

## SPECIAL REPORT

**ASVCP guidelines: quality assurance for point-of-care testing in veterinary medicine**Bente Flatland<sup>1</sup>, Kathleen P. Freeman<sup>2</sup>, Linda M. Vap<sup>3</sup>, Kendal E. Harr<sup>4</sup>

<sup>1</sup>Department of Biomedical and Diagnostic Sciences, College of Veterinary Medicine, University of Tennessee, Knoxville, TN, USA; <sup>2</sup>IDEXX Laboratories, Wetherby, West Yorkshire, UK; <sup>3</sup>Department of Microbiology, Immunology, and Pathology, College of Veterinary Medicine and Biomedical Sciences, Colorado State University, Fort Collins, CO, USA; and <sup>4</sup>URIKA, LLC, Mukilteo, WA, USA

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**Correspondence**

Dr. Bente Flatland, Department of Biomedical and Diagnostic Sciences, College of Veterinary Medicine, University of Tennessee, 2407 River Drive, Knoxville, TN 37996, USA  
E-mail: bflatlan@utk.edu

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**Abstract:** *Point-of-care testing* (POCT) refers to any laboratory testing performed outside the conventional reference laboratory and implies close proximity to patients. Instrumental POCT systems consist of small, handheld or benchtop analyzers. These have potential utility in many veterinary settings, including private clinics, academic veterinary medical centers, the community (eg, remote area veterinary medical teams), and for research applications in academia, government, and industry. Concern about the quality of veterinary in-clinic testing has been expressed in published veterinary literature; however, little guidance focusing on POCT is available. Recognizing this void, the ASVCP formed a subcommittee in 2009 charged with developing quality assurance (QA) guidelines for veterinary POCT. Guidelines were developed through literature review and a consensus process. Major recommendations include (1) taking a formalized approach to POCT within the facility, (2) use of written policies, standard operating procedures, forms, and logs, (3) operator training, including periodic assessment of skills, (4) assessment of instrument analytical performance and use of both statistical quality control and external quality assessment programs, (5) use of properly established or validated reference intervals, (6) and ensuring accurate patient results reporting. Where possible, given instrument analytical performance, use of a validated  $1_{3s}$  control rule for interpretation of control data is recommended. These guidelines are aimed at veterinarians and veterinary technicians seeking to improve management of POCT in their clinical or research setting, and address QA of small chemistry and hematology instruments. These guidelines are not intended to be all-inclusive; rather, they provide a minimum standard for maintenance of POCT instruments in the veterinary setting.

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## Introduction

The term *point-of-care testing* (POCT) broadly refers to any laboratory testing performed outside the conventional reference laboratory and implies close proximity to patients (a.k.a. "bedside," "near-patient," "decentralized," "extra-laboratory," or "in-clinic," testing).<sup>1-3</sup> POCT instruments are numerous and varied in technological complexity. POCT can be divided into non-instrumental systems (eg, reagent test strips); small, hand-held analyzers (eg, glucometers); and desktop or benchtop instruments (eg, automated hematology or chemistry analyzers).<sup>3</sup>

Lack of governmental regulation of veterinary clinical laboratory medicine means that veterinarians must demonstrate a commitment to quality assurance (QA) and quality control (QC) from within the profession.<sup>4</sup> Concern about the quality of veterinary in-clinic testing has been expressed by veterinarians themselves in published literature;<sup>5,6</sup> however, little, if any, concise and practical guidance is available to veterinary practitioners on this topic. Veterinary guidelines and textbooks are aimed at laboratory professionals and complex laboratory equipment such as found in reference laboratories. In the authors' experience, laboratory QA/QC instruction in veterinary curricula is scant, leaving new graduates with little training in how to establish, evaluate, and maintain the quality of in-clinic laboratory testing. Acknowledging this void, the Quality and Laboratory Standards (QALS) Committee of the American Society for Veterinary

Clinical Pathology (ASVCP) formed a POCT subcommittee in 2009 to develop guidelines for POCT in veterinary medicine. Given the numerous laboratory tests that can be performed in veterinary practice, the POCT subcommittee excluded from consideration non-instrumental test systems and focused instead on instrumental test systems.

## Guideline Scope

These guidelines predominantly apply to handheld and bench top hematology and chemistry instruments measuring multiple analytes. Glucometer use will be addressed in a separate ASVCP guideline. Such instruments have potential utility in many veterinary settings, including private practice, academic veterinary medical centers, the community (eg, remote area veterinary medical or disaster response teams), and for research applications in academia, government, and industry. These guidelines are aimed at veterinarians and veterinary technicians seeking to improve management of POCT in their particular clinical or research setting. These guidelines are not intended to be all-inclusive; rather, they provide a minimum standard for maintenance of POCT instruments in the veterinary setting. As additional scientific studies become available and POCT instruments and analytical performance capability evolve, these guidelines may change; guideline revision is anticipated approximately every 10 years. A glossary of terms and definitions used can be found in Appendix 1 at the end of this article.

## A Formalized Approach to Veterinary Point-of-Care Testing

Veterinary settings of all sizes offering in-clinic laboratory testing should establish a formalized approach to POCT management that includes a written quality plan or manual. The quality plan should address the hospital's environment (patient population served, type of testing offered, etc.), facilities, personnel, equipment, and working policies and procedures. The quality plan may be part of a more comprehensive quality manual that also includes detailed policies, chains of command, standard operating procedures (SOPs), and forms covering all aspects of laboratory function (operational management, analysis, reporting, and QA).<sup>7</sup> It is recommended that all veterinary facilities operating POCT develop and use such documents, and that documents be maintained according to a document control policy that ensures only current, approved document

copies are in circulation. Recommendations concerning quality documentation can be found in other resources.<sup>7</sup>

Academic veterinary medical teaching hospitals and large specialty practices should form a POCT committee or working group that oversees POCT policies and instrument acquisition, maintenance, and quality management. All major stakeholders in POCT should be represented in such a body (eg, clinicians, nurses/technicians, medical technologists, medical records, billing, and information technology). Suggestions regarding composition, responsibilities, and function of POCT committees and working groups are available.<sup>2,3,8</sup> The individual veterinary facility should decide whether any POCT committee's role is primarily as an advisory body or whether it also has a policing and enforcement role.

### General Quality Assurance Recommendations

The goal of QA procedures is to minimize error in all phases of laboratory testing (pre-analytical, analytical, and post-analytical). QA measures involve many "common sense" practices and procedures routinely used in well-run hospital and laboratories.

#### Personnel (Instrument Operators)

Adequate equipment operator training is an essential component of QA and generation of accurate laboratory results.<sup>4</sup> The hospital manager should ensure that all personnel performing laboratory testing are properly trained, and provision should be made for both initial training and continuing education. Examination audits (competency assessments) should be carried out by the manager (or another qualified individual) to document competence. Audits should follow initial training and be performed periodically thereafter at the manager's discretion. Maintenance of written operator training logs or other training records is also recommended.<sup>9</sup> Audits and logs should be archived such that retrospective evaluation is possible; relevant state, national, and professional accreditation requirements should be met.

#### Instrument Maintenance

Manufacturer's recommendations for maintenance and cleaning of equipment should be followed and documented. Instrument performance studies (to characterize an instrument's imprecision, bias, and total error [TE]) should be carried out immediately following instrument purchase/set-up and a period of

operator familiarization, but before the instrument is used routinely to evaluate patient samples. Follow-up instrument performance studies are recommended at a minimum annually thereafter (more often if needed) to ensure that analytical performance does not deteriorate with instrument aging or other events in the life of the instrument that could influence analytical performance (parts replacement, software upgrades, etc.). An instrument log should be maintained and kept near the instrument to document any problems with the instrument or its results, any trouble-shooting performed, and any corrective action(s) taken as a result. Efficacy of corrective actions should be confirmed in writing and archived in the instrument log.<sup>9</sup>

### Other Quality Assurance Procedures

Procedures discussed in this section that do not involve analysis of numerical data are sometimes referred to as *non-statistical QA*. These procedures are an essential component of veterinary laboratory quality systems, particularly given the variety of species, physiologic differences, and disease manifestations that veterinarians routinely encounter.<sup>7</sup> Recommended QA procedures are summarized in Table 1; all veterinary

**Table 1.** Procedures recommended for general quality assurance of veterinary point-of-care testing.

Chemistry and Hematology Testing
Use of written policies, standard operating procedures, and forms
Use of only non-expired, properly stored and handled reagents and quality control materials
Documentation of personnel training
Documentation of instrument maintenance and repairs
Regular monitoring of water quality and electrical power supply
Regular monitoring (and verification/documentation of proper function) of ancillary laboratory equipment (eg, temperature of refrigerators, freezers, and water baths, and performance of pipettes, centrifuges, balances, and timers)
Use of repeat criteria*
Use of medical review criteria*
Awareness/monitoring of trends in patient data
Use of properly established (or properly transferred and validated) reference intervals for patient data interpretation†
Hematology Testing Only
Use of blood smear review
Correlation of calculated HCT and PCV (spun hematocrit)
Correlation of HGB, HCT, and MCHC
Regular monitoring (and verification/documentation of proper function) of microscope, refractometer, and microhematocrit centrifuge. Romanowsky stains should be kept fresh and free of microbial contamination

\*For definition, see glossary of terms.

†For additional information, see Friedrichs et al.<sup>12</sup>

laboratories, regardless of their size or complexity, should have such procedures in place.

Interpretation of unexpected, abnormal laboratory data in clinically healthy patients presents a challenge. Knowledge of test result patterns and implementation of repeat criteria and medical review criteria are important QA measures that may help veterinarians judge the significance of abnormal laboratory results in apparently healthy animals. In some cases, repeat testing on a second specimen may be needed to demonstrate the validity and persistence of an abnormal finding. The degree of abnormality in the result and the likelihood of clinical significance (in the clinician's estimation) may also be important factors in determining if further investigation or continued monitoring should be undertaken.

### Patient Results Interpretation and Reporting

Patient data should be interpreted in light of properly established (or properly transferred and validated) reference intervals. More information about reference intervals is available in other resources.<sup>10–12</sup>

If patient results (instrument print-outs or electronic data) are not pasted directly into a paper medical record or transferred electronically (downloaded) to a computerized hospital information system, then a system should exist to verify accuracy of transcribed results. Corrected results should be clearly identified, in the event that a reported result is revised. Manually entered (handwritten or typed) annotations should be initialed and dated. Information concerning sample characteristics (eg, lipemia, hemolysis, or other discoloration) should be included with patient results. If there is potential for interference based on POCT manufacturer information (eg, user manual), then affected results should be highlighted or flagged in some way (if this is not already done automatically by the instrument).

Archiving and backup of electronic patient data must exist to insure integrity over time as required by law. Additionally, paper documentation of patient data must use ink that will last for the legally required duration. Carbon-burned print produced by some instrument printers will fade and is not adequate for patient data archiving.

### Chemistry Instruments

Analytical methods used by small, handheld and benchtop chemistry instruments are various and are reviewed elsewhere.<sup>13</sup> Factors that may influence

selection of a particular POCT chemistry instrument include are presented in Table 2.

### Instrument Maintenance

In addition to general instrument recommendations above, the light source of chemistry instruments should be checked regularly according to manufacturer's instructions to ensure that deterioration, which could result in erroneous results, is not present. The light source should be replaced as needed. Periodic software updates should be performed as needed and recommended by the manufacturer.

### Quality Assurance and Quality Control

In addition to general QA recommendations given above, QC options for POCT chemistry instruments include monitoring results of any internal instrument QC functions, analysis of one or more quality control materials (QCM, "running controls"), participation in external quality assessment (proficiency testing) programs, and comparability testing (eg, comparison of results from an in-clinic instrument with those of a reference laboratory).

#### *Internal Instrument Quality Control Functions*

In this context, *internal* means "internal to the instrument." Built-in instrument QC functions (electronic and other) may include QC samples, measuring system function checks, electronic system checks, and calibration checks.<sup>14</sup> Internal instrument QC functions provide important data that should be reviewed regularly and that may be used for trouble-shooting aberrant laboratory results. Importantly, veterinarians must realize that internal instrument QC functions monitor only certain aspects of the testing process and do not simultaneously assess the entire analytical system (instrument, reagents, and operator).<sup>15,16</sup> Most often, it is the operator that is not assessed by these functions. Assessment of reagent variables by internal QC functions varies by instrument. Internal instrument QC functions should not be considered a substitute for the external QC options discussed below, but should be used in addition to them.<sup>15,16</sup>

#### *External Quality Control ("Running Controls")*

*Quality Control Materials.* In this context, *external* means "external to the instrument." The best way to determine whether a laboratory instrument is performing adequately is to measure material having known analyte concentrations/activities.<sup>5</sup> Use of QCM is the

**Table 2.** Factors that may influence POCT chemistry and hematology instrument selection.

Instrument	Direct & Indirect Costs	Other
Size/footprint of instrument	Instrument purchase or lease	Training and continuing education provided by instrument manufacturer/supplier
Environmental requirements of instrument*	Reagents, including cost, shelf-life¶, storage requirements, and whether liquid or lyophilized**	Technical support provided by instrument manufacturer/supplier
Ambulatory capability of instrument†	Quality control materials, including availability, cost, shelf-life¶, storage requirements and whether liquid or lyophilized**	Time needed to manage inventory
Whether multiple or single analytes are measured	Cost and length of maintenance or service contracts	Waste generated by instrument use (type, amount, disposal requirements)
Species capability (ie, whether validated for the species of interest)	Cost of participation in an external quality assessment (proficiency testing) program, if available	Infection control considerations
Type of unit device used by instrument (if applicable)‡ For hematology instruments, how extensive is the WBC differential count (3-part or 5-part) and availability of certain measurands (eg, reticulocyte count or RBC indices)		Instrument reputation based on feedback from other users and/or as published in medical literature
Sample type, volume requirements, & processing speed (turnaround time & throughput capability)		
Ease of instrument and software operation, including flags§ and ease of trouble-shooting		
Patient and control data presentation, storage, and retrieval		
Analytical performance		
Presence and type of internal (electronic or other) quality control functions		
Maintenance required, including quality control procedures (“running controls”)		

\*Examples of environmental requirements include temperature, humidity, and vibration.

†Ambulatory capability is relevant to settings requiring instrument transport (eg, ambulatory practices, remote area veterinary medical and disaster response teams).

‡Unit device refers to cartridges, slides, strips, and rotors (or other single-use devices required for sample analysis).

§Instrument flags are codes or symbols alerting the operator to abnormal patient values or operational problems.

¶When considering reagent and quality control materials, both open and closed container shelf-life should be considered.

\*\*Liquid materials may be used as is; lyophilized materials require reconstitution.

only way to confirm proper function of the entire POCT system, including instrument, reagents, and operator.

QCM are available through biochemistry supply companies worldwide and may be designated as assayed or non-assayed materials.<sup>17</sup> Use of assayed QCM is recommended. For assayed QCMs, the manufacturer reports a mean analyte concentration (frequently with a range and standard deviation) for each analyte in the QCM package insert, together with relevant analytical methods used.<sup>17</sup> Veterinarians should ideally purchase QCM having a mean determined by the same analytical method(s) as used by the instrument in question. Manufacturers of the QCM should supply information regarding compatibility and use of their product with specific instruments, and manufacturer's recommendations should be followed. All commercially available QCM have a lot and/or batch

number and an expiration date. QCM degrade over time, and expiration dates must be observed. QCM should be stored and handled as directed by the manufacturer.<sup>16</sup>

Using a minimum of 2 levels of QCM (normal and one abnormal) is recommended for all instrument performance studies, including external quality assessment (proficiency testing).<sup>18</sup> Using 3 levels of QCM (low, normal, and high) may be preferred during in-clinic instrument performance evaluation (eg, at instrument purchase and set-up, or during annual performance reevaluation) to demonstrate performance over a wider range of medically relevant values. Routine daily monitoring of instrument performance (routine “running of controls”) should also be performed with at least one level of QCM following instrument set-up and initial performance evaluation.<sup>18,9</sup> Whether a normal or an abnormal control (or both) is



used for daily running of controls may depend upon instrument type and the patient population served; instrument manufacturer recommendations should also be followed. Optimally, consultation with a QC specialist and QC validation should be used to determine the number of QCM levels used (typically one, 2, or 3). Justification for the number of QCM used during routine monitoring should be documented in the instrument log. QC data should be recorded and archived for 2 years or as required by law.<sup>20</sup>

*Interpreting Control Data.* Data generated by analysis of QCM (control data) should be interpreted at the time of analysis. These should also be archived and evaluated periodically over time. Three major options for interpreting control data exist: (1) comparison to QCM manufacturer's assayed range, (2) use of control charts, and (3) in light of one or more validated *control rules*. A simple control rule can be adapted for use with POCT,<sup>19</sup> and the third option is ideally recommended. Use of a validated control rule (or rules) requires instrument performance evaluation, selection of a quality requirement, and a process called *QC validation*.

Control data should always be inspected for instrument error flags, and flagged results should be investigated. Similarly, control data for each analyte should always be compared to the QCM manufacturer's assayed range; data outside the assayed range likely reflect egregious analytical error and should be investigated. However, manufacturer's reported ranges may be wide, and using the QCM manufacturer's assayed range as the only control limits during interpretation of control data is not recommended. When using the QCM manufacturer's assayed range as the only control limits, it is possible that excessive analytical error (based on a quality requirement) for a particular POCT could occur and yet control results could still be within the QCM manufacturer's reported range. In other words, using QCM manufacturer's assayed ranges as the only control limits is insensitive and may allow clinically significant analytical error to go undetected. Rather, control data should be interpreted in light of a quality requirement, knowledge of the given POCT's analytical performance capability, and adequate sensitivity and specificity for detecting analytical error.

Control data may be archived and periodically graphed for visual inspection of trends over time. Control charts (eg, Levey-Jennings charts, which plot the date or run number on the *x*-axis, and analyte concentration on the *y*-axis) are useful for spotting marked deviations from the mean as well as data drifts (trends) or shifts over time that should prompt investigation of instrument function. When using control charts, data

are typically considered unacceptable ("out of control") if results fall outside the interval defined by a specified multiple of the standard deviation from the mean of the data (eg,  $\pm 2$  standard deviations [SD], or  $\pm 3SD$ ).<sup>21</sup> Some instrument software packages may create control charts automatically.

Interpretation of control data using validated mathematical rules is known as *statistical QC* because it employs mathematical *control rules* to establish *control limits*, outside of which control data are considered unacceptable ("out of control"). Statistical QC is the most sensitive and specific way to detect analytical error because it is tailored to a particular instrument and its analytical performance capability. Sensitivity (probability of error detection,  $P_{ed}$ ) and specificity (probability of false rejection,  $P_{fr}$ ) of control rules for detecting analytical error hinge on 3 factors: (1) the chosen quality requirement, (2) the control rule(s) that is/are selected, and (3) the number of QCM that are analyzed each time controls are run. Clearly, running 2 levels of QCM each time controls are run yields more data about analyzer performance than running only one level of QCM. However, to minimize the cost and time involved, using fewer levels of QCM is preferred if QC validation has demonstrated that using fewer QCM can provide enough information to detect analytical error with reasonable certainty.

How are control rules selected and the number of QCM levels decided upon? Broadly speaking, QC validation has 3 phases: for a given instrument, for each analyte measured, (1) choose a quality requirement (allowable TE, or  $TE_a$ , is recommended, and recommendations are available from ASVCP<sup>22</sup>), (2) do an instrument performance study and calculate observed TE ( $TE_{obs}$ ), and (3) if analytical performance is acceptable ( $TE_{obs} < TE_a$ ), choose an appropriate control rule and number of QCM levels. Selecting appropriate control rules requires a QC validation tool (eg, commercially available software,<sup>23</sup> specially designed tables,<sup>19</sup> or specially designed charts<sup>24</sup>); consultation with a QC specialist is ideally recommended. The control rule called  $1_{3s}$  is recommended for POCT; this rule states that a control data point is considered unacceptable ("out-of-control") if it falls outside the range of  $\pm 3$  SD from the mean of the control data. Any one data point outside  $\pm 3$  SD is a rule "violation," leads to "rejection" of that QC run, and should prompt trouble-shooting of instrument function.<sup>18,19</sup> Once any instrument malfunction has been corrected, QCM should be measured one more time. Patient samples should not be measured until repeat analysis of QCM demonstrates acceptable ("in-control") results for all analytes. All corrective actions should be documented in the instru-

ment log. Using one or 2 levels of QCM is recommended for POCT. Veterinary practitioners may use Table S1, which includes  $TE_a$  values currently recommended by ASVCP,<sup>22</sup> to determine if analytical performance of their own particular POCT is robust enough such that  $1_{3s}$  and one or 2 levels of QCM may be used with the recommended sensitivity and specificity for analytical error detection.

It is recommended that the  $1_{3s}$  rule detects analytical error with  $P_{cd} \geq 85\%$  and a  $P_{fr} \leq 5\%$ .<sup>18,19,25</sup> This level of error detection means that, during routine QC, the  $1_{3s}$  rule has a  $\geq 85\%$  chance of detecting analytical error and a  $\leq 5\%$  chance of falsely rejecting control data that are, in fact, acceptable. How successfully the  $1_{3s}$  rule performs for a given analyte and a given instrument, and whether one or 2 levels of QCM are needed, is dictated by that instrument's analytical performance. For instruments having good analytical performance, only one QCM level will be needed; for those with less good performance, 2 levels of QCM will be needed (or analytes may not be "QC-able" at all).

During QC validation, a crucial question for chemistry instruments measuring multiple analytes is "how many analytes are 'QC-able' using  $1_{3s}$ ?" That is, for how many of the measured analytes can  $1_{3s}$  be applied with the desired sensitivity and specificity for detecting analytical error ( $P_{cd} \geq 85\%$  and a  $P_{fr} \leq 5\%$ )? This question should be investigated using both one and 2 levels of QCM. If one level of QCM provides desired  $P_{cd}$  and  $P_{fr}$ , stop there. If not, investigate whether 2 levels of QCM will provide adequate error detection. A POCT instrument does not "qualify" for statistical QC (ie, statistical QC should not be performed) if the  $1_{3s}$  rule cannot provide  $P_{cd} \geq 85\%$  and a  $P_{fr} \leq 5\%$  for  $> 75\%$  of measured analytes using 2 levels of QCM. While it is true that other candidate control rules could be evaluated in this situation, it is likely that other statistical solutions will not be easy or cost-effective. Therefore, if statistical QC using  $1_{3s}$  is not possible at the recommended  $P_{cd}$  and  $P_{fr}$  for at least 75% of measured analytes, and instrument analytical performance cannot be improved (based on consultation with the manufacturer  $\pm$  a QC specialist), then instrument replacement should be considered. Alternatively, instrument performance could be monitored using other means, including non-statistical methods (Table 1), participation in an external quality assessment (proficiency testing) program, or through comparability testing (see below).<sup>18</sup>

*How Often to Run Controls.* The longer the interval between control runs, the more difficult it is to detect

trends or shifts in instrument analytical performance. This is particularly true for low-volume laboratory settings evaluating few patient samples, since, in those settings, there are not sufficient patient data to help detect abnormal trends and shifts. Each hospital or clinic must ponder the "cost" (actual financial costs of repeating samples, potential liability of making medical decisions using poor quality laboratory data, costs to client relations, etc.) of infrequent QC and managing laboratory results generated between an acceptable and an unacceptable QC event. Clinics operating laboratory instruments connected to a laboratory information system may be able to work with instrument manufacturers to receive QC services and feedback via remotely monitored patient and/or control data.<sup>26</sup>

Recommendations for QC frequency of POCT is complicated by the fact that many POCT (particularly instruments measuring biochemical analytes) utilize single-use, disposable cartridges, cassettes, rotors, slides, or strips. These "unit devices" vary in complexity and may contain electrodes, microfluidic networks, reagents, and/or mechanisms for separating or aliquoting samples.<sup>27</sup> POCT using unit devices also vary in complexity and may or may not contain pipettes or tubing that could be subject to malfunction (plugs, leaks, etc.). A single POCT may utilize multiple unit devices measuring different analytes (eg, cartridges, cassettes, rotors, or slides offering different "profiles" or "panels"). Such devices present several dilemmas:

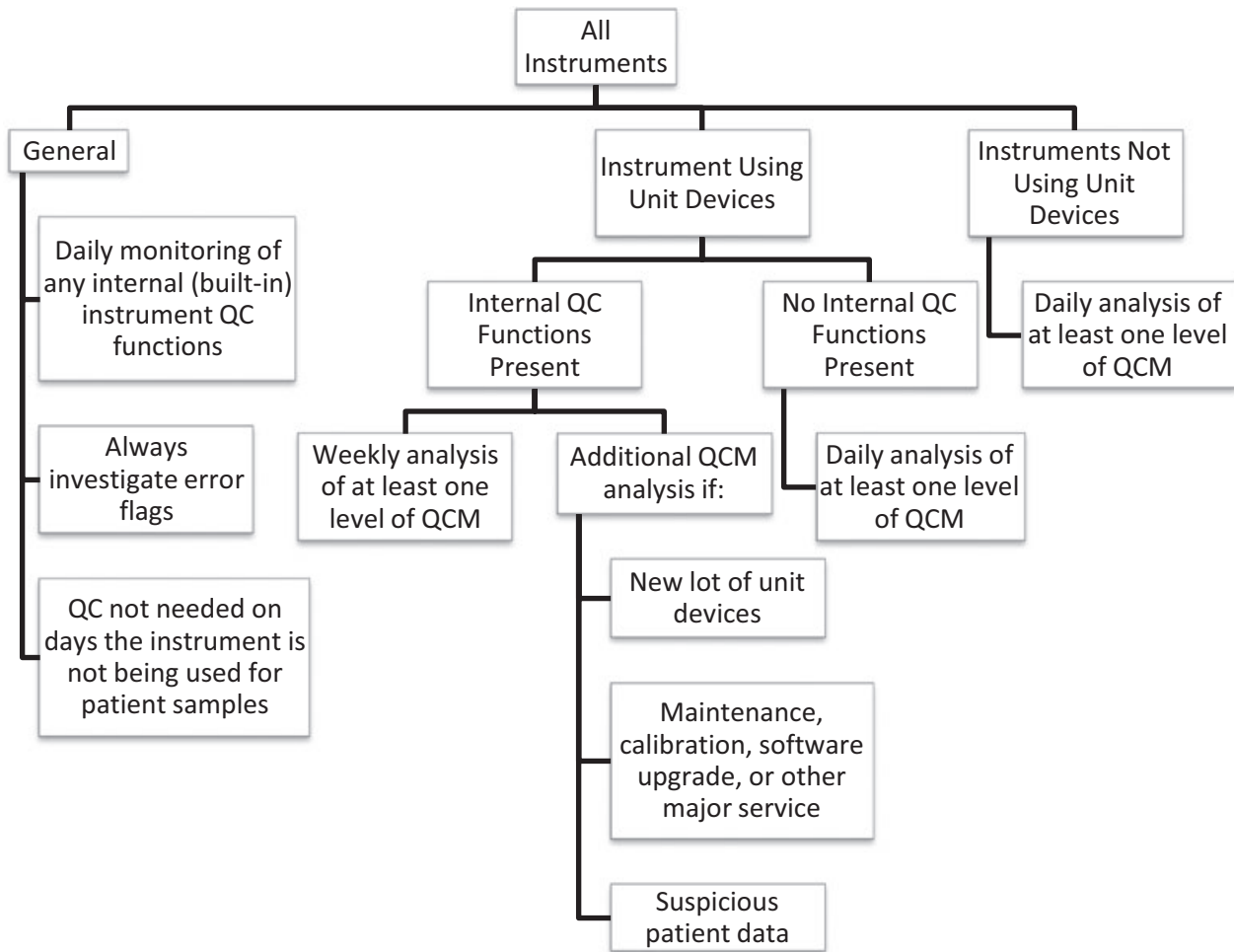
- If external QC is done, a unit device must be used for each QC run, adding to the overall total cost of laboratory testing.
- If external QC is done, a QC run only evaluates quality of that one particular unit device. If resulting control data are acceptable ("in control"), it is assumed that other unit devices from the same lot have similar quality and are also appropriate for patient use. This is generally true; however, quality can vary from unit device to unit device, even within the same lot.
- Unit devices may or may not contain internal QC functions that assess reagents or other components of the analytical process. Information about efficacy of such internal QC functions may not be available if it is considered proprietary by the manufacturer.

Making recommendations concerning necessity and frequency of external QC for unit use POCT devices ideally requires risk assessment on an individual clinic or laboratory basis. Such devices may require monitoring via external quality assessment (proficiency testing) program participation.

Daily analysis of QCM (ie, at least every 24 hours, or each day an instrument is to be used for patient samples) is recommended by most laboratorians.<sup>28</sup> This recommendation was made specifically for larger, more complex laboratory analyzers using liquid reagents. POCT instrument manufacturer/supplier recommendations for frequency of analyzing QCM vary widely and may be as infrequent as monthly, may be based on the volume of testing, or may be based on changes in unit device lot numbers. The more frequent the monitoring of instruments, the greater the likelihood that analytical error is detected before erroneous patient results are reported.<sup>14</sup> In the authors' experience, QC intervals greater than weekly do not provide adequate control data. A formalized, risk-assessment-based approach to quality management is currently uncommon in veterinary laboratories and clinics, but should be considered and could be used to tailor the general

recommendations given below. Consultation with a QC specialist may be of benefit in helping assess risks if this approach is used. Recommendations for QC frequency of veterinary POCT instruments are presented in Figure 1. Actual QC frequency may be tailored to the individual clinic setting based on the estimated risk of error occurring, instrument analytical performance capability, stability of analytical performance over time, and consultation with a QC specialist. Justification for QC frequency should be documented in the instrument log and relevant SOPs.

*Quality Control Material Lot Number Changes.* If control data are being monitored using control charts or control rule(s) then the control limits used to ascertain whether control data are acceptable are derived from the mean and SD of the control data. QCM from differ-



**Figure 1.** Recommended frequency for quality control material analysis for veterinary point-of-care instruments. QCM indicates quality control material.

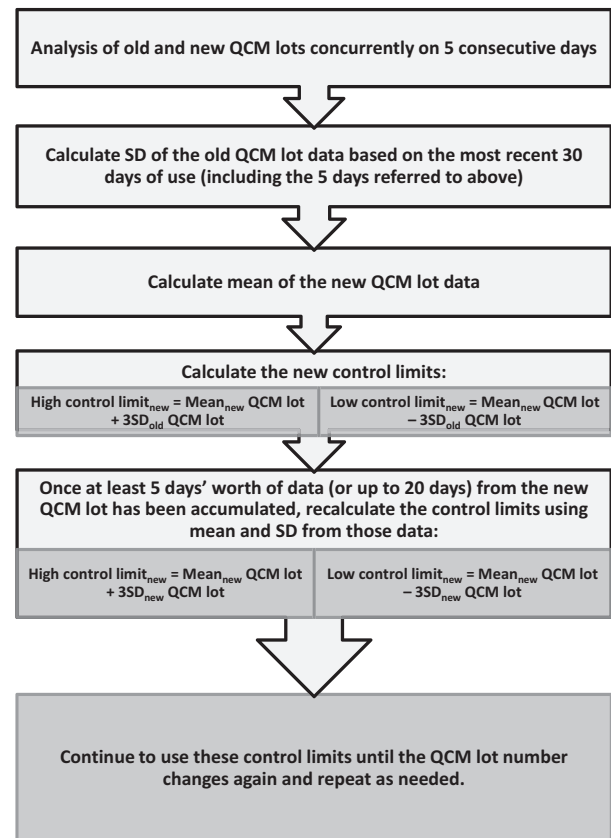


ent lots may not have the exact same analyte concentrations, although these should be close. This issue impacts QC because changing QCM lots (and thus analyte concentrations in the QCM) alters the control limits (by altering mean and SD of the data) used to decide if QC data are “in-control” or “out-of-control.”<sup>29,30</sup> Instrument recalibration (as may occur with software updates and other adjustments) also impacts QC, because recalibration may alter how the instrument measures and may impact mean and SD of the control data.

Obviously, the longer one lot of QCM can be used, the less frequently control limits must be recalculated. Ideally, a clinic or laboratory should purchase (or reserve with the manufacturer, based on estimated needs over the course of a year) enough of one QCM lot to last for an entire year. This may or may not be possible, depending upon stability of the QCM and manufacturer production schedules. Chemistry QCM lots may be available for 12 months or longer. If QCM lots are changed only once per year, recalculation of control limits (which requires repeat measurement of QCM) can be combined with the annual reassessment of instrument performance capability. Steps facilitating QCM lot changes are presented in Figure 2. These steps should be carried out before completely running out of the old QCM lot, such that sufficient material is available. During the changeover period, control data from the old QCM lot should be used to determine whether instrument performance is “in control” or “out of control.” Steps given in Figure 2 assume use of the  $I_{3\sigma}$  control rule; obviously, use of an alternate rule requires that calculations in steps 4 and 5 be done accordingly.

#### *External Quality Assessment (Proficiency Testing) Programs and Comparability Testing*

In this context, *external* means “external to the veterinary clinic or laboratory.” In addition to regular in-clinic QC, participation in an external quality assessment (EQA) program is recommended to ensure quality of POCT results. At least quarterly (periodic) participation is recommended; less frequent participation is unlikely to yield useful data. A limitation of this recommendation for POCT is that most current EQA programs available to veterinarians (and supplying veterinary samples) cater to reference laboratories, and an appropriate peer group may be difficult to find for POCT. More EQA programs aimed at veterinary POCT and veterinary in-clinic laboratories are needed.



**Figure 2.** Recommended sequence for control limit recalculation following quality control material lot number changes or instrument recalibration.<sup>17,19,29</sup>

In human medicine, “comparability” refers to agreement between patient results for a given analyte using different measurement procedures (different instruments or analytical methods) within one health care system.<sup>31</sup> Timing of comparability testing can be frequent (eg, daily, weekly), periodic (eg, quarterly, biannually), or “special-cause” testing. Special-cause testing is performed in response to an alert from a QC procedure or other triggering event.<sup>31</sup> In veterinary medicine, a common scenario initiating special-cause-comparability testing is the desire to check an unexpected or aberrant patient result from an in-clinic analyzer by sending an aliquot of that patient’s sample to a reference laboratory.

Regularly scheduled frequent or periodic comparability testing (monthly or quarterly) using a stable patient sample or QCM potentially could be used by a veterinary clinic to monitor analytical performance of its in-clinic instruments. An ASVCP guideline regarding EQA and comparability testing is forth-

coming, and specific recommendations will be made therein.

## Hematology Instruments

Analytical methods used by small, handheld and benchtop hematology instruments are various and are reviewed elsewhere.<sup>13,32,33</sup> Factors that may influence selection of a particular POCT hematology instrument include are presented in Table 2.

### Unique Aspects of Hematology Testing

In addition to numerical results (cell counts and indices) reported by automated hematology analyzers, evaluation of blood cell morphology is a critical aspect of hematology testing. In general, enumeration of hemic cells from birds, reptiles, amphibians, and fish is not supported by manufacturers of automated hematology analyzers due to the presence of nucleated RBCs and thrombocytes in these species that interfere with instrument counting functions.<sup>34</sup> Hemocytometers and specialized pipette systems are used for exotic animal hematology and are not covered by these guidelines. More information about exotic animal hematology can be found in other resources.<sup>9,35,36</sup> Recommendations presented herein specifically refer to hematology testing of mammalian blood samples.

### Quality Assurance and Quality Control

#### *Running Controls and Statistical Quality Assurance*

The QA/QC recommendations made above for chemistry instruments also apply to hematology instruments. A recent veterinary publication showed that it is possible to perform statistical QC of chemistry instruments in the in-clinic setting using a 1<sub>3s</sub> control rule and one or 2 QCM.<sup>19</sup> Presumably, this control rule can also be considered for statistical QC of hematology instruments (following the recommendations presented above), although more studies are needed. Hematology instruments do not use unit devices and may or may not have internal QC functions, depending upon the instrument. Daily QC consisting of measuring at least one level of assayed QCM is recommended for impedance and light scatter-based instruments, in addition to daily monitoring of any internal QC functions the instrument may possess.

#### *Non-Statistical Quality Assurance and the Importance of Blood Smear Review*

Non-statistical quality assurance procedures relevant to hematology testing are presented in Table 1. Ideally, blood smears should be reviewed for all CBCs performed by the clinic. At minimum, blood smears should be reviewed for CBCs from clinically ill patients and CBCs yielding unexpected or suspicious results. Blood smears should be prepared by appropriately trained personnel as soon as possible after collection and stored at room temperature. Only smears of good to excellent quality (having a smooth, uniform, feathered edge, with no holes or gaps in the film of blood) should be examined. Blood smears must be kept away from moisture and formalin fumes. Smears should be stained with a Romanowsky stain that is fresh and uncontaminated by debris or microorganisms.<sup>32</sup> A qualified individual such as a veterinarian or veterinary technician should assess the respective densities and morphology of RBCs, WBCs, and platelets to look for platelet clumping, and compare their subjective impression of the blood smear to numerical data as well as any instrument flags, histograms, or cytograms from the analyzer. Unexpected or suspicious instrument data call for more critical smear review, further evaluation of the patient by the veterinarian, evaluation of the instrument by manufacturer's technical support, and/or referral of the sample to a clinical pathology laboratory.

Criteria should be in place to guide use of manual WBC differential counts in place of the automated differential counts, and medical review criteria should be used; suggested criteria are presented in Tables 3 and 4. If nucleated RBC (nRBC) are not included in the 100-cell manual nucleated differential cell count but are rather counted additionally, and if  $> 5$  nRBCs/100 WBCs are identified, the automated total WBC concentration should be corrected<sup>32</sup>, and the absolute leukocyte concentrations should be recalculated using the corrected total WBC count. If nRBC are included in the differential count, corrected WBC counts should be calculated, but absolute leukocyte concentrations do not need to be recalculated. If immature granulocytes are observed, the manual leukocyte differential count should divide neutrophils into segmented and band forms (and earlier forms if also seen), and leukocyte absolute counts should be corrected. If toxic change is observed, this should be noted. Blood smear review should be performed anytime there is suspicion that automated leukocyte differential counts are inaccurate (eg, if there is a lack of clear distinction between cell types on histograms or cytograms).

**Table 3.** Criteria for Performing an In-Clinic Manual WBC Differential Count by Trained Personnel.

Presence of...	Suggested Cut-Off Value	Comments
Nucleated RBCs (nRBCs)	If more than rare nRBC	Perform and report a manual differential count. Correct automated total WBC for the number of nRBC (see text)
Neutrophil left shift	> 1 band and/or immature granulocytes (eg, metamyelocyte) observed	Perform and report a manual differential count, enumerating neutrophil forms (segmented, band, metamyelocyte, etc.) separately
Unclassified (unidentified) cells	Any	Perform and report a manual differential count, enumerating the unclassified cells in an "other" category. Describe morphology of the unclassified cells. Recalculate absolute differential results
Subjective impression that automated WBC differential count may not be accurate	N/A	If for any reason the automated WBC differential count is suspect, perform a manual WBC differential count to verify it

N/A indicates not applicable.

**Table 4.** Suggested criteria for medical review of blood smears and concurrent CBC data. Blood smears and EDTA-anticoagulated blood should be sent to a board-certified clinical pathologist as needed to confirm abnormal findings.

Blood Smear	Criteria Triggering a Review
Background	Unusual background matrix Unusual background color Organisms or suspected organisms
RBC	Moderate to marked poikilocytosis of any kind; moderate to severe anemias Reticulocytosis Any Heinz bodies in a non-feline species; > 10% Heinz bodies in cats Any non-routine* inclusions (including organisms or suspected organisms) Basophilic stippling, siderocytes, or Howell-Jolly bodies in dog 5 nRBC/100 WBC (or > 10% nRBC if included in the differential count) in non-equine species; any nRBC in horses Abnormal MCV
WBC	Left shift in which bands are $\geq 3\%$ of observed leukocytes, or any left shift in which neutrophil precursors less mature than bands are observed; Leukopenia < 3,000 WBC/ $\mu\text{L}$ Any left shift where immature neutrophil forms outnumber segmented neutrophils Leukocytosis > 30,000 WBC/ $\mu\text{L}$ in non-ruminants; leukocytosis > 15,000 WBC/ $\mu\text{L}$ in ruminants and horses Lymphocytosis > 10,000 cells/ $\mu\text{L}$ ; Monocytosis > 2,000 cells/ $\mu\text{L}$ ; Eosinophilia > 2,000 cells/ $\mu\text{L}$ ; Basophilia > 1,000 cells/ $\mu\text{L}$ Any unclassified cells Any organisms or suspected organisms Presence of vacuoles in non-monocytes and abnormal granulation in any leukocyte, other than toxic granulation in neutrophils
Platelets	Platelet count > 900,000 cells/ $\mu\text{L}$ (except pigs and ruminants); moderate to severe thrombocytopenia < 100,000 cells/ $\mu\text{L}$ Abnormal MPV (if reported by instrument) Suspected inclusions or abnormal granulation

\*Low numbers of Howell-Jolly bodies are occasionally found in blood from healthy cats and horses, but not dogs.

nRBC indicates nucleated RBC; MPV, mean platelet volume.

Certain morphologic changes (eg, presence of RBC poikilocytosis, Heinz bodies, neutrophil toxic change, hemoparasites and other infectious organisms) simply cannot be detected by automated analyzers (of any type), and evaluation of a well-made blood smear is not only an essential QA procedure but may additionally be diagnostic. Other morphologic changes in hemic cells may either go undetected by automated instruments or trigger instrument flags or abnormalities in histograms or cytograms, and blood smear

review is required to clarify and further elucidate the abnormality (eg, presence of nRBCs, neutrophil left shift, basophilia, neoplastic cells, and clumped, large, or misshapen platelets). Blood smear preparation and evaluation technique influences interpretation, and personnel must have proper training in recognizing normal and pathologic cells in blood of the different veterinary species. Instruction is available in published literature, and interested readers are referred to other resources.<sup>37,38</sup>

*Hematocrit and Microhematocrit.* Performing a PCV (spun HCT) and plasma protein measurement with each CBC is recommended. A spun microhematocrit tube can be used to evaluate plasma characteristics (eg, look for lipemia, hemolysis, or icterus) and confirm the automated HCT. Because a small amount of plasma and some platelets and leukocytes become trapped within the RBC column inside a microhematocrit tube, PCV may be slightly higher than HCT as reported by the POCT.<sup>39</sup> If concurrent PCV and HCT values disagree by greater than 3 L/L, results from both methods should be investigated for potential error.

When MCHC is within the reference interval, the numerical value of the measured blood HGB concentration should be approximately one-third of the HCT numerical value<sup>39</sup>; if MCHC is abnormal, this relationship may not hold true. If MCHC is within the reference interval (or close to it) and HGB does not approximately equal one third of the HCT numerical value, then both HGB and HCT results should be investigated for sources of error. Increased MCHC is almost always an artifact and should prompt investigation for hemolysis, lipemia, or Heinz bodies.<sup>39</sup> Hemolysis falsely decreases the RBC concentration and HCT or PCV. Excessive lipemia may falsely increase HGB concentration. Either situation results in a falsely increased MCHC and MCH. Plasma should be evaluated for lipemia and hemolysis by inspecting the microhematocrit tube after centrifugation for a concurrent PCV. The level of lipemia or hemolysis can be reported in a semi-quantitative fashion as slight, moderate, marked, or 1+, 2+, 3+. If evidence for these artifacts is lacking, appropriate instrument operation should be confirmed by measuring QCM and technical services should be contacted as needed for assistance.

Periodic (quarterly) external quality assessment (proficiency testing) or comparability testing of hematology instrumentation is recommended to confirm instrument function, reagent stability, and comparability to an appropriate peer group or reference laboratory. If sending an aliquot of patient sample to a reference laboratory to compare results from an in-house hematology instrument, this should be done within 24 hours of sample acquisition. The blood sample should be refrigerated (4°C) immediately following in-clinic analysis until arrival at the reference laboratory.<sup>40</sup> Air-dried, stained blood smears are stable specimens and may last for years if protected from light and moisture (particularly if a coverslip is applied to the stained smear using an appropriate adhesive). Smears that are shipped to reference laboratories for review

should be protected from condensation, freezing, and formalin fumes.<sup>9</sup>

#### *Proper Hematology Sample Handling*

- 1 *Proper sample tube and tube filling.* Blood for CBCs should be collected into EDTA (lavender-top) tubes.<sup>40</sup> Tubes are available containing EDTA in liquid (K<sub>2</sub>-EDTA) or spray-dried (K<sub>3</sub>-EDTA) forms. K<sub>2</sub>-EDTA is recommended.<sup>41</sup> EDTA liquid inside blood collection tubes can dilute samples by 1-2% or more, depending on volume of blood added. Underfilling these tubes can significantly decrease PCV as a result of RBC shrinkage in the presence of the highly osmolar EDTA. In addition, excess EDTA can falsely increase plasma protein if determined by refractometry, especially in samples from patients with low plasma protein concentration. Filling tubes at least half full is recommended, as this is unlikely to alter clinical interpretation. Small volume (pediatric) tubes are available and should be used for smaller animals.
- 2 *Proper sample mixing.* Mixing the collection tube by gentle inversion 8-10 times immediately after filling is recommended to avoid clotting of the sample. When samples rest in a test tube rack, erythrocytes settle to the bottom of the sample tube, leaving nucleated cells and platelets concentrated at the top. Sufficient sample mixing is therefore also crucial immediately prior to sample analysis. The net effect of settling in improperly mixed samples will vary with the location of the instrument needle aspirating the aliquot to be measured.<sup>37</sup>
- 3 *Rejection of clotted samples.* Samples containing grossly visible clots should be rejected. The effect of clotting on cell concentrations will be proportional to the clot size and/or number but cannot be accurately predicted by visual inspection of the clot. Small clots may not be grossly visible but can be detected by gently stirring the sample prior to analysis with one or several clean, wooden applicator sticks, as clots will adhere to the stick. In addition to affecting cell counts because they trap cells, clots may cause mechanical problems; aspiration of small clots may plug tubing in the analyzer, altering the accuracy of results for the current or subsequent sample(s).<sup>39</sup> If sample clotting is observed, the sample should be rejected and a new sample should be obtained.

#### *Sample Characteristics That May Adversely Affect the Quality of CBC Data*

Certain sample characteristics may adversely affect the quality of CBC data and are reasons for sample rejection or annotation of CBC results:

- 1 *Platelet activation, resulting in clumping*, may occur during venipuncture and sample handling and may cause falsely decreased automated platelet counts.<sup>42</sup> Unexpectedly low platelet counts (based on patient condition and other clinical information) should prompt evaluation of a blood smear to look for platelet clumping. The authors have observed that presence, number, and size of platelet clumps are not always reproducible between smears made from the same blood sample. If large clumps are observed on smear review and/or a low automated platelet count (regardless of the degree of observed clumping) requires confirmation, a fresh blood sample should be drawn (using atraumatic venipuncture and conscientious sample handling) and analyzed. Samples from animals having increased numbers of large platelets in circulation may also yield falsely low automated platelet counts, because analyzers using impedance methods may not be able to distinguish large platelets from RBCs.<sup>43</sup>
- 2 *Agglutination of RBCs* may falsely lower RBC concentration and falsely increase MCV<sup>39</sup>; while its effect on HCT and MCHC is variable. If severe, agglutination may be detected by examining the sample collection tube walls for grossly visible aggregates. Significant rouleaux can mimic agglutination; distinguishing between these can usually be accomplished with a saline dispersion test, where blood is added to saline on a glass slide to achieve approximately a 1:4 (or greater) dilution and examined under the microscope.<sup>39</sup> Rouleaux should dissipate while agglutination remains.
- 3 *Marked numbers of Heinz bodies or nRBCs* may render the sample turbid, falsely increasing HGB concentration and subsequently MCHC and MCH, particularly in anemic patients.<sup>44</sup> Heinz bodies may be detected on routine blood smear review and can be confirmed using new methylene blue staining.<sup>39</sup> Presence of Heinz bodies should be noted semiquantitatively (eg, mild, moderate or marked) or reported as the percentage of RBCs affected on the CBC report.

#### *Patient Results Reporting*

CBC results known to be inaccurate should not be reported.<sup>9</sup> Any observed sample clotting (or other problem with sample quality) should be recorded on the laboratory data report and included in the patient medical record. Automated platelet counts should not be reported if significant platelet clumping is observed on blood smear review; rather, platelets should simply be reported as “clumped”; a semiquantitative estimate

such as “clumped, appear adequate” (or increased or decreased, as appropriate) may be added.

Results of the blood smear review should be recorded on or near instrument print-outs of numerical data or on a CBC form, and such annotations should be initialed and dated. Whether an automated or manual differential WBC count is used for patient management should be clearly indicated. If computerized medical records are used, CBC data, annotations, and comments should be added into the hospital information system for each patient.

## Summary

A formalized and comprehensive approach to the quality management of POCT is recommended in all veterinary settings, and it is the ASVCP's recommendation that any facility performing veterinary POCT should implement a comprehensive laboratory quality management program. Facilities should document laboratory quality procedures by means of a written quality plan or manual that includes policies, SOPs, and forms. Logs and records (eg, instrument performance logs, instrument maintenance logs, and operator training logs) and audit results (eg, of operator examination audits) should be maintained and archived. Equipment operator training and assessment should be documented and ongoing. Internal instrument QC functions, external QC procedures (measurement of QCM and interpretation of control data, participation in an EQA program, comparability testing), and non-statistical QA procedures should routinely be used. Reference intervals for patient data interpretation should be validated, and measures should be in place to ensure accurate patient results reporting. A list of relevant resources and example forms and logs can be found with the on-line version of this guideline document, published at <http://www.asvcp.org/pubs/qas/index.cfm>.

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## Supporting Information

Additional Supporting Information may be found in the online version of this article:

**Table S1.** Instrument Performance Specifications: Requirement for Application of the  $1_{3s}$  Control Rule Using  $TE_a$  Values Recommended by ASVCP.

## Appendix 1

### Glossary of Terms

**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)** – Total systematic error, which includes constant and proportional bias. Bias is the difference between the measured result and some measure of the “true” value (e.g. as measured by a reference method or as defined by a known standard). The term *bias* has a specific meaning in the statistical t-test and in difference plot analysis, where bias (expressed in analyte units) equals the difference between the mean values of 2 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

$$\text{Bias}\% = \frac{\text{Mean}_{\text{target}} - \text{Mean}_{\text{measured}}}{\text{Mean}_{\text{target}}} \times 100$$

Bias can be positive or negative; when used to calculate observed total error, the absolute value is used. Recommendations made in this guideline focus on using a known mean concentration of commercially available assayed control material as the target mean, since control materials are most easily accessible and cost-effective for privately practicing veterinarians. In clinical pathology laboratories, best practice dictates that target means be based on data from method comparison to a true reference method (“definitive” method) or known concentration of certified reference material.<sup>1,2</sup> Target

means may also be based on peer group means from external quality assessment (EQA, or proficiency testing) program data.

**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).<sup>3</sup>

**Bias, proportional** – When the magnitude of systematic error changes as the analyte concentration changes. Often, error increases as the analyte concentration increases, but the reverse may also be true.<sup>3</sup>

**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 material 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 within one health care system that process samples from the same patients. Comparability testing is done to ensure that measurements are similar and can be used interchangeably without causing clinical error. Total allowable error (TE<sub>a</sub>) can be used as a basis for judging acceptability of comparability testing results.<sup>4,5</sup>

**Control data** – Data obtained when one or more quality control material (s)(QCM) is/are measured. **Control charts** are graphical displays of control data, plotting time (in days) on the *x*-axis and analyte concentration on the *y*-axis. Control charts are useful for assessing how far away individual data points are from the mean and for spotting drifts (shifts) or trends in results. **Levey-Jennings charts** are a popular type of control chart that use mean  $\pm$  a multiple of the standard deviation as the control limits (measure of acceptable data).<sup>6</sup>

**Control level** – “Level” refers to analyte concentration/activity (eg, low, normal, or high) in the QCM. “Running 2 level controls” refers to using two different

QCM (eg, one having predominantly normal analyte concentrations/activities and one having predominantly abnormal analyte concentrations/activities) in a given quality control (QC) procedure.

**Control limits** – The high and low values outside which control data are considered unacceptable (“out-of-control”). For example, in the 1<sub>3s</sub> rule recommended in these guidelines, control limits are defined as mean  $\pm$  3 standard deviations. A single control data point outside the range mean  $\pm$  3 standard deviations is said to “violate” the 1<sub>3s</sub> rule. Use of control rules is sometimes referred to as **statistical QC**.

**Control rule** – A rule used during analysis of control data to determine whether said control data are acceptable (“in control”) or unacceptable (“out-of-control”). Control rules are sometimes referred to as “Westgard Rules”.<sup>7</sup> Additional information about control rule nomenclature can be found in other resources.<sup>7,8</sup>

**Control run** – Measurement of one or more QCM following a specified interval (after a specified number of patient samples, after a specified duration of instrument operation [eg, laboratory shift]).

**CV (coefficient of variation)** – A measurement of imprecision (random error); mathematically, CV is standard deviation (SD) divided by the mean (mathematical average) and expressed as a percentage:

$$CV(\%) = \frac{SD}{Mean} \times 100$$

**External Quality Assessment (aka external quality assurance, EQA, or proficiency testing, PT)** – A program which determines total testing performance by comparing a laboratory’s 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.<sup>9</sup>

**External QC** – QC procedures performed by laboratory or veterinary clinic staff that are external to (ie, not built or programmed into) the laboratory instrument. Measuring quality control materials (QCM) is a common example of external QC.

**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 (expressed as percent). (Also see *precision*.)

**In-Clinic QC** – QC procedures performed by the veterinarian or veterinary staff which include both internal and external QC procedures, such as measurement of quality control materials, participation in an EQA program, and/or comparability testing.

**Internal QC** – QC functions that are internal to (ie, built and programmed into) laboratory instruments and assess the analytical processes of those instruments.

**Instrument performance study** – A study performed to characterize an instrument's analytical performance capability, represented by bias (inaccuracy) and imprecision (random error). Instrument performance studies provide data needed for calculation of observed total error ( $TE_{obs}$ ) and quality control (QC) validation (including ensuring that an instrument can perform to the desired quality requirement). In human laboratory medicine, it is recommended that assessment of imprecision and bias be based on repeat measurement of at least 20 samples.<sup>10,11</sup> This recommendation has been modified to 5 replications for veterinary point-of-care testing.<sup>12,13</sup>

**Mean** – Mathematical average of values measured.

**$P_{ed}$  (probability of error detection)** – The “diagnostic sensitivity” of a control rule for detecting analytical error. High  $P_{ed}$  means that analytical error is reliably detected;  $P_{ed} \geq 90\%$  is recommended in human laboratory medicine.<sup>14</sup>  $P_{ed} \geq 85\%$  is recommended as a minimum for veterinary point-of-care testing (POCT).<sup>12,13</sup>

**$P_{fr}$  (probability of false rejection)** – The “diagnostic specificity” of a control rule for detecting analytical error. Low  $P_{fr}$  means that there is a low probability of falsely rejecting control data (ie, of thinking that control data are unacceptable when in fact they do not represent analytical error).  $P_{fr} \leq 5\%$  (ie, a diagnostic specificity of  $> 95\%$ ) is recommended in human laboratory medicine and is also recommended for veterinary POCT.<sup>12–14</sup>

**POCT (point-of-care test or testing)** – Laboratory testing performed outside the traditional clinical pathology laboratory (a.k.a. “reference laboratory”).

**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).

**QA (quality assurance or assessment)** – Laboratory procedures that monitor and improve laboratory performance and seek to minimize all types of laboratory error (pre-analytical, analytical, and post-analytical). QA involves quality planning, implementation, monitoring, and assessment, and includes many “common sense” procedures (personnel training, use of standard operating procedures, etc.) routinely utilized in well-run laboratories and clinics.

**QALS (Quality Assurance and Laboratory Standards Committee of the ASVCP)** – The ASVCP

committee charged with “encouraging and promoting the establishment of standards for the performance of laboratory procedures on veterinary samples.”<sup>15</sup>

**QC (quality control)** – Laboratory procedures that monitor the analytical performance of instruments and detect error (predominantly analytical). May refer to measurement of quality control materials (QCM) by the instrument operator with subsequent analysis of control data<sup>16</sup> or internal instrument QC functions that monitor analytical processes.

**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  $\pm Z * SD$ . (Also see definition of Z score.)

**Quality control validation** – The process of selecting control rules based on a quality requirement, known instrument analytical performance, and desired sensitivity ( $P_{ed}$ ) and specificity ( $P_{fr}$ ) for detecting analytical error. QC validation allows robust detection of analytical error because selected rules are *tailored* to the individual instrument and chosen quality requirement. Allowable total error ( $TE_a$ ) is a commonly used quality requirement.

**Quality Plan** – A concise written statement summarizing the philosophy and framework upon which a facility's quality management program is based.<sup>17</sup>

**Quality Requirement** – A benchmark or standard to which the analytical performance of a laboratory instrument is compared. The quality requirement recommended for POCT in these guidelines is expressed as allowable total error ( $TE_a$ ).<sup>5</sup>

**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*.)

$$s = \sqrt{\frac{\sum(x_i - \bar{x})^2}{(n - 1)}}$$

**SOP (standard operating procedure)** – A written document that provides information about a process or



task. An SOP for laboratory testing may provide a variety of information, but should include detailed instructions for carrying out a laboratory procedure. Use of SOPs helps ensure that laboratory procedures are carried out in a standardized and consistent manner. Suggestions for SOP content can be found in the general ASVCP quality assurance guideline.<sup>15,18</sup>

**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 (eg, some pre-analytical variation, biologic variation, and other factors) that contribute to variation seen in patient results. Total error components that are under direct supervision or control of the laboratory are bias and imprecision.

**TE<sub>a</sub> (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 insure clinical usefulness.

**TE<sub>obs</sub> (observed or calculated total error)** – The sum of measured random error (imprecision) and measured systematic error (bias or inaccuracy). TE<sub>obs</sub> is defined in this guideline as:

If expressed in units of %,

$$\text{TE}_{\text{obs}} = 2\text{CV} + \text{absolute bias}\%$$

If expressed in analyte units,

$$\text{TE}_{\text{obs}} = 2\text{SD} + \text{absolute mean difference}$$

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. The value 2 is a Z score (see below).

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

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

**Z score (a.k.a. Z value, normal score, or standard normal deviate)** – In statistics, a number indicating how far away an individual value in a dataset is from the mean.<sup>19</sup> The Z score reflects probability of (or confidence in) the TE<sub>obs</sub> estimate. A Z value of 2 produces roughly a 95% 2-tailed confidence interval for a given estimate.

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