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Quality Management

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OBJECTIVES

To understand the three phases of the total testing process

To understand factors affecting quality of test ordering, specimen collection, and patient satisfaction

To understand basic statistical processes involved in monitoring analytical performance

To understand factors affecting test turnaround time

To understand the role of corrected and incomplete reports in quality management

To understand systems for document control

Quality has to be caused, not controlled.

Philip Crosby, Reflections on Quality

Quality management is a system for continuously analyzing, improving, and reexamining resources, processes, and services within an organization (7, 25, 34, 36, 43, 92, 94, 98, 127). This is accomplished by defining quality indicators that are measured and analyzed either over time or compared to similar or identical indicators from other departments or organizations (benchmarking) (100). The primary objective of quality management is to achieve the best possible outcome. Quality indicators provide information on which to base strategies for improvement, and quality is achieved by reducing variability by standardizing these processes across the organization. Managing the development and implementation of a quality program requires a global understanding of the various resources, processes, and outcomes associated with laboratory medicine as well as healthcare systems and their regulatory environment in general (32).

The design of a quality management system depends in large part on expected outcomes. For example, processes involving identification of patient specimens for blood transfusion purposes are much more rigorous than processes for identifying patient specimens for general chemistry testing because the possible risk of a poor outcome from a misidentified specimen is substantially higher for the former (72). Fortunately, poor outcomes from laboratory errors are uncommon. The frequency of laboratory mistakes is estimated to be about 1 per 1,000 patient visits in which laboratory testing is performed. Of these errors, only about a quarter of mistakes are judged to have any impact on patient management, and very few are associated with any significant adverse patient outcome (24, 87). In 2005 a 5-week prospective study of patient and

specimen identification errors at 120 (primarily hospital) laboratories documented 345 adverse events arising from 6,100 identification errors (126). More than 70% of the adverse events resulted in significant patient inconveniences with no known change in treatment or outcome.

Developing an effective quality management program is challenging because the goal of the program (good outcomes) is often difficult to quantify and may involve processes that are not directly under the laboratory manager's control (73). In this context, quality assessment of laboratory medicine should be viewed as part of the organization's total quality plan. The "total testing process" is a concept that provides a comprehensive working model for evaluating the components of the laboratory's quality management plan as an interdependent component of the organization's total quality improvement program (54, 84, 103, 104, 135).

The total testing process consists of three phases. The first phase, the preanalytical phase, involves all the various processes and resources that precede the measuring step. This phase includes proper ordering and test selection by the clinician, patient preparation, specimen collection, identification, transport and/or storage, and premeasurement laboratory processing.

The second phase, the analytical phase, involves managing the reliability of instruments and reagents used for measuring patient specimens and obtaining test results. This phase relies heavily on statistical quality control processes to reduce errors and variation in test measurements. Quality management of the analytical phase is the most standardized and regulated and has therefore received the most attention. The fewest errors occur during this part of the testing cycle. For example, various studies have shown that only 13 to 32% of laboratory errors are due to analytical problems (9). Howanitz et al. (51) have suggested that the heavy focus on laboratory quality control processes has diverted attention and resources away from other equally important quality objectives associated with the pre- and postanalytical phases of testing.

The last phase, postanalytical, involves reporting, interpretation, and clinical use of test results. Application of different quality management processes may involve one or a combination of all three phases. For example, turnaround time and examination of reasons for corrected reports are important quality indicators that may cross over any or all phases of the testing process.

The College of American Pathologists (CAP) (http://www.cap.org) provides numerous management tools to assist laboratories with quality improvement. Two in particular, the Q-Probes and Q-Tracks programs, focus on pre- and postanalytical phases of the testing process (100, 138). Several standardized monitors are provided each year to participants. The Q-Probes program provides a series of cross-sectional quality assurance studies with peer evaluations, while the Q-Tracks program provides continuous quality monitors for tracking changes over time. These programs have substantial value for benchmarking performance and tracking improvement. Table 21.1 shows the 2011 Q-Probes and Q-Tracks monitors. A broad range of Q-Probes studies from the last 15 years is available from the CAP for use by laboratories. These predesigned quality assurance studies are linked with historical data for benchmarking performance and can be a useful supplement to a laboratory's quality program.

Organizational structure, personnel information, and utilization management as well as laboratory safety are important components of the total quality management plan and are discussed in other chapters. In addition, many of the laboratory's quality management procedures conducted in clinical laboratories today have been mandated by regulatory and accreditation requirements. Participating in on-site laboratory inspections and appropriate external proficiency programs is required to comply with government regulations (see chapter 5, this volume).

Quality Management of Preanalytical Processes

Even the most accurate measurement using the most up-to-date technology by a highly trained technologist may cause an untoward clinical outcome if the wrong test is ordered or the specimen is compromised prior to analysis (28, 67, 68, 95, 116). The preanalytical phase of the testing cycle is complex and is prone to the most variation and the highest proportion of errors (24, 64, 110). For example, one study uncovered only 0.47% erroneous results arising from 40,490 stat tests performed for critical-care patients. Of these erroneous results, 68% occurred during the preanalytical phase of testing, compared to 13% of errors during the analytical phase and 18% in the postanalytical phase. About one-quarter of all erroneous results led to unnecessary additional testing or therapy (91).

Test Selection and Ordering

The first step in the testing process occurs at the moment of test selection. While the majority of laboratory testing is ordered by physicians and nurse clinicians, other groups, including pharmacists in some jurisdictions, can order tests. Information on laboratory testing is expansive and involves knowledge of the indications for testing, including test sensitivity and specificity for the patient's condition or diagnosis. Many tests are performed for monitoring or screening, so frequency of test ordering may need to be considered. Multiple clinical guidelines provide expert opinions about clinical indications for testing based on specific signs, symptoms, or suspected disorders (27, 78). However, implementation of these guidelines has proven difficult (11). Some approaches for managing the

Table 21.1 CAP Q-Tracks and Q-Probes quality assurance program, 2011[a]

Q-Tracks

Patient Identification Accuracy (QT1)
Assess the incidence of wristband errors within individual institutions, compare performance between participating institutions, and identify improvement opportunities.

Blood Culture Contamination (QT2)
Determine the rate of blood culture contamination using standardized criteria for classifying contaminants.

Laboratory Specimen Acceptability (QT3)
Identify and characterize unacceptable blood specimens that are submitted to the chemistry and hematology sections of the clinical laboratory for testing.

In-Date Blood Product Wastage (QT4)
Compare the rates of blood product wastage (i.e., units discarded in-date) in participating hospitals and track rates of improvement over time.

Satisfaction with Outpatient Specimen Collection (QT7)
Assess patient satisfaction with outpatient phlebotomy services by measuring patients' assessment of waiting time, level of discomfort, courteous treatment, and overall satisfaction.

Stat Test Turnaround Time Outliers (QT8)
Monitor the frequency with which stat test turnaround time intervals exceed institutional stat test turnaround time expectations.

Critical Values Reporting (QT10)
Evaluate the documentation of successful critical values reporting in the general laboratory for both inpatients and outpatients according to the laboratory's policy.

Turnaround Time (TAT) for Troponin (QT15)
Determine the median order-to-report turnaround time of troponin (I or T) ordered on patients presenting to emergency departments (EDs) with signs and symptoms of acute myocardial injury.

Corrected Results (QT16)
Monitor the number of corrected test results within individual institutions and compare performance with that of all institutions and those institutions similar to yours.

Outpatient Order Entry Errors (QT17)
Measure the incidence of incorrectly interpreted and entered outpatient physician test orders, compare performance across institutions, and track performance over time.

Specimen Acceptability in Blood Bank (QT18)
Identify and characterize incorrectly collected and labeled blood specimens submitted to the blood bank for testing.

Q-Probes

Laboratory Services for Emergency Department (QP111)
Measure order-to-report turnaround times for laboratory tests requested from the ED and measure ED physician satisfaction with the provided TAT.

Appropriateness of Plasma Transfusions (QP112)
Assess the conformance of plasma transfusion practice to institutional guidelines and assess the posttransfusion coagulation testing documentation and extent of coagulation correction achieved.

Clinical Consequences of Specimen Rejection (QP114)
Quantify the effect of laboratory specimen rejection on the delay in test result availability. Determine the effect on test result availability by (i) the reason for specimen rejection, (ii) the detection method for mislabeled specimens, and (iii) the laboratory's policy regarding resolution of improperly labeled specimens.

[a] CAP (http://www.cap.org).

quality of test selection include monitoring the frequency of testing use by algorithms and instituting test restriction policies (59). Limits can be established for test ordering frequency. Thus, for a slowly changing analyte like hemoglobin A1c (used to monitor glucose control in diabetics), some healthcare systems cancel any new test order if the hemoglobin A1c is ordered within 28 days of the last test (75). Some laboratory information systems can notify the clinician about potential excess ordering patterns when the number of tests (e.g., two serum cholesterol orders within a week) exceeds a predetermined number (4, 117). Use of algorithms in which indications for ordering a test depend on the results of another test or other patient parameters can be effective. Examples include deferring serological testing for acute hepatitis A when alanine aminotransaminase is normal or deferring ova and parasite examinations in patients who have been hospitalized for more than three days (82). To promote optimal test usage, a multifaceted approach is recommended, including clinician education about laboratory testing, controls on ordering, and feedback about the individual clinician's test utilization (108). New Zealand offers such a program for its general practitioners that combines physician education and utilization feedback; initial results have been dramatic (120).

Preanalytical errors associated with ordering tests include inaccuracies or omissions when transcribing from paper requisitions into a laboratory computer system, tests performed but not actually ordered, associating the order with the wrong physician, and mistakes with assigning priority status to the order (e.g., stat, routine). Of all tests ordered, about 2% are not completed because of these problems (124). In one study involving 660 laboratories, 4.8% of about 115,000 outpatient orders resulted in mistakes (125). The most common was assignment of the wrong physician with an order, and the least common was test priority assignment. High test volume, verbal orders, and lack of laboratory policies and procedures to ensure a high-quality order entry process were associated with higher error rates.

While ordering errors and inappropriate test requests should be tracked and trends should be investigated, major advances in improving the quality of test selection will depend on advances in healthcare information systems strengthening their ability to assist clinicians based on other information in the patient's electronic record (4, 44, 93). Schiff reported that 2% of patients with a laboratory diagnosis of hypothyroidism were not informed of this finding by their clinician. Another 5% with hypothyroidism were lost to follow-up, and patients with thyroid replacement therapy were not considered (97). Computer linkage of laboratory data to a pharmacy database would decrease such issues and improve patient safety. Use of computerized test ordering directly by the physician reduces clerical and transcription errors associated with paper requisitions, reduces

costs, and improves utilization (106, 118). Electronic access to patients' imaging and laboratory results is not a panacea; physicians who were able to access their patients' radiology and laboratory results online tended to order more tests, especially radiologic tests (77).

Quality of Specimen Collection

Laboratory test results may be affected by the patient's condition at the time of specimen collection, as well as by the materials and procedures used for specimen collection (80). These types of errors may be easily overlooked and lead to inaccurate test interpretations or incomplete testing due to specimen rejection (e.g., hemolysis), insufficient volume, or incorrect collection containers. In one study that examined more than 800,000 outpatient visits at 210 facilities, about 0.4% of phlebotomy procedures were unsuccessful (31). The most common causes in order of frequency were nonfasting patient, missing orders, unsuccessful phlebotomy procedure, patient left collection area, and patient not prepared for test (other than nonfasting status). Of the successful blood collections, 0.26% of specimens were unsuitable for testing. In order of decreasing frequency, this was caused by hemolyzed specimen, insufficient specimen volume, clotting of anticoagulated specimen, lost specimen, mislabeling, and rejection based on delta check failure. Other studies have shown that about 0.35% of specimens submitted for chemistry examinations are rejected, with hemolysis being the most common reason, and about 0.45% of specimens received for hematology testing are rejected, with specimen clotting being the most common reason (56, 57). The quality of coagulation testing depends greatly on good collection technique and full sampling (1, 64). A review of videotaped phlebotomies showed that 4 of 10 phlebotomists did not mix their filled blood tubes and 2 of 10 delayed mixing (45). Delayed mixing of filled plasma separator tubes can cause artifactual increases in troponin and hCG (115).

Well-documented and validated specimen collection procedures used by trained phlebotomy and nursing staff are key factors to prevent preanalytical errors from affecting the overall quality of the testing process (6, 8). It is important to provide patients with detailed instructions about preparation prior to collecting the specimen and then to make sure the instructions were followed. For example, two consecutive studies have found that between 25 and 34% of toxic serum digoxin levels were likely falsely elevated due to specimen collection too soon after patients ingested their medication (49). These falsely high results can be avoided by instructing phlebotomists to ask patients when they last took a digoxin pill to determine if a specimen collection should be deferred to a later time. To mitigate the problem of falsely elevated digoxin results in northern Alberta, an interdisciplinary team of a clinical biochemist, pharmacists, and clinicians mandated evening digoxin dosing. This nocturnal dosing coupled with the usual morning therapeutic monitoring has resulted in very few incorrectly timed digoxins (D. LeGatt, personal communication). Phlebotomists should always ask if a patient is fasting prior to collecting a specimen for triglyceride, as false elevation of serum triglyceride occurs in specimens collected from nonfasting patients, making this determination meaningless. Measuring total creatinine on 24-h urine specimens helps determine whether a complete 24-h collection was obtained, and this can be monitored as a quality indicator.

Special attention must be given to the collection of specimens for microbiological examinations. Poor-quality specimens that are collected improperly or inappropriately will produce useless or even misleading results that may be misinterpreted as having significance to patient care (134). In some cases, specimen quality can be evaluated by smear examinations before cultures are performed, and specimens may be deferred from testing if judged to be of poor quality (83). For example, excessive epithelial cells seen on a Gram stain from a sputum specimen suggest that the specimen contents are from the mouth rather than the lower respiratory tract; this may warrant rejection of the specimen for culture. Another example, the failure to collect a sufficient number of sputum specimens, is the most common cause of delayed diagnosis of tuberculosis in HIV-infected patients (37, 76).

While contaminated cultures from sterile sources cannot be completely eliminated, they can be reduced with good aseptic collection techniques. Proper sterile preparation of the venipuncture site with the correct materials and careful collection procedures by a properly trained phlebotomist significantly reduce the cost of blood culture contamination, which varies up to fivefold between laboratories (42, 69, 102, 107, 130). Blood collection processes have important implications for costs and outcomes. A preliminary false-positive blood culture results in additional costs of $4,000 per episode because of prolongation of hospitalization and concomitant laboratory testing and therapies (3). Finally, the specimen may be collected properly, but there may be insufficient blood volume or inadequate specimen numbers to provide the highest-quality result. For example, collection of solitary rather than multiple blood cultures makes it difficult to differentiate contamination from true bacteremia when coagulase-negative *Staphylococcus* sp. is isolated (99).

It is critically important that specimens be labeled correctly and properly. The frequency and reasons for incorrect patient identification should be part of the laboratory's quality assessment program. Delta checking (see Use of Patient Data for Quality Control) is a method in which the laboratory manager establishes parameters in the laboratory information system that flag current patient results that differ substantially from previous results (53, 62, 63). Generally, delta checks are not very helpful in highly

automated laboratories because of the relative absence of sample mix-up and analytic error. Delta checks also lack utility for most analytes because of large expected changes in these analytes (e.g., glucose). Other analytes are more sensitive (e.g., red blood cell mean corpuscular volume). Depending on how the parameters are set, only a small proportion of delta check investigations will uncover specimen mix-up errors in today's healthcare organizations, where the median identification error rate is 4 per 10,000 (88, 105, 114, 126).

Patient and Client Satisfaction

Typically, the only direct experience patients have with the laboratory is during phlebotomy. Patient satisfaction with this experience is an important preanalytical quality measurement. This is determined by patient surveys as well as objective parameters such as patient waiting times or number of self-reported hematomas (47), number of needlesticks, and even the cleanliness of the phlebotomy area (22).

Laboratories should also conduct nurse and physician satisfaction surveys. Excessively long turnaround time is usually the most significant concern expressed by both physicians and nurses (54, 57, 111). Esoteric test turnaround time has been associated with low levels of physician satisfaction (55). Nurse customers were the least satisfied with test turnaround time in the intensive care units and emergency departments (58). Setting up a hotline through which clients can report potential problems or errors and make inquiries may help large laboratories improve customer support services. It is useful to track this information to look for trends or ideas for quality improvement.

Specimen Transport, Storage, Receipt, and Preanalytical Processing

Specimens can deteriorate through prolonged delays or failure to maintain proper conditions during transport. Some tests (e.g., urine culture, coagulation tests) are more susceptible than others to processing delays. The World Health Organization has published a very useful comprehensive monograph that documents the stability of anticoagulated blood and serum and plasma specimens (137).

It is difficult to monitor transport times or even collection time when the collection is not under the control of the laboratory. Specimens that are lost or mishandled in other ways (e.g., broken tube) during transport or preanalytical laboratory processing should be tracked as a quality indicator (see Corrected and Incomplete Reports). Specifications for specimen transport and storage based on stability of analytes should be validated and documented.

Accurate identification of the specimen throughout the testing process is facilitated by the use of bar codes that can be scanned by laboratory instruments prior to testing (119). Bar codes are significantly more reliable than the manual entry of specimen information. Bar-coded specimens prevent errors due to misplacement of specimens into instruments or when aliquoting specimens into secondary containers. Bar code systems work best when integrated into the blood collection process with wristband (inpatient) or identification card (outpatient) positive patient identification schemes. Finally, significant error reduction can be accomplished with the implementation of robotic technology for the automated handling of all aspects of preanalytical within-laboratory specimen processing (10, 46).

Quality Management of Analytical Processes

Quality management of the analytical phase involves reducing inaccuracy and imprecision (variability) of test methods as much as possible (109). Attention to standardizing test procedures and monitoring method performance with a well-designed quality control system are the key elements for meeting this management goal. Appropriate method selection and proper training are additional factors that are important for success.

Method Selection and Evaluation

Method selection is laboratory dependent and based on characteristics that best fit internal goals for cost, timeliness, and reliability (see chapter 27, this volume). These characteristics include type of specimen required, sample volume, run size, population to be tested, instrument capacity, analysis time, personnel requirements, existing equipment, safety, utilities (e.g., electrical, water), and space requirements. The complexity of analysis, including calibration, stability of reagents and controls, sensitivity and specificity of the method, linear range of analysis, and interferences, as well as types of internal and external proficiency systems, are factors that may affect method selection decisions. In the United States, most laboratory methods require review of rigorous premarket evaluations and approval by the U.S. Food and Drug Administration (FDA). As a result, implementation of FDA-approved tests is usually relatively straightforward. Validation and implementation of non-FDA-approved methods can be much more complex and labor-intensive and require substantially more development and evaluation, as well as resources. Sometimes, the best decision is to outsource a test when rapid turnaround time is not necessary, test volume is low, or it is difficult to maintain an acceptable quality of proficiency.

Method evaluation and implementation involves assessing the analytical process statistically by the use of control materials, establishing or validating the reference (normal) range of the population being tested, documenting the procedure in writing (both for laboratory use and

another document for client use), and training personnel (Table 21.2). When a new method is introduced, it must be compared to the old method before bringing it into use. All procedure changes, training, and analytical performance data from the previous method should be documented, and clients should be notified of changes affecting interpretation of results.

Quality Control

The term "quality control" describes the approach used to monitor the analytical process to ensure that the test results meet their quality requirements. Quality control includes establishing specifications for the analytical process, monitoring the analytical process to determine conformance to these specifications, and taking any necessary corrective actions to bring the analytical process into conformance (16).

The primary quality characteristic that is monitored during the analytical process is the deviation of an analytical measurement from expected. If the size of this deviation (also known as error) is large, the analytical process may be defective and thus must be investigated. Errors can be classified as systematic (resulting in a shift) or random (resulting in increased imprecision). They may also be classified as persistent or intermittent. Other typically monitored quality characteristics of the analytical process include specific instrument checks that are usually unique to a particular instrument.

The deviation of the analytical measurement from the expected value is usually monitored by repetitively assaying one or more levels of quality control specimen. The results of testing these commercially prepared, stabilized control specimens are compared to a range of expected values calculated as the mean and variance (standard deviation) of these measurements. If the quality control result deviates significantly as defined by quality control rules (see below), routine analysis is suspended, the analytical run is investigated, and corrective action is taken.

Usually two or three different control levels are used. In hematology and hormone (ligand) measurements, it is standard to use three levels; in general chemistry, two levels are standard. As a rule, it is better to have more measurements on fewer control products. Laboratories may also compare their own quality control results to those generated in other laboratories using the same lot of control materials and instrument/reagent systems. This information is provided by most commercial manufacturers of quality control materials and provides a way to assess bias and imprecision of the laboratory's methods relative to others' tests performed under similar quality control conditions (Fig. 21.1). Quality control systems for microbiological and serological testing are primarily qualitative in nature. Control testing is performed to check the performance of media, biochemical reactions (positive or negative), immunological reactions, or expected growth in the presence of antibiotics (susceptibility testing). In molecular microbiology, more than three standards are typically used to generate standard curves for quantitative measurements and are combined with two or three density levels (e.g., low, mid, and high density), external positive controls, or standards.

Quality Control Rules

Quality control rules developed for the clinical laboratory originated in the early 1950s with Levey-Jennings charts. These charts were implemented with three standard deviation (SD) limits for the mean and range of two controls analyzed just twice per week. By the 1960s, the limits had been reduced to two SD for single controls (Fig. 21.2). In the next decade, statistical quality control rules were implemented to help reduce the number of false rejections. Table 21.3 shows some of the common quality control rules used to evaluate control measurements today. Westgard et al. have developed a nomenclature for these control rules and devised graphical summaries (power function curves) of their sensitivity and specificity (131, 132). For most applications of clinical laboratory quality control, a combination of the 1-3SD and the 2-2SD control rules is adequate. The 1-3SD rule can detect increases in random error and large systematic errors, while the 2-2SD control rule detects moderate-sized systematic errors. This quality control combination is relatively simple to implement and has a relatively low false rejection probability. Figure 21.3 shows how the 1-3SD and the 2-2SD control rules are applied at one laboratory. On highly precise analyzers, the analytical variation of some analytes may be so small that violations of the 1-3SD or 2-2SD rules can be

Table 21.2 Method evaluation and implementation

Stage I
Prepare and document procedure
Validate linearity and calibration
Determine within-run imprecision
Evaluate for interferences
Stage II
Determine between-day imprecision
Compare to old method
Evaluate acceptability of imprecision and bias
Perform or validate reference range(s)
Stage III
Establish final quality control ranges, critical values, and delta checks
Train personnel
Complete and sign procedure documents
Notify clients of any significant changes in method

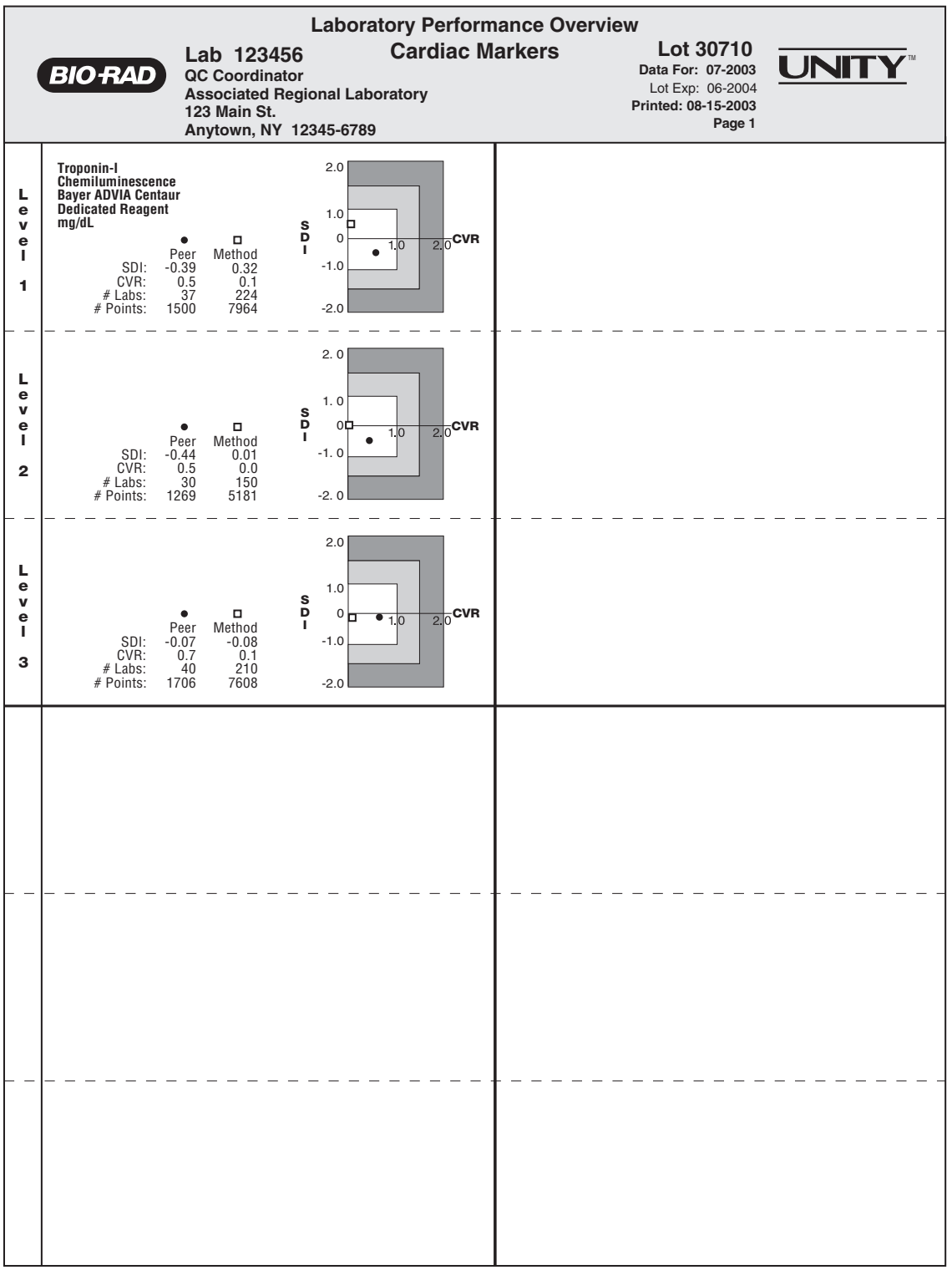

Figure 21.1 Examples of interlaboratory quality control reports. (A) The SDI (a peer-based measure of bias) and CVR (a peer-based estimator of precision) are combined as an *x, y* coordinate within three performance zones: acceptable, acceptable to marginal, and marginal.

(continued)

Laboratory Comparison Report
Cardiac Markers

BIO-RAD

Lab 123456
QC Coordinator
Associated Regional Laboratory
123 Main St.
Anytown, NY 12345-6789

Lot 30710
Data For: 01-2003
Lot Exp: 06-2004
Printed: 08-15-2003
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UNITY™

The following statistics are derived from user-supplied data and are provided by Bio-Rad Laboratories as a service to customers. Such action does not imply support of reported analytes and test methods. Refer to the package insert for specific analyte claims and stability information.
Peer group statistics contained in this report may not be used without the express written consent of Bio-Rad Laboratories.

Analyte / Method / Units / Temp / Instrument/Kit / Reagent			Level 1 Mon	Level 1 Cum	Level 2 Mon	Level 2 Cum	Level 3 Mon	Level 3 Cum
Troponin-I								
Chemiluminescence ng/mL								
Bayer ADVIA Centaur								
Dedicated Reagent								
	Your Lab	Mean	1.49	1.60	10.78	11.08	38.94	38.17
		SD	0.053	0.074	0.332	0.405	1.60	1.49
		CV	3.6	4.6	3.1	3.7	4.1	3.9
		(Peer) CVR	0.5	0.6	0.5	0.6	0.7	0.7
		(Method) CVR	0.1	0.1	0.0	0.1	0.1	0.1
		(Peer) SDI	-0.39	0.27	-0.44	0.03	-0.07	-0.28
		(Method) SDI	0.32	0.37	0.01	-0.03	-0.08	-0.17
		# Points	4	151	4	151	4	151
	Peer Group	Mean	1.53	1.57	11.08	11.06	39.10	38.78
		SD	0.102	0.111	0.677	0.635	2.14	2.20
		CV	6.7	7.1	6.1	5.7	5.5	5.7
		# Points	1500	5889	1269	4917	1706	6900
		# Labs	37	39	30	32	40	41
Group Values by Method		Mean	1.21	1.23	10.70	11.34	40.46	41.98
		SD	.0866	.100	.786	1.023	1.901	2.294
		CV	7.15	8.13	7.35	9.02	4.70	5.46
		# Points	7964	37806	5181	25366	7608	35479
		# Labs	224	254	150	179	210	238

Figure 21.1 *(continued)* (B) Reports provide monthly and cumulative statistics for the laboratory and between-laboratory comparisons with a peer group. Report includes mean, standard deviation, coefficient of variation, CVR, SDI, number of data points, and number of laboratories. CVR, coefficient of variation ratio, a ratio of laboratory imprecision to peer group imprecision. A value less than 1 indicates better than average imprecision; a value greater than 1 indicates more than average imprecision compared to the peer group. doi:10.1128/9781555817282.ch21.f1

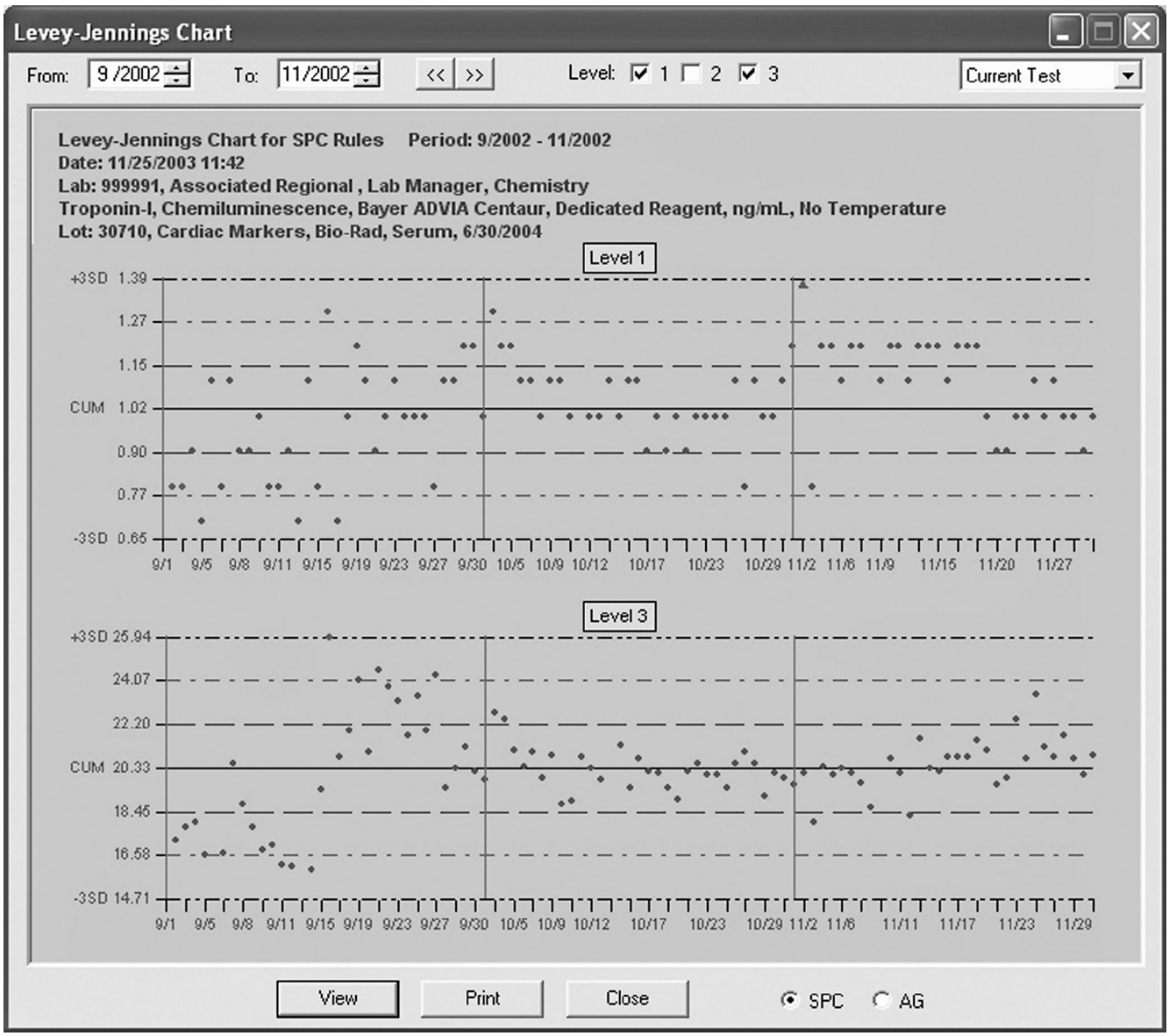

Figure 21.2 Quality control charts. doi:10.1128/9781555817282.ch21.f2

caused by very small errors that would not affect the clinical interpretation of the test result. For these tests, it might be reasonable to expand the control limits and diminish the frequency of attempts at correction and prevention of these small errors. Variations of these rules have been adapted for testing platforms in quantitative molecular microbiology (66).

Frequency of Quality Control Analysis

The more frequently control products are analyzed, the more quickly analytical errors can be detected, investigated, and corrected. For some tests, government regulations specify the longest period over which controls need not be analyzed. While many laboratories analyze controls more frequently, the government-mandated period tends to become a de facto standard for control analysis. The average time to detect a persistent error has been shown to be one-half of the period between control analyses (90). Thus, if the period between control analyses is 24 h, an error may impair laboratory testing for an average of 12 h before being detected. It is possible to shorten the interval between control analyses without increasing the number of controls analyzed. Rather than analyzing several controls one after another, each control can be tested at different times of the day. As a result, the period between control testing is shortened. For example, rather than analyze three blood gas controls every 24 h, one can be tested every 8 h. Using this control analysis schedule, the average time to detect a persistent error will be 4 h.

Table 21.3 Common quality control rules

1-2SD	Use as a rejection or warning when one control observation exceeds the $x - (\pm 2SD)$ control limits; usually used as a warning.	Overused. Should only be used with manual assays with low number of analytes/control materials.
1-3SD	Reject a run when one control observation exceeds the $x - (\pm 3SD)$ control limits.	Detects random error and large systematic error.
1-3.5SD	Reject a run when one control observation exceeds the $x - \pm(3.5SD)$ control limits.	Detects large random and systematic error. Use only with highly precise assays.
1-4SD	Reject a run when one control observation exceeds the $x - \pm(4SD)$ control limits.	Detects large random and systematic error. Use only with highly precise assays.
2-2SD	Reject a run when two consecutive control observations are on the same side of the mean and exceed the $x - (+2SD)$ or $x - (-2SD)$ control limits.	Detects systematic error.
4-1SD	Reject a run when four consecutive control observations are on the same side of the mean and exceed either the $x - (+1SD)$ or $x - (-1SD)$ control limits.	Detects small systematic error; very few applications.
10*x*	Reject a run when 10 consecutive control observations are on the same side of the mean.	Detects very small errors; do not use.
R-4SD	Reject a run if the range or difference between the maximum and minimum control observation out of the last 4 to 6 control observations exceeds 4SD.	Detects random errors; use within run.
x-0.01	Reject a run if the mean of the last *N* control observations exceeds the control limits that give a 1% frequency of false rejection ($p_{fr} = 0.01$).	Underutilized
R-0.01	Reject a run if the range of the last *N* control observations exceeds the control limits that give a 1% frequency of false rejection ($p_{fr} = 0.01$).	Underutilized

Some laboratories do not analyze quality control specimens on a periodic basis; rather, the number of controls analyzed depends on the number of patient specimens run. Because reference laboratories can analyze large numbers of specimens over the course of a day, regular but infrequent control analysis may result in large numbers of samples being analyzed with minimal information provided about the run quality. As such, many reference laboratories test their patient samples in batches, with a specific number of controls analyzed in each batch. Only when the quality control specimens are within quality control limits is the batch of patient results reported. Some authors have suggested that for high-volume multichannel chemistry analyzers, control specimens be tested between every 30 and 100 patient specimens (85). Some referral laboratories do not use specimen number to establish quality control frequency; they test quality control specimens more frequently, e.g., each hour.

Specification of MAE

The primary function of quality control is to maintain a stable analytic process. Once the process is stable, then any required improvements can be implemented. Specifications for maximum allowable error (MAE) provide information about the adequacy of an analytic system for patient care. MAE represents the magnitude of total error that can be tolerated without invalidating the medical usefulness of the result. The analytical quality of a test can be evaluated by comparing its total analytic error to the MAE; this is a method for setting goals for the analytical performance of a laboratory test.

Several different approaches have been used for determining the MAE of laboratory tests. One of the first was offered in 1963 (121) by Tonks, who insightfully suggested that the MAE be based on interindividual variation. For most analytes, he suggested that the MAE should be no greater than one-quarter of the analyte's reference interval (normal range) (121). Cotlove et al. proposed that the MAE should be less than one-half of the intraindividual range (29). Ricos et al. tabulated MAEs for over 300 different analytes based on biological variation and associated method biases and imprecisions (96).

Table 21.4 compares the MAE for select analytes to typical amounts of imprecision of current laboratory analyzers. There is tremendous variation in the MAEs, ranging from around 1% for serum sodium to 30% for various urine assays. The MAE/imprecision ratio is a measure of the analytical quality of the test method. The ratio can be thought of as the magnitude of shift, expressed in standard deviations, which will render a test measurement unfit for medical usage. Thus, for sodium, whose ratio is approximately 1, just a 1% shift in measured sodium might make the measurement too inaccurate for serial monitoring. Sodium is an extreme example because its plasma concentration is tightly controlled by multiple feedback mechanisms. Where a test's MAE/imprecision ratio is less than 2.5, it is highly desirable

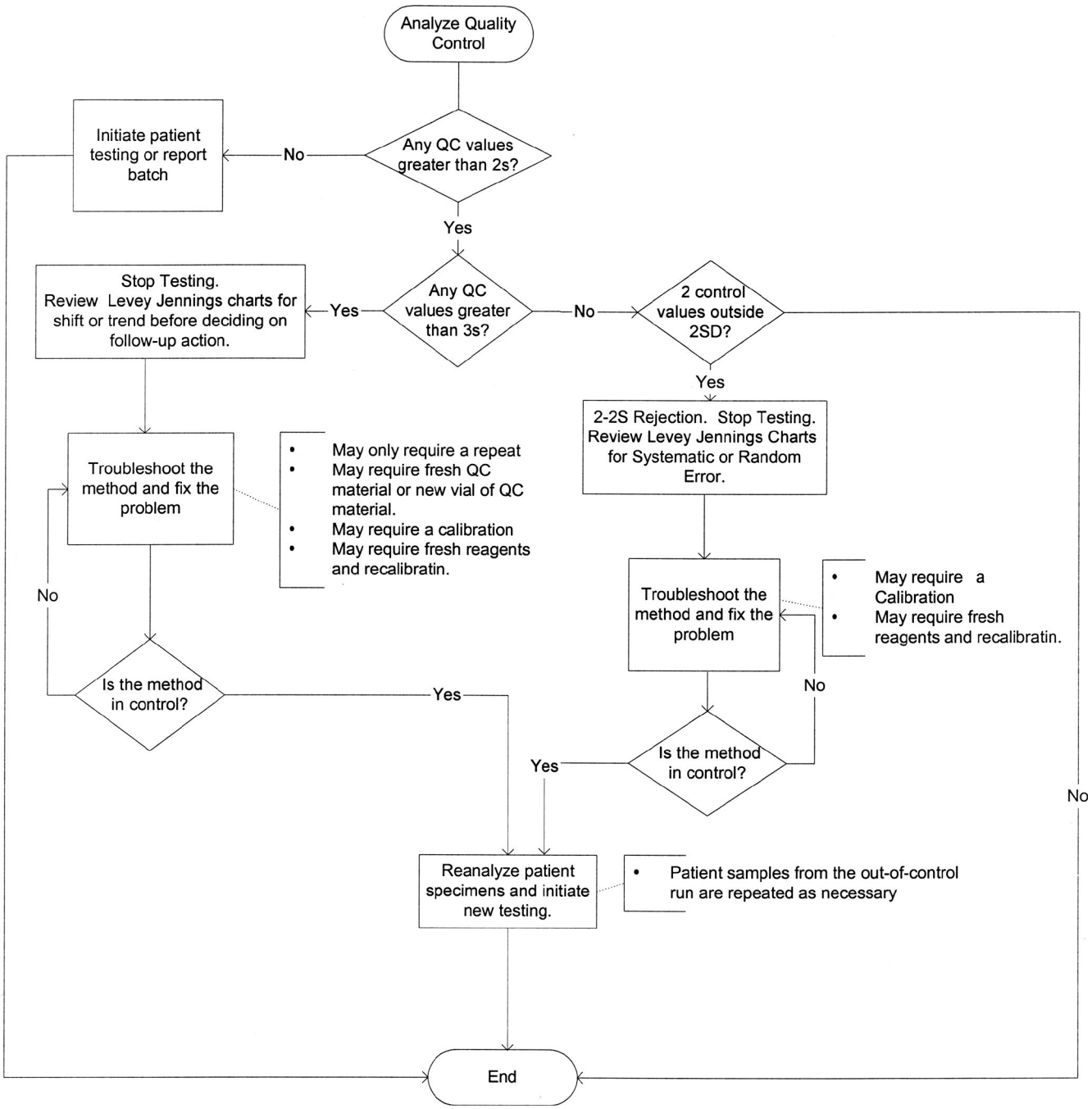

Figure 21.3 Flow chart showing implementation of the 2-2SD/1-3SD control procedure. Courtesy of Tammy Hofer. doi:10.1128/9781555817282.ch21.f3

that the manufacturer reduce the method's imprecision. This is a better approach than adding extra quality control samples to attempt to detect small analytical errors on a system that has insufficient reproducibility. Such effort is highly frustrating and, in the authors' opinion, generally nonproductive. For analytes with MAE/imprecision ratios of 2.5 or less, we recommend the combination of the 1-3SD and 2-2SD rules, possibly combined with the R-4SD rule. Table 21.5 shows recommended quality control rules for various MAE/imprecision ratios. Whenever possible, the laboratory manager should deploy instruments that provide tests with MAE/imprecision ratios that exceed 3.5. For analytical systems with high MAE/imprecision ratios, it is possible to employ control rules with very low false

Table 21.4 Comparison of MAEs derived from physiological variation to typical instrument imprecisions

Analyte	MAE (%), 95% limits	Typical imprecision (%)	MAE (%)/imprecision
Serum albumin	3.9	1.5	2.6
Urinary albumin	46.1	8	5.8
Urinary creatinine, 24 h	6.9	2.5	2.8
Activated partial thromboplastin time	4.5	3	1.5
Hemoglobin	4.1	0.8	5.1
Serum sodium	0.9	0.8	1.1
Urinary sodium, 24 h	28.8	4	7.2

rejection probabilities, such as 1-3SD or 1-3.5SD or even 1-4SD (21).

Unfortunately, selection of analyte-specific control rules can require variations in the timing of quality control testing. Alterations in control frequency are difficult because many quality control analytes are measured together on a single instrument. It is almost impossible in a busy hospital laboratory to schedule more frequent analyte-specific quality control testing and interpretation. At this time, very few instruments can automatically sample and analyze on-board quality control material on a per analyte basis. As a result, most laboratories use the same schedule of control analysis for all of the analytes measured. Some laboratories apply analyte-specific quality control rules through the use of a sophisticated laboratory information system or instrument-based quality control systems.

Use of Patient Data for Quality Control

Virtually all laboratories that perform patient specimen testing for ongoing care must alert the caregiver of any results that are critical (sufficiently outside of their usual physiological limits such that they are incompatible with life). Each laboratory must have a critical value list that specifies the limits for alerting the caregiver (60, 61, 89, 128). In the past, many areas of the clinical laboratory have repeated testing in the most timely manner if the initial results were "critical." This kind of a check (sometimes called a limit check) delays the reporting of the critical value to the caregiver. As successive generations of analyzers become more precise, and as laboratories determine that the repeat values are substantially the same, more laboratories are ending the practice of confirming the critical value. Such decisions should be data driven; if an evaluation of the last 50 to 100 critical-value repeats does not yield clinically significant differences, the laboratory director can confidently suspend this increasingly non-value-added practice.

For analytes exhibiting large random errors (usually in the low-volume, manual laboratory), specimens should be analyzed in duplicate with the average reported as long as the difference between duplicates does not exceed certain limits—originally around ±15%, but presently around ±5%. Some laboratories use duplicate analyses of another type: patient-sample comparisons. These comparisons require the regular analysis of split samples on identical or dissimilar instruments that measure the same analyte. Differences between instruments that exceed predetermined limits are investigated and corrected (19, 79). Too often, these comparisons are performed retrospectively and contribute little to quality improvement. We recommend that the analyst enter the patient comparison data into an active database; outlying data should be signaled immediately to the analyst and laboratory supervisor. Such prospective analysis can easily be followed by reanalysis of another sample, adjustment of calibration, perhaps widening of the acceptable differences, and rarely, instrument replacement.

The average of patient (AOP) data is another control procedure that uses patient data. In AOP, an error condition is signaled when the average of consecutive centrally distributed patient data is beyond the control limits established for the average of the patient data. The assumption underlying AOP is that the patient population is stable. Any shift would thus be secondary to an analytical shift. The error-detection capabilities of AOP depend on several factors (17). The most important are the number of patient results averaged and the variances of the patient population and analytical method. Using averages of patient endocrine data has demonstrated high error-detection capabilities for thyroid testing (33). However, AOP is not commonly used for clinical chemistry. In contrast, AOP

Table 21.5 Control rules that can be used for various MAE/imprecision ratios[a]

MAE/imprecision	Control rule
2 to 4	Multirule consisting of combination of 1-3SD, 2-2SD, and R-4SD (2 or 3 control levels at start-up)
3.5 to 5	1-2.5SD (2 or 3 control levels at start-up)
4.5 to 7	1-3SD or 1-3.5SD (2 or 3 control levels at start-up)

[a]Adapted with permission from reference 14.

has been used extensively in hematology to monitor patient red blood cell indices and, indirectly, their constituent measurements, hemoglobin and red blood cell count, as well as hematocrit (23, 65, 74). The primary limitation of AOP in the hospital laboratory is the lack of randomization in the order of receipt and analysis of patient samples. In hematology, for example, the averaging of a large number of specimens from a neonatal unit or a hematology unit can cause the red blood cell indices to inappropriately indicate an out-of-control situation. In clinical chemistry, analysis of specimens primarily from renal units will cause large shifts in the AOP of creatinine, glucose, and urea nitrogen. In referral laboratory testing, there is "natural randomization" of patient specimens, and AOP is a powerful tool in guaranteeing acceptable analytical performance (20). Hospital laboratory AOP is significantly influenced by longer-term, within-day and within-week trends. Overnight and over weekends, less testing is ordered; this weekend and nightly testing is performed on more acutely ill patients. As a result, these evening and weekend AOPs will demonstrate elevated glucose, lower sodium, lower protein, and lower calcium averages (13).

One other quality control approach uses patient data: the delta check, in which the most recent result for a patient is compared to the previous value. The difference between consecutive laboratory values (deltas) is calculated and compared to previously established limits (62). A difference that exceeds these limits is investigated; this difference is either the result of specimen mix-up or real changes in the patient's test results. The difference is usually calculated in two ways: as a numerical difference (current value minus last value) and as a percentage difference (numerical difference times 100 divided by the current value). There is a tremendous range in the true positive rate of delta check methods depending on the analyte and its delta limit (133). While delta checks are almost universally applied, there is a high cost in investigating the many false positives, especially in tertiary-care hospital populations in which there are large excursions in laboratory values secondary to disease or therapy.

External Quality Control (Proficiency Testing)

Proficiency-testing programs provide samples of unknown concentrations of analytes to participating laboratories. Their purpose is to evaluate the ability of laboratory personnel to achieve the correct analysis. Participation in these programs is usually government-mandated, with the premise that acceptable performance indicates proficiency in patient specimen analysis. This assumes that proficiency specimens are comparable to and treated the same as patient specimens. Acceptable performance is determined by some form of consensus by peer comparisons using "fixed limits," which are expressed either in measurement units of the analyte (e.g., $\pm$0.5 mmol/liter from the mean for potassium) or as percentages (e.g., $\pm$10% for total cholesterol) (122). Statistically defined limits of acceptability are used for a far smaller number of methods (e.g., thyroid-stimulating hormone) (Table 21.6). The standard deviation index (SDI) is used for this purpose and is calculated as the numerical difference between an individual laboratory's results and the mean of all laboratory results, divided by the standard deviation of all laboratory means. For these analytes, the participant result is acceptable if it falls within $\pm$3 SDI of the group mean.

Table 21.6 CLIA testing criteria for acceptable external proficiency testing performance

Test or analyte	Acceptable performance (+ target value)
Chemistry, toxicology	
Alanine aminotransferase	20%
Albumin	10%
Alcohol, blood	25%
Alkaline phosphatase	30%
Alpha-1 antitrypsin	3 SD
Alpha-fetoprotein	3 SD
Amylase	30%
Anti-HIV	Reactive or nonreactive
Antinuclear antibody	2 dilution or positive/negative
Antistreptolysin O	2 dilution or positive/negative
Aspartate aminotransferase	20%
Bilirubin, total	0.4 mg/dl or 20%
Blood lead	10% or 4 mg/dl
Blood gas pO_2	3 SD
Blood gas pCO_2	5 mmHg or 8%

(continued)

Table 21.6 CLIA testing criteria for acceptable external proficiency testing performance *(continued)*

Test or analyte	Acceptable performance (+ target value)
Blood gas pH	0.04
Calcium, total	1.0 mg/dl
Carbamazepine	25%
Chloride	5%
Cholesterol, total	10%
CK isoenzymes	MB present or absent, or 3 SD
Complement C4	3 SD
Complement C3	3 SD
Cortisol	25%
Creatine kinase	30%
Creatinine	0.3 mg/dl or 15%
Digoxin	20% or 0.2 ng/ml
Ethosuximide	20%
Free thyroxine	3 SD
Gentamicin	25%
Glucose	6 mg/dl or 10%
HDL cholesterol	30%
Hepatitis (HBsAg, anti-HBc, HBeAg)	Reactive, positive or nonreactive, negative
Human chorionic gonadotropin (HCG)	3 SD or positive/negative
Immunoglobulin A (IgA)	3 SD
IgE	3 SD
IgG	25%
IgM	3 SD
Infectious mononucleosis	2 dilution or positive/negative
Iron	20%
Lactate dehydrogenase	20%
Lithium	0.3 mEq/liter or 20% (greater)
Magnesium	25%
Phenobarbital	20%
Phenytoin	25%
Potassium	0.5 mEq/liter
Primidone	25%
Procainamide (and metabolite)	25%
Quinidine	25%
Rheumatoid factor	2 dilution or positive/negative
Rubella	2 dilution or positive/negative
Sodium	4 mEq/liter
T3 uptake	3 SD
Theophylline	25%
Thyroid stimulating hormone	3 SD
Thyroxine	20% or 1.0 mg/dl
Tobramycin	25%
Total protein	10%
Triglycerides	25%
Triiodothyronine (T3)	3 SD
Urea nitrogen	2 mg/dl or 9%
Uric acid	17%
Valproic acid	25%

(continued)

Table 21.6 *(continued)*

Test or analyte	Acceptable performance (+ target value)
Hematology	
Cell identification	80% or greater consensus on identification
White cell differential	3 SD based on leukocyte percentage
Erythrocyte count	6%
Hematocrit	6%
Hemoglobin	7%
Leukocyte count	15%
Platelet count	25%
Fibrinogen	20%
Partial thromboplastin time	15%
Prothrombin time	15%

An alternative multirule system has been developed to evaluate proficiency test results (12, 15, 18). The alternative method is simple and can be used by pathologists, doctorate-level scientists, and medical technologists. The most current approach is illustrated in Fig. 21.4. When significant deviations are detected in a set of five survey results (the mean of the five results exceeding +1.5 SDI, or the range of the observations exceeding 4 SDI, or at least one observation exceeding 75% of the total allowable error), the laboratory records, including the internal quality control results, should be reviewed. Mix-ups of proficiency specimens or of proficiency and clinical specimens should be ruled out.

Whenever possible, aliquots of the survey specimens should be frozen and saved. If the survey results differ significantly from those obtained on peer instruments, these aliquots should be reassayed. Results that still deviate

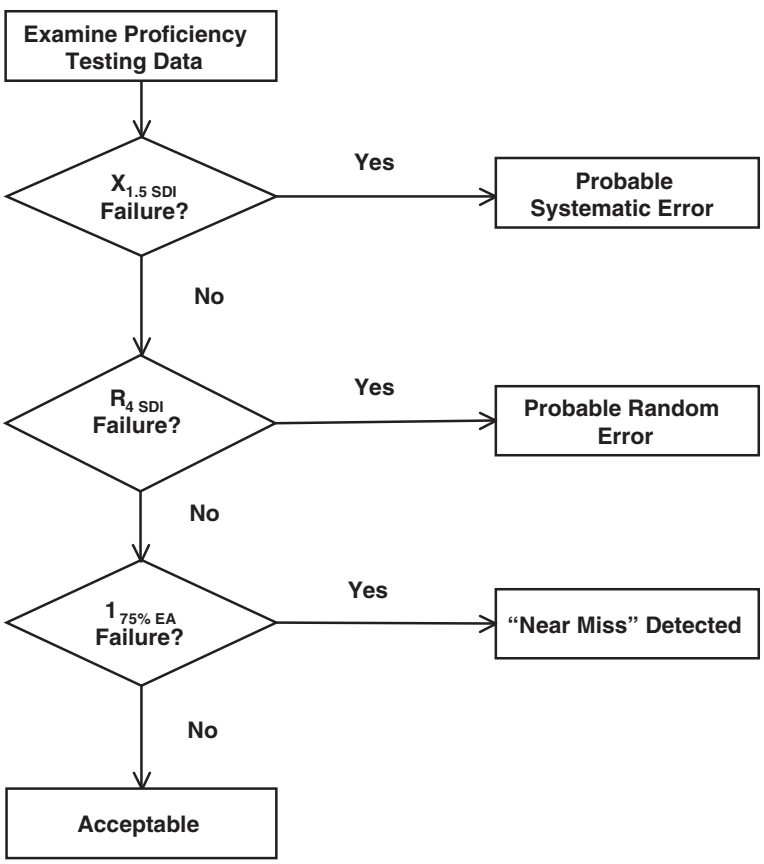

Figure 21.4 Flow chart illustrating proficiency test review, from reference 14 with permission. doi:10.1128/9781555817282.ch21.f4

significantly after retesting can indicate a long-term bias. If the deviations are variable in magnitude and direction, there may be a problem with imprecision (random error). In the event that repeat analysis yields satisfactory results, the error probably represented a random error or transient bias encountered during the testing period.

Quality Management of Postanalytical Processes

The two most important factors affecting the postanalytical phase of the testing process are test reporting and result interpretation (113, 129). One source of inaccurate reporting is clerical errors due to data entry mistakes. Laboratory instrument interfaces with computer reporting capabilities prevent most of these types of errors. Phone reports have a relatively high rate of errors and should be avoided if possible. To mitigate such errors, both The Joint Commission and CAP require the healthcare provider to read back the information conveyed during the telephone reporting of patient critical values. If computer reporting is unavailable, printed results should be promptly delivered to the patient's chart or physician's office. Whenever possible, calculations should be done by preprogrammed computer systems.

Procedures for defining and reporting critical laboratory test results must be developed and periodically reviewed by the laboratory director in conjunction with the medical staff to ensure that clinicians are immediately notified about abnormal results when necessary (35, 70, 71). Common examples of critical values that require immediate notification include severe hypo- or hyperglycemia, thrombocytopenia, and positive blood cultures. Failure to notify a clinician of a critical test result is a serious quality failure and requires investigation.

Quality management of results utilization and proper test interpretation is underdeveloped at this time. For example, the appropriateness and timeliness of treatment of patients with serious infections improve when the laboratory actively broadcasts the findings of clinically significant bacterial culture results (30, 101). Recent publications, such as those using PCR or peptide nucleic acid fluorescence in situ hybridization (PNA-FISH), document the laboratory's ability to provide postanalytical impact (5, 38–40, 136).

Turnaround Time

Excessively prolonged laboratory test turnaround time is one of the most common complaints voiced to the laboratory manager (55, 58). The slow delivery of laboratory results is associated with increased diagnostic uncertainty and delays in patient management. From an outcome perspective, slow test turnaround times lead to longer waiting times for the patient or incomplete information at the time of a clinical encounter. Pressure to provide test results more rapidly has led, in part, to the growth of point-of-care testing by nonlaboratory personnel outside of the main clinical laboratory. As a general rule, faster service is associated with higher costs and sometimes lower quality of test results. Therefore, it is the laboratory manager's responsibility to determine the most effective testing process and testing schedules that will provide the most cost-effective and reliable results within a clinically appropriate time frame.

Evaluation of test turnaround time is an important component of the laboratory's quality assurance program (50, 123). Turnaround time involves all stages of the testing process and is a good way to globally assess performance. Table 21.7 shows the major intervals in the testing process that are potential bottlenecks for delayed testing. Measurement of turnaround time can involve any of these intervals, although the typical measurement is usually specimen collection to result reporting or specimen delivery to result reporting. Typically, the distribution of turnaround times is shifted to the right with a few cases of prolonged times due to various factors such as verification protocols, dilutions, or instrument malfunction. Therefore, simply taking an average of all turnaround time measurements is misleading. A more appropriate measure is to examine the percentage of outlier turnaround times (86, 112). These are also the events that will most likely be noticed and be of concern to clinicians. The key to this approach is to establish an appropriate target for turnaround time based on the goals of the clinical staff and the capabilities of the laboratory and facilities infrastructure (48). For example, in one study involving 496 hospitals, about 90% of stat tests from the emergency department were completed in less than 70 min. Test ordering and specimen collection accounted for nearly 60% of all reasons for delays (112).

Corrected and Incomplete Reports

Corrected reports are an important indicator of a failure in one or more laboratory processes. They are analogous to shipping a defective part in the manufacturing

Table 21.7 Stages in the testing cycle where turnaround time may be measured

Order received and recorded
Patient registration
Specimen collection
Specimen delivery
Specimen processing
Test
Result verification
Result reporting
Interpretation by clinician

industry. Fortunately, only about 4% of these errors have a significant impact on patient care (52). The largest proportion tend to be associated with hematology testing, while the fewest are documented in transfusion medicine. Prior to a result being reported, any number of quality processes may come into play to prevent incorrect results from being reported. However, after the result is verified and reported, the defective result has the potential to affect patient outcome. Incorrect results may be detected in a variety of ways, including input from the physician about a clinical inconsistency, a delta check that uncovers a mislabeled sample that was previously tested, delayed recognition of a significant quality control failure, or a clerical error found during routine supervisory review. All corrected reports should be treated as opportunities to reexamine and improve processes to prevent recurrences of the same problem.

Incomplete reporting of results arises from about 2% of orders received by laboratories (124). This may occur for a variety of reasons that involve the total testing process, including improper specimen collection, an unavailable patient, broken tube, lost specimen, misinterpretation of the order, an interfering substance in the specimen, or failure to provide the result in the patient record. Whenever possible, incomplete testing should be reported to the clinician as soon as possible so that testing can be repeated, if necessary. As with corrected reports, incomplete tests should be monitored and examined with the goal of modifying processes to prevent future occurrences.

Document Control

Clinical laboratories process and handle an enormous amount of information each day. These processes require an organized approach for controlling, organizing, and retaining this information and making it readily accessible to busy laboratory staff and laboratory inspectors. Document control can be a challenge to manage; electronic software packages are available to help the laboratory manage its documents. Nationally, the top three laboratory deficiencies identified during CAP on-site inspections in the years 1998 to 2001 were related to document control items (41). The Joint Commission inspection of laboratories yields similar results, especially when off-site or multisite laboratories are involved. A document control policy should state the intent and direction the laboratory takes to document and record the structure it uses for creating, revising, approving, distributing, storing, retrieving, and destroying documents. Using the Clinical and Laboratory Standards Institute Quality Systems approach, documents are broken down into 12 quality system essentials (Table 21.8) to provide laboratories with a mechanism to manage the information required to provide quality laboratory services (26).

Table 21.8 CLSI quality system essentials[a]

Organization	
	Leadership's commitment to laboratory quality and quality plan
	Organizational charts, definitions, responsibilities, and relationships
Customer focus	
	Identifies laboratory customers and expectations and a means to monitor
Facilities and safety	
	Overall safety plan with regard to facility and staff safety and emergency response planning
Personnel	
	Hiring, training, competency, qualifications, job/position descriptions
Purchasing and inventory	
	Supplier agreements to provide needed inventory and verification of incoming supplies.
Equipment	
	Selection and installation, equipment list, validation records, operation/maintenance checks
Process management	
	The path of workflow to make the most efficient use of laboratory resources.
Documents and records	
	Policies, processes, and standard operating procedures that control the creation, revision, approving, distribution, storing, retrieving, and destruction of laboratory documents
Information management	
	Confidentiality and security of patient information
Nonconforming event management	
	Reporting and analyzing of events that do not adhere to laboratory policies, processes, or standards
Assessments	
	Internal and external monitoring to ensure laboratory meets requirements
	External proficiency testing, accreditation, and quality indicators
Continual improvement	
	Identifying opportunities to continually look for ways to improve

[a]See reference 26.

Summary

Clinical laboratories are required to have in place a comprehensive quality program. This requires managing the quality of a wide spectrum of resources, procedures, and services by continuously evaluating quality indicators and making adjustments to improve laboratory performance and patient outcomes. The program involves ongoing inspection of the total testing process, from the time a test is ordered until the results are utilized. The quality program is supported by a robust document control system and is conducted by measurement and analysis of indicators to provide information to guide improvement.

KEY POINTS

- Quality management is a system for continuously analyzing, improving, and reexamining resources, processes, and services within an organization.
- The total testing process provides a comprehensive working model for evaluating the components of the laboratory's quality management plan as an interdependent component of the organization's total quality improvement program.
- Well-documented procedures and trained phlebotomy and nursing staff are key factors for ensuring quality of specimen collection.
- Patient satisfaction is an important quality indicator.
- Quality control is a method for establishing specifications for an analytical process, assessing the procedures, monitoring conformance by statistical analysis, and taking corrective actions to bring the procedures into conformance.
- The two most important factors affecting the postanalytical phase of the testing process are test reporting and result interpretation.
- Turnaround time, corrected reports, and incomplete testing are important indicators for monitoring the total testing process.
- A document control policy should state the intent and direction the laboratory takes to document and record the structure it uses for creating, revising, distributing, storing, retrieving, and destroying documents.

GLOSSARY

Accuracy Agreement between the best estimate of a quantity and its true value.

Analyte Sample to be measured.

Analytical error The difference between the result of an analytical method and the true value.

Analytical method Set of written instructions that describe the procedure, materials, and equipment necessary for the analyst to obtain a result.

Analytical range The range of concentration or other quantity in the specimen over which the method is applicable without modification.

Bias Systematic error that describes the difference between measured and true or assigned value.

Calibration Process of using standards of known concentration to establish a relationship between the measured signal from the instrument and analyte concentration.

Coefficient of variation A measure of variance expressed as a percentage of the mean ([standard deviation/mean] $\times 100$).

Confidence interval Expected range of values within a group with a specified probability.

Constant systematic error An error that is always in the same direction and of the same magnitude, even as the concentration of analyte changes.

Control limit A range of expected values that, if exceeded, warns of random and/or systematic error in an analytical process.

Control material Specimen that is repeatedly analyzed, with test results statistically analyzed to monitor method performance.

Delta check Rule-based method to compare a patient's current test result to a previous measurement to check for unexpected differences that might be due to analytical or nonanalytical errors in the testing process.

Error Deviation of measured concentration from expected or true value.

Gaussian distribution A random distribution of values described by their average and variance (standard deviation); used to describe analytical imprecision.

Imprecision Analytical variance, usually expressed as the standard deviation or coefficient of variation ([standard deviation/mean] $\times 100$).

Interference One or more specimen constituents that cause bias by affecting the analytical method.

Matrix Total constituents of the specimen that may affect the analytical process.

Maximum allowable error (MAE) Amount of error associated with an analytical method that can be tolerated without invalidating the medical usefulness of the result.

Mean Arithmetic average of a set of values.

Medical usefulness limits Quality control limits derived from clinical application of results rather than statistical imprecision of the method.

Normal range See reference range.

Proportional systematic error An error that is always in one direction and whose magnitude is a percentage of the concentration of analyte being measured.

Quality assurance A systematic approach to continuously analyzing, improving, and reexamining the total testing process.

Quality control A process for monitoring assay performance to detect deviations from expected outcomes.

Random error A variance from expected that is not reproducible or predictable.

Recovery Amount (usually expressed as percentage) of known quantity of an analyte that is measured when added to a specimen.

Reference range Test results that are within expected parameters for about 95% of all individuals in a defined healthy population. Values outside of the range are classified as abnormal and may be associated with a pathological condition.

Sample Part of specimen that is measured.

Sensitivity, analytical The lowest detection limit of an assay; sometimes measured as the concentration of an analyte that can be differentiated from a blank within a 95% confidence interval.

Specificity, analytical The ability of an analytical method to determine solely the component(s) it purports to measure.

Standard Material of known or assigned concentration used for assay calibration.

Standard deviation A statistic that describes the amount of variance of a set of measurements about the mean value. It is used to describe the random error of an analytical method.

Turnaround time The interval between the beginning of one event to the end of another event in the total testing process. Typically measured as the collection to reporting time or as the receipt of specimen in laboratory to reporting time.

Variance Standard deviation squared. Assuming all sources of error are independent of each other, total error is the sum of variances of individual sources of error.

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APPENDIX 21.1 Regulations, Guidelines, and Information with Application to a Clinical Laboratory

A listing of relevant regulations grouped according to the regulatory agency from which they are issued.

FDA

http://www.fda.gov/scienceresearch/specialtopics/runningclinicaltrials/ucm155713.htm (accessed May 7, 2013)

21 CFR 11, Electronic Records; Electronic Signatures, Subpart B—Electronic Records

21 CFR 58, Good Laboratory Practice for Nonclinical Laboratory Studies

- 58.185 Reporting of nonclinical laboratory study results
- 58.190 Storage and retrieval of records and data
- 58.195 Retention of records

21 CFR 211, Current Good Manufacturing Practice for Finished Pharmaceuticals

- Subpart J—Records and Reports (211.180–211.198)

21 CFR 600, Biological Products, General

- 600.12 Records

21 CFR 606, Current Good Manufacturing Practice for Blood and Blood Components

- 606.100 Standard operating procedures
- Subpart I—Records and Reports (606.160–606.171)

21 CFR 640, Additional Standards for Human Blood and Blood Products

- 640.72 Records

21 CFR 803, Medical Device Reporting of Adverse Events and Certain Malfunctions

- 803.17–803.18 Written MDR procedures, Files

21 CFR 820, Good Manufacturing Practice, Quality System Regulation

- Subpart M—Records (820.180–820.198)

Department of Labor: Occupational Safety and Health Administration (OSHA)

29 CFR 1904, Recording and Reporting Occupational Injuries and Illnesses

- 1904.6 Retention of records
- 1904.9 Falsification or failure to keep records or reports

29 CFR 1910 Occupational Safety and Health Standards

- Appendix C to 1910.120
  - 4. Training (records)
  - 8. Medical surveillance programs (records)

Department of Health and Human Services: Center for Medicare and Medicaid Services (CMS)

42 CFR 493, Laboratory Requirements (CLIA 88)

- 493.1107 Test—Records
- 493.1201(b) Written quality control procedures
- 493.1202(c)(2) Procedure manual, moderate-complexity testing
- 493.1211 Procedure manual, high-complexity testing
- 493.1221 Quality Control—Records
- 493.1721 Quality Assurance—Records

Department of Health and Human Services, Public Health

42 CFR 72, Interstate Shipment of Etiologic Agents

Department of Transportation

49 CFR 171–7 Shipment of Hazardous Materials

Department of Labor

29 CFR 71—Protection of individual privacy and access to records under the Privacy Act of 1974

Miscellaneous sources (specifics not listed)

American Association of Blood Banks: http://www.aabb.org (accessed 5/7/13)

CDC Guidelines: http://www.cdc.gov (accessed 5/7/13)

Clinical Laboratory Standards Institute (CLSI): http://www.clsi.org (accessed 5/7/13)

College of American Pathologists (CAP): http://www.cap.org (accessed 5/7/13)

FDA Guidelines, Guidances, and Memoranda: http://www.fda.gov/ (accessed 5/7/13)

Federal Register, multiple sources: https://www.federalregister.gov/ (accessed 5/7/13)

International Organization for Standardization (ISO): http://www.iso.org/iso/home/standards/management-standards/iso_9000.htm (accessed 5/7/13)

The Joint Commission: http://www.jointcommission.org (accessed 5/7/13)

APPENDIX 21.2 CAP Laboratory Inspection Checklist Associated with Quality Management

The checklist is comprised of declarative statements for which the laboratory must show evidence of compliance. The checklist provides "notes" that provide further detail on the declarative statements.

Quality Improvement

GEN.13806 The laboratory has a documented quality management (QM) program.

GEN.16902 For laboratories that have been CAP accredited for more than 12 months, the QM plan is implemented as designed and is reviewed annually for effectiveness.

GEN.20100 The QM program covers all areas of the laboratory and all beneficiaries of service.

GEN.20208 The QM system includes a program to identify and evaluate errors, incidents and other problems that may interfere with patient care services.

GEN.20316 The QM program includes monitoring key indicators of quality in the pre-analytic, analytic, and post-analytic phases.

GEN.20325 The laboratory has a procedure for employees and patients to communicate concerns about quality and safety to management.

GEN.23584 The laboratory conducts an interim self-inspection and documents efforts to correct deficiencies identified during the process.

Quality Management of Preanalytic Processes: Test Selection and Ordering

GEN.40000 There is a procedure manual or other source for the complete collection and handling instructions of all laboratory specimens.

GEN.40016 There is documentation of at least biennial review of the specimen collection/handling procedure manual by the current laboratory director or designee.

GEN.40050 The specimen collection manual is distributed to all specimen-collecting areas within the hospital (nursing stations, operating room, emergency room, out-patient areas) AND to areas outside the main laboratory (such as physicians' offices or other laboratories).

GEN.40100 The specimen collection manual includes instructions for all of the following elements, as applicable

1. Preparation of the patient
2. Type of collection container and amount of specimen to be collected
3. Need for special timing for collection (e.g., creatinine clearance)
4. Types and amounts of preservatives or anticoagulants
5. Need for special handling between time of collection and time received by the laboratory (e.g., refrigeration, immediate delivery)
6. Proper specimen labeling
7. Need for appropriate clinical data, when indicated

GEN.40125 For specimens sent to reference laboratories, the referring laboratory properly follows all requisition, collection and handling specifications of the reference laboratory.

GEN.40470 There is documentation that all personnel performing patient blood collection have been trained in collection techniques and in the proper selection and use of equipment/supplies.

GEN.40490 The individual collecting the specimen positively identifies the patient before collecting a specimen.

GEN.40935 The laboratory has a policy that personnel receiving verbal or phone orders read back the entire order to verify accuracy of transcription.

GEN.40938 The laboratory has a policy on confirmation of test orders that may be unclear (e.g., orders using non-standard or non-specific terms).

Quality of Specimen Collection

GEN.40505 There is a mechanism to provide feedback to the collector of the specimen on issues related to specimen quality.

GEN.40825 There is a system to positively identify all patient specimens, specimen types, and aliquots at all times.

GEN.43750 The system provides for comments on specimen quality that might compromise the accuracy of analytic results (e.g., hemolyzed, lipemic).

GEN.40535 There is an adequate process for monitoring the quality of submitted specimens, correcting problems identified in specimen transportation, and improving performance of clients or offices that frequently submit specimens improperly.

Patient and Client Satisfaction

GEN.20335 Referring physicians'/clients' or patients' satisfaction with laboratory service was measured within the past two years.

Quality Management of Analytic Processes

GEN.30000 There is a written quality control program that clearly defines policies and procedures for monitoring analytic performance.

GEN.30070 If the laboratory performs test procedures for which neither calibration nor control materials are available, procedures are established to verify the reliability of patient test results.

Proficiency Testing (PT)

COM.010000 The laboratory has written procedures for proficiency testing sufficient for the extent and complexity of testing done in the laboratory.

(continued)

APPENDIX 21.2 CAP Laboratory Inspection Checklist Associated with Quality Management *(continued)*

COM.01100 The laboratory has a procedure for assessing its performance on PT challenges that were intended to be graded but were not.

COM.01500 For tests for which CAP does not require PT, the laboratory at least semi-annually 1) participates in external PT, or 2) exercises an alternative performance assessment system for determining the reliability for analytic testing.

COM.01600 The laboratory integrates all proficiency testing samples within the routine laboratory workload, and those samples are analyzed by personnel who routinely test patient/client samples, using the same primary method systems as for patient/client/donor samples.

COM.01700 There is ongoing evaluation of PT and alternative assessment results, with prompt corrective action taken for unacceptable results.

COM.01800 There is a policy that prohibits interlaboratory communication about proficiency testing samples until after the deadline for submission of data to the proficiency testing provider.

COM.01900 There is a policy that prohibits referral of proficiency testing specimens to another laboratory.

Quality Management of Postanalytic Processes: Reporting

GEN.43825 Manual and automated result entries are verified before final acceptance and reporting by the computer.

COM.30000 The laboratory has procedures for immediate notification of a physician (or other clinical personnel responsible for the patient's care) when results of designated tests exceed established "alert" or "critical" values that are important for prompt patient management decisions.

COM.30100 When critical results are communicated verbally or by phone, there is a policy that laboratory personnel ask for a verification "read-back" of the results.

Turnaround Time

GEN.41345 Has the laboratory defined turnaround times (i.e., the interval between specimen receipt by laboratory personnel and results reporting) for each of its tests, and does it have a policy for notifying the requester when testing is delayed?

Corrected and Incomplete Reports

GEN.41307 When errors are detected in patient test reports, the laboratory promptly notifies responsible clinical personnel or reference laboratory as applicable and issues a corrected report.

GEN.41310 All revised reports of previously reported, incorrect patient results are identified as revised, and both the revised and original data are clearly identified as such.

Document Control

GEN.20375 The laboratory has a document control system.

GEN.20377 Laboratory records and materials are retained for an appropriate time.