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# Laboratory Quality Control Based on Risk Management; Approved Guideline

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

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



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*Advancing Quality in Health Care Testing*

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### Abstract

Clinical and Laboratory Standards Institute document EP23-A—*Laboratory Quality Control Based on Risk Management; Approved Guideline* provides guidance to laboratories on the development of quality control plans for measuring systems. Regulatory requirements, information provided by the manufacturer, information pertaining to the laboratory environment, and medical requirements for the test results are evaluated, using risk management principles, to develop a quality control plan tailored to the particular combination of measuring system, laboratory environment, and clinical application. The effectiveness of the laboratory quality control plan is monitored to detect trends, identify corrective actions, and provide continuous quality improvement. The advantages and limitations of various quality control processes are considered.

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## Foreword

Although the manufacturer is responsible for quality in design of its measuring system and reagents, the laboratory and, ultimately, the laboratory director are accountable for the quality of test results. To establish effective quality control (QC), laboratories should process an array of information (regulatory requirements, manufacturer-provided information, the laboratory's environment, and the medical applications of tests performed) through a risk assessment process. This process identifies potential weaknesses in the measuring system and 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 in consideration of the clinical use of a laboratory result. This document provides guidance to laboratories for establishing a quality control plan (QCP). Once developed, the QCP is monitored for effectiveness and modified as unanticipated failure modes or underestimated risks of error are discovered or as particular control procedures are no longer required once sufficient objective data demonstrating reliable performance have been established. The advantages and limitations of a variety of QC measures are discussed to help the laboratory develop a QCP that is appropriate for its particular measuring system, laboratory, and clinical environment.

Compliance with EP23 may not satisfy the requirements of all regulatory, accreditation, or certification bodies. Laboratories need to comply with all applicable requirements in the development of their QCPs.

## Key Words

Quality control, risk assessment, risk management



# Laboratory Quality Control Based on Risk Management; Approved Guideline

## 1 Scope

This document 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 manufacturer and identified by the laboratory, applicable regulatory and accreditation requirements, and the individual health care and laboratory setting are considered in development of the QCP. This document is intended to guide laboratories in determining quality control (QC) procedures that are both appropriate and effective for the test being performed.

This document may not satisfy the requirements of all regulatory, accreditation, or certification bodies. Laboratories need to comply with all applicable requirements in the development of their QCPs.

## 2 Introduction

### 2.1 Quality Control Plan

Health care providers need test results that are relevant, accurate, and reliable for patient care. A number of factors can adversely affect the quality of test results and present a risk of harm to the patient, from failures of the measuring system, to operator errors, to environmental conditions. Failure is used in this document in the context of risk management and means, in the broadest sense, a case when the system does not meet the user's expectation. 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 may produce an incorrect result, and incorrect use of a measuring system that may 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 document 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. QC in this context 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 to mitigate and prevent errors in testing that describes the practices, resources, and sequences of specified activities to control the quality of a particular measuring system or measurement process to ensure intended purposes are met. The laboratory establishes QCPs to prevent failures and to detect nonconformities that may occur before incorrect results are reported to health care providers and clinical action is taken.

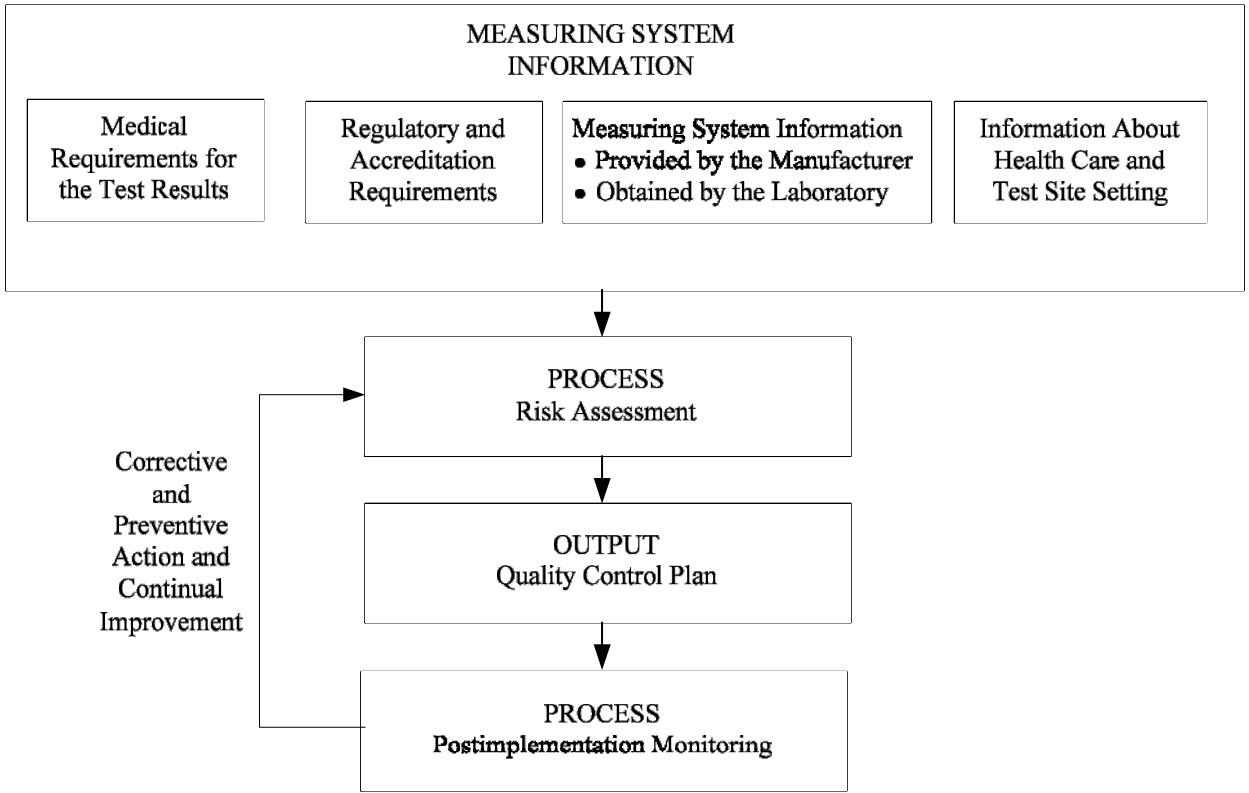
Development of a QCP requires an understanding of the preexamination (preanalytical), examination (analytical), and postexamination (postanalytical) processes, and identification of the weaknesses (potential failure modes) in these processes where failures can impact a given measuring system and potentially cause patient harm. Although this guideline addresses the examination phase, it is important to recognize that preexamination (preanalytical) and postexamination (postanalytical) processes are also important and may directly influence the acceptability of a measurement result. For example, sample collection, transport, and handling may contribute to the acceptability of a reported result.

The laboratory should manage risk by implementing QCPs that serve to ensure test result quality is appropriate for clinical use of the information by:

- 1) Monitoring the testing process for the occurrence of errors
- 2) Introducing control procedures to mitigate the occurrence of errors

Given the variety of testing performed in a typical health care facility, with particular measuring systems, examination (analytical) procedures, laboratory environments, and clinical applications, laboratories need guidance to determine effective combinations of control strategies to achieve reliable test results. This document 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 1) collecting the necessary information from manufacturers, literature, regulatory and accreditation agencies, the laboratory's particular environment, and the clinical application of test results; 2) conducting a risk assessment; and 3) identifying effective control measures to reduce risk.

In the risk management process, attempts are first made to identify and eliminate the causes of potential process and system failures before implementing measures to detect failures and/or their effects (eg, incorrect test results). Activities to monitor ongoing performance are directed toward the identification of unpredicted events that cause risks, modification of the QCP, and continual improvement (CI). Figure 1 depicts schematically the inputs needed to develop and continually improve a QCP.

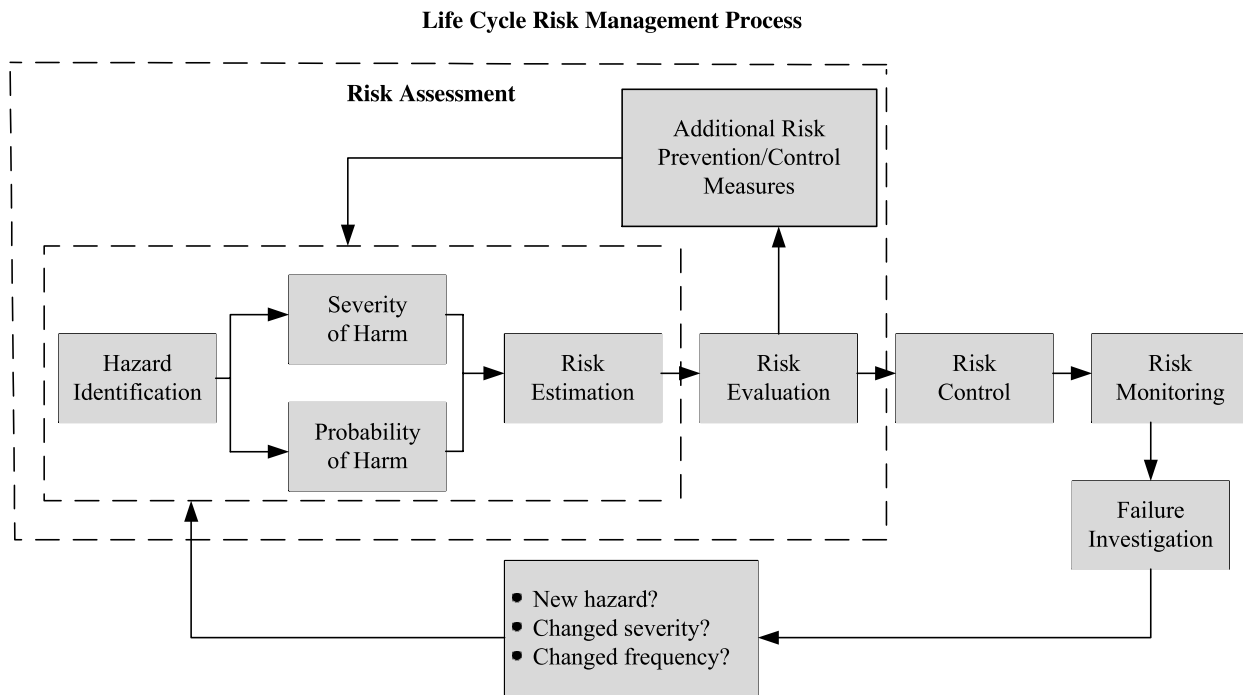


**Figure 1. Process to Develop and Continually Improve a QCP.** (The terms *corrective and preventive action* and *continual improvement* are referred to as CAPA and CI, respectively, in risk management literature.)

2.2 Risk Management

Application of risk management to the entire life cycle of a laboratory measuring system is described for manufacturers in ISO 14971.<sup>1</sup> The principles described are adapted in this document for use by laboratories to develop a QCP for measuring systems currently in use or introduced in a health care setting.

Risk assessment, the central component of the overall risk management process, is based on the analysis (identifying hazards and estimating the probability and severity of harm) and evaluation of the risks that can result from a measuring system failure, as shown in the following flow chart in Figure 2.



**Figure 2. Risk Management Process**

During the risk analysis process, each laboratory should consider how built-in and laboratory-applied control procedures for a measuring system reduce the risk of harm from an erroneous result, a delayed result, or the nondelivery of a result. Analysis of the risk of harm should take into consideration information on the measuring system (see Section 6.2), information about the laboratory (see Section 6.3), and the performance required for the medical applications of the test results (see Section 6.4). Risk estimation is the combination of the probability of occurrence of harm and the severity of that harm. Risk estimation should take into account the hazardous situations that could occur from incorrect test results or delays in treatment.

Residual risk is that risk which remains after all control measures have been implemented to prevent and/or mitigate those adverse events that cannot be avoided by improvement of the measuring system, its components, processes, or personnel competencies. A determination of the acceptability of this residual risk of harm 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 in terms of financial liability of the treating parties vs known benefits to the patient. All laboratory tests have some residual risk associated with them. Therefore, if the known residual risk is found to be unacceptable, then a determination should be made as to the feasibility of adding more risk control measures vs avoiding the risk by not implementing the test or the particular measuring system being considered.

A QCP is developed to reduce residual risk (see Section 7.4), first by 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 control procedures required to achieve a clinically acceptable risk of harm to a patient. The final QCP should also comply with all regulatory and accreditation requirements.

Once the QCP is implemented, any future incidences of measuring system failure are investigated in order to determine the sources of failure and whether modification of the QCP is required (see Section 8). If a new hazard is identified or if the severity or probability of harm is greater than anticipated, the output of risk monitoring feeds back to the appropriate step in the risk analysis process, and risk control procedures are revised to reduce the risk.

The laboratory is ultimately responsible for ensuring that the testing processes and the QCPs have the capability to provide the analytical quality of results required for patient care.

### 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 blood-borne pathogens. Standard and universal precaution guidelines are available from the Centers for Disease Control and Prevention.<sup>2</sup> 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.<sup>3</sup>

### 4 Terminology

#### 4.1 A Note on 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 the United States, Europe, and elsewhere; that these differences are reflected in CLSI, International Organization for Standardization (ISO), and European Committee for Standardization (CEN) documents; and that legally required use of terms, regional usage, and different consensus timelines are all important considerations in the harmonization process. In light of this, CLSI’s consensus process for development and revision of standards and guidelines focuses on harmonization of terms to facilitate the global application of standards and guidelines.

To align the usage of terminology in this document with that of ISO, the term *accuracy*, in its metrological sense, refers to closeness of agreement between a measured quantity value and a true quantity value of a measurand, and comprises both random and systematic effects applied to one result. *Trueness* is used in this document when referring to the “closeness of the agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value”; the measurement of trueness is usually expressed in terms of *bias*, which is recognized as the estimate of a systematic error. *Precision* is defined as the “closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions.” As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low. For its numerical expression, the term *imprecision* is used, which is the “dispersion of a set of replicate measurements or values expressed quantitatively by a statistic, such as standard deviation or coefficient of variation.” In addition, different components of precision are defined in EP23, primarily *repeatability*, ie, “measurement precision under a set of repeatability conditions of measurement,” whereas *reproducibility* describes the condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects. Finally, it is important to note that in EP23, the term *error* (ie, deviation from truth, accuracy, or

correctness; includes mistakes) includes, but is used in a much broader sense than, the VIM<sup>4</sup> term *error of measurement*, (ie, measured quantity value minus a reference quantity value).

## 4.2 Definitions

**acceptable risk** – a state achieved in a measuring system where 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—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 (JCGM 200:2008).<sup>4</sup>

**analyte** – component represented in the name of a measurable quantity (ISO 17511)<sup>5</sup>; **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 (ISO 17511).<sup>5</sup>

**bias (of measurement)** – estimate of a systematic measurement error (JCGM 200:2008).<sup>4</sup>

**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 (JCGM 200:2008)<sup>4</sup>; **NOTE:** 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.

**continual improvement (CI)** – recurring activity to increase the ability to fulfill requirements (ISO 9000 [3.2.13])<sup>6</sup>; **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 in order to provide added benefits to the customer and organization.<sup>7</sup>

**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 action** – action to eliminate the cause of a detected nonconformity or other undesirable situation (ISO 9000 [3.6.5])<sup>6</sup>; **NOTE 1:** There can be more than one cause for a nonconformity; **NOTE 2:** Corrective action is taken to prevent recurrence, whereas preventive action (ISO 9000 [3.6.4])<sup>6</sup> is taken to prevent occurrence.

**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** – measured quantity value minus a reference quantity value (JCGM 200:2008)<sup>4</sup>; deviation from truth, accuracy, or correctness; includes mistakes; **NOTE:** It is important to note that in EP23, the term “error” includes, but is used in a much broader sense than, the VIM<sup>4</sup> term “error of measurement.”

**examination** – set of operations having the object of determining the value or characteristics of a property (ISO 15189)<sup>8</sup>; 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 is observed; generally describes the way the failure occurs and its impact on equipment operation.<sup>9</sup>

**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.<sup>10</sup>

**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** – physical injury or damage to the health of people, or damage to property or the environment (ISO/IEC Guide 51)<sup>11</sup>; **NOTE:** In this guideline, damage to property or the environment is considered harmful only if that damage directly harms people.

**hazard** – potential source of harm (ISO/IEC Guide 51).<sup>11</sup>

**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 (GHTF/SG1/N045:2008).<sup>12</sup>

**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** – information supplied by the manufacturer with an *in vitro* diagnostic medical device concerning the safe and proper use of the reagent(s) or the safe and correct operation, maintenance, and basic troubleshooting of the instrument (ISO 15197).<sup>13</sup>

**laboratory director** – competent person(s) with responsibility for, and authority over, a laboratory (ISO 15189)<sup>8</sup>; **NOTE 1:** For the purposes of ISO 15189,<sup>8</sup> the person or persons referred to are designated collectively as laboratory director; **NOTE 2:** National, regional, and local regulations may apply with regard to qualifications and training (ISO 15189).<sup>8</sup>

**matrix (of a material system)** – totality of components of a material system except the analyte (ISO 17511).<sup>5</sup>

**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 (ISO 17511).<sup>5</sup>

**measurand** – quantity intended to be measured (JCGM 200:2008)<sup>4</sup>; **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 (JCGM 200:2008)<sup>4</sup>; **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 (JCGM 200:2008).<sup>4</sup>

**measuring system** – set of one or more measuring instruments and often other devices, including any reagent and supply, assembled and adapted to give information used to generate measured quantity values within specified intervals for quantities of specified kinds (JCGM 200:2008)<sup>4</sup>; **NOTE:** A measuring system may consist of only one measuring instrument (JCGM 200:2008).<sup>4</sup>

**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.<sup>14</sup>

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

**precision (measurement)** – closeness of agreement between indications or measured quantity values obtained by replicate measurements on the same or similar objects under specified conditions (JCGM 200:2008)<sup>4</sup>; **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 (JCGM 200:2008)<sup>4</sup>; **NOTE 2:** The ‘specified conditions’ can be, for example, repeatability conditions of measurement, intermediate precision conditions of measurement, or reproducibility conditions of measurement (see ISO 5725-3:1994)<sup>15</sup> (JCGM 200:2008)<sup>4</sup>; **NOTE 3:** Measurement precision is used to define measurement repeatability, intermediate measurement precision, and measurement reproducibility (JCGM 200:2008).<sup>4</sup>

**preventive action** – action to eliminate the cause of a potential nonconformity or any other undesirable potential situation (ISO 9000 [3.6.4])<sup>6</sup>; **NOTE 1:** There can be more than one cause for a potential nonconformity; **NOTE 2:** Preventive action is taken to prevent occurrence, whereas corrective action (ISO 9000 [3.6.4])<sup>6</sup> is taken to prevent recurrence.

**process mapping** – graphical descriptions of processes that include detailed flow charts, workflow diagrams, and value stream maps.

**quality** – degree to which a set of inherent characteristics fulfills requirements (ISO 9000).<sup>6</sup>

**quality assurance** – part of quality management focused on providing confidence that quality requirements will be fulfilled (ISO 9000).<sup>6</sup>

**quality control (QC)** – part of quality management focused on fulfilling quality requirements (ISO 9000)<sup>6</sup>; **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:** This includes the operational techniques and activities that are used to fulfill requirements for quality; **NOTE 3:** In clinical laboratory testing, QC includes the procedures intended to monitor the performance of a test procedure to ensure reliable results.

**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.

**quality control sample** – a stable sample designed to simulate a patient sample.

**quality management system (QMS)** – management system to direct and control an organization with regard to quality (ISO 9000)<sup>6</sup>; **NOTE 1:** Systematic and process-oriented efforts are essential to meet quality objectives; **NOTE 2:** For the purposes of ISO 15189, the “quality” referred to in this definition relates to matters of both management and technical competence (ISO 15189)<sup>8</sup>; **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: Documents and Records, Organization, Personnel, Equipment, Purchasing and Inventory, Process Management, Information Management, Nonconforming Event Management, Assessments, Continual Improvement, Customer Focus, and Facilities and Safety.

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

**repeatability (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) under a set of repeatability conditions of measurement (condition of measurement, out of a set of conditions 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) (JCGM 200:2008).<sup>4</sup>

**reproducibility (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) under reproducibility conditions of measurement (condition of measurement, out of a set of conditions that includes different locations, operators, measuring systems, and replicate measurements on the same or similar objects) (JCGM 200:2008).<sup>4</sup>

**residual risk** – risk remaining after risk control measures have been taken (ISO 14971).<sup>1</sup>

**risk** – combination of the probability of occurrence of harm and the severity of that harm (ISO/IEC Guide 51).<sup>11</sup>

**risk analysis** – systematic use of available information to identify hazards and to estimate the risk (ISO/IEC Guide 51)<sup>11</sup>; **NOTE:** Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm (ISO 15189).<sup>8</sup>

**risk assessment** – overall process comprising a risk analysis and a risk evaluation (ISO/IEC Guide 51).<sup>11</sup>

**risk estimation** – process used to assign values to the probability of occurrence of harm and the severity of that harm (ISO 14971).<sup>1</sup>

**risk evaluation** – process of comparing the estimated risk against given risk criteria to determine the acceptability of the risk (ISO 14971).<sup>1</sup>

**risk management** – systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk (ISO 14971).<sup>1</sup>

**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 (ISO 15189)<sup>8</sup>; **EXAMPLE:** A portion of serum taken from a specimen of coagulated blood.

**severity** – measure of the possible consequences of a hazard (ISO 14971).<sup>1</sup>

**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; **NOTE:** In some countries, the term “specimen” may be used to mean a sample of biological origin intended for examination by a medical laboratory.

**stability** – the ability of an *in vitro* diagnostic (IVD) reagent to maintain its performance characteristics consistent 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 instruments or measuring systems after calibration.

**system** – set of interrelated or interacting elements (ISO 9000).<sup>6</sup>

**systematic error (of measurement)** – component of measurement error that in replicate measurements remains constant or varies in a predictable manner (JCGM 200:2008)<sup>4</sup>; **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 (JCGM 200:2008)<sup>4</sup>; **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 (JCGM 200:2008)<sup>4</sup>; **NOTE 3:** Systematic measurement error equals measurement error minus random measurement error (JCGM 200:2008).<sup>4</sup>

**test** – determination of one or more characteristics according to a procedure (ISO 9000).<sup>6</sup>

**trueness (measurement)** – closeness of agreement between the average of an infinite number of replicate measured quantity values and a reference quantity value (JCGM 200:2008)<sup>4</sup>; **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 (modified from ISO 17511).<sup>5</sup>

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

**use error** – an error whose root cause derives from an aberration in the process.

**user** – the laboratory or person using the measuring system.

**value stream mapping** – a lean manufacturing technique used to analyze the flow of materials and information currently required to bring a product or service to a consumer.

### 4.3 Abbreviations and Acronyms

|    |                          |
|----|--------------------------|
| CI | continual improvement    |
| CV | coefficient of variation |

|     |                                                |
|-----|------------------------------------------------|
| EQA | external quality assessment                    |
| ISO | International Organization for Standardization |
| IVD | <i>in vitro</i> diagnostic                     |
| LIS | laboratory information system                  |
| PT  | proficiency testing                            |
| QC  | quality control                                |
| QCP | quality control plan                           |
| QMS | quality management system                      |
| UPS | uninterruptible power supply                   |

## 5 Quality Control Toolbox

Using the appropriate combination of QC “tools” allows a laboratory to develop a comprehensive QCP that can effectively monitor and evaluate the performance of a measuring system. This section provides a brief description of some of the established QC tools that are part of a well-designed QCP.

Each QC tool has strengths and weaknesses. There is no perfect QC tool that consistently prevents or detects all failures. Understanding their strengths and weaknesses allows use of the tools to effectively reduce risk. This section briefly describes the QC tools and outlines their strengths and weaknesses.

### 5.1 Analysis of Quality Control Samples

#### 5.1.1 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 of testing QC samples is that measuring system failures or errors and use errors that would negatively influence the testing of patient samples also affect the results obtained with the QC samples for many (but importantly, not all) failure modes.

The use of QC samples to monitor a measuring system involves establishing the mean and standard deviation 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 for each measuring system:

- The frequency of QC sample test events
- The type and number of QC samples tested per test event
- The statistical QC limits used to evaluate the results
- The frequency of periodic review for detecting shifts and trends
- The actions taken when results exceed acceptable limits

In 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 may remain undetected until the next control event. Furthermore, when an error is detected, it may 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 impact of errors on patient care), the stability of the analyte or measurand, stability of the examination

(analytical) process, the number of patient samples processed between QC events, and frequency of calibration will influence the maximum interval between control events.

If a number of laboratories use the same measuring system and the same lot of QC samples, the results obtained may be pooled to provide peer group comparisons between laboratories. See Section 5.1.2 for a discussion of interlaboratory comparisons.

In evaluating the effectiveness of QC samples, consider the following:

- 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 may not be challenged by the control procedure (eg, phlebotomy and sample collection).
- QC samples may not mimic patient samples in all properties. Matrix effects may exist due to noncommutability of a QC sample with clinical samples, which could cause incorrect inferences about the measuring system results for patient samples, eg, QC results following a reagent lot change may not mirror the performance with patient samples.<sup>16</sup> Also, QC samples may 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 a long shelf life are needed to avoid frequent crossover evaluations between lots. Adequate stability once the container is opened should also be considered. Measurand (analyte) instability is a potential source of variability that can confound interpretation of a QC result.
- If an assay is sensitive to contamination or degradation, eg, molecular testing, it may be appropriate to consider one-time-use vials of control material.

Information to establish and maintain an effective QC strategy for quantitative tests using QC samples is contained in CLSI document C24.<sup>17</sup>

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 (analyte) values can be used to verify method performance.

In addition, undetected bias and excessive imprecision are risks. The frequency of QC sample procedures must be designed to have a high probability of detecting an error that exceeds a stated medically allowable error limit. At the least, the ability of the QC procedures to detect an error that exceeds a medically allowable error limit should be evaluated.

### 5.1.2 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. 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 [analyte] availability) apply.

Before Internet reporting of interlaboratory summaries, interlaboratory comparisons could be used only for retrospective checks of performance stability. However, Internet-based interlaboratory programs now provide timelier data analysis and feedback.

### **5.1.3 Trueness Controls**

Target values may also be assigned to reference (or QC sample) materials by reference measurement laboratories using certified primary reference measurement procedures. These control samples may be used to verify the trueness of a laboratory's measuring system, as long as 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.

### **5.1.4 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 give individual laboratories a means of determining 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.

### **5.1.5 Control Materials Without Assigned Values (Unassayed Quality Control Samples)**

Unassayed control material is widely used in clinical laboratories. It is generally less expensive than assayed control material and is used to evaluate accuracy and precision. Unassayed QC material has no assigned analyte values provided by the manufacturer and is not linked to specific assay/measuring systems. The end user assigns expected results to unassayed QC material. The manufacturer may indicate whether a specific analyte is present or absent in the QC material preparation without indicating an expected assay result.

### **5.1.6 Frequency of Quality Control Sample Testing**

The optimal frequency of performing QC sample procedures depends on built-in and other controls for a given measuring system, the stability of that measuring system, and conditions in the laboratory identified through risk assessment that could affect the reliability of testing such as staff turnover, and the clinical risk of harm to a patient if an erroneous result is reported and acted on. The frequency of control 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 may have received incorrect results. For example, a laboratory that evaluates the examination (analytical) process every eight hours will identify a systematic error condition much earlier than a laboratory that monitors the examination process every 24 hours. However, the total number of specimens tested in a time interval may also influence the frequency of monitoring. For example, a laboratory that tests 2000 samples in one 24-hour period might perform control procedures several times a day, whereas a laboratory that tests 50 samples in an eight-hour shift might perform control procedures at the beginning and end of a shift. The complex relationship between the frequency of QC sample testing,

frequency of false rejection, and the quality of patient results has been explored by Parvin and colleagues.<sup>18-20</sup>

## **5.2 Controls Built Into the Measuring System**

### **5.2.1 Integrated Quality Control Samples**

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

Information concerning these integrated QC samples and their effectiveness in risk mitigation should be included in the information obtained from the manufacturer. Note that 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 manufacturer and determine (1) 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 specimen sampling step, and (2) whether 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 may be optimized for a specific measuring system. For example, a QC sample may be too closely related to the calibrators, so it does not simulate routine patient samples and cannot serve as an effective control.

### **5.2.2 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 may 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, may be monitored.

Modern measuring systems may also incorporate procedures for the detection of use errors. These may include detection of sample underfills, overfills, bubbles, and clots; use of the wrong anticoagulant; sample hemolysis; and out-of-specification ambient temperature, pressure, or humidity; as well as other potential use errors. Measuring systems may 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, may be included in the information obtained from the manufacturer.

Measuring system function checks may 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 manufacturer should indicate which functions are critical to producing accurate results, as well as which are monitored and which are not.

### **5.2.3 Electronic System Checks**

Some measuring systems include software algorithms that check certain 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 manufacturer. The information should

indicate which components and functions are monitored electronically and which are not, and how reliably the system checks can prevent incorrect results.

#### **5.2.4 Calibration Checks**

Automated calibration checks are intended to detect certain calibration problems before running QC samples 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 manufacturer or derived from previous valid calibrations.

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

Note that calibration checks may detect calibrations that fall outside expected statistical ranges, but may not verify that a calibration meets traceability requirements.

### **5.3 Control Techniques Using Patient Test Results**

#### **5.3.1 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.

In most cases, patient sample testing eliminates matrix effects. Principal limitations are that some analytes or measurands may 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.

#### **5.3.2 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 distribution of test results are relatively stable. This technique eliminates matrix effects and can detect systematic errors.<sup>21,22</sup>

The effectiveness of using aggregated patient results is dependent on using an adequate number of results to calculate the aggregated value. The necessary number of results for effective performance varies between measurands (analytes) and may 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 (analytes), but may be difficult to implement in real time. Robust estimation and/or outlier rejection techniques may be required for successful monitoring.<sup>23</sup> Changing patient populations and their effect on the overall distribution of results may limit the effectiveness of this technique. For example, the addition of an oncology population to the patient mix will alter the distribution of hematology results.

### 5.3.3 Identifying Implausible Values

Implausible values are results that are considered physiologically impossible or so improbable they are simply not believable. They could 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 a short sample volume). In practice, 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 influences that cause large deviations from the expected values. Although many health care providers would 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 (analytes). For many, it is difficult to select a limit that would not suppress valid results or trigger too many false alerts. The time required 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. Effective use as a QC tool requires implementation via laboratory information system (LIS), middleware, or other computer system.

### 5.3.4 Delta Checks

A delta check evaluates 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.

Delta checks may be useful for detecting sample mislabeling or improperly collected samples. Delta checks detect measurement errors only when they are large.<sup>24,25</sup> They provide an additional safeguard in case a health care provider might not question an unexpected result.

Establishing and verifying optimal delta check limits can be difficult. The delta or degree of difference that is significant may vary over the entire range of concentrations for a given measurand (analyte). The variation is also dependent on the time interval between samples. The same delta values may not apply to all patient populations.

The time required to investigate false-positive delta checks can be extensive and may require obtaining additional clinical information to differentiate true errors from false-positive errors. Manual implementation is not practical. Effective use as a QC tool requires implementation via LIS, middleware, or other computer system.

### 5.3.5 Correlation of Multiple Analytes in the Same Sample

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

pathological conditions. The time required to investigate false-positive alerts can be extensive and may require obtaining clinical information to differentiate true errors from false-positive errors.

## 6 Information Gathering for Risk Assessment

To conduct a risk analysis, the laboratory should systematically identify the potential failure modes, determine the possible failure causes, estimate the probability that the failures would occur, estimate the probability that each failure would lead to a hazardous situation (eg, a clinically incorrect result reported to a health care provider), estimate the severity of harm that could arise from the hazardous situation, and estimate the likelihood that harm would come to a patient.

To perform the risk analysis, the laboratory should collect information, where available, from the following sources in Table 1. If a laboratory needs additional information from the manufacturer to develop a QCP, it should contact the manufacturer and request that information.

**Table 1. Sources for Collecting Information for Risk Analysis**

| Information                                                                                                                                                                                                                                                                                                                                                                                                                                              | Source                                                             |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|
| Regulatory and accreditation requirements <ul style="list-style-type: none"> <li>• Mandated QC procedures</li> <li>• Required quality assurance activities</li> <li>• Regulatory agency recall and device failure notifications</li> </ul>                                                                                                                                                                                                               | Regulatory authorities; accreditation agencies                     |
| Measuring system information <ul style="list-style-type: none"> <li>• Intended use (including limitations, warnings, and precautions)</li> <li>• Environmental requirements</li> <li>• Instructions for calibration, maintenance, use, and reagent storage</li> <li>• Calibrator traceability information</li> <li>• QC features</li> <li>• Risk mitigation recommendations</li> </ul>                                                                   | <i>In vitro</i> diagnostic (IVD) manufacturer                      |
| Laboratory information <ul style="list-style-type: none"> <li>• Environmental conditions, including facilities and utilities, and existing controls</li> <li>• Installation/operational qualification reports</li> <li>• Operator training and competency</li> <li>• Internal performance evaluation/verification data</li> <li>• External performance data (eg, proficiency test results)</li> <li>• Process map covering the steps analyzed</li> </ul> | Laboratory                                                         |
| Publications and reports from laboratory peers <ul style="list-style-type: none"> <li>• Published performance evaluations</li> <li>• Published clinical studies</li> <li>• Other users (eg, user groups, listservs, forums)</li> </ul>                                                                                                                                                                                                                   | Laboratory                                                         |
| Clinical information <ul style="list-style-type: none"> <li>• Clinical applications for use of a test result</li> <li>• Biological reference intervals and clinical decision levels</li> <li>• Foreseeable medical errors that could result from incorrect, delayed, or no results</li> <li>• The severity of patient harm that would result from the hazardous situations</li> </ul>                                                                    | Laboratory, in consultation with medical users of the test results |

Appendix A provides a checklist for establishing a QCP based on information collected for risk analysis, which is outlined in Table 1.

### 6.1 Regulatory and Accreditation Requirements

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

## **6.2 Information About the Measuring System**

### **6.2.1 Information Obtained From the Manufacturer**

Manufacturers should provide adequate instructions for use. These instructions typically include the intended use, test procedure, technical performance, maintenance, and storage recommendations (temperature, humidity, and light), environmental conditions of operation, limitations, and other information needed to properly install, verify, and use the measuring system.

Awareness of key risk mitigation features for the measuring system is another important piece of information necessary for development of an appropriate and effective QCP. If a laboratory needs additional information from the manufacturer to develop a QCP, it should contact the manufacturer and request detailed information.

#### **6.2.1.1 Laboratory-Developed Tests**

For laboratory-developed tests or laboratory-modified tests, the laboratory is responsible for determining and documenting information analogous to that of IVD manufacturers listed in Table 1.

### **6.2.2 Information Obtained by the Laboratory**

Measuring system performance data, generated by sources independent of the manufacturer, may be available from:

- In-house generated evaluation data
- Interlaboratory comparison programs provided by suppliers of QC samples
- External quality assessment (EQA) or proficiency testing (PT) programs
- Evaluation in the peer-reviewed literature

## **6.3 Information About the Laboratory**

### **6.3.1 Laboratory Environment**

When the laboratory is following the manufacturer's instructions for use, the laboratory needs to assess how conditions specific to the laboratory could affect the measuring system. Examples of potential environmental hazards are dust, temperature, humidity, electrical or water quality, and atmospheric pressure. The QCP should reflect these conditions and their potential influence on the test results.

### **6.3.2 Operator Training and Competency**

Operator training and competency (see CLSI document GP21<sup>26</sup>) can affect the quality of patient test results and the following should be assessed:

- Employee 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 organization policies
- Technical laboratory skills
- Competence of temporary personnel

- Education, licensure, and/or certification
- Visual acuity, color perception, and hearing impairment
- Operator fatigue

The effectiveness of the laboratory's quality management system (QMS) in addressing the personnel knowledge and skills should be considered when the laboratory is developing the QCP. See CLSI document GP26<sup>27</sup> for more information on the personnel component of the quality system essentials. The laboratory should include personnel performing testing at sites outside the main laboratory if the main laboratory is responsible for the quality of testing in remote sites. The laboratory should be sensitive to the fact that personnel who perform testing outside the main laboratory may have limited laboratory training and/or less competence in performing testing. The QCP may need to reflect such conditions, depending on the susceptibility of the measuring system to user influence.

### 6.3.3 Frequency of Patient Testing

The QCP should take into account the frequency with which patient testing is performed. Operators may 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 of a measuring system leads to operator competency. Consequently, when a test is not performed often in a laboratory, consider the need for more frequent QC sample testing. Give consideration to the simplicity/complexity of the procedure and whether the procedure is fully automated, semiautomated, or manual. Dilutions, extractions, calculations, and maintenance of measuring systems and support equipment (refrigerators, centrifuges, balances), for example, can be challenging to operators. Manual steps typically pose more risks than automated processes owing to the greater likelihood of use errors.

## 6.4 Information About the Clinical Application

The laboratory should consider the intended medical uses and potential impacts of a patient's test result when creating the QCP. Development of the QCP may require consultation with the health care providers using the test results. Factors to consider include the 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 (signs and symptoms) influence the interpretation of the test results; and whether any medical actions in response to an erroneous test result are likely to lead to serious harm.

Consider the amount of time that typically lapses between reporting a test result and a health care provider taking action based on that result when developing the QCP. When a result is likely to be acted on immediately, such as might occur in the emergency department, intensive care unit, or the operating room, it is advisable to focus the QCP on preventing incorrect results, because there will be no time to issue a corrected report for an erroneous result. For example, a blood gas or electrolyte result may 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 may be less stringent.

## 6.5 Process Mapping

It is useful to break down the total measuring process into steps to facilitate identification of weak points and allow the laboratory to recognize potential failure modes that could present significant risks to patients, and to identify opportunities in the process to control them.<sup>28</sup> For effectiveness, process mapping should provide a useful level of detail.

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

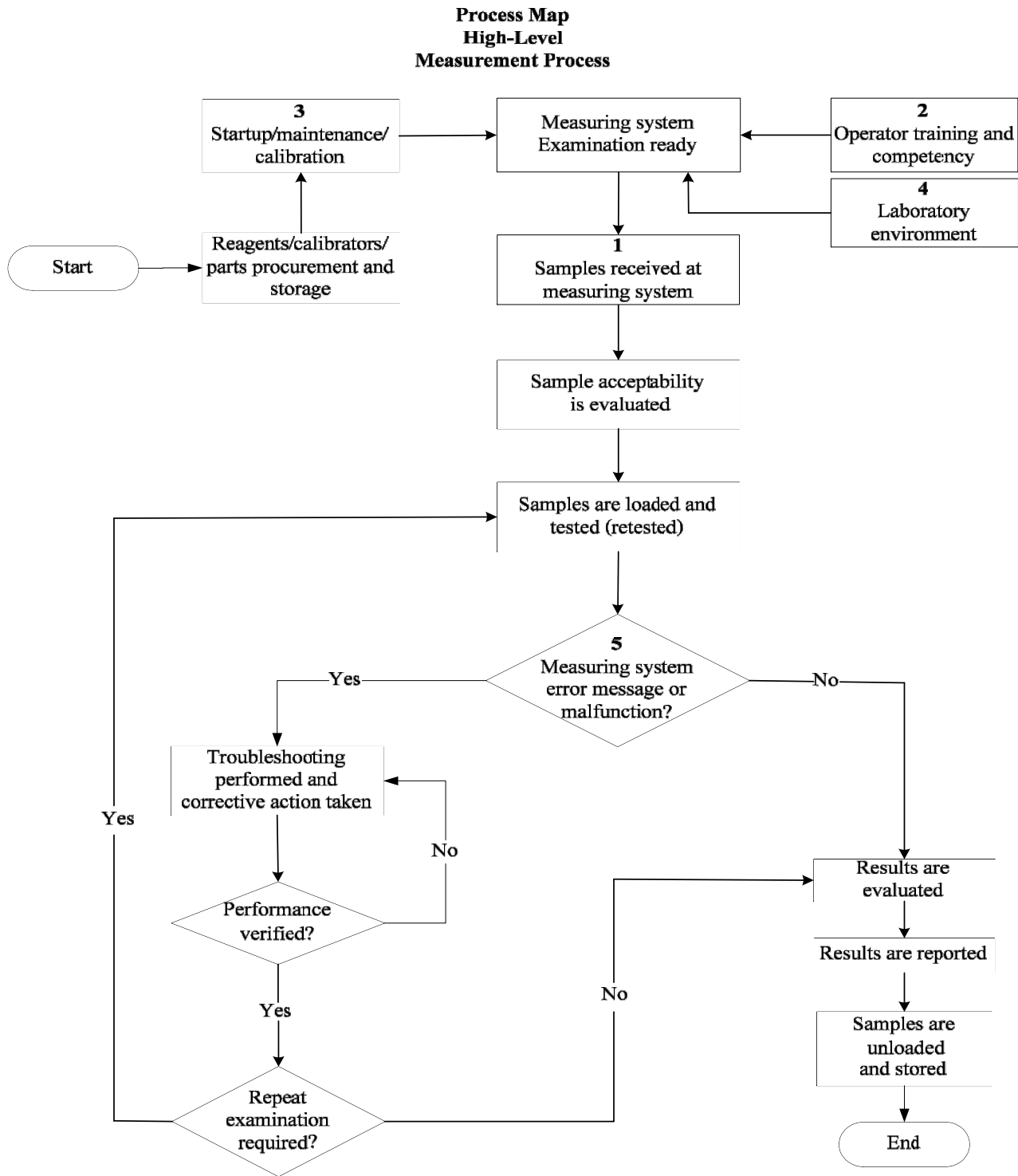
**Table 2. Key Processes in the Laboratory Path of Workflow (from CLSI document GP02)<sup>29</sup>**

| Preexamination (Preanalytical) Processes                                                                                                                                                                                              | Examination (Analytical) Processes                                                                                                | Postexamination (Postanalytical) Processes                                                                                                                                            |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"> <li>• Examination ordering</li> <li>• Sample collection and labeling</li> <li>• Sample transport</li> <li>• Sample receipt and accessioning</li> <li>• Preexamination sample processing</li> </ul> | <ul style="list-style-type: none"> <li>• Examination</li> <li>• Results review and follow-up</li> <li>• Medical review</li> </ul> | <ul style="list-style-type: none"> <li>• Results reporting</li> <li>• Results archiving</li> <li>• Sample archiving</li> <li>• Charging for examinations, where applicable</li> </ul> |

The following bulleted list provides some considerations for developing a process map when conducting a measurement on an automated measuring system. In many cases, the same logic may apply to a group of analytes performed on a single measuring system or to a group of identical measuring systems used within a health care environment. A single QCP may apply to a measuring system or multiple measuring systems, or to individual analytes.

- Operator training and competency – An operator is trained to operate the measuring system and required to demonstrate competency to follow the manufacturer’s instructions for use.
- Reagent/calibrator/parts procurement and storage – Reagents and calibrators are obtained from the manufacturer and distributors, and stored in the laboratory according to the manufacturer’s instructions.
- Patient sample acceptability evaluation – A sample should be available in the appropriate collection tube and processed as required.
- Startup – The measuring system is set up and verified as operational before testing of patient samples can occur.
- Calibration – The measuring system is calibrated and its performance is evaluated to verify the measuring system is functioning within specification.
- Loading and testing of patient samples – For analysis, the operator places a prepared specimen tube on the measuring system intake component where the bar code label may be read to identify the specific patient sample, or a load list may be prepared to identify the sequence of samples.
- 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 analyte concentration by comparing the response to the calibration function.
- 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 displayed.

A high-level measurement process map is shown in Figure 3. Many of these processes are common to other measuring systems.



**Figure 3. Example of Process Map.** The intent of this process map is to help identify potential stages or steps in the process that may require subsequent failure mode analysis. The stages or steps can be used to identify control points for which procedures can be included in the QCP for the measuring system. The numbers in the process map boxes are examples linking to specific branches in the fishbone diagram to identify potential failure modes (see Figure 4).

The identified potential failure modes in this process are shown in the fishbone diagram in Figure 4. A fishbone diagram identifies the possible causes of failure modes and their effects. In this example, failures

are identified that could lead to incorrect test results. The components of the measuring system (and their potential sources of failure) include the sample (integrity and presentation), the operator (inadequate training, incompetency, and staffing), the reagent/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, because these are control processes. This is an example and is not all-inclusive. CLSI document EP18<sup>30</sup> provides a detailed list of potential sources of failure (potential failure modes).

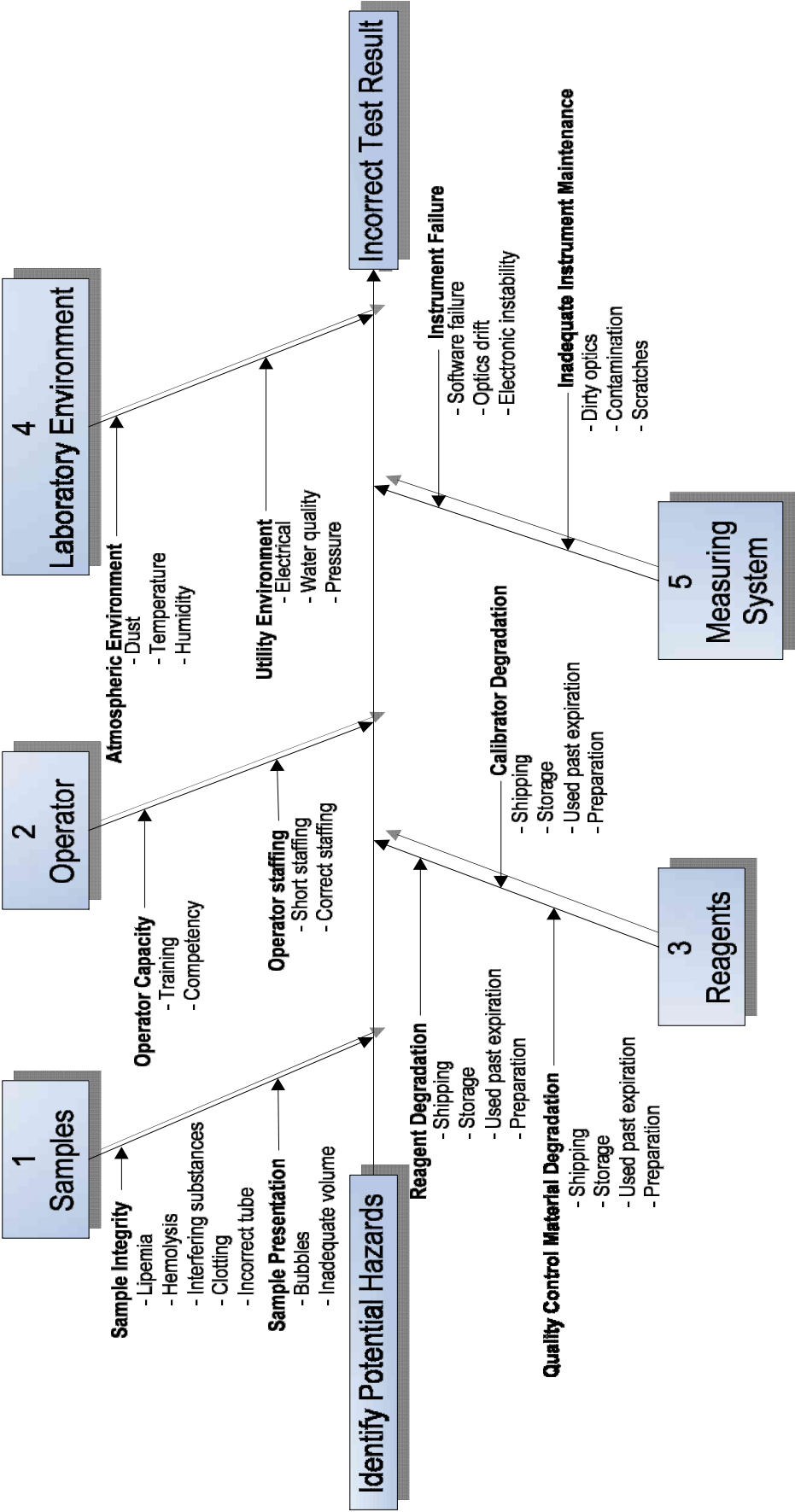


Figure 4. Fishbone Diagram for Identification of Potential Failure Modes<sup>a</sup>

<sup>a</sup>This fishbone diagram is an example; it is not all-inclusive.

7 Developing the Quality Control Plan

The overall process for assessing risk and establishing a QCP is shown schematically in Figure 5. Numbering in the flow diagram corresponds to upcoming sections in EP23.

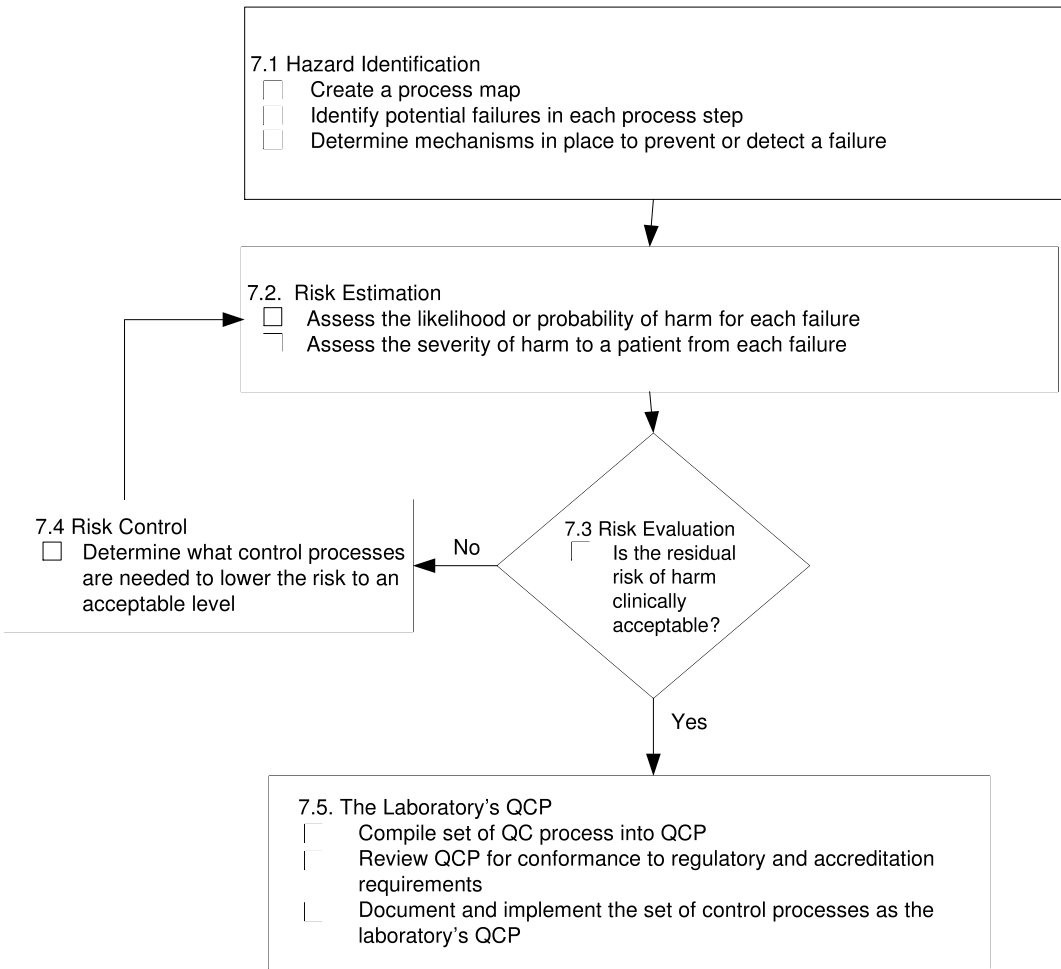


Figure 5. Risk Assessment

7.1 Hazard Identification

The first step in risk analysis is to identify the potential hazards and their causes. The laboratory should map the total testing process in detail and collect the information discussed in Section 6. This information is used to identify potential failure modes in the testing process that could affect patient care and allow the laboratory to identify appropriate control points to prevent and/or detect the failures.

7.1.1 Review of Information Obtained From the Manufacturer

The information obtained from the manufacturer (see Section 6.2.1) should be reviewed to identify potential failure modes in the process. It may not be necessary, or even practical, to document all possible failure modes in a measuring system. Some failures would clearly create hazards (ie, incorrect results or delays in testing). Other failures may be prevented by design of the measuring system.

Ideally, manufacturers identify important potential failure modes that could affect the reliability of test results, describe the features that were 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 failure modes and information that describes the effectiveness and limitations of the mitigation to reduce the likelihood of failures may be provided in manufacturers' instructions for use and operator manuals (see Table 1).

The QCP described in this document relies on information obtained from the measuring system manufacturer. Laboratories should evaluate the information and confirm that any risk mitigation features are appropriate to meet patient care needs. One way to organize the information obtained from the manufacturer might be as follows:

| Targeted Failure Mode (Hazard) | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | Control Process Effective? | The QCP Actions Required to Address Known Limitations | Residual Risk Acceptable? (Yes/No) |
|--------------------------------|------------------------------------------------|----------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|
|--------------------------------|------------------------------------------------|----------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|

As laboratories review manufacturers' information, they should be aware that the information may not have been reviewed or verified by a regulatory, accreditation, or certification body. Laboratories need to critically assess the information provided by manufacturers and apply their own knowledge of measuring systems to the risk analyses.

### 7.1.2 Review of Information About the Laboratory Environment

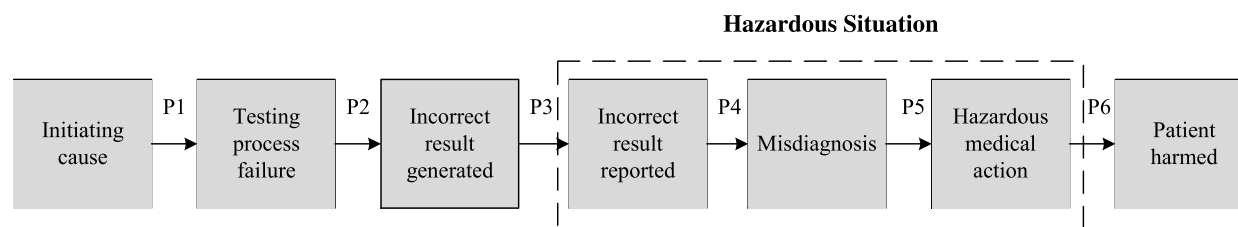
The laboratory should confirm and document that the manufacturer's specifications for the facility where the testing is performed, including all installed utilities, are met. Potential failure modes and use errors that might occur from variables under the laboratory's control are identified. The laboratory may capture these failures in a fishbone diagram, as shown in Figure 4. The information about the specific laboratory setting (see Section 6.3) is included in the risk assessment.

## 7.2 Risk Estimation

The next step in the risk analysis is to determine the degree of risk associated with the hazards. This is done by assigning values to the probability of occurrence of harm associated with an identified hazard and the severity of that harm.

### 7.2.1 Probability of Harm

Once potential failure modes are identified, an estimate of the likelihood or probability of harm is needed. Because the harm arising from an incorrect or delayed test result is indirect, estimating the probability of harm from a failure in the testing process requires an understanding of the laboratory's QMS and the way particular test results are used by health care providers. The overall probability of harm from the use of many laboratory measuring systems may be substantially lower than the probability of the failure because not every instance of failure will lead to patient harm. A representative sequence of events is illustrated in Figure 6. In Figure 6, the medical action may not be hazardous; it may be an absence of action, but it is an inappropriate medical action based on the erroneous test result.



**Figure 6. Sequence of Events Creating Risk of Harm for a Patient (Example)**

A probability is associated with each of the steps in the sequence (signified as P1 to P6 in Figure 6). The existing controls built into the measuring system and the laboratory's existing QMS are taken into account when estimating the risks, but one cannot assume that a built-in or user-applied control is 100% effective in preventing or detecting a failure unless supported by data.

A quantitative estimate of the expected failure rate (P1) is desirable, but sufficient data may not be available. Similarly, the probabilities associated with the other steps in the sequence may not easily be quantifiable. In such cases, a descriptive semiquantitative approach is used to estimate the probabilities, ie, create descriptive categories, so there is no confusion over what is meant by a term. An example of a semiquantitative descriptive scoring from ISO 14971<sup>1</sup> is:

- 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

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 due to 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 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 result:

- Historical failure data
- Method evaluation/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 result:

- Medical literature
- Medical judgment
- Consultation

- Other users (eg, user groups, listservs, forums)
- Regulatory agency recall and device failure notifications

### 7.2.2 Severity of Harm

The consequences of a failure include an incorrect result, a delayed result, or no result, all of which could lead to a hazardous situation for a patient. For example, if the result contributed to a misdiagnosis, the patient harm may occur by an inappropriate treatment or the lack of appropriate treatment. The significance of each failure is evaluated as the severity of harm that could occur to a patient if a hazardous situation occurred. Estimating the severity of harm requires the judgment of the laboratory, in collaboration with the clinical care providers who use the test results.

Key considerations include the following items:

- What will a care provider do with the result?
- What other information is used to corroborate the test result?
- How likely is the care provider to get a confirmatory test result before acting on a result?
- How quickly will the results lead to a medical decision?
- What interventions are initiated for a patient based on the result?
- What risk of harm is caused by an inappropriate intervention?
- How severe might that harm be?
- What is the liability?
- Will the patient suffer mental anguish?

If the laboratory is unable to assess all of these key considerations, the laboratory should assume the most harmful scenarios. Severity of harm is described using a semiquantitative scale of severity levels, such as suggested in ISO 14971<sup>1</sup>:

- 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

The laboratory should select the number of levels needed to represent the range of possible severities. However, too many levels can result in debates over meaningless differences.

## 7.3 Risk Evaluation

The probability or likelihood of a failure leading to harm combined with the severity of that harm is used to evaluate the risk to a patient. Risk evaluation is the process of comparing the estimated risk with an assessment of clinically acceptable risk. The evaluation should take into account the medical benefits of the test and what is achievable in the current state of the art. Acceptable risk may be ascertained through a process of ongoing literature review, expert consultation, local experience, and cooperative evaluation with clinical providers and risk managers. The laboratory, in consultation with health care providers, is responsible for making the determination whether the residual risk of harm, 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 of harm 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 axis. 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 is reached regarding the risk of harm. An example risk matrix from ISO 14971<sup>1</sup> is shown in Table 3.

**Table 3. Risk Acceptability Matrix**

|                            | <i>Severity of Harm</i> |                     |                     |                     |                     |
|----------------------------|-------------------------|---------------------|---------------------|---------------------|---------------------|
| <i>Probability of Harm</i> | <i>Negligible</i>       | <i>Minor</i>        | <i>Serious</i>      | <i>Critical</i>     | <i>Catastrophic</i> |
| <i>Frequent</i>            | <i>unacceptable</i>     | <i>unacceptable</i> | <i>unacceptable</i> | <i>unacceptable</i> | <i>unacceptable</i> |
| <i>Probable</i>            | acceptable              | <i>unacceptable</i> | <i>unacceptable</i> | <i>unacceptable</i> | <i>unacceptable</i> |
| <i>Occasional</i>          | acceptable              | acceptable          | acceptable          | <i>unacceptable</i> | <i>unacceptable</i> |
| <i>Remote</i>              | acceptable              | acceptable          | acceptable          | acceptable          | <i>unacceptable</i> |
| <i>Improbable</i>          | acceptable              | acceptable          | acceptable          | acceptable          | acceptable          |

## 7.4 Risk Control

Each of the failure modes identified by the risk analysis as presenting unacceptable risk requires control 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 practical.

The laboratory should evaluate the risk control measures implemented to address each failure mode, such as specific mitigations provided by the manufacturer and the QC tools described in Section 5, 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 will need to identify additional control 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 risk analysis until the overall residual risk of the test has been reduced as low as practical and is clinically acceptable.

## 7.5 The Laboratory’s Quality Control Plan

Once the residual risk is considered acceptable, then the laboratory includes the control measures as a component of the laboratory’s QCP. Each control or user-required action is added to the Laboratory Risk Assessment and QCP Table as one element of the laboratory’s QCP for the testing process for a specific measurand (analyte).

There may 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, or both, and that the manufacturer’s instructions for use are followed. If not, modify the QCP 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 manufacturers’ recommended instructions, the laboratory can implement the QCP.

The laboratory’s risk assessment and QCP table offers a summary of the decision-making process or rationale used in developing the QCP for use in troubleshooting and for responding to health care provider inquiries. Laboratory inspectors may use this information in determining if the laboratory’s QCP is appropriate.

In many cases, the QCP developed for a given measurand (analyte) may apply to a group of measurands (analytes) performed on a single measuring system or to a group of identical measuring systems used within a health care environment. A single QCP may apply to individual measurands (analytes), all measurands (analytes) assayed using a measuring system, and/or to multiple identical measuring systems.

## **7.6 Example of Laboratory Risk Assessment for Glucose Concentration Measurement on an Automated Measuring System**

An example of risk assessment and the development of a laboratory-specific QCP are provided in the appendixes. The example (glucose concentration measurement on an automated measuring system) illustrates the process of developing a QCP. Note the examples are not comprehensive but include a number of typical aspects to illustrate the process of risk assessment and aggregation of QC elements into a QCP.

Appendix B is a detailed assessment of risk by the laboratory based on the information provided by the following entities: the measuring system manufacturer; the laboratory, regarding its own particular testing environment, the health care setting, and the clinical application of the test result; and the local regulatory requirements.

Appendix C is a table that combines all of the rows from Appendix B, without the detailed explanation of the risk assessment process, showing how the information is organized to document the risk assessment and mitigation assessment processes and provide a record to support the laboratory's QCP.

Appendix D is the QCP developed from the individual components of the QC procedures from Appendixes B and C. Appendix D combines control elements for specific risks that are identical so there is no redundancy in the final components of the QCP. Each component of the QCP is evaluated for conformance to manufacturer instructions and regulatory requirements. The output of Appendix D is the laboratory's QCP for implementation. Note that this is an example format and that other formats are acceptable. Also note that this QCP example is illustrative of the process and is not intended to include all control elements that might be needed for a complete QCP. In addition, when groups of measurands (analytes) are measured using a single measuring system, it may be reasonable to develop a single QCP for the measuring system that includes the requirements for each measurand integrated with components that are common to the measuring system.

## **8 Postimplementation Monitoring of the Quality Control Plan**

As part of its QMS, a laboratory should establish a review system for monitoring quality benchmarks, or the effectiveness of the QCP over time. One quality benchmark that could be monitored is the frequency of a specific error over time to ensure that the QCP effectively reduces the frequency of error occurrence.<sup>31,32</sup> Unacceptable performance will trigger an investigation to identify the root cause and potentially trigger appropriate modifications to the QCP. This surveillance system should be part of the corrective action process. In addition, identification of opportunities to reduce acceptable risks even further is part of the CI program for the laboratory.

The laboratory should ensure appropriate communication and implementation of any manufacturer updates, recalls, or field corrections (eg, calibrator value adjustments), as well as an assessment of any impact on reported test results.

### **8.1 Evaluation of the Effectiveness of the Laboratory Quality Control Plan**

An effective QCP will optimize the probability of detecting an error while minimizing the probability of false error detection. Long-term monitoring of the effectiveness of an implemented QCP may include:

- a) Evaluation of the performance of the QCP at scheduled intervals to verify that occurrences of unacceptable precision or bias were identified with the expected effectiveness and efficiency.
- b) Reviewing 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 quality system policies, practices, and procedures. If the investigation shows that the results were incorrect, an evaluation of the QCP should address why the failure was not prevented or detected, whether the risk to patients is still acceptable, and whether changes to the QCP are required.
- c) Tracking the frequency of complaints and investigations to ensure that failures are being recognized and problems do not recur.

## 8.2 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 of the unacceptable performance. Whenever unacceptable performance is identified, assess the impact on patient care and document it as part of a review of the original risk assessment. If the risk is unacceptable, determine the cause of the unacceptable performance, the corrective action necessary to prevent similar failures in the future, and then update the risk assessment with the new information and modify the QCP as needed to reduce the residual risk from that component of potential failure.

The following are examples of typical corrective actions:

- When the problem is failure of one of the measuring system's built-in controls, additional preventive maintenance procedures and/or new control processes might be necessary.
- If the failure is due to environmental causes, the measuring system may need changing, the laboratory setting may need adaptation, or enhanced monitoring of laboratory environment may need implementation.
- When operator errors are traced to gaps in written procedures or incomplete training, it may be possible to revise the procedure and eliminate the opportunities for error; otherwise, the training program may need alteration to ensure that operators are fully trained and aware of the cause of the failure and are competent to perform the test.
- The laboratory should, after some period of time, revisit the issue to ensure that the corrective action remains effective. Appendix E provides an example of how a laboratory may begin documenting a QCP and making modifications to the QCP.

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

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## Appendix A. Quick Guide Checklist for Establishing a Quality Control Plan Based on Risk Management

Recent advances in technology have significantly enhanced the accuracy and reliability of certain measuring systems. In recognition of these advances, regulatory and accreditation bodies may provide opportunities for laboratories to establish a quality control plan (QCP) based on risk assessments. Appropriate site-specific QCPs can be established through a systematic analysis and evaluation of factors that can adversely affect the quality of test results, and by using an assortment of quality control (QC) tools to mitigate patient risk. The particular combination of measuring system, laboratory, or test site environment and clinical application should be considered when establishing a QCP. Some of the factors considered by the laboratory are listed in this checklist that may provide a useful overview of a laboratory's complete QCP. Additional guidance can be found in CLSI document EP18.<sup>1</sup>

### Measuring System and Analytes:

|                                                                                                                                                                                                                                                         |                          |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| <b>A. Information Gathering.</b>                                                                                                                                                                                                                        |                          |
| 1. <b>Regulatory and accreditation requirements permit site-specific QCPs.</b>                                                                                                                                                                          | <input type="checkbox"/> |
| 2. <b>Measuring system information</b>                                                                                                                                                                                                                  |                          |
| a. The provision of adequate instructions from the manufacturer for using its methodology with its packaged measuring system                                                                                                                            | <input type="checkbox"/> |
| b. Manufacturer's information regarding the scope and effectiveness of built-in controls and recommended QC procedures                                                                                                                                  | <input type="checkbox"/> |
| 3. <b>Factors impacting the test methodology that were considered include:</b>                                                                                                                                                                          |                          |
| <i><b>Specimen, Reagent, and Operator Considerations:</b></i>                                                                                                                                                                                           |                          |
| a. Specimen type, volume, quality, storage, and handling                                                                                                                                                                                                | <input type="checkbox"/> |
| b. Shipment, storage, and interchange of reagents between kits                                                                                                                                                                                          | <input type="checkbox"/> |
| c. Training of testing personnel and periodic monitoring of competency                                                                                                                                                                                  | <input type="checkbox"/> |
| <i><b>Examination Considerations:</b></i>                                                                                                                                                                                                               |                          |
| a. Stable calibration over time                                                                                                                                                                                                                         | <input type="checkbox"/> |
| b. Negligible sample carryover between tests                                                                                                                                                                                                            | <input type="checkbox"/> |
| c. Minimization of visual misinterpretation of test results, through training and competency assessment                                                                                                                                                 | <input type="checkbox"/> |
| d. Implementation of procedures to ensure reagent lots are used within the expiration date                                                                                                                                                              | <input type="checkbox"/> |
| e. Including timing for warm-up or analysis in the procedure                                                                                                                                                                                            | <input type="checkbox"/> |
| f. Risk from air bubbles, low-volume samples, specimen excess, clots, wrong calibration code, or incorrect reagent                                                                                                                                      | <input type="checkbox"/> |
| g. Software, timer, power source, and mechanical systems                                                                                                                                                                                                | <input type="checkbox"/> |
| h. Exposure to radio frequency/electromagnetic interferences                                                                                                                                                                                            | <input type="checkbox"/> |
| <i><b>Physical Considerations:</b></i>                                                                                                                                                                                                                  |                          |
| a. Room temperature, humidity, and light levels                                                                                                                                                                                                         | <input type="checkbox"/> |
| b. Location, altitude, level of work surface, and vibration                                                                                                                                                                                             | <input type="checkbox"/> |
| c. Controlling environmental parameters for mobile testing of patients                                                                                                                                                                                  | <input type="checkbox"/> |
| <i><b>Other Factors Considered:</b></i>                                                                                                                                                                                                                 |                          |
| _____                                                                                                                                                                                                                                                   | <input type="checkbox"/> |
| _____                                                                                                                                                                                                                                                   | <input type="checkbox"/> |
| 4. <b>Health care-specific factors.</b> QCP considers the consequences of an incorrect, delayed, or unavailable result; whether results are acted upon immediately; and whether the result is used for screening, diagnosis, and/or patient management. | <input type="checkbox"/> |



## Appendix B. The Laboratory Risk Assessment: Example Glucose Measurement Using an Automated Measuring System

Appendix B includes a description of a hypothetical risk assessment process considered by the laboratory for glucose measurement using an automated measuring system. Each row of the risk assessment table is presented as individual hazards (potential failure modes). Appendix C presents the complete risk assessment summary table without the supporting text and discussion.

Note that this appendix is intended as an illustrative example and does not include all possible risks. This example and analysis may not be applicable to all laboratory situations and should not be used as a quality control plan (QCP) for any specific laboratory. The example illustrated using glucose is intended to demonstrate the logic in constructing a risk assessment. In many cases, the same logic may apply to a group of measurands (analytes) performed on a single measuring system and/or to a group of identical measuring systems used within a health care environment. A single QCP may apply to individual measurands (analytes), to multiple measurands (analytes) assayed using a single measuring system, and/or to multiple measuring systems.

Using the glucose measurement with an automated measuring system as an example, the laboratory has collected the applicable laboratory regulations and accreditation requirements, the manufacturer-provided information, and the information about the laboratory setting and clinical application of the test results.

The description of the measuring system is as follows: a benchtop, laboratory-automated, multianalyte measuring system, using reagent cartridges (liquid reagents packed in either 200- or 1000-test configurations), quality control (QC) samples, manufacturer-supplied calibrators, and built-in control processes.

The manufacturer recommends in its instructions for use that two concentrations of QC samples be assayed, at a minimum, on receipt of reagents, with each new calibration, and after major maintenance. Manual calibration is performed at the following times: 1) weekly; 2) with reagent lot changes; 3) when QC sample results fail to meet acceptance criteria; or 4) following major maintenance.

The laboratory risk assessment first considers each identified risk or potential failure mode and whether the measuring system features or control procedures (recommended actions) mitigate the risk to a clinically acceptable level in the context of the laboratory's setting. Specifically, the laboratory determines if the residual risk (probability and severity of harm) to the patient is acceptable. If not, the laboratory develops additional control features to reduce the residual risk to clinically acceptable levels. In addition to the manufacturer-provided information, additional risks or potential failure modes that need assessment may be identified by the laboratory. The laboratory needs to assess risk in consideration of the laboratory setting and intended clinical use of the results.

In this example, the QCP is modified based on different requirements in two laboratory settings: an inpatient, acute hospital environment and an outpatient clinic setting. Both laboratory settings are under the purview of the same laboratory management. The first setting is a central hospital laboratory for analysis of stat and routine glucose tests sent to the central laboratory from hospitalized inpatients. The central laboratory performs 500 glucose tests a day and is staffed by experienced medical technologists with minimal staff turnover. This measuring system is used for the diagnosis of diabetes, for verification of point-of-care testing glucose meters when results do not match clinical symptoms, and for support of emergency room, operating room, neonatal, and intensive care units. The second laboratory setting is an outpatient clinic laboratory for a practice of 10 health care providers that requests 20 to 25 glucose tests a day. The clinic laboratory is staffed by nursing aides (with one to two years of clinical training, but little laboratory experience) and has a high staff turnover, with the average staff member staying only six months. This measuring system is used to support all glucose testing needs in the clinic, including diagnosis of diabetes and occasional stat testing for patient consultation while in the office.

**Appendix B. (Continued)****Row #1**

The first targeted failure mode the laboratory addressed in this example was incorrect results due to reagent deterioration during shipment. The manufacturer-recommended action for mitigating this risk is to analyze QC samples on receipt of each new shipment. This information was found in the package insert. Limitations of this recommended action and further laboratory-determined actions required to address these limitations are indicated in the table below.

| <b>An Illustrative Example of a Glucose Measurement With an Automated Measuring System</b> |                                                                |                                                                                                |                                                                    |                                   |                                                                |                                           |
|--------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|-----------------------------------|----------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                               | <b>Targeted Failure Mode (Hazard)</b>                          | <b>Measuring System Feature or Recommended Action</b>                                          | <b>Known Limitations of Feature or Recommended Action</b>          | <b>Control Process Effective?</b> | <b>Actions Required to Address Known Limitations (the QCP)</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>1</b>                                                                                   | Incorrect results due to 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 may incorrectly assess assay integrity. |                                   |                                                                |                                           |

Key considerations in the laboratory's assessment of the risk for incorrect results due to reagent degradation during shipment include:

- Manufacturer-recommended storage conditions are 2 to 8 °C. There is no assurance that these conditions were maintained during shipment. Verify conditions of cold packs upon receipt. Analyze QC samples to verify performance.
- Limitation – QC samples may fail to detect reagent problem if QC samples have degraded or are used outside of expiration date. The laboratory should check expiration date, check that open vial use is within stability claim, and store QC samples as recommended. The laboratory should be confident that it can comply with these recommendations. An outpatient clinic laboratory with high staff turnover will encounter more challenges in monitoring temperatures and storage conditions than a hospital laboratory with stable staff dedicated to laboratory testing. Consider continuous temperature monitoring with alarms for refrigerators in outpatient clinics.
- QC sample result acceptance criteria should reflect performance in the laboratory setting. Although manufacturer-suggested acceptance ranges may be useful to verify that performance claims are met, each laboratory should establish specific acceptance criteria based on repeat analysis of the same lot of QC sample over several days, measuring system calibrations, and with different operators. For this example, the laboratory should analyze the QC sample over time at both the central hospital laboratory and the outpatient clinic laboratory, and set acceptance criteria based on the performance of the QC samples at these sites. For this example, during implementation, the central hospital laboratory did set laboratory-specific QC ranges while the outpatient clinic chose to use the manufacturer's package insert limits.
- Residual risk assessment with QC samples, laboratory-developed QC ranges, and storage monitoring in place:
  - Probability of harm – remote – QC samples should detect a deteriorated lot of reagent
  - Severity of harm – serious – if QC sample results should miss a reagent problem
  - Residual risk – acceptable

**Appendix B. (Continued)**

These control strategies are summarized in the “QCP Actions Required to Address Known Limitations” column.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                |                                                                                                |                                                                    |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                          | <b>Measuring System Feature or Recommended Action</b>                                          | <b>Known Limitations of Feature or Recommended Action</b>          | <b>Control Process Effective?</b>                                               | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>1</b>                                                                                 | Incorrect results due to 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 may incorrectly assess assay integrity. | N/A – No automated control process to detect reagent stability during shipment. | <u>Follow manufacturer’s recommendations:</u><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><u>Laboratory-implemented control processes:</u><br>– Implement continuous temperature monitoring for outpatient clinics.<br>– Ensure QC samples are within expiration date and within the open vial stability claim.<br>– Check condition of the cold packs upon reagent shipment receipt.<br>– Ensure QC sample range criteria are appropriate for the clinical setting. | Yes                                       |

**Appendix B. (Continued)****Row #2**

A risk of incorrect results due to calibrator degradation (error during calibration) is identified.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                   |                                                                                                                                      |                                                                                                            |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>             | <b>Measuring System Feature or Recommended Action</b>                                                                                | <b>Known Limitations of Feature or Recommended Action</b>                                                  | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>2</b>                                                                                 | Incorrect results due to calibrator deterioration | Software monitors calibrator integrity (absorbance measurement of calibrator reaction is within preset measurement response limits). | Measuring system performance could drift between QC sample measurement and subsequent recalibration event. |                                   |                                                              |                                           |

- The manufacturer's owner's manual describes an internal control process that monitors calibration absorbance readings and ensures that measurement response for the calibration is within a predetermined acceptable range or the system will produce an error message and prevent patient testing.
- The manufacturer recommends analysis of QC samples after each calibration to verify system performance.
- Limitation – Measuring system performance has the potential to change between a QC sample measurement and a subsequent calibration event. Calibration drift would not be detected by the internal control process because drift follows a recalibration event.
- QC results within the acceptable ranges can verify measuring system stability and should bracket major events like calibration. The manufacturer recommends weekly calibration, with QC samples analyzed after calibration. More frequent analysis of QC samples, eg, every three days, would provide the laboratory assurance that the system is stable and calibration has not drifted between calibration events. This heightened analysis of QC samples would be more important during initial implementation of the measuring system and could be stopped once the laboratory has collected sufficient data and gained a comfort level with the measuring system's stability over time. The laboratory also recommends that QC samples should be measured before calibration in order to verify measuring system performance before a change in assay conditions, and a possible correction of a calibration drift, caused by a new calibration event.
- Analysis of external quality assessment (EQA) or proficiency testing (PT) samples can verify the accuracy of the laboratory's measuring system calibration by comparing performance against other peer laboratories using the same measuring system and reagents.
- Residual risk with internal calibration monitoring and QC sample analysis before, after, and with interim analysis between calibration events:

**Appendix B. (Continued)**

- Probability of harm – remote – that both internal software control process and QC samples would not detect a calibration error due to calibrator degradation or drift between calibration events
- Severity of harm – critical – if a calibration error occurs
- Residual risk – acceptable

Analysis of QC samples before, after, and with interim analysis between calibration events is added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                   |                                                                                                                                      |                                                                                                            |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                           |
|------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>             | <b>Measuring System Feature or Recommended Action</b>                                                                                | <b>Known Limitations of Feature or Recommended Action</b>                                                  | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>2</b>                                                                                 | Incorrect results due to calibrator deterioration | Software monitors calibrator integrity (absorbance measurement of calibrator reaction is within preset measurement response limits). | Measuring system performance could drift between QC sample measurement and subsequent recalibration event. | Partial                           | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Verify calibration by testing QC samples after each calibration event.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Analyze QC samples before each calibration to verify system performance before change in conditions from calibration.</li> <li>– Analyze QC samples every three days to monitor for calibration drift until laboratory collects sufficient data to establish confidence with measuring system stability over time.</li> <li>– Participate in EQA or PT program to compare performance against other peer laboratories.</li> </ul> | Yes                                       |

**Appendix B. (Continued)****Row #3**

The potential for incorrect results from data entry errors is identified. This error could involve the incorrect entry of specimen identifiers, calibration factors, reagent types, and other critical information required for correct analysis.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                  |                                                       |                                                                                                        |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>            | <b>Measuring System Feature or Recommended Action</b> | <b>Known Limitations of Feature or Recommended Action</b>                                              | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>3</b>                                                                                 | Incorrect results due to sample data entry error | Bar code reader ensures correct data entry.           | Bar code misread – rare event. Manual entry errors are more frequent than bar coded data entry errors. |                                   |                                                              |                                           |

- Measuring system has an internal bar code reader for specimens and reagents/calibrator information.
- Limitation – Bar code reader failures are rare, but manual entry errors occur more frequently. The laboratory needs a documented procedure for how to verify manual entries and staff members need to be trained on this procedure. Staff with less laboratory experience, as in the outpatient laboratory, may be less likely to understand the potential for error from manual data entry. Training will need to emphasize the consequences of data entry errors and how checking manual data entry can reduce the probability of error.
- Bar coding systems are more reliable than manual data entry. The laboratory recommends use of bar coding to minimize manual data entry whenever possible.
- Residual risk using bar code reader:
  - The probability of harm is remote with bar code entry.
    - Harm is probable with manual data entry, unless training emphasizes the need to verify manual entries.
  - The severity of harm is serious if a data entry error occurs from either manual or bar code entry.
  - Residual risk is:
    - Unacceptable with manual data entry alone, as the potential for harm is probable and serious.
    - Acceptable with manual entry and double-checking, which results in an occasional probability of harm.
    - Acceptable with bar code entry, which results in a remote probability of harm.

**Appendix B. (Continued)**

These control strategies (ie, use bar code reader, implement procedural step to train staff to verify manual entries) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                  |                                                       |                                                                                                        |                                   |                                                                                                                                                                             |                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------------|-------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>            | <b>Measuring System Feature or Recommended Action</b> | <b>Known Limitations of Feature or Recommended Action</b>                                              | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>3</b>                                                                                 | Incorrect results due to sample data entry error | Bar code reader ensures correct data entry.           | Bar code misread – rare event. Manual entry errors are more frequent than bar coded data entry errors. | Yes, unless manual entry.         | <u>Manufacturer recommendations:</u><br>– Use bar codes for data entry.<br><u>Laboratory-implemented control processes:</u><br>– Train staff to verify manual data entries. | Yes                                       |

**Row #4**

The risk of a result error from a low-volume sample is assessed.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                            |                                                                                                                                                                                                                                               |                                                                                          |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>      | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                         | <b>Known Limitations of Feature or Recommended Action</b>                                | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>4</b>                                                                                 | Incorrect results due to low-volume sample | Low-volume sample detector identifies samples with low volumes. Optical sensor detects meniscus in pipettor to ensure that the sample volume is at the appropriate level or a system error will be generated and no result will be displayed. | System may fail to detect a slightly low-volume sample and generate an incorrect result. |                                   |                                                              |                                           |

**Appendix B. (Continued)**

- An internal optical sensor checks for adequate specimen volume. A review of the manufacturer's labeling and technical documents, in addition to inquiring with the manufacturer, finds that specimens with volumes causing more than a 10% error will have results suppressed. Is 10% bias sufficient for diagnosis and/or monitoring as the maximum error tolerance that could pass the system check? Consultation with clinicians indicates that 10% error is acceptable for their use of the results.
- Limitation – The laboratory should monitor trends for receiving specimens with low volumes by tracking the frequency of system error messages and counseling staff involved in specimen collection when trends occur. Visual inspection can help catch low-volume specimens before they are placed on the analyzer. This may be more of a problem in the pediatric population (where smaller samples are collected) and may delay discharge and/or treatment while waiting for collection of a second sample with adequate volume.
- Residual risk with optical sensor procedure for checking specimen volumes and operator training on the procedure:
  - Probability of harm – remote – that both sensor and operator would fail to detect low volume
  - Severity of harm – serious – if a low-volume specimen is analyzed with falsely decreased results
  - Residual risk – acceptable

These control strategies (ie, low-volume sample detector, implementation of procedural step to check specimen volumes and counsel staff collecting specimens) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                            |                                                                                                                                                                                                                                               |                                                                                          |                                   |                                                                                                                                                                                                                                                                                                                                                                                                       |                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>      | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                         | <b>Known Limitations of Feature or Recommended Action</b>                                | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                          | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>4</b>                                                                                 | Incorrect results due to low-volume sample | Low-volume sample detector identifies samples with low volumes. Optical sensor detects meniscus in pipettor to ensure that the sample volume is at the appropriate level or a system error will be generated and no result will be displayed. | System may fail to detect a slightly low-volume sample and generate an incorrect result. | Partial                           | <u>Manufacturer recommendations:</u><br>None – automated low-volume sample detector.<br><u>Laboratory-implemented control processes:</u><br>– Monitor frequency of low-volume error messages and counsel staff collecting specimens.<br>– Implement procedural step to examine pediatric samples to ensure that adequate volume of sample is presented to measuring system; train staff on procedure. | Yes                                       |

**Appendix B. (Continued)****Row #5**

Specimen clots can present a source of risk of a result error.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                |                                                                                                                       |                                                    |                            |                                                       |                                    |
|-----------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                 | Measuring System Feature or Recommended Action                                                                        | Known Limitations of Feature or Recommended Action | Control Process Effective? | The QCP Actions Required to Address Known Limitations | Residual Risk Acceptable? (Yes/No) |
| 5                                                                                 | Incorrect results due to clots from the sample | Sample pressure monitored in probe. Measuring system software identifies signals indicative of the presence of clots. | Small microclots may not be detected.              |                            |                                                       |                                    |

- The measuring system monitors pressure in the sample probe. The manufacturer requires routine maintenance to clear the sample probe of any protein build-up and ensure optimum monitoring of probe pressure.
- Limitation – Small microclots may not be detected. The laboratory does not know the effects of microclots on glucose results. A higher frequency of clotted specimens may occur when staff does not mix specimens well immediately after phlebotomy, or if specimens are not allowed sufficient time to clot before centrifugation and processing. Staff members with less experience in phlebotomy and processing generate more problem specimens. Consider monitoring the frequency of clot errors displayed by the measuring system and counseling/retraining staff responsible for collecting and processing those specimens.
- With a risk of error from missing small clots, the laboratory recommends implementing the procedural step to check specimens for clots before analysis, training staff on this procedure, and performing routine maintenance, as recommended by the manufacturer. Note that major maintenance can alter measuring system conditions; therefore, QC samples should be analyzed before the maintenance to ensure no defect in the measuring system has occurred since the last time QC samples were analyzed, and after major maintenance to ensure that maintenance did not affect test results.
- Residual risk with pressure sensor and procedural step to check specimens for clots with operator training on the procedure:
  - Probability of harm – occasional – that both sensor and operator would fail to detect a clotted specimen
  - Severity of harm – serious – unsure the effect of microclots that may be missed
  - Residual risk – acceptable

**Appendix B. (Continued)**

These control strategies (pressure sensor and procedural step to train staff to check for specimen clots) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                |                                                                                                                       |                                                           |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                           |
|------------------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>          | <b>Measuring System Feature or Recommended Action</b>                                                                 | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                  | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>5</b>                                                                                 | Incorrect results due to clots from the sample | Sample pressure monitored in probe. Measuring system software identifies signals indicative of the presence of clots. | Small microclots may not be detected.                     | Partial                           | <u>Manufacturer recommendations:</u><br>Perform routine maintenance so pressure sensor can function optimally to detect clots.<br><u>Laboratory-implemented control processes:</u><br>– Implement procedural step to inspect samples for visible clots and train staff on this procedure.<br>– Monitor frequency of system clot errors and follow up with staff collecting or processing samples.<br>– Analyze QC samples before and after major maintenance. | Yes                                       |

**Appendix B. (Continued)****Row #6**

The manufacturer indicates a risk of incorrect results due to sample carryover.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                           |                                                                                                                                                |                                                                                                                       |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>     | <b>Measuring System Feature or Recommended Action</b>                                                                                          | <b>Known Limitations of Feature or Recommended Action</b>                                                             | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>6</b>                                                                                 | Incorrect results due to sample carryover | Use disposable cuvettes and wash mechanism for probes. The wash mechanism removes residual glucose left over from a high-concentration sample. | Inadequate washing following a high glucose concentration sample can cause false elevations in the subsequent sample. |                                   |                                                              |                                           |

- The measuring system uses disposable cuvettes that prevent carryover from a previous analysis. The measuring system also has a washing mechanism to reduce the likelihood of sample carryover from probes. The manufacturer recommends analyzing QC samples and performing routine maintenance to remove protein build-up and ensure that the probes are regularly inspected, cleaned, and replaced as needed.
- The laboratory identifies major maintenance procedures, such as probe maintenance, that can alter measuring system conditions; QC samples should be analyzed before and after major maintenance to ensure that maintenance did not affect test results.
- The laboratory conducted a carryover study and demonstrated clinically acceptable bias for samples following a patient specimen with a glucose concentration of 480 mg/dL (26.7 mmol/L).
- Limitation – Washing fails to clear a high glucose sample, resulting in carryover. The manufacturer recommendations to run QC samples periodically and to perform routine maintenance will not entirely mitigate this risk of carryover. These are only preventive actions to ensure that the probes are clean and the wash mechanism is functioning. The laboratory should reassay any specimen that follows a specimen with glucose higher than 480 mg/dL (26.7 mmol/L).
- The risk of sample carryover is greater when the laboratory receives a higher number of samples with elevated glucose >480 mg/dL (26.7 mmol/L). A hospital laboratory may receive several specimens a day with elevated glucose results, whereas an outpatient clinic laboratory may only see an elevated glucose result once every several days/weeks. If the probability of a person missing a high glucose and failing to repeat the following specimen is estimated at 1 in 100; the frequency of missing a high glucose specimen in the hospital central laboratory or the clinic is frequent (defined in Section 7.2.1 as once per week).

**Appendix B. (Continued)**

- A “frequent” frequency, combined with a serious severity, is clinically unacceptable. Both the clinic and hospital laboratories should determine additional mitigations.
- The required mitigation is to repeat the measurement of any specimen that follows a specimen with glucose greater than 480 mg/dL (26.7 mmol/L) before releasing results to the health care provider. Additional mitigations include analyzing all glucose results without autoverification to allow for review before release, or to not autoverify any results with glucose greater than 480 mg/dL (26.7 mmol/L), or to create a laboratory information system (LIS) notification to operators to alert them when a glucose concentration is >480 mg/dL (26.7 mmol/L).
- Residual risk with disposable cuvettes, probe wash mechanism, laboratory specimen repeat policy, and the LIS notifying operators of specimens with glucose >480 mg/dL (26.7 mmol/L):
  - Probability of harm – occasional – operator may miss the LIS notification and not repeat the sample following a specimen with glucose >480 mg/dL (26.7 mmol/L)
  - Severity of harm – serious – bias is unknown for samples >480 mg/dL (26.7 mmol/L)
  - Residual risk – acceptable

These control strategies (ie, use wash mechanism and implement specimen rerun policy with LIS alert after high glucose) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                           |                                                                                                                                                |                                                                                                                       |                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                         |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>     | <b>Measuring System Feature or Recommended Action</b>                                                                                          | <b>Known Limitations of Feature or Recommended Action</b>                                                             | <b>Control Process Effective?</b>                     | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                            | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>6</b>                                                                                 | Incorrect results due to sample carryover | Use disposable cuvettes and wash mechanism for probes. The wash mechanism removes residual glucose left over from a high-concentration sample. | Inadequate washing following a high glucose concentration sample can cause false elevations in the subsequent sample. | Partial – requires additional laboratory mitigations. | <u>Manufacturer recommendations:</u><br>– Perform routine maintenance.<br><u>Laboratory-implemented control processes:</u><br>– Analyze QC samples before and after maintenance to verify system performance before and after a major system change.<br>– Repeat any sample that follows a glucose >480 mg/dL (26.7 mmol/L).<br>– Report results without autoverification and use the LIS to notify operator of high glucose specimens. | Yes                                       |

**Appendix B. (Continued)****Row #7**

The laboratory notes a risk of introducing a measuring system problem or failure condition during maintenance procedures.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                 |                                                |                                                                                                    |                            |                                                       |                                    |
|-----------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                  | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action                                                 | Control Process Effective? | The QCP Actions Required to Address Known Limitations | Residual Risk Acceptable? (Yes/No) |
| 7                                                                                 | Fault condition caused by maintenance procedure | Recalibrate after major maintenance.           | Recalibration may not correct all possible conditions that could be introduced during maintenance. |                            |                                                       |                                    |

- The manufacturer recommends recalibrating after major maintenance.
- Limitation – Recalibration may not mitigate all the possible problems that could be introduced during maintenance (including incorrectly performed maintenance). The laboratory recommends analyzing QC samples before and after major maintenance to document measuring system performance. Major maintenance needs definition, but typically includes cleaning or replacing any component that can affect the chemical reaction and/or the signal measured by the measuring system.
- Measuring QC samples before maintenance is important to verify acceptable performance since the last QC sample event and before the measuring system condition is altered by the maintenance.
- Residual risk with recalibration following major maintenance and measuring QC samples before and after major maintenance:
  - Probability of harm – remote – that recalibration and analysis of QC samples would not detect a measuring system problem or failure
  - Severity of harm – critical – if maintenance introduces a measuring system problem or failure
  - Residual risk – acceptable

**Appendix B. (Continued)**

These control strategies (ie, recalibration and QC sample measurement before and after maintenance) are added to the Laboratory Risk Assessment table.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                 |                                                |                                                                                                    |                                     |                                                                                                                                                                                                               |                                    |
|-----------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------|----------------------------------------------------------------------------------------------------|-------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                  | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action                                                 | Control Process Effective?          | The QCP Actions Required to Address Known Limitations                                                                                                                                                         | Residual Risk Acceptable? (Yes/No) |
| 7                                                                                 | Fault condition caused by maintenance procedure | Recalibrate after major maintenance.           | Recalibration may not correct all possible conditions that could be introduced during maintenance. | N/A – No automated control process. | <u>Manufacturer recommendations:</u><br>– Recalibrate following major maintenance.<br><u>Laboratory-implemented control processes:</u><br>– Analyze QC samples before and after major maintenance procedures. | Yes                                |

**Row #8**

The use of expired reagents presents a risk of incorrect results. There are two sources of reagent expiration: use beyond the manufacturer's unopened storage expiration date, and open cartridge stability (which is 60 days).

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                  |                                                                                   |                                                    |                            |                                                       |                                    |
|-----------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------|----------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                   | Measuring System Feature or Recommended Action                                    | Known Limitations of Feature or Recommended Action | Control Process Effective? | The QCP Actions Required to Address Known Limitations | Residual Risk Acceptable? (Yes/No) |
| 8                                                                                 | Incorrect results due to use of expired reagents | Bar code entry of reagent information. Software prevents use of expired reagents. | Does not detect open bottle expiration.            |                            |                                                       |                                    |

- The measuring system uses bar coded expiration dates, preventing use of a reagent beyond the manufacturer's expiration. However, there is the possibility of using reagents beyond the open bottle stability, so the laboratory recommends including a step in the procedure to check reagent open bottle dating each day of use and implementing operator training on this step.
- Limitations – Bar coded expiration dates only prevent use of reagents beyond manufacturer expiration date for storage; open bottle stability is not automatically checked.

**Appendix B. (Continued)**

- Residual risk with bar coded expiration dates, inclusion of procedural step to check reagent open cartridge expiration dates daily, and implementation of operator training:
  - Probability of harm – occasional – that operator compliance would miss expired open cartridge stability dating
  - Severity of harm – serious – consequences of using reagent outside of open bottle stability are unknown but are expected to cause erroneous results
  - Residual risk – acceptable

These control strategies (ie, bar coded reagent expiration date, and the practice of an operator checking the open bottle stability expiration date) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                  |                                                                                   |                                                           |                                                                                                 |                                                                                                                                                                                                                                                                                                                                               |                                           |
|------------------------------------------------------------------------------------------|--------------------------------------------------|-----------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>            | <b>Measuring System Feature or Recommended Action</b>                             | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>                                                               | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                  | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>8</b>                                                                                 | Incorrect results due to use of expired reagents | Bar code entry of reagent information. Software prevents use of expired reagents. | Does not detect open bottle expiration.                   | Partial bar coding prevents use of expired reagents but does not monitor open bottle stability. | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Bar coded reagent cartridges prevent use past expiration date.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Include procedural step to monitor open bottle expiration dates and train staff.</li> </ul> | Yes                                       |

**Appendix B. (Continued)****Row #9**

There is a potential risk of incorrect results from use of reagents that have deteriorated prematurely during storage conditions or after opening.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                       |                                                                                                                                                                                       |                                                           |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                 | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                 | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>9</b>                                                                                 | Incorrect results due to use of deteriorated reagents | Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank. Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration.            |                                   |                                                              |                                           |

- The measuring system monitors absorbance reading of reagent blank. Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance blank. A system error message will display if reagent blank absorbance readings are out of preset limits.
- Limitations – This feature does not automatically monitor reagent storage or expiration dates, or the length of time an open reagent is used (see rows #1 and #8).
- Besides the other system control processes (ie, monitoring storage conditions, bar coded and open bottle reagent expiration checks), periodic analysis of QC samples can directly verify reagent and measuring system performance. The manufacturer only recommends analysis of QC samples upon receipt of reagent shipments, and after calibration or major maintenance. The laboratory should monitor for measuring system error messages and increase the frequency of QC sample analysis whenever there is an increased frequency of error messages.
- In addition, QC samples should be analyzed more frequently during initial operation, to ensure system stability after new operator training. The laboratory selects a QC sample frequency of once every three days for the hospital laboratory where testing is conducted by experienced medical technologists, and once every day for the outpatient clinic with high staff turnover for the first three months after implementing the measuring system. If no trends are detected, both laboratories will decrease the frequency of QC analysis to before and after weekly calibration.
- Residual risk with blank absorbance monitor:
  - Probability of harm – remote – that blank absorbance monitor and other control strategies (evaluating reagent shipments upon receipt, monitoring refrigerator temperatures, and daily checking for open bottle expiration date) would not detect reagent degradation

**Appendix B. (Continued)**

- Severity of harm – serious – if reagent degrades
- Residual risk – acceptable

These control strategies (ie, measuring system blank absorbance monitor and previously discussed reagent control processes) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                       |                                                                                                                                                                                          |                                                           |                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                 | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                    | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>                                                          | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>9</b>                                                                                 | Incorrect results due to 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 – requires additional control processes to monitor reagent storage and expiration. | <u>Manufacturer recommendations:</u><br>– Automated reagent blank measurement.<br><u>Laboratory-implemented control processes:</u><br>– See row #8 – bar coded reagent expiration dates and staff monitoring open bottle stability.<br>– See row #1 – 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 three days in hospital laboratory (for first three months of system use). | Yes                                       |

**Appendix B. (Continued)****Row #10**

Another possible source for risk of incorrect results is spectrophotometric drift. Causes of spectrophotometric drift include optics deterioration, lamp intensity changes, and detector changes that alter the baseline absorbance measurements of the system and affect the accuracy of results.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                   |                                                                                                                                                                                                                                                      |                                                           |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>             | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                                | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>10</b>                                                                                | Incorrect results due to spectrophotometric drift | Automated monitoring of spectrophotometric system. Two levels of electronic control. Software monitors lamp intensity and resets baseline before every test; a second control uses an optic filter to monitor absorbance signal each day of testing. |                                                           |                                   |                                                              |                                           |

- According to information in the manufacturer's instrument user manual, the measuring system monitors two levels of electronic optical controls. One level measures lamp intensity to reset baseline before each test. A second level control passes an optical filter between the lamp and detector to mimic a high range absorbance when the measuring system is turned on and every 24 hours of continuous operation. The baseline lamp intensity and optical filter controls should be within preset ranges or an error message will be displayed.
- Limitations – The laboratory should follow maintenance schedule, replacing lamps when necessary.
- The laboratory should monitor for measuring system error messages and increase the frequency of QC sample analysis whenever there is an increased frequency of error messages. The laboratory notes that QC samples also need to be assayed before maintenance to verify assay performance stability since the last QC sample analysis, and after maintenance to verify that there was no change in assay performance from the maintenance event (lamp replacement is considered major maintenance).

**Appendix B. (Continued)**

- Residual risk with electronic controls and laboratory maintenance schedule to replace lamps when necessary:
  - Probability of harm – improbable – of not detecting a serious optics problem
  - Severity of harm – serious – if a lamp intensity drift occurs
  - Residual risk – acceptable

These control strategies (ie, electronic controls, maintenance to replace lamps when necessary) are added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                   |                                                                                                                                                                                                                                                      |                                                           |                                   |                                                                                                                                                                                                                                                                                            |                                           |
|------------------------------------------------------------------------------------------|---------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>             | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                                | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                               | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>10</b>                                                                                | Incorrect results due to spectrophotometric drift | Automated monitoring of spectrophotometric system. Two levels of electronic control. Software monitors lamp intensity and resets baseline before every test; a second control uses an optic filter to monitor absorbance signal each day of testing. |                                                           |                                   | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Maintenance schedule to replace lamps.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Analyze QC samples before and after lamp replacement.</li> </ul> | Yes                                       |

**Appendix B. (Continued)****Row #11**

A risk of incorrect results from the operator inadvertently changing measuring system settings is assessed. This could occur if the operator changes critical settings, such as calibration factors, reagent volumes, probe wash parameters, units, or other settings that would affect test results.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                      |                                                                                                 |                                                           |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                                | <b>Measuring System Feature or Recommended Action</b>                                           | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>11</b>                                                                                | Incorrect results due to operator changing measuring system settings | Password control over settings. Operator cannot change settings; requires authorized personnel. | Operators learn supervisor password.                      |                                   |                                                              |                                           |

- The measuring system has supervisor password control over the settings, preventing general operator access to change settings.
- Limitation – Operators learn supervisor password. The laboratory should ensure that staff members do not share passwords and that passwords are changed periodically to maintain security.
- Residual risk with password control of measuring system settings:
  - Probability of harm – remote – that an operator changes settings
  - Severity of harm – critical – if settings are changed
  - Residual risk – acceptable

The control strategy (ie, password control) is added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                      |                                                                                                 |                                                           |                                   |                                                                                                                                                                                                       |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                                | <b>Measuring System Feature or Recommended Action</b>                                           | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                          | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>11</b>                                                                                | Incorrect results due to operator changing measuring system settings | Password control over settings. Operator cannot change settings; requires authorized personnel. | Operators learn supervisor password.                      | Yes                               | <u>Manufacturer recommendations:</u><br>– Use password security features.<br><u>Laboratory-implemented control processes:</u><br>– Do not share supervisor password and change password periodically. | Yes                                       |

**Appendix B. (Continued)****Row #12**

The laboratory notes a risk of operating the measuring system outside of manufacturer specifications for temperature and humidity (ie, high temperatures and humidity in the summer, colder temperatures in the winter).

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                                                                |                                                              |                                                           |                                   |                                                              |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------|-----------------------------------|--------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                                                                          | <b>Measuring System Feature or Recommended Action</b>        | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b> | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>12</b>                                                                                | Incorrect results due to operating the measuring system outside of manufacturer's environmental specifications | Only operate measuring system within defined specifications. | No internal environmental monitoring                      |                                   |                                                              |                                           |

- The measuring system does not automatically check if the temperature and humidity are within operating specifications. The laboratory recommends monitoring critical environmental conditions, room temperature, and humidity, and providing adequate ventilation for the measuring system to prevent overheating.
- The laboratory recommends installing continuous temperature/humidity monitoring with an accompanying alarm, which will sound if conditions are outside of the operating range.
- Limitations – Monitoring of critical environmental variables should ensure operation within the manufacturer's specifications. The hospital central laboratory is already well controlled and is monitored by the Engineering/Facilities Department for both temperature and humidity; however, the outpatient clinic is in an older building and experiences wider temperature and humidity fluctuations. Recommend installing continuous monitoring of temperature and humidity with alarms in the outpatient clinic, and training staff in the use of this equipment, and propose actions to take if conditions fall outside of the manufacturer's recommendations.
- Residual risk with laboratory environmental monitoring:
  - Probability of harm – remote – that conditions will fall outside of manufacturer's recommendations without action
  - Severity of harm – serious – unknown effects if operating measuring system outside of manufacturer recommended environmental conditions but are expected to cause erroneous results
  - Residual risk – acceptable

**Appendix B. (Continued)**

This control strategy (ie, environmental monitoring for temperature and humidity) is added to the Laboratory Risk Assessment table.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                                                                                |                                                              |                                                    |                                    |                                                                                                                                                                                                                                                                      |                                    |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                                                                                 | Measuring System Feature or Recommended Action               | Known Limitations of Feature or Recommended Action | Control Process Effective?         | The QCP Actions Required to Address Known Limitations                                                                                                                                                                                                                | Residual Risk Acceptable? (Yes/No) |
| 12                                                                                | Incorrect results due to operating the measuring system outside of manufacturer's environmental specifications | Only operate measuring system within defined specifications. | No internal environmental monitoring               | N/A – No environmental monitoring. | <u>Manufacturer recommendations:</u><br>– Operate measuring system within defined specifications.<br><u>Laboratory-implemented control processes:</u><br>– Monitor room temperature and humidity.<br>– Use automated environmental monitoring for outpatient clinic. | Yes                                |

**Row #13**

The laboratory notes the risk of incorrect results due to power fluctuations.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                            |                                                |                                                    |                            |                                                       |                                    |
|-----------------------------------------------------------------------------------|------------------------------------------------------------|------------------------------------------------|----------------------------------------------------|----------------------------|-------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                             | Measuring System Feature or Recommended Action | Known Limitations of Feature or Recommended Action | Control Process Effective? | The QCP Actions Required to Address Known Limitations | Residual Risk Acceptable? (Yes/No) |
| 13                                                                                | Incorrect or unavailable results due to power fluctuations | Protect the system from power fluctuations.    | No internal system checks on power fluctuations    |                            |                                                       |                                    |

- The measuring system does not have built-in checks to ensure that power fluctuation is within specifications. The hospital central laboratory has emergency power supply outlets that both condition and provide backup power should a power outage or interruption occur. This safeguard allows the technologists to complete the analysis of samples without interruption. However, the outpatient clinic is not connected to the hospital's emergency power. The laboratory recommends the purchase of an uninterruptible power supply (UPS)/surge protector to condition the electricity supplied to the measuring system and to provide backup power in the outpatient clinic in case of a power outage to allow completion of tests in progress before shutting off the measuring system.
- Limitations – UPS batteries can fail. Check battery function at least annually, and replace batteries as required by the manufacturer.

**Appendix B. (Continued)**

- Residual risk with UPS power supply and surge protection:
  - Probability of harm – remote – that the laboratory will experience a power surge or outage, and the UPS will fail
  - Severity of harm – serious, unknown effect of power surge or failure on measuring system and test results but are expected to cause erroneous or unavailable results
  - Residual risk – acceptable

This control strategy (ie, UPS power supply and surge protection) is added to the Laboratory Risk Assessment table.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                            |                                                       |                                                           |                                                           |                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                           |
|------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                      | <b>Measuring System Feature or Recommended Action</b> | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>                         | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                     | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>13</b>                                                                                | Incorrect or unavailable results due to power fluctuations | Protect the system from power fluctuations.           | No internal system checks on power fluctuations           | N/A – No system control processes for power fluctuations. | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Protect the measuring system from power fluctuations.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Use emergency power outlets in hospital.</li> <li>– Purchase a UPS for measuring system in outpatient clinic.</li> <li>– Monitor UPS battery function and replace as needed.</li> </ul> | Yes                                       |

## Appendix C. Summary of Laboratory Risk Assessment Table. Example: Glucose Measurement on an Automated Measuring System

This table is the same as the one created row by row in Appendix B, but does not include the explanatory text on how the table was constructed. This table is an example of the documentation that would be created as a result of the risk assessment process. Note this table is not the laboratory's quality control plan (QCP). Appendix B evaluates each potential risk separately, and there is overlap in the QCP strategies that address each risk. Appendix D shows the QCP that is created by aggregating common strategies in Appendix C into a set of particular elements that constitute an executable QCP.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                                |                                                                                                                  |                                                                                    |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                    |
|-----------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                                 | Measuring System Feature or Recommended Action                                                                   | Known Limitations of Feature or Recommended Action                                 | Control Process Effective?                                                      | The QCP Actions Required to Address Known Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         | Residual Risk Acceptable? (Yes/No) |
| 1                                                                                 | Incorrect results due to reagent deterioration during shipment | Test quality control (QC) samples that were not in the same shipment as the reagent, on receipt of new shipment. | Deterioration of quality control QC sample may incorrectly assess assay integrity. | N/A – No automated control process to detect reagent stability during shipment. | <u>Follow manufacturer's recommendations:</u><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><u>Laboratory-implemented control processes:</u><br>– Implement continuous temperature monitoring for outpatient clinics.<br>– Ensure QC samples are within expiration date and within the open vial stability claim.<br>– Check condition of the cold packs upon reagent shipment receipt.<br>– Ensure QC sample range criteria are appropriate for the clinical setting. | Yes                                |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                   |                                                                                                                                      |                                                                                                            |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |                                           |
|------------------------------------------------------------------------------------------|---------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------|-----------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>             | <b>Measuring System Feature or Recommended Action</b>                                                                                | <b>Known Limitations of Feature or Recommended Action</b>                                                  | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>2</b>                                                                                 | Incorrect results due to calibrator deterioration | Software monitors calibrator integrity (absorbance measurement of calibrator reaction is within preset measurement response limits). | Measuring system performance could drift between QC sample measurement and subsequent recalibration event. | Partial                           | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Verify calibration by testing QC samples after each calibration event.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Analyze QC samples before each calibration to verify system performance before change in conditions from calibration.</li> <li>– Analyze QC samples every three days to monitor for calibration drift until laboratory collects sufficient data to establish confidence with measuring system stability over time.</li> <li>– Participate in external quality assessment (EQA) or proficiency testing program to compare performance against other peer laboratories.</li> </ul> | Yes                                       |
| <b>3</b>                                                                                 | Incorrect results due to sample data entry error  | Bar code reader ensures correct data entry.                                                                                          | Bar code misread – rare event. Manual entry errors are more frequent than bar coded data entry errors.     | Yes, unless manual entry.         | <u>Manufacturer recommendations:</u> <ul style="list-style-type: none"> <li>– Use bar codes for data entry.</li> </ul> <u>Laboratory-implemented control processes:</u> <ul style="list-style-type: none"> <li>– Train staff to verify manual data entries.</li> </ul>                                                                                                                                                                                                                                                                                                                                                                                                                                                                     | Yes                                       |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                |                                                                                                                                                                                                                                               |                                                                                          |                                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                           |
|------------------------------------------------------------------------------------------|------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|-----------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>          | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                         | <b>Known Limitations of Feature or Recommended Action</b>                                | <b>Control Process Effective?</b> | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                  | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>4</b>                                                                                 | Incorrect results due to low-volume sample     | Low-volume sample detector identifies samples with low volumes. Optical sensor detects meniscus in pipettor to ensure that the sample volume is at the appropriate level or a system error will be generated and no result will be displayed. | System may fail to detect a slightly low-volume sample and generate an incorrect result. | Partial                           | <u>Manufacturer recommendations:</u><br>None – automated low-volume sample detector.<br><u>Laboratory-implemented control processes:</u><br>– Monitor frequency of low-volume error messages and counsel staff collecting specimens.<br>– Implement procedural step to examine pediatric samples to ensure that adequate volume of sample is presented to measuring system; train staff on procedure.                                                         | Yes                                       |
| <b>5</b>                                                                                 | Incorrect results due to clots from the sample | Sample pressure monitored in probe. Measuring system software identifies signals indicative of the presence of clots.                                                                                                                         | Small microclots may not be detected.                                                    | Partial                           | <u>Manufacturer recommendations:</u><br>Perform routine maintenance so pressure sensor can function optimally to detect clots.<br><u>Laboratory-implemented control processes:</u><br>– Implement procedural step to inspect samples for visible clots and train staff on this procedure.<br>– Monitor frequency of system clot errors and follow up with staff collecting or processing samples.<br>– Analyze QC samples before and after major maintenance. | Yes                                       |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                 |                                                                                                                                                |                                                                                                                       |                                                       |                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>           | <b>Measuring System Feature or Recommended Action</b>                                                                                          | <b>Known Limitations of Feature or Recommended Action</b>                                                             | <b>Control Process Effective?</b>                     | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>6</b>                                                                                 | Incorrect results due to sample carryover       | Use disposable cuvettes and wash mechanism for probes. The wash mechanism removes residual glucose left over from a high-concentration sample. | Inadequate washing following a high glucose concentration sample can cause false elevations in the subsequent sample. | Partial – requires additional laboratory mitigations. | <u>Manufacturer recommendations:</u><br>– Perform routine maintenance.<br><u>Laboratory-implemented control processes:</u><br>– Analyze QC samples before and after maintenance to verify system performance before and after a major system change.<br>– Repeat any sample that follows a glucose >480 mg/dL (26.7 mmol/L).<br>– Report results without autoverification and use the laboratory information system to notify operator of high glucose specimens. | Yes                                       |
| <b>7</b>                                                                                 | Fault condition caused by maintenance procedure | Recalibrate after major maintenance.                                                                                                           | Recalibration may not correct all possible conditions that could be introduced during maintenance.                    | N/A – No automated control process.                   | <u>Manufacturer recommendations:</u><br>– Recalibrate following major maintenance.<br><u>Laboratory-implemented control processes:</u><br>– Analyze QC samples before and after major maintenance procedures.                                                                                                                                                                                                                                                     | Yes                                       |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                       |                                                                                                                                                                                       |                                                           |                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                           |
|------------------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                 | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                 | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>                                                               | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                      | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>8</b>                                                                                 | Incorrect results due to use of expired reagents      | Bar code entry of reagent information. Software prevents use of expired reagents.                                                                                                     | Does not detect open bottle expiration.                   | Partial bar coding prevents use of expired reagents but does not monitor open bottle stability. | <u>Manufacturer recommendations:</u><br>– Bar coded reagent cartridges prevent use past expiration date.<br><u>Laboratory-implemented control processes:</u><br>– Include procedural step to monitor open bottle expiration dates and train staff.                                                                                                                                                                                                                                                                                | Yes                                       |
| <b>9</b>                                                                                 | Incorrect results due to use of deteriorated reagents | Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank. Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration.            | Partial – requires additional control processes to monitor reagent storage and expiration.      | <u>Manufacturer recommendations:</u><br>– Automated reagent blank measurement.<br><u>Laboratory-implemented control processes:</u><br>– See row #8 – bar coded reagent expiration dates and staff monitoring open bottle stability.<br>– See row #1 – 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 three days in hospital laboratory (for first three months of system use). | Yes                                       |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                                                                |                                                                                                                                                                                                                                                      |                                                           |                                    |                                                                                                                                                                                                                                                                      |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------|------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                                                                          | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                                                                                | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>  | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                         | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>10</b>                                                                                | Incorrect results due to spectrophotometric drift                                                              | Automated monitoring of spectrophotometric system. Two levels of electronic control. Software monitors lamp intensity and resets baseline before every test; a second control uses an optic filter to monitor absorbance signal each day of testing. |                                                           |                                    | <u>Manufacturer recommendations:</u><br>– Maintenance schedule to replace lamps.<br><u>Laboratory-implemented control processes:</u><br>– Analyze QC samples before and after lamp replacement.                                                                      | Yes                                       |
| <b>11</b>                                                                                | Incorrect results due to operator changing measuring system settings                                           | Password control over settings. Operator cannot change settings; requires authorized personnel.                                                                                                                                                      | Operators learn supervisor password.                      | Yes                                | <u>Manufacturer recommendations:</u><br>– Use password security features.<br><u>Laboratory-implemented control processes:</u><br>– Do not share supervisor password and change password periodically.                                                                | Yes                                       |
| <b>12</b>                                                                                | Incorrect results due to operating the measuring system outside of manufacturer's environmental specifications | Only operate measuring system within defined specifications.                                                                                                                                                                                         | No internal environmental monitoring.                     | N/A – No environmental monitoring. | <u>Manufacturer recommendations:</u><br>– Operate measuring system within defined specifications.<br><u>Laboratory-implemented control processes:</u><br>– Monitor room temperature and humidity.<br>– Use automated environmental monitoring for outpatient clinic. | Yes                                       |

**Appendix C. (Continued)**

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                            |                                                       |                                                           |                                                           |                                                                                                                                                                                                                                                                                                                                                           |                                           |
|------------------------------------------------------------------------------------------|------------------------------------------------------------|-------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                      | <b>Measuring System Feature or Recommended Action</b> | <b>Known Limitations of Feature or Recommended Action</b> | <b>Control Process Effective?</b>                         | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                              | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>13</b>                                                                                | Incorrect or unavailable results due to power fluctuations | Protect the system from power fluctuations.           | No internal system checks on power fluctuations           | N/A – No system control processes for power fluctuations. | <u>Manufacturer recommendations:</u><br>– Protect the measuring system from power fluctuations.<br><u>Laboratory-implemented control processes:</u><br>– Use emergency power outlets in hospital.<br>– Purchase an uninterruptible power supply (UPS) for measuring system in outpatient clinic.<br>– Monitor UPS battery function and replace as needed. | Yes                                       |

## **Appendix D. The Quality Control Plan Developed From the Individual Components of the Quality Control Strategies From Appendixes B and C. Example: Glucose Measurement on an Automated Measuring System**

This appendix organizes individual components from the analysis performed in Appendix B to create the laboratory's quality control plan (QCP). Note that this appendix is intended as an illustrative example and addresses only those risks that were assessed in Appendixes B and C.

There have been recent advances in technology and in recognition of these advances, regulatory and accreditation bodies may provide opportunities for laboratories to establish QCP based on risk assessments. Therefore, this QCP centers on the risk assessment process developed by the laboratory. This process includes following the manufacturer's recommendation for analyzing quality control (QC) samples (ie, analyzed on receipt of new shipments of reagents, with each calibration, after major maintenance, or whenever the performance of the measuring system is in question). Also note that in this example, the measuring system has two electronic control processes each day of testing: 1) the baseline lamp intensity, and 2) the optical filter absorbance check. Analysis of QC samples is conducted per the manufacturer's recommendations, at the minimum, and the laboratory has additional recommendations for analysis of QC samples before and after calibration and maintenance, and at least every three days that testing is performed.

The QCP is summarized for implementation as:

### *Electronic Controls*

- Electronic controls perform automatically every 24 hours.

### *QC Samples*

- Analyze two levels of QC samples that were not in the same shipment as the reagents on receipt of new reagents.
- Ensure QC sample acceptance criteria are appropriate for the clinical setting.
- Analyze two levels of QC samples before and after each calibration.
- Analyze two levels of QC samples before and after major maintenance.
- Analyze two levels of QC samples at least every three days that testing is performed.
- During initial three months of implementation, analyze two levels of QC samples daily in the outpatient clinic, and every three days in the hospital laboratory.

### *External Quality Assessment (EQA) or Proficiency Testing (PT)*

- Participate in EQA or PT program to assess overall system performance and compare against other peer laboratories. Note that frequency of EQA or PT is determined by the provider or by local or national regulations.

### *Calibration*

- After major maintenance
- Weekly or with reagent lot changes

## **Appendix D. (Continued)**

### *Maintenance*

- Follow manufacturer's schedule (emphasize checking probe cleaning and lamp intensities).
- Monitor refrigerator temperature daily (implement continuous temperature monitoring for outpatient clinic).
- Monitor temperature and humidity at all laboratory locations (install continuous temperature and humidity monitoring with alarm at outpatient clinic).
- Install uninterruptible power supply (UPS)/surge protector at outpatient clinic laboratory and monitor UPS battery function.

### *Training*

- Monitor refrigerator temperature daily.
- Check condition of the cold packs on receipt of new shipments of reagents.
- Double-check manual data entries, and stress consequences of incorrect data entry.
- Check for low-volume sample and clots before testing, and monitor frequency of measuring system error messages, which may indicate the need for staff counseling.
- Repeat next sample following a sample with glucose >480 mg/dL (26.7 mmol/L) to check for specimen carryover (until sufficient data is collected to demonstrate the effectiveness of probe washing in reducing the potential risk from carryover).
- Check open dating and stress consequences of using degraded or expired reagents, QC samples, and calibrators.
- Change measuring system passwords periodically and do not share system passwords.

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

Scenario: A 10-member health care provider group practice with an automated glucose measuring system in an office laboratory. Clinical medical assistants perform glucose testing. This health care provider's office is using a quality control plan (QCP) as developed in Appendix B and shown in Appendix D.

A 45-year-old diabetic woman visits the clinic, complaining of 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 room. Her admission glucose measured in the hospital's clinical laboratory is 420 mg/dL (23.3 mmol/L). The 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 quality control (QC) sample results were within acceptable limits over the past six months. No measuring system error messages requiring operator intervention were obtained. Review of the QCP identified that the office laboratory was using two concentrations of QC samples at 70 mg/dL (3.9 mmol/L) (with a product insert acceptance range of 56–84 mg/dL [3.1–4.6 mmol/L], 10% coefficient of variation [CV]) and 250 mg/dL (13.8 mmol/L) (with a product insert acceptable range of 200–300 mg/dL [11.1–16.7 mmol/L], 10% CV). QC samples were analyzed as recommended, before and after calibration and every three days of patient testing. The outpatient clinic verified performance within QC package insert acceptance ranges with each shipment of reagents, choosing to use package insert QC limits as the laboratory's acceptance limits for each lot.

The original patient specimen 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; a result of 421 mg/dL (23.2 mmol/L) was obtained.

This confirmed discrepancy prompted a review of the QC sample data for the last six 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 last six weeks in which all values were below the mean, with the last four 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 ranges may have compromised the laboratory's ability to detect reagent degradation, or 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 range criteria were appropriate for the clinic setting.

Possible causes of measurement error: incorrect calibration, or incorrect calibrator value if a recalibration had occurred; calibration drift; reagent deterioration; measuring system failure.

**Appendix E. (Continued)**

Further investigation: The measuring system was recalibrated with fresh reagents from the same lot, and from the same vial of calibrator that had been used for the past two 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 opening its container. However, other possible causes are not excluded without further 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.

Conclusions of the investigation:

1. The automated built-in reagent monitoring system failed to detect the reagent deterioration.
  - Cause: To be determined by the manufacturer.
  - Contributing cause: The laboratory failed to verify that the control sample range criteria were appropriate for the clinical setting.
2. QC testing at two levels of glucose using the package insert acceptable ranges 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).
  - Immediate cause: The laboratory failed to implement appropriate acceptance limits (ie, laboratory-specific limits determined statistically from QC sample results). This 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.
  - Root causes: The laboratory's QCP failed (1) to require implementation of appropriately determined control limits, and (2) to verify that the glucose control limits were adequate for the medical use of the test results.

Corrective actions:

1. 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.
2. Instituted weekly correlation testing of five patient samples with the main laboratory.

**Appendix E. (Continued)**

Row #1 of the Laboratory Risk Assessment table in Appendix B describes the potential risk of reagent deterioration during shipment, the laboratory's actions to address validation of reagents upon receipt, and control strategies to manage storage within manufacturer's specifications.

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                |                                                                                                |                                                                    |                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------|------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|---------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                          | <b>Measuring System Feature or Recommended Action</b>                                          | <b>Known Limitations of Feature or Recommended Action</b>          | <b>Control Process Effective?</b>                                               | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>1</b>                                                                                 | Incorrect results due to 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 may incorrectly assess assay integrity. | N/A – No automated control process to detect reagent stability during shipment. | <u>Follow manufacturer's recommendations:</u><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><u>Laboratory-implemented control processes:</u><br>– Implement continuous temperature monitoring for outpatient clinics.<br>– Ensure QC samples are within expiration date and within the open vial stability claim.<br>– Check condition of the cold packs upon reagent shipment receipt.<br>– Ensure QC sample range criteria are appropriate for the clinical setting. | Yes                                       |

**Appendix E. (Continued)**

Row #9 of the Laboratory Risk Assessment table in Appendix B refers to the automated control that detects reagent deterioration based on the reagent blank absorbance and the laboratory's actions to manage open bottle stability.

| An Illustrative Example of a Glucose Measurement on an Automated Measuring System |                                                       |                                                                                                                                                                                       |                                                    |                                                                                            |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                    |
|-----------------------------------------------------------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| Row #                                                                             | Targeted Failure Mode (Hazard)                        | Measuring System Feature or Recommended Action                                                                                                                                        | Known Limitations of Feature or Recommended Action | Control Process Effective?                                                                 | The QCP Actions Required to Address Known Limitations                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Residual Risk Acceptable? (Yes/No) |
| 9                                                                                 | Incorrect results due to use of deteriorated reagents | Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank. Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration.     | Partial – requires additional control processes to monitor reagent storage and expiration. | <u>Manufacturer recommendations:</u><br>– Automated reagent blank measurement.<br><u>Laboratory-implemented control processes:</u><br>– See row #8 – bar coded reagent expiration dates and staff monitoring open bottle stability.<br>– See row #1 – 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 three days in hospital laboratory (for first three months of system use). | Yes                                |

**Appendix E. (Continued)**

The investigation showed that the automated control, a blank absorbance monitor, was insufficient to detect reagent deterioration and prevent incorrect results being reported before clinical action. In addition, the QC ranges were not adequate to detect a trend in measuring system reagent performance. Therefore, the risk analysis (see rows #1 and #9 in Appendix B) was modified as indicated by bolded text:

| <b>An Illustrative Example of a Glucose Measurement on an Automated Measuring System</b> |                                                                |                                                                                                                                                                                       |                                                                    |                                                                                            |                                                                                                                                                                                                                                                           |                                           |
|------------------------------------------------------------------------------------------|----------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------|--------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| <b>Row #</b>                                                                             | <b>Targeted Failure Mode (Hazard)</b>                          | <b>Measuring System Feature or Recommended Action</b>                                                                                                                                 | <b>Known Limitations of Feature or Recommended Action</b>          | <b>Control Process Effective?</b>                                                          | <b>The QCP Actions Required to Address Known Limitations</b>                                                                                                                                                                                              | <b>Residual Risk Acceptable? (Yes/No)</b> |
| <b>1</b>                                                                                 | Incorrect results due to 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 may incorrectly assess assay integrity. | N/A – No automated control process to detect reagent stability during shipment.            | <p>– Ensure QC sample range criteria are appropriate for the clinical setting.</p> <p><b>– Ensure QCP is followed in all laboratory settings and site-specific QC sample limits are developed instead of using package insert criteria.</b></p>           | Yes                                       |
| <b>9</b>                                                                                 | Incorrect results due to use of deteriorated reagents          | Discoloration of reagent occurs with deterioration and is detected by measurement of the absorbance of the reagent blank. Periodic QC sample measurement verifies system performance. | Does not detect reagent storage or expiration.                     | Partial – requires additional control processes to monitor reagent storage and expiration. | <p>– Analyze QC samples daily in outpatient clinic and once every three days in hospital laboratory (for first three months of system use).</p> <p><b>– Correlate five patient samples weekly between the clinic and central hospital laboratory.</b></p> | Yes                                       |

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## The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The quality management system 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 as follows:

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

EP23-A addresses the QSE indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

| Organization | Customer Focus | Facilities and Safety | Personnel    | Purchasing and Inventory | Equipment | Process Management       | Documents and Records | Information Management | Nonconforming Event Management | Assessments  | Continual Improvement |
|--------------|----------------|-----------------------|--------------|--------------------------|-----------|--------------------------|-----------------------|------------------------|--------------------------------|--------------|-----------------------|
| GP26         | GP26           | GP26<br>M29           | GP21<br>GP26 | GP26                     | GP26      | X<br>C24<br>EP18<br>GP26 | GP02<br>GP26          | GP02<br>GP26           | EP18<br>GP26                   | EP18<br>GP26 | EP18<br>GP26          |

## Path of Workflow

A path of workflow is the description of the necessary processes to deliver the particular product or service that the organization or entity provides. A laboratory path of workflow consists of the sequential processes: preexamination, examination, and postexamination and their respective sequential subprocesses. All laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

EP23-A addresses the clinical laboratory path of workflow steps indicated by an “X.” For a description of the document listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

| Preexamination       |                   |                  |                           | Examination |                              |                | Postexamination                 |                   |
|----------------------|-------------------|------------------|---------------------------|-------------|------------------------------|----------------|---------------------------------|-------------------|
| Examination ordering | Sample collection | Sample transport | Sample receipt/processing | Examination | Results review and follow-up | Interpretation | Results reporting and archiving | Sample management |
| GP26                 | GP26              | GP26             | GP26                      | X<br>GP26   | X<br>GP26                    | X<br>GP26      | GP26                            | GP26              |

## Related CLSI Reference Materials\*

- C24-A3**      **Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions; Approved Guideline—Third Edition (2006).** This guideline provides definitions of analytical intervals, planning of quality control procedures, and guidance for quality control applications.
- EP18-A2**      **Risk Management Techniques to Identify and Control Laboratory Error Sources; Approved Guideline—Second Edition (2009).** This guideline describes risk management techniques that will aid in identifying, understanding, and managing sources of failure (potential failure modes) and help to ensure correct results. Although intended primarily for *in vitro* diagnostics, this document will also serve as a reference for clinical laboratory managers and supervisors who wish to learn about risk management techniques and processes.
- GP02-A5**      **Laboratory Documents: Development and Control; Approved Guideline—Fifth Edition (2006).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the medical laboratory community.
- GP21-A3**      **Training and Competence Assessment; Approved Guideline—Third Edition (2009).** This document provides background information and recommended processes for the development of training and competence assessment programs that meet quality and regulatory objectives.
- GP26-A4**      **Quality Management System: A Model for Laboratory Services; Approved Guideline—Fourth Edition (2011).** This document provides a model for medical laboratories that will assist with implementation and maintenance of an effective quality management system.
- M29-A3**      **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005).** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

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\* CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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Centers for Medicare & Medicaid Services  
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MA Dept. of Public Health Laboratories  
Malaria Research Training Center  
Marion County Public Health Department  
Meuhedet Central Lab  
Ministry of Health and Social Welfare - Tanzania  
Mongolian Agency for Standardization and Metrology  
Namibia Institute of Pathology  
National Cancer Institute, OBBR, NIH  
National Food Institute Technical University of Denmark  
National Health Laboratory Service C/O F&M Import & Export Services  
National HIV & Retrovirology Lab  
Public Health Agency of Canada  
National Institute of Health-Maputo, Mozambique  
National Institute of Standards and Technology  
National Pathology Accreditation Advisory Council  
New York State Dept. of Health  
Ontario Agency for Health Protection and Promotion  
Pennsylvania Dept. of Health  
SA Pathology  
Saskatchewan Health-Provincial Laboratory  
Scientific Institute of Public Health  
State of Alabama  
State of Wyoming Public Health Laboratory  
The Nathan S. Kline Institute  
University of Iowa, Hygienic Lab  
US Naval Medical Research Unit #3  
USAMC - AFRIMS

Industry Members

Company  
3M Medical Division  
Abbott  
Abbott Diabetes Care  
Abbott Point of Care Inc.  
Access Genetics  
Aderans Research  
AdvaMed  
Akonn Biosystems  
Ammirati Regulatory Consulting  
Anapharm, Inc.  
AspenBio Pharma, Inc.  
Astellas Pharma  
AstraZeneca Pharmaceuticals  
Astute Medical, Inc.  
Ativa Medical  
Axis-Shield PoC AS  
Bayer Healthcare, LLC Diagnostic Division  
BD  
BD Biosciences - San Jose, CA  
BD Diagnostic Systems  
BD Vacutainer Systems  
Beaufort Advisors, LLC  
Beckman Coulter Cellular Analysis Business Center  
Beckman Coulter, Inc.  
Beth Goldstein Consultant  
Bio-Rad Laboratories, Inc.  
Bio-Rad Laboratories, Inc. - France  
Bioanalyse, Ltd.  
Biocartis  
BioDevelopment S.r.l.  
Biohit Oyj.  
Biomedica Laboratories SDN BHD  
bioMérieux, Inc.  
Blaine Healthcare Associates, Inc.  
BRI Consultants Limited  
Calloway Laboratories  
Canon U.S. Life Sciences, Inc.  
CBI Inc.  
Cempra Pharmaceuticals, Inc.  
Cepheid  
Cerilliant Corp.  
Compliance Insight, Inc.  
Constitution Medical Inc  
Controllab  
Copan Diagnostics Inc.

Crescendo Bioscience  
Cubist Pharmaceuticals, Inc.  
Dahl-Chase Pathology Associates PA  
Diagnostica Stago  
DX Assays Pte Ltd.  
Eiken Chemical Company, Ltd.  
Elanco Animal Health  
Elkin Simson Consulting Services  
Emika Consulting  
EndPoint Associates, LLC  
Enigma Diagnostics  
Eurofins Medinet  
Evidia Biosciences Inc.  
EXACT Sciences Corporation  
Gen-Probe  
Genefluidics  
Genzyme Diagnostics  
GlaxoSmithKline  
Greiner Bio-One Inc.  
Himedia Labs Ltd  
HistoGenex N.V.  
Hospital Sungai Buloh  
Icon Laboratories, Inc.  
Innovotech, Inc.  
Instrumentation Laboratory  
Integrated BioBank  
IntelligentMDx, Inc.  
Intuity Medical  
ITC Corp  
Japan Assn. of Clinical Reagents Industries  
Johnson & Johnson Pharmaceutical Research & Develop., L.L.C.  
Kaiser Permanente  
KoreaBIO  
Krouwer Consulting  
Lab PMM  
Laboratory Specialists, Inc.  
LifeLabs  
LifeScan, Inc.  
Liofilchem SRL  
LipoScience, Inc.  
Maine Standards Company, LLC  
Marketing MicroScan & Molecular Korea-Siemens Healthcare  
Masimo Corp.  
Masimo Labs  
Mbio Diagnostics, Inc.  
MDxHealth SA  
Medical Device Consultants, Inc.  
Merek & Company, Inc.  
Merial Limited  
Meso Scale Diagnostics, LLC.  
Micromyx, LLC  
Molecular Response  
Moscow Antidoping Agency  
Nanosphere, Inc.  
Nihon Kohden Corporation  
Nissui Pharmaceutical Co., Ltd.  
NJK & Associates, Inc.  
NorDx - Scarborough Campus  
Nova Biomedical Corporation  
NovaBiotics  
Novartis Institutes for Biomedical Research  
Optimer Pharmaceuticals, Inc.  
Ortho-Clinical Diagnostics, Inc.  
Ortho-McNeil, Inc.  
Oxryase, Inc.  
Paratek Pharmaceuticals, Inc.  
PathCare Pathology Laboratory  
PerkinElmer Genetics, Inc.  
Pfizer Animal Health  
Pfizer Inc  
Pfizer Italia Srl  
Phadia AB  
Philips Healthcare Incubator  
PPD  
ProteoGenix, Inc.  
QML Pathology  
Quotient Bioresearch Ltd.  
R-Biopharm AG  
Radiometer America, Inc.  
Roche Diagnostics GmbH  
Roche Diagnostics, Inc.  
Roche Molecular Systems  
RPL Laboratory Solutions, Inc.  
DBA RPL Compliance Solutions  
Sanofi Pasteur  
Sarstedt, Inc.  
Seventh Sense Biosystems  
Siemens Healthcare Diagnostics Inc.  
Siemens Healthcare Diagnostics Products GmbH  
Soloy Laboratory Consulting Services, Llc  
SomaLogic  
Sphere Medical Holding Limited  
Streck Laboratories, Inc.  
Super Religare Laboratories Ltd  
Sysmex America, Inc.  
Sysmex Corporation - Japan  
Tetraphase Pharmaceuticals

The Clinical Microbiology Institute  
The Medicines Company  
TheraDoe  
Theranos  
Theravance Inc.  
Thermo Fisher Scientific  
Thermo Fisher Scientific, Oxoid Products  
Thermo Fisher Scientific, Remel  
Transasia Bio-Medicals Limited  
Trek Diagnostic Systems  
Tulip Group  
Ventana Medical Systems Inc.  
VeracYTE, Inc.  
Vivacta  
Watson Pharmaceuticals  
Wellstat Diagnostics, LLC  
XDX, Inc.

Associate Active

31st Medical Group SGSL (AE)  
3rd Medical Group (AK)  
48th Medical Group/MDSS RAF Lakenheath (AE)  
55th Medical Group/SGSAL (NE)  
59th MDW/859th MDTs/MTL Wilford Hall Medical Center (TX)  
81st MDSS/SGSAL (MS)  
82 MDG/SGCL Sheppard AFB (TX)  
Academisch Ziekenhuis-VUB UZ Brussel (Belgium)  
ACL Laboratories (IL)  
ACL Laboratories (WI)  
Adams County Hospital (OH)  
Adena Regional Medical Center Hospital (OH)  
Affiliated Laboratory, Inc. (ME)  
Akron Children's Hospital (OH)  
Al Ain Hospital (Abu Dhabi, United Arab Emirates)  
Al Hada Armed Forces Hospital/TAIF/KSA (Saudi Arabia)  
Al Noor Hospital (United Arab Emirates)  
Al Rahba Hospital (United Arab Emirates)  
Alameda County Medical Center (CA)  
Albany Medical Center Hospital (NY)  
Albemarle Hospital (NC)  
Alexandra Hospital (Singapore)  
All Children's Hospital (FL)  
Allegiance Health (MI)  
Alpena Regional Medical Center (MI)  
Alta Bates Summit Medical Center (CA)  
Alverno Clinical Laboratories, Inc. (IN)  
American Esoteric Laboratories (AEL) (TN)  
American University of Beirut Medical Center (NJ)  
Anand Diagnostic Laboratory (India)  
Anne Arundel Medical Center (MD)  
Antech Diagnostics (CA)  
Antelope Valley Hospital District (CA)  
Appalachian Regional Healthcare System (NC)  
Arkansas Children's Hospital (AR)  
Arkansas Dept of Health Public Health Laboratory (AR)  
Arkansas Methodist Medical Center (AR)  
Arnot Ogden Medical Center Laboratory (NY)  
Artemis Health, Inc. (CA)  
ARUP Laboratories (UT)  
Asan Medical Center (Korea, Republic Of)  
Asante Health System (OR)  
Ashley County Medical Center (AR)  
Asiri Group of Hospitals Ltd. (Sri Lanka)  
Aspen Valley Hospital (CO)  
ASPETAR (Qatar Orthopedic and Sports Medicine Hospital) (Qatar)  
Aspirus Wausau Hospital (WI)  
Auburn Regional Medical Center (WA)  
Augusta Health (VA)  
Aultman Hospital (OH)  
Avera McKennan Hospital & University Health Center (SD)  
AZ Sint-Jan (Belgium)  
Azienda Ospedale Di Lecco (Italy)  
Azienda Ospedaliera Padova (Italy)  
Baptist Hospital of Miami (FL)  
Baptist Memorial Health Care Corporation - Hospital Laboratories Works (TN)  
Barnes-Jewish Hospital (MO)  
Bassett Healthcare (NY)  
Baton Rouge General (LA)  
Baxter Regional Medical Center (AR)  
BayCare Health System (FL)  
Baylor Health Care System (TX)  
Bayou Pathology, APMC (LA)  
Baystate Medical Center (MA)  
BC Biomedical Laboratories (BC, Canada)

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|----------------------------------------------------------------------------|------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Beloit Memorial Hospital (WI)                                              | Cornwall Community Hospital (ON, Canada)                                     | Hoag Memorial Hospital Presbyterian (CA)                                                          | Long Island Jewish Medical Center (NY)                                     |
| Berg Diagnostics (MA)                                                      | Covance CLS (IN)                                                             | Hoboken University Medical Center (NJ)                                                            | Louisiana Office of Public Health Laboratory (LA)                          |
| Beth Israel Medical Center (NY)                                            | Covenant Medical Center (TX)                                                 | Holy Cross Hospital-Lab (MD)                                                                      | Louisiana State University Medical Ctr. (LA)                               |
| Bio-Reference Laboratories (NJ)                                            | Creighton Medical Lab (NE)                                                   | Holy Name Hospital (NJ)                                                                           | Lower Columbia Pathologists, P.S. (WA)                                     |
| Blanchard Valley Hospital (OH)                                             | Crozer-Chester Medical Center (PA)                                           | Hôpital de la Cité-de-La-Santé De Laval (Quebec, Canada)                                          | Lower Mainland Laboratories (BC, Canada)                                   |
| Bon Secours Health Partners (VA)                                           | Cumberland Medical Center (TN)                                               | Hôpital du Haut-Richelieu (PQ, Canada)                                                            | Lyndon B. Johnson General Hospital (TX)                                    |
| Bonnyville Health Center (AB, Canada)                                      | Darwin Library NT Territory Health Services (NT, Australia)                  | Hôpital Maisonneuve-Rosemont (PQ, Canada)                                                         | Maccabi Medical Care and Health Fund (Israel)                              |
| Boston Medical Center (MA)                                                 | David Grant Medical Center (CA)                                              | Hôpital Santa Cabrini Ospedale (PQ, Canada)                                                       | Mafraq Hospital (United Arab Emirates)                                     |
| Boulder Community Hospital (CO)                                            | Daviness Community Hospital (IN)                                             | Horizon Health Network (N.B., Canada)                                                             | Magnolia Regional Health Center (MS)                                       |
| Boyce & Bynum Pathology Labs (MO)                                          | Deaconess Hospital Laboratory (IN)                                           | Hospital Albert Einstein (SP, Brazil)                                                             | Main Line Clinical Laboratories, Inc. (PA)                                 |
| Brant Community Healthcare System/Brant General Hospital (Ontario, Canada) | Dean Medical Center (WI)                                                     | Hospital Sacre-Coeur de Montreal (Quebec, Canada)                                                 | Lankenau Hospital (PA)                                                     |
| Bremerton Naval Hospital (WA)                                              | Denver Health & Hospital Authority (CO)                                      | Hôtel-Dieu Grace Hospital Library (ON, Canada)                                                    | Makerere University Walter Reed Project                                    |
| Brian All Good Community Hospital/121 Combat (AP)                          | DHHS NC State Lab of Public Health (NC)                                      | Hunter Area Pathology Service (Australia)                                                         | Makerere University Medical School (Uganda)                                |
| Bridgeport Hospital (CT)                                                   | DiagnoSearch Life Sciences Inc. (Maharashtra, India)                         | Hunter Labs (CA)                                                                                  | Marquette General Hospital (MI)                                            |
| Brooke Army Medical Center (TX)                                            | Diagnostic Laboratory Services, Inc. (HI)                                    | Huntington Memorial Hospital (CA)                                                                 | Marshfield Clinic (WI)                                                     |
| Broward General Medical Center (FL)                                        | Diagnostic Services of Manitoba (MB, Canada)                                 | Imelda Hospital (Belgium)                                                                         | Martha Jefferson Hospital (VA)                                             |
| Cadham Provincial Laboratory-MB Health (MB, Canada)                        | Dimensions Healthcare System Prince George's Hospital Center (MD)            | Indiana River Memorial Hospital (FL)                                                              | Martin Luther King, Jr./Drew Medical Center (CA)                           |
| Calgary Laboratory Services (AB, Canada)                                   | DMC University Laboratories (MI)                                             | Indiana University Health Bloomington Hospital (IN)                                               | Martin Memorial Health Systems (FL)                                        |
| California Pacific Medical Center (CA)                                     | Drake Center (OH)                                                            | Indiana University Health Care-Pathology Laboratory (IN)                                          | Mary Hitchcock Memorial Hospital (NH)                                      |
| Cambridge Health Alliance (MA)                                             | Driscoll Children's Hospital (TX)                                            | Inova Central Laboratory (VA)                                                                     | Mary Washington Hospital (VA)                                              |
| Cape Fear Valley Medical Center Laboratory (NC)                            | DUHS Clinical Laboratories Franklin Site (NC)                                | Institut fur Stand. und Dok. im Med. Lab. (Germany)                                               | Mater Health Services - Pathology (Australia)                              |
| Capital Coast Health (New Zealand)                                         | Dynacare Laboratory (WI)                                                     | Institut National de Santé Publique Du Quebec Centre de Doc. - INSPQ (PQ, Canada)                 | Maxwell Air Force Base (AL)                                                |
| Capital Health - Regional Laboratory Services (AB, Canada)                 | Dynacare NW, Inc - Seattle (WA)                                              | Institute Health Laboratories (PR)                                                                | Mayo Clinic (MN)                                                           |
| Capital Health System Mercer Campus (NJ)                                   | DynaLIFE (AB, Canada)                                                        | Institute of Clinical Pathology and Medical Research (Australia)                                  | MCG Health (GA)                                                            |
| Caritas Norwood Hospital (MA)                                              | E. A. Conway Medical Center (LA)                                             | Institute of Laboratory Medicine                                                                  | Meadows Regional Medical Center (GA)                                       |
| Carl R. Darnall Army Medical Center Department of Pathology (TX)           | East Georgia Regional Medical Center (GA)                                    | Landsipitali Univ. Hospital (Iceland)                                                             | Medical Center Hospital (TX)                                               |
| Carolina Medical Laboratory (NC)                                           | East Texas Medical Center-Pittsburg (TX)                                     | Institute of Medical & Veterinary Science (SA, Australia)                                         | Medical Center of Louisiana At NO-Charity (LA)                             |
| Carolinas Healthcare System (NC)                                           | Eastern Health - Health Sciences Centre (NL, Canada)                         | Intermountain Health Care Lab Services (UT)                                                       | Medical Centre Ljubljana (Slovenia)                                        |
| Carpenter S.A. de C.V. (D.F., Mexico)                                      | Eastern Health Pathology (Victoria, Australia)                               | International Health Management Associates, Inc. (IL)                                             | Medical College of Virginia Hospital (VA)                                  |
| Catholic Health Initiatives (KY)                                           | Easton Hospital (PA)                                                         | Irwin Army Community Hospital (KS)                                                                | Medical University of South Carolina (SC)                                  |
| Cedars-Sinai Medical Center (CA)                                           | Edward Hospital (IL)                                                         | Jackson County Memorial Hospital (OK)                                                             | Memorial Hermann Healthcare System (TX)                                    |
| Cenetron Diagnostics (TX)                                                  | Effingham Hospital (GA)                                                      | Jackson Memorial Hospital (FL)                                                                    | Memorial Medical Center (IL)                                               |
| Central Baptist Hospital (KY)                                              | Elmhurst Hospital Center (NY)                                                | Jackson Purchase Medical Center (KY)                                                              | Memorial Medical Center (PA)                                               |
| Central Kansas Medical Center (KS)                                         | Emory University Hospital (GA)                                               | Jessa Ziekenhuis VZW (Belgium)                                                                    | Memorial Regional Hospital (FL)                                            |
| Centre Hospitalier Anna-Laberge (Quebec, Canada)                           | Evangelical Community Hospital (PA)                                          | John C. Lincoln Hospital - N.MT. (AZ)                                                             | Mercy Franciscan Mt. Airy (OH)                                             |
| Centre Hospitalier Regional De Trois Rivières (PQ, Canada)                 | Evans Army Community Hospital (CO)                                           | John F. Kennedy Medical Center (NJ)                                                               | Mercy Hospital & Medical Center (IL)                                       |
| Centro Médico Imbanaco (Colombia)                                          | Exeter Hospital (NH)                                                         | John H. Stroger, Jr. Hospital of Cook County (IL)                                                 | Methodist Dallas Medical Center (TX)                                       |
| Chaleur Regional Hospital (NB, Canada)                                     | Exosome Diagnostics, Inc. (MN)                                               | Johns Hopkins Medical Institutions (MD)                                                           | Methodist Hospital (TX)                                                    |
| Chang Gung Memorial Hospital (Taiwan)                                      | Federal Medical Center (MN)                                                  | Johnson City Medical Center Hospital (TN)                                                         | Methodist Hospital Park Nicollet Health Services (MN)                      |
| Changhua Christian Hospital (Taiwan)                                       | First Health of the Carolinas Moore Regional Hospital (NC)                   | JPS Health Network (TX)                                                                           | Methodist Hospital Pathology (NE)                                          |
| Changi General Hospital (Singapore)                                        | Fletcher Allen Health Care (VT)                                              | Kailos Genetics (AL)                                                                              | MetroHealth Medical Center (OH)                                            |
| Chatham - Kent Health Alliance (ON, Canada)                                | Fleury S.A. (Brazil)                                                         | Kaiser Permanente (MD)                                                                            | Metropolitan Hospital Center (NY)                                          |
| Chesapeake General Hospital (VA)                                           | Florida Hospital (FL)                                                        | Kaiser Permanente Medical Care (CA)                                                               | Metropolitan Medical Laboratory, PLC (IA)                                  |
| Chester County Hospital (PA)                                               | Fox Chase Cancer Center (PA)                                                 | Kenora-Rainy River Reg. Lab. Program (ON, Canada)                                                 | Miami Children's Hospital (FL)                                             |
| Children's Healthcare of Atlanta (GA)                                      | Fraser Health Authority Royal Columbian Hospital Site (BC, Canada)           | King Abdulaziz Hospital, Al Ahsa Dept. of Pathology & Laboratory Medicine (AI-hasa, Saudi Arabia) | Mid Michigan Medical Center - Midland (MI)                                 |
| Childrens Hosp. - Kings Daughters (VA)                                     | Gamma-Dynacare Laboratories (ON, Canada)                                     | King Fahad Specialist Hospital-Dammam, K.S.A. (Eastern Region, Saudi Arabia)                      | Middelheim General Hospital (Belgium)                                      |
| Children's Hospital & Research Center At Oakland (CA)                      | Garden City Hospital (MI)                                                    | King Faisal Specialist Hospital & Research Center (Saudi Arabia)                                  | Middlesex Hospital (CT)                                                    |
| Childrens Hospital Los Angeles (CA)                                        | Garfield Medical Center (CA)                                                 | King Hussein Cancer Center (Jordan)                                                               | Mike O'Callaghan Federal Hospital (NV)                                     |
| Children's Hospital Medical Center (OH)                                    | Gaston Memorial Hospital (NC)                                                | King's Daughters Medical Center (KY)                                                              | Minneapolis Medical Research Foundation (MN)                               |
| Children's Hospital of Central California (CA)                             | Geisinger Medical Center (PA)                                                | Kinston General Hospital (ON, Canada)                                                             | Mississippi Baptist Medical Center (MS)                                    |
| Children's Hospital of Orange County (CA)                                  | Genesis Healthcare System (OH)                                               | Laboratória Médico Santa Luzia Ltda (Brazil)                                                      | Mississippi Public Health Lab (MS)                                         |
| Children's Hospital of Philadelphia (PA)                                   | George Washington University Hospital (DC)                                   | Laboratory Alliance of Central New York (NY)                                                      | Monongalia General Hospital (WV)                                           |
| Childrens Hospital of Wisconsin (WI)                                       | Gestión de Calidad (Argentina)                                               | Laboratory Corporation of America (NJ)                                                            | Montreal General Hospital (Quebec)                                         |
| Children's Hospitals and Clinics (MN)                                      | Ghent University Hospital (Belgium)                                          | Laboratory Medicin Dalarna (Dalarna, Sweden)                                                      | Mouwassat Hospital (GA, Saudi Arabia)                                      |
| Children's Medical Center (OH)                                             | Good Shepherd Medical Center (TX)                                            | LabPlus Auckland District Health Board (New Zealand)                                              | Mt. Carmel Health System (OH)                                              |
| Children's Medical Center (TX)                                             | Grana S.A. (TX)                                                              | LAC/USC Medical Center (CA)                                                                       | Mt. Sinai Hospital (ON, Canada)                                            |
| Christiana Care Health Services (DE)                                       | Grand Marquis Co., LTD (Taiwan)                                              | Lafayette General Medical Center (LA)                                                             | Mt. Sinai Hospital - New York (NY)                                         |
| CHU - Saint Pierre (Belgium)                                               | Grand River Hospital (ON, Canada)                                            | Lakeland Regional Medical Center (FL)                                                             | Naples Community Hospital (FL)                                             |
| CHU Sainte-Justine (Quebec, Canada)                                        | Grand Strand Regional Medical Center (SC)                                    | Lancaster General Hospital (PA)                                                                   | Nassau County Medical Center (NY)                                          |
| CHUM Hospital Saint-Luc (Quebec, Canada)                                   | Group Health Cooperative (WA)                                                | Landstuhl Regional Medical Center (Germany)                                                       | National B Virus Resource Laboratory (GA)                                  |
| City of Hope National Medical Center (CA)                                  | Gundersen Lutheran Medical Center (WI)                                       | Langley Air Force Base (VA)                                                                       | National Cancer Center (Korea, Republic Of)                                |
| Cleveland Clinic (OH)                                                      | Guthrie Clinic Laboratories (PA)                                             | LeBonheur Children's Hospital (TN)                                                                | National Institutes of Health, Clinical Center (MD)                        |
| Clinica Alemana De Santiago (Chile)                                        | Hôtel-Dieu de Lévis (PQ, Canada)                                             | Legacy Laboratory Services (OR)                                                                   | National Naval Medical Center (MD)                                         |
| Clinical and Laboratory Standards Institute (PA)                           | Halton Healthcare Services (ON, Canada)                                      | Letherbridge Regional Hospital (AB, Canada)                                                       | National University Hospital Department of Laboratory Medicine (Singapore) |
| Clinical Labs of Hawaii (HI)                                               | Hamad Medical Corporation (Qatar)                                            | Lewis-Gale Medical Center (VA)                                                                    | National University of Ireland, Galway (NUIG) (Ireland)                    |
| Clinical Labs of Hawaii (HI)                                               | Hamilton Regional Laboratory Medicine Program - St. Joseph's (ON, Canada)    | Lexington Medical Center (SC)                                                                     | Nationwide Children's Hospital (OH)                                        |
| College of Physicians and Surgeons of Alberta (AB, Canada)                 | Hanover General Hospital (PA)                                                | L'Hotel-Dieu de Québec (PQ, Canada)                                                               | Naval Hospital Oak Harbor (WA)                                             |
| Collingwood General & Marine Hospital (ON, Canada)                         | Harford Memorial Hospital (MD)                                               | Licking Memorial Hospital (OH)                                                                    | Naval Medical Center Portsmouth (VA)                                       |
| Commonwealth of Kentucky (KY)                                              | Harris Methodist Fort Worth (TX)                                             | LifeBridge Health Sinai Hospital (MD)                                                             | Naval Medical Clinic Hawaii (HI)                                           |
| Commonwealth of Virginia (DCLS) (VA)                                       | Harris Methodist Hospital Southwest (TX)                                     | LifeLabs Medical Laboratory Services (BC, Canada)                                                 | NB Department of Health (NB, Canada)                                       |
| Community Hospital (IN)                                                    | Hartford Hospital (CT)                                                       | Loma Linda University Medical Center (LLUMC) (CA)                                                 | New England Baptist Hospital (MA)                                          |
| Community Hospital of the Monterey Peninsula (CA)                          | Health Network Lab (PA)                                                      | Long Beach Memorial Medical Center-LBMMC (CA)                                                     | New Lexington Clinic (KY)                                                  |
| Community Medical Center (NJ)                                              | Health Sciences Research Institute (Japan)                                   |                                                                                                   | New York City Department of Health and Mental Hygiene (NY)                 |
| Community Memorial Hospital (WI)                                           | Health Waikato (New Zealand)                                                 |                                                                                                   | New York Presbyterian Hospital (NY)                                        |
| Complexe Hospitalier de la Sagamie (Quebec, Canada)                        | Heartland Health (MO)                                                        |                                                                                                   | New York University Medical Center (NY)                                    |
| CompuNet Clinical Laboratories Quest Diagnostics JV (OH)                   | Heidelberg Army Hospital (AE)                                                |                                                                                                   | Newark Beth Israel Medical Center (NJ)                                     |
| Concord Hospital (NH)                                                      | Helen Hayes Hospital (NY)                                                    |                                                                                                   | Newfoundland Public Health Laboratory (NL, Canada)                         |
| Consultants Laboratory of WI LLC (WI)                                      | Helix (Russian Federation)                                                   |                                                                                                   | Nor-Lea General Hospital (NM)                                              |
| Contra Costa Regional Medical Center (CA)                                  | Henry Ford Hospital (MI)                                                     |                                                                                                   | North Carolina Baptist Hospital (NC)                                       |
| Cook Children's Medical Center (TX)                                        | Henry M. Jackson Foundation for the Advancement of Military Medicine-MD (MD) |                                                                                                   | North District Hospital (China)                                            |
| Cookeville Regional Medical Center (TN)                                    | Hi-Desert Medical Center (CA)                                                |                                                                                                   | North Mississippi Medical Center (MS)                                      |
|                                                                            | Highlands Medical Center (AL)                                                |                                                                                                   | North Shore Hospital Laboratory (New Zealand)                              |
|                                                                            | HJF Naval Infectious Diseases Diagnostic Laboratory (MD)                     |                                                                                                   |                                                                            |

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| North Shore-Long Island Jewish Health System Laboratories (NY)                | Sahlgrenska Universitetssjukhuset (Sweden)                                       | Swedish Edmonds Hospital (WA)                                   | University of Colorado Health Sciences Center (CO)                 |
| Northridge Hospital Medical Center (CA)                                       | Saint Francis Hospital & Medical Center (CT)                                     | Swedish Medical Center (CO)                                     | University of Colorado Hospital (CO)                               |
| Northside Hospital (GA)                                                       | Saint Mary’s Regional Medical Center (NV)                                        | Sydney South West Pathology Service                             | University of Illinois Medical Center (IL)                         |
| Northside Medical Center (OH)                                                 | Saints Memorial Medical Center (MA)                                              | Liverpool Hospital (NSW, Australia)                             | University of Iowa Hospitals and Clinics (IA)                      |
| Northwest Texas Hospital (TX)                                                 | Salem Memorial District Hospital (MO)                                            | T.J. Samson Community Hospital (KY)                             | University of Kentucky Medical Center (KY)                         |
| Northwestern Memorial Hospital (IL)                                           | Sampson Regional Medical Center (NC)                                             | Taichung Veterans General Hospital (Taiwan)                     | University of Maryland Medical System (MD)                         |
| Norton Healthcare (KY)                                                        | Samsung Medical Center (Korea, Republic Of)                                      | Taiwan Society of Laboratory Medicine (Taiwan)                  | University of Minnesota Medical Center- Fairview (MN)              |
| Ocean County Medical Laboratories (NJ)                                        | San Francisco General Hospital- University of California San Francisco (CA)      | Tallaght Hospital (Ireland)                                     | University of Missouri Hospital (MO)                               |
| Ochsner Clinic Foundation (LA)                                                | Sanford USD Medical Center (SD)                                                  | Tartu University Clinics (Estonia)                              | University of Pennsylvania Health System (PA)                      |
| Ohio State University Hospitals (OH)                                          | Santa Clara Valley Medical Center (CA)                                           | Temple Univ. Hospital - Parkinson Pav. (PA)                     | University of Pittsburgh Medical Center (PA)                       |
| Ohio Valley Medical Center (WV)                                               | SARL Laboratoire Caron (France)                                                  | Tenet Healthcare (PA)                                           | University of Texas Health Center (TX)                             |
| Onze Lieve Vrouweziekenhuis (Belgium)                                         | Scott & White Memorial Hospital (TX)                                             | Texas Children’s Hospital (TX)                                  | University of the Ryukyus (Japan)                                  |
| Ordre Professionnel Des Technologistes Médicaux Du Quebec (Quebec, Canada)    | Seattle Children’s Hospital/Children’s Hospital and Regional Medical Center (WA) | Texas Department of State Health Services (TX)                  | University of Virginia Medical Center (VA)                         |
| Orebro University Hospital (Sweden)                                           | Sebastian River Medical Center (FL)                                              | Texas Health Presbyterian Hospital Dallas (TX)                  | UPMC Bedford Memorial (PA)                                         |
| Orlando Health (FL)                                                           | Seoul National University Hospital (Korea, Republic Of)                          | The AGA Khan University Hospital (Pakistan)                     | US Naval Hospital Naples ( )                                       |
| Ospedale Casa Sollievo Della Sofferenza - IRCCS (Italy)                       | Seoul St. Mary’s Hospital (Korea, Republic Of)                                   | The Brooklyn Hospital Center (NY)                               | UZ-KUL Medical Center (Belgium)                                    |
| Our Lady’s Hospital For Sick Children (Ireland)                               | Seton Medical Center (CA)                                                        | The Charlotte Hungerford Hospital (CT)                          | VA (Asheville) Medical Center (NC)                                 |
| Palmetto Baptist Medical Center (SC)                                          | Sharp Health Care Laboratory Services (CA)                                       | The Children’s Mercy Hospital (MO)                              | VA (Bay Pines) Medical Center (FL)                                 |
| Pamela Youde Nethersole Eastern Hospital (Hong Kong East Cluster) (Hong Kong) | Sheik Kalifa Medical City (United Arab Emirates)                                 | The Cooley Dickinson Hospital, Inc. (MA)                        | VA (Central Texas) Veterans Health Care System (TX)                |
| Pathgroup (TN)                                                                | Shore Memorial Hospital (NJ)                                                     | The Credit Valley Hospital (ON, Canada)                         | VA (Chillicothe) Medical Center (OH)                               |
| Pathlab (IA)                                                                  | Singapore General Hospital (Singapore)                                           | The Hospital for Sick Children (ON, Canada)                     | VA (Cincinnati) Medical Center (OH)                                |
| Pathology and Cytology Laboratories, Inc. (KY)                                | South Bend Medical Foundation (IN)                                               | The Medical Center of Aurora (CO)                               | VA (Dallas) Medical Center (TX)                                    |
| Pathology Associates Medical Lab. (WA)                                        | South Eastern Area Laboratory Services (NSW, Australia)                          | The Michener Inst. for Applied Health Sciences (ON, Canada)     | VA (Dayton) Medical Center (OH)                                    |
| Pathology Inc. (CA)                                                           | South Miami Hospital (FL)                                                        | The Naval Hospital of Jacksonville (FL)                         | VA (Indianapolis) Medical Center (IN)                              |
| Penn State Hershey Medical Center (PA)                                        | Southern Community Laboratories (Canterbury, New Zealand)                        | The Nebraska Medical Center (NE)                                | VA (Iowa City) Medical Center (IA)                                 |
| Pennsylvania Hospital (PA)                                                    | Southern Health Care Network (Australia)                                         | The Ottawa Hospital (ON, Canada)                                | VA (Miami) Medical Center (FL)                                     |
| Peterborough Regional Health Centre (ON, Canada)                              | Southwest Healthcare System (CA)                                                 | The Permanente Medical Group (CA)                               | VA (Tampa) Hospital (FL)                                           |
| PHS Indian Hospital - Pine Ridge (SD)                                         | Spectra East (NJ)                                                                | The Toledo Hospital (OH)                                        | Valley Health / Winchester Medical Center (VA)                     |
| Piedmont Hospital (GA)                                                        | Spectra Laboratories (CA)                                                        | The University of Texas Medical Branch (TX)                     | Vancouver Island Health Authority (SI) (BC, Canada)                |
| Pitt County Memorial Hospital (NC)                                            | St. Agnes Healthcare (MD)                                                        | Thomas Jefferson University Hospital, Inc. (PA)                 | Vanderbilt University Medical Center (TN)                          |
| Potomac Hospital (VA)                                                         | St. Anthony Hospital (OK)                                                        | Timmins and District Hospital (ON, Canada)                      | Via Christi Regional Medical Center (KS)                           |
| Prairie Lakes Hospital (SD)                                                   | St. Barnabas Medical Center (NJ)                                                 | Tokyo Metro. Res. Lab of Public Health (Japan)                  | Viracor-IBT Reference Laboratory (MO)                              |
| Presbyterian Hospital - Laboratory (NC)                                       | St. Elizabeth Community Hospital (CA)                                            | Touro Infirmary (LA)                                            | Virginia Regional Medical Center (MN)                              |
| Presbyterian/St. Luke’s Medical Center (CO)                                   | St. Eustache Hospital (Quebec, Canada)                                           | TriCore Reference Laboratories (NM)                             | Virtua - West Jersey Hospital (NJ)                                 |
| Prince of Wales Hospital (Hong Kong, China)                                   | St. Francis Hospital (SC)                                                        | Trident Medical Center (SC)                                     | WakeMed (NC)                                                       |
| Princess Margaret Hospital (Hong Kong, China)                                 | St. Francis Memorial Hospital (CA)                                               | Trinity Medical Center (AL)                                     | Walter Reed Army Medical Center (DC)                               |
| Providence Alaska Medical Center (AK)                                         | St. John Hospital and Medical Center (MI)                                        | Tripler Army Medical Center (HI)                                | Warren Hospital (NJ)                                               |
| Providence Health Services, Regional Laboratory (OR)                          | St. John’s Episcopal Hospital (NY)                                               | Tuen Mun Hospital, Hospital Authority (China)                   | Washington Hospital Center (DC)                                    |
| Provincial Laboratory for Public Health (AB, Canada)                          | St. John’s Hospital & Health Center (CA)                                         | Tufts Medical Center Hospital (MA)                              | Washington Hospital Healthcare System (CA)                         |
| Queen Elizabeth Hospital (P.E.I, Canada)                                      | St. John’s Mercy Medical Center (MO)                                             | Tulane Medical Center Hospital & Clinic (LA)                    | Waterbury Hospital (CT)                                            |
| Queen Elizabeth Hospital (China)                                              | St. Joseph Mercy Hospital (MI)                                                   | Turku University Central Hospital (Finland)                     | Waterford Regional Hospital (Ireland)                              |
| Queensland Health Pathology Services (Australia)                              | St. Jude Children’s Research Hospital (TN)                                       | Twin Lakes Regional Medical Center (KY)                         | Wayne Memorial Hospital (NC)                                       |
| Queensway Carleton Hospital (ON, Canada)                                      | St. Luke’s Hospital (IA)                                                         | UCI Medical Center (CA)                                         | Weirton Medical Center (WV)                                        |
| Quest Diagnostics, Incorporated (CA)                                          | St. Luke’s Hospital (PA)                                                         | UCLA Medical Center Clinical Laboratories (CA)                  | West China Second University Hospital, Sichuan University (China)  |
| Quintiles Laboratories, Ltd. (GA)                                             | St. Mary Medical Center (CA)                                                     | UCSD Medical Center (CA)                                        | West Jefferson Medical Center (LA)                                 |
| Rady Children’s Hospital San Diego (CA)                                       | St. Mary’s Hospital (WI)                                                         | UCSF Medical Center China Basin (CA)                            | West Penn Allegheny Health System- Allegheny General Hospital (PA) |
| Ramathibodi Hospital (Thailand)                                               | St. Michael’s Medical Center, Inc. (NJ)                                          | UMC of El Paso- Laboratory (TX)                                 | West Shore Medical Center (MI)                                     |
| Redington-Fairview General Hospital (ME)                                      | St. Tammany Parish Hospital (LA)                                                 | UMC of Southern Nevada (NV)                                     | West Valley Medical Center Laboratory (ID)                         |
| Regions Hospital (MN)                                                         | Stanford Hospital and Clinics (CA)                                               | UNC Hospitals (NC)                                              | Westchester Medical Center (NY)                                    |
| Reid Hospital & Health Care Services (IN)                                     | Stanton Territorial Health Authority (NT, Canada)                                | Unidad de Patologia Clinica (Mexico)                            | Western Baptist Hospital (KY)                                      |
| Reinier De Graaf Groep (Netherlands)                                          | State of Connecticut Department of Public Health (CT)                            | Union Clinical Laboratory (Taiwan)                              | Western Healthcare Corporation (NL, Canada)                        |
| Renown Regional Medical Center (NV)                                           | State of Ohio/Corrections Medical Center Laboratory (OH)                         | United Christian Hospital (Kowloon, Hong Kong)                  | Wheaton Franciscan Laboratories (WI)                               |
| Research Medical Center (MO)                                                  | State of Washington Public Health Labs (WA)                                      | United States Air Force School of Aerospace Medicine / PHE (TX) | Wheeling Hospital (WV)                                             |
| Response Genetics, Inc. (CA)                                                  | Stillwater Medical Center (OK)                                                   | Unity HealthCare (IA)                                           | White Memorial Medical Center (CA)                                 |
| RIPAS Hospital (Brunei-Mauria, Brunei Darussalam)                             | Stony Brook University Hospital (NY)                                             | Universitair Ziekenhuis Antwerpen (Belgium)                     | Whitehorse General Hospital (YT, Canada)                           |
| Riverside County Regional Medical Center (CA)                                 | Stormont-Vail Regional Medical Ctr. (KS)                                         | University College Hospital (Ireland)                           | William Beaumont Army Medical Center (TX)                          |
| Riverside Health System (VA)                                                  | Strong Memorial Hospital (NY)                                                    | University Hospital (GA)                                        | William Beaumont Hospital (MI)                                     |
| Riverside Methodist Hospital (OH)                                             | Sudbury Regional Hospital (ON, Canada)                                           | University Hospital Center Sherbrooke (CHUS) (Quebec)           | William Osler Health Centre (ON, Canada)                           |
| Riyadh Armed Forces Hospital, Sulaymainia (Saudi Arabia)                      | Sunnybrook Health Sciences Centre (ON, Canada)                                   | University Medical Center at Princeton (NJ)                     | Winchester Hospital (MA)                                           |
| Rockford Memorial Hospital (IL)                                               | Sunrise Hospital and Medical Center (NV)                                         | University of Alabama Hospital Lab (AL)                         | Winn Army Community Hospital (GA)                                  |
| Royal Victoria Hospital (ON, Canada)                                          |                                                                                  | University of Chicago Hospitals Laboratories (IL)               | Wishard Health Sciences (IN)                                       |
| SAAD Specialist Hospital (Saudi Arabia)                                       |                                                                                  |                                                                 | Womack Army Medical Center Department of Pathology (NC)            |
| Sacred Heart Hospital (WI)                                                    |                                                                                  |                                                                 | York Hospital (PA)                                                 |
| Sacred Heart Hospital (FL)                                                    |                                                                                  |                                                                 | Yukon-Kuskokwim Delta Regional Hospital (AK)                       |



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