ASVCP Guidelines
Allowable Total Error

Biochemistry

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Developed by the Quality Assurance and Laboratory Standards (QALS) Committee of the ASVCP

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1 SCOPE

As all laboratory equipment ages and contains components that may degrade with time, initial and periodically scheduled external quality assessment is required to verify accurate and precise results over the life of the instrument. As veterinary patients may present to general practitioners and then to referral hospitals (both of which may perform in-clinic blood work, using different instruments), and given that general practitioners may send blood work to reference laboratories, there is a need for comparability of results across instruments and methods. Allowable total error (TEa) is a simple comparative quality concept used to define acceptable analytical performance. These guidelines make recommendations for determination and interpretation of TEa for commonly measured analytes in major domestic species (cats, dogs, and horses) for equipment commonly used in veterinary diagnostic medicine.

TEa values recommended herein are aimed at all veterinary settings, both private in-clinic laboratories using point-of-care analyzers and larger reference laboratories using more complex equipment. TEa can be used for (1) assessment of an individual instrument’s analytical performance which is of benefit if one uses this information during instrument selection or assessment of in clinic instrument performance (2) QC validation (as illustrated in Rishniw, et al.), and (3) as a measure of agreement or comparability of results from different laboratories (e.g. the in-clinic analyzer and the reference laboratory). These guidelines define a straightforward approach to assessment of instrument analytical performance. Use of TEa for internal QC validation is not explained fully in this document. Further detail is available in the Point of Care Guidelines for Quality Assurance, Section 2- Chemistry (http://www.asvcp.org/pubs/qas/index.cfm as of December 2013).

2 DEFINITIONS

Accuracy – Closeness of agreement between the results of a measurement and the true concentration of the analyte. Accuracy is the opposite of inaccuracy, or bias.

Alpha Error – Probability of falsely rejecting the null hypothesis (typically defined as health in medicine) when it is true; false positive.

Beta Error – Probability of falsely rejecting the alternative hypothesis (typically defined as disease) when it is true; false negative.

Bias (a.k.a. inaccuracy) – is the difference between the measured result and the concentration of a known standard. Generally used to describe the inaccuracy of a method relative to a comparative method in a method comparison experiment. The term bias in difference plot analysis (expressed in analyte units) equals the difference between the mean values of the two methods being compared or the average of all the differences between the paired sample values. Bias may also be expressed as a percentage according to the formula bias(%) = \text{mean}_{\text{target}} − \text{mean}_{\text{measured}}/\text{mean}_{\text{target}} \times 100. Total systematic error includes constant and proportional bias.
Bias, constant – When the degree of systematic error remains the same over the range of analyte concentrations (i.e., results of one method are consistently above or below another method).

Bias, proportional – When the magnitude of systematic error changes as the analyte concentration changes.

Calibration – The process of testing and adjusting how a laboratory instrument or test system measures a substance by comparing it to a known substance (the calibrator) and subsequently defining the association between the instrument/test system and the value of the calibrator.

Calibrator – A sample intended by its manufacturer to be used to define the association of a laboratory instrument measurement to a known value. (See calibration.)

Coefficient of Variation (CV) – A measurement of imprecision (random error), biologic variation, or other variability in a population; mathematically, CV is standard deviation divided by the mean and expressed as a percentage.

Commutability - is the equivalence of results of different measurement procedures using a reference material and representative samples from healthy and diseased individuals.

Comparability Testing – Comparison of test results from two or more instruments within the same laboratory or from laboratories at different sites that process samples from the same patients to ensure that measurements are similar and can be used interchangeably without causing clinical error. Total allowable error is one tool that is used in comparability testing.

External Quality Assessment (a.k.a. External Quality Assurance, EQA, or Proficiency Testing) – A program which determines total testing performance by comparing a laboratory or clinic’s test result (including interpretation of results) to a known standard or to an appropriate peer group mean generated from an inter-laboratory comparison in which multiple laboratories measure the same sample using the same test methods, reagents and controls.[CLSI GP27 A2, http://www.oie.int/fileadmin/Home/eng/Health_standards/tahm/0.04_GLOSSARY.pdf]

NOTE: The primary objective of EQA or PT is to evaluate the laboratory’s proficiency to measure a particular analyte.

Imprecision (a.k.a. random error or random variation) – Lack of repeatability or reproducibility of the same result; represented by the standard deviation (in units of the test) or coefficient of variation (in units of percent).

Instrument performance study – A study performed to characterize an instrument’s analytical performance, represented by bias (inaccuracy) and imprecision (random error). Data from an instrument performance study can be used to calculate an instrument’s observed total error (see total error).
Mean – Average of values measured.

Precision – Closeness of agreement between independent, repeated results obtained from the same sample under specific conditions. These may be derived in the same day (intraday) or on different days (between or interday).

Quality Assurance (a.k.a. quality assessment, QA) – Procedures which monitor and improve laboratory performance. QA includes quality planning, implementation, monitoring, and assessment. QA includes many “common sense” procedures (personnel training, use of standard operating procedures, etc.) routinely performed in well-run laboratories and clinics to minimize pre-analytical, analytical, and post-analytical error.

Quality Control (QC) – Procedures which monitor analytical performance of instruments and detect analytical error. QC typically refers to use of quality control materials and analysis of resulting control data. Control data analysis may include graphs (control charts, such as Levy-Jennings charts) and use of statistical rules (control rules, or Westgard rules) to determine whether control data are acceptable (in control) or unacceptable (out of control). QC validation is the process of choosing controls rules based on known analytical performance and a desired quality requirement.

Quality Control Material (QCM) – A material intended by its manufacturer to be used for QC of laboratory testing. Measurement of QCM monitors the entire test system (operator, reagents, and instrument analytical function). QCM may be used to carry out an instrument performance study or to monitor routine analytical performance. An assayed QCM is one for which the manufacturer provides expected results for specific instruments or methods. These results include a range and/or mean, standard deviation, and CV. Range may be the mean +/- Z * SD. (Also see definition of Z score.)

Quality Requirement – A benchmark to which the analytical performance of a laboratory instrument is compared. Also see allowable total error (TEa).

Standard Deviation (SD) – A measure of variability or diversity associated with random error or imprecision. SD shows how much variation or dispersion there is from the mean (average or other expected value) during repeated measures. A small SD indicates that data points tend to be very close to the mean, whereas a large SD indicates that the data points are spread over a wide range of values. SD is the square root of a dataset’s variance. (Also see imprecision.)

\[
s = \sqrt{\frac{\sum (x_i - \overline{x})^2}{n - 1}}
\]

TE (total error, a.k.a. total analytical error) – The sum of random error (imprecision) and systematic error (bias or inaccuracy). This term may also incorporate other sources of error (e.g., some pre-analytical variation, biologic variation, and other factors) that contribute to variation seen in patient results.
**TE**<sub>obs</sub> (observed or calculated total error) - The sum of measured random error (imprecision) and systematic error (bias/inaccuracy can be calculated from instrument performance data according to the formula), as defined in this guideline, **2CV + bias(%) or 2SD + bias (analyte units)**. TE<sub>obs</sub> must be calculated for each analyte, is unique to an individual instrument/method, and may vary with analyte concentration or activity.

**TEa** (allowable or desirable total error) – A quality requirement that sets a limit for combined imprecision (random error) and bias (inaccuracy, or systematic error) that are tolerable in a single measurement or single test result to ensure clinical usefulness. Tables for allowable total error are found on page 6.

**Type I error** – False positive or alpha error (see alpha error)

**Type 2 error** – False negative or beta error (see beta error)

**Z score** – Unitless number that is a coefficient indicating the number of standard deviations from mean. The z score (aka standard score, z value) is arbitrary in ATE and dependent upon the stringency desired for the test. This ASVCP consensus approved guideline as well as CLIA documentation assign the z score of 2 for calculation of TEa in laboratory medicine.

### 3 ALLOWABLE TOTAL ERROR FOR VETERINARY REFERENCE LABORATORY AND POINT OF CARE EQUIPMENT
<table>
<thead>
<tr>
<th>Analyte</th>
<th>Low Analyte Values</th>
<th>Within RI</th>
<th>High Values</th>
<th>CLIA Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Albumin</td>
<td>15%</td>
<td>15%</td>
<td>15%</td>
<td>10%</td>
</tr>
<tr>
<td>Alkaline Phosphatase</td>
<td>NCR</td>
<td>25% (20% desirable)</td>
<td>25% (20% desirable)</td>
<td>30%</td>
</tr>
<tr>
<td>Alanine Amino Transferase</td>
<td>NCR</td>
<td>25%</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Ammonia</td>
<td>NCR</td>
<td>20%</td>
<td>20%</td>
<td>Not found</td>
</tr>
<tr>
<td>Amylase</td>
<td>NCR</td>
<td>25%</td>
<td>25%</td>
<td>30%</td>
</tr>
<tr>
<td>Aspartate Amino Transferase</td>
<td>NCR</td>
<td>30%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Bicarbonate</td>
<td>20% (15% desirable)</td>
<td>20% (15% desirable)</td>
<td>20% (15% desirable)</td>
<td>10% (RCPA) to 20% (CAP)</td>
</tr>
<tr>
<td>Bile Acids</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>None found</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
<td>10%</td>
</tr>
<tr>
<td>Chloride</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
<td>5%</td>
</tr>
<tr>
<td>Creatine Kinase</td>
<td>NCR</td>
<td>30%</td>
<td>30%</td>
<td>30%</td>
</tr>
<tr>
<td>Creatinine</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>0.5mmol/L</td>
</tr>
<tr>
<td>Gamma Glutamyl Transferase</td>
<td>NCR</td>
<td>20%</td>
<td>20%</td>
<td>15% (RCPA) to 30% (CFX)</td>
</tr>
<tr>
<td>Glutamate Dehydrogenase</td>
<td>NCR</td>
<td>30%</td>
<td>25%, &gt;90IU 20%</td>
<td>None found</td>
</tr>
<tr>
<td>Glucose</td>
<td>10%</td>
<td>20%</td>
<td>20%</td>
<td>6% Low, 10% High</td>
</tr>
<tr>
<td>Iron</td>
<td>30% (15% desired)</td>
<td>30%</td>
<td>30%</td>
<td>20%</td>
</tr>
<tr>
<td>Potassium</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
<td>0.5mmol/L</td>
</tr>
<tr>
<td>Lactate</td>
<td>NCR</td>
<td>40%</td>
<td>40%</td>
<td>10 (RCPA) to 30% (CFX)</td>
</tr>
<tr>
<td>LDH</td>
<td>NCR</td>
<td>20%</td>
<td>20%</td>
<td>20%</td>
</tr>
<tr>
<td>Magnesium</td>
<td>15% desirable, 20% acceptable</td>
<td>15% desirable, 20% acceptable</td>
<td>15% desirable, 20% acceptable</td>
<td>25%</td>
</tr>
<tr>
<td>Sodium</td>
<td>10%</td>
<td>5%</td>
<td>5%</td>
<td>4mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>20%</td>
<td>15%</td>
<td>15%</td>
<td>10-23% (CAP)</td>
</tr>
<tr>
<td>Sorbitol Dehydrogenase</td>
<td>NCR</td>
<td>25%</td>
<td>25%</td>
<td>None found</td>
</tr>
<tr>
<td>Total Bilirubin</td>
<td>NCR</td>
<td>30% (25% desirable)</td>
<td>30% (25% desirable)</td>
<td>0.4 mg/dl, 20%</td>
</tr>
<tr>
<td>Total Calcium</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>2% (BV) to 8% (CFX)</td>
</tr>
<tr>
<td>Total Protein</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>NCR</td>
<td>25%</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>Troponin</td>
<td>NCR</td>
<td>70%</td>
<td>70%</td>
<td>20%CV maximal with around 50% TEa if calculated</td>
</tr>
<tr>
<td>Urea</td>
<td>15%</td>
<td>12%</td>
<td>12%</td>
<td>2mg/dl, 9%</td>
</tr>
<tr>
<td>Uric acid</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>17%</td>
</tr>
</tbody>
</table>
NCR - Not Clinically Relevant. Three to five boarded clinicians (ACVIM or ECVIM with various specialties) gave opinions upon clinically desired TEa at low, mid, and high analyte concentrations and activities, except for Troponin where the opinion of a single cardiologist was used. Total allowable error was calculated directly from reference equipment used by QALS members using the equation 2CV + bias% = TEa% to ensure that TEa was possible.

CFX - Canadian Fixed Limits, The College of Physicians and Surgeons of Saskatchewan
RCPA - Royal College of Pathologists of Australasia and the Australasian Clinical Biochemist association Quality Assurance Program

Table 1 References
4 QUALITY ASSESSMENT

4.1 Introduction

Quality assessment includes selection and evaluation of instrument/method performance in order to ensure that validated, reliable, and robust methods appropriate for the species being tested are in use. (Flatland, 2010) In-clinic quality control (QC) validation and reference interval generation are part of the instrument/method validation and verification process. (Friedrich, et al., 2012, website: ASVCP POCA, General QA guidelines, and reference interval recommendations found here http://www.asvcp.org/pubs/qas/index.cfm). Once instruments/methods are judged to be suitable for routine testing, QA ensures that ongoing instrument performance is stable and that the errors inherent to the instrument/methods do not exceed levels that would invalidate the interpretation of test results. Important QA tools include regular quality control (QC) procedures and participation in an external quality assurance (proficiency testing) program.

The concept of quality requirements is the foundation for quality planning. Quality requirements can help guide interpretation of laboratory test results because they provide perspective about variability of results within an acceptable interval and potential significance of abnormal findings. [Westgard website] A hierarchy of quality requirements has been proposed [Kenny 1999], and the most stringent quality requirements are based on clinical outcomes and clinical decision thresholds. Quality requirements may also be based on data about biologic variation of an analyte, analytical performance criteria (e.g., as mandated by CLIA for human medicine [CLIA website]), expert opinion and/or technological state-of-the-art (Kenny 1999).

A commonly used quality requirement is allowable or desirable total error (TEa), which is derived from medically important analyte concentrations or clinical decision thresholds. TEa can be used to aid instrument selection if manufacturer’s claims for instrument performance are available. TEa can also be compared to an instrument’s calculated or observed total error (TEobs) to help determine whether that instrument’s analytical performance is adequate. (Farr and Freeman, 2008) If analytical performance is deemed adequate, TEa can further be used during QC validation of that instrument. Finally, TEa can be used to guide comparison of test results across laboratories and clinics using the same or different analytical methods. TEa can be used to help interpret results from external quality assurance (proficiency testing) programs or to help interpret results of comparability testing, where a reference laboratory is used to “check” in-clinic or other laboratory results. Additional information about TEa can be found in [CLSI- C54-A, 2008]

It is important to realize that TEa may differ with

- Species - TEa for a given analyte may be different for dogs vs. cats vs. horses
- Analyte concentration - TEa may differ at low, within reference interval, or high analyte concentrations
- Clinical use - TEa may differ at different cut-off values for “normal” or at different clinical decision thresholds
- Type of laboratory –TEa for the same analyte may differ for reference laboratories, veterinary practices, toxicology laboratories, and other industry laboratories, as these serve different animal populations, different clinical needs, and may use different instruments/methods.
4.2 Quality Control Material

The purpose of analyzing QCM (in-clinic or within-laboratory QC) is to detect excessive analytical error that deviates from expected instrument performance, given stable operation in a routine setting.[Westgard, 2010] Comparability testing among methods or instruments is used to investigate external quality assessment failure (e.g., disparate results between the clinic or laboratory’s mean and the peer group mean). Common causes of noncomparability of results (results for the same sample that differ significantly) include sample transport and storage effects as well as other pre-analytical effects, instrument failure or drift, reagent degradation, differences in calibration, imprecision, different analytical methodologies, and more.

Both in-clinic QC and external quality assessment (proficiency testing) require different levels (concentrations, activities, etc.) of measurement dependent upon the instrument, reference intervals, expected changes due to disease, and species evaluated at the facility. All commercially available QCM have a lot number (batch number) and expiration date. QCM degrade over time, and expiration dates must be strictly observed. QCM should be stored and handled appropriately, as directed by the manufacturer.[Bellamy, 2000] QCM from different lots may not have the exact same analyte concentrations. This impacts QC because it alters the control limits used to decide if QC data are in-control or out-of-control.[Westgard, 2010]

In a previous study, a minimum of two “levels” (analyte concentrations/activities) of assayed QCM were found to be adequate for external quality assessment in the form of instrument/method performance valuations for in clinic analyzers. [Rishniw, et al., 2012] Evaluation of these materials with levels of analytes at or near those of clinical decision values and/or reference interval limits should be conducted at least biannually. If a sufficient supply of QCM can be reserved for an entire year, use of the same QCM for the entire year is ideally recommended.

Artificially prepared QCM may not behave in exactly the same manner as patient samples. However, as QCM are likely to be more stable than patient samples, these may be preferred to assess reagent or instrument drift. QCM may be purchased from a number of companies. (See Section 8)

Multiple factors may influence the choice of the assayed QCM, including but not limited to:

1) Commutability across instruments/methods
2) Numbers, types and levels of analytes present within the materials
3) Shelf-life/stability
4) Cost
5) Other factors as determined by the laboratory director

4.3 Frequency

In order to ensure ongoing production of reliable laboratory results that enable quality diagnostic medicine over time on the same instrument or between instruments, both in-clinic or within laboratory quality control
and external quality assessment (proficiency testing) must be performed regularly in order to detect changes in analyte measurement resulting from pre-analytical, analytical, or post-analytical error.

**The frequency of inter-instrument quality assessment (comparability testing) can be categorized as:**

Frequent monitoring (e.g., daily, weekly); periodic monitoring (e.g., quarterly, biannually); and special cause testing.

Recommended frequency of monitoring may vary between laboratories and clinics. In general, frequent internal quality control (daily or weekly) and periodic external quality assurance/proficiency testing (quarterly) should be performed. [Lester, et al., 2013] Special cause testing may be initiated if there is suspicion of inaccurate measurement of patient samples and concern for accurate diagnosis. While special cause testing and a subsequent quality investigation may successfully identify sources of error, laboratories and clinics are encouraged not to rely on special cause testing as their sole method of quality assessment. Special cause testing is not adequate as the sole method of quality assessment for any instrument as there is significant likelihood of misdiagnosis of patients.

Periodic quality control is performed when frequent monitoring is deemed unnecessary because the measurement systems involved are stable and the risk of errors in the clinical interpretation due to noncomparable (disparate) results is low. Determination of stability should be assessed with knowledge of the assay, knowledge of reagent stability, clinical experience and consistent monitoring of the assay for a minimum of 30 days. Special cause testing is performed in response to an alert from a monitoring procedure or other triggering event. [CLSI C54-A] The frequency of external QA monitoring/proficiency testing can be determined by the QC specialist based on the number of samples analyzed per day, known inherent drift of the analytical method, perception of previous problems noted in the laboratory, cost of reagents, and other factors. Reference laboratories are likely to have a QA specialist on staff who can make decisions about frequency of proficiency testing; private practices are encouraged to consult with the instrument manufacturer or a board-certified veterinary clinical pathologist with expertise in QA.

### 4.4 Handling and Transport

The stability of external QCM during transport to the laboratory and storage within the laboratory need to be carefully considered. QCM that are transported or stored under inappropriate conditions may lead to errors during comparability studies. Conditions of storage, including temperature, light, humidity, duration, etc. must be monitored to ensure stability of QCM, and conditions known to alter the stability of the QCM should be avoided. For example, repeated freeze-thaw cycles encountered with “frost-free” freezers lead to degradation of QCM analytes and should be avoided. Instead, liquid QCM typically are stored in -70°C freezers to ensure stability for extended time of storage. Manufacturer’s recommendations regarding storage should be followed and included in Standard Operating Procedures. All QCM should be labeled with an expiry date and promptly discarded upon reaching this date. No expired QCM or reagents (including rotors or cartridges) should be used. If the stability of the QCM is suspected to be compromised, it should be discarded and replaced. Backdating of instruments to use outdated reagent or QCM should never be performed. Even under
appropriate conditions of transport and storage, analyte results may vary over the lifetime of the QCM while yet remaining within the expected intervals. Therefore, when performing comparability studies on different analyzers, QCM should be analyzed at approximately the same time. This may require splitting and shipping of QCM in aliquots instead of analyzing the QCM on different days at different facilities.

Transportation of products with variable environmental conditions and time to measurement also may change concentrations of the analytes. These must be controlled and, if there is known compromise of the QCM, e.g. excessive heating, repeated freeze-thaw cycles, etc., the QCM should be replaced. Additionally, if different analyzers are to be compared, it is recommended to prepare aliquots and coordinate the testing so all aliquots are measured at approximately the same time, i.e. within 4-6 hours. In the authors experience with in-clinic QA at veterinary clinics, procurement of frozen liquid control specimens is preferable rather than lyophilized control materials that need to be reconstituted. This helps minimize pipetting, contamination, or other errors that may be introduced by dilution of lyophilized control materials.

5 ALLOWSABLE TOTAL ERROR

Westgard was the first to introduce the concept of total error in 1974 [Westgard, 1974, Whitehead, 1977]. Analytical imprecision (reproducibility of the result) and bias (systematic error) were combined into a single measure of the uncertainty of a test result. The ideal situation is to have highly accurate and precise measurement, i.e. low bias and low CV or SD, respectively. Westgard originally used TE = bias(%) + 1.65CV, but a coefficient for the CV as high as 6 has been used by some authors for method validation studies.[Westgard, 1996]

For the purpose of this document, we define total allowable error as bias(%) + 2CV which is consistent with CLIA recommendations. (CLIA '88 Proficiency Testing Limits, U.S. Federal Register). If units of the test are used, then the equation, bias (expressed in units of the test) + 2SD, is used to calculate allowable total error.

5.1 Instrument performance evaluation: Calculation of CV, SD, bias, and calculated or observed Total Error (TEobs)

More detailed instrument performance evaluation and validation procedures are commonly used in reference laboratories where determination of bias and CV should be carried out within recommended ASVCP guidelines and at the discretion of the quality control specialist. The following guidelines are provided for in-clinic laboratories but many of the general principles apply to all types of laboratories conducting veterinary testing.

The following instrument performance evaluation may be performed when:

1) a new instrument is being considered for purchase
2) a new instrument is evaluated to ensure that it performs according to manufacturer’s claims
3) there is routine internal quality control of an instrument, conducted to ensure adequate ongoing performance
4) evaluating performance as part of an external quality assurance (proficiency) program.

CV for purposes of determination of calculated TE (TEobs) should be determined from precision studies using quality control materials at various levels of analytes, known standards and/or patient samples.

Three methods that may be used:
1. Comparison with target values provided by manufacturers of assayed quality control materials. An assayed QCM may be repeatedly measured for 5 days to determine mean, bias, SD and coefficient of variation. In this situation, the mean of the results should be compared to the assayed mean to determine bias. These data can then be used to calculate total error (TEobs) of the analyte. The assayed QCM should be specific for the equipment and methods being evaluated; the instrument manufacturer should be consulted if there is any doubt regarding QCM suitability. Please consult the manufacturer to insure that it is appropriate for the equipment and methods.
2. Based on comparison with known gold standards for various analytes (standards provided by external regulating or governmental agencies or other specialist resources)
3. Comparison with peer group means in an external QA program participation. This typically must be done using an external quality assessment program that is employed to help insure quality laboratory results. While some external quality assurance programs use assayed materials in human medicine, typically in veterinary medicine, unassayed materials are used and there is reliance on the peer group mean. Peer group is defined by same instrument and/or method as that upon which the result is obtained. An external quality assessment using comparison with a peer group is dependent on inclusion of sufficient numbers of instruments included in the peer group as well as other laboratories’ maintenance of equipment and quality control.

This approach is best suited for ongoing instrument performance evaluation following initial and annual instrument evaluations conducted using assayed QCM or known standards.

As external quality control programs currently in existence are method specific and methods used by in-clinic laboratories are frequently not represented at the time of this document, option 3 is often not available to the in-clinic laboratory. The following steps are designed for quality assurance assessment for the in-clinic laboratory but may also be used as a very basic guideline by reference laboratories. Further information for complete review by reference laboratories is available at www.westgard.com, in the ASVCP General QA guidelines, and in CLSI documents as needed. All steps should be carried out by appropriately trained personnel who are knowledgeable regarding the analyzer’s operation and the facility’s quality assessment program. Calculations can easily be carried out using commercially available software programs. Calculations should be performed for each analyte and each QCM.
1. Measure each QCM daily for a minimum of five days. [Rishniw 2012] Five repetitions in one day is possible but does not incorporate potential interday variation that may be found when assessing samples from hospitalized patients. Using these data, for each QCM and each analyte, calculate
   a. Mean (average)
   b. Standard deviation (SD)
   c. Coefficient of variation (CV). This value represents between-day (interassay) imprecision of the analyzer.

\[
CV (\%) = \frac{SD}{\text{Mean}} \times 100
\]

The mean, SD, and CV of the analyzer derived from these QC data are referred to as the calculated or observed SD, and CV.

2. Calculate the analyzer’s measured bias using the measured mean and the QCM manufacturer’s reported mean for the assayed control material (using same instrument and/or method as that used by the analyzer) according to the formula:

\[
\text{Bias}\% = \frac{\text{Mean}_{\text{manufacturer}} - \text{Mean}_{\text{measured}}}{\text{Mean}_{\text{manufacturer}}} \times 100
\]

(QCM manufacturer’s reported means are commonly found in the QCM package insert, categorized according to the instrument and method producing the assayed values.) Measured bias may be a positive or a negative number, depending upon whether the analyzer’s results are lower or higher than the manufacturer’s reported mean. If bias is a negative number (e.g., –5.0%), then the absolute number (5.0%) should be used in step 4, below.

3. Calculate the analyzer’s observed total error (TE_{obs}), using measured CV and measured bias, according to the formula:

\[
\text{TE}_{\text{obs}} = 2CV + \text{Bias}\%
\]

4. Compare measured TE_{obs} to TEa. If TE_{obs} < TEa (or very close to it), then the quality requirement is met and instrument is considered suitable for measurement of that analyte. If TE_{obs} > TEa, then several options exist (see below).
5.2 TEobs Interpretation and Assessment of External Quality Assessment Results

Calculated total error (TEobs) for all analytes determined on in-house or reference lab equipment should be compared to the ASVCP total allowable error guidelines found in Table 1. If calculated allowable total error for all concentrations is less than that which is acceptable (TEa), then instrument performance is satisfactory and no further assessment for that analyte is required. If calculated total allowable error (TEobs) is greater than that which is acceptable (TEa), attempts should be made to identify and correct causes of imprecision (high CV) and inaccuracy (high bias). (Lester, 2013) Use of special calculations, such as the Quality Goal Index (Parry, 2005 and 2006) may be helpful in determining if the poor performance is due to imprecision, bias, or a combination of both.

If these sources of error cannot be corrected or if problems occur repeatedly, the manufacturer of the instrument and/or a boarded clinical pathologist with expertise in QA should be called upon for further assessment. Further assessment may include attempts to improve performance capability by analyzer adjustments, operator training, replacement of reagent with new reagent or different manufacturer product, or, potentially, analyzer replacement. Alternately, the initial quality requirements may be relaxed. This is not recommended but is possible only if potential additional error can be tolerated in diagnostic judgment. This requires education of ALL clinicians using the analyzer regarding amended total allowable error of the analyte(s) in question. Any changes outside of the recommended TEa in this document must be justified and documented in a laboratory handbook. This should be done only upon consultation with a boarded veterinary clinical pathologist.

5.3 Total Allowable Error Specifications Based on Clinical Decision Limits

In order to establish the total allowable error guidelines provided in this document, clinicians were surveyed to determine their expectations of analytical quality required for confident management of their patients using standard diagnostic paradigms. The goal was to reach a clinical consensus that would result in minimal alpha or beta error as a result of analytical error. The advantage of this approach was that it was based on clinical experience and therefore acceptable to clinicians in their diagnostic framework. However, some clinicians’ expectations for quality requirement could not be achieved based on analytical performance of current, commonly used instruments. Therefore, some of the total allowable errors listed (e.g. ALP and magnesium) reflect the current technological state-of-the-art rather than clinician’s opinions. Additionally, some clinical decision limits are anticipated to change over time as analytical performance improves and disease diagnosis is further refined. Consequently, this document will be reviewed and revised in the future.

5.4 Bias, CV and Total Allowable Error Specifications Based on Biological Variation
Biological variation may also be used to establish bias, CV and total allowable error guidelines. [Oosterhuis, 2011] While biological variation was considered in selection of quality requirements, for several analytes, such as ALT, a biologic variation-based quality requirement was too stringent given the analytical performance that is currently possible with most diagnostic instruments. Therefore, while data on biological variation are presented in Addendum 1 for informational purposes, these are not recommended as guidelines to ensure adequate instrument performance. Some instrument/method performance may be achievable using these calculated specifications, while others may not. Improvements in instrument/method performance in the future may allow improved quality requirements based on biologic variation. The data from this table are based on studies conducted in dogs, primarily by a single group of clinical researchers. Additional studies in other species may help us better understand the needs for instrument/method performance of other species.

6 REFERENCES IN TEXT


Clinical Laboratory Improvement Amendments of 1988 (CLIA), Public Law 100-578.


7 WEB RESOURCES

7.1 Veterinary Information Network Resources

Total Allowable Error Calculator http://www.vin.com/doc/?id=5200884


VIN Rounds: VIN Study Results Of In-Clinic And Reference Laboratory Quality http://www.vin.com/Members/Proceedings/Proceedings.plx?CID=ECVIM2011&PID=67918&O=VIN
7.2 ASVCP Resources

American Society for Veterinary Clinical Pathology General Quality Assurance Guideline.
American Society for Veterinary Clinical Pathology Reference Interval Guideline.
American Society for Veterinary Clinical Pathology Point of Care Guideline.

7.3 Human Medical Resources

www.westgard.com

8 VETERINARY QUALITY ASSURANCE PROGRAM RESOURCES and QUALITY CONTROL MATERIALS

Bio-Rad Laboratories, Clinical Diagnostic Group

CLIA(Human Medical) approved proficiency testing programs:

College of American Pathologists
http://www.cap.org/apps/cap.portal?_nfpb=true&_pageLabel=accreditation

Insight Interlaboratory Quality Assessment Program from Sysmex

Urika, LLC Quality Assurance Division
www.urikapathology.com

Veterinary Laboratory Association Quality Assurance Program
http://www.vlaqap.org/
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barbara.vonbeust@bluewin.ch
RAC liason
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<th>Bias Des⁸</th>
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RECOMMENDATIONS FOR ANALYTICAL COEFFICIENT OF VARIATION, BIAS AND TOTAL ERROR BASED ON BIOLOGIC VARIATION OF VARIOUS BIOCHEMICAL AND HAEMATOLOGICAL ANALYTES IN DOGS

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CV = coefficient of variation.

CVa = analytical CV

CVi = within dog CV

CVg = between dog CV

Superscript Designations:

A = CV Opt = recommended optimal analytical CV based on CVa ≤ 0.25CVi

B = CV Des = recommended desirable analytical CV based on CVa ≤ 0.5 CVi

C = CV min = recommended minimally acceptable analytical CV based on CVa ≤ 0.75 CVi

D = Bias opt = recommended optimal Bias based on B ≤ 0.125(CVi + CVg)1/2

E = Bias Des = recommended desirable Bias based on B ≤ 0.250 (CVi + CVg)1/2

F = Bias min = recommended minimally acceptable Bias based on B ≤ 0.375(CVi + CVg)1/2

G = TE Opt = recommended optimal TE based on TEa ≤ 1.65(0.25CVi) + 0.125(CVi + CVg)1/2

H = TE Des = recommended desirable TE based on TEa ≤ 1.65 (0.50CVi) + 0.250 (CVi + CVg)1/2

I = TE min = recommended minimally acceptable TE based on TEa ≤ 1.65 (0.75CVi) + 0.375(CVi + CVg)1/2

RECOMMENDATIONS FOR ANALYTICAL COEFFICIENT OF VARIATION, BIAS AND TOTAL ERROR BASED ON BIOLOGIC VARIATION OF VARIOUS BIOCHEMICAL AND HAEMATOLOGICAL ANALYTES IN DOGS


L = Alt TE min = recommended desirable TE based on TEa \leq 1.65 (CV Min) – calculation from Oosterhuis, WP, Gross Overestimation of Total Error Based on Biologic Variation, Letter to the Editor, Clin Chem 57:9 (2011), pp. 1334-1336.


2 = Calculation formulas from:
   (b) Fraser, CG. Chapter 2: Quality Specifications, Biological Variation: From Principles to Practice. AACC Press. 2001., p.29-66.


4 = Index of individuality (II) = CVb / square root of (CVi^2 + CVa^2). Interpretation: > 1.7 = high index of individuality; reference change value likely to provide better determination of significant difference in sequential analyses; use of 95% population-based reference interval may hamper diagnostic sensitivity. <0.7 = low index of individuality; use of 95% population-based reference interval is valid. Between 0.7 – 1.7 = reference change value may be of benefit in determining significant difference in sequential analyses.

Note: the II will change with assays having a CVa different from that presented in this table. See CG Fraser, Biologic Variation: From Principles to Practice. AACC Press, 2001, p. 29-66.

5 = categories of II = High (>1.7), intermediate (0.7-1.7), low (<0.7)
ASVCP Guidelines:

Allowable Total Error

Version 1.0 (July 2013)

Worksheet

The purpose of this checklist is to facilitate practical application of the Allowable Total Error Guideline.

Developed by the American Society for Veterinary Clinical Pathology (ASVCP) Quality Assurance and Laboratory Standards (QALS) Committee

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Allowable Total Error Worksheet

1. Calculate analyzer precision by performing a minimum of n=5 repetitions. (More repetitions are preferred.) Repetitions should be performed identically to standard analysis of patient samples, using the same personnel, instrument, reagents, etc. Calculate coefficient of variation (CV%). One can use excel or any other basic statistics program to calculate standard deviation.

\[
CV (\%) = \left( \frac{\text{Standard deviation}}{\text{Mean}} \right) \times 100
\]

2. Calculate analyzer bias from known standard/control material (Mean_{target}) or deviation from population mean and measured mean from Step #1 (Mean_{measured}) using equation:

\[
\text{Bias}(\%) = \left( \frac{\text{Mean}_{target} - \text{Mean}_{measured}}{\text{Mean}_{target}} \right) \times 100
\]

3. Calculate Total Error (TE_{obs}) using the following formula. Use the absolute bias result (i.e., positive number only).

\[
\text{TE}_{obs} = 2CV (\%) + \text{Bias} (\%)
\]

4. Compare TE_{obs} calculated in the laboratory with TE_{a} in Table 1 of the ASVCP Guidelines for TE_{a}.
   a. If TE_{obs} < TE_{a}
      i. The quality assessment passes and no further action is needed
   b. If TE_{obs} > TE_{a}
      i. Report results to Quality Assurance Personnel/Committee.
      ii. Investigate pre-analytical and procedural factors (e.g., sample quality, instrument SOP, operator proficiency) that may have impacted performance and correct as needed. Reassess instrument performance following correction.
      iii. If no pre-analytical or procedural factors are identified that can be addressed and corrected, management should report findings to the manufacturer of the instrument so that any needed maintenance, repairs, or replacement may be evaluated and implemented.
      iv. Clinicians whose results may be impacted should be notified in writing.

5. All Total Error assessments should be catalogued in a written and/or digital archive accessible to personnel who may operate the instrument or interpret the results. (Quality Assurance for Point of Care Testing Guidelines, 2013)