EP18-P2
Vol. 27 No. 23
Replaces EP18-A
Vol. 22 No. 28

Risk Management Techniques to Identify and Control Laboratory Error Sources; Proposed Guideline—Second Edition

PLEASE

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This proposed document is published for wide and thorough review in the new, accelerated Clinical and Laboratory Standards Institute (CLSI) consensus-review process. The document will undergo concurrent consensus review, Board review, and delegate voting (ie, candidate for advancement) for 60 days.

Please send your comments on scope, approach, and technical and editorial content to CLSI.

Comment period ends

29 October 2007

The subcommittee responsible for this document will assess all comments received by the end of the comment period. Based on this assessment, a new version of the document will be issued. Readers are encouraged to send their comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087-1898 USA; Fax: +610.688.0700, or to the following e-mail address: customerservice@clsi.org

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COMMENT

This guideline recommends risk management techniques that will aid in identifying, understanding, and managing sources of error (potential failure modes) and help to ensure correct results. It is targeted for those involved in supervision of laboratory-testing quality management, and it addresses issues related to specimen collection through reporting of results.

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

Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS) is an international, interdisciplinary, nonprofit, standards-developing, and educational organization that promotes the development and use of voluntary consensus standards and guidelines within the health care community. It is recognized worldwide for the application of its unique consensus process in the development of standards and guidelines for patient testing and related health care issues. Our process is based on the principle that consensus is an effective and cost-effective way to improve patient testing and health care services.

In addition to developing and promoting the use of voluntary consensus standards and guidelines, we provide an open and unbiased forum to address critical issues affecting the quality of patient testing and health care.

PUBLICATIONS

A document is published as a standard, guideline, or committee report.

Standard A document developed through the consensus process that clearly identifies specific, essential requirements for materials, methods, or practices for use in an unmodified form. A standard may, in addition, contain discretionary elements, which are clearly identified.

Guideline A document developed through the consensus process describing criteria for a general operating practice, procedure, or material for voluntary use. A guideline may be used as written or modified by the user to fit specific needs.

Report A document that has not been subjected to consensus review and is released by the Board of Directors.

CONSENSUS PROCESS

The CLSI voluntary consensus process is a protocol establishing formal criteria for:

- the authorization of a project
- the development and open review of documents
- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

Most documents are subject to two levels of consensus—"proposed" and "approved." Depending on the need for field evaluation or data collection, documents may also be made available for review at an intermediate consensus level.

Proposed A consensus document undergoes the first stage of review by the health care community as a proposed standard or guideline. The document should receive a wide and thorough technical review, including an overall review of its scope, approach, and utility, and a line-by-line review of its technical and editorial content.

Approved An approved standard or guideline has achieved consensus within the health care community. It should be reviewed to assess the utility of the final document, to ensure attainment of consensus (ie, that comments on earlier versions have been satisfactorily addressed), and to identify the need for additional consensus documents.

Our standards and guidelines represent a consensus opinion on good practices and reflect the substantial agreement by materially affected, competent, and interested parties obtained by following CLSI's established consensus procedures. Provisions in CLSI standards and guidelines may be more or less stringent than applicable regulations. Consequently, conformance to this voluntary consensus document does not relieve the user of responsibility for compliance with applicable regulations.

COMMENTS

The comments of users are essential to the consensus process. Anyone may submit a comment, and all comments are addressed, according to the consensus process, by the committee that wrote the document. All comments, including those that result in a change to the document when published at the next consensus level and those that do not result in a change, are responded to by the committee in an appendix to the document. Readers are strongly encouraged to comment in any form and at any time on any document. Address comments to Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, PA 19087, USA.

VOLUNTEER PARTICIPATION

Health care professionals in all specialties are urged to volunteer for participation in CLSI projects. Please contact us at customerservice@clsi.org or +610.688.0100 for additional information on committee participation.

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Risk Management Techniques to Identify and Control Laboratory Error Sources; Proposed Guideline—Second Edition

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Abstract

Clinical and Laboratory Standards Institute document EP18-P2—*Risk Management Techniques to Identify and Control Laboratory Error Sources; Proposed Guideline—Second Edition* recommends a quality management system for *in vitro* diagnostic test systems that is based on expert opinion, is practical to implement, and is applicable to various devices and settings, so sources of error (potential failure modes) are identified, understood, and managed. This system will assist device manufacturers, users, regulators, and accrediting agencies in assuring correct results. It addresses regulatory considerations (eg, principles and accountability), recommends the development of a partnership between users and manufacturers, provides a source-of-errors matrix, and suggests approaches to quality monitoring/identification of the problems.

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Foreword

In vitro diagnostic devices (IVDs) play a crucial role in patient care, and the quality and reliability of IVD results are paramount. However, all devices and methods may be subject to preanalytical, analytical, and postanalytical error. The relative importance and probability (ie, the risk) of a specific error condition will vary with the device design, the user, the medical application, and the operating environment. A single quality assurance and control (QA/QC) regimen that optimally mitigates risk for all devices does not exist. As a greater variety of devices and tests become available to meet clinical demands in various environments, including outside the traditional laboratory at the point of patient care (POC), there is a pressing need to assure and control quality in the most effective and efficient manner. Such QA/QC regimens should be based on the characteristics of the device in use, taking into consideration local variables, such as the intended use of the test and the testing environment. Furthermore, QA/QC procedures should be developed systematically using established quality management tools, such as Failure Modes and Effects Analysis (FMEA) and Failure Reporting, Analysis, and Corrective Action Systems (FRACAS).

This document is one in a series of three CLSI documents concurrently undergoing revision or development that address risk assessment and implementation of quality control strategies to mitigate risks of error. This series of documents includes the current revision of this guideline, EP18—*Risk Management Techniques to Identify and Control Laboratory Error Sources*, and two new guidelines under development, EP22-P—*Presentation of Manufacturers' Risk Mitigation Information for Users of* In Vitro *Diagnostic Devices*, and EP23-P—*User-Defined QC Protocols for* In Vitro *Diagnostic Devices Based on Manufacturer's Risk Mitigation Information and the User's Environment.* One common example ties together the three documents and highlights the key features of each document. The interrelationship of the three documents is summarized below.

*EP18—*Risk Management Techniques to Identify and Control Laboratory Error Sources* is intended to provide manufacturers and laboratory professionals with systematic tools for risk management, particularly FMEA and FRACAS. (The components of FRACAS are sometimes known by other names, such as *complaint monitoring* and *corrective and preventative action* (CAPA) systems.) EP18 will discuss the use of FMEA by manufacturers to identify potential sources of error and impose all applicable measures to control those errors. A laboratory should use the information provided by a manufacturer, apply FMEA and FRACAS to identify residual errors, and apply control measures.

*EP22-P—*Presentation of Manufacturers' Risk Mitigation Information for Users of* In Vitro *Diagnostic Devices* provides guidance to manufacturers on the establishment and disclosure of information to users regarding the scope and effectiveness of design features intended to mitigate risk of potential device failures. This information includes the risk associated with such failures, how the QC design features operate, and the studies done to verify the effectiveness of those features.

*EP23-P—*User-Defined QC Protocols for* In Vitro *Diagnostic Devices Based on Manufacturer's Risk Mitigation Information and the User's Environment* describes how a user can integrate manufacturer's risk mitigation information with the unique characteristics of their environment to develop effective quality control protocols for *in vitro* diagnostic devices. Environmental characteristics can include unique factors, such as personnel competency, testing location, temperature, etc., that can impact test results.

* **NOTE:** Recommended revised Titles and Scopes have not yet been approved by the respective committees and will be modified if required in future drafts.

The previous version of this document, EP18-A—*Quality Management for Unit-Use Testing*, was limited to unit-use devices (see Appendix E on Unit-Use Devices). The impetus for the original document was that:

"Conventional quality assurance and quality control methods in and of themselves do not assure quality. A one-size-fits-all or prescribed quality control testing protocol such as "two levels per day of use" may not be appropriate for all testing systems. The diversity among regulatory requirements, accreditation practices, and user needs, coupled with the financial aspects of this QC method, led to the formation of the CLSI Subcommittee on Unit-Use Testing.

It is the subcommittee's intent to provide a comprehensive and flexible guideline that will enable users, manufacturers, and regulators to identify potential sources of errors in unit-use test systems and implement processes to manage these errors using new quality management models."

-Reference EP18-A

The original subcommittee anticipated that a broader-based guideline could be created that would address both unit-use and multiuse systems. Accordingly, the current revision of EP18, *Quality Management for Unit-Use Testing*, is applicable to all IVD devices.

Invitation for Participation in the Consensus Process

An important aspect of the development of this and all CLSI documents should be emphasized, and that is the consensus process. Within the context and operation of CLSI, the term "consensus" means more than agreement. In the context of document development, "consensus" is a process by which CLSI, its members, and interested parties (1) have the opportunity to review and to comment on any CLSI publication; and (2) are assured that their comments will be given serious, competent consideration. Any CLSI document will evolve as will technology affecting laboratory or health care procedures, methods, and protocols; and therefore, is expected to undergo cycles of evaluation and modification.

The Area Committee on Evaluation Protocols has attempted to engage the broadest possible worldwide representation in committee deliberations. Consequently, it is reasonable to expect that issues remain unresolved at the time of publication at the proposed level. The review and comment process is the mechanism for resolving such issues.

The CLSI voluntary consensus process is dependent upon the expertise of worldwide reviewers whose comments add value to the effort. At the end of a 60-day comment period, each subcommittee is obligated to review all comments and to respond in writing to all which are substantive. Where appropriate, modifications will be made to the document, and all comments along with the subcommittee's responses will be included as an appendix to the document when it is published at the next consensus level.

A Note on Terminology

CLSI, as a global leader in standardization and harmonization, is firmly committed to achieving global harmonization wherever 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, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and is an area of immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In the context of this guideline, it is necessary to point out that several terms are used differently in the USA and other countries, notably those in Europe.

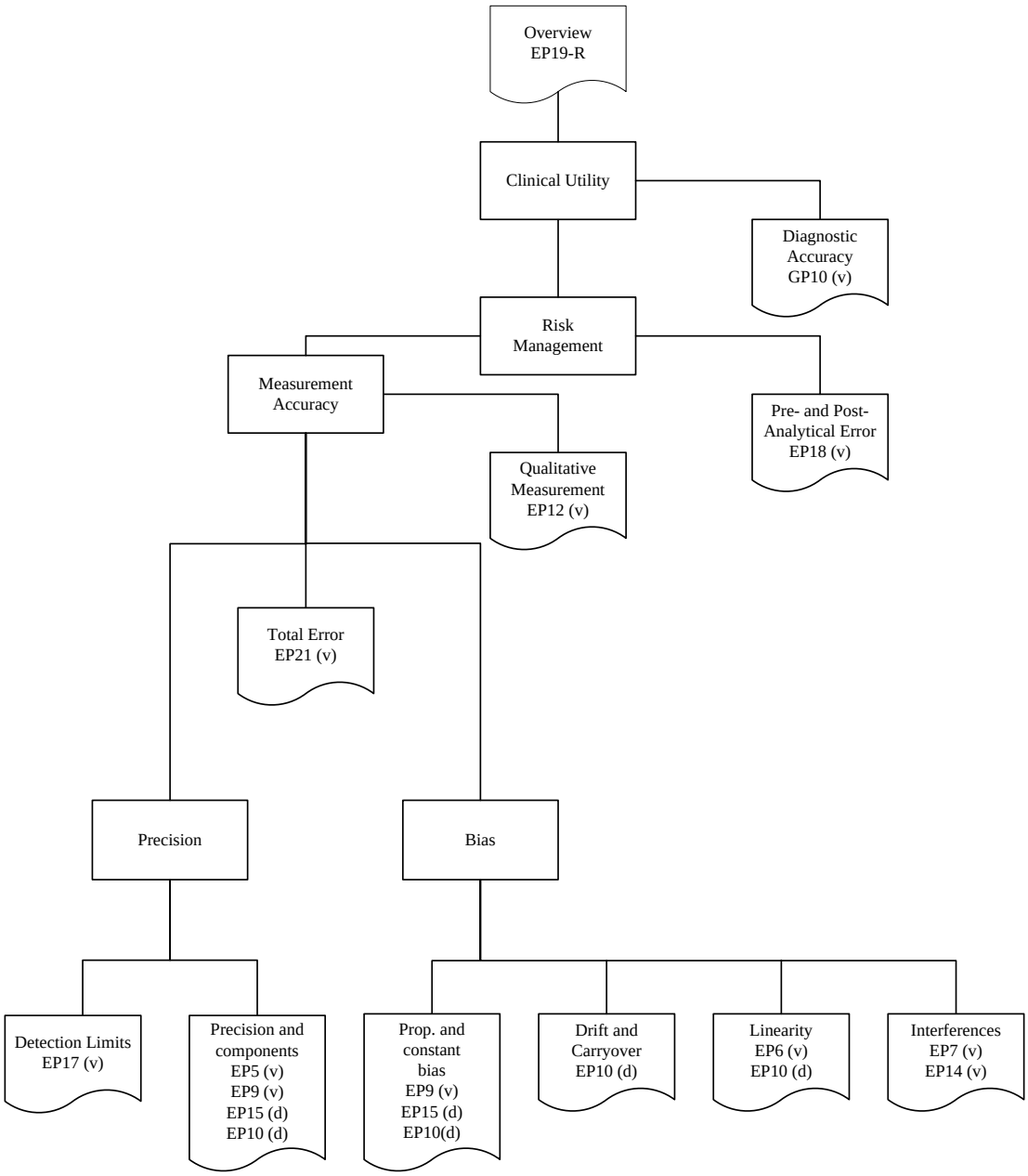
In order to align the usage of terms to ISO, the term *trueness* is used in this document when referring to the closeness of the agreement between the average value from a large series of measurements and an accepted reference value. The term *accuracy*, in its metrological sense, refers to the closeness of the

agreement between the result of a (single) measurement and a true value of a measurand, thus comprising both random and systematic effects.

Key Words

Quality assurance, quality control, quality management, quality system

Laboratory Error Sources and CLSI Evaluation Protocols Documents



Documents marked (d) provide guidance for demonstrating that a source of measurement inaccuracy is within acceptable limits. Documents marked (v) provide guidance for more rigorous evaluation of inaccuracy components.

Laboratory Error Sources and CLSI Evaluation Protocols Documents.[a] This figure illustrates the relationship among parameters estimated by EP documents. Items higher up in the figure are more comprehensive, whereas lower-level items are more specific. Overall, the figure is much like a cause-and-effect diagram. Documents marked (d) provide guidance for demonstrating that a source of measurement inaccuracy is within acceptable limits. Documents marked (v) provide guidance for more rigorous evaluation of inaccuracy components.

[a] For a description of each of the documents listed, please see the Related CLSI/NCCLS Publications section at the end of this document.

The laboratory sources of error figure on the preceding page is based on a figure that has appeared in the following publication: Krouwer JS. Estimating total analytical error and its sources: techniques to improve method evaluation. *Arch Pathol Lab Med.* 1992;116:726-731.[1] Reprinted with permission from the American Medical Association.

Risk Management Techniques to Identify and Control Laboratory Error Sources; Proposed Guideline—Second Edition

1 Scope

This document provides guidance for risk assessment procedures that are based on best practices, practical to implement; applicable to all diagnostics assays; and scientifically based so sources of error are identified, understood, and managed. This guidance will aid device manufacturers and users in ensuring correct results.

The scope of this guideline comprises testing components, locations, and users. Specifically, the testing components include:

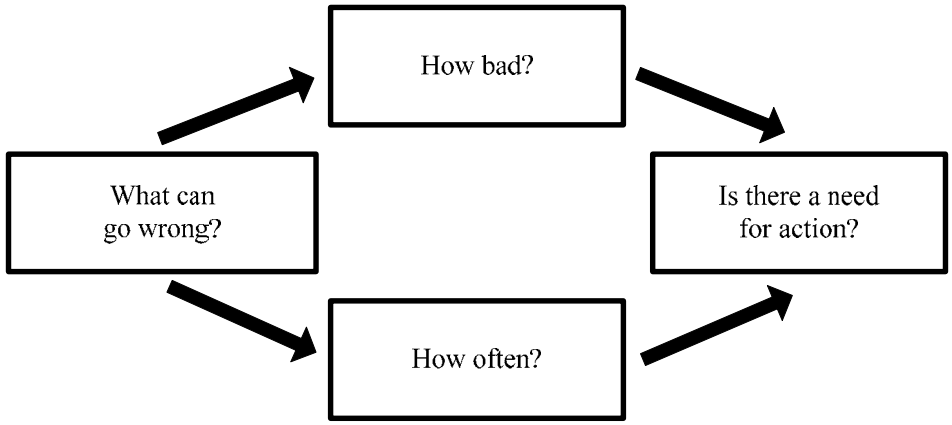
- specimen collection;
- sample presentation;
- instrument/reagents;
- result/readout/raw data;
- preliminary review; and
- integration into the patient record.

This guideline applies to IVD test systems used by providers of health care services in any setting.

2 Introduction

Diagnostic testing presents unique challenges to manufacturers, users, regulators, and accrediting agencies. Manufacturers and the clinical laboratory are faced with the task of keeping systems operational and producing results (reliability) as well as ensuring that the results meet minimum accuracy standards (performance). ***Any*** error source can affect the accuracy and/or reliability of a result.

Risk management attempts to answer the four questions in the following figure.



From National Patient Safety Agency. *Healthcare risk assessment made easy.* March 2007:3. Available at: www.npsa.nhs.uk.

For each **hazard** identified, it is important to decide whether it is significant and whether appropriate and sufficient controls or contingencies are in place to ensure that the **risk** is effectively minimized.

Hazard: a situation with the potential to cause harm

Risk: the combination of likelihood and consequence of hazards being realized

Many evaluation protocols documents have focused on evaluating parameters that affect accuracy, such as linearity[2], precision[3], and bias.[4] EP18 takes a more global approach regarding accuracy and reliability by using risk analysis methods to ensure that:

- the risk of potential errors has been lowered to an acceptable level; and
- the recurrence of observed errors has been reduced to an acceptable rate.

These risk analysis methods are part of a quality assurance program.

The following basic concepts directed the development of this guideline:

Diagnostic devices are extremely diverse in their technology, design, and function. Every test system is subject to certain preanalytical (pre-examination), analytical (examination), and postanalytical (post-examination) errors. The relative importance and likelihood of these errors varies with the device, the specimen, the user, and the environment. In addition, a high level of variability exists in terms of skill and knowledge level among end users. The hospital or commercial laboratory IVD user is often more skilled and knowledgeable in laboratory techniques than the average user of a point-of-care device.

Based upon the assessment of the guiding concepts outlined above, the guideline follows a systems approach to quality management.[5] The phases of the testing process are defined, and the potential as well as any observed sources of error within each phase are identified.

The number of potential and observed errors is large; this makes it important to prioritize efforts to reduce risk, as resources are limited. For example, some errors are almost certain to cause patient harm (eg, an erroneous hypoglycemic result when the patient is hypoglycemic), whereas a result that must be repeated but is not time sensitive will only raise cost. The effect of patient harm is usually more severe than the effect of increased cost. With the classification of severity and probability (or frequency) of occurrence, one can prioritize the importance of events with Pareto analysis. It is also likely—though not certain—

that the most severe events are potential (eg, they have not been observed), whereas less severe events are often observed. It is important to conduct both FMEA (to reduce the risk of potential error events) and FRACAS (to reduce the rate of observed error events), because each risk analysis process has a different focus.

Section 7 lists components of a quality management system (see the related CLSI document on this subject for a more detailed account of these components[6]). These components provide examples of types of control measures (mitigations) that can be used to prevent errors.

This guideline illustrates the following concepts with examples of each in the appendixes:

- generic sources-of-errors matrix is presented for manufacturers to consider when designing systems and using FMEA as a design review aid

- the use of FMEA is explained as a way to reduce the risk of potential errors and includes
  - an example of a completed FMEA by a manufacturer
  - an example of a completed FMEA by a clinical laboratory

- the use of FRACAS is explained as a way to reduce the rate of observed errors and includes
  - an example of a completed FRACAS by a clinical laboratory

The key to the success of this approach is cooperation and open exchange of information among manufacturers and IVD users. In this way, high-quality patient care can be delivered through the competent use of accurate and reliable testing systems.

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 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 US Centers for Disease Control and Prevention.[7] For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to the related CLSI document.[8]

4 Terminology

4.1 Definitions

analyte – component represented in the name of a measurable quantity (ISO 17511).[9]

bias of measurements – difference between the observed results of measurement and a true value of the measurand; **NOTE 1:** There may be one or more systematic error components contributing to the bias; **NOTE 2:** Bias is a measure of the degree of trueness; **NOTE 3:** An estimate of bias is the average value of a series of measurements minus a reference value [ISO 5725-1].[10]

corrective action – action to eliminate the cause of a detected nonconformity or other undesirable situation; **NOTE 1:** There can be more than one cause for a nonconformity; **NOTE 2:** Corrective action is taken to prevent recurrence whereas preventive action is taken to prevent occurrence; **NOTE 3:** There

is a distinction between correction and corrective action; a correction removes a nonconformity while a corrective action removes the cause of the nonconformity [ISO 9000].[11]

error grid – An error grid is a graphical display of differences between an assay and reference; **NOTE:** These differences are divided into zones A, B, C, and so on, with higher letters indicating differences that could lead clinicians to make incorrect medical decision that could harm patients.

failure – A failure in the broadest sense is a case when the system does not meet the user's expectation; **NOTE:** 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.

failure mode and effects analysis (FMEA) – systematic review of an instrument system or process that examines how failures can affect the instrument system or process; **NOTE 1:** FMEA involves identification of potential failure modes, determining the consequences of each failure, and reviewing the control measures implemented to prevent or detect the failure; **NOTE 2:** If estimating the criticality of the failures and the risk of harm is part of the analysis, the technique is called "failure mode, effect, and criticality analysis" (FMECA); **NOTE 3:** FMEA is considered a "bottoms-up" analysis.

fault tree analysis (FTA) – systematic review of an instrument or system to identify potential sources of failure that starts by assuming a main system failure and determines what could cause it; **NOTE 1:** FTA is considered a "top-down" analysis; **NOTE 2:** FTA is more efficient than FMEA for analyzing combinations of failure events and human-use errors; **NOTE 3:** FTA and FMEA are often used together to evaluate complex systems for a comprehensive top-down and bottom-up risk analysis.

FRACAS (Failure Reporting And Corrective Action System) –a process whereby a system is tested and failures are observed and classified by severity and frequency of occurrence. The failures ranked by criticality, the product of severity and frequency of occurrence. The most important problems are corrected. The failure rate is measured in this closed loop process unless the failure rate goal has been met.

hazard – a situation with the potential to cause harm.

hazard analysis – study of the chains of cause and effect between identified hazards, the hazardous situations to which they might lead, and the resulting harm; **NOTE:** The purpose of a hazard analysis is to derive sufficient information for the assessment of the risks involved and the identification of preventive measures [IEC 615081 (modified)].[12]

***in vitro* diagnostic medical device** – medical device intended by the manufacturer to be used for *in vitro* examination of specimens derived from the human body to provide information that may be used for diagnostic, monitoring or compatibility purposes; EXAMPLES: IVD medical devices include reagents, calibrators, sample collection and storage devices, control materials, and related instruments or apparatus; **NOTE:** May be used alone or in combination with other IVD medical devices [ISO/DIS 18113-1].[13]

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 an error 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.

information supplied by the manufacturer – labeling written, printed or graphic matter affixed to a medical device or any of its containers or wrappers, or, provided for use with a medical device, related to

identification, technical description, and use of the IVD medical device, but excluding shipping documents; EXAMPLES: labels, instructions for use [ISO/DIS 18113-1].[13]

instructions for use – information supplied by the manufacturer concerning the safe and proper use of an IVD medical device; **NOTE:** This includes directions for use, operator's manual maintenance, troubleshooting, warnings and precautions, and disposal information [ISO/DIS 18113-1].[13]

intended use – objective intent of the manufacturer or other legal entity or person, under whose name the device is placed on the market, in respect of the application and performance of the device, as indicated in the labeling and promotional material; **NOTE 1:** Intent may be determined by the manufacturer's expressions or shown by the circumstances surrounding the distribution of the article; **NOTE 2:** A statement that identifies the target population for which the IVD medical device is intended is called the Indications for Use [ISO/DIS 18113-1].[13]

malfunction – failure of the product to meet its performance specifications or otherwise perform as intended; **NOTE:** Performance specifications include all claims made in the labeling of the product [21 CFR 803.3 (n)].[14]

measurand – particular quantity subject to measurement; **NOTE 1:** The specification of a measurand may require statements about quantities such as time, temperature and pressure. EXAMPLES: In the type of quantity "mass of protein in 24-hour urine," "protein" is the analyte. In "concentration of glucose in plasma," "glucose" is the analyte. In both cases the long phrase designates the measurand [VIM: 1993].[15]

measurement – set of operations having the object of determining a value of a quantity **NOTE:** The operations may be performed automatically [VIM:1993].[15]

outlier – the observation in a sample, so far separated in value from the remainder as to suggest that it may be from a different population, or the result of an error in measurement (ISO3534-1/93)[16]; **NOTE 1:** (WHO-BS)[17] defines this as "A number of a set of values that is inconsistent with the other numbers of the set"; **NOTE 2:** Statistical tests can be used to identify outliers, but frequently the "common-sense" judgment of the analyst is substituted.

performance characteristic – one of the parameters used to define the performance of an *in vitro* diagnostic medical device; EXAMPLES specificity, precision, limit of detection [SO/DIS 18113-1].[14]

preventive maintenance – regularly scheduled service, as defined by the manufacturer, intended to prevent failures and ensure continued optimal operation of equipment. The term *preventive maintenance* is used to differentiate these activities from maintenance performed to repair a problem after it has occurred; EXAMPLES: calibration, replacement of batteries, replacement of parts at the end of their normal life expectancy, and responses to normal wear and tear.

point-of-care (POC) testing – testing that is performed near or at the site of the patient; **NOTE:** Testing performed outside a central laboratory environment, generally nearer to, or at the site of the patient/client.

preventive action – action to eliminate the cause of a potential nonconformity or other undesirable potential situation; **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 is taken to prevent recurrence [ISO 9000].[11]

quality assurance – part of quality management focused on providing confidence that quality requirements will be fulfilled; [ISO 9000][11] EXAMPLES: Recordkeeping, calibration, equipment maintenance, quality control, proficiency testing, and training; **NOTE:** These activities include

monitoring, evaluating, taking preventative and corrective actions, if necessary, and monitoring the corrective actions for the preanalytical, analytical, and postanalytical phases.

quality control – part of quality management focused on fulfilling quality requirements; [ISO 9000][11] **NOTE 1:** This includes the operational techniques and activities that are used to fulfill requirements for quality; **NOTE 2:** In clinical laboratory testing, quality control includes the procedures intended to monitor the performance of a test procedure to ensure reliable results.

quality management – coordinated activities to direct and control an organization with regard to quality; **NOTE:** Direction and control with regard to quality generally includes establishment of the quality policy and quality objectives, quality planning, quality control, quality assurance and quality improvement. See ISO 15189 for clinical laboratory quality management system [ISO 9000].[11]

quality management system – management system to direct and control an organization with regard to quality; **NOTE:** A quality management system typically includes the organizational structure, resources, processes, and procedures needed to implement quality management [ISO 9000].[11]

residual risk – risk remaining after risk control (mitigation) measures have been taken [ISO 14971].[18]

risk – combination of the probability of occurrence of harm and the severity of that harm [ISO/IEC Guide 51][19]; **NOTE:** In this document, the term criticality is used as a synonym of risk.

risk analysis – systematic use of available information to identify hazards and to estimate the risk [ISO/IEC Guide 51][19]; **NOTE:** Risk analysis includes examination of different sequences of events that can produce hazardous situations and harm.

risk assessment – overall process comprising a risk analysis and a risk evaluation [ISO/IEC Guide 51].[19]

risk management – systematic application of management policies, procedures, and practices to the tasks of analyzing, evaluating, controlling, and monitoring risk [ISO 14971].[18]

sample – one or more parts taken from a system, and intended to provide information on the system, often to serve as a basis for decision on the system or its production; EXAMPLE: a portion of serum taken from a specimen of coagulated blood [ISO 15189].[20]

severity of harm – measure of the possible consequences of a hazard [ISO14971].[18]

specimen – 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 [ISO/DIS 18113-1].[13]

stability – ability of an IVD medical device to maintain its properties within the limits specified by the manufacturer; EXAMPLES: Stability applies to reagents, calibrators, or controls when stored, transported, or used in specified conditions; lyophilized materials after reconstitution and/or preparation of working solutions; materials after opening a sealed container; measurement systems after calibration; **NOTE 1:** Stability of an IVD reagent or measurement system is normally quantified with respect to time; **NOTE 2:** Stability may be quantified in terms of the time over which a performance characteristic changes by a stated amount [ISO/DIS 18113-1].[13]

system – set of interrelated or interacting elements [ISO 9000].[11]

test – determination of one or more characteristics according to a procedure [ISO 9000].[11]

trueness - closeness of agreement between the average value obtained from a large series of test results and an accepted reference value; [ISO 3534-1][16]; **NOTE:** Trueness is usually expressed numerically by the statistical measure bias, which is inversely related to trueness.

uncertainty of measurement – parameter, associated with the result of a measurement, which characterizes the dispersion of the values that could reasonably be attributed to the measurand; **NOTE 1:** Measurement uncertainty quantitatively characterizes the knowledge about the measurand, based on the information used; **NOTE 2:** Measurement uncertainty characterizes the dispersion of a set or distribution of quantity values for the measurand. The dispersion is due to definitional uncertainty of the measurand and random and systematic effects in the measurement; **NOTE 3:** The parameter may be, for example, a standard deviation called standard measurement uncertainty (or a given multiple of it), or the half-width of an interval, having a stated coverage probability; **NOTE 4:** It is understood that the result of the measurement is the best estimate of the value of the measurand, and that all components of uncertainty, including those arising from systematic effects, such as components associated with corrections and reference standards, contribute to the dispersion parameter that characterizes the dispersion of the quantity values that are being attributed to a measurand, based on the information used; **NOTE 5:** Some components of uncertainty may be evaluated from the statistical distribution of the results of series of measurements and can be characterized by "experimental standard deviations." Other components may be evaluated from assumed probability distributions based on experience or other information and can also be characterized by standard deviations; **NOTE 6:** Depending upon its intended use, an expanded measurement uncertainty of a measurement result may be given with a stated coverage factor, giving a coverage interval intended to contain the value of the measurand with high probability, or encompass a stated large fraction of the dispersed quantity values that are being attributed to the measurand [GUM:1995].[21]

unit-use test system – IVD medical device in which reagents, calibrators, and other reaction components supplied in a disposal carrier require no user preparation prior to the analysis; **NOTE:** IVD medical device in which all reagents and reaction components, calibrators, sample conduits, and vessels are supplied in discrete units to be used in the examination of a single sample.

4.2 Acronyms/Abbreviations

IVD	*in vitro* device
FMEA	Failure Mode Effects Analysis
FMECA	Failure Mode Effects Criticality Analysis
FRACAS	Failure Reporting and Corrective Action System
FTA	Fault Tree Analysis
HFMEA	Health care Failure Mode Effects Analysis
POC	Point of Care
QA	Quality Assurance
QC	Quality Control

5 User-Manufacturer Quality Partnership

The objective of a quality management program is to verify that all test system components are performing as specified by the manufacturer and are doing so at a quality level acceptable to the user. The FMEA table (System-Specific Sources of Error Matrix) is the recommended quality tool to be used by manufacturers to identify and lessen potential failure modes, while both the FMEA and FRACAS tables are the recommended quality tools for the laboratory users to identify potential causes of erroneous results that must be controlled. This section outlines the responsibilities of each partner and defines the nature of the partnership between manufacturers and users of testing systems.

5.1 Manufacturer's Responsibility

The FMEA, also referred to as a system-specific sources of error matrix table, can be used as a starting point. The manufacturer's responsibility is to design the testing system to eliminate or minimize significant sources of error as much as possible, then to disclose those that remain. Additional sources of error that are not in the table may often be identified after the test system is in operation. Analyte-specific, as well as system-specific, sources of error should be included. Once the errors have been identified, the manufacturer should develop recommendations for managing these sources of error with consideration given to the nature of the error's impact, the device capabilities, any operator requirements, and the type and frequency of applicable quality monitoring. The risk analysis, which may include items listed in Appendix A, should be analyzed; those risks not mitigated by the manufacturer should be disclosed in the information supplied by the manufacturer to the user.

The following list provides suggested steps for the manufacturer in completing an FMEA:

- Review the generic FMEA table shown in Appendix A.
- Identify applicable failure modes.
- Add other sources of error specific to the device/analyte, not in Appendix A.
- Determine effects of each failure mode (eg, negative bias, positive outlier, etc.).
- Explain the potential impact of each effect on the clinical outcome.
- Design device to eliminate/minimize risk (ie, criticality of failure x probability of occurrence).
- Evaluate device to verify level of effectiveness.
- Identify and evaluate remaining risks.
- Determine further corrective actions required for acceptable risk level (training, labeling, QC protocol).
- Provide information and recommendations in product labeling/information supplied by the manufacturer. Manufacturers are encouraged to disclose significant sources of error and recommended methods of control following this (EP18) guideline.

5.2 User's Responsibility

The IVD user has responsibilities to develop a quality management system that is specific to each testing system and the setting in which each is being used. For the test system to perform within its intended use (within performance characteristics and limitations of use), the user must follow the manufacturer's directions. Laboratories must remember, however, that they must first satisfy the jurisdictional regulatory requirements. The user bears the ultimate responsibility for determining the frequency, level, and rules for surrogate (external) quality control used in its own unique laboratory environment. The user also bears responsibility for establishment of performance characteristics and any other limitations if deviating from the manufacturer's instructions.

A quality management system should provide the appropriate details to ensure that the quality assurance program can identify and manage possible sources of error associated with all clinical testing. The user is responsible for development of a documented quality assurance program appropriate for each testing system. The FMEA table may be used as a checklist or as a tool to help identify potential errors in a testing system so that an appropriate QA program can address them. The user should carefully review the manufacturer's instructions for use and all other product labeling, and identify applicable failure modes that the laboratory's QA program must address. A completed FMEA table will define all anticipated significant sources of error associated with a particular system and how to monitor, detect, and manage (eliminate/minimize) these identified sources of error. A separate FMEA table should be completed for each type of IVD device utilized by a testing facility.

The following is a step-by-step guide to completing a laboratory FMEA table:

(1) The user should review the manufacturer's instructions for use and identify any additional sources of error that the laboratory must control. If the user needs additional information and recommendations, he/she should contact the manufacturer.

(2) Compare the manufacturer's risk analysis information and QC recommendations (FMEA table) to the generic FMEA table (Appendix A) information to determine if the manufacturer's information is compatible with the laboratory's specific analytical/clinical needs and the intended test setting. Add omitted and additional possible sources of error as they are determined to be relevant for the use and setting.

(3) Complete the table columns for all identified sources of error. Identify where additional quality control measures are necessary and how these sources should be managed; Appendix C may be used as a guide for this step. Obtain supporting data as needed from the manufacturer. The criteria for determining which quality monitors to use and at what frequency to implement them is determined by factors specific for the facility. Such factors may include: regulatory requirements; laboratory director specifications; device sensitivity/specificity; device past performance record; competency level of testing operators; reporting mechanisms; and frequency of device utilization.

(4) Determine what additional steps may be necessary in eliminating or reducing the risks of error identified by the FMEA table if the manufacturer's recommend quality control procedures do not appear to monitor for these errors.

(5) Implement all applicable quality monitoring (see Section 6.6.4.3, Applicable Quality Monitoring) at the frequencies specified in the laboratory FMEA table.

(6) Periodically review and evaluate the quality management system to ensure all sources of error are identified and managed at an acceptable rate. Complete and evaluate the FRACAS table (Appendix D) to update acceptable quality monitors and frequencies to improve outcomes.

6 FMEA and FRACAS

6.1 Description of FMEA and FRACAS

For both manufacturers and users (eg, clinical laboratories) both FMEA and FRACAS are important techniques to prevent failures. Their use is recommended as follows:

Site	Phase	FMEA	FRACAS
Manufacturer	Product being designed	✓	
	Product being tested		✓
Clinical laboratory	Product being evaluated	✓	
	Product in use		✓

A manufacturer conducts an FMEA ideally at the *start* of product design. The purpose of this FMEA is to brainstorm potential errors and to ensure that control measures are implemented in the design.

A clinical laboratory FMEA would be conducted before an assay or an instrument system is implemented. Here, one looks at the potential errors suggested by the manufacturer that may affect a clinical laboratory. The laboratory brainstorms to determine whether there are any additional potential errors and whether existing control measures in place are adequate and if not, what control measures need to be implemented. Note that many laboratory processes are common to a collection of assays, so an FMEA covering every aspect of an assay does not have to be performed for every assay.

A manufacturer performs FRACAS after initial product design but before product release to correct observed errors.

A clinical laboratory conducts a FRACAS after an assay is implemented to correct observed errors. For a laboratory, a FRACAS could be set up for the entire laboratory or by department.

6.2 Definition and Purpose

FMEA is a process whose output is a table that contains a list of potential failure modes, in the pre-analytical, analytical, and postanalytical phases of testing, that cause erroneous results. The table may be completed with information from the manufacturer and user describing the relevance of each applicable source of error with potential to cause erroneous results. Some items may not apply to a particular test type or format.

The purpose of an FMEA is to aid the manufacturer and user in considering and identifying possible sources of error applicable to a particular test system. Once a source of error is identified, its criticality can be assessed. For important errors, controls (also called *mitigations*) can be implemented to reduce the risk of errors.

FRACAS is different from FMEA in that rather than postulating a list of potential failure modes, failures that actually have occurred are captured in FRACAS, and the controls applied are called *corrective actions*.

For both FMEA and FRACAS, it is helpful to maintain results in a database. When this is not feasible, a spreadsheet is an alternative.

The timing of FMEA and FRACAS with respect to a process is shown in the following figure.

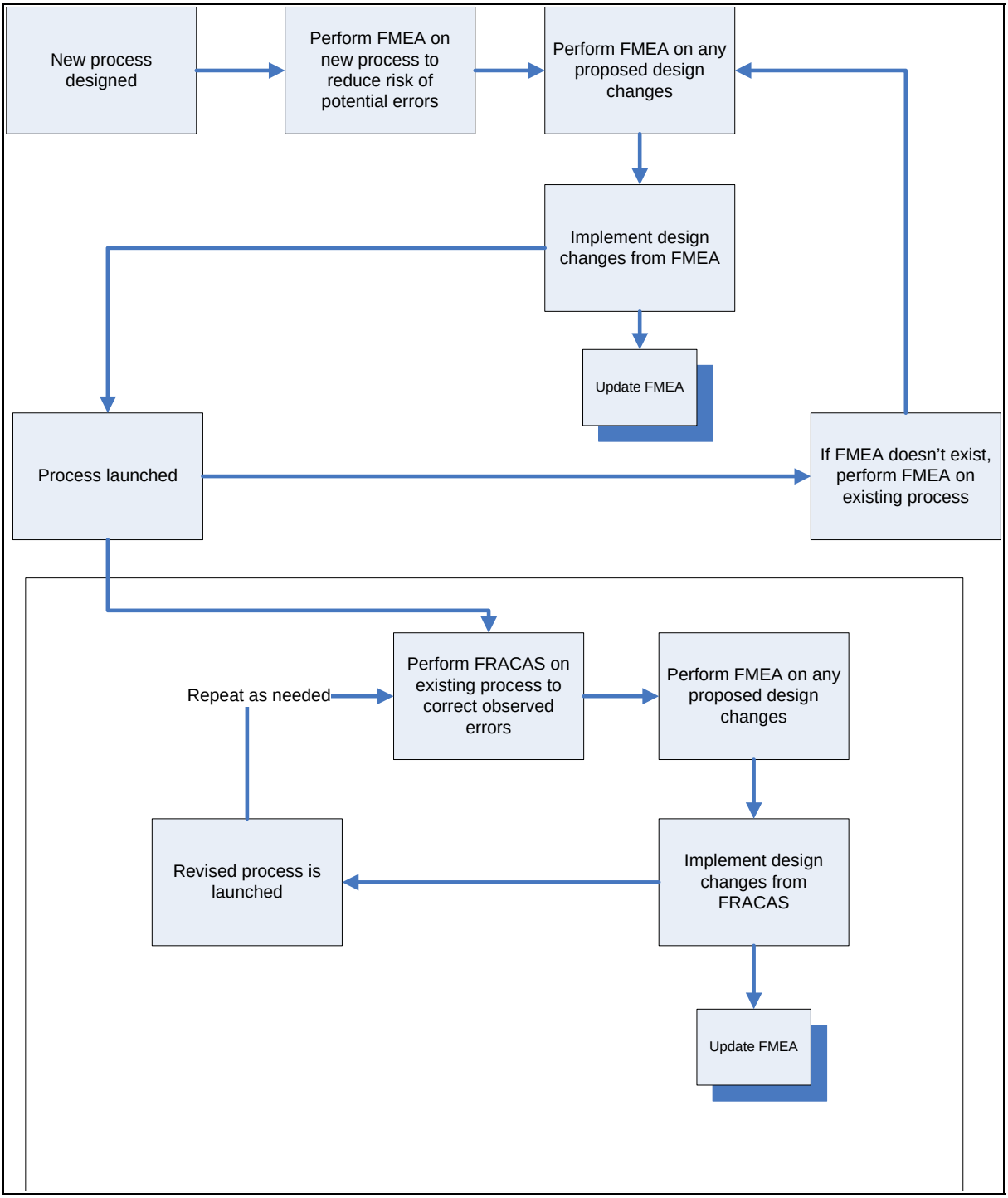


Figure 1. When to Perform FMEA and FRACAS for a Process

6.3 Some General Guidelines for FMEA and FRACAS

6.3.1 A Note on What are and are not Failures

Whereas it is always up to the FMEA or FRACAS team to decide what are or are not errors, one should try to be as conservative as possible. Thus, if a user ignored the manufacturer's instructions on when to recalibrate, this might not be considered an error for the manufacturer, but it would be an error for the clinical laboratory. On the other hand, if the manufacturer suggested that every result be verified against the clinical status of the patient, these would be unreasonable instructions and a resulting error would be the responsibility of the manufacturer.

As another example, some failures will occur at interfaces. If a clinician makes an incorrect medical decision, but could have benefited from better information provided in a laboratory report, then one could partially attribute this problem to the clinical laboratory.

Note that there is a trend to report analytical performance as limits that contain 95% of the differences between an assay result and a suitable reference. This is completely outside the concept of FMEA or FRACAS, which focuses on reporting severe errors.[22]

6.3.2 Avoid Multiple Entries for a Row

In an FMEA or FRACAS table, multiple entries within a row are undesirable. For example, if multiple causes are listed for failure mode, it will be unclear which control measures apply to which cause. If multiple effects are listed, it will be unclear which severities apply, and so on.

6.3.3 Consider Different Types of Control Measures or Corrective Actions

To prevent the effects of errors, one can either prevent the error, or detect and recover from an error that occurs and thereby prevent the effect of the error. One must be open-minded in deciding which strategy is optimal (prevention, detection/recovery, or both). Cost and effectiveness are factors to be considered.

6.4 Description of FMEA Table Entries

The main items in an FMEA are:

6.4.1 Process Step or Component

The process step or product component column describes both the function of the process step (or product component), which contains the failure, and a description of the failure. It is labeled in Appendix A as "step or component in which error occurs" and is helpful for identifying which steps in a process have the most problems.

6.4.2 The Root Cause(s) of the Failure Modes (Errors)

6.4.2.1 "Potential Source of Error" Columns—FMEA

The potential sources of error column is used to list the potential failure modes. Although one could start out with a blank FMEA, the EP18 potential sources of error column contains a list of potential failure modes with six categories. Each category corresponds to the different phases of the testing process. This grouping provides finer discrimination than the traditional classification of preanalytical, analytical, and postanalytical errors.

Note that in Appendix A, these sources of error are *causes*. That is, the actual observed error might be different. For example, the first error source listed in Appendix A is contamination; this is a cause. The actual error (also called *failure*) that would be observed would possibly be an incorrect result, although it is also possible that no failure would be observed. If it were possible for the instrument system to detect sample contamination during analysis—which is unlikely—the observed error would be a system message. Whether a failure is observed or not, a possible failure effect is reporting an incorrect result.

Appendix B illustrates a sample, filled-out FMEA table. Typically, an actual FMEA is a more abbreviated and focused evaluation of the specific system than the conceptual FMEA in Appendix A.

6.4.2.1.1 Specimen Collection

Specimen collection applies to possible error causes occurring during patient preparation, sample collection, transport, and storage prior to measurement; this includes inappropriate sample selection (eg, wrong sample type or presence of known interferents).

6.4.2.1.2 Sample Presentation

Sample presentation applies to possible errors occurring during specimen preparation (eg, during dilution) and during mixing with reagents or introduction into the unit-use device.

6.4.2.1.3 Instrument/Reagents

Instrument/reagent applies to possible error causes occurring during measurement, due to problems with instrument, reagent, or user procedure (eg, outdated reagent or electromagnetic interference).

6.4.2.1.4 Results/Readout/Raw Data

Results/readout/raw data applies to potential error causes occurring during and at the conclusion of the measurement phase (eg, incorrect instrument mode setting or misinterpretation of a visual result by the user).

6.4.2.1.5 Review

Review of results applies to potential error causes occurring after measurement is complete, while judging validity of the measurement process and results (eg, failure to recognize alert value or instrument diagnostic/malfunction warning, or physiologically impossible results).

6.4.2.1.6 Integration into the Patient Record

Integration into the patient record applies to potential error causes occurring during sample result storage and transfer to patient medical records (eg, transcription mistakes).

6.4.3 The Failure Mode

Given that one has a list of failure mode causes, one wants to know what failure will actually be observed.

6.4.4 The Effect of the Failure Event

For any error, there is a possible cascade of downstream events. In FMEA or FRACAS, one of the downstream events is selected as the effect of the event.

For the effect of incorrect clinical laboratory results on patient safety, one must consider what happens after the clinician has the results. The clinical consequences are beyond the scope of this document. Clinical consequences are considered in "error grid," approaches, such as the Clarke[23] or Parkes[24] error grid for glucose.

This means that one can assess severity if one knows where an incorrect result will fall on an error grid. If one only knows that an incorrect result will be produced (but not its location on an error grid), then one must use the highest severity in the grid.

Typically, with respect to patient harm, there are two possible effects:

- an incorrect result, which could lead to a clinician making an incorrect medical decision; or
- a delayed result (eg, when no result is produced).

Note that other nonpatient harmful effects are possible, such as increase in cost to the laboratory, threat to accreditation, or a complaint.

6.4.5 Applicability to System (Yes or No)

The example provided in Appendix A is meant to be a starting point, showing a generic list of possible errors that occur in many testing systems. The laboratory must select those that apply to the testing system under consideration (including the intended testing site) and add or delete those errors that are or are not applicable.

6.4.6 Criticality

Criticality is the product of severity times probability (FMEA) or frequency of occurrence (FRACAS). Criticality is used to prepare a Pareto chart, which is a table or chart of the errors ranked by criticality.

6.4.7 The Severity of the Event

The severity is based on the *effect* of the failure event (see Section 6.4.6). Typically, one uses a scale of 1 to 4, where 4 is the most severe event. The Veteran's Administration has a suggested list of severities.[25]

Since there are only two possible patient harm effects for diagnostic assays, it is suggested that an incorrect result has severity 4 and a delayed result has severity 3. These may need to be modified depending on the assay.

6.4.8 The Probability of Occurrence

In FMEA, one needs to assess the probability of occurrence of the failure event. This may be based on actual data from similar systems or may be based on judgment. The probability is the estimated number of times that the box "Error Effect Observed" occurs in Figure 2. With successful detection and recovery processes, the number of Error Event Observed (error effects are themselves events) is often lower than the number of "Error Event Occurs." One typically uses a scale of 1 to 4, where 4 is more likely than a 1, with the meaning of each number described by the Veteran's Administration.[25]

6.5 Description of FRACAS Table Entries

6.5.1 Failure Mode Column

In FRACAS, one does not list *potential* sources of error (eg, causes); one simply lists *observed* errors. Although this sounds simple, it is actually quite difficult; if not enough attention is paid to this step, errors will be undercounted. Note that all errors (errors are synonymous with failures), regardless of their severity, need to be reported. The sources for reporting errors include:

- *customer complaints*—for example, complaints from clinicians;
- *electronic means*—for example, turnaround-time errors could be obtained from the laboratory computer system. Thus, a result that exceeds its time to report result goal is an error, regardless of whether it is accompanied by a complaint; and
- *observation* –includes human errors and often needs to be facilitated by having the right policies in place.

Finally, for all of this to work, the laboratory needs training and staff to administer the program.

6.5.2 Failure Mode Effect Column

See Section 6.5.6, Frequency of Occurrence Column.

6.5.3 Failure Mode Cause Column

The root cause is an explanation of how the error might occur. More than one root cause is possible.

Note that a root cause for a FRACAS error can be unknown.

6.5.4 Criticality Column

See Section 6.5.6, Frequency of Occurrence Column.

6.5.5 Severity Column

See Section 6.4.7, The Severity of the Event.

6.5.6 Frequency of Occurrence Column

In FRACAS, one simply counts the frequency of occurrence of each error, where again, one is using the box “Error Effect Observed” in Figure 2.

As an example, take the error cause, inadequate sample. Laboratories have a process step whereby, before a sample is analyzed, it is visually inspected. If the sample is detected to be inadequate, a delay occurs. One has a 1 to 1 correspondence, in this case, between the observed error (inadequate sample) and its effect (delay). As a similar example, assume an incorrect result was reported, and upon investigation, the sample (which was still available) was found to be inadequate. Here, the effect is incorrect result reported, and each instance that occurs is counted. The cause is inadequate sample *and* detection failure during the sample check.

In FRACAS, one can also calculate actual rates. Thus, in a typical health care FMEA, probability is expressed as a semiquantitative variable, whereas in FRACAS, occurrence is quantitative and expressed as a rate.

FRACAS, by definition, contains only observed events; however, FMEA can contain both potential and observed events. This can create some potential ranking problems and is one reason to perform FMEA separately from FRACAS. When two criticalities are identical, the FRACAS event is more important than an FMEA event, because the FRACAS event *has* occurred. However, it is dangerous to focus entirely on observed events—some high-severity events that have never occurred could still benefit from process improvement.

6.6 Control Measures (FMEA) or Corrective Action (FRACAS)

An important concept in both FMEA and FRACAS is that control measures (mitigations or corrective actions) implemented to improve criticality usually don't change the severity of the effect of an event; they most often only reduce its probability (FMEA) or frequency (FRACAS) of occurrence.

Note that in Appendix C, Clinical Laboratory FMEA (Manufacturer-completed Part), a suggested clinical laboratory action is provided.

6.6.1 Failure Event Prevention

A control or corrective action step that prevents a failure step from occurring or reduces its likelihood involves changing a process step or product component. For example, a computer physician order entry (CPOE) system will prevent an error due to illegible handwriting. Of course, if an error has been prevented, the effect of that error is eliminated.

6.6.2 Failure Event Detection

A detection step is used to alert staff that an error has occurred. Detection steps do not prevent errors; they prevent the effect of an error from being realized. For example, if an inadequate sample has been prepared, a step to examine specimens can detect this error and prevent the specimen from being analyzed and causing an incorrect result to be reported. Another example is running QC, which detects an out-of-control condition.

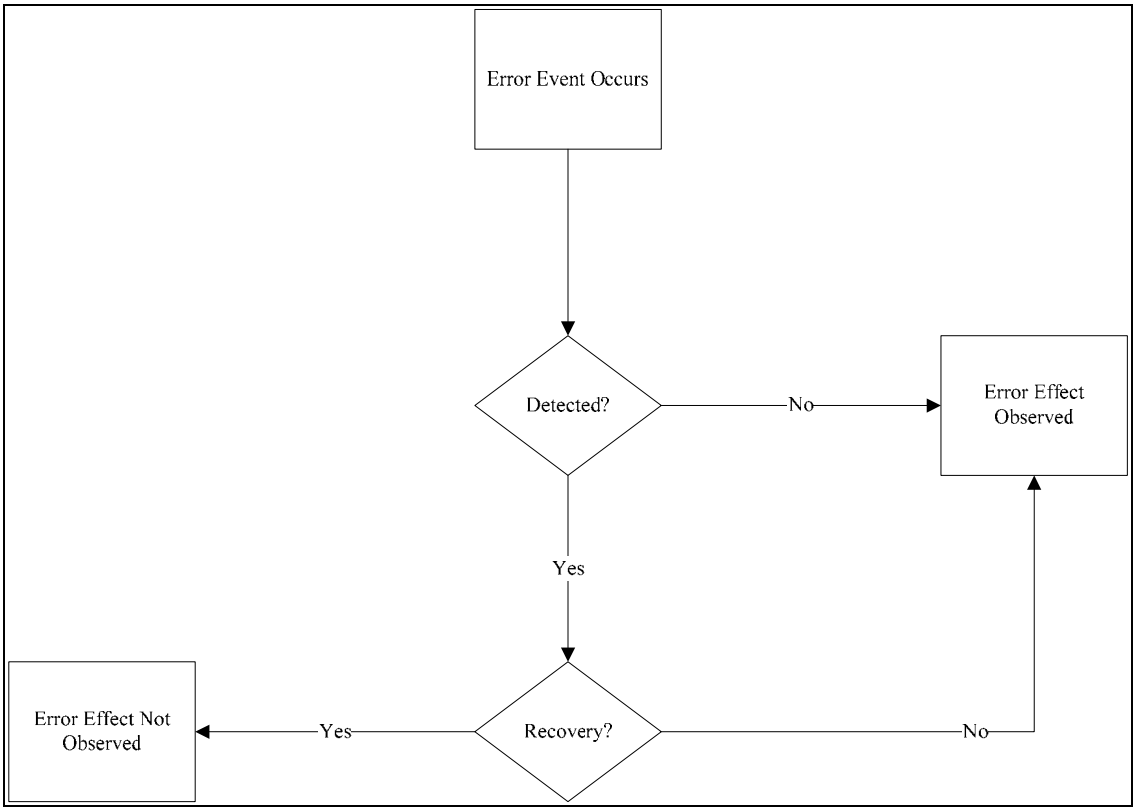


Figure 2. Detection and Recovery Can Prevent the Effect of an Error

Note that detection steps are similar to the accuracy of a medical test, as shown by the following table. Since one does not know the outcome of the "truth" column in routine use, one performs the detection step. One can evaluate the accuracy of the detection step by a study in which truth is determined.

Truth	Detection was positive	Detection was negative
Error occurred	Correct result*	False negative
Error did not occur	False positive	Correct result†

* A correct result means that an error occurred and was detected.

† Here, a correct result means that an error did not occur and no error was detected.

For example, one can independently audit the detection step to establish a "truth" column and thereby calculate all cells in the preceding table to validate the detection step.

6.6.3 Failure Event Recovery

A recovery step is always preceded with a detection step; that is, given an error has been detected, a recovery step is needed to prevent the effect of the initial error. In the inadequate specimen example, a recovery step would be to notify the source of the inadequate sample and to prevent the specimen from being analyzed. In the QC example, patient samples would be rerun.

Although recovery steps seem obvious and foolproof, this is not always the case. Hospitals are continuously being notified of product recalls (this may be considered a detection step). It is up to the hospital to act on these recalls (this is a recovery step). See the related CLSI document on this subject.[26]

6.6.4 Examples of Control/Corrective Action

Each of the items listed in Section 6.4.2, The Root Cause(s) of the Failure Modes (Errors), represent examples of measures to prevent, detect, or recover from failures. When such steps are put in place before failures occur, they are the result of FMEA; if they are implemented after failures occur, they are the result of a FRACAS evaluation. Note that more than one solution to prevent a failure can be used, and the solutions can come from different areas. For example, in blood gas, training is used to educate operators that samples should be drawn without air bubbles. Devices can also contain systems to detect air bubbles.

6.6.4.1 Device Capabilities

This is a description of how and when the instrument or device prevents or detects the error. (For example, does the device include visual indicators of reagent viability as a means of prevention? Does the device include low-battery alarms as a means of detection?)

6.6.4.2 Training/Laboratory Procedure Requirements

This is a description of requirements for the user in developing or modifying laboratory procedures and training requirements, not with regard to manufacturer's instructions for use, but to address issues concerning error detection and elimination. Use of this information will promote training that ensures the safe, effective handling and operation of the test system. It includes training in all aspects of the measurement, ranging from specimen collection and handling to integration of results into the patient record.

6.6.4.3 Applicable Quality Monitoring

This is a description of quality monitoring and assessment appropriate to minimize and/or detect the errors that have not been prevented by device design, including quality assurance procedures to measure and monitor control results; monitor proficiency testing (internal and external); review records; and assess personnel for competency and need for retraining.

6.6.4.4 Frequency of Monitoring

The user is responsible for completing this column to ensure that the source of error is monitored at a frequency that optimizes error detection. The user should consider the nature of the error's impact and the cost of detection. Additional information on determining the detection and impact of an error can be determined by using an FMEA. The manufacturer may make recommendations in this column, but it is the responsibility of the user to make the final determination in accordance with all relevant regulations.

6.7 Validation (FMEA)

Validation is an outcome measure, such as an audit function, that ensures the corrective action has been implemented. See Appendixes B and C for examples.

6.8 Rate Measure (FRACAS)

To evaluate FRACAS, one measures the error rate before and after implementing corrective actions. Error rates are often stated as errors events per million total events.

6.9 Other Considerations

6.9.1 Consequences of Implementing a Control Measure or Corrective Action

Before implementing a control measure (FMEA) or corrective action (FRACAS), one should investigate possible errors that will occur due to the process or product change being implemented. This amounts to conducting an FMEA on the proposed change.

6.10 Pareto Analysis

Pareto analysis, which is represented by either a table or chart, is a way to show the most important problems. It is carried out by sorting in descending value, the Criticality column in either FMEA or FRACAS. Pareto analysis is important, because both manufacturers and clinical laboratories have limited resources and these must be focused on the most important problems.

6.11 More on FRACAS for Clinical Laboratories

This section outlines all of the elements of a FRACAS. FRACAS has a long history in the defense, auto, and aerospace industries but is largely unknown in clinical laboratories, although some of what constitutes a FRACAS is being practiced now under different names by clinical laboratories. However, until all of the elements of a FRACAS are carried out, a clinical laboratory cannot claim that FRACAS is being accomplished, nor will the benefits of a FRACAS be realized.

6.11.1 Existing FRACAS-Related Activities for Clinical Laboratories

Whereas there have not been any reports of FRACAS for clinical laboratories, there have been reports of FRACAS-like activities.[27,28] In these reports, the majority of FRACAS work has been carried out; namely, to collect all laboratory errors. Of interest is the classification of human errors as either cognitive or noncognitive.[29] A cognitive error is one in which a calculation error is made or an error results due to lack of knowledge. A noncognitive error, which is also called a “slip,” is caused when someone inadvertently makes a mistake for an activity that is routine and doesn’t require much thought. This classification is useful in designing correction actions, since noncognitive errors are considered to be nonpreventable can be dealt with by detection recovery schemes, whereas cognitive errors are considered to be preventable and can be dealt with by training.

What is lacking in these reports with respect to FRACAS is that the classifications do not focus on criticality (severity times frequency of occurrence). Moreover, some of the classifications are at best questionable, such as “active vs latent,” “preventability status,” and “adverse vs potentially adverse event.” For example, regarding adverse events, reporting a low glucose result in error that is really high glucose is a severe error from a laboratory standpoint, regardless of whether it turns out to actually have patient harm (an adverse event), as factors are involved outside of laboratory’s control. These reports also do not have goals for error rates, and the rates themselves are not generally combined—one simply has a long list of errors.

6.11.2 FRACAS Goals

A FRACAS goal describes a desired error rate to be achieved. Some attributes of the error rate are:

- the error rate is a combined error rate from ***all*** errors in the clinical laboratory
  - If the FRACAS is restricted to patient harm, then “all errors” mean only those errors that can cause patient harm.

- Errors are combined based on the criticality of each error (severity times frequency of occurrence).

- The error rate goal is also normalized for usage, such as errors per million tests.

- the error rate goal is nonzero
  - One often hears that a desired error rate goal is zero (eg, zero defects). Although everyone wants zero defects, it is an unachievable goal.

The combined error rate goal in a FRACAS differs from the list of targeted errors in a pay-for-performance program. (**NOTE:** "Pay for performance" is a system to financially reward improvements in selected performance measures.[30]) Although it is possible that the targeted errors in a pay-for-performance program will be the same as the top errors in a Pareto chart in FRACAS, there is no guarantee that this will happen. The top list of errors from a Pareto chart may be different for different clinical laboratories. The advantage of FRACAS is it is informed from the data, whereas a pay- for-performance program relies on a committee to determine the list of errors to be slated for improvement.

The *observed* patient harm error rate caused by the clinical laboratory will likely be an underestimate of the true patient harm error rate caused by the clinical laboratory, since some patient harm caused by the clinical laboratory will not always be traceable to the clinical laboratory. For example, Cole describes patient harm due to incorrect hCG results.[31] If harm occurred in a subsequent medical procedure, it is possible that the initial hCG error would not have been detected and the source of medical error would have been totally ascribed to the subsequent medical procedure.

6.11.3 FRACAS Data Collection

A list of possible error data sources is described in Section 6.5.1, Failure Mode Column. Further details regarding those sources are:

- *customer complaints* –often defined by laboratory or hospital policy;

- *electronic means* - bedside turnaround-time, including any error that can be captured by electronic means, such as failed QC; and

- *observation* - having the right policies in place is crucial and can be facilitated by programs such as recommended by Marx.[32]

6.11.4 FRACAS Data Categorization

As observed errors are reported, they must be categorized with respect to severity; this is often accomplished by having a team meet regularly (the frequency of meetings is often dictated by the number of errors that occur). The team reviews each error and decides what is and is not an error, and classifies the error's severity.

There will be many issues that arise from these meetings, and to list all of the possibilities is beyond the scope of this guideline; however, here are some examples:

QC that is outside the limits is an example of an error that has been detected, and presumably the effect of the error (eg, patient harm) has been prevented. How one treats this failed QC depends on the likelihood that QC will detect the error. For example, if it is estimated that QC will detect the error 90% of the time and miss the error 10% of the time, then this failed QC can be added to the overall error rate by "weighting" its contribution by multiplying its criticality by 0.10.

A near-miss implies that an important error has been prevented by a detection recovery (see Figure 2). However, if the detection happened by chance (unplanned detection), then the near miss should be counted as an error, since the likelihood of detection was low.

6.11.5 FRACAS Reports

It is desirable to have a person serve as an administrator for the FRACAS process. All FRACAS events are maintained in a FRACAS program, which often relies on a database, or at a minimum, a spreadsheet. Outputs from this process are FRACAS reports, which include:

- a Pareto table or chart, which ranks errors according to their criticality; and
- the current overall error rate.

— Projections of when and what error rate reductions will be achieved are often facilitated by models such as reliability growth[33] and Duane plots.[34]

6.11.6 FRACAS Corrective Action Teams

For the list of errors at the top of the Pareto chart, a separate corrective action team is usually formed for each class of error to decide how to reduce the error rate of that specific class. When the corrective action is implemented, one can determine the efficacy of the corrective action by observing the error rate for that error, before and after implementing the corrective action. One must be aware that some corrective actions can increase the error rate for other areas.

6.12 Aids to Facilitate FMEA and FRACAS

See also Section 7, Components of a Quality Management System, for descriptions of additional aids.

6.12.1 Flowcharts

A flowchart is a graphical representation of the process. Visualizing process steps can be helpful in brainstorming potential errors.

6.12.2 Fault Tree Analysis

A limitation of FMEA is that it is a table, and each failure mode is “flattened” in that only cause and effect are shown. In reality, the relationship between cause and effect can be more than a chain of three connected events.

For example, inadequate specimen is an error, the effect of which can be an incorrect result. A cause of this error can be failure of the detection step in which specimens are evaluated. The problem is that this is where a typical FMEA stops, but the detection step failure can have a chain of connected causes for its failure.

A fault tree can be helpful in informing an FMEA, because a fault tree is a graphical way of illustrating the cause and effect relationships of an error and its effects. Fault trees use “gates,” which show the difference between unique causes (OR gate) and multiple causes (AND gate). A more complete description of fault trees is beyond the scope of this document.

6.12.2.1 Alternatives to Fault Trees

Other graphical tools, similar to fault trees, include cause-and-effect and fishbone diagrams.

7 Components of a Quality Management System

The goal of quality management is to prevent and detect *critical failures*[35] and *hazards* in the testing cycle. The type of quality management that is employed should depend upon reliability and risk analysis and supported by appropriate risk management techniques such as *FMEA (Failure Mode and Effects Analysis), FMECA* (*Failure Mode, Effects, and Criticality Analysis),* and *FRACAS (Failure Reporting and Corrective Action System).* Additional risk management techniques are the *PHA (Preliminary Hazard Analysis), FTA (Fault Tree Analysis), HAZOP (Hazard and Operability Study),* and *HACCP (Hazard Analysis and Critical Control Point).*[18]

7.1 Standard Operating Procedures

Each test should have a written procedure that covers all aspects of the testing cycle. This procedure should be written in language that is familiar to the intended users and should be readily available to users when testing is performed. The procedure should include the following elements that are applicable to the specific test system:

- principle and/or purpose of the test;
- patient preparation requirements;
- specimen requirements and collection methods;
- all reagents and supplies used in testing or quality assessment;
- instrumentation;
- calibration protocols and schedules;
- specific directions for use, including result reporting;
- expected values, interpretation of values, definition and handling of alert values;
- expected error or uncertainty;
- the maximum permissible total error or uncertainty;
- frequency and tolerance of quality control;
- risk management procedures, tables, and data including:

  — failure modes and effects;
  — hazards in normal use;
  — hazards in fault conditions;
  — estimated risks to patients;
  — estimated failure rate or mean time to failure;
  — estimated critical failure rate or mean time to critical failure;
  — preventive, recovery, and corrective actions;
  — critical control points;
  — residual risk;
  — acceptable risk;
  — instructions for reporting critical failures, hazards and harms; and
  — instructions for assessing the critical failures, hazards and harms database;

- procedural notes;
- method limitations;
- references;
- effective date and review schedule;
- distribution; and
- author.

In general, causes of failure that are detected by the operator, dependent on proper technique, and/or managed by training should be contained in the procedure. A system should exist to ensure that procedures are current and that procedural changes are made in a controlled fashion.

7.2 Training and Competency

Operators performing analytical tests should have training both in the systems involved and the applied risk management techniques or have worked under the supervision of an experienced laboratorian until they have satisfactorily demonstrated proficiency for each procedure. The degree of training depends upon both the background of the individual who will be performing the testing and the analytical systems being employed. When selecting the system, the level of training (eg, the complexity of the system, the degree of technique dependence, etc.) that is required to implement a new method or instrument should be considered.

Training should cover the following subjects, the significance of which depends upon the personnel and the test system being used:

- theory of instrument/device/test system;
- specimen collection/preservation/transport;
- testing procedure;
- statistical quality control concepts, principles, and procedures; and
- risk management concepts, principles, and procedures, including:

    — failure mode and effects;
    — failures, critical failures, and hazards in normal use, including sources and degree of error or uncertainty (preanalytic, analytic, postanalytic);
    — failures, critical failures, and hazards in fault conditions;
    — estimated risks to patients;
    — estimated failure rate or mean time to failure;
    — estimated critical failure rate or mean time to critical failure;
    — preventive, recovery, and corrective actions, emphasizing preventive maintenance;
    — critical control points;
    — residual risk;
    — acceptable risk;
    — detection, analysis, documentation, and reporting of failures and hazards and harms; and
    — accessability to the critical failures, hazards, and harms database.

There are several sources of training available:

- manufacturers via on-site training, telephone, and internet assistance;
- local hospital laboratory or commercial laboratory;
- medical technologists or other trained personnel available as part-time consultants; and
- workshops and training seminars.

Training may be available from the manufacturer. The use of manufacturer-provided training is recommended. Site-specific needs and procedures should be considered and the training supplemented to address them. Some form of competency assessment should be included in order to determine the effectiveness of training.

Evaluating the competency of all testing personnel and ensuring the staff's continuing competency to perform tests and report tests promptly, accurately, and proficiently are essential components of a quality testing system. Individuals must demonstrate competency in performing the procedure, and evidence of

this competency must be documented. Evaluation of the competency of the staff may include, among other procedures, the following:

- direct observation of routine patient test performance, including patient preparation (if applicable), specimen handling, specimen processing, and testing;
- monitoring the recording and reporting of test results;
- review of intermediate test results or worksheets, QC records, proficiency testing results, and preventive maintenance records;
- direct observation of performance of instrument maintenance and function checks;
- assessment of test performance through testing of previously analyzed specimens, internal blind testing samples, or external proficiency testing samples;
- assessment of problem-solving skills;
- assessment of application of the appropriate risk management techniques; and
- evaluation and documentation of the performance of persons responsible for testing, and providing such documentation to the testing personnel manager.

Testing personnel should be assessed for competency at least annually. Sources of operator error that have a critical impact on the test result should be included in each assessment. Competency testing should occur more frequently if individuals are having difficulty with test performance.

7.3 Ongoing Process Control

The goal of process control is to verify that all system components are performing as specified by the manufacturer and at a quality level acceptable to the user. System components include the operator, the instrument, the reagents, the sample, and the environment. Various forms of controls test different parts of the process. (For additional procedures for test validation, refer to the related CLSI document on this subject.[36])

At a minimum, process controls should be performed as specified by the manufacturer and in agreement with the local, regional, or national regulations. Users may implement additional controls. The types selected should check the components most vulnerable to failure. Periodically, material should be used that verifies all system components at one time under usual testing conditions. The composition and frequency of such testing should be defined by considering the following characteristics:

- estimated total error or uncertainty of the test system;
- maximum permissible total error or uncertainty;
- risk analysis, including:
  - failure modes and effects;
  - hazards in normal use;
  - hazards in fault conditions;
  - estimated risks to patients;
  - estimated failure rate or mean time to failure;
  - estimated critical failure rate or mean time to critical failure;
  - estimated probability of hazards;
  - estimated probability of harm;

— estimated severity of harm;
— acceptable risk; and
— acceptable residual risk;

- available control materials;
- cost of the process control;
- operator experience with the test system; and
- institutional experience with the test system.

7.3.1 Acceptance Testing

When there is a significant change in the test system beyond that for which the system is validated (eg, a new lot of reagents, a change in the environment, or a new test operator), appropriate quality control testing should be performed to show that the change is acceptable. Sufficient replicate testing of control materials must be done to ensure that a failure, if caused by the change, will be detected. The less uncertain an assay, the fewer replicates are necessary to detect a problem. The laboratory director determines the maximum acceptable total error or uncertainty in the results (the effect), taking into account the maximum medically permissible total error or uncertainty.

7.3.2 Periodic Conventional Quality Control

Some form of ongoing quality control using control materials, and in some cases, patients' samples, should be performed periodically with the goals of assessing system stability.

7.3.3 Split Samples

The trueness of a testing system is initially established by recovery studies, and by comparison to a method that is traceable to a recognized standard. These tests are performed by the manufacturer as a part of its design control process. Periodic comparison studies ensure that bias does not gradually increase and go undetected by conventional quality control systems. In a split-sample study, clinical specimens are collected, split into aliquots, and analyzed using both methods. If possible, specimens should be fresh, cover the analytical range of interest, and represent a variety of medical conditions. A split-sample study may be employed when stable control materials are not available, or as a supplemental procedure when the source of an error or uncertainty cannot be identified from available control data. The frequency of split sampling should be established by each institution.

7.3.4 Other Forms of Quality Control

7.3.4.1 Electronic QC

Electronic quality control devices are test simulators that monitor and/or report on the function of the test system. Some electronic QC devices provide numerical results as a simulated test. Others provide a "pass/fail" based on the performance of the device being monitored.

When a device is equipped with electronic QC, the manufacturer should explain the parts of the device that are tested by the electronic QC. The user should use this information to evaluate any additional device components or parts of the testing procedure that may produce failures that need monitoring throughout the entire testing process and add them to the QC scheme.

7.3.4.2 Onboard QC

Onboard QC is quality control that is performed by the system automatically without any action required by the user. The advantages of this type of quality control are that QC preparation errors are avoided, and the onboard QC is convenient.

7.3.5 Proficiency Testing

Laboratories should be enrolled in a proficiency testing program for all analytes for which proficiency testing is available. By treating such specimens similarly to routine patient samples, proficiency samples may provide an overall assessment of the testing process.

7.3.6 Delta Checks

Delta checks consist of a comparison of the patient's current test result to the patient's last result, looking for a significant difference. What defines a significant difference depends on the analyte and the precision of the method and is determined by the staff at each facility. If a significant difference is detected, the result is then correlated to the patient's current clinical condition. A significant difference in a test result in a clinically stable patient may indicate a problem with the measurement.

7.3.7 Clinical Surveillance

Monitoring patient test results is a direct form of process control and can provide additional information useful in monitoring both device performance and operator competency. The most effective procedure is retrospective clinical correlation of test results with the clinical status of the patient. A major advantage in testing at the point of care is that the individual performing the test has the ability to correlate test results with the patient's condition. In an individual patient, clinical correlation can help identify spurious or unlikely test results that may not be evident with conventional quality control procedures. Health care workers should be encouraged to report test discrepancies to the laboratory director for further investigation.

7.3.8 Environmental Monitoring

Environmental monitoring encompasses all conditions surrounding the use of a device/method that ultimately determines test performance. It is essential to apply appropriate risk management techniques—to recognize, monitor, establish critical limits, and control environmental factors associated with a testing device/method. A list of the more obvious environmental monitoring topics is in the "sources of error" matrix.

A device/method manufacturer has a responsibility to identify environmental monitoring factors that would potentially impact the test performance in normal and usual operating conditions.

The user has a responsibility to identify environmental factors that may impact test performance but may not be identified by the manufacturer. When such factors are identified, the user must determine the critical limits and frequencies at which to monitor identified factors to ensure optimal device/method performance.

Users are responsible for adhering to any and all applicable regulatory requirements associated with a particular device/method. Regulatory requirements may include environmental factors that must be monitored at specified frequencies and within certain limits. In addition, users have a responsibility to provide quality feedback to manufacturers, so they can correct design deficiencies and support continuous product development.

7.4 Preventive Maintenance

Analytical systems should be maintained according to the manufacturer's procedures and the applied risk management techniques.

When preventive maintenance is performed, it must be clearly documented in the system records.

7.5 Failure, Hazard, and Harm Reporting[35,37]

Reporting and subsequent analysis of possible failures in the testing cycle can reveal process failures that are difficult to detect by other means. The mechanism for reporting these failures should be simple and should be encouraged as a means to improve processes rather than as a means to affix blame. Reports should be analyzed using risk management techniques to see if changes can be made to prevent failures.

Hazardous situations and harms are required to be reported to regulatory agencies in some countries. Users should also report them to the manufacturer, along with other failures, such as defective devices, inaccurate or unreadable product labeling, packaging or product mix-up, or stability problems, etc. Manufacturers are obligated under regulatory and quality management system standards to investigate all complaints and take corrective and preventative action where appropriate and to improve product design.

7.5.1 Failures Database

A database for each device or test should be developed by the manufacturer with the reported failures and the estimated respective rates.

Failures are required to be reported to regulatory agencies in some countries. It would be very helpful if the database could be accessible by the users of the device.

7.6 Auditing

Periodic auditing is to search for concealed (eg, willful neglect to follow rules) or not immediately apparent failures in the testing cycle that need recovery or corrective action.

Most often, this quality monitoring method is used for record review, such as QC records, records of test results, and risk management records. Auditing should test compliance to operating and risk management procedures. Auditing may be particularly helpful in assessing test-reporting mechanisms to see if test results are actually being recorded in the patient's medical record. An audit may cover all aspects of the testing cycle or may be focused on one particular portion. It can validate the QC process. It can reveal whether or not a failure, hazard, or harm exists; some sense of the frequency of the failure, hazard, or harm; and reasons for their occurrence. It can validate the failures, hazards, and harms recovery, correction, and reporting, as well as the access to the respective database of Section 7.5.1, Failures Database.

Audits may be performed on a regular, scheduled basis or may be initiated in response to a reported critical failure, hazard, or harm. Prior to the audit, a threshold for acceptable performance should be determined. If the audit yields findings that fall below the threshold, quality improvement or corrective actions should be undertaken. Solutions should ultimately be assessed for effectiveness in improving performance.

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Explanation of the Appendixes

The appendixes contain the following examples:

Appendix A – This is a list of possible failure modes that could occur, in an FMEA format. It is intended to be used by a manufacturer to ensure that these failures modes are considered and, where appropriate, controls put in place.

Appendix B – This is an example of an FMEA that has been completed by a manufacturer.

Appendix C – This is an FMEA taken from Appendix B, but with only the sections that would apply to a clinical laboratory (in most cases, these will be the user section). In this FMEA, the manufacturer has recommended actions for the clinical laboratory. Part of this FMEA is completed by the clinical laboratory.

Appendix D – This is a FRACAS provided by a clinical laboratory.

Appendix E – An explanation for why this document's scope is expanded to include all diagnostic devices and not just one unit use.

Appendix A. Example of a "System-Specific Sources of Error" Matrix – an FMEA

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
1 Specimen Collection											
		1.1 Contamination									
		1.1.1 Alcohol									
		1.1.2 Other Cleansing Agent									
		1.1.3 Anticoagulants in Lines									
		1.1.4 Intravenous Fluids									
		1.1.5 Admixture with Other Fluids/Materials									
		1.2 Inadequate Sample									
		1.2.1 Poor Circulation at Sample Site									
		1.2.2 Poor Vascular Access									
		1.2.3 Not Enough Collected									
		1.2.4 Poor Technique									
		1.2.5 Too Much Collected									
		1.3 Hemolysis									
		1.4 Incorrect Patient Drawn									
		1.5 Inappropriate Sample									
		1.5.1 Arterial vs Venous vs Capillary									
		1.5.2 Whole Blood vs Plasma									
		1.5.3 Sample in Wrong Container or Syringe/Wrong Additives									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		1.5.4 Fasting vs Nonfasting									
		1.5.5 Clotted Sample									
		1.5.6 Inappropriate Time of Collection									
		1.6 Patient Condition Inappropriate for Testing Method									
		1.6.1 Hematocrit Too High or Too Low									
		1.6.2 Oxygen Too Low or Too Unstable									
		1.6.3 Medications Interfere With Method									
		1.6.4 Lipemia									
		1.6.5 Too Dilute Urine									
		1.7 Improper Patient Preparation									
2 Sample Presentation		2.1 Incorrect Procedure/ Technique									
		2.1.1 Contamination									
		2.2 Incorrect Sample Presented									
		2.2.1 Sample Type									
		2.2.2 Failure to Appropriately Dilute Sample									
		2.2.3 Failure to Remove Excess Particulate Matter									
		2.2.4 Incorrect Sample Temperature									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		2.2.5 Improper Handling of Stored Specimens									
		2.3 Too Long Delay From Collection to Analysis									
		2.4 Sample Inadequately Mixed									
		2.5 Sample Inadequately Mixed With Reagents									
		2.6 Inappropriate Amount of Sample Presented									
		2.6.1 Insufficient Volume									
		2.6.2 Excessive Volume									
		2.7 Introduction of Air Bubbles									
		2.8 Incorrect Patient Identification Information Entered Into Instrument									
3 Instrument/ Reagents		3.1 Adverse Environmental Conditions									
		3.1.1 Temperature									
		3.1.2 Humidity									
		3.1.3 Shock/ Vibration									
		3.1.4 Static Electricity									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		3.1.5 Radio Frequency Interference/ Electromagnetic Interference									
		3.1.6 Light Intensity									
		3.1.7 Barometric Pressure/Altitude									
		3.1.8 Inadequate Warm-Up Time									
		3.1.9 Low Power									
		3.2 Outdated Reagents									
		3.3 Improper Reagent Shipment									
		3.4 Improper Reagent Storage									
		3.5 Incorrectly Prepared Reagents									
		3.6 Incorrect Use of Reagents									
		3.7 Reagent Contamination									
		3.8 Deterioration of Reagent Lots Over Time									
		3.9 Lot-to-Lot Variability									
		3.10 Sample-Related Reagent Failure									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		3.10.1 Interfering Substances									
		3.10.2 Excessive Analyte Concentrate (hook or prozone effects)									
		3.10.3 Unusual pH									
		3.10.4 Unusual Viscosity									
		3.10.5 Unusual Particulate Load									
		3.11 Electronic Simulator Malfunction									
		3.12 Improper Control Shipment									
		3.13 Improper Control Storage									
		3.14 Inadequate Mixing of Controls									
		3.15 Improper Calibration									
		3.16 Poor Precision									
		3.17 Poor Trueness /Correlation With Laboratory Method									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		3.17.1 Bias									
		3.17.2 Interferences									
		3.18 Incorrect Analysis Mode									
		3.18.1 Controls vs Patient Samples									
		3.18.2 Incorrect Analyte Selected									
		3.18.3 Incorrectly Programming Parameters									
		3.19 Sample Carryover									
		3.20 Instrument Error									
		3.21 Instrument Failure									
		3.21.1 Software Computation									
		3.21.2 Drift Between Calibration and Analysis									
		3.21.3 Loss of Calibration									
		3.21.4 Electronic Instability									
		3.21.5 Readout Device Error									
		3.21.6 Loss/ Corruption of Data									
		3.22 Instrument/ Reagent Performance Not Verified Prior to Use									
		3.22.1 Initial Instrument Implementation									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		3.22.2 Instrument Repair/ Maintenance									
		3.22.3 Battery Changes									
		3.22.4 Reagent Lot Changes									
		3.22.5 Routine Use									
		3.23 Improperly Functioning Instrument Not Removed From Service									
		3.24 Inadequate Instrument Maintenance/ Handling									
		3.24.1 Dirty Optics									
		3.24.2 Scratches									
		3.24.3 Fogging									
		3.24.4 Instrument Trauma									
		3.25 Patient's Personal Equipment Used									
		3.26 Complicated Procedure									
		3.27 Incorrect Technique									
4 Results/ Readout/ Raw Data		4.1 Visual Misinterpretation									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		4.2 Incorrect Setting for Units of Measure									
		4.3 Incorrect Mode Setting									
		4.3.1 Neonatal vs Whole Blood vs Plasma vs Urine									
		4.3.2 Control vs Patient Sample									
		4.3.3 Incorrect Programming									
		4.4 Accidental Loss of Data									
		4.5 Calculation Required									
5 Preliminary Review		5.1 Improper Interpretation of Control Results									
		5.2 Outlier/Nonsense Result Not Recognized									
		5.3 Result Outside of Linear Range Not Recognized									
		5.4 Alert Value Not Recognized									
		5.5 Need for a Confirmatory Sample Not Recognized									
		5.6 Effect of Preanalytical Variables Not Recognized									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		5.7 Instrument Malfunction Not Recognized									
		5.8 Interference Not Recognized									
6 Integration/ Report Into Chart		6.1 No Result Recorded									
		6.2 Result Recorded in Incorrect Patient Chart									
		6.3 Incorrect Information Recorded									
		6.3.1 Data									
		6.3.2 Time									
		6.3.3 Result									
		6.4 Information Unreadable									
		6.5 No Aids for Clinical Interpretation									
		6.5.1 Reference Interval									
		6.5.2 Alert Limits									
		6.5.3 Previous Patient Results									
		6.6 Inconsistent Location of Reporting/Result Difficult to Find in Chart									

Appendix A. (Continued)

Potential Sources of Error					Criticality			Controls			Validation
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**App.? (Y/N)**	**S**	**P**	**C**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
		6.7 Result Temporarily Unavailable Due to Reporting Mechanism (computer delay)									

Appendix B. An Example of a Manufacturer's FMEA

The severity and probability ratings that follow are the first step in identifying the potential effects of identified failure modes and failure mode causes. Use the definitions to classify the severity of the failure as minor, moderate, major, or catastrophic; then classify the probable frequency of the failure as remote, uncommon, occasional, or frequent. For consistency, remember to use the definitions provided. Criticality is the product of severity and probability of occurrence.

Severity Rating

Event Severity	Rating
Failure could cause death or catastrophic injury	4
Failure could cause major injury	3
Failure could cause moderate injury	2
Failure could cause minor injury	1

Step 4B: Probability Rating

Event Probability	Rating
Frequent: Likely to occur immediately or within a short period (may happen several times in one year)	4
Occasional: Probably will occur (may happen several times in 1 to 2 years)	3
Uncommon: Possible to occur (may happen sometime in 2 to 5 years)	2
Remote: Unlikely to occur (may happen sometime in 5 to 30 years)	1

The HFMEA Scoring Matrix Criticality

The HFMEA Scoring Matrix				
Probability	Severity			
	Catastrophic (4)	Major (3)	Moderate (2)	Minor (1)
Frequent (4)	16	12	8	4
Occasional (3)	12	9	6	3
Uncommon (2)	8	6	4	2
Remote (1)	4	3	2	1

Appendix B. (Continued)

This example is a molecular assay.

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Manufacturing (User)	Missing Reagent	Reagent 1 not loaded in test system.	No result or false negative	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit to ensure compliance.
	Missing Reagent 2	Reagent 2 not loaded in test system.	No result or false negative	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit to ensure compliance.
	Missing Control Reagent 1	Control Reagent 1 not loaded in test system.	No result	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit monthly to ensure compliance.
	Partial Reagent 1	Reagent 1 in test system not complete.	No result or false negative	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit to ensure compliance.
	Partial Reagent 2	Reagent 2 in test system not complete.	No result or false negative	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit to ensure compliance.
	Partial Control Reagent 1	Control Reagent 1 in test system not complete.	No result	3	2	6	Revise training or add detection to system	Inspect system prior to analysis to ensure installed reagents.	Replace reagent before running system.	Audit to ensure compliance.
	Missing critical part	Critical part not loaded in test system.	Partial reaction assembly. No result or false negative	3	1	3	Revise training or add detection to system	Inspect system prior to analysis to ensure installed components.	Replace part before running system.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	Error	Cause	Effect	S*	P	C	PREVENTION	DETECTION	RECOVERY	
	Contaminated manufacturing area	Cartridge/cassette/tube contamination.	No result or false negative	3	2	6	Revise training or add detection to system	Inspect system prior to analysis. Implement internal controls.	Rerun with another cartridge/ cassette/tube.	Review QC records monthly.
	Contaminated reagents	Cross-contamination with other products in manufacturing.	False positive	3	2	6	Revise training or add detection to system	Ensure that QC is acceptable prior to analysis.	Rerun with another reagent.	Review QC records monthly.
Reagents	Poor or no reaction	Improperly manufactured.	No result or false negative	3	2	6	Revise training or add detection to system	Verify expiration date/storage conditions. Ensure that QC is acceptable prior to analysis.	Rerun with another reagent.	Review QC records monthly.
	Poor or no reaction	Degradation due to improper storage/shipping conditions by distributor.	No result or false negative	3	2	6	Revise training or add detection to system	Verify expiration date/storage conditions. Ensure that QC is acceptable prior to analysis.	Rerun with another reagent.	Review QC records monthly.
	Poor or no reaction	Degradation due to improper storage by user.	No result or false negative	3	4	12	Revise training or add detection to system	Verify expiration date/storage conditions.	Rerun with another reagent.	Review QC records monthly.
Internal control 1	Internal control 1 fails	Improperly manufactured	No result	3	2	6	Revise training or add detection to system	Verify expiration date/storage conditions.	Rerun with another control.	Review QC records monthly.
Internal control 2	Internal control 2 fails	Degradation due to improper storage/shipping conditions by distributor.	No result	3	2	6	Revise training or add detection to system	Verify expiration date and storage conditions.	Rerun with another control.	Review QC records monthly.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Internal control 2	Internal control 2 fails	Degradation due to improper storage by user	No result	3	4	12	Provide storage instructions.	Conduct stability studies.	Rerun with another lot number of control.	Review QC records monthly.
Stop reagent	Stop reagent fails	Improperly manufactured	No result	3	2	6	Revise training or add detection to system.	Verify expiration date/storage conditions	Rerun with another reagent.	Review QC records monthly.
Stop reagent	Stop reagent fails	Degradation due to improper storage/shipping conditions by distributor	No result	3	2	6	Provide storage instructions.	Conduct shipping studies.	Rerun with another reagent.	Review QC records monthly.
Stop reagent	Stop reagent fails	Degradation due to improper storage by user	No result	3	4	12	Provide storage instructions.	Conduct stability instructions.	Rerun with another reagent.	Review monthly QC records.
Internal Control 3	Internal control 3 fails	Improperly manufactured	No result	3	2	6	Test each lot.	Verify expiration date/storage conditions	Rerun with another control.	Review QC records monthly.
Internal control 3	Internal control 3 fails	Degradation due to improper storage/shipping conditions by distributor	No result	3	2	6	Shipping studies	Conduct stability studies.	Rerun with another control.	Review QC records monthly.
Internal control 3	Internal control 3 fails	Degradation due to improper storage by user	No result	3	4	12	Provide storage instructions.	Conduct stability studies.	Rerun with another control.	Review QC records monthly.
Sample collection device	Incorrect sampling procedure	Incorrect sample collection	Patient symptoms/harm	3	3	9	Conduct phlebotomy training.	False result detected through manual review	Rerun with a properly collected sample.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Sample collection device	Incorrect collection device used	A collection device other than that specified is used	Questionable results	3	3	9	Conduct phlebotomy training. Labeling requires correct collection device. Institution must validate off-label use.	False result detected through manual review	Rerun using correct device.	Audit monthly to ensure compliance.
Sample collection device	No collection device available	Facility has run out of collection devices	Inability to run test	3	3	9	Maintain a supply of collection devices at manufacturer site for rapid shipment.			Manufacturer tracks collection device vs assay orders
Sample collection device	PCR inhibition	Interfering substances in collection device	False negative	3	2	6	Validate collection device. Implement internal controls.	False result detected through manual review.	Rerun sample.	Review QC records monthly.
Sample collection	Incorrect sampling procedure	Wrong or incorrectly prepared sampling site	Possible sample inhibition	3	3	9	Operator training. Provide instructions on proper sampling procedure.	False result detected through manual review.	Rerun sample.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Sample collection	Incorrect sampling procedure	Collection device not used correctly	Possible impact on test performance	3	3	9	Labeling. Operator training. Provide instructions on proper sampling procedure.	False result detected through manual review	Rerun with a newly collected sample.	Audit to ensure compliance.
Sample collection	Sample kept too long	Sample not used within recommended time	Possible impact on test performance	3	3	9	Provide operator training. Provide instructions on proper sampling procedure. Package insert to state that collection device may be stored at TEMP for up to TIME or TEMP for up to TIME, and discarded thereafter.	False result	Reduced likelihood of impact on test performance due to prolonged storage of collection device.	Audit to ensure compliance.
Sample collection	Incorrect sampling procedure	Improper sample collected	Possible impact on test performance	3	4	12	Labeling Operator training Provide instructions on proper sampling procedure.	False result detected through manual review	Rerun with a newly collected sample.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	Error	Cause	Effect	S*	P	C	PREVENTION	DETECTION	RECOVERY	
Specimen	Inhibition	Specimen contaminated	False negative	3	3	9	Operator training	False result detected through manual review	Rerun with a newly collected sample.	Review QC records monthly
Specimen	Sample contamination	Sample contaminated with target	False positive	3	3	9	Implement internal controls.	False result detected through manual review	Rerun with a newly collected sample.	Review QC records monthly.
Specimen	Inhibition	Presence of inhibitors in specimen.	No result or false negative	3	3	9	Implement internal controls.	False result detected through manual review	Rerun with a newly collected sample.	Review QC records monthly.
Sample prep	Reproducibility	Sample prep not as reproducible as reference.	No result or false negative	3	3	9	Tested at EVT, reproducibility better than reference Validate assay.	False result detected through manual review	Poor reproducibility highly improbable. Rerun with a newly collected sample.	Review QC records monthly.
Sample prep	Recovery	Sample recovery less than 50% of reference.	No result or false negative	4	2	8	Tested at Tech Feas, recovery is equivalent to or better than reference. Validate assay.	False result detected through manual review	Poor sample recovery highly improbable. Rerun with a newly collected sample.	Review QC records monthly.
Sample prep	Sensitivity	Clinical sensitivity less than reference.	No result or false negative	4	2	8	Test in beta and clinical study. Validate assay.			Review QC records monthly.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Sample prep	Sample volume	Sample volume insufficient for retest.	Inability to run retest	3	2	6	Collect excess sample. Validate assay. Implement internal controls.	False result detected through manual review	Rerun with a newly collected sample.	Audit to ensure compliance.
User	Poor or no reaction	Inadequate labelling or instructions.	No result or false negative	3	2	6	Multiple reviews of labeling and instructions Implement internal controls. Test in clinical study.	False result detected through manual review	Rerun using correct instructions.	Multiple reviews of labeling and instructions.
User	Poor or no reaction	Overly complicated instructions.	No result or false negative	3	2	6	Multiple reviews of labeling and instructions Internal controls Test in clinical study.	False result detected through manual review	Rerun using correct instructions.	Multiple reviews of labeling and instructions.
User	Poor or no reaction	Unavailability of instructions.	No result or false negative	3	2	6	On-line help Tech support Implement internal controls. Test in clinical study.	False result detected through manual review	Rerun using correct instructions.	Multiple reviews of labeling and instructions.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	Error	Cause	Effect	S*	P	C	PREVENTION	DETECTION	RECOVERY	
User	Poor or no reaction	Unskilled or untrained personnel.	No result or false negative	3	3	9	CLIA complexity level. Operator training Implement internal controls.	False result detected through manual review	Rerun with trained personnel.	Audit to ensure compliance.
User	Poor or no reaction	Uses test system which has been knocked over after adding reagents.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls.	False result detected through manual review	Rerun using replaced reagents.	Audit to ensure compliance.
User	Contamination	Spills test system after adding buffers.	Work area becomes contaminated with reagents.	3	3	9	Operator training Implement internal controls.	False result detected through manual review	Rerun using replaced reagents.	Audit to ensure compliance.
User	Poor or no reaction	Spills test system after adding buffers.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls.	False result detected through manual review	Rerun using replaced buffers.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	Error	Cause	Effect	S*	P	C	PREVENTION	DETECTION	RECOVERY	
User	Poor or no reaction	Puts buffers in wrong locations.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls	False result detected through manual review	Rerun using replaced buffers.	Audit to ensure compliance.
User	Poor or no reaction	Omits buffers.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls	False result detected through manual review	Rerun using buffers.	Audit to ensure compliance.
User	Poor or no reaction	Omits buffer 2.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls	False result detected through manual review	Rerun using replaced buffers.	Audit to ensure compliance.
User	Poor or no reaction	Omits buffer 1.	No result or false negative	3	3	9	Labeling Operator training Implement internal controls	False result detected through manual review	Rerun using replaced buffers	Audit to ensure compliance.
User	Poor or no reaction	Putting sample in wrong location in test system.	No result or false negative	6	2	6	Labeling Operator training Design test system so sample only goes in correct location			Audit monthly to ensure compliance.
User	Poor or no reaction	Sample blocks instrument access.	No result	3	3	9	Labeling Operator training	Software aborts run if the parameters exceed the defined limit	Repeat sample Rerun with a redrawn sample.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
User	Poor or no reaction	Improper handling of the sample (instruction for use not followed).	No result or false negative	3	3	9	Labeling Operator training	False result detected through manual review	Repeat sample Rerun with a redrawn sample	Audit to ensure compliance.
User	Poor or no reaction	Operator omits sample.	No result or false negative	3	3	9	Labeling, Operator training	No result	Add sample and run test.	Audit to ensure compliance.
User	Incorrect specimen tested	Improper identification of specimen.	Result is reported for wrong sample	3	3	9	Label sample and test system for traceability. Labeling Operator training.			Audit to ensure compliance.
User	Incorrect specimen tested	Specimen mix-up.	Result is reported for wrong sample	3	3	9	Label sample and test system for traceability. Labeling Operator training			Audit to ensure compliance.
User	Incorrect specimen tested	Specimen reaction loaded in wrong site in instrument.	Result is reported for wrong sample	3	3	9	Labeling Operator training Software allows only one site to be loaded at a time.	False result detected through manual review	Rerun using correct specimen.	Audit to ensure compliance.
User	Incorrect label placement	Operator places label over instrument access port.	Run will not start.	3	3	9	Labeling Operator training	Run will not start	Operator will need to remove label, replace assay, and restart run.	Multiple reviews of labeling and instructions.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
User	Incorrect label placement	Operator places label over instrument access. Plunger punctures label and debris enters test system.	No or false negative	3	3	9	Implement internal controls.			Multiple reviews of labeling and instructions.
User	Operator interpretation	Operator deduces result from data (s)he sees from invalid run.	False negative or false positive	3	2	6	Labeling Operator training Data from invalid runs available only to senior users; all others see only "ND."			Audit to ensure compliance.
User	Operator error	User selects wrong assay.	No result, false negative, or false positive	2	2	4	Only the assay that matches the test ID is available for selection. For another assay, retest uses the same protocol as the screen.	Unable to enter test results.	Rerun sample using correct assay.	Audit to ensure compliance.
User	Operator error	User stops run and restarts it.	No result, false negative, or false positive	2	2	4	Require confirmation to stop run. Software detects duplicate test system ID, run will not restart.			Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Assay	Assay performance	Target fails before internal controls	False negative	3	2	6	Characterize assay. Optimize internal controls relative to target.			Audit to ensure compliance.
Assay	Assay performance	Internal controls fail to detect assay assembly	No or false negative	3	2	6	Internal controls Implement signal thresholds. Validate instrument performance.			Audit to ensure compliance.
Quality systems	Qualification of system in user's facility	IQ/OQ/PO not yet developed.	Inability of user to verify system performance	2	2	4	Develop procedure, ID proficiency panels, or other means of qualification.			Audit to ensure compliance.
Labeling	Bar code/RFD information	Bar code/RFD can't be read.	Inability to run test	2	2	4	Provide alternate means of entering information.	Inability to recognize accession number.	Reprint a new label and then rerun sample.	Audit to ensure compliance.
System	Data lost	Laptop computer goes into "sleep" mode during run and does not accept data when it wakes up.	No result	2	2	4	Software disables "sleep" mode.		Operator will need to enter information manually.	Audit to ensure compliance.

Appendix B. (Continued)

Potential Sources of Error				Criticality			Recommended Risk Reduction Measures			Outcome Measure
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**S***	**P**	**C**	**PREVENTION**	**DETECTION**	**RECOVERY**	
Vendor	Contaminated manufacturing or filling area	Buffer(s) contaminated.	No result or false negative	3	2	6	Vendor qualification, shelf life studies. Implement internal controls. Test at incoming inspection.			Audit to ensure compliance.

*The severity assigned for each failure cause is the one associated with the greatest potential hazard.
NOTE: Hazard effect shown is for worst case situation.

Appendix C. Laboratory FMEA: Manufacturer completed part and Clinical Laboratory completed part

Total quality assurance of a laboratory testing device requires an understanding of the device operation; how the device will be utilized in patient care; and an assessment of the laboratory's unique environment, including the potential for error and consequences from an error occurring. These errors can arise anywhere in the preanalytic, analytic, or postanalytic phases of the testing process, and can occur from mistakes during analysis, from operator oversights, or from environmental factors.

This example is an automated real-time nucleic acid amplification system that is being implemented in a small community hospital affiliated with a large group physician practice (50 physicians) and several small physician office laboratories (one to three physicians) for patient screening and diagnosis for infectious and sexually transmitted diseases. Based on the device's results, clinicians will prescribe potentially hazardous antibiotics (like gentamicin) and report communicable diseases to the State Department of Public Health. As such, the results of this device must be highly accurate and reliable on the first analysis. The device will be operated by medical technologists in the main hospital laboratory and possibly by nursing in the group practice. This health system has decentralized phlebotomy, and all specimens are collected by nursing or other clinical staff.

Errors that could affect test results during analysis could come from reagent failure or mistakes in device operation. Typical analytic errors include the use of outdated reagents, improper loading of reagent into device, applying too much or too little sample to the device, incorrect sample application resulting in bubbles, movement of device during operation, or power failure during analysis. A primary concern with nucleic amplification systems, because of the sensitivity of the method, is contamination of the sample with extraneous DNA, either from other patients or the environment. Scrupulous pipetting, glove changes, and even air handling is often recommended to separate DNA extraction from amplification steps and to prevent false-positive results. This nucleic acid amplification system is self-contained and performs the extraction, amplification, and detection steps in a single, closed system that minimizes the potential for contamination once the sample is introduced. Operator training is the most important step to ensuring proper operation of the device; however, the device also contains electronic and internal controls that test the device operation and viability of the reagents with each test. The internal controls also check the integrity of sample (too much, too little, viscosity, bubbles) through comparison of target analyte recovery and result timing compared to internal control parameters. Outdated reagents or inhibitors in the specimen that would prevent amplification can also be detected by the internal controls. Electronic and internal controls would also fail to generate a patient result if the device were opened, moved, or experienced a power failure during operation.

Operator-induced errors are another concern when developing a quality assurance program for a new device. Patient identification, sample collection, sample transportation, and specimen loading onto the device are all potential sources of error that can affect test results. Patient identification when conducted by clinical staff rather than trained phlebotomists is a concern, because sample collection is a side task to the primary focus of clinicians—the patient. Clinicians may not make the task of sample collection the center of their attention as dedicated phlebotomists do. In this example, the hospital and clinic implementing the nucleic acid amplification device have decentralized phlebotomy, so there is a greater chance of collecting a specimen from the wrong patient, mislabeling, collecting in an inappropriate preservative, transportation delays, and other collection errors. The manufacturer of this device has engineered many of these errors out of the system by requiring a special collection device for this test. This requirement prevents the possibility of collection in the wrong tube type and reduces errors surrounding application of the sample to the testing device; however, operators can still make mistakes in patient identification, labeling, and most importantly, preanalytic contamination of the specimen during phlebotomy. Extraneous DNA from other patients or outside the specimen could lead to false positives, so operator training on collection technique for this particular device may be even more important than with other laboratory tests. Postanalytic errors in interpretation and transcription of results are further concerns.

Appendix C. (Continued)

Tests requiring operators to interpret a number as positive or negative create sources of potential error; however, this device eliminates that possibility by producing a qualitative result printout as either positive or negative. The remaining concerns would be the variability around the positive cutoff (ie, the possibility of indeterminate specimens with borderline results) and errors in transcription of results to the medical record that could be reduced by the purchase of electronic interfaces that automate the resulting process.

Environmental factors are a third area for potential error to consider when developing a quality assurance program. Operation of the device or exposure of reagents to extremes of temperature could compromise results. Fortunately, the presence of electronic controls would sense operation outside of temperature limits, and internal controls would warn if reagents have degraded. Operator training will be needed to monitor storage temperatures in the laboratory and to test new shipments of reagents before use in patient testing.

The following table summarizes the laboratory FMEA for the nucleic acid amplification system example.

Appendix C. (Continued)

←——————————**Manufacturer completed section** ——————————→ ←—**Clinical laboratory completed section** ———→

Items in **BOLD** and shading are new control measures, as a result of this FMEA. Items not in bold and shading are existing control measures

Manufacturer completed section				**Clinical laboratory completed section**							
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**C**	**S**	**P**	**Recomm. Action from manuf.**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
Analytic	Reagents fail – poor or no reaction	Outdated	Incorrect result	6	3	2	Verify expiration date/storage conditions; rerun with another assay	Operator training to check dates	Manual operator checks; Failed internal and surrogate QC	Rerun patients	Audit that operators have been trained. Periodically monitor and trend for expired reagents.
Analytic	Enzyme fails – possible inhibition	Specimen drug or other inhibitor	Incorrect result	4	4	1	**Rerun with another specimen; dilute to minimize inhibition**	Operator training to recognize unusual results	Manual review for unusual results	Dilute patient specimen and repeat or request new specimen	Audit that operators have been trained. Monitor and trend for specimen issues.
Analytic	Internal controls fail	Reagent or analyzer	No result	1	1	1	Rerun with another assay	Operator training	Automatic	Repeat analysis	Audit that operators have been trained. Monitor for frequency of internal QC failure
Analytic	Target/analyte recovery low	Reagent, analyzer, pipette, or calibrator failure	Low result	8	4	2	Rerun with another specimen	Maintain analyzer, monitor calibration.	Check surrogate QC recovery or proficiency surveys.	Recalibrate maintain analyzer, repeat samples	Audit that operators have been trained. Monitor for QC failure.
Analytic	Sample volume insufficient for retest	Quantity of sample not sufficient for analysis (QNS)	No result	1	1	1	Collect excess sample per labeling	Publish minimum sample requirement to allow for analysis and retest.	Unable to analyze specimen	Request new sample.	Monitor for frequency of QNS.

Appendix C. (Continued)

Manufacturer completed section				Clinical laboratory completed section							
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**C**	**S**	**P**	**Recomm. Action from manuf.**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
Analytic	Pressure too high	Reagent line clogged or twisted	Analyzer and internal QC failure	3	3	1	Validate instrument performance	Routine maintenance	Analyzer or internal QC failure	Perform maintenance and repeat analysis	Audit frequency of maintenance; monitor for frequency of error
Analytic	Pressure too low	Reagent line broke or leaking	Analyzer and internal QC failure	3	3	1	Validate instrument performance	Routine maintenance	Analyzer or internal QC failure	Perform maintenance and repeat analysis.	Audit frequency of maintenance; monitor for frequency of error.
Operator	Too much specimen	Specimen overflow	Analyzer error	2	1	2	Evaluate read-out; dilute specimen and rerun.	Operator training	Analyzer error	Repeat analysis.	Audit operator training; monitor for frequency of error.
Operator	Too little specimen	Specimen quantity not sufficient for analysis (QNS)	Analyzer error	2	1	2	Evaluate read-out; concentrate specimen and rerun; use another specimen.	Operator training	Analyzer error	Repeat analysis.	Audit operator training; monitor for frequency of error.
Operator	Specimen inserted incorrectly into test system	Specimen turned so analyzer can't read barcode	Analyzer error	2	1	2	Training, instructions	Operator training	Analyzer error	Reinsert specimen and start analysis.	Audit operator training; monitor for frequency of error.
Operator	Wrong collection device used	Incorrect tube type	Incorrect result	1	1	1	Do not use collection device other than what is provided unless validated first.	Operator training on proper specimen collection	Specimen arrives in wrong collection container	Request a new specimen.	Audit operator training; monitor for frequency of error.

Appendix C. (Continued)

Manufacturer completed section				Clinical laboratory completed section							
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**C**	**S**	**P**	**Recomm. Action from manuf.**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
Operator	Specimen not collected correctly	Specimen clotted or incorrect tube type	Incorrect result	1	1	1	Training, instructions	Operator training on proper specimen collection, monitor specimen conditions on arrival to lab	Specimen arrives in wrong container or clotted	Request new specimen.	Audit operator training; monitor for frequency of error.
Operator	Specimen contaminated with target/analyte carry-over	Improper specimen handling	Incorrect result	4	4	1	Change gloves when handling different specimens.	Operator training; clean work area; maintain sterile technique	Surrogate QC or proficiency test failure	Repeat analysis.	Audit frequency of surrogate QC; monitor frequency of error.
Operator	Wrong assay system used for test	Operator interrupted, selected wrong test	Result on a different test	1	1	1	Verify test system matches what is entered on computer.	Operator training; locate analyzer where techs are not interrupted	Wrong test after analysis	Repeat analysis with correct test.	Audit operator training; monitor for frequency of error.
Operator	Specimen added to wrong place in assay system	Operator error	No result	1	1	1	Assay designed so specimen, if collected properly, does not fit anywhere but proper insertion point.	Operator training	Analyzer error	Reinsert specimen and start analysis.	Audit operator training and competency.
Operator	Reagents added incorrectly/omitted	Operator error	No result	1	1	1	Training, instructions	Operator training	Analyzer error, internal QC failure	Reinsert reagents and start analysis.	Audit operator training and competency.
Operator	Assay system not inserted correctly into instrument	Operator error	Analyzer error	1	1	1	Reinsert and restart.	Operator training	Analyzer error	Reinsert reagents and start analysis.	Audit operator training and competency.

Appendix C. (Continued)

Manufacturer completed section				Clinical laboratory completed section							
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**C**	**S**	**P**	**Recomm. Action from manuf.**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
Operator	Assay system knocked over/dropped after reagents added	Analyzer bumped	Incorrect result	3	3	1	If spill, consider new assay system.	Locate analyzer in low traffic area of lab.	Analyzer error	Repeat analysis.	Monitor for frequency of error.
Operator	Specimen omitted	Skipped sample	No result	1	1	1	Visually inspect assay before loading into instrument.	Place analyzer in quiet space; allow techs uninterrupted time for test analysis.	No result	Repeat analysis.	Audit operator training; monitor for frequency of error.
Operator	Incorrect label placement; blocks instrument access	Analyzer unable to read barcode to recognize reagent	No result	1	1	1	Remove label; replace assay system and restart run.	Operator training	Analyzer error	Repeat analysis.	Operator training; monitor for frequency of error.
Operator	Debris in assay	Clot or particle from rubber stopper	Incorrect result	4	2	2	Determine source of debris; rerun with new assay.	Check samples before placing on analyzer.	Clot and sample liquid sensor failure	Repeat with filtered or centrifuged sample; request new sample.	Samples checked before analysis; monitor for frequency of clot or liquid sensor failures.
Operator	Run stopped and restarted	Power failure	No results	2	2	1	Rerun with new assay.	Plug analyzer into continuous or backup power source.	Analyzer error message; internal QC failure	Repeat analysis.	Monitor for frequency of power failures.
Environmental	Work area contaminated with target/analyte	Supplies (pipettes, tubes) contaminated with samples; Carry-over	Incorrect result	8	4	1	Do not open a closed test system where reactions are run.	Clean work area regularly, maintain disposable sterility.	Surrogate QC or proficiency surveys	Repeat analysis.	Audit frequency of surrogate QC; monitor for QC and proficiency failures.

Appendix C. (Continued)

Manufacturer completed section				Clinical laboratory completed section							
Step or component in which error occurs	**Error**	**Cause**	**Effect**	**C**	**S**	**P**	**Recomm. Action from manuf.**	**Prevention**	**Detection**	**Recovery**	**Outcome measure**
Environmental	**Sample shipping/storage issues**	**Freezing or heating**	**Incorrect or no result**	**6**	**2**	**3**	**Verify storage/shipment under recommended conditions.**	**Monitor condition of specimens on receipt and storage conditions in lab.**	**Use freeze and temp monitors in courier cartons; consider shipping surrogate QC with specimens.**	**Request a new specimen for affected patients.**	Audit that shipping and storage conditions followed.
Additional Items added by the clinical laboratory											

C=Criticality = SxP; S=Severity (1-5); P=Probability (1-5), where 5 is most severe and most likely.

Appendix D. Example of a FRACAS

This is a constructed example of a FRACAS. It represents observed errors that occur in a clinical laboratory using all of the FRACAS steps described in Section 6. Whereas there are literature examples on laboratory errors, none of these examples contain all FRACAS elements. It is hoped to replace this constructed example with a real one in a revision.

Step (comp.) in which error occurs	Error	Cause	Effect	C	S	F	Prevention	Detection	Recovery	Error rate before corrective action	Error rate after corrective action
Preanalytic *(Pre-examination)*	Incorrect patient ID, specimen mislabeling	Labeling specimen outside patient's room	Results mixed with another patient	8	4	2	Revise labeling policy; staff retraining	Monitor for labeling issues on specimen arrival to lab.	Reject questionable specimens; request redraw.		
	Test not ordered	Use of physician order entry (POE) and manual execution of orders	Results not available for patient care				Phlebotomist & lab staff to close out all POEs at the end of each shift	Monitor POE pending list.	Request draw by the phlebotomist.		
Reagent shipments	Freezing and heating of reagents during shipment	Exposure during shipping	Reagent failure, erroneous results on patient specimens	12	4	3	Manufacturer implemented shipping monitor; perform additional surrogate QC, and verify test performance with patient samples for new shipments.	Verifying freeze and temperature monitor in shipping carton on arrival	Reject questionable shipments prior to patient testing.		
	Prolonged retention at room temperature	Multiple receipt points at the hospital, ie, Receiving Dept, from where it is routed to laboratory	Reagent deterioration; shift/drift in QC and patient test results				Consolidate receipt at hospital to facilitate prompt storage of reagents at appropriate temperature.	Include receipt date/time and storage date/time in QA log; review monthly.	Review monthly QA log to ensure prompt storage at appropriate temperature; use QC performance to monitor drift/shift.		

Appendix D. (Continued)

Step (comp.) in which error occurs	Error	Cause	Effect	C	S	F	Prevention	Detection	Recovery	Error rate before corrective action	Error rate after corrective action
Analytic *(Examination)*	Analyzer overheating	Operation during summer in clinic without air-conditioning	Analyzer error	12	4	3	Move analyzer to controlled temperature.	Analyzer error	Analysis not available during summer until clinic purchases air-conditioning		
	Analyzer shut down during operation	Room temperature higher than upper limit for analyzer	Drift/shift in test results as room temperature changes; erroneous test results				Evaluate total BTU of heat generated by all analyzers in lab, service A/C, and/or use air duct to vent heat out of lab.	Monitor room temperature.	Alternate use of high BTU analyzers until other long-term corrections are implemented.		
	Quality of water	Use of Type 2 instead of Type 1 water	Increased imprecision with CV% > 2x expected				Ensure that vendors specify type of water during initial sale and comply with the specifications.	Monitor daily QC and proficiency survey. Monitor quality of water on a schedule.			
Postanalytic *(Postexamination)*	Request to analyze after 7 days on stored serum	Outpatient facility had delay in results, test was not ordered, request to add to existing specimen (12 days old)	Potential erroneous result	4	4	1	Extend time that add-ons can be requested.	Current computer system monitors of storage time	Storage time extended for certain assays		

Appendix E. A Note on Unit-Use Devices

The scope of the original EP18 document was limited to unit-use devices, defined as a *"testing system where reagents, calibrators, and wash solutions are typically segregated as one test, without interaction of reagents, calibrators, and wash solutions from test to test, and the container where the test is performed is always discarded after each test."* The document's main focus was on devices used at the point of care (POC), although it should be noted that such devices are also used in the main clinical laboratory.

The original EP18 committee recognized that traditional approaches to quality control were not always preferable for unit-use devices, and that alternative approaches had the potential to be better matched to the design and characteristics of a particular device. In addition, traditional surrogate sample statistical quality control could be unnecessarily expensive and difficult for users to perform outside the traditional clinical laboratory.

The debate and confusion about the most appropriate approach to quality control for these devices led to the creation of EP18, which was intended to provide guidance for clinical users to *"develop a comprehensive, yet individualized, quality management program based on the unit-use test system and the specific setting in which it will be utilized."*

In developing such a quality program, some specific aspects of unit-use systems need to be considered. To begin with, it may be helpful to consider three types of failures (applicable to any measurement system):

Single sample errors are transient error conditions that result in measurement error in a given measurement, but the error condition does not persist to affect following measurements. Examples include interference in a patient sample and noisy signals.

Persistent error conditions are characterized by an unacceptable change(s) in the measurement system that potentially affects all subsequent measurements until the error condition is corrected. Whereas the adverse impact of an undetected single sample error condition is limited to one test result, undetected persistent error conditions continue to adversely affect test results until the error condition is detected. Examples include systematic calibration errors, degraded sensing elements due to protein deposition, and fluid flow blockages due to sample clot formation.

Reliability – An error occurs preventing the device from reporting a result. This may be a hardware error such as a failed power supply or a system-suppressed result, whereby software has detected that there is something wrong with one or more aspects of the test cycle, so the result is not reported. Note that reliability errors can be either persistent or single sample errors.

Failures of unit-use test systems can be further categorized as those that affect the single-use components of the test system and those that affect the reusable components of the test system.

Error conditions associated with the single-use portion of the test system are typically single-sample errors (if the error occurs in an individual unit), but can also be persistent (or "batch") error conditions if a batch of units is affected. Because reagents, calibrators, and wash solutions are segregated by individual test and because any points of contact samples have with the system are discarded after each test, potential sources of persistent error conditions due to use of the device over time may be significantly reduced compared to an analogous multiuse design.

Appendix E. (Continued)

Error conditions associated with the reusable portion of the test system may result in single-sample errors or persistent error conditions. Similar to the discussion above, because contact between the reusable part of the device and patient samples is avoided, certain potential sources of persistent error conditions due to use of the device over time may be significantly reduced compared to an analogous multiuse design.

Using a quality management approach to establish quality control procedures, the potential sources of error are considered and the optimal QC tools are selected to effectively and efficiently mitigate risk. The choice of quality control methodology for unit-use devices is not conceptually different than that for multiuse devices, but the potential sources of error may be markedly different. As a result, there may be, for example, an increased emphasis on detecting single-sample errors using automated “internal” QC methods. Such methods are not new, having been used since assays were automated, but they have increased in complexity with the increased electronic and computing capacity of modern devices.

In addition to internal QC methods, “traditional” surrogate-sample statistical quality control may be used to detect persistent out-of-control error conditions for both the single-use and reusable components of unit-use devices. However, traditional QC is *not* generally very effective in detecting single-sample errors.

Some persistent errors in the unit-use portion of the system, such as a bad batch of devices caused by adverse shipment conditions, can be addressed by acceptance sampling. Such methods can detect failures that affect a high proportion of the batch. However, it is impractical for the clinical laboratory to perform acceptance sampling to detect low-percentage error rates, because to guarantee with high confidence a high proportion of a lot will not exhibit errors usually requires very large samples sizes.

Clinical and Laboratory Standards Institute consensus procedures include an appeals process that is described in detail in Section 8 of the Administrative Procedures. For further information, contact CLSI or visit our website at www.clsi.org.

Summary of Consensus Comments and Committee Responses

EP18-A: *Quality Management for Unit-Use Testing; Approved Guideline*

Appendix A. Example of a "System-Specific Sources of Error" Matrix

1. For clarity, I suggest considering renaming the following error source matrix columns and their occurrences in the text. An alternative to this is to describe somewhere how each error source matrix name related to a traditional FMECA name. A suggested format follows.

   For criticality and probability some examples would have to be given, such as: criticality—severe: wrong patient result, medium: result not processed, etc., and probability—highly unlikely: less than 0.001%, possible: less than 1%, etc.

Potential Sources of Error	**Appli-cable Y/N?**	**Effect of Error**	**Criticality or Error**	**Proba-bility of Error**	**Detection of Error**		**Mitigation of Error**	
					Quality Monitoring and Frequency if Applicable	**Other**	**Training/ Labor-atory Require-ments**	**Other**

- **Revisions made in Appendix A have addressed this comment.**

NOTES

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 approach is based on the model presented in the most current edition of CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care.* 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 quality system essentials (QSEs) are:

Documents & Records	Equipment	Information Management	Process Improvement
Organization	Purchasing & Inventory	Occurrence Management	Service & Satisfaction
Personnel	Process Control	Assessment	Facilities & Safety

EP18-P2 addresses the quality system essentials (QSEs) indicated by an "X." For a description of the other documents listed in the grid, please refer to the Related CLSI/NCCLS Publications section on the following page.

Documents & Records	Organization	Personnel	Equipment	Purchasing & Inventory	Process Control	Information Management	Occurrence Management	Assessment	Process Improvement	Service & Satisfaction	Facilities & Safety
GP2 GP26	GP26	GP26	GP26 HS11	GP26	X EP5 EP6 EP7 EP9 EP10 EP12 EP14 EP15 EP19 EP21 GP10 GP26 M29	GP2 GP26	X GP26 GP32	X EP10 GP26	X EP7 GP26	GP26	GP26 M29

Adapted from CLSI/NCCLS document HS1—*A Quality Management System Model for Health Care.*

Related CLSI/NCCLS Publications*

EP5-A2 **Evaluation of Precision Performance of Quantitative Measurement Methods; Approved Guideline—Second Edition.** This document provides guidance for designing an experiment to evaluate the precision performance of quantitative measurement methods; recommendations on comparing the resulting precision estimates with manufacturers' precision performance claims and determining when such comparisons are valid; as well as manufacturers' guidelines for establishing claims.

EP6-A **Evaluation of the Linearity of Quantitative Measurement Procedures: A Statistical Approach; Approved Guideline.** This document provides guidance for characterizing the linearity of a method during a method evaluation; for checking linearity as part of routine quality assurance; and for determining and stating a manufacturer's claim for linear range.

EP7-A2 **Interference Testing in Clinical Chemistry; Approved Guideline—Second Edition (2005).** This document provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interfering substances on clinical chemistry test results.

EP9-A2 **Method Comparison and Bias Estimation Using Patient Samples; Approved Guideline—Second Edition (2002).** This document addresses procedures for determining the bias between two clinical methods, and the design of a method comparison experiment using split patient samples and data analysis.

EP10-A3 **Preliminary Evaluation of Quantitative Clinical Laboratory Measurement Procedures; Approved Guideline—Third Edition (2006).** This guideline provides experimental design and data analysis for preliminary evaluation of the performance of a measurement procedure or device.

EP12-A **User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline (2002).** This document provides a protocol designed to optimize the experimental design for the evaluation of qualitative tests; to better measure performance; and to provide a structured data analysis.

EP14-A2 **Evaluation of Matrix Effects; Approved Guideline—Second Edition (2005).** This document provides guidance for evaluating the bias in analyte measurements that is due to the sample matrix (physiological or artificial) when two measurement procedures are compared.

EP15-A2 **User Verification of Performance for Precision and Trueness; Approved Guideline—Second Edition (2006).** This document describes the demonstration of method precision and trueness for clinical laboratory quantitative methods utilizing a protocol designed to be completed within five working days or less.

EP19-R **A Framework for CLSI Evaluation Protocols; A Report (2002).** This report describes the different types of performance studies that are conducted to evaluate clinical assays.

EP21-A **Estimation of Total Analytical Error for Clinical Laboratory Methods; Approved Guideline (2003).** This document provides manufacturers and end users with a means to estimate total analytical error for an assay. A data collection protocol and an analysis method which can be used to judge the clinical acceptability of new methods using patient specimens are included. These tools can also monitor an assay's total analytical error by using quality control samples.

GP2-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.

GP10-A **Assessment of the Clinical Accuracy of Laboratory Tests Using Receiver Operating Characteristic (ROC) Plots; Approved Guideline (1995).** This document provides a protocol for evaluating the accuracy of a test to discriminate between two subclasses of subjects where there is some clinically relevant reason to separate them. In addition to the use of ROC plots, the importance of defining the question, selecting the sample group, and determining the "true" clinical state are emphasized.

GP26-A3 **Application of a Quality Management System Model for Laboratory Services; Approved Guideline—Third Edition.** This guideline describes the clinical laboratory's path of workflow and provides information for laboratory operations that will assist the laboratory in improving its processes and meeting government and accreditation requirements.

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* Proposed-level documents are being advanced through the Clinical and Laboratory Standards Institute consensus process; therefore, readers should refer to the most recent editions.

GP32-P **Management of Nonconforming Laboratory Events; Proposed Guideline (2007).** This guideline provides an outline and the content for developing a program to manage a health care service's nonconforming events that is based on the principles of quality management and patient safety.

HS1-A2 **A Quality Management System Model for Health Care; Approved Guideline—Second Edition.** This document provides a model for providers of health care services that will assist with implementation and maintenance of effective quality management systems.

HS11-A **A Model for Managing Medical Device Alerts (Hazards and Recalls) for Healthcare Organizations; Approved Guideline.** This document provides a framework for health care delivery organizations to respond to externally generated notifications of medical device hazards and recalls while focusing on the quality constructs of process control, occurrence management, and process improvement.

M29-A3 **Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition.** 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.

NOTES

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Children's Hospital & Research Center at Oakland (CA)
Children's Hospital Medical Center (OH)
Children's Memorial Hospital (IL)
Childrens Hosp.- Kings Daughters (VA)
Childrens Hospital Los Angeles (CA)
Childrens Hospital of Wisconsin (WI)
Chilton Memorial Hospital (NJ)
Christiana Care Health Services (DE)
CHUM Hopital Saint-Luc (Canada)
City of Hope National Medical Center (CA)
Clarian Health – Clarian Pathology Laboratory (IN)

Cleveland Clinic Health System Eastern Region (OH)
Clinical Labs of Hawaii (HI)
CLSI Laboratories, Univ. Pittsburgh Med. Ctr. (PA)
Commonwealth of Kentucky
Community Care 5 (OH)
Community Hospital (IN)
Community Hospital of the Monterey Peninsula (CA)
Connolly Hospital (Ireland)
Consultants Laboratory of WI LLC (WI)
Contra Costa Regional Medical Center (CA)
Corpus Christi Medical Center (TX)
Covance CLS (IN)
Covance Evansville (IN)
Creighton Medical Laboratories (NE)
Creighton University Medical Center (NE)
Cross Cancer Institute (Canada)
Darwin Library NT Territory Health Services (Australia)
David Grant Medical Center (CA)
Daviess Community Hospital (IN)
Dekalb Memorial Hospital (IN)
DeWitt Healthcare Network (USA Meddac) (VA)
DHHS NC State Lab of Public Health (NC)
Diagnostic Laboratory Services, Inc. (HI)
Diagnostic Services of Manitoba (Canada)
Diagnósticos da América S/A (Sao Paulo)
Dianon Systems/Lab Corp. (OK)
Dr. Everette Chalmers Regional Hospital (NB)
Driscoll Children's Hospital (TX)
DSI of Bucks County (PA)
DUHS Clinical Laboratories (NC)
Dundy County Hospital (NE)
Dwight D. Eisenhower Medical Center (KS)
Edward Hospital (IL)
EMH Regional Medical Center (OH)
Emory University Hospital (GA)
Evangelical Community Hospital (PA)
Evanston Hospital (IL)
Exeter Hospital (NH)
Federal Medical Center (MN)
Firelands Regional Medical Center (OH)
First Health of the Carolinas Moore Regional Hospital (NC)
Fisher-Titus Memorial Hospital (OH)
Flaget Memorial Hospital (KY)
Fletcher Allen Health Care (VT)
Fleury S.A. (Brazil)
Foote Hospital (MI)
Fort St. John General Hospital (Canada)
Forum Health Northside Medical Center (OH)
Fox Chase Cancer Center (PA)
Gamma-Dynacare Laboratories (Canada)
Gamma Dynacare Medical Laboratories (Ontario, Canada)
Garden City Hospital (MI)
Geisinger Medical Center (Danville, PA)
Geisinger South Wilkes Barre Laboratory (PA)
Genesis Healthcare System (OH)
George Washington University Hospital (DC)
Good Samaritan Hospital (NE)
Good Shepherd Medical Center (TX)
Grand Strand Reg. Medical Center (SC)
Haga Teaching Hospital (Netherlands)
Hagerstown Medical Laboratory (MD)
Hamad Medical Corporation (Qatar)
Harris Methodist Fort Worth (TX)
Hartford Hospital (CT)
Harford Memorial Hospital (MD)
Health Network Lab (PA)
Health Partners Laboratories Bon Secours Richmond (VA)
Health Waikato (New Zealand)
Heartland Health (MO)
Heidelberg Army Hospital (APO, AE)
Hema-Quebec (Canada)
Henry Ford Hospital (MI)
Hi-Desert Medical Center (CA)
Hoag Memorial Hospital Presbyterian (CA)
Holy Cross Hospital (MD)
Holy Family Medical Center (WI)
Holy Spirit Hospital (PA)
Hopital Cite de La Sante De Laval (Canada)
Hôpital Maisonneuve - Rosemont (Montreal, Canada)
Hôpital Sacré-Coeur de Montreal (Quebec, Canada)
Hôpital Sainte - Justine (Quebec)
Hopital Santa Cabrini Ospedale (Canada)
Hospital Albert Einstein (Brazil)
Hospital de Dirino Espirito Santa (Portugal)
Hospital De Sousa Martins (Guarda) (Portugal)
Hôtel Dieu Grace Hospital Library (Windsor, ON, Canada)
Humility of Mary Health Partners (OH)
Hunter Area Pathology Service (Australia)
Hunterdon Medical Center (NJ)
Icon Laboratories (Ireland)
IGate Clinical Research Intl., Pvt., LTD (India)
Imelda Hospital (Belgium)
Indiana University - Chlamydia Laboratory (IN)
Inova Fairfax Hospital (VA)
Institut fur Stand. und Dok. im Med. Lab. (Germany)
Institut National de Santé Publique du Quebec Centre de Doc. – INSPQ (Canada)
Institute of Clinical Pathology and Medical Research (Australia)
Integrated Regional Laboratories South Florida (FL)
International Health Management Associates, Inc. (IL)
Island Hospital (WA)
Jackson Health System (FL)
Jackson Hospital & Clinic, Inc. (AL)
Jackson Purchase Medical Center (KY)
Jacobi Medical Center (NY)
John C. Lincoln Hospital (AZ)
John F. Kennedy Medical Center (NJ)
John H. Stroger, Jr. Hospital of Cook County (IL)
John Muir Medical Center (CA)
John T. Mather Memorial Hospital (NY)
Johns Hopkins Medical Institutions (MD)
Johns Hopkins University (MD)
Kadlec Medical Center (WA)
Kaiser Permanente (CA)
Kaiser Permanente (MD)
Kangnam St. Mary's Hospital (Korea)
Keller Army Community Hospital (NY)
Kenora-Rainy River Reg. Lab. Program (Canada)
King Fahad National Guard Health Affairs King Abdulaziz Medical City (Saudi Arabia)
King Faisal Specialist Hospital (MD)
Kingston General Hospital (Canada)
Kosciusko Laboratory (IN)
Lab Medico Santa Luzia LTDA (Brazil)
LabCorp (NC)
Labette Health (KS)
Laboratory Alliance of Central New York (NY)
LabPlus Auckland Healthcare Services Limited (New Zealand)
Lakeland Regional Medical Center (FL)
Landstuhl Regional Medical Center (APO, AE)
Langlade Memorial Hospital (WI)
LeBonheur Children's Medical Center (TN)
Legacy Laboratory Services (OR)
Lethbridge Regional Hospital (Canada)
Lewis-Gale Medical Center (VA)
L'Hotel-Dieu de Quebec (Quebec, Canada)
Licking Memorial Hospital (OH)
LifeBridge Health Sinai Hospital (MD)
Long Beach Memorial Medical Center (CA)
Los Angeles County Public Health Lab. (CA)
Louis A Johnson Medical Center (WV)
Louisiana State University Medical Ctr. (LA)
Lourdes Hospital (KY)
Madison Parish Hospital (LA)
Magruder Memorial Hospital (OH)
Manipal AcuNova (India)
Marquette General Hospital (MI)
Marshfield Clinic (WI)
Martin Luther King, Jr. Harbor Hospital (CA)
Martin Memorial Health Systems (FL)
Marymount Medical Center (KY)
Massachusetts General Hospital (MA)
Massachusetts General Hospital Division of Laboratory Medicine (MA)
Maxwell Air Force Base (AL)
MDS Laboratories (Canada)
MDS Metro Laboratory Services (BC, Canada)
Meadows Regional Medical Center (GA)
Mease Countryside Hospital (FL)
Mease Dunedin Hospital (FL)
Medical Center of Louisiana at NO-Charity (LA)
Medical Centre Ljubljana (Slovenia)
Medical College of Virginia Hospital (VA)
Medical Specialists (IN)
Medical Univ. of South Carolina (SC)
Memorial Health Center, Inc. (WI)
Memorial Hermann Healthcare System (TX)
Memorial Hospital (OH)
Memorial Hospital Miramar (FL)
Memorial Hospital Pembroke (FL)
Memorial Hospital West (FL)
Memorial Medical Center (PA)
Memorial Regional Hospital (FL)
Mercy Hospital (ME)
Mercy Medical Center (CO)
Mercy Medical Center (ID)
Mercy Medical Center (OR)
Methodist Hospital (MN)
Methodist Hospital (TX)
Methodist Hospital Pathology (NE)
Mississippi Public Health Lab (MS)
Monmouth Medical Center (NJ)
Montefiore Medical Center (NY)
Montreal General Hospital (Canada)
Morton Plant Hospital (FL)
Mt. Sinai Hospital (NY)
Nassau County Medical Center (NY)
National Cancer Institute (MD)
National Healthcare Group (Singapore)
National Institutes of Health, Clinical Center (MD)
National Naval Medical Center (MD)
National University Hospital Department of Laboratory Medicine (Singapore)
Naval Hospital Cherry Point Laboratory (NC)
Naval Hospital Oak Harbor (WA)
New England Fertility Institute (CT)
New Lexington Clinic (KY)
New York City Department of Health and Mental Hygiene (NY)
New York-Presbyterian Hospital (NY)
New York University Medical Center (NY)
Newark Beth Israel Medical Center (NJ)
North Bay Hospital (FL)
North Carolina Baptist Hospital (NC)
North Coast Clinical Laboratory, Inc. (OH)
North Mississippi Medical Center (MS)
North Shore Hospital Laboratory (Auckland, New Zealand)
North Shore-Long Island Jewish Health System Laboratories (NY)
Northeast Pathologists, Inc. (MO)
Northern Plains Laboratory (ND)
Northridge Hospital Medical Center (CA)
Northwest Texas Hospital (TX)
Northwestern Memorial Hospital (IL)
Norton Healthcare (KY)
Ochsner Clinic Foundation (LA)
Oklahoma Heart Hospital, LLC (OK)
Onze Lieve Vrouw Ziekenhuis (Belgium)
Ordre Professionel Des Technologistes Medicaux Du Quebec (Quebec)
Orlando Regional Healthcare System (FL)
Our Lady of Lourdes Medical Center (NJ)
Our Lady of Lourdes Reg. Medical Ctr. (LA)
Our Lady of the Way Hospital (KY)
Our Lady's Hospital for Sick Children (Ireland)
Overlake Hospital Medical Center (WA)
Pathologists Associated (IN)
Pathology and Cytology Laboratories, Inc. (KY)
Pathology Associates Medical Laboratories (WA)
PathWest (Nedlands, WA)
PathWest (Subiaco, WA)
PCA Southeast (TN)
Pediatrix Screening Inc. (PA)
Pennsylvania Hospital (PA)
Penrose St. Francis Health Services (CO)
Perry County Memorial Hospital (IN)
Peterborough Regional Health Centre (Canada)
Physicians Reference Laboratory (KS)
Pitt County Memorial Hospital (NC)
PPD (KY)
Presbyterian Hospital of Dallas (TX)
Presbyterian/St. Luke's Medical Center (CO)
Prince George Medical Lab (Prince George, BC)
Providence Health Care (Canada)
Providence Medford Medical Center (OR)
Provincial Health Services Authority (Vancouver, BC, Canada)
Provincial Laboratory for Public Health (Edmonton, AB, Canada)
Queen Elizabeth Hospital (Canada)
Queensland Health Pathology Services (Australia)
Quest Diagnostics, Inc
Quest Diagnostics, Inc (San Juan Capistrano, CA)
Quest Diagnostics JV (IN, OH, PA)
Quest Diagnostics Laboratories (WA)
Quintiles Laboratories, Ltd. (GA)
Rady Children's Hospital San Diego (CA)
Redington-Fairview General Hospital (ME)
Régie Régionale Dela Santé Beaséjour (Canada)
Regional Health Authority - Central Manitoba Inc (Canada)
Regional Health Authority Four (RHA4) (Canada)
Regions Hospital (MN)
Research Medical Center (MO)
Riverside Methodist Hospital (OH)
Riverview Hospital (WI)
Riyadh Armed Forces Hospital, Sulaymainia (Riyadh, Saudi Arabia)
Robert Wood Johnson University Hospital (NJ)
Roxborough Memorial Hospital (PA)
SAAD Specialist Hospital (Saudi Arabia)
Sahlgrenska Universitetssjukhuset (Sweden)
Saint Elizabeth Regional Medical Center (NE)
Saint Francis Hospital & Medical Center (CT)
St. Agnes Healthcare (MD)
St. Anthony Hospital (OK)
St. Anthony Hospital Central Laboratory (CO)
St. Anthony's Hospital (FL)
St. Barnabas Medical Center (NJ)
St. Christopher's Hospital for Children (PA)
St. Francis Medical Center (MN)
St. John Hospital and Medical Center (MI)
St. John's Hospital & Health Ctr. (CA)
St. Johns Hospital (MO)
St. Joseph Medical Center (MD)
St. Joseph Mercy Hospital (MI)
St. Joseph's Hospital (FL)
St. Joseph's Hospital & Health Center (ND)
St. Joseph's Medical Center (CA)
St. Joseph's Regional Medical Center (NJ)
St. Jude Children's Research Hospital (TN)
St. Louis University Hospital (MO)
St. Luke's Hospital (PA)
St. Luke's Hospital (IA)
St. Margaret Memorial Hospital (PA)
St. Mary Medical Center (CA)
St. Mary's Health Center (MO)
St. Mary's Healthcare (SD)
St. Mary's Medical Center (IN)
St. Michael's Hospital Diagnostic Laboratories & Pathology (Canada)

San Francisco General Hospital-University of California San Francisco (CA)
Scott & White Memorial Hospital (TX)
Seoul Clinical Laboratories (Korea)
Seton Medical Center (CA)
Shands at the University of Florida
Shape Healthcare Clinic (APO, AE)
Sheik Kalifa Medical City (UAE)
Shore Memorial Hospital (NJ)
Shriners Hospitals for Children (SC)
Singapore General Hospital (Singapore)
SJRMC Plymouth Laboratory (IN)
Seoul National University Hospital (Korea)
Sonora Quest JV (AZ)
South Bend Medical Foundation (IN)
South County Hospital (RI)
South Dakota State Health Laboratory (SD)
South Florida Baptist Hospital (FL)
South Texas Laboratory (TX)
Southern Health Care Network (Australia)
Southwest Nova District Health Authority (Canada)
Specialty Laboratories, Inc. (CA)
Starke Memorial Hospital Laboratory (IN)
State of Connecticut Department of Public Health (CT)
State of Washington Public Health Labs
Steele Memorial Hospital (ID)
Stillwater Medical Center (OK)
Stony Brook University Hospital (NY)
Stormont-Vail Regional Medical Center (KS)
Stratford General Hospital (Canada)
Sunnybrook Health Science Center (ON, Canada)
Swedish Medical Center (CO)
Taipei Veterans General Hospital (Taiwan)
Taiwan Society of Laboratory Medicine
Tampa General Hospital (FL)
Temple Univ. Hospital - Parkinson Pav. (PA)
Texas Department of State Health Services (TX)
The Bermuda Hospitals Board (Bermuda)
The Community Hospital (OH)
The Credit Valley Hospital (Canada)
The Hospital for Sick Children (Canada)
The Nebraska Medical Center (NE)
The New York Hospital Medical Center of Queens (NY)
The Ottawa Hospital (Canada)
The Permanente Medical Group (CA)
The Toledo Hospital (OH)
The University of Texas Medical Branch (TX)
Thomason Hospital (TX)
Timmins and District Hospital (Canada)
Touro Infirmary (LA)
Tri-Cities Laboratory (WA)
Tripler Army Medical Center (HI)
Tufts New England Medical Center Hospital (MA)
UCLA Medical Center Clinical Laboratories (CA)
UCSD Medical Center (CA)
UCSF Medical Center China Basin (CA)
UMC of Southern Nevada (NV)
UNC Hospitals (NC)
Union Clinical Laboratory (Taiwan)
United Clinical Laboratories (IA)
Unity HealthCare (IA)
Universita Campus Bio-Medico (Italy)
Universitair Ziekenhuis Antwerpen (Belgium)
University College Hospital (Ireland)
University of Alabama-Birmingham Hospital (AL)
University of Arkansas for Medical Sci. (AR)
University of Colorado Health Sciences Center (CO)
University of Colorado Hospital
University of Illinois Medical Center (IL)
University of Kentucky Med. Ctr. (KY)
University of Maryland Medical System
University of Medicine & Dentistry, NJ
University Hosp. (NJ)
University of MN Medical Center - Fairview
University of Missouri Hospital (MO)
University of MS Medical Center (MS)
University of the Ryukyus (Japan)
University of Virginia Medical Center
University of Washington
U.S. Army Health Clinic – Vicenza (APO, AE)
US LABS, Inc. (CA)
U.S.A. Meddac (Pathology Division) (MO)
U.T. Health Center (TX)
UW Hospital (WI)
UZ-KUL Medical Center (Belgium)
VA (Asheville) Medical Center (NC)
VA (Bay Pines) Medical Center (FL)
VA (Chillicothe) Medical Center (OH)
VA (Cincinnati) Medical Center (OH)
VA (Colmery-O'Neil) Medical Center (KS)
VA (Dallas) Medical Center (TX)
VA (Decatur) Medical Center (GA)
VA (Fayetteville) Medical Center (AR)
VA (Iowa City) Medical Center (IA)
VA (Long Beach) Medical Center (CA)
VA New Jersey Health Care System (NJ)
VA (Phoenix) Medical Center (AZ)
VA (San Diego) Medical Center (CA)
VA (Tucson) Medical Center (AZ)
Valley Health (VA)
Vancouver Hospital and Health Sciences Center (BC, Canada)
Vanderbilt University Medical Center (TN)
Virga Jessezieukenhuis (Belgium)
Virginia Regional Medical Center (MN)
ViroMed Laboratories (LabCorp) (MN)
WakeMed (NC)
Walter Reed Army Medical Center (DC)
Warren Hospital (NJ)
Waterbury Hospital (CT)
Waterford Regional Hospital (Ireland)
Weirton Medical Center (WV)
Wellstar Cobb Hospital Laboratory (GA)
Wellstar Douglas Hospital Laboratory (GA)
Wellstar Health System (GA)
Wellstar Paulding Hospital (GA)
Wellstar Windy Hill Hospital Laboratory (GA)
West China Second University Hospital, Sichuan University (P.R. China)
West Valley Medical Center Laboratory (ID)
Westchester Medical Center (NY)
Wheaton Franciscan & Midwest Clinical Laboratories (WI)
Wheeling Hospital (WV)
Whitehorse General Hospital (Canada)
William Beaumont Army Medical Center (TX)
William Beaumont Hospital (MI)
Winchester Hospital (MA)
Womack Army Medical Center (NC)
Women's Health Laboratory (TX)
Woodlawn Hospital (IN)
York Hospital (PA)

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