



## 21120.517 Analytical Quality Control - Quality Control Procedures 4.3

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Copy of version 4.3 (approved and current)

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#### Comments for version 4.0 (last major revision)

Update CLS coordinator responsibilities

#### Comments for version 4.3 (this revision)

Updated Warnings per FDA guidance

#### Approval and Periodic Review Signatures

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(b) (6)

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(b) (6)

Next revision:  
Formatting - keep sections and tables together, use page breaks Some old (b) (4) document numbers are still in the text (b) (4)

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(b) (6)

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Approvals and periodic reviews that occurred before this document was added to the (b) (4) Document Control system may not be listed.

#### Prior History

Migrating into (b) (4)

Replaces QS-Ana-0008 V2.0. General updatea ;and clarifications.

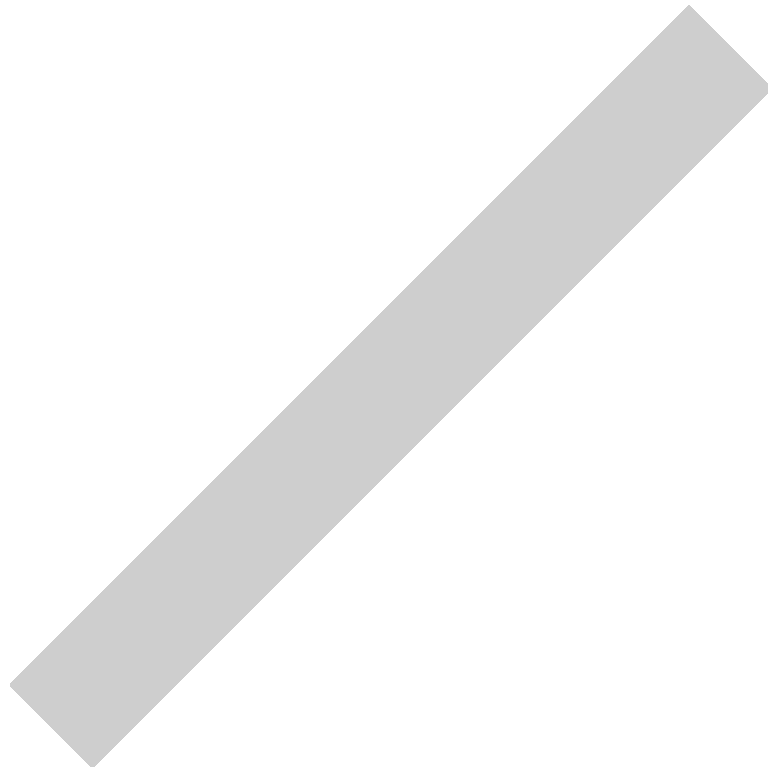
#### Version History

Version	Status	Type	Date Added	Date Effective	Date Retired
4.3	Approved and Current	Minor revision	16-Oct-2020	16-Oct-2020	Indefinite
4.2	Retired	Minor revision	13-Oct-2020	13-Oct-2020	16-Oct-2020
4.1	Retired	Minor revision	13-Jul-2018	13-Jul-2018	13-Oct-2020
4.0	Retired	Major revision	03-Jul-2018	13-Jul-2018	13-Jul-2018
3.0	Retired	Major revision	04-Apr-2017	18-Apr-2017	13-Jul-2018
2.2	Retired	Minor revision	19-Dec-2016	20-Dec-2016	18-Apr-2017

2.1	Retired	Minor revision	13-Feb-2015	13-Feb-2015	20-Dec-2016
2.0	Retired	Major revision	11-Jun-2014	01-Aug-2014	13-Feb-2015
1.0	Retired	First version in Document Control	13-Nov-2012	29-Mar-2012	01-Aug-2014

## Linked Documents

- 21120.369 Analytical Quality Control - Assay Calibration and Calibration Verification
- 21120.516 Monthly QC Review Log
- 21120.1275 Allergen Specific IgE by ImmunoCAP 1000
- 21120.1276 Allergen-Specific IgG by ImmunoCAP 1000
- 21120.1277 Allergen-Specific IgG4 by ImmunoCAP 1000
- 21120.1278 Total IgE by ImmunoCAP 1000
- 21120.1281 Allergen-Specific IgA by ImmunoCAP 100
- 21120.2583 Procedure for TVEC TCID50 Assay



## Objective

A quality control program is necessary to ensure that a test method is consistently producing reliable results over time. Appropriate quality control (QC) procedures involve each person working in the laboratory and provide a means of detection for the failure of test reagents and instruments, changes in the operating environment and operator errors.

An assay quality control program includes the following elements:

- Establishment of assay performance specifications as a basis for acceptance or rejection of test data.
- Contemporaneous documentation of reagent traceability, instrumentation, operator identity, and QC data.
- Monitoring of QC sample performance over time by the use of control charts, as applicable.
- Failure investigations and trend analysis.
- Implementation of corrective actions when problems are discovered.

This document provides a set of guidelines for establishing effective QC procedures for laboratory test methods.

## Scope

Quality control is the process of ensuring and documenting that a test system is operating within pre-determined performance requirements and correcting deviations from those requirements.

Approved quality control procedures are required for all laboratory test systems. There are many aspects to managing an effective Quality Control program, some of which require daily or monthly actions and review. Each of these is important and essential to the success in our QC program's ability to detect changes in the quality of testing that could adversely impact patient results. The overall review of QC data is a shared responsibility that features unique roles as described below.

Quality control procedures for clinical studies are governed by the BioPharma sponsor and may differ from the procedures outlined in this document.

## Responsibilities

Testing personnel have primary responsibility for:

- Adhering to established QC procedures on a daily basis on every run of patient or study samples.
- Ensuring that QC materials are prepared and handled properly so as to provide technically relevant results for each run.
- Ensuring that QC specimens are placed at appropriate intervals in the run according to established method SOPs.
- Ensuring that the QC material being tested is of the appropriate “in-use” lot number and expiration date.
- Ensuring that QC samples are tested in the same manner as patient or study specimens as per SOP (no repeat testing or special handling that only applies to QC samples is allowed unless specifically noted in the Laboratory Method SOP for that assay).

- Ensuring that QC material and patient samples within the same run are tested by the same personnel.
- Ensures that QC results are within acceptable limits prior to releasing patient or study results for reporting.
- Evaluating patient or study sample results for unusual values, shifts or trends that may indicate a potential problem with the testing system not indicated by out of range control results.
- Ensures that all QC results (both in-range and out of range values) are entered into the appropriate QC database for each run so that results may be tracked and evaluated for assay performance over time.
- Signing/initialing all paper logs and forms as appropriate to indicate the steps performed.

CLS Coordinators (with Supervisors oversight) and/or Supervisors are responsible for:

Reviewing data for the assessment of new lots of QC material before they are placed into use and ensuring that the new lots are set up in the QC database.

- Ensuring that QC procedures are followed during sample testing runs.
- Provide problem solving assistance to testing personnel and the Technical Supervisor as needed.
- Monitor control charts and initiate appropriate corrective actions when deviations or problems are found

The associate serving as the supervisor over a test system or group of tests has primary responsibility for:

- The monthly review of QC data and information for shifts or trends month to month.
- Ensuring that each SOP for which they are responsible contains the correct QC information, including frequency, limits, and QC rules for acceptance/rejection.
- Ensuring the review of patient data summaries for assays for which they are responsible to assess trending month to month and year over year are being completed on a regular and timely basis (at least monthly) as applicable.
- Reviewing QC ranges for appropriateness. Documenting causes/reasons for any changes that might be necessary.

## Procedure

## Establishment of Test Acceptance Specifications

- For FDA-cleared test systems in clinical laboratory use, at a minimum, the acceptance/rejection criteria provided by the manufacturer's instructions will be used.
- If the manufacturer's criteria are not stringent or comprehensive enough for the use of the test in our laboratory, the Laboratory reserves the right to implement stricter QC acceptance criteria with the approval of Laboratory Director.

- Each laboratory test method SOP must have a QC section describing quality specifications which must be met for the assay run to be accepted and specimen results reported. The acceptance/rejection specifications should be consistent with the performance characteristics of the test system that were verified during validation.
- Use the following guidelines to establish performance specifications for a test method:
- If a calibration curve is generated, there should be a specification for one or more curve attributes such as:
  - Minimum signal range: depends on type of method and sensitivity required
  - Curve-fit assessed by regression statistic ( $R$  or  $R^2$ ):  $R$  values of  $>0.98$  are generally recommended
  - Curve-fit assessed by calculated vs. observed values for individual calibrators: observed values should be very close to the expected value for at least (b) (4) of the calibrators; the degree of tolerance will depend on the variance of the particular method.
- The maximum allowable signal generated by a blank sample ("0" concentration of analyte in the normal specimen matrix) should be specified.
- QC results that are within 2 Standard Deviations (SD) for a test for which a statistically valid range has been established is grounds for acceptance of all patient or study samples within that run to be accepted and reported so long as no other unusual or unexpected result flags or concerns exist

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appropriate for use with the test system and specimen types being analyzed.

- One method for meeting this requirement would be to get approval from the manufacturer in writing that the proposed control material is suitable for use with the test system and keeping a dated approval record on file (clearly indicating the manufacturer's approval) with the initial control validation data and analysis of approval.
- Make sure the number and concentration levels of the control samples meet CLIA requirements.
- Additional QC samples prepared by the laboratory may be included if deemed desirable.

#### Test Systems Developed or Modified by the Laboratory

- At least two controls (QC samples) at different concentration levels must be provided for each test method.
  - Three levels should be used for all quantitative or semi-quantitative methods when available.
  - At least one control must be in the negative range and at least one in the positive range for all qualitative methods.
- Each control must have a stated value (target or mean) and an acceptance range. See SOP 21120.370 *Analytical Quality Control - Preparation of QC Samples and Establishment of Control Ranges*.
- A complete set of controls must be assayed at least once each day the test is performed.
- For batched assays such as micro-well plate enzyme-linked immunosorbent assay (ELISA) methods, a complete set of controls must be included in each test run or sample batch. If multiple plates are run in a batch, controls must be included on each plate. Either:
  - Include a complete set of controls on each plate (recommended), or
  - Disperse controls among all plates, at least two levels per plate.
- For non-batched methods or random-access assay formats a complete set of QC samples should be assayed at pre-determined sample intervals, at a minimum the full set of QC samples must be included at the beginning and end of the each test run.

**Note:** In cases where the manufacturer specifies more frequent QC determinations within a plate based assay, the manufacturer's recommendations will supersede the QC frequency noted above.

#### Documentation of Quality Control

- For each test run, the information listed below must be recorded. The record can be paper (Test Record form), or electronic as in the use of the Quality Control tracking software, or a combination of the two.

**Note:** for QC results entered into the laboratory's QC database, QC data do not need to be handwritten or hand-recorded. All QC data will be recorded into the QC

database along with any associated corrective actions as needed.

- Date(s) the test run was started and finished and a unique identifier for the test run (e.g. consecutive run number). Use of testing date alone as the identifier is discouraged since for some tests more than one run may be performed in a single day.
  - Identity of the reagents and other materials used in the assay run including a description of the reagent (name and part or catalog number) and the specific lot used. The expiration date of the reagent should also be recorded when possible.
  - Identity of specific instruments and equipment by serial number or inventory number.
  - Identity of all operator(s) who performed the steps in the test procedure.
  - Record of critical procedural data such as measurements, timing, temperatures, instrument settings, etc.
  - A checklist of the QC specifications indicating the result for each and whether the run passed or failed.
  - Written or electronically recorded justification and supervisory approval of any deviations from QC specifications that were made in order to accept the results.
  - Space to document reasons for test failure, the need for re-assay of specimens, corrective actions taken.
  - Dated signature of a laboratory supervisor (CLS Coordinator or higher) who reviewed the record of the test run.
- At the time of the assay, or as soon after completion as practical, the values obtained for control samples must be entered into the database used for control charting. The control sample results will be entered for all test runs that are completed.
  - The test records and results must be reviewed and approved as described below before results are reported to the client.
  - QC records must be preserved for a minimum of two years in accordance with the retention periods required in 21120.269 *Records Management*.

Review and  
Verification

Once a testing run has been completed, perform the following data reviews:

- Testing Personnel-
  - Fill out the QC section of the test record form (where applicable) with all required information and enter results into the appropriate QC database. Note: Not all assays include a test record form.
  - Make sure any deviations from the SOP, operator errors, equipment problems or other anomalies are written down on the run record (where applicable).
- A second Clinical Laboratory Scientist (CLS), CLS Coordinator or General Supervisor-
  - Check records for accuracy, completeness.

- Check QC results to verify pass/fail status.
  - Check any results which were manually transcribed from data forms into the results database for transcription errors.
  - Sign the QC Record form (where applicable) to indicate acceptance/rejection of the run and enter result review/approval into the QC database.
- Technical Supervisor, as indicated-
    - Approve any deviations from procedure or QC acceptance specifications.
    - Provide written justification and approval for overriding any QC specifications.
    - Verify results in QC database.

#### Use of Control Charts to Monitor Assay Performance

Control charts are a means of monitoring assay performance over time and changes in reagent lots, operators, etc. Control charts can provide valuable information about trends and discontinuities which can be helpful in discrimination between random and non-random variability of a test method and in analyzing the causes of out-of-specification results. The typical control chart used for tracking assay performance is the Levy-Jennings plot of values obtained over the life of a specific lot of QC sample material.

The control charting function of the QC software will be the primary means used for monitoring all quantitative test methods in routine laboratory use. Maintain a separate chart for each lot of each QC level of each instrument or test system for each analyte.

In order for the control chart to be used effectively in detecting deviations or errors, the QC sample mean and range values must not be changed once they are established in the system except under the conditions described in the section on revising control ranges found in 21120.371, *QC Failure Analysis and Corrective and Preventive Actions* procedure. With approval of the Laboratory Director a provisional range based on a small number of values may be used initially until the standard number of results (b) (4) is accumulated to establish the permanent mean and range.

The QC system is set up specifically with the acceptance/rejection rules defined in this SOP and all out of range results will be flagged accordingly. The acceptance/rejection rules are universal in regards to all quantitative assays as they are written in this SOP unless otherwise specified in the individual method SOP.

Testing Personnel who perform tests and CLS Coordinators and/or Supervisors with responsibility for test methods are responsible for entering QC sample results into the QC database in a timely manner, as required. Certain assays have QC data delivered through an interface.

Supervisors are responsible for monitoring control charts on at least a monthly basis to ensure that assays under their supervision are maintained in a state of control and that the test is reporting reliable results.

Failures, significant control trending, calibration issues and other problems detected by the assay monitoring process must be reported to the Supervisor or Technical Supervisor in

charge of supervising the specific test as appropriate.

The cause of failures must be determined and appropriate corrective and preventive actions must be taken. See 21120.371 for *Failure Analysis and Corrective and Preventive Action* procedures.

The General Supervisor and Laboratory Director are responsible for monthly review of QC data for completeness and accuracy of records and to assess any issues or potential issues related to the data, ranges or instrument to instrument biases that may be evident by such review. Appropriate review records must be kept on file and active management of QC issues must be demonstrated and documented such that the test system remains stable and suitable for producing accurate patient and study test results. Records are kept on file by the supervisors in charge of each assay or group of assays for which they are responsible.

## Warnings

- The Viracor SARS-CoV-2 assay has not been FDA cleared or approved;
- The Viracor SARS-CoV-2 assay has been authorized by FDA under an EUA for use by the authorized laboratory: Viracor Eurofins Clinical Diagnostics Laboratory located at 1001 NW Technology Dr., Lee's Summit, MO, certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, and meet the requirements to perform high complexity tests;
- The Viracor SARS-CoV-2 assay has been authorized only for the detection of nucleic acid from SARS-CoV-2, not for any other viruses or pathogens; and
- The Viracor SARS-CoV-2 assay is only authorized for the duration of the declaration that circumstances exist justifying the authorization of emergency use of in vitro diagnostics for detection and/or diagnosis of COVID-19 under Section 564(b)(1) of the Federal Food, Drug and Cosmetic Act, 21 U.S.C. § 360bbb-3(b)(1), unless the authorization is terminated or revoked sooner.

## References

CLIA Regulations on Control Procedures; 42 CFR Part 493.1256

## Appendices

Monthly QC Review Log