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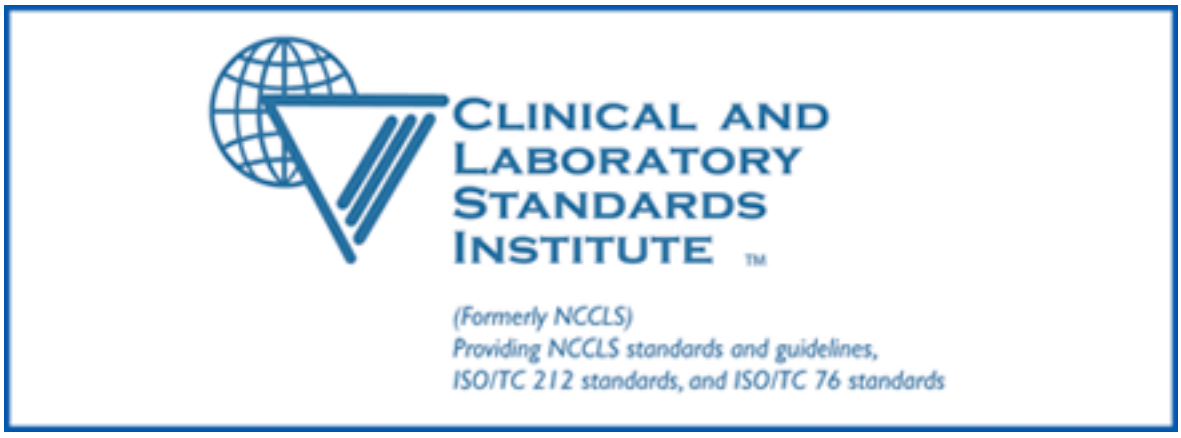
Quality Management for Unit-Use Testing; Approved Guideline



This guideline recommends a quality management system for unit-use devices that will aid in the identification, understanding, and management of 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 NCCLS consensus process.

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- the revision of documents in response to comments by users
- the acceptance of a document as a consensus standard or guideline.

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Healthcare professionals in all specialties are urged to volunteer for participation in NCCLS projects. Please contact the NCCLS Executive Offices for additional information on committee participation.

Quality Management for Unit-Use Testing; Approved Guideline

Abstract

NCCLS document EP18-A—*Quality Management for Unit-Use Testing; Approved Guideline* recommends a quality management system for unit-use test devices that is based on expert opinion, is practical to implement, and is applicable to various devices and settings, so that 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 (e.g., 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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Quality Management for Unit-Use Testing; Approved Guideline

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David L. Phillips, Chairholder
Paula J. Santrach, M.D., Vice-Chairholder
Anne Belanger, M.T.(ASCP), M.A.
Veronica Calvin
Cecelia S. Hinkel, M.T.(ASCP)
Wendell R. O'Neal, Ph.D.
James O. Westgard, Ph.D.
Ronald J. Whitley, Ph.D.

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Daniel W. Tholen, M.S **Vice-Chairholder**	**Statistical Services** **Traverse City, Michigan**

Subcommittee on Unit-Use Testing

David L. Phillips **Chairholder**	**LifeScan** **Carmel, Indiana**
Paula J. Santrach, M.D. **Vice-Chairholder**	**Mayo Clinic** **Rochester, Minnesota**
Anne Belanger, M.A., M.T.(ASCP)	Healthcare Standards Consultants Warrenville, Illinois
Veronica Calvin	FDA Ctr. for Devices/Rad. Health Rockville, Maryland
Cecelia S. Hinkel, M.T.(ASCP)	Centers for Medicare and Medicaid Services Finksburg, Maryland
Wendell R. O'Neal, Ph.D.	The Whisk Group & Hlth. Alliance of Greater Cincinnati Cincinnati, Ohio
James O. Westgard, Ph.D.	University of Wisconsin Madison, Wisconsin
Ronald J. Whitley, Ph.D.	University of Kentucky Medical Center Lexington, Kentucky

Advisors

John A. Boffa, B.L.D.	American Association of Bioanalysts Howell, New Jersey
A. Wayne Bruce, Ph.D.	University of ND School of Med. & Health Sciences Grand Forks, North Dakota
Louis J. Dunka, Jr., Ph.D.	LifeScan, Inc. Milpitas, California

Advisors (Continued)

JoAnn Edlow	Dade International Glasgow Newark, Delaware
Sharon S. Ehrmeyer, Ph.D.	University of Wisconsin Madison, Wisconsin
Ellis Jacobs, Ph.D., CABCC, FACB	The Mount Sinai Hospital-NYU Medical Center New York, New York
Sharon K. Lappalainen	Centers for Medicare & Medicaid Services Baltimore, Maryland
Lowry J. Messenger, Ph.D.	LXN Corporation San Diego, California
Anthony O. Okorodudu, Ph.D.	University of Texas Medical Branch Galveston, Texas
Bob Schoen, Ph.D.	Abbott Laboratories Abbott Park, Illinois
James K. Tusa, Ph.D.	AVL Scientific Corp. Roswell, Georgia
Antonius L. van Kessel, B.Sc. RCPT	Stanford University Medical Center Los Altos, California
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Foreword

Unit-use testing has existed for many years. Conventional methods and lyophilized or aqueous materials were generally used for quality control and quality assurance. Because these materials were readily available and generally accepted as capable of ensuring trueness and precision, they became part of the quality assurance program for early unit-use test systems such as urine dipsticks.

The concepts of quality control over the last half-century have developed in two primary directions. The first is the more familiar, in which a continuous process that generates measurements is monitored to determine whether the process is stable or is headed out of control. The concepts of statistical quality control were applied to the clinical laboratory with the introduction of Levey-Jennings charts, with many subsequent statistical and interpretation enhancements developed to provide additional capabilities of process control to the clinical laboratory measurement process. Similar quality control practices are also used by manufacturers to release lots of reagents, including unit-use reagents. This quality control regimen guards against continuous processes that drift or become unstable, generating trends or increased imprecision.

The second area of quality control is acceptance sampling, where a "lot" of individual items is sampled to determine that an acceptable level of performance has been obtained. Continuous variable measurement, as used in process control, uses quantitative measurements which have standard deviations and means. Acceptance sampling (in its simplest and most common applications) classifies items in two discrete categories: defective and valid. Use of acceptance sampling protects against failures that appear to occur randomly. These failures can occur from a continuous process that has no detectable mean shift and in some cases no detectable increased imprecision, e.g., they can occur in conventional diagnostic analyzers that exhibit acceptable, conventional quality control.

In the clinical laboratory, only the first of these two general areas has found wide application, whereas acceptance sampling is sometimes used by manufacturers in release criteria for reagent lots. With the introduction of unit-use devices for clinical sample testing, it is necessary to incorporate the concepts of the second type of quality control. The assumptions and implications of each approach are different, and it is now necessary to combine both approaches for many of the new *in vitro* devices now in the marketplace. Two varieties of systems are currently in use for quality control of the unit-use device. One system consists of self-contained unit-use disposable devices; the other is a combination of a unit-use disposable device (test strip, cassette, disk, card, etc.) and a reader (reflectance meter, fluorescence, spectrophotometry device, etc).

No conventional quality control (QC) method and material can completely control any test system. With some devices, quality control in clinical laboratories that is used to detect process changes may be less relevant for unit-use systems, assuming that the manufacturer has carried out conventional quality control during manufacturing. This is because the additional "process" that takes place in a conventional diagnostic analyzer at a clinical laboratory has already occurred for a unit-use system in the manufacturing environment, rather than the clinical laboratory. Acceptance sampling, while impractical for clinical laboratories, is also carried out by manufacturers when appropriate.

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 NCCLS 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.

Foreword (Continued)

The subcommittee has limited the discussions within this document to unit-use test systems. While it is the committee's expectation that the guideline will be used primarily to address the issues around point-of-care (POC) devices that utilize single-use disposables, EP18 should not be considered as exclusive to unit-use systems. However, as these concepts are further refined with actual experience, an additional, perhaps broader-based guideline could be undertaken to address multiuse systems and include all aspects of statistical process control and error reduction.

Key Words

Quality assurance, quality control, quality management, quality system, unit-use system

A Note on Terminology

NCCLS, 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. NCCLS 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 NCCLS, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all obstacles to harmonization. In light of this, NCCLS 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 to 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.

The Quality System Approach

NCCLS subscribes to a quality 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 through a gap analysis. The approach is based on the model presented in the most current edition of NCCLS HS1—*A Quality System Model for Health Care.* The quality system approach applies a core set of "quality system essentials (QSEs)," basic to any organization, to all operations in any healthcare service's path of workflow. 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:

QSEs

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

EP18-A addresses the following quality system essentials (QSEs):

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

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

Quality Management for Unit-Use Testing; Approved Guideline

1 Introduction

Unit-use testing presents unique challenges to manufacturers, users, regulators, and accrediting agencies in terms of quality control and quality assurance. Conventional schemes of quality control, with strictly defined materials and frequency, are not always applicable to unit-use test systems due to the very nature of these devices. Furthermore, quality assurance and oversight take on new dimensions with the utilization of many of these test systems outside traditional laboratory test settings, and with test performance by a variety of healthcare personnel.

Even though the committee considered the use of all unit-use (point-of-care) test systems in this guideline, the primary focus is the use of these unit-use systems within professional settings, i.e., hospitals, physician offices, etc. and not for patient self-testing or in-home testing. It is in the professional settings that the healthcare professional has assumed the responsibility of ensuring the quality of the testing system. Moreover, these testing sites are subject to regular and routine inspections or surveys by various accrediting agencies. Therefore, some guidance as to how to deal with various test system errors is important. It is no less important in self-testing situations, but it is the patient along with his/her physician that is responsible for the quality of the testing system. Further, there is no organization that requires and monitors the patient's compliance to any quality systems. However, as technology becomes more advanced by making test systems simpler to operate for the layperson, some portions of this guideline may become appropriate for review and use by the individual consumer.

The following basic concepts directed the development of this guideline:

- Unit-use devices are extremely diverse in their technology, design, and function. Every unit-use test system is subject to certain preanalytical, analytical, and postanalytical 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 the end users of the unit-use device as opposed to the user in the hospital or commercial laboratory. While it is evident that all *in vitro* diagnostic (IVD) devices are subject to these issues, this document focuses strictly on unit-use test devices and may be expanded in future versions.

- A single quality control/quality assurance regimen cannot be developed to cover all unit-use test systems (as well as most, if not all IVD systems) and detect all possible errors.

- The principles of traditional, statistical quality control need to be customized and adapted for the unit-use test system. It is impractical to consume large numbers of unit-use systems needed to detect the low rate of defects found in properly designed, manufactured, shipped, and stored unit-use systems. A multitier approach to quality control and quality assurance has been proposed within this document. This approach provides the user with the means to inspect goods upon arrival through the use of limited acceptance sampling to detect variables such as shipping conditions, lot changes, and new operators. It also allows for further quality assurance testing when device results deviate from established QC control ranges, and it allows for an assessment of operator competency. Periodic quality control also serves as an indicator of operator competency.

- Quality control/assurance programs may evolve with increasing experience with the unit-use test system. These programs should focus on errors which may occur relatively frequently and/or have the potential for significant clinical impact.

The more simple an *in vitro* device might be to use, the more demanding the design requirements for robustness of the analytic process and the stability of the system.

Based upon the assessment of the guiding concepts outlined above, the subcommittee based this guideline on a systems approach to quality management.[1] The phases of the testing process are defined, and the potential sources of error within each phase are identified.

A generic "sources of error" matrix is presented and suggestions for practical management/monitoring are described. The expectation is that a manufacturer will evaluate this list of potential failure modes during the design and development of each new product and identify those that are relevant. Failure mode, effects, and criticality analysis (FMECA)[2] and hazard analyses should consider whether each of the listed failure modes is relevant to the device under design. The device's design should lessen to the extent possible any resulting hazards that present an unacceptable risk to patients, users, or other individuals. Any remaining failure modes shall be clearly and unambiguously disclosed in the product labeling/instructions for use. Clinical users can 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. Regulatory and accrediting agencies can use both the generic and customized matrices to assess the appropriateness of these programs.

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

2 Scope

The intent of the subcommittee is to develop a guideline for establishing a quality management system for unit-use test systems that is practical to implement; applicable to various devices and settings; and scientifically based so that "sources of error" are identified, understood, and managed. This system will aid device manufacturers and users in assuring correct results.

The characteristics of a unit-use test are:

- The container where the test is performed is always discarded after each test.

- Reagents, calibrators, and wash solutions are typically segregated as one test. There is no interaction of reagents, calibrators, and wash solutions from test to test.

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

- Testing Components

  — Specimen collection
  — Sample presentation
  — Instrument/reagents
  — Result/readout/raw data
  — Preliminary review
  — Integration into the patient record

- Locations and Users

This guideline applies to unit-use test systems utilized by healthcare providers in any setting.

3 Definitions[a]

Error, *n* - A test result where the difference between the measured value and the true value is larger than laboratory-specified or manufacturer-specified tolerances; that is, a result that could lead to inappropriate patient management; **NOTES:** a) This definition is a combination of VIM 3.10 "measurement error" and VIM5.21 "maximum permissible error"; b) In this document, the term "error" is used broadly to include all potential failure modes. This includes measurement error (the difference between the test result and the true value), which may or may not exceed specified tolerances; it also includes operator mistakes, instrument failure or defects, and environmental conditions that can create "errors" as defined above. Where possible, the document is exact in stating the type of error, but does not do so where the meaning is clear and the exact term is unnecessarily wordy or awkward.

Failure mode, effect, and criticality analysis (FMECA), *n* – A systematic review of a system or product involving three phases: identification of potential failures, assessing the impact on total system/product performance of that failure, and the criticality of that failure; **NOTES**: a**)** The analysis also includes a review(s) of the steps taken to guard against the failure or to mitigate its effect; b) The procedure is sometimes referred to as a "bottoms-up" analysis; c) If no criticality or severity is part of the analysis, the term FMEA is used.

Fault tree analysis (FTA), *n* – A systematic review of a system or product to identify sources of potential failure; particularly useful in safety and reliability analyses; **NOTES**: a) First, a list of potential failure modes is developed. For each, an analysis is conducted to (i) determine the primary causes; (ii) the secondary causes behind the primary causes; and (iii) possibilities to mitigate the primary and the secondary causes; b) The procedure is sometimes referred to as a "top-down" analysis; c) The causes for a top-level event are enumerated through a series of Boolean logic gates.

Hazard analysis, *n* - A fault tree analysis used in medical devices, whereby the top-level event is related to patient safety, operator safety, or an environmental hazard.

Quality assurance, *n* - Planned and systematic activities to provide adequate confidence that requirements for quality will be met.

Quality control, *n* - Operational techniques and activities that are used to fulfill requirements for quality.

Quality management, *n* - All activities of the overall management function that determine the quality policy, objectives and responsibilities, and implement them by means such as quality planning, quality control, quality assurance, and quality improvement within the quality system.

Quality system, *n* - The organizational structure, resources, processes, and procedures needed to implement quality management.

Source of error, *n* – A component of the measurement method, device, or operator practice that creates risk for patients, users, or other individuals.

Source of error matrix, *n* – A generic FMECA diagram prepared for unit-use medical devices.

Trueness, *n* - The closeness of agreement between the average value obtained from a large series of test results and an accepted reference value.

[a] Some of these definitions are found in NCCLS document NRSCL8—*Terminology and Definitions for Use in NCCLS Documents.* For complete definitions and detailed source information, please refer to the most current edition of that document.

Unit-use system, *n* – 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.

4 User-Manufacturer Quality Partnership

The objective of the quality management program is to verify that all system components are performing as specified by the manufacturer and are doing so at a quality level acceptable to the user. The sources of error matrix is the recommended quality tool to be used by manufacturers to identify and lessen potential failure modes and by 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.

4.1 Manufacturer's Responsibility

The "sources of error" matrix can be used as a starting point. The manufacturer's responsibility is to design the system to eliminate or minimize sources of error as much as possible, then to disclose those that remain. Additional sources of error that are not on the matrix may be identified. Analyte-specific, as well as system-specific, sources of error should be included. Once the applicable factors 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 and those risks not mitigated by the manufacturer should be disclosed in the information supplied by the manufacturer. Specific details on quality control as to the level and/or frequency of testing should be provided in the information supplied by the manufacturer.

The following list provides suggested steps for the completion of the "sources of error" matrix:

- Review "sources of error" matrix/checklist (Appendix A).
- Identify applicable failure modes.
- Add other sources of error specific to the analyte/device.
- Determine effects of each failure mode (e.g., negative bias, positive outlier, etc.).
- Determine the clinical significance of each effect.
- Design device to eliminate/minimize risk (i.e., criticality of failure x probability of occurrence).
- Evaluate device to verify 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.

4.2 User's Responsibility

The user has responsibilities to develop a quality management system that is specific to the testing system and the setting in which each device is being used. For the test system to perform within its intended use, performance characteristics, and limitations, the user must follow manufacturer directions. The user bears responsibility for establishment of performance characteristics if deviating from manufacturer instructions.

A quality assurance program elaborates with definitive details how to identify and manage possible sources of error associated with clinical testing. The user is responsible for development of a documented

quality assurance program appropriate for each testing system. The sources of error matrix may be used as a tool to help define a facility's quality assurance (QA) program. The sources of error matrix may be used as a checklist or as a tool to help identify potential failure modes so that they can be addressed by the manufacturer or by the user.

The user should carefully review the manufacturer's instructions for use and identify applicable failure modes that the laboratory's QA program must address. A completed "sources of error" matrix will define all possible sources of error associated with a particular system and how to monitor, detect, and manage (minimize/eliminate) identified sources of error. A separate "source of error" matrix should be completed for each type of unit-use device utilized by each facility.

The following is a step-by-step guide to completing the "sources of error" matrix:

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

(2) Compare the manufacturer's summary of failure modes to the sources of error matrix (Appendix A) information to determine if the manufacturer's information is compatible with the analytical/clinical needs and test setting. Add omitted and additional possible sources of error as they are determined to be relevant for the use and setting.

(3) Complete all matrix columns for all identified sources of error. Identify where additional quality control measures are necessary and how these sources should be managed. 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) Revise, add, delete and/or create QA programs, standard operating procedures, training protocols, and other facility policies as necessary based on the information derived from the completed sources of error matrix.

(5) Implement all applicable quality monitoring (see Section 5.2.6) at the frequencies specified in the "sources of error" matrix.

(6) Periodically review and evaluate the quality management system (QMS) to ensure sources of error are identified and managed at an acceptable rate. Reestablish acceptable quality monitors and frequencies to monitor sources of error to improve outcomes.

5 Description and Use of "Sources of Error" Matrix

5.1 Definition and Purpose

The "sources of error" matrix (see Appendix A) is a table that contains a list of potential failure modes in the preanalytical, analytical, and postanalytical phases of unit-use device testing, causing erroneous results. The chart 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 the “sources of error” matrix is to aid the manufacturer and user in considering and identifying possible sources of error applicable to a particular unit-use test system. Once a source of error is identified, its relevance can be assessed to determine how and at what frequency it will be monitored.

5.2 Contents of Matrix

5.2.1 "Potential Source of Error" Column

This column contains 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.

Appendix B illustrates a sample "sources of error matrix" for a typical unit-use test system. Typically, a specific source of error matrix is a more abbreviated and focused evaluation of the specific system than that which is demonstrated in the appendix.

5.2.1.1 Specimen Collection

Specimen collection applies to possible errors occurring during patient preparation, sample collection, transport, and storage prior to measurement. This includes inappropriate sample selection, (e.g., wrong sample type or presence of known interferents).

5.2.1.2 Sample Presentation

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

5.2.1.3 Instrument/Reagents

Instrument/reagent applies to possible errors occurring during measurement, due to problems with instrument, reagent, or user procedure (e.g., outdated reagent or electromagnetic interference).

5.2.1.4 Results/Readout/Raw Data

Results/readout/raw data applies to potential errors occurring at the conclusion of the measurement phase (e.g., incorrect instrument mode setting or misinterpretation of a visual result by the user).

5.2.1.5 Preliminary Review

Preliminary review applies to potential errors occurring after measurement is complete, while judging validity of the measurement process and results (e.g., failure to recognize alert value or instrument diagnostic/ malfunction warning, or physiologically impossible results).

5.2.1.6 Integration into the Patient Record

Integration into the patient record applies to potential errors occurring during sample result storage and transfer to patient medical records (e.g., transcription mistakes).

5.2.2 Applicability to System (Yes or No)

The identified source of error either applies or does not apply to the unit-use device systems.

5.2.3 Nature of Impact

This is a description of how the result is perturbed or impacted by the sources of error. In the case of a multianalyte test, a pattern may emerge and should be described. (For example, does air contamination of a blood gas sample cause low PCO_2? Does it cause elevated pH? Does it cause biased PO_2?)

5.2.4 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?)

5.2.5 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 unit-use 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.

5.2.6 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. This includes 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.

5.2.7 Frequency of Monitoring

The user is responsible for completing this column to ensure that the source of error is monitored at a frequency which optimizes error detection. The user should consider the nature of the impact of the error and the cost of detection. Additional information on determining the detection and impact of an error can be determined by using a failure mode, effects, and criticality analysis (FMECA). 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 Components of a Quality Management System

The goal of quality management is to prevent and detect problems in the testing cycle.[3] (Please refer to the most current version of NCCLS document HS1— *A Quality System Model for Health Care* for additional information.) The type of quality management that is employed is dependent upon the nature of the error that needs to be detected. The frequency and extent of monitoring should be determined by both the severity of the error, should it occur, and the likelihood that the error will occur. Since the sources of error vary based on the particular unit-use device and how it is applied, the monitoring program must be designed to fit each situation.

6.1 Standard Operating Procedures

Each unit test should have a written procedure which 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. (Please refer to the most current version of NCCLS

document GP2—*Clinical Laboratory Technical Procedure Manuals* for additional information.) The procedure should include the following elements that are applicable to the specific unit-use test:

- 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, troubleshooting, and corrective actions;
- frequency and tolerance of controls, including instructions for corrective action;
- expected values, interpretation of values, definition and handling of alert values;
- procedural notes;
- method limitations;
- references;
- effective date and review schedule;
- distribution; and
- author.

In general, sources of error 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.

6.2 Training and Competency

Operators performing unit-use tests should have training in the systems involved 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 (e.g., 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 each topic depends upon the personnel and the test system being used.

- theory of instrument/device/test system;
- specimen collection/preservation/transport;
- instrument maintenance;
- quality control principles and procedures;
- testing procedure;
- sources and degree of error (preanalytic, analytic, postanalytic); and
- clinical significance.

There are several sources of training available:

- manufacturers via on-site training and telephone 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 of 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; and
- evaluation and documentation of the performance of persons responsible for testing, and providing such documentation to the testing personnel manager.

If a source of operator procedure error has been identified that is not detected by the system, periodic liquid control testing should be included in the evaluation of user competency. The recommended QC scheme/procedure is indicated below.

- Frequent operators (those performing the tests at least once per week) would perform traditional liquid (i.e., not electronic) quality control at least once per week.
- Those operators who perform the tests less frequently (less than once per week) would perform quality control with every day of testing. These recommendations would serve as a starting point for quality control testing frequency and could be modified by each institution based on their data and experience. As quality control testing intervals lengthen, reagent stability should be considered.
- Users should follow the manufacturer's recommendation for periodic liquid QC with a default frequency of no longer than $1/10^{th}$ the labeled stability of a product if the manufacturer does not provide frequency information.
- If secondary storage conditions occur, QC should be run at the manufacturer's recommended interval or approximately midway through the secondary storage interval.
- Unit-use devices have reagent stability of greater than one year; this recommendation means (in practical terms) that testing should be performed no less than approximately once every month.

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.

6.3 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 most recent version of GP29—*Assessment of Laboratory Tests When Proficiency Testing is Not Available*.)

At a minimum, process controls should be performed as specified by the manufacturer. 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:

- anticipated failures and likelihood of occurrence;
- available control materials;
- operator experience with the test system;
- institutional experience with the test system;
- the medical impact of the test results; and
- occurrence of improper handling (e.g., dropped device, excess heat, etc.).

6.3.1 Acceptance Testing

When there is a change in the test system (e.g., 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 must be done to ensure that a problem, if caused by the change, will be detected. The more precise an assay, the fewer replicates that are necessary to detect a problem. The laboratory director determines the maximum acceptable shift in the results (the effect). For example, if the assay is so precise that the standard deviation or coefficient of variation is only one-third of the effect, then only triplicate measurements need to be made for acceptance testing. (Please refer to the most current version of NCCLS document EP7—*Interference Testing in Clinical Chemistry*.) This testing should be done with two levels of control material or consistent with manufacturer's recommendations. Patient samples may be used for acceptance testing, particularly if the test method is subject to a matrix effect.

6.3.2 Periodic Quality Control (Traditional, Liquid Quality Control)

Some form of ongoing quality control should be performed periodically with the goals of assessing system stability and operator competency (see Section 6.2). This ongoing quality control may involve testing of control material, testing of split patient samples, and/or testing of external proficiency samples.

6.3.3 Split Samples

The trueness of unit-use devices is initially established by recovery and interference studies, and by comparison to a method that is traceable to a recognized standard or to another trueness basis. These tests are performed by the manufacturer as a part of design control and government submission processes. Periodic comparison studies ensure that systematic errors do 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 a measurement error cannot be identified from available control data. The frequency of split sampling should be established by each institution.

6.3.4 Other Forms of Quality Control

6.3.4.1 Electronic QC

Electronic quality control (EQC) devices are test simulators that monitor and/or report on the function of the test system. Some EQC 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 which are tested by the EQC. The user should use this information to evaluate any additional errors that need to be tested for in the entire testing process; and add them to the QC scheme. When appropriate, if the test system and alternate QC are separate components, the above mentioned should prevail.

If the components are integrated, then follow instructions from the second paragraph, above.

6.3.5 Preventive Maintenance

Single-unit devices that are self-contained (e.g., pregnancy tests) have no maintenance required by the tester. Single-unit devices or cartridges used in combination with other devices or readers, such as reflectance meters, should be maintained according to the manufacturer's procedures. Examples of preventive maintenance may include, but are not limited to the following:

- periodic cleaning;
- frequent pipet checks;
- part replacements (e.g., electrical, mechanical); and
- calibration.

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

6.3.6 Proficiency Testing

All types of unit-use testing should be enrolled in a proficiency testing program if one is available. Alternatively, split patient samples may be used in a similar fashion. By treating such specimens similarly to routine patient samples, proficiency samples may provide an overall assessment of the testing process.

6.3.7 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.

6.3.8 Environmental Monitoring

Environmental monitoring encompasses all conditions surrounding the use of a device/method which ultimately determines test performance. It is essential to recognize, monitor, and establish limits on

environmental monitoring 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 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 to enable them to correct design deficiencies and support continuous product development.

6.3.9 Clinical Surveillance

Monitoring of 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 traditional quality control procedures. Healthcare workers should be encouraged to report test discrepancies to the laboratory director for further investigation.

6.4 Error and Incident Reporting[4,5]

Reporting and subsequent analysis of variations, errors, and problems in the testing cycle can reveal process problems that are difficult to detect by other means. The mechanism for reporting these errors or problems should be simple. Reporting of these process variations should be encouraged as a means to improve processes rather than as a means to affix blame. Reports should be analyzed from a systems perspective to see if changes can be made to prevent errors or "mistake-proof" the process.

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

6.5 Auditing

The purpose of periodic auditing is a search for concealed or not immediately apparent problems in the testing cycle that need improvement or corrective action. Most often, this quality monitoring method is used for record review, such as QC records and records of test results. 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 reveal whether or not a problem exists, some sense of the frequency of the problem, and reasons for problem occurrence. Audits may be performed on a regular, scheduled basis or may be initiated in response to a reported problem. 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 action should be undertaken. Solutions should ultimately be assessed for effectiveness in improving performance.

References

[1] ANSI/ASQC Q90004-1-1994. Quality Management and Quality System Elements - Guidelines.

[2] MIL-STD 1629A. United States Military. *Procedures for Performing a Failure Mode, Effects, and Criticality Analysis.* Philadelphia, PA: Document Automation and Production Service; 1980.

[3] ISO 8402:1994. Quality management and quality assurance—vocabulary. Geneva, Switzerland: International Organization for Standardization; 1994.

[4] Motschman TL, Santrach PJ, Moore SB. Error/incident management and its practical application. In: Duckett JB, Woods LL, Santrach PJ, eds. *Quality in Action*. Bethesda, MD: American Association of Blood Banks; 1996.

[5] ISO 13485:1996. Quality systems – medical devices – particular requirements for the application of ISO 9001. Geneva, Switzerland: International Organization for Standardization; 1996.

Additional Reference

ISO 14971:2000. Medical devices—application of risk management to medical devices. Geneva, Switzerland: International Organization for Standardization; 2000.

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

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
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					
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					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
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 Dilute Urine					
1.6.6 Dehydration/Hemodilution					
1.6.7 Shock					
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					
2.2.5 Improper Handling of Stored Specimens					
2.3 Long Delay from Collection to Analysis					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
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					
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					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
3.3 Improper Reagent Shipment					
3.4 Improper Reagent Storage					
3.5 Incorrectly Prepared Reagents					
3.6 Incorrect Use of Reagents					
3.7 Reagent Contamination					
3.8 Deterioration of Reagent Lots Over Time					
3.9 Lot-to-Lot Variability					
3.10 Sample-Related Reagent Failure					
3.10.1 Interfering Substances					
3.10.2 Excessive Analyte Concentrate (hook or prozone effects)					
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					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
3.16 Poor Precision					
3.17 Poor Trueness /Correlation with Laboratory Method					
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					
3.22.2 Instrument Repair/Maintenance					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
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					
4.1.1 Color					
4.1.2 Number					
4.2 Incorrect Setting for Units of Measure					
4.3 Incorrect Mode Setting					
4.3.1 Neonatal vs. Whole Blood vs. Plasma					
4.3.2 Control vs. Patient Sample					
4.3.3 Incorrect Programming					
4.4 Accidental Loss of Data					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
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					
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					

Appendix A. (Continued)

Potential Sources of Error	Applicable Y/N?	Nature of Impact	Training/Laboratory Procedure Requirements	Applicable Quality Monitoring	Frequency of Monitoring
6.5 No Aids for Clinical Interpretation					
6.5.1 Reference Range					
6.5.2 Alert Limits					
6.5.3 Previous Patient Results					
6.6 Inconsistent Location of Reporting/Result Difficult to Find in Chart					
6.7 Result Temporarily Unavailable Due to Reporting Mechanism (computer delay)					

Appendix B. Example of an Applicable Error Summary Sheet

Source of Error	Method of Control
Sample Presentation	
Incorrect sample presented (something other than serum)	Training
Incorrect sample handling/processing (incorrect storage, particulate matter, failure to dilute)	Training; reader flags; appearance of membrane; controls out of range
Incorrect sample preparation (mistake in mixing with pretreatment solution, incorrect preparation of control samples)	Controls out of range; visual appearance of assay zones
Wrong sample volume	Controls out of range
Incorrect introduction of sample to device (dropwise vs. bolus, inadequate distribution on membrane)	Controls out of range; visual appearance of assay zones
Reagents	
Wrong temperature	Controls out of range
Contaminated	Appearance of membrane; controls out of limits range
Improper storage	Controls out of range
Incorrect use of reagents (mixing different lots of reagents)	Controls out of range; appearance of membrane
Deterioration of reagents over time	Controls out of range; trend charts
Lot-to-lot reagent variability	Trend charts
Interfering substance in sample	Internal controls out of range
Heterophilic sample	Internal controls out of range
Testing Environment	
Adverse laboratory temperature	Controls out of range
Adverse air flow	Controls out of range

Appendix B. (Continued)

Source of Error	Method of Control
Performance	
Improper calibration	Controls out of range
Poor precision	Controls out of range
Poor trueness	Trend charts
Incorrect value entered for high calibrator	Controls out of range
Technique	
Incorrect assay technique	Controls out of range
Inadequate technician training	Training
Sample carryover (failure to change pipette tip between samples)	Training
Reusing cylinders	Training
Instrument (Reader)	
Reader not calibrated before use	Controls out of range
Compromised optics (scratched, dirty, fogged)	Controls out of range
Power supply failure	Message given on reader
Compromised calibration cylinder (dirty, scratched)	Controls out of range
Instrument maintenance (broken door)	Controls out of range
Incorrect instrument use (opening door too soon, trauma to reader)	Controls out of range

NCCLS consensus procedures include an appeals process that is described in detail in Section 9 of the Administrative Procedures. For further information contact the Executive Offices or visit our website at www.nccls.org.

Summary of Comments and Subcommittee Responses

EP18-P: *Quality Management for Unit-Use Testing; Proposed Guideline*

Foreword

1. At the end of the Foreword, the committee asks whether EP18 should be broadened in scope to cover process control issues for *in vitro* devices in general. While the ultimate goals for quality management are the same for unit-use and multiuse systems, we believe that the seminal concept in EP18 is that the unique characteristics of unit-use systems require a different approach to quality management, including a broadened use of acceptance testing and a more limited role for traditional liquid quality control. At least until these concepts are digested, accepted, and possibly developed more fully, EP18 should remain focused on quality management for unit-use systems. Possibly a new, upper-level or broad-based guideline could be developed to include all aspects of statistical process control and error reduction.

- **The reviewer's comments are acknowledged, but the subcommittee is not entirely in agreement. The committee has incorporated the following changes to the cited paragraph:**

  "The subcommittee has limited the discussions within this document to unit-use test systems. While it is the committee's expectation that the guideline will be used primarily to address the issues around point-of-care (POC) devices that utilize single-use disposables, EP18 should not be considered as exclusive to unit-use systems. However, as these concepts are further refined with actual experience, an additional, perhaps broader-based guideline could be undertaken to address multiuse systems and include all aspects of statistical process control and error reduction."

Introduction

2. The presentation of the concept of acceptance sampling is unclear, because the introduction appears to be referring only to acceptance sampling for attributes while Section 6.3.1 appears to be referring only to acceptance sampling for variables. The difference between the two is paramount, since acceptance sampling for attributes occurring at low frequency (such as point defects in manufacturing) is highly impractical for end users and, therefore, must be the responsibility of the manufacturer, while acceptance sampling for variables may be quite practical for end users, as described in Section 6.3.1.

- **The subcommittee agrees with this distinction between the two kinds of acceptance sampling. The following modification to the third bullet in the Introduction has been made:**

  "It is impractical to consume large numbers of unit-use systems needed to detect the low rate of defects found in properly designed, manufactured, shipped, and stored unit-use systems. A multitier approach to quality control and quality assurance has been proposed within this document. This approach provides the user with the means to inspect goods upon arrival *through the use of limited acceptance sampling to detect variables such as shipping conditions, lot changes, and new operators*."

3. In the Introduction (page 1, last paragraph) the sources of error matrix is described as a "partial list of potential failure modes" while in Section 5.1 it is described as a "comprehensive list." Both adjectives could be dropped, since the list is further qualified in both places.

- **The subcommittee agrees with the comment. The suggested revisions have been incorporated.**

Section 4.1

4. Manufacturers do embed most, if not all, information needed to create an error matrix in manuals, package inserts, and end-user training. This information should be "clearly and unambiguously disclosed in the product labeling/instructions for use." Unfortunately, the competitive nature of our business makes us, the manufacturers, reluctant to point out a source of error that might appear to be a weakness in our systems. Somehow we have to get a consensus agreement to include an error matrix in our labeling, and EP18 is a very positive start.

- **The subcommittee agrees with the comment and believes that manufacturers will see the value of "truth in labeling" and be forthcoming with information for the device operators that will allow them to focus on error identification and reduction/elimination.**

Section 4.2

5. Number 6: Add to the end of the last sentence, "and efficiency."

- **The subcommittee appreciates the comment; however, inclusion of this recommendation is outside the goal and scope of the guideline.**

Section 5.1

6. Change "unexpected results" to "erroneous results," since unexpected results may indeed reflect a patient's true condition.

- **The subcommittee agrees with the comment. The suggested revision has been incorporated.**

Section 5.2.4

7. Device Capabilities: This paragraph does not include more sophisticated capabilities. An additional example could be added, such as: Does the device have on-line quality checks for adverse operating conditions, operator errors, and reagents and analyzers that are performing outside of specifications with clearly displayed descriptions and resolutions to the detected errors?

- **The examples used were selected to simply illustrate the definition of device capabilities; hence, sophisticated device examples are not included. Many other examples could be used but are not felt to be necessary for clarification.**

Section 5.2.7

8. Frequency of Monitoring: After the first sentence add a sentence to convey the concept that the nature of the impact of error and the cost of detection should be considered. If the nature of the impact is minor, an attempt to detect the error 100% of the time would probably be inefficient.

- **The subcommittee agrees with the comment. The following text has been incorporated:**

"The user should consider the nature of the impact of the error and the cost of detection. Additional information on determining the detection and impact of an error can be determined by using a failure mode, effects, and criticality analysis (FMECA)."

Section 6.2

9. We have difficulty with the emphasis put on quality control sample testing as the best way to assess the competency of end users. One reason for this is that our analyzer incorporates real-time quality checks that detect operator errors and incorporates real-time operator error reports. We are very much in agreement that operator competency must be assessed periodically, but we disagree that the best way to accomplish this is by using traditional quality control schemes. We would appreciate the committee's consideration of the following changes to Section 6.2.

a. Place the paragraph beginning "Evaluation of the competency of all testing personnel and ensuring the staff's continuing competency…" before the paragraph beginning "Frequent operators (those performing the tests at least once per week)…"

- **The subcommittee agrees with the comment. The suggested revision has been incorporated.**

b. In the above paragraph, change the wording of the sentence, "The procedures for evaluation of the competency of the staff should include, but are not limited to, the following:" to "Evaluation of the competency of the staff could include, among other procedures, the following:"

- **The subcommittee agrees with the comment. The suggested revision has been incorporated.**

c. Add before the paragraph beginning "Frequent operators (those performing the tests at least once per week)…" the following sentence, " If a source of operator procedure error has been identified that is not detected by the system, periodic liquid control testing should be included in the evaluation of user competency."

(Even for a system susceptible to operator error, the use of liquid controls is problematic. Blood gas controls require very different handling from patient samples, and they do not assess preanalytical error which for unit-use tests is the more likely source of error.)

- **The subcommittee agrees with the comment. The suggested revision has been incorporated.**

d. Remove from the above paragraph on operator competency the information about reagent stability beginning with the sentence, "As quality control testing intervals lengthen, reagent stability should be considered." Place this information in Section 6.3.2 and title this section "Traditional, Liquid Quality Control." Then delete the reference to operator competence in this section, since it is covered in Section 6.2. If this change is made, references to split patient samples and external proficiency samples should also be deleted from this section, since they are covered in Sections 6.3.3 and 6.3.6.

- **The subcommittee appreciates the comments. However, the subcommittee believes the current format is clear.**

e. $1/10^{th}$ may be too frequent if the user has established that the system/test unit is very stable. I don't like the inclusion of a specific frequency interval. Performing QC frequently increases costs but usually does not improve the quality of the final test result.

- **The text has been modified to suggest that users follow the manufacturer's recommendation for periodic liquid QC with a default frequency of no longer than $1/10^{th}$ the labeled stability of a product if the manufacturer does not provide frequency information. If secondary storage**

conditions occur, QC should be run at the manufacturer's recommended interval or approximately midway through the secondary storage interval.

Section 6.3

10. We have no essential problem with the recommendation that the quality control testing interval should be no longer than 1/10th the stability stated by the manufacturer. However, the rational for this recommendation appears to be no more absolute, in a statistical sense, than the 24-hour limit imposed on traditional QC programs and could eventually be outdated by ongoing improvements in systems, reagents, and error detection software. While gaining a new consensus for an NCCLS recommendation is relatively straightforward, changing a recommendation once it is incorporated into a CLIA standard is not. To avoid this, the recommendation could be to follow the manufacturer's recommendation for periodic liquid QC with a default frequency of no longer than 1/10th the labeled stability of a product if the manufacturer does not provide frequency information. It is the manufacturer's responsibility to ensure that the recommended frequency is suitable, based on the stability and quality system of the device, to assure the reliability of results.

    In addition, we would not want to see the 1/10th QC limit applied to the two-week room temperature shelf life. Again, we appreciate the fact that a guideline must be generic enough to cover all systems in use now and in the near future and that it cannot address individual systems. However, since to be most affective the quality system must be tailored to the characteristics of the individual system, the manufacturer's recommendations should override generic recommendations.

- **See response to Comment 9(e).**

11. For consistency, the terms "dual split patient samples" and "known patient samples" should be changed to "split patient samples."

- **The subcommittee agrees with the comment. The suggested revision has been incorporated.**

Section 6.3.4

12. Add paragraph 6.3.4.2, Automated Real-time (or On-line) Quality Checks, to address the extent to which a system's ability to detect environmental, operator, unit-use device, and analyzer errors influences the frequency at which liquid control samples need to be tested. A recommendation could be made to validate the manufacturer's claims to detect these errors. Validation could be a period during which liquid control samples are tested on a frequent basis with results examined for shifts, drifts, or errors not detected by the system. Validation could also include specific challenges of the detection software, such as underfilling a cartridge or using an analyzer outside its specified operating conditions.

    This paragraph would compliment and expand upon paragraph 5.2.4, Device Capabilities, under Contents of Matrix, which does not address the capabilities of more sophisticated devices.

- **The subcommittee believes the underlying concern has been appropriately addressed, as NCCLS document EP18—*Quality Management for Unit-Use Testing* provides users with a reasonable approach for monitoring ongoing performance of unit-use devices. Additional validation of specific manufacturer's claims is beyond the scope of the document.**

Summary of Delegate Comments and Subcommittee Responses

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

General

1. Our concerns revolve around the information that is requested for the risk tables. It is our position that much of the requested information is proprietary in nature. For each of our products, we complete a risk assessment, as required by QSR. Identified risks are mitigated by various methods. Residual risks are carefully considered for acceptability. It is our responsibility to determine what level of residual risk is acceptable to our company as liability. We believe that, if a user follows our instructions for use as written, than any risks associated with the use of the product are minimal. Users must assess their own levels of risk if they deviate from our instructions. Although we agree in principle that users may wish to understand areas where residual risk could be present, we believe that this kind of information would be inappropriately exploited by marketing representatives, thus leading to gross levels of misunderstanding by the users. We support ISO 15198 "Clinical Laboratory Medicine—Validation of manufacturer's recommendations for user quality control." This document also leads the user through an assessment of a product, considering aspects such as pre-examination errors, examination errors such as sample handling, QC, calibration, maintenance, stability, and post examination errors. The document helps the user develop a validation plan and protocol. This document is appropriate, since it considers products from the user's perspective, rather than the manufacturer's. Both ISO 15198 and NCCLS EP18-A address similar aspects, we support the use of the ISO document.

- **It is not the intent of this guideline to either compel or suggest that the manufacturer disclose proprietary information. This is left to the discretion of the individual company. The suggestion here is that the manufacturer inform the user/operator of any potential error, and provide information as to how the manufacturer has mitigated the risk of the error. In some instances, the user/operator may not be satisfied with the information contained in the package insert or other information generally available from the manufacturer. Thus, the user/operator may request additional information to help determine if additional testing or monitoring is necessary locally. It is then left up to the manufacturer whether or not to provide the requested information. As is stated above "Users must assess their own levels of risk if they deviate from our instructions." Indeed, users must assess their own level of risk even when not deviating from the manufacturer's instructions and some users/operators may request additional information on the test system to assess this level.**

2. We disagree with this document for a number of reasons, including the intrusiveness into company confidential data. The document, as proposed, offers little value to most users but creates an onerous, and in our opinion, an unnecessary amount of data to be provided by IVD manufacturers. We firmly believe this information proposed to be shared with users, is redundant to extensive prior regulatory findings. The subcommittee should also be aware of widespread rejection of this document by other IVD manufacturers. We recommend this document be sent back to the subcommittee and that the document be rewritten with input from users, regulatory, and industry representatives.

- **See response to Comment 1. The NCCLS process is especially suited for developing guidelines because of its ability to mobilize specific expertise and its adherence to balanced participation. Experts from NCCLS's core constituencies (i.e., government, professions, and industry) were included as members of the subcommittee. It is the belief of the subcommittee that, based on the number and contents of the comments received to date, there is not a "widespread rejection of this document by other IVD manufacturers."**

Section 4.1

3. The introduction of the document states the following, “Any remaining failure modes shall be clearly and unambiguously disclosed in the product labeling/instructions for use.” We support this idea. However, it is problematic for a manufacturer to supply the entire Appendix A as indicated in the document. This information is provided to government agencies that request it for a product submission and approval process. If risk is determined to offset the benefit of putting the product on the market, the product is not approved for sale. This information would be too lengthy to include in product information for the majority of devices. The risk analysis is prepared by manufacturers as a requirement of quality system and is open to review by the regulatory agencies that require it. It is important to focus information for use on details that are important to the user, not provide extraneous information that is not helpful. For this reason, it is suggested that details as to the errors that are not mitigated by the design of the product or the manufacturing process be made available in the information supplied by the manufacturer with suggested recommendations. Also, disclosure should include special warnings or precautions of which the user should be made of aware.

   Therefore, we recommend deleting the sentence that reads, "This information should then be summarized for the user (see Table 1)" and replacing it with the following sentence, “The risk analysis, which may include the items listed in Appendix A should be analyzed and those risks not mitigated by the manufacturer shall be disclosed in the information supplied by the manufacturer. Specific details on QC as to the level and/or frequency of testing should be provided in the information supplied by the manufacturer.”

- **The text has been modified as suggested.**

4. For the same reasons stated above in Comment 2, we recommend changing the final row in Table 1 to read as follows, "Provide information and recommendations in product labeling information supplied by the manufacturer. Manufacturers are encouraged to disclose significant sources of error and recommend methods of control following this (EP18) guideline.

- **The text has been modified as suggested.**

Section 4.2

5. The user should not expect that the manufacturer be able to provide a complete risk analysis. These documents are very lengthy and are too extensive to publish and keep current to all users. The essential safety information, however, is disclosed in the information supplied by the manufacturer as a requirement of most government agencies for approval to market the product. This safety information is diligently reviewed by government agencies before allowing the product on the market. It is important that the user be provided the recommendations for user QC that then covers the errors that are not mitigated in other ways. The precautions and warnings section of current product information supplies this information. This allows the user to complete the review of Appendix A and put the appropriate quality assurance system in place to mitigate the possible sources of errors disclosed in the information for use.

   Therefore, we recommend deleting the sentence that reads, “The sources of error matrix may be used as a tool to help define a facility’s quality assurance (QA) program” and replacing it with the following, “The manufacturer’s recommendations on appropriate QC provide a basis for the user to define a facility’s quality assurance program.”

- **The current language has been maintained. The user’s quality assurance program should not be based solely on manufacturer’s QC recommendations. Users may also need to consider other sources of error not mitigated by product design or QC, particularly preanalytical and**

postanalytical issues that may be institution specific. The manufacturer chooses how much of the matrix to reveal; this guideline does not infer complete disclosure of all items in the matrix. The user may also need to know more than just the QC recommendations, as they may not cover all preanalytical and postanalytical concerns.

6. If the manufacturer is following this document, the information regarding error reduction will be provided in the information for use. Therefore, we recommend deleting the sentence that reads, "If the manufacturer has not adequately described potential failure modes in its labeling, or recommended ways to control them, then the customer should contact the manufacturer and ask for the information."

- **The subcommittee believes this to be an implied conclusion. However, the text has been revised to read, "If the customer needs additional information and recommendations, they should contact the manufacturer."**

7. All safety information that the manufacturers supply is furnished in the information that is supplied with the product. It is important to the manufacturer that every customer receives this important information. The manufacturer cannot set up a system pertaining to safety of the device, which provides certain information to some users, while others do not receive the information. Therefore, we recommend deleting the sentence that reads, "Obtain supporting data as needed from the manufacturer."

- **Some users are more diligent in managing their quality systems than others. Therefore, some will require the information while others won't. The subcommittee believes there is no additional requirement or implied obligation on the part of the manufacturer by inclusion of this sentence.**

Section 5.2.1

8. More clarity is needed between the use of Appendix A versus Appendix B. Is Appendix B something that would be used by manufacturer to provide the information in the information for use, or the error matrix that the user would complete?

- **Appendix A is intended to provided manufacturers and users with a suggested checklist of potential sources of error and is not intended to be comprehensive. Appendix B is an example of what a test system matrix might look like when completed by either the manufacturer or the user. Appendix B is provided as an example of a sources of error matrix when using Appendix A as a "filter."**

Section 6.1

9. It is not always a requirement, that a separate SOP be developed for certain tests. After first sentence, we recommend adding the following statement, "This may be in the form of the manufacturer's instructions for use." Addition of the recommended statement allows for this provision.

- **Use of the manufacturer's instructions for use does not take into account local procedures regarding preanalytical and postanalytical aspects of testing. The subcommittee does not encourage the use of inserts (i.e., manufacturer's instructions for use) *only*, as the scope of this document extends beyond the analytical phase. Additionally, such a recommendation is contrary to most accreditation requirements. Therefore, the text has been maintained.**

Section 6.2

10. Some systems do not require formal training by a laboratorian or the manufacturer. Sample devices are tested by the manufacturer before being marketed to assure the intended user can operate the system by reading the instructions provided with the device. Other devices are more complicated and require formal training. The suggested change allows for a continuum of complexity of devices providing the user with necessary training, but does restrict new technology.

    Therefore, we recommend changing the first sentence of the section to read, "Operators performing simple unit-use tests may have trained themselves using the information supplied with the product, (for example, in the United States, waived tests). For more complex tests, formal training may be required for operators until they have satisfactorily demonstrated proficiency for each procedure."

- **The subcommittee disagrees with the recommended text change since it ignores pre- and postanalytical aspects of testing at the local site. Additionally, if there is more than one individual performing the same test, there needs to be some check on consistency of performance of all aspects of testing, not just quality control. The phrase "formal training" has been changed to "training," to provide more flexibility for the user.**

11. Some systems are simple and easy to use and should not have the added burden put on the user when there is no benefit to having "formal training." Testing is also done by the manufacturer to allow the information supplied to be the only training that is necessary. This testing is documented in the government clearance application submission and the product is approved/cleared with this intended purpose. Therefore, we recommend adding the following as a bullet in the third paragraph: "reading the information supplied by the manufacturer may be sufficient for simple, easy to use devices."

- **Manufacturer's information may not take into consideration the preanalytical and postanalytical aspects of the test that may be unique to that institution or testing site. Therefore, the text has been maintained.**

12. Change the first sentence in the fifth paragraph to read, "Individuals must demonstrate competency in performing the procedure, and evidence of this competency must be documented, if required by regulatory requirements."

- **This guideline is designed to aid in the development and promotion of a quality system approach to testing (not necessarily just to meet regulatory requirements). Therefore, the text has been maintained.**

13. Modify the second sentence of paragraph 6 as follows:

    "An example of a proposed QC scheme/procedure is indicated below:

    - Frequent operators (those performing the test at least once per week)…
    - Those operators who perform the test less frequently…
    - Users should follow the manufacturer's recommendations for periodic….
    - If secondary storage conditions occur…
    - Unit use devices have reagent stability of greater than one year…"

- **The subcommittee agrees with the commenter and has incorporated this change. Also, the first sentence has been modified to read, "The recommended QC scheme/procedure is indicated below."**

Section 6.3.1

14. This acceptance testing seems only to apply to quantitative assays. It is not necessary for a user to carry out this extensive testing for unit use devices since the manufacturer specifications for lot release is set to test for this type of change. If the product being manufactured does not meet specification and therefore not meet claims stated in the information supplied by the manufacturer, then that lot is rejected and does not ship to the end user.

    Therefore, we recommend modifying the first sentence to read, "When there is a change in a quantitative test system (e.g., a shift in standardization, a new environment that has not previously been validated by the manufacturer, or a new test operator)…"

- **The text has been maintained. This section addresses any type of testing (i.e., quantitative or qualitative—although, a potential problem is perhaps easier to detect in a quantitative test). This section deals with acceptance testing after a device has passed the manufacturer's quality assurance testing process and is designed to help determine when a product may have been stressed beyond its limits during shipment to the end user.**

15. The manufacturer is required to set specifications for release of product lots as a requirement of a quality system. This testing allows for product that will meet published claims throughout the expiration date to be approved for shipping to users. All other product that falls outside these specifications is rejected and not allowed to ship to the end user. It is redundant and expensive to have the user retest product to this extent. The user should understand what the risk is in receiving product and do testing that is in alignment with the quality goals.

    We recommend deleting the sentence that reads, "For example, if the assay is so precise that the standard deviation or coefficient of variation is only one-third…NCCLS document EP7-Interference Testing in Clinical Chemistry)," and modifying the subsequent sentence to read, "This testing should be done consistent with manufacturer's recommendations."

- **The manufacturer does not necessarily supply recommendations regarding acceptance testing. Therefore, the sentence has been maintained.**

Section 6.3.3

16. It is important to make it clear to the user that it is not expected or anticipated that these tests would be repeated in each laboratory or at each site performing the test. We recommend modifying the first sentence to read, "The trueness of unit-use devices is initially established by recovery and interference studies and by comparison to a method that is traceable to a recognized standard or to another trueness basis. These tests are performed by the manufacturer as part of design control and government submission processes."

- **The text has been modified as suggested.**

Section 6.3.4.1

17. Delete the sentences that read, "EQC devices specifically monitor the instrument only, since the disposable portion of the test system is a single-use item and cannot be run simultaneously with the EQC device. In these situations, an additional (non-electronic) quality control material should be tested at specific intervals to test the device and disposable portion together." These sentences as written could limit future technology advances in electronic QC. These statements should be removed in order to avoid this unintended restriction on advances in technology.

Then, add the following sentence after the first paragraph, "When a device is equipped with electronic QC, the manufacturer should explain the parts of the device which are tested by the EQC and the user should take this information and evaluate what additional errors need to be tested for the entire testing process and add these to the QC schemes."

It could be added, "When appropriate, if the test system and alternate QC are separate components the above method should prevail. If the components are integrated, then follow the second paragraph instructions.

- **The text has been modified as suggested.**

Related NCCLS Publications*

AST2-A **Point-of-Care *In Vitro* Diagnostic (IVD) Testing; Approved Guideline (1999).** This document provides users of *in vitro* diagnostic devices outside the clinical laboratory with the guidance they need to produce reliable results comparable to those obtained in the clinical laboratory.

AST4-A **Blood Glucose Testing in Settings Without Laboratory Support; Approved Guideline (1999).** This document provides recommendations for personnel performing blood glucose testing at sites outside the traditional clinical laboratory, addressing test performance, quality control, personnel training, and administrative responsibilities.

C24-A2 **Statistical Quality Control for Quantitative Measurements: Principles and Definitions; Approved Guideline—Second Edition (1999).** This guideline provides definitions of analytical intervals, plans for quality control procedures, and guidance for quality control applications.

C30-A **Ancillary (Bedside) Blood Glucose Testing in Acute and Chronic Care Facilities; Approved Guideline (1994).** This document offers guidelines for performance of bedside blood glucose testing with emphasis on quality control, training, and administrative responsibility.

EP7-A **Interference Testing in Clinical Chemistry; Approved Guideline (2002).** This guideline provides background information and procedures for characterizing the effects of interfering substances on test results.

GP2-A4 **Clinical Laboratory Technical Procedure Manuals; Approved Guideline—Fourth Edition (2002).** This document provides guidance on development, review, approval, management, and use of policy, process, and procedure documents in the laboratory testing community.

GP21-A **Training Verification for Laboratory Personnel; Approved Guideline (1995).** This document provides background and recommends an infrastructure for developing a training verification program that meets quality/regulatory objectives.

NRSCL8-A **Terminology and Definitions for Use in NCCLS Documents; Approved Standard (1998).** This document provides standard definitions for use in NCCLS standards and guidelines, and for submitting candidate reference methods and materials to the National Reference System for the Clinical Laboratory (NRSCL).

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

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NCCLS ▾ 940 West Valley Road ▾ Suite 1400 ▾ Wayne, PA 19087 ▾ USA ▾ PHONE 610.688.0100
FAX 610.688.0700 ▾ E-MAIL: exoffice@nccls.org ▾ WEBSITE: www.nccls.org ▾ ISBN 1-56238-481-3