

Current quality assurance concepts and considerations for quality control of in-clinic biochemistry testing

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Quality assurance is an implied concept inherent in every consumer's purchase of a product or service. In laboratory testing, quality assurance encompasses preanalytic (sampling, transport, and handling prior to testing), analytic (measurement), and postanalytic (reporting and interpretation) factors. Quality-assurance programs require that procedures are in place to detect errors in all 3 components and that the procedures are characterized by both documentation and correction of errors. There are regulatory bodies that provide mandatory standards for and regulation of human medical laboratories. No such regulations exist for veterinary laboratory testing. The American Society for Veterinary Clinical Pathology (ASVCP) Quality Assurance and Laboratory Standards Committee was formed in 1996 in response to concerns of ASVCP members about quality assurance and quality control in laboratories performing veterinary testing. Guidelines for veterinary laboratory testing have been developed by the ASVCP. The purpose of this report was to provide an overview of selected quality-assurance concepts and to provide recommendations for quality control for in-clinic biochemistry testing in general veterinary practice. (*J Am Vet Med Assoc* 2013;242:182–192)

All clinicians expect that the results obtained from the diagnostic tests they perform on their patients are accurate and precise, so that correct clinical decisions can be made to manage their patients. Obtaining results that are inaccurate or imprecise can lead to incorrect diagnoses, inappropriate courses of action, and, potentially, patient harm. These expectations apply to in-clinic biochemistry analyzer systems, which have proliferated in general veterinary practice over the past decade. However, despite the popularity of these analyzers, quality-assurance programs and QC systems have been largely neglected in general veterinary practice, with most clinicians relying on manufacturers' claims and occasional calibration of equipment to ensure diagnostic test quality.

Quality assurance is an implied concept inherent in every consumer's purchase of a product or service. Many of the initial quality-assurance procedures came from the manufacturing sector and were the result of the need to produce products that were cost effective and did not fail.¹ Quality-assurance systems were then discussed and applied over time in human diagnostic laboratories beginning in the 1950s² and subsequently implemented in veterinary laboratories. These programs have changed and evolved along with new procedures, statistical concepts, and evaluations of system

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ABBREVIATIONS

ALT	Alanine aminotransferase
ASVCP	American Society for Veterinary Clinical Pathology
CV	Coefficient of variation
QC	Quality control
QCM	Quality control material
TEa	Total allowable error
TEc	Total calculated error

flaws, with the goal of ensuring that each and every result is correct.

In laboratory testing, quality assurance encompasses 3 major components: preanalytic (sampling, transport, and handling prior to testing), analytic (measurement), and postanalytic (reporting and interpretation) factors. Quality-assurance programs require that procedures are in place to detect errors in all 3 components and that the procedures are characterized by both documentation and correction of errors.

There are regulatory bodies that provide mandatory standards for and regulation of human medical laboratories as well as numerous accreditation bodies.^{3,4} In concert with the regulation of these laboratories, there are regulations governing the production of medical testing devices, including standards of performance.^{5,6} No such regulations exist for veterinary laboratory testing.

The ASVCP Quality Assurance and Laboratory Standards Committee was formed in 1996 in response to concerns of ASVCP members about quality assur-

ance and QC in laboratories performing veterinary testing. The committee was charged as follows: “to encourage and promote the establishment of standards for the performance of laboratory procedures” on veterinary samples. Guidelines for veterinary laboratory testing have been developed by the ASVCP, the most recent of which are now posted on the ASVCP website⁷ and as summary reports in the veterinary literature.⁸

Laboratory quality assurance is a robust field of inquiry and interest in human medicine, and there has recently been increased interest in laboratory quality assurance in veterinary medicine.^{9–18}

Most recently, a study¹⁹ examined the real-world precision, accuracy, and sources of error of in-clinic and reference laboratory biochemistry testing. On the basis of evidence provided in that study¹⁹ and the current resurgence of interest in QC and quality assurance by various veterinary hospital–certifying organizations and other veterinary organizations,^{20–23} specific recommendations for quality assurance and QC for in-clinic biochemistry testing are warranted.

The purpose of this report is to provide an overview of selected quality-assurance concepts and to provide recommendations for QC for in-clinic biochemistry testing in general veterinary practice.

Background, historical perspective, and need for quality awareness in veterinary laboratory testing

The ideal in-clinic veterinary biochemistry analyzers would be accurate, precise, and easy to use and would detect and correct errors identified during the testing process. Many commercially available systems are marketed as “plug and play” technology. Traditionally, the need for QC has not been addressed in marketing materials or user manuals. Some analyzers have built-in checks of electronic components, but the traditional QC approach that assesses all aspects of the analytic process (operator, analyzer, and reagents) is lacking. Veterinarians have primarily relied on the manufacturers’ claims of validity of a particular analyzer for use with various species, but information about the basis for such validations and independent examinations of such claims are conspicuously sparse. The lack of emphasis placed on quality assurance and QC as an intrinsic and ongoing component of veterinary education and practice, coupled with a similar lack of emphasis during marketing and sale of such analyzers, represents a potential risk to veterinary patients and, consequently, a potential risk of litigation by aggrieved clients. This lack of emphasis is further complicated by a paucity of personnel in veterinary clinics who are trained in laboratory instrumentation, procedures, and QC.

Recommendations for basic quality assurance and QC have recently been included by some manufacturers of in-clinic laboratory analyzers. Education regarding quality assurance and QC is becoming more prevalent at veterinary meetings, and guidelines for veterinary laboratory testing quality assurance and QC are now provided by the ASVCP.⁷ However, these can only be effective if adopted by the manufacturers of in-clinic laboratory analyzers and veterinarians using their analyzers in clinical practice.

Astute clinicians evaluate and address disparities between the results obtained and their clinical appraisal

of sick patients, rather than accepting laboratory results without such consideration. However, the use of in-clinic laboratory testing to detect subclinical or occult disease in animals without clinical signs as part of routine wellness or preanesthetic testing allows for no possibility to correlate findings with clinical signs because no clinical signs are present. The veracity of these laboratory results cannot be determined by simple reassessment of the complete clinical picture. Ignoring abnormal laboratory results in an animal with a normal clinical assessment (ie, assuming false-positive laboratory results and discounting them) raises the issue of why the laboratory tests were run at all if abnormal results are to be routinely discarded. Alternatively, clinicians are obliged to pursue abnormal results, possibly at considerable expense to the owner and potential risk to the patient, to confirm or refute the initial abnormal result. Similarly, clinicians might be unable to determine whether a normal test result for a clinically normal animal is a true-negative or false-negative finding. Therefore, systems to help ensure production of reliable, accurate, and precise results in which the clinician has the confidence to allow decisions to be made about further investigations, treatment, or monitoring are of paramount importance.

A specific focus of laboratory quality-assurance programs is error detection. Analytic errors can occur because of inaccuracy (systematic error or bias) or imprecision (random error). Properly run quality-assurance programs are designed to detect these errors in a timely manner, reducing unnecessary additional testing or inappropriate and potentially harmful treatment.

Concepts critical to the understanding of laboratory testing quality

Several key concepts of laboratory testing quality are important for understanding the quality-assurance recommendations described later in this paper and are as follows: quality requirements for laboratory testing, performance characteristics of laboratory analyzers, relationship of laboratory analyzer performance to quality requirements, principles of statistical QC, and customization of statistical QC on the basis of analyzer performance.

Quality requirements for laboratory testing—Quality requirements provide a basis for judging the performance of an analyzer or method for laboratory testing. Quality requirements for testing may vary with the type of laboratory, the clientele, the species being evaluated, the use of the laboratory results, the concentrations of analytes, the clinical decision levels with each analyte, and the capability of current analyzers.²⁴

Clinical decision levels (also termed clinical decision limits or clinical decision thresholds) are the concentrations or activities (when dealing with enzymes) of each analyte that trigger a medical decision (ie, to treat or not treat the patient or to pursue additional diagnostic testing). This is also described as a concentration or activity that distinguishes 2 populations: those with disease and those without disease. To establish a consensus on clinical decision levels, there must be an objective assessment of the test characteristics that includes an appreciation of the precision, accuracy, and performance of both the test and the equipment and the defined reference intervals that are relevant to the population tested.

Total allowable error, a standard quality requirement concept, can be applied to data obtained from the use of assayed QCM from which SDs and CVs are determined by accessible computer programs.^a Relevant TEa values both as percentages and actual concentrations have been developed for use in human diagnostic laboratories and are part of the analyzer and methodology evaluation necessary to comply with laboratory testing standards. One purpose of this report is to familiarize veterinary clinicians with this concept and outline ways to implement TEa and basic QC procedures for in-house laboratories.

Total allowable error encompasses multiple possible sources of error, including imprecision, bias, and other sources of variation. The TEa can vary considerably, depending on the analyte and the clinical decision levels of interest, and no single value applies across all analytes. The TEa should be examined at concentrations of the analyte that represent or reflect clinical decision levels because it is at these levels that interpretation of results is most clinically critical. For example, if the clinical decision level for sodium concentration is 140 mEq/L, the suggested TEa is $\pm 5\%$ (± 7 mEq/L), resulting in a range of 133 to 147 mEq/L. This range typically falls within that included in the reference interval for sodium concentration and helps ensure that an analyzer result of 140 mEq/L would not be so erroneous that it could actually be abnormal (eg, 130 mEq/L) or misinterpreted as abnormal. On the other hand, the TEa for ALT activity at a clinical decision level of 60 U/L could be 100% (± 60 U/L) and with a reference range of 0 to 120 U/L would not alter the interpretation of the result; ALT activities of 60 and 120 U/L would both be correctly interpreted as normal. There is no need to examine TEa for analyte concentrations having no clinical significance, as the example of a low ALT activity demonstrates (equally nonsensical would be examination of TEa for ALT activity $> 1,000$ U/L because clinicians would not be concerned about results above this value being accurate for the purposes of clinical decision making). Examples of a method to determine TEa and the application to several analytes are summarized (Table 1).

A conference held in Stockholm in 1999 provided a consensus developed by laboratory experts from 27 countries regarding a hierarchy upon which quality requirements should be based (Table 2).²⁵ This consensus presents a 5-tiered approach to establishing quality requirements, with the highest level attained through evaluation of the effects of analytic performance on clinical outcomes in specific clinical settings. The second level of the hierarchy is based on evaluation of the effect of analytic performance on clinical decisions in general, on the basis of biological variation and analysis of clinicians' opinions. The third level within the hierarchy is published professional recommendations from national and international expert bodies or from expert local groups of individuals. These 2 latter levels are represented by 2 reports^{13,14} in the veterinary literature and have been commented on in a brief communication.²⁴

The fourth level of the hierarchy is represented by performance goals set by regulatory bodies or providers of external quality-assurance programs. This level does not currently apply in veterinary medicine because of the absence of regulations for veterinary laboratory testing.

The fifth and lowest level of the hierarchy is goals based on current state of the art, reflected by data from external quality assurance or proficiency testing schemes and current publications on methodology. This area is also underdeveloped in veterinary medicine.

Performance characteristics of laboratory analyzers—Any consumer who purchases a product subsequently assesses the quality of the product (consciously or subconsciously) on the basis of his or her experience with the product and expectations derived from education, experience, or marketing of that product. Practical consumerism and the principles of good laboratory practice dictate that an initial assessment of a new analyzer should be performed to ensure that the analyzer is performing properly out of the box.

The types of studies usually conducted within reference laboratories are extensive and traditionally include evaluation of the reportable ranges for analytes, precision studies, and studies to determine the amount and type of bias that is present with stable analyzer performance.²⁶ The goal of such evaluations is to determine the amount of variation or error that can occur with testing and to ensure that this amount of error is less than the levels acceptable for interpretation of the test based on established quality requirements. The first step involves a familiarization period with the analyzer consisting of training of personnel and establishing stable performance. Following this familiarization period, the analyzer is evaluated to determine the magnitude of the error components (accuracy and precision) that would be present in the later analysis of patient samples. These are expressed as bias and SD or CV. Laboratory personnel use these data to evaluate the performance capability of the analyzer for each analyte over a range of values of clinical interest by determining the TEc via the formula $\text{bias} + 2 \text{CV}$ (which accounts for the 95% confidence interval for potential errors that may occur).¹⁹ Other methods for determining TEc are also used in laboratories and depend on the level of confidence in error detection that is required.²⁷ If the TEc is found to be less than the predetermined TEa (ie, $\text{TEc} < \text{TEa}$) for a particular analyte at several clinical decision levels, the performance of the analyzer is considered acceptable for that analyte. This process is repeated for every analyte measured by the analyzer. Clinicians should be concerned if no, or only a few, analytes are considered acceptable and consider rejecting the analyzer as unsuitable for use in veterinary testing. The TEa can be calculated with different formulas, and guidelines for TEa are currently under development by the Quality Assurance and Laboratory Standards Committee of the ASVCP. Essentially, the calculation reflects the degree of variation in the analyte value that will impact clinical decisions (Table 2).

If the TEc is found to be greater than the predetermined TEa (ie, $\text{TEc} > \text{TEa}$) for 1 or several analytes, several options exist. The laboratory can choose to do the following:

- Attempt to improve performance capability through analyzer adjustments, operator training, or analyzer replacement. This incurs additional time and expense since the same evaluation needs to be re-

Table 1—Examples of approaches to determine quality requirements on the basis of clinical interpretation and use of laboratory results.

Example	Analyte (result of interest)	Basis	Calculation of desirable TEa
1	Albumin (slightly decreased)	Many reference intervals for albumin will have a lower limit around 25 g/L. A slight decrease in albumin based on the clinical decision level (the level considered likely to need further investigation) is 22.5 g/L.	<p>Determination of quality requirement, expressed as desirable TEa (TEa_d), at a clinical decision level of 22.5 g/L:</p> $TEa_d (\%) = \frac{ lower\ limit\ of\ reference\ interval - clinical\ decision\ level }{clinical\ decision\ level} \cdot 100$ $= \frac{ 25.0 - 22.5 }{22.5} \cdot 100 = \frac{2.25}{22.5} \cdot 100 = 11\%$
2	Albumin (moderately decreased)	The clinical decision level of interest for moderately low albumin is considered to be 18 g/L. This is at or approaching the concentration at which colloidal osmotic pressure may be sufficiently decreased to result in effusion. This concentration warrants further investigation if an underlying cause has not been determined and may warrant treatment if effusion or other clinical signs are present.	<p>Determination of quality requirement, expressed as desirable TEa (TEa_d), at a clinical decision level of 18 g/L:</p> $TEa_d (\%) = \frac{ clinical\ decision\ level\ of\ interest - closest\ clinical\ decision\ level }{clinical\ decision\ level\ of\ interest} \cdot 100$ $= \frac{ 18 - 22.5 }{18} \cdot 100 = \frac{4.5}{18} \cdot 100 = 25\%$
3	ALT (slightly increased)	Usually, an increase in ALT is considered of clinical importance if a persistent elevation of 2X the upper reference limit is identified. The upper limit of many reference intervals for ALT is approximately 120 U/L. So the clinical decision level for a slight increase in ALT is 240 U/L.	<p>Determination of quality requirement, expressed as desirable TEa (TEa_d), at a clinical decision level of 240 U/L:</p> $TEa_d (\%) = \frac{ lower\ limit\ of\ reference\ interval - clinical\ decision\ level }{clinical\ decision\ level} \cdot 100$ $= \frac{ 120 - 240 }{240} \cdot 100 = \frac{120}{240} \cdot 100 = 50\%$
4	ALT (within reference interval)	The reference interval for ALT is sometimes expressed as 0 to 120 U/L or < 120 U/L. It is considered desirable to be able to differentiate a value that is in the middle of the reference interval from that which is approaching the upper limit of the reference interval, so the midreference interval is used as 1 clinical decision level and the upper limit of the reference interval is used as the second clinical decision level.	<p>Determination of quality requirement, expressed as desirable TEa (TEa_d), at a clinical decision level of 60 U/L:</p> $TEa_d (\%) = \frac{ clinical\ decision\ level\ of\ interest - closest\ clinical\ decision\ level }{clinical\ decision\ level\ of\ interest} \cdot 100$ $= \frac{ 60 - 120 }{60} \cdot 100 = \frac{60}{60} \cdot 100 = 100\%$ <p>The TEa_d for values within the reference interval could also be calculated with the clinical decision level as the upper limit of the reference interval (120 U/L), as follows:</p> $TEa_d (\%) = \frac{ clinical\ decision\ level\ of\ interest - closest\ clinical\ decision\ level }{clinical\ decision\ level\ of\ interest} \cdot 100$ $= \frac{ 120 - 60 }{120} \cdot 100 = \frac{60}{120} \cdot 100 = 50\%$

peated following adjustments, training, or analyzer replacement to determine whether these have been successful in improving the analyzer performance.

- Relax the initial quality requirements (increase the desired TEa). This is possible only if there is room for additional error in interpretation of the patient results. Education of all clinicians who use the in-clinic analyzer regarding desirable interpretation criteria and analyzer capability is important in guiding interpretation of routine results, repeated test results, or results obtained from serial monitoring of patients.

Alteration of quality requirements can be considered if the alteration does not invalidate the interpretation of the patient results or if the additional error in-

herent in such an alteration is taken into account when interpreting the results. Since there are few current recommendations for quality requirements for analytes used in veterinary testing, deviation from quality requirements from those which may be recommended by others (such as the upcoming recommendations of the ASVCP Methods Validation Subcommittee) ultimately rests with the clinician's personal decision regarding the use of the results. Consultation with a clinical pathologist who is experienced and interested in quality assurance of laboratory testing is strongly recommended to help implement this decision-making process. Clinicians inexperienced in QC should not attempt to alter TEa without consultation, as this might invalidate the results they obtain for a particular analyte.

Table 2—Hierarchy of quality requirements determined by the Stockholm conference, 1999.²⁵

Level within the hierarchy (I = highest; V = lowest)	Basis for quality requirement	Comments
I	Effect of analytic performance on clinical outcomes in specific clinical settings	Studies currently lacking in veterinary medicine
II	Effect of analytic performance on clinical decisions on the basis of data from components' biological variation and data from analysis of clinicians' opinions	Some basis for this in veterinary medicine
III	Published professional recommendations from national and international expert bodies or expert local groups or individuals	Currently the strongest support in veterinary medicine
IV	Performance goals set by regulatory bodies and organizers of external quality assessment schemes	Not applicable in veterinary medicine owing to lack of regulation
V	Goals based on the current state of the art as demonstrated by data from external quality assurance or proficiency testing schemes or publications on methodology	Data limited or not currently available for in-clinic instrumentation or methodology

For example, consider the desirable TEa for albumin concentration of 11% at a clinical decision level of 22.5 g/L (2.25 g/dL). The reference interval for albumin concentration is 25 to 42 g/L (2.5 to 4.2 g/dL).

At a TEa of 11%, the clinician is willing to accept results ranging from 20.0 to 25.0 g/L (2.0 to 2.5 g/dL) as being not different from the true concentration of 22.5 g/L (2.25 g/dL; $22.5 \pm 11\% = 22.5 \pm 2.5 = 20.0$ to 25.0 g/L). The extreme at 1 end of this range is 25.0 g/L, which is the lower limit of the reference interval. A result of 25 g/L (2.5 g/dL) may not warrant further diagnostic investigation or treatment; however, it may prompt continued monitoring to ensure the albumin concentration is not continuing to decrease. Alternatively, a result of 20 g/L (2.0 g/dl) is likely to prompt prompt diagnostic investigation and even treatment.

If the initial analyzer evaluation for a particular analyzer determined bias for albumin concentration at the clinical decision level of 22.5 g/L to be 5% and the CV to be 3.5%, the following formula results: $TEc = \text{absolute bias (\%)} + 2(CV) = 5 + 2(3.5) = 5 + 7 = 12\%$. In this example, the TEc (12%) is greater than TEa (11%). This may trigger rejection of the analyzer method since the performance does not result in the desirable quality (desirable TEa). However, because the TEc is close to the 11% desirable TEa, it might be reasonable to examine whether a slight revision of the quality requirement (desirable TEa) is acceptable or not (in other words, whether it will highly impact interpretation of an albumin concentration near 22.5 g/L).

If the TEa is adjusted upward to 12%, the range of albumin concentrations around the clinical decision level (22.5 g/L) is now higher at 19.8 to 25.2 g/L. The upper end of this range (25.2 g/L) is still at the low end of the reference interval (25 g/L), which warrants further monitoring to determine whether the albumin concentration will fall below the reference interval. A result at the low end of this error range (eg, 19.8 g/L) would likely instigate further investigation as to under-

lying cause. Therefore, the relaxation of the TEa from 11% to 12% is acceptable on the basis of the clinical interpretation of the test and is unlikely to adversely affect patient care. Whereas the more strict quality requirement of 11% may be preferred, if other aspects of the analyzer and its performance are acceptable, the relaxation of the quality requirement to 12% for slightly low albumin concentration should be considered.

In this example, the relaxation of the TEa is an acceptable alternative and the knowledge of the potential total error can be taken into account when evaluating albumin results. Knowledge of the potential total error may help the clinician in the decision-making process and provide sound evidence for additional diagnostic investigations. Such concepts are complex and can be difficult to grasp for many clinicians; therefore, clinicians examining quality requirements and analyzer performance would be well advised to consult clinical pathologists trained in the concepts of statistical QC and allowable error determination to help establish appropriate measures of analyzer performance.

Principles of statistical QC—Statistical QC involves running 1 or more well-characterized QCMs to make decisions regarding the stability and acceptability of analyzer performance. In reference laboratories, this is usually done at least once daily with the start-up of analyzers at the beginning of a shift. Additional controls may be run throughout the shift or at the end of the shift, depending on analyses of analyzer stability, known problematic conditions, other factors, and the philosophy of the laboratory leadership.^{28,29} Statistical QC provides the means to detect changes in operating systems (methods, reagents, and operator) that indicate potential problems that need to be addressed prior to analyzing patient samples. Decision criteria regarding the acceptability of control material data as a reflection of stable and reliable performance are expressed as control rules.³⁰ Ideally, the statistical control rules that are

applied should provide a high probability of error detection with a low probability of false rejection. This means that if excessive error is present, statistical QC should alert the laboratory personnel of the possibility of a problem and, if no problems exist, no false alarm should be raised.³¹

The probabilities of error detection and false rejection for a particular analyte at a given clinical decision level depend on 3 factors: the quality requirement for the test (ie, TEa), the bias, and the SD or CV for the analyte in question. The mathematical bases for these factors have been studied in detail, and both manual and computerized programs have been developed to help determine the best approaches to making decisions about specific control rules and numbers of control materials that should be used to assess operating system performance.³² The process of determining which control rules should be applied to achieve a high probability of error detection and low probability of false rejection on the basis of the performance capability of a particular analyzer is called QC validation.

The report by Rishniw et al¹⁹ provides a definition of in-clinic statistical QC that allows a simple, economical, easily understood way to determine performance acceptability. This system requires application of only 1 simple control rule that accepts values up to 3 SDs from the mean (labelled a 1_{3s} rule). This means that any result falling within 3 SDs from an established mean for a control material is considered acceptable performance or within control; conversely, any result falling outside of 3 SDs from the established mean for a control material is considered unacceptable performance and outside the control. Either 1 or 2 levels of QCM are needed to achieve a high probability of error detection (> 85% with 1 control material and > 90% with 2 control materials) and a low probability of false rejection (virtually 0% with either 1 or 2 control materials). A table within the report by Rishniw et al¹⁹ provides data extrapolated from a designing software program that was used to determine whether those analytes were suitable for in-clinic QC when the quality requirement (TEa) and performance characteristics of bias and CV are known by use of the single 1_{3s} control rule for either 1 or 2 levels of QCM.

The determination of bias and CV via assayed QCM should be an integral part of the initial assessment of an analyzer. Not all analytes or analyzers will be suitable for statistical QC with this approach because a high degree of both accuracy (determined by bias) and precision (determined by CV) is required to have a high probability of error detection (Ped) and low probability of false rejection (Pfr). If high numbers of analytes are determined to be unsuitable for in-clinic QC, several options exist and may be used in combination³³:

- Work with the analyzer manufacturer to determine if a reason for poor analyzer performance can be identified and to enable as large a number of analytes as possible to be subjected to statistical QC by in-clinic QC specifications. This might require substituting the current unit for a different unit if no specific fault can be identified. Additional evaluation of the new analyzer will be required to determine if it has performance that allows a larger

number of analytes to be suitable for statistical QC according to in-clinic QC specifications.

- If adequate performance based on predetermined TEa is not achievable, then consider evaluation of a new analyzer, either of the same type or from another manufacturer. It should be acknowledged that a different analyzer might or might not perform suitably and that additional time and expense are required for further evaluations. Such investment may be preferable to dissatisfaction with inaccurate and imprecise results that may be produced by some analyzers.
- Revise the TEa requirements. There are some analytes for which a wide error range may not make a clinically significant difference (eg, ALP), whereas other analytes, such as electrolytes, require narrow ranges. Clinicians unfamiliar with QC principles should consult a clinical pathologist trained in analyzer QC prior to revising TEa requirements to prevent inappropriate adjustments. Some analytes may not meet desirable TEa requirements, but, when considered in the context of the performance of the analyzer with multiple analytes, may be considered an acceptable compromise, and any differences in desirable TEa and calculated TEa should be taken into account when interpreting those analytes.
- Consult board-certified clinical pathologists with an interest in quality assurance to help determine the best approaches for statistical and nonstatistical QC and in overall planning and implementation of a quality system designed to provide assurance of quality in laboratory testing. These specialists are in the unique position of an interface between medicine and the laboratory and are well trained in the correlation of data with clinical findings.

When statistical QC cannot be relied on to provide peace of mind regarding production of accurate and reliable results, nonstatistical QC (ie, nonstatistical quality-assurance procedures) should be used to help ensure that accurate results are produced. Nonstatistical QC may include a variety of aspects, such as correlation of clinical findings with laboratory results, correlation of a laboratory result with other laboratory results assessing the same or different organ systems, criteria for repeat testing, medical review criteria for defined levels of results, and criteria to define the need to send the sample to the reference laboratory for comparative testing. Evaluation of all patient results for single and multiple analytes generated for a given time period (daily or weekly, depending on the volume of testing) may also be used to help determine if there are detectable errors, trends in results, or other findings that may reflect unacceptable quality in laboratory testing. Participation in an external quality assurance (proficiency testing) scheme aids in comparing the performance of the individual analyzer with the performance of a peer group using the same analyzer or method of testing.

Participation in an external quality-assurance program is a necessary component of quality assurance. The authors recognize that at this time, clinicians using in-clinic analyzers have little opportunity to participate

in comprehensive external quality-assurance programs that are applicable to their laboratory practice.

Reliable external quality-assurance programs exist for the major reference laboratory biochemical analyzers. The commonly used in-clinic analyzers are poorly represented in most quality-assurance programs used by reference laboratories. Local, limited quality-assurance programs for in-clinic analyzers exist in some countries (eg, United Kingdom), but participation is voluntary and represents only a fraction of the total in-clinic analyzers that potentially could participate. Additionally, many of these are rudimentary and do not routinely encompass statistical QC methods but merely compare performance of an individual analyzer with similar analyzers. Therefore, international standards with known accurate measurement and ranges of measurement need to be developed for in-clinic quality assurance.

Customization of statistical QC on the basis of analyzer performance—The performance capability has been shown to differ considerably amongst in-clinic biochemistry analyzers of the same and different types.¹⁹ Analysis of assayed QCMs that have been validated by sources other than the analyzer manufacturer provides the most accurate assessment of performance because it allows comparison of the clinician's analyzer with other identical analyzers or at least analyzers that use the same methods, including QCMs that cover the clinically relevant decision levels. Simply deferring to the analyzer manufacturer's range for a given QCM might or might not provide the high probability of error detection and low probability of false rejection a clinician desires. Basing statistical QC decisions on the actual performance of the analyzer and quality requirements acceptable to the in-clinic laboratory provides a sound evidence-linked basis for these practices and does not rely on the manufacturer of the analyzer to provide ongoing assurance of quality of the testing. Instead, the responsibility for ongoing quality assessment and quality assurance for in-clinic testing should rest with those who are actually generating the results and working with the analyzers on a daily basis. The use of assayed QCM is a basic step toward analyzer evaluation. Although the in-clinic analyzer may not have been evaluated with the assayed QCM, similar types of analyzers and methodologies will be represented and can be used to provide an estimate of the acceptable ranges that the analyzer should achieve.

Considerations for quality assurance for in-clinic biochemistry testing

The following describes in a stepwise manner how to apply the concepts discussed in the opening sections to in-clinic biochemistry testing. These concepts apply to each test performed and are for the specific purpose of determining the consistency of the instrument. These are considered a baseline evaluation of the instrument. These concepts are not intended to evaluate a specific setting or methodology evaluation that is required to verify tests for their use in different species.

1. Perform an initial assessment of an in-clinic biochemistry analyzer, following a period of

familiarization and satisfaction with early performance by use of control materials and patient samples and assurance of initial stable performance.

- a. This initial analyzer assessment should consist of evaluation of at least 2 (and preferably 3) assayed QCMs daily for 5 days to characterize the performance of the analyzer across a range of analyte values.
- b. From these data, the mean, SD, and CV should be calculated for each QCM for each analyte. The bias should be calculated relative to the mean of the assayed QCM. Using the manufacturer-provided assayed QCM mean to calculate bias is only valid if that mean was generated by use of the same analyzer or analytic method as the analyzer being evaluated. The TEC should be calculated with the formula absolute bias (%) + 2(CV), and the results should be compared with the desired or suggested TEa for each analyte.^{19,a}
- c. If performance is deemed to be adequate relative to TEa (TEC < TEa or close to it), then the performance characteristics can be used to determine those analytes suitable for statistical QC.¹⁹
- d. The results should be evaluated to determine the acceptability of the performance of the analyzer and whether or not it is suitable for the needs of the in-clinic laboratory at this point. If the performance is not considered suitable, then additional investigation to determine the reason and whether an in-clinic analyzer of the same or other type is capable of performing at the required level is needed.
- e. Determine the number of assayed QCMs to be used for routine QC procedures. In most cases, at least 2 QCMs are advised to span a range of clinical decision levels.
- f. Arrange with the QCM manufacturer to provide enough material to last for a year (interval between analyzer assessments). Initial discussions with the manufacturer of the QCM should be undertaken prior to the initial evaluation to ensure that this option is available for the QCMs selected at its completion. This is important because analyte concentrations in QCM vary from batch to batch, which impacts analyses by changing the TEa and clinical decision limits.
- g. For those analytes suitable for statistical QC, determine the frequency of QC testing and method of recording of QC results. Documentation should be kept of the lot or batch number of QCM, frequency of QC performance, trouble-shooting and corrective actions taken, and subsequent monitoring to determine the efficacy of corrective actions in eliminating problems. Daily QC is the standard in both veterinary and human reference laboratories and, as such, should

be considered as a comparable standard for in-clinic veterinary testing. Pet owners likely desire no lesser standard of care and quality in testing conducted for their pets than that used for their own laboratory results. Therefore, perform QC, using an aliquot of the QCM, any day that you analyze patient samples. If a clinician elects less frequent QC, patient results generated between an acceptable QC result and an unacceptable QC result must be considered suspect. It is not possible to know when analyzer performance has deteriorated if QC is not run with reasonable frequency. Current American Animal Hospital Association guidelines require at least weekly QC for biochemical in-clinic analyzers.

2. Repeat the analyzer performance study described above annually to determine that adequate performance is sustained and that statistical QC continues to be appropriate for the various analytes. Ideally, this evaluation should coincide with any software updates since these updates have the potential to change the analyzer performance capability.
3. Use caution in comparison of results obtained by in-clinic analyzers and the reference laboratory, particularly when different methods of analysis are used. If evaluation of the results obtained by both laboratories indicates a discrepancy, the clinic-based result \pm TEa will aid in determining if the reference laboratory result and the clinic range are in agreement. Other comparison methods might be applicable and have been reviewed.¹⁸
4. Participate in an external quality-assurance (proficiency testing) program where possible to help ensure accuracy of results, particularly for those analytes that are deemed to not be suitable for statistical QC. Inquiries prior to participation in such a scheme should ensure that other users of the same analyzer or method are represented in order to have an appropriate peer group for comparison.
5. Develop a written quality plan, policies, analyzer log, standard operating procedures, and forms for quality assurance and statistical and nonstatistical QC for the in-clinic laboratory.
6. Consult with a board-certified clinical pathologist with an interest in quality assurance and analyzer evaluation to determine the most appropriate methods of QC for your situation.
7. Provide ongoing education for veterinarians, veterinary technicians, and other clinic personnel serving as analyzer operators regarding quality assurance and QC for in-clinic laboratory testing.

Discussion

In-clinic QC for biochemical analyzers requires a compromise between what is currently being performed in most veterinary clinics (ie, nothing or almost nothing)

and what is done in reference laboratories. Our recommendations provide a reasonable platform for clinicians with in-clinic analyzers to begin performing QC on currently owned analyzers and to consider remedial steps should performance be found insufficient. Unfortunately, there are very few programs available for veterinary in-clinic QC; because the concept is in its infancy, a few certifying organizations (American Animal Hospital Association and Royal College of Veterinary Surgeons) are recommending that clinics comply with QC guidelines to maintain certification, with a view to imposing mandatory QC in the future for hospital certification. Only by undertaking quality assessment and implementing quality requirements (albeit, at considerable expense) can clinicians with in-clinic analyzers become confident of the performance of their analyzers and the veracity of their results. Unfortunately, some of the recommendations in the present report are currently difficult to comply with because the infrastructure either does not exist or is rudimentary. For example, external quality-assurance programs that focus on common in-clinic analyzers still need to be established to allow clinicians to meaningfully compare the performance of their analyzers with that of their peers, using clinically relevant QCM.

Our recommendation of using only 5 days of data to calculate bias, SD, and CV provides a clinically relevant estimate of analyzer performance characteristics over time. Whereas veterinary reference laboratories use 20 data points to determine these estimates (this produces narrower confidence limits),^{7,8} the use of 5 days of data is a compromise based on willingness of in-clinic laboratories to invest time, money, and effort into characterizing analyzer performance for clinical use and ability to generate meaningful data. Each day of a QC analysis represents a snapshot of laboratory performance, similar to that obtained with a single examination of a veterinary patient. As with any such examinations, confidence in the accuracy and validity of such a snapshot is obtained with serial examinations over longer periods of time to truly become aware of the ongoing general competency of the veterinary laboratory.

Whereas statistical QC is desired, not all analytes with all analyzers will be suitable for statistical QC. It is apparent from a prior clinical study¹⁹ that some in-clinic analyzers perform too poorly to allow statistical QC to be used as the primary means of detecting variation that would invalidate interpretation of a result according to the defined criteria for in-clinic QC. The prior study¹⁹ found that some individual analyzers had as few as 16% or as many as 87% of the analytes amenable to statistical QC.

Clinicians using in-clinic analyzers should recognize that daily oversight of the equipment, calibrations (not done with all analyzers), proper control of the reagents, and training of the personnel should be standard operating procedure and that tests should only be performed by clinic staff who have been appropriately trained and designated for this set of tasks. Additionally, analyzer manufacturers should provide documentation as to the accuracy and precision of their equipment as a matter of routine. Any improvements in analyzer performance and minimization of variation among analyzers of the same and different manufacturers rest with the

manufacturer of the analyzer. Training and education of veterinary personnel in all aspects of laboratory quality planning, implementation, analyzer evaluation, and QC are needed and should be provided by analyzer manufacturers, clinical pathology organizations, and veterinary organizations involved with continuing education.

This report provides a basis for ongoing evaluations of in-clinic laboratory performance and a commitment to ongoing quality assessment and quality improvement within the in-clinic laboratory. Continuing education is needed for veterinary practitioners and veterinary technicians to increase understanding of the concepts of quality assurance for in-clinic laboratory testing. Additionally, as QC data become more commonplace for in-clinic analyzers, clinicians considering purchase of new equipment will be able to compare mean analyzer performance for different analyzers and analyzer manufacturers will have to improve analyzer performance to maintain or improve market share.

Clinicians should realize that maintaining an in-clinic biochemical analyzer is not a matter of simply installing the analyzer, but requires diligent QC, which can be labor-intensive and costly. Understanding the limitations, sources of error, and overall performance of any particular analyzer will assist clinicians in minimizing false negative results and optimizing error detection for their patients' biochemical testing. This will help provide for the best possible patient care.

a. Microsoft Excel 2007, Microsoft Corp, Redmond, Wash.

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Glossary appears on following pages.

Accuracy—Closeness of the agreement between the observed result from measurement of an analyte and a true value of the analyte as determined by a reference standard method. May be expressed in the same units as the result, as the difference between the true value and the observed value, or as a percentage of the true value that the difference represents; expressed the latter way, the quantity is more correctly termed inaccuracy or bias. In the context of the analyzer or method validation referred to in this report, the terms random error, systematic error, and total error are generally used to clarify the intent and meaning. *See* also precision, imprecision, inaccuracy, total error, and bias.

Assayed QCM—A QCM for which the manufacturer has determined the results expected for different analytes using specified analyzers and methods. These so-called bottle values are summarized on product information sheets and most often include the mean and 2-SD range for each analyte and for each analyzer or method of analysis. The assayed means for each analyte are useful for selecting QCM. Analyzer-specific mean, 2 SD, and CV should be generated by each user on the basis of repeated analyses of the QCM, rather than relying on the manufacturer's 2-SD range.

Bias, inaccuracy, systematic error—Amount of variation between an observed result and some measure of the true value. Generally used to describe the inaccuracy of a method relative to a comparative method in a method comparison experiment. Can also be estimated by comparison of an observed result with the mean of an assayed control material determined by the same analyzer or method or by comparison with the mean obtained in a quality-assurance program by the group of participants using the same analyzer or method. *See* estimating bias.

Clinically significant, clinically significant difference—Used in instrument and method evaluation (validation) to describe a difference or error in a test result that is larger than allowable for the medical use of a test. A clinically significant difference is an important conclusion when judging the acceptability of analyzer or method performance, in contrast to a statistically significant difference, which only infers that a difference is larger than the experimental uncertainty of the data.

Clinical decision level, decision level, clinical decision limit, clinical decision threshold—A concentration of analyte for which medical interpretation is critical for patient care. Often these represent values of test results that prompt further monitoring, investigations, or treatment. There may be several different clinical decision levels for a particular analyte.

Coefficient of variation, CV—The relative SD; ie, the SD expressed as a percentage of the mean ($CV = 100 \times [SD/mean]$). It is a reflection of imprecision in repeated results.

Control rule—Criteria used in statistical QC to determine if instrument, reagent, and operator performance are exhibiting stable performance. If the result of a QCM analysis falls within the limits of the control rule, then the system (instrument, reagents, and operator) is determined to be in control and suitable for determining patient results. If the result of a QCM analysis falls outside the limits of the control rule, then the system is determined to be out of control and further investigation to determine if unstable performance of the system is truly present, its underlying cause, and correction of the problem prior to analyzing patient samples is needed. Example: in this paper, in-clinic QC specifications recommend use of a 1_{3s} control rule. This means that if a result for a particular analyte obtained using a QCM falls within 3 SDs of the previously determined mean of that analyte, that system is in control. If the result of a particular analyte obtained using a QCM falls outside of 3 SDs of the previously determined mean of that analyte, the system is out of control.

Estimating bias—Bias is the systematic difference between a measured and control (or expected) value. Bias is calculated by obtaining a mean for a measured QCM analyte on a particular analyzer (from 5 or more repeat analyses), and comparing it to the assayed mean for that QCM analyte (provided by the QCM manufacturer or external quality-assurance program). Bias can be a positive or negative value. Absolute bias, expressed as a percentage, is most commonly determined when examining bias:

$$|\% \text{ Bias}| = \left| \frac{\bar{X}_{\text{measured}} - \bar{X}_{\text{assayed}}}{\bar{X}_{\text{assayed}}} \right| \cdot 100$$

Example:

A QC run for ALP activity yields the following 5 measured values: 140, 142, 141, 145, and 142 U/L. The assayed QCM mean for this QCM lot for ALP activity (using the same analyzer or same methodology) is 138 U/L.

$$\bar{X}_{\text{measured}} = \frac{(140 + 142 + 141 + 145 + 142)}{5} = 142$$

$$\bar{X}_{\text{assayed}} = 138$$

Therefore, actual bias = $142 - 138 = 4$ U/L (note, this value has a positive direction; this is a positive bias of 4 U/L), while

$$|\% \text{ Bias}| = \left| \frac{142 - 138}{138} \right| \cdot 100 = 2.89\%$$

(Note, this value does not define a direction of the bias.)

Imprecision—The random dispersion of a set of replicate measurements expressed quantitatively by a statistic, such as SD (expressed in units of the analyte) or CV (expressed as a percentage).

Inaccuracy—Numeric difference between the mean of a set of replicate measurements and the true value. This difference (positive or negative) may be expressed in the units in which the quantity is measured or as a percentage of the true value. *See* bias, accuracy, total error.

In-clinic QC—Approach to statistical QC for in-clinic laboratories based on use of a simple control rule with low numbers of QCMs in order to achieve peace of mind with regard to production of accurate and reliable laboratory results. For example, a 1_{3s} rule with either 1 or 2 QCMs should allow the clinician to achieve a high probability of error detection (> 0.85 with 1 QCM or > 0.9 with 2 QCMs) and low probability of false rejection (0.0).

Glossary continued on next page.

Lot number—An alphanumeric or symbolic identification placed on the label of the QCM or reagents by the manufacturer that enables the manufacturing history of the product to be traced. Also called batch number.

Nonstatistical QC—Those aspects of QC in which statistics are not applied. These may include many alternative procedures, such as preventive maintenance, instrument function checks, correlation of results with other clinical and laboratory findings, repeated analyses according to predetermined criteria, medical review of results based on predetermined criteria, or performance of other confirmatory tests if initial results meet predetermined criteria. These efforts help ensure daily production of accurate and reliable results.

Precision—Closeness of agreement between results obtained by replicate measurements of a specimen, under specified conditions.

Probability for error detection (Ped)—A statistical evaluation to describe how often an analytic run is rejected when results contain an error. This is similar to sensitivity in diagnostic test evaluation. Ideally, Ped should be 1.0 for errors that are clinically important. In practice, we generally aim for a Ped of ≥ 0.90 when selecting and designing QC procedures.

Probability for false rejection (Pfr)—A statistical evaluation to indicate how often a run will be rejected when there really are no errors. This is similar to specificity in diagnostic test evaluation. Ideally, Pfr should be 0.00. In practice, we generally aim for a Pfr of ≤ 0.05 .

Quality assurance—Planned and systematic activities to provide confidence in the performance of quality requirements. This includes all monitoring activities, detection of products or results not meeting quality requirements, and actions taken to ensure that problems are rectified in order to maintain quality specifications. These things are undertaken as part of the quality management system of the laboratory.

Quality-assurance program, external quality-assurance program, proficiency testing program, interlaboratory QC program—Organizations external to the laboratory that provide testing materials for comparison of results with those of a peer group using the same analyzer or method. The frequency of external quality-assurance events will differ, depending on the provider. The range of values represented in the events should cover a range of clinically significant values. The emphasis of quality-assurance programs is on determination of accuracy and inaccuracy relative to the peer group using the same analyzer or method, but other indices of performance may be included.

QC—A generic term that refers to the monitoring and assessment of laboratory testing processes to identify problems and maintain performance. Quality control typically involves the daily efforts taken to ensure that stable performance is maintained and that accurate results are produced on a daily basis. Often divided into the components of statistical QC and nonstatistical QC. See statistical QC and nonstatistical QC.

QCM—Solution of analytes of previously characterized concentration, ideally reflecting clinical decision levels, used for performing statistical QC. See also assayed QCM.

Random error—An unpredictable error that occurs because of variations in the technical or mechanical operation of analyzers. Some analyzers may be more prone to produce random errors than are others. See also imprecision.

Statistical QC—Those aspects of QC in which statistics are applied, in contrast to the broader scope of QC, which includes many other procedures, such as preventive maintenance, instrument function checks, and performance validation tests. Statistical QC procedures are often used to monitor routine performance of a method and to alert the laboratory when the performance of a method changes. Statistical QC should provide a high Ped and low Pfr. See also nonstatistical QC.

Systematic error—An error that is always in 1 direction and is predictable, in contrast to random errors that may be either positive or negative and whose direction cannot be predicted. See bias.

Target value—Used in proficiency testing to designate the so-called correct value, estimated by the mean of all participant responses, after removal of outliers, or by the mean established by definitive or reference methods. A QCM may also have a target value, reflected by the mean provided by the manufacturer and represented in the package insert.

Total allowable error (TEa)—Also called desirable TEa. A quality requirement that sets a limit for the total amount of error that is tolerable in a single measurement or single test result. Total error is different for each analyte and for different concentrations of the analyte and should be based on the amount of variation that may invalidate the clinical interpretation of a test result or change the diagnostic category or actions taken as a result of the interpretation of a test result.

Total calculated error (TEc)—Measurement derived from performance evaluation of an instrument in order to determine if performance is acceptable on the basis of established quality requirements, usually expressed as TEa. Total calculated error is determined by the following formula:

$$\text{TEc (\%)} = \text{Bias (\%)} + 2 \text{ CV (\%)}$$