How to Design an In-House Quality Control Plan for your Laboratory

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In the past 15 years, there has been a large move to perform more analysis of veterinary samples in-clinic. Indeed, in a 2007 VIN survey, >85% of clinics had some form of in-clinic laboratory. This has been driven by marketing campaigns by the large retailers of laboratory equipment that state all of the positive factors. There is the potential for improved turn-around time especially in after-hours clinics where they are most needed. Decreased transport and handling of samples, which can add artefact and error, would also result in significant improvement in accurate and precise results. Additionally, certain analysis such as coagulation factors and urinalysis are temperature and time dependent. These and other similar analyses would benefit from a high quality, well-validated in-clinic assays with a good quality assurance program. The hope in the clinics is that the purchase of laboratory equipment also increases revenue to the clinic by keeping laboratory work in the clinic revenue stream.

What these marketing campaigns frequently do not address is quality control of laboratory samples which is legally mandated for the same equipment in human medicine. This has been overlooked in large part as the added cost is perceived to be a deterrent for purchase of equipment. Veterinarians do not receive training during their veterinary medical education which would enable them to manage the equipment that they purchase. Indeed, few clinical pathology courses teach quality assurance to veterinary students at all. Veterinarians are therefore poorly prepared to be a discerning consumer when sales representatives from the major companies come to sell their wares. They are dependent on QA/QC education from manufacturers, which is important, but should be just one facet of the quality assurance knowledgebase in the facility if there is to be an in-house laboratory. They also are taken unaware when sales representatives try to sell them different products which include reagent contracts and lack any mention of an appropriate quality assurance program. The appropriate costs of a well-managed laboratory are frequently grossly underestimated. Practitioners have been caught in reagent purchase requirements which are very costly as they are not familiar with actual usage and expiry of these products. This can result in the use of expired reagent which is obviously against all guidelines and results in imprecise, inaccurate and poor quality results.

So how do we move forward during our busy day to construct and effectively manage an in-house laboratory? The answer step by step, one builds the foundation. Quality assurance (QA) is the overall system for assuring the quality of laboratory test results. QA includes monitoring and assessment of all laboratory systems and procedures, with the objective of identifying problems, making corrections, and continuously improving the quality of testing service such that pre-analytical, analytical, and post analytical error are minimized. Internal and in-clinic quality control (QC) validation and reference interval generation are part of the instrument/method validation and verification process. (See ASVCP POCA, General QA guidelines, and reference intervals found here http://www.asvcp.org/pubs/qas/index.cfm) 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 training and assessment of personnel, regular quality control (QC) procedures and participation in an external quality assurance (proficiency testing) program.

Actually sitting down and constructing a management plan, though it seems like more time and work, typically results in significant cost savings due to adequately managed reagent and time savings as a direct result of better trained personnel, better communication, written plans and SOPs. This is of course in addition to decreased error in sample measurement.

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. A hierarchy of quality requirements has been proposed, and the most stringent quality requirements are based on clinical outcomes and clinical decision thresholds.

Quality laboratory medicine requires continual maintenance through a quality assurance program. A recent study by Rishniw and others suggested that performance of in-clinic biochemical analyzers was significantly worse than that of reference laboratories, and that individual in-clinic analyzers of most common makes periodically and unpredictably failed quality assurance. Additionally, certain analytes tended to be problematic with most analyzers. In all cases, the clinicians participating in that study were unaware of the accuracy and precision of their own in-clinic analyzers, and did not routinely undertake quality control measures to examine and validate performance. Subsequently, recommendations for quality assurance in veterinary practice were developed, and have been recently published.

In a recent 2007 VIN survey, practitioners obviously desired quality results, however when it comes down to specifics, there appears to be a lack of knowledge how to implement the level of quality control necessary to obtain them. This is an outline of where to begin.

A. Create standards or management policies for your business and criteria for the standards.
    1. Use federal, state regulations, ASVCP guidelines and client contractual obligations as a starting point.
    2. Review best practices through AAHA, ASVCP, and AAVLD and determine how you can strive to achieve them. Align your criteria with accreditation standards, even if you do not pursue accreditation. These will become the basis of your policies and procedures.
B. Create a quality program/management description.
    1. This document should include:
        a. a mission statement,
        b. company reporting structure
        c. annual program evaluation process
        d. goals
        e. business practices and specific policies relevant to the quality program's scope.
C. Create policies and standard operating procedures (SOPs) according to manufacturer's recommendations and current ASVCP guidelines.
D. Establish a plan for in-clinic and external quality assessment of equipment according to ASVCP guidelines.
    1. In-clinic quality assessment includes controls analyzed according to a schedule that is appropriate for the equipment. Actual frequency and controls required varies greatly between specific instruments from daily to internal QC performed by manufacturer technicians. Ask your manufacturer about available QC packages. If they say that they don't have any, buy another instrument.
    2. According to the ASVCP Point of Care guidelines external quality assessment should be performed at least biannually.
E. Work with various leaders (e.g. department chairs, clinical pathologists, head technologists, business managers, etc) to develop workflows and standard operating procedures that support your quality program and meet high principles for running your business.
F. Train staff and hold refreshers to ensure workflows are understood, implemented and meeting the needs of your business.
    1. Use written policies and SOPs as training tools. Have staff sign off on these so they may be referred to if there are any misunderstandings at a later date.
G. Establish a quality committee that include employees from multiple departments/areas. Consider external participants, such as clients or referral veterinarians, who can provide subjective feedback. This committee and regular meetings assures that any issues are quickly addressed
    1. Meet on a quarterly basis to review quality reports, trends and improvement activities.
    2. The data the committee reviews should include quality metrics, sales/revenue reports, satisfaction survey results and other screening tools relevant to your business..
H. Implement corrective action plans when results are unsatisfactory and performance needs improvement. Hold management accountable for developing action plans and achieving results. Continue monitoring to ensure that your company is providing the best possible products and services.

Reference intervals

Reference intervals are a cornerstone of modern day diagnosis which are taken for granted and poorly understood. Asking the correct questions can change understanding and use of your laboratory report. Are your reference intervals correct for your patient? Are they method, species, and population specific? Where did they come from and were they generated according to current ASVCP guidelines? Is partitioning required to improve acuity of diagnosis? You need to ask your laboratory for this information if it is not apparent to you on your record. According to current guidelines, if there is any deviation from normal generation in statistical or population analysis, this must be directly annotated on the report. If RI generation has been in accordance with guidelines, this should be available to the clinician in a written report (RI study summary document). This information may include, but is not limited to: Reference population demographics and number of reference subjects sampled, subject preparation and time or season of collection, if relevant, sample type and handling, confidence intervals around the reference limits. If you are unaware of the specifics of the reference intervals you are currently using, please ask! The numbers that you use likely on a daily basis for diagnosis are typed in by a technician from data generated by one or a handful of hopefully qualified quality assurance specialists (a.k.a. human beings who make mistakes).

When was the last time that the reference interval was reviewed and revalidated? Current recommendations are revision every 3-5 years. Even at reputable institutions this can be problematic. Recently at UC Davis, it was realized that bovine hematology reference intervals that were used and essentially disregarded by clinicians as most results were "out of bounds" were last evaluated in the 1950s. Amazing what written archives sitting on a slightly older emeritus professor's shelf found by an exuberant veterinary student can elucidate; not likely to happen in the digital age.

In clinic equipment

In a 2007 VIN survey, only approximately 25% of 371 practitioners had developed/validated the reference intervals they were currently using, meaning that the majority of respondents were not in compliance with current ASVCP recommendations.

Validation of existing reference intervals, potentially supplied to you by your manufacturer should be verified for your population and for your individual instrument. In order to do this, ASVCP guidelines recommend:

Several issues should be scrutinized when external RI are considered for transference.

- The appropriateness of the reference population with respect to age, sex, breed, geography, physiology, etc.
- 1.2 Differences in pre-analytical techniques, such as patient preparation and collection method.
- 1.3 Differences in test methodology
- 1.4 Differences in instrument accuracy and imprecision (analytical quality).
- 1.5 Differences in laboratory quality by the laboratory donating the RI and the laboratory adopting them.

If significant differences are detected in the above areas, transference may not be appropriate. Many RI studies are not well documented and often lack the detailed information necessary to determine the appropriateness of transference."

The following validation procedure is relatively quick and straightforward. Evaluate 20 samples from normal animals representative of the clinic's own patient population against the candidate RI. If there are any outliers that are suspected to be diseased, they should be eliminated and additional samples collected. If ≤ 2 of the 20 values fall outside the candidate RI, it is considered transferable. If > 2 of the original 20 values fall outside the candidate RI, transference is rejected for that analyte. This is basically a binomial test and will not determine whether the transferred RI is too wide for the receiving laboratory. If all 20 samples fall within the candidate RI, it may be inappropriately wide for the adopting laboratory. When this occurs, another 20 samples should be evaluated. The probability that all 20 results will be within the candidate RI is about 0.36, and with 40 samples the probability falls to about 0.13. If all 40 samples fall within the candidate RI, then it is likely too wide and de novo RI should be determined.

Table 1. Procedural steps for de novo determination of RI for new methods or new populations.
(Page 27 of ASVCP reference interval guideline, references are to said guideline.)
http://www.asvcp.org/pubs/pdf/RI%20Guidelines%20For%20ASVCP%20website (Accessed September 2012)

1. Perform literature search for information about analytes to be measured (preliminary investigation).
2. Define reference population and establish selection, inclusion and exclusion criteria (Section 1 and Table 1).
3. Develop questionnaire to be completed by examining clinician, owner/caretaker or both in order to determine if reference individual fits the selection or partitioning criteria (Section 2).
4. Determine number of reference individuals available or the number required to establish reference intervals with desired level of certainty (as reflected by 90% CI around the reference limits) (Section 3).
5. Select reference individuals, preferably by direct methods (Section 4).
6. Collect and handle reference samples in standardized manner (Section 5).
7. Analyze reference samples using well-controlled methods (Section 6 and 7).
8. Prepare histogram (Section 8).
9. Identify outliers (Section 9). This may require prior transformation to appropriately apply outlier detection methods and may need to be repeated after initial outliers are eliminated.
10. Determine distribution of reference data (Gaussian or non-Gaussian) (Section 10). If using parametric methods, transform data if it is not Gaussian and retest distribution. Transformation may improve the performance of the robust method. Nonparametric methods do not require any particular distribution.
11. Calculate upper and lower reference limits using an appropriate statistical method based on distribution of data and number of samples (Section 11 and Table 2). Calculate confidence intervals for the upper and lower reference limits.
12. Determine the need for partitioning only if there are sufficient numbers of reference samples or there is evidence for clinical importance (Section 12).
13. Document all previous steps for a comprehensive reference interval summary report (Section 13)

References

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Additional Resources

The College of Veterinarians of Ontario; Guideline: Ordering, Performing and Interpreting Laboratory Tests in Veterinary Clinical Practice. Available at: http://www.cvo.org/uploadattachments/Laboratorytestsguideline.pdf. Accessed September, 2012.

http://www.asvcp.org/pubs/qas/index.cfm (Accessed September, 2012)

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