



Establishing Quality Control Target Values and Standard Deviations for Hematology Instrumentation

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WHO REQUIRES IT AND WHAT THEY REQUIRE

Regulatory agencies require the use of Quality Control (QC) materials to assess the validity of results on patient specimens. Laboratories are required to ensure that the basic QC practices used in their facilities meet or exceed the regulations put forth by these agencies.

REGULATORY BODIES REQUIRE THE USE OF QUALITY CONTROL

The Centers for Medicare & Medicaid Services (CMS) regulates all laboratory testing (except research) performed on humans in the U.S. through the Clinical Laboratory Improvement Amendments (CLIA). For laboratories subject to CLIA-88, for quantitative procedures, two control materials of different concentrations should be tested at least once each day that patient specimens are assayed. For each QC procedure employed, the laboratory must have appropriate QC ranges. CLIA deems it good laboratory practice for the individual laboratory to establish its own means and ranges.

U.S.-based regulations state laboratories must establish their own means and ranges for their instruments.

However, officials at the Division of Laboratory Services (the federal agency that administers the CLIA regulations) have stated, “We are aware that for smaller laboratories, performing a limited volume of testing, this may not be practical, and they may use the manufacturer’s suggested ranges, provided these are suitable for the methodology and instrument used by the laboratory. The CLIA regulation at 493.1256(d)(10) requires a laboratory to establish or verify the criteria for acceptability of all control materials. When control materials providing quantitative results are used, statistical parameters (for example, mean and standard deviation) for each batch or lot number of control materials must be defined and available. The laboratory may use the stated value of a commercially assayed control material provided the stated value is for the methodology and instrumentation employed by the laboratory and is verified by the laboratory.”

The key phrase is “smaller laboratories performing a limited volume of testing.” These laboratories, which would be exempt from establishing their own means and ranges, would operate only on a limited basis. They would be running more QC samples than patient samples. The number of laboratories meeting these requirements would be small. For the majority of laboratories, establishing lab specific means and ranges is required.

The published assay range is a range of means.

The published assay means and ranges of a commercial hematology control are considered a range of means. The expected ranges listed represent estimates of variation due to different laboratories, instrument calibration, maintenance, reagents and operator technique. The laboratory’s calculated means should fall within the ranges listed on the published assay. All QC results for an individual laboratory do not need to fall within the published assay range.

International consensus is reached on the establishment of lab-specific means.

In June 2010, the Clinical Laboratory and Standards Institute (CLSI), an international educational organization that promotes the development and use of standards and guidelines within healthcare communities, released document H26-A2, *Validation, Verification and Quality Assurance of Automated Hematology Analyzers*, Approved Standard - Second Edition. This document reinforces the importance of establishing laboratory-specific quality control means and ranges.

THE JOINT COMMISSION

The Joint Commission on Accreditation of Health Care Facilities (JCAHO), in a Q&A item on their web site, stated:

The standards require each laboratory to establish its own control ranges through repetitive testing. However, there is an allowance to use manufacturer ranges when the following conditions are met:

1. The stated values correspond to the method and instrument used by the laboratory, and
2. The mean obtained by the laboratory reflects the manufacturer's stated mean, and
3. The Laboratory Medical Director assures the range is narrow enough to detect clinically significant error.

Determination of QC protocols is ultimately the responsibility of the Laboratory Medical Director.

Manufacturer ranges may also be implemented if a test is used so infrequently that calculation of valid statistics is not possible. In settings where there is a high reproducibility (precise instrumentation, limited testing personnel), the laboratory's own calculated standard deviation (SD) may be small. When compared with the manufacturer ranges, a laboratory may find that the range spans more than the commonly used ± 2 SD. Using the laboratory's calculated ± 2 SD may produce unnecessarily narrow ranges, causing the testing personnel to frequently repeat QC and investigate when the control performs outside the laboratory's range, but within the manufacturer's range. Alternatively, the full manufacturer range may be too broad to promote the detection of clinically significant error. Selection of the appropriate range is a balance between these two ends of the spectrum.

CAP REQUIREMENTS

The College of American Pathologists (CAP) Hematology and Coagulation checklist states that at least two different analytic levels of control must be analyzed and recorded during each 24 hours of the analyzer's use. For each QC procedure employed, the laboratory must have appropriate QC ranges. For example, expected recovery ranges for commercial control materials are NOT the same as between-run SD ranges and are probably too wide for daily QC of a single instrument. The laboratory should calculate its own imprecision statistics for each instrument. The lab should also consider the following, per the survey checklist:

HEMATOLOGY 20035 PHASE II

Are tolerance limits (numeric and/or non-numeric) fully defined and documented for all hematology and coagulation control procedures?

NOTE: *The goal is to have scientifically valid, logical "action limits" for quality control procedures that promptly alert the technologist of the need for immediate evaluation of the particular assay, including initiation of corrective action, before release of patient results.*

HEM.25870 PHASE II

If commercially ASSAYED controls are used for CBC instruments, do control values correspond to the methodology and have target values (mean and QC ranges) been verified or established by the laboratory?

NOTE: Most commercial controls have expected recovery ranges for each parameter, provided by the manufacturer. The mean of such ranges may not be the exact target value in a given laboratory. Each laboratory should assign its own initial target value, based on initial analysis of the material; this target value should fall within the recovery range supplied by the manufacturer, but need not exactly match the package insert mean. The laboratory should establish specific recovery ranges that accommodate known changes in product attributes, assuming that calibration status has not changed.

DETERMINING TARGET VALUES AND STANDARD DEVIATIONS

Streck supports CLSI Document C24, *Statistical Quality Control for Quantitative Measurement Procedures: Principles and Definitions*, for establishing each laboratory's individual target values and ranges, and CLIA Title 42 part 493 subpart K, *Quality Systems for Nonwaived Testing*, Section 493.1256, *Standard Control Procedures*.

CLSI document C24, Section 5.3, states that assigned values used by the manufacturer should only be used as a guide. Actual values for the mean and standard deviation must be established by serial testing in the laboratory. The observed mean should fall within the range published by the manufacturer. External peer-comparison programs provide useful measures of the means and SDs observed in other laboratories. C-24 gives guidance, outside the scope of this document, on how to implement a solid QC strategy based on performance goals.

Establishing laboratory-specific means and standard deviations is not a difficult process.

Here is a brief procedure for establishing target values and Standard Deviation (SD) requirements:

1. Analyze the control a minimum of 20 times across several days. Testing conditions should mimic routine testing as closely as possible.
2. Take the average of these runs.
3. This average should be within the range stated on the assay sheet and is considered the established target value.
4. Calculate a two Standard Deviation range from the results.
5. Incorporate this SD range around the established target value and monitor throughout the dating of the product.
6. The target value and SD measurements should be tracked and updated once sufficient data is collected.

Most hematology instruments have quality control files that will calculate these means and ranges automatically. Peer comparison programs such as Streck's *STATS*® are helpful in providing historical lab SD calculations.

EVIDENCE-BASED CONTROL RANGES

When control limits are properly calculated and implemented, the lab can be confident in its procedure to detect measurement errors at a high rate with a low false rejection rate, based on the performance characteristics of their particular method. The best response to an out-of-control result is to investigate the entire procedure to identify possible root cause(s), define fail-safe solutions to eliminate the cause(s), and prevent the same problem from occurring in the future. The worst response would be to repeat the control until it lands within range as this becomes testing the controls.

Once the lab has established an initial mean and range, as described in the previous section of this paper, it is important to re-evaluate the criteria after a full lot of data, and continue to evaluate on an ongoing basis and to ensure that the control ranges are appropriate for the particular test method. Applying too narrow limits or all-encompassing SD ranges for all test methods may lead to false alarms, repeat control testing, which leads to waste of control and tech time and reduced lab productivity. Applying too broad ranges may lead to accepting too many results that really should be evaluated and to potentially missing errors.

Evidence-Based Control Ranges are:

- Not assay sheet limits or stand-alone rules
- Built using performance goals, bias and precision of the test method
- Specific to the instrument or method, level of control, and parameter
- Designed to identify issues with an instrument or method

The best Quality Control Rule approach to monitor performance defines the relevant clinical requirements for quality testing while integrating a high error detection rate and low false rejection rate.

LOT-TO-LOT CORRELATIONS

CLSI H26-A2 states that new lots of control material should be assayed in parallel with the current lot in use before the expiration of the current lot. Here is a brief procedure to transition to a new lot:

1. Set up new QC files for each control level of the new lot.
2. Verify the new lot by running each level of control three times in its respective file. Ensure that the mean values of the three runs fall within the ranges published on the manufacturer assay, “without any regard to matching any published ‘mean’ value.”
3. Run each level twice a day for 3-5 days to calculate new mean values for each measurand.
4. Compare the calculated mean values for each level to the range specified on the manufacturer assay sheet.
5. If the calculated mean is within range, enter it as the expected mean. Once the values are updated in the QC files, these files are used for the remainder of the dating period.

SITUATIONS THAT REQUIRE ADJUSTING QUALITY CONTROL TARGET VALUES

Some hematology parameters, such as MCV, will increase slightly over time. CAP gives guidance on how to accommodate this:

*Most commercial controls have expected recovery ranges for each parameter, provided by the manufacturer. The mean of such ranges should lie within the recovery range supplied by the manufacturer, but need not exactly match the package insert mean. **The laboratory should establish specific recovery ranges that accommodate known changes in product attributes, assuming that calibration status has not changed.***

Means of parameters that change over time may be handled differently.

If it is known that the MCV rises 2 units over the life of the control, it is acceptable to raise the mean by half this change to accommodate the known rise.

For example, if the initial mean is calculated at 84 and the historical 2 SD is 4, the lab could establish a target value of 85, with a range of 81-89. This will allow the values to start below the mean, rise through the mean and finish above the mean. The cumulative mean calculated at the end of the product life should fall within the lab's established criteria.

QC material can be influenced by changes in measurement conditions that may not affect patient results. QC material comprised of biological components with a matrix that resemble patient samples fall in this category. As indicated in CLSI C24, some changes in QC results are artifacts of the interaction of the reagent or changes in measurement procedure components that are sometimes unidentifiable. When this situation occurs, "failure to update the target value when needed introduces an artifactual bias that negatively affects the ability of the QC acceptable criteria to identify erroneous measurement conditions." It is recommended that the lab test patient samples and determine if there is a critical difference to the measurement condition that would alter a decision made for patient care. If no clinical difference, the change in the measurement condition is accepted and the QC target value is updated.

QUALITY CONTROL FOR ANALYZERS WITH TWO SAMPLE MODES OR PATHWAYS

Analyzers with multiple sample modes require additional QC.

The following recommendation for quality control of two sample modes is taken from the JCAHO web site Q&A forum:

Since there are two distinct sample pathways, QC is required for each sample mode according to the parameters established in the hematology standards. This would mean (for JCAHO purposes) performance of at least one control every eight hours of patient testing and performance of at least two levels of commercial controls every 24 hours of patient testing.

The following are CAP requirements for analyzers using different pathways:

- Two levels of control at every 24 hours of patient testing for analyzers that perform body fluid cell count using the same pathways as CBC testing.
- For analyzers using different pathways for CBC and body fluid cell counts, two levels of control at every 24 hours of patient testing is required for each pathway, i.e., two sets of control (it is as if there are two separate analyzers).

SUMMARY

Establishing laboratory means and ranges does not need to be a tedious task.

Regulatory agencies require the use of Quality Control (QC) materials to assess the validity of results on patient specimens. This is achieved by a QC strategy that considers the frequency of QC and the use of appropriate QC rules. The CLIA minimum is to assay at least two levels of control material every 24 hours. Most laboratories are required to establish target values and standard deviations for the parameters tested and reported for patients. The published assay range for a given control is the range in which a laboratory's mean must fall to be considered acceptable. The determination of mean and range does not have to be a difficult process. Most hematology analyzers and Laboratory Information Systems (LIS) have software to accomplish this task fairly effortlessly.

REFERENCES

1. Clinical and Laboratory Standards Institute - www.clsi.org
2. Clinical Laboratory Improvement Amendments - www.cms.gov/CLIA
3. College of American Pathologists - www.cap.org
4. The Joint Commission - www.jointcommission.org