Every patient deserves the GOLD STANDARD ...

Clinical Biochemical Genetics Checklist

CAP Accreditation Program

07.28.2015
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ON-LINE CHECKLIST AVAILABILITY

Participants of the CAP accreditation programs may download the checklists from the CAP website (www.cap.org) by logging into e-LAB Solutions. They are available in different checklist types and formatting options, including:

- Master — contains ALL of the requirements and instructions available in PDF, Word/XML or Excel formats
- Custom — customized based on the laboratory’s activity (test) menu; available in PDF, Word/XML or Excel formats
- Changes Only — contains only those requirements with significant changes since the previous checklist edition in a track changes format to show the differences; in PDF version only. Requirements that have been moved or merged appear in a table at the end of the file.

SUMMARY OF CHECKLIST EDITION CHANGES
Clinical Biochemical Genetics Checklist
07/28/2015 Edition

The information below includes a listing of checklist requirements with significant changes in the current edition and previous edition of this checklist. The list is separated into three categories:

1. New
2. Revised:  
   - Modifications that may require a change in policy, procedure, or process for continued compliance; or  
   - A change to the Phase
3. Deleted/Moved/Merged:
   - Deleted  
   - Moved — Relocation of a requirement into a different checklist (requirements that have been resequenced within the same checklist are not listed)  
   - Merged — The combining of similar requirements

NOTE: The listing of requirements below is from the Master version of the checklist. The customized checklist version created for on-site inspections and self-evaluations may not list all of these requirements.

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INTRODUCTION

This checklist is used in conjunction with the All Common and Laboratory General Checklists to inspect a clinical biochemical genetics laboratory section or department.

The Clinical Biochemical Genetics Checklist covers aspects of clinical biochemical genetic testing performed for the diagnosis of inborn errors of metabolism (IEM), including, but not limited to, the analysis of amino acids, organic acids, enzymes involved in intermediary metabolism, carnitine and acylcarnitines, acylglycines, CSF neurotransmitters, sugars, glycosaminoglycans and glycoproteins. Biochemical tests for the identification of heterozygotes of IEMs and newborn screening for IEMs are also covered.

Note for non-US laboratories: Checklist requirements apply to all laboratories unless a specific disclaimer of exclusion is stated in the checklist.

CLINICAL BIOCHEMICAL GENETICS GENERAL ISSUES

QUALITY MANAGEMENT AND QUALITY CONTROL

GENERAL ISSUES

Inspector Instructions:

- Sampling of patient results with review by the laboratory director or qualified designee within the turnaround time specified

CBG.10900  Result Review  Phase I

The results of tests are reviewed by the laboratory director or qualified designee within the turnaround time specified by the laboratory’s standard operating procedure.

NOTE: In the case of clinically significant abnormal results, there must be a procedure for rapid communication to and receipt by the laboratory director or qualified designee.
CALIBRATION AND STANDARDS

Inspector Instructions:

- Sampling of calibration and AMR policies and procedures
- Sampling of calibration/calibration verification records
- Sampling of AMR verification records
- Sampling of patient reports/worksheets for verification of results outside of AMR
- Semiannual instrument correlation records

- Sampling of calibration materials (quality)

- What is your course of action if calibration is unacceptable?
- When was the last time you performed a calibration procedure and how did you verify the calibration?
- What is your course of action when results fall outside the AMR?

- Further evaluate the responses, corrective actions, and resolutions for unacceptable calibration, and unacceptable calibration verification

This introduction discusses the processes of calibration, calibration verification, and analytical measurement range verification (AMR).

DEFINITIONS:

CALIBRATION is the set of operations that establish, under specified conditions, the relationship between reagent system/instrument response and the corresponding concentration/activity values of an analyte. Calibration procedures are typically specified in the manufacturer’s instructions, but may also be established by the laboratory.

CALIBRATION VERIFICATION denotes the process of confirming that the current calibration settings for each analyte remain valid for a test system. If calibration verification confirms that the current calibration settings for each analyte are valid, it is not necessary to perform a complete calibration or recalibration of the test system. Each laboratory must define limits for accepting or rejecting tests of calibration verification. Calibration verification can be accomplished in several ways. If the manufacturer provides a calibration validation or verification process, it should be followed. Other techniques include (1) assay of the current method calibration materials as unknown specimens, and determination that the correct target values are recovered, and (2) assay of matrix-appropriate materials with target values that are specific for the test system.

REQUIRED FREQUENCY OF CALIBRATION VERIFICATION
Laboratories must calibrate a test system when it is first placed in service and perform calibration verification at least every six months thereafter. However, a laboratory may opt to recalibrate a test system (rather than perform calibration verification) at least every six months. If a test system has been recalibrated then it is NOT necessary to also perform calibration verification sooner than six months following recalibration. In addition to
this six-month schedule, calibration verification or recalibration is required (regardless of the length of time since last performed) immediately if any of the following occurs:

1. A change of reagent lots for chemically or physically active or critical components, unless the laboratory can demonstrate that the use of different lots does not affect the accuracy of patient/client test results, and the range used to report patient/client test data
2. If QC materials reflect an unusual trend or shift, or are outside of the laboratory's acceptable limits, and other means of assessing and correcting unacceptable control values fails to identify and correct the problem
3. After major maintenance or service. The Laboratory Director must determine what constitutes major maintenance or service.
4. When recommended by the manufacturer

MATERIALS SUITABLE FOR CALIBRATION VERIFICATION

Materials for calibration verification must have a matrix appropriate for the clinical specimens assayed by that method and target values appropriate for the measurement system. Suitable materials may include, but are not limited to:

1. Calibrators used to calibrate the analytical system
2. Materials provided by the analytical measurement system vendor for the purpose of calibration verification
3. Previously tested unaltered patient/client specimens
4. Primary or secondary standards or reference materials with matrix characteristics and target values appropriate for the method
5. Third party general purpose reference materials that are suitable for verification of calibration following reagent lot changes if the material is listed in the package insert or claimed by the method manufacturer to be commutable with patient specimens for the method. A commutable reference material is one that gives the same numeric result as would a patient specimen containing the same quantity of analyte in the analytic method under discussion; i.e., matrix effects are absent. Commutability between a reference material and patient specimens can be demonstrated using the protocol in CLSI EP14-A3
6. Proficiency testing material or proficiency testing validated material with matrix characteristics and target values appropriate for the method

In general, routine control materials are not suitable for calibration verification, except in situations where the material is specifically designated by the method manufacturer as suitable for verification of the method's calibration process.

In some instances suitable calibration materials may not be available, e.g., when the analyte is unstable. In these cases, calibration and calibration verification may not be possible, and therefore at least two samples from normal patients should be analyzed along with the patient samples submitted for testing, to verify that the normal patient samples have results in the normal range.

ANALYTICAL MEASUREMENT RANGE

DEFINITIONS:

The ANALYTICAL MEASUREMENT RANGE (AMR) is the range of analyte values that a method can directly measure on the specimen without any dilution, concentration, or other pretreatment not part of the usual assay process.

LINEARITY AND THE AMR

An important concept in verifying the AMR is that a plot of measured values from test samples vs. their actual (or expected) concentration or relative concentrations must be linear within defined acceptance criteria over the AMR. Verifying linearity using such a plot verifies the AMR. Beyond the limits of the AMR, there may not be a linear relationship between measured and actual analyte concentrations, and test results may therefore be unreliable. For patient samples, only measured values that fall within the AMR (or can be brought into the AMR by sample dilution or concentration) should be reported. Values that fall outside the AMR may be reported
as "less than" or "greater than" the limits of the AMR (see the note below, Patent Samples with Unusually High Concentrations of Analyte).

AMR VERIFICATION

Minimum requirements can be met by using matrix appropriate materials, which include the low, mid and high concentration or activity range of the AMR and recovering appropriate target values, within defined acceptance criteria. Records of AMR verification must be available.

The best practice for AMR verification is to demonstrate a linear relationship, within defined acceptance criteria, between measured concentrations of analytes and expected values for a set of four or more matrix-appropriate samples that cover the AMR.

AMR verification may be accomplished through the calibration procedure under certain circumstances. It is not necessary to perform a separate AMR verification if the calibration of an assay includes calibrators that span the full range of the AMR, with low, midpoint and high values (i.e. three points) included. A one-point or two-point calibration does not include all of the necessary points to validate the AMR.

REQUIRED FREQUENCY OF AMR VERIFICATION
When initially introducing a new method, it is necessary to verify the AMR independently from the calibration procedure. In this situation, suitable materials for the AMR verification include those listed below (see OTHER MATERIALS SUITABLE FOR AMR VERIFICATION). Additionally, when multipoint calibration that spans the AMR is utilized, a set of calibrators from a different lot number than that used to calibrate the system may be suitable for independent AMR verification.

The AMR must be verified at least every six months after a method is initially placed in service and following the criteria defined in the checklist. If multipoint calibrators that span the AMR are used for calibration/calibration verification, it is not necessary to independently verify the AMR, as long as the system is calibrated at least every six months.

OTHER MATERIALS SUITABLE FOR AMR VERIFICATION
The materials used for AMR verification must be known to have matrix characteristics appropriate for the method. The matrix of the sample (i.e. the environment in which the sample is suspended or dissolved) may influence the measurement of the analyte. In many cases, the method manufacturer will recommend suitable materials. The verification must include specimens, which at a minimum, are near the low, midpoint, and high values of the AMR. Suitable materials for AMR verification include the following:

1. Linearity material of appropriate matrix, e.g. CAP CVL Survey-based or other suitable linearity verification material
2. Previously tested patient/client specimens, that may be altered by admixture with other specimens, dilution, spiking in known amounts of an analyte, or other technique
3. Primary or secondary standards or reference materials with matrix characteristics and target values appropriate for the method
4. Patient samples that have reference method assigned target values
5. Control materials, if they adequately span the AMR and have method specific target values

CLOSENESS OF SAMPLE CONCENTRATIONS OR ACTIVITIES TO THE UPPER AND LOWER LIMITS OF THE AMR
When verifying the AMR, it is required that materials used are near the upper and lower limits of the AMR. Factors to consider in verifying the AMR are the expected analytic imprecision near the limits, the clinical impact of errors near the limits, and the availability of test specimens near the limits. It may be difficult to obtain specimens with values near the limits for some analytes. In such cases, reasonable procedures should be adopted based on available specimen materials. The method manufacturer's instructions for verifying the AMR should be followed, when available. The Laboratory Director must define limits for accepting or rejecting verification tests of the AMR.

PATIENT SAMPLES WITH UNUSUALLY HIGH CONCENTRATIONS OF ANALYTE
In the case of samples with very high concentrations or activities of an analyte, very large dilutions may be required to bring the concentration or activity into the AMR. Making large dilutions of patient samples can introduce error, and the Laboratory Director should establish appropriate volumes of sample and diluent to be used to minimize dilution errors. For example, pipetting 1 µL of a sample is difficult to do accurately and larger sample and diluent volumes should be specified. Note that for some analytes, an acceptable dilution protocol may not exist because dilution would alter the analyte or the matrix causing erroneous results, e.g. free drugs or free hormones. Also note that for some analytes, there may be no clinical relevance to reporting a numeric result greater than a stated value. If it is not possible to achieve a measured value that is within the AMR by using allowable dilutions, or there is no clinical value to reporting a higher value, then the result may be reported as “greater than” the value of the highest allowable dilution.

**REVISED** 07/28/2015

CALIBRATION PROCEDURE

Calibration procedures for each test system are appropriate, and the calibration records are reviewed for acceptability.

NOTE: Calibration must be performed following manufacturer’s instructions, at minimum, including the number, type, and concentration of calibration materials and criteria for acceptable performance. The calibration procedure must define the limits of acceptable variation, e.g. +/- 20% of the expected value. These limits should be applied to all standard and control samples run after the calibration is performed. The procedure should also specify the actions to be taken if a control or standard sample falls outside the defined range. For some analytes (e.g. enzymes) calibration is limited to the product of the reaction, rather than the enzyme concentration or activity itself.

REFERENCES

CBG.11800 Calibration Materials

High quality materials with test system and matrix-appropriate target values are used for calibration and calibration verification whenever possible.

NOTE: Calibration materials establish the relationship between method/instrument response and the corresponding concentration/activities of an analyte. They have defined analyte target values and appropriate matrix characteristics for the clinical specimens and specific assay method. Many instrument systems require calibration materials with system-specific target values to produce accurate results for clinical specimens.

Evidence of Compliance:
✓ Written policy defining appropriate calibration/calibration verification materials

REFERENCES
1) ISO 17511:2003 In vitro diagnostic medical devices--Measurement of quantities in biological samples--Metrological traceability of values assigned to calibrators and control materials.
Criteria are established for frequency of recalibration or calibration verification, and the acceptability of results.

NOTE: Criteria typically include:

1. At changes of reagent lots for chemically or physically active or critical components, unless the laboratory can demonstrate that the use of different lots does not affect the accuracy of patient/client test results and the range used to report patient/client test data
2. If QC materials reflect an unusual trend or shift or are outside of the laboratory’s acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem
3. After major maintenance or service
4. When recommended by the manufacturer
5. At least every six months

Evidence of Compliance:

✓ Written procedure defining the method, frequency and limits of acceptability of calibration verification for each instrument/test system AND
✓ Records of calibration verification documented at defined frequency

REFERENCES

**REVISED** 07/28/2015

CBG.12200 Recalibration Phase II

The test system is recalibrated when calibration verification fails to meet the established criteria of the laboratory.

Evidence of Compliance:

✓ Written policy defining criteria for recalibration AND
✓ Records of recalibration, if calibration or calibration verification has failed

REFERENCES

CBG.12300 AMR Verification Phase II

Verification of the analytical measurement range (AMR) is performed with matrix-appropriate materials, which include, at minimum, the low, mid and high range of the AMR, appropriate acceptance criteria are defined, and the process is recorded and reviewed.

NOTE: The AMR must be verified at least every six months after a method is initially placed in service and if any of the following occur:

1. A change of reagent lots for chemically or physically active or critical components, unless the laboratory can demonstrate that the use of different lots does not affect the accuracy of patient/client test results, and the range used to report patient/client test data
2. If QC materials reflect an unusual trend or shift or are outside of the laboratory’s acceptable limits, and other means of assessing and correcting unacceptable control values fail to identify and correct the problem
3. After major preventive maintenance or change of a critical instrument component
4. When recommended by the manufacturer

The AMR must be verified at least every six months. It is not necessary for every analyte in a multiple-analyte procedure* to be verified in this way; it is acceptable to verify a clinically important subset of analytes, or one or more analytes representing groups with the same chemical characteristics. For example, in automated amino acid analysis, the laboratory may verify a single amino acid eluted with each buffer.

*A laboratory test that detects or measures multiple similar compounds, such as organic acids or amino acids. It does not refer to a multiple-test chemistry panel.

Evidence of Compliance:
✓ Written policy for AMR verification defining the types of materials used, frequency and acceptability criteria

REFERENCES

CBG.12500 Diluted or Concentrated Samples Phase II

If a result is greater than or less than the AMR, a numeric value is not reported unless the sample is processed by dilution, a mixing procedure or concentration so that the result falls within the AMR.

NOTE:
1. A measured value that is outside the AMR may be unreliable and should not be reported in routine practice. Dilution, a mixing procedure* or concentration of a sample may be required to achieve a measured analyte activity or concentration that falls within the AMR. The result must be within the AMR before it is mathematically corrected by the concentration or dilution factor to obtain a reportable numeric result.
2. For each analyte, the composition of the diluent solution and the appropriate volumes of sample and diluent must be specified in the procedure manual. Specifying acceptable volumes is intended to ensure that the volumes pipetted are large enough to be accurate without introducing errors in the dilution ratio.
3. All dilutions, whether automatic or manual, should be performed in a way that ensures that the diluted specimen reacts similarly to the original specimen in the assay system. For some analytes, demonstrating that more than one dilution ratio similarly recovers the elevated concentration may be helpful.
4. This checklist requirement does not apply if the concentration or activity of the analyte that is outside the AMR is reported as "greater than" or "less than" the limits of the AMR.

*This procedure is termed the "method of standard additions." In this procedure, a known quantity (such as a control) is mixed with the unknown, and the concentration of the mixture is measured. If equal volumes of the two samples are used, the result is multiplied by two, the concentration of the known subtracted, and the concentration of the unknown is the difference.

Evidence of Compliance:
✓ Patient reports or worksheets

CBG.12600 Maximum Dilution Phase II

For analytes that may have results falling outside the limits of the AMR, the laboratory procedure specifies the maximum dilution that may be performed to obtain a reportable numeric result.

NOTE:
1. For each analyte, the laboratory procedure defines the maximum dilution that falls within the AMR and that can be subsequently corrected by the dilution factor to
obtain a reportable numeric result. Note that for some analytes, an acceptable
dilution procedure may not exist because dilution would alter the analyte or the
matrix causing erroneous results, e.g. free drugs or free hormones. Also note that,
for some analytes, there may be no clinical relevance to reporting a numeric result
greater than a stated value.

2. Analytes for which a dilution procedure is unable to bring the activity or concentration
into the AMR should be reported as "greater than" the highest estimated values.

3. Establishment of allowable dilutions is performed when a method is first placed into
service and is reviewed biennially thereafter as part of the procedure manual review
by the Laboratory Director or designee. The laboratory director is responsible for
establishing the maximum allowable dilution of samples that will yield a credible
laboratory result for clinical use.

Evidence of Compliance:
✓ Patient reports or worksheets

CONTROLS

Controls are used to ensure that a test system is performing correctly. Traditionally, controls are samples that
act as surrogates for patient/client specimens, periodically processed like a patient/client sample to monitor
the ongoing performance of the entire analytic process. Under certain circumstances, other types of controls
(electronic, procedural, built-in) may be used. (Details are in the checklist requirements in this section, below.)

CONTROLS – NONWAIVED TESTS

Inspector Instructions:

- Sampling of quality control policies and procedures
- Sampling of QC records

- How do you determine when quality control is unacceptable and when corrective
  actions are needed?
- How does your laboratory verify or establish acceptable quality control ranges?
- What is your course of action when monthly precision data change significantly from
  the previous month’s data?
- What is your course of action when you perform test procedures that do not have
  commercially available calibration or control materials?

- Select several occurrences in which QC is out of range and follow records to
determine if the steps taken follow the laboratory procedures for corrective action

**REVISED** 04/21/2014
CBG.12800 Daily QC - Nonwaived Tests

Appropriate controls are run each day of patient testing for quantitative and qualitative
tests.
NOTE: Controls should verify assay performance at relevant decision points. The selection of
these points may be based on clinical or analytical criteria.

Daily external controls must be run as follows:

- For quantitative tests, two controls at two different concentrations must be run
daily or with each batch of samples/reagents, unless a different requirement is
specifically required by this checklist. Analytes selected are based on availability
of materials.
- For qualitative tests, a negative control and a positive control (when available)
must be run daily or with each batch.

Control testing is not necessary on days when patient testing is not performed.

Evidence of Compliance:
✓ Records of QC results

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Medicare, Medicaid and CLIA programs;
   CLIA fee collection; correction and final rule. Fed Register. 2003(Jan 24);5232 [42CFR493.1256(d)(3) (i, ii)]
   Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2006
   2000;113:240-248
4) Clinical and Laboratory Standards Institute (CLSI). User Protocol for Evaluation of Qualitative Test Performance; Approved Guideline
   Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, 2008.

CBG.12900 QC Acceptable Range Verification Phase II

For quantitative tests, a valid acceptable range has been established or verified for each
lot of control material.

NOTE: For unassayed controls, the laboratory must establish a valid acceptable range by
repetitive analysis in runs that include previously tested control material. For assayed controls,
the laboratory must verify the acceptability ranges supplied by the manufacturer.

Evidence of Compliance:
✓ Written procedure to establish or verify control ranges AND
✓ Records for control range verification of each lot

REFERENCES
1) Clinical and Laboratory Standards Institute. Evaluation of Precision Performance of Quantitative Measurement Methods; Approved
2) Clinical and Laboratory Standards Institute. User Verification of Performance to Precision and Trueness; Approved Guideline. 3rd ed.
3) Ross JW, Lawson NS. Analytic goals, concentration relationships, and the state of the art of clinical laboratory precision. Arch Pathol
   Lab Med 1995;119:495-513
4) Steindel SJ, Tetraut G. Quality control practices for calcium, cholesterol, digoxin, and hemoglobin. A College of American
   Pathologists Q-Probes study in 505 hospital laboratories. Arch Pathol Lab Med 1998;122:401-408
5) Clinical and Laboratory Standards Institute (CLSI). Risk Management Techniques to Identify and Control Error Sources - Approved
   Valley Road, Suite 1400, Wayne, PA, 19087-1898, USA, 2009.

CBG.13000 Calibrator Preparation Phase II

If the laboratory prepares calibrators and controls in-house, these materials are prepared
separately.

NOTE: In general, calibrators should not be used as QC materials. If calibrators are used as
controls, then different preparations should be used for these two functions.

Evidence of Compliance:
✓ Written policy for in-house preparation of calibrators and controls
CBG.13100  Calibrators as Controls  Phase I

If a calibrator obtained from an outside supplier is used as a control, it is a different lot number from that used to calibrate the method.

NOTE: In general, calibrators should not be used as QC materials. However, this practice may be necessary for some methods when a separate control product is not available. In such cases, the calibrator used as a control must be from a different lot number than that used to calibrate the method.

Evidence of Compliance:
✓ Written policy for the use of calibrators as controls AND
✓ QC/calibrator records

REFERENCES

CBG.13200  Validation of Accuracy  Phase II

If the laboratory performs test procedures for which calibration and control materials are not commercially available, written procedures have been established to validate the accuracy of patient/client test results.

NOTE: In clinical biochemical genetics laboratories calibrators and control materials are not available for some of the analytes detected in complex metabolic profiles. As these analytes often have critical clinical significance, it is acceptable to use surrogate calibrations (using compounds with similar structure) to generate quantitative results used in the context of pattern recognition and profile interpretation. When surrogate calibrators are used, their use and the basis of their use should be validated and documented.

REFERENCES

CBG.13300  QC Data  Phase II

Quality control data are organized and presented so they can be evaluated daily by the technical staff to detect problems, trends, etc.

NOTE: Results of controls must be recorded or plotted to readily detect a malfunction in the instrument or in the analytic system. These control records must be readily available to the person performing the test.

REFERENCES

CBG.13400  Numeric QC Data  Phase I

For numeric QC data, quality control statistics (e.g. SD, CV, or other appropriate statistics) are calculated monthly to define and monitor analytic imprecision.

NOTE: The laboratory must evaluate the imprecision statistics (e.g. SD, CV, or other appropriate statistics) monthly to confirm that the test system is performing within acceptable limits. For whole blood methods, where stabilized whole blood or other suitable material is not available for QC, such statistics may be generated from previous patient/client samples using the SD of duplicate pairs.
This checklist requirement does not apply to external controls run only to verify new lots/shipments of test materials. However, the laboratory should have defined acceptable limits for such controls (either from the manufacturer, or developed by the laboratory).

Evidence of Compliance:
- Written procedure for monitoring analytic imprecision including statistical analysis of data
  AND
- QC records showing monthly monitoring for imprecision

REFERENCES
1) Mukherjee KL. Introductory mathematics for the clinical laboratory. Chicago, IL: American Society of Clinical Pathology, 1979:81-94

CBG.13500 QC Corrective Action

There are records of corrective action when control results exceed defined acceptability limits.

NOTE: In the case of complex metabolic profiles as seen in clinical biochemical genetics laboratories, controls of analytes of clinical significance should meet the laboratory’s overall criteria for acceptability.

Patient/client test results obtained in an analytically unacceptable test run or since the last acceptable test run must be re-evaluated to determine if there is a significant clinical difference in patient/client results. Re-evaluation may or may not include re-testing patient samples, depending on the circumstances.

Even if patient samples are no longer available, test results can be re-evaluated to search for evidence of an out-of-control condition that might have affected patient results. For example, evaluation could include comparison of patient means for the run in question to historical patient means, and/or review of selected patient results against previous results to see if there are consistent biases (all results higher or lower currently than previously) for the test(s) in question.

REFERENCES

CBG.13600 QC Handling

Control specimens are tested in the same manner and by the same personnel as patient/client samples.

NOTE: QC specimens must be analyzed by personnel who routinely perform patient/client testing - this does not imply that each operator must perform QC daily, so long as each instrument and/or test system has QC performed at required frequencies, and all analysts participate in QC on a regular basis. To the extent possible, all steps of the testing process must be controlled, recognizing that pre-analytic and post-analytic variables may differ from those encountered with patient/clients.

For newborn screening testing, good laboratory practice is to punch controls and patient blood specimens with the same equipment.

**REVISED** 04/21/2014
Evidence of Compliance:
✓ Records reflecting that QC is run by the same personnel performing patient testing

REFERENCES
2) ibid. 2003(Jan 24):3708[42CFR493.1256(d)(7-8)]

CBG.13700 QC Confirmation of Acceptability

The results of controls are reviewed for acceptability before reporting results.

NOTE: Control results must be reviewed before reporting patient/client results. It is implicit in quality control that patient/client test results will not be reported when controls do not yield acceptable results. Controls must be run prior to reporting patient results after a change of analytically critical reagents, major preventive maintenance, or change of a critical instrument component.

Evidence of Compliance:
✓ Records showing confirmation of acceptability of QC

REFERENCES
2) ibid. 2003(Jan 24):3708[42CFR493.1256(d)(6)]

**REVISED** 04/21/2014

CBG.13800 Monthly QC Review

Quality control data are reviewed and assessed at least monthly by the laboratory director or designee.

NOTE: The review of quality control data must be recorded and include follow-up for outliers, trends, or omissions that were not previously addressed.

The QC data for tests performed less frequently than once per month should be reviewed when the tests are performed.

Evidence of Compliance:
✓ Records of QC review including follow-up for outliers, trends or omissions

METHODS, INSTRUMENT SYSTEMS, AND EQUIPMENT

The checklist requirements in this section should be used in conjunction with the requirements in the All Common Checklist relating to instruments and equipment.

Inspector Instructions:
- If problems are identified during the review of the methods, instrument systems, and equipment or when asking questions, further evaluate the laboratory’s responses, corrective actions and resolutions
- Select a representative assay and follow the entire process from specimen receipt to final result reporting
ENZYME ASSAYS

Inspector Instructions:

- Sampling of enzyme assay policies and procedures
- Sampling of control, calibration curve records
- Sampling of patient reports for completeness

CBG.14100 Control for Interference

Appropriate blanks are included in each run.

*NOTE: Blanks should be employed to control for interference from two sources: background activity related to the reagents and non-enzymatic conversion of substrate to product.*

CBG.14200 QC-Calibration Curve

Standards are used to create a calibration curve for each run.

CBG.14300 QC-Controls

Controls are analyzed with each run.

*NOTE: Ideally at least one affected control and one normal control sample are analyzed with each run. However, samples from affected patients may not always be available, and the use of inactivated samples (i.e. samples that have been heated or treated in some other way to inactivate the enzyme of interest) is an acceptable alternative.*

CBG.14400 Defined Ranges

A normal range, disease range, and, if appropriate, a carrier range are defined for each assay.

*NOTE: Reference ranges should be established by the laboratory based on its own analysis of samples from multiple individuals. For rare diseases, it may not be possible for the laboratory to establish its own disease (“affected”) range. In this case, it is permissible to use levels from the literature or other laboratories performing the test, as long as these are based on the same analytic method.*

Evidence of Compliance:

✓ Records of establishment of reference ranges OR
✓ Literature to support reference ranges

REFERENCES


CBG.14500 Report Content

Laboratory reports include an interpretation of the result that reflects the presence or absence of the disease (or carrier state), possible limitations of the test, and, if appropriate, recommendations for additional testing.
CHROMATOGRAPHY AND MASS SPECTROMETRY

THIN LAYER CHROMATOGRAPHY (TLC)

Inspector Instructions:
- Sampling of TLC policies and procedures
- Sampling of control, standards/calibrator records

CBG.14600  Standard/Calibration Materials  Phase II
Appropriate standards, calibrators, or controls (as applicable) are included with each TLC plate.

NOTE: Appropriate standards must include compounds that test the chromatographic range of the TLC plate, and that test all phases of the staining/development system. This may consist of a standard solution, previously tested positive patient samples, or dot that contains appropriate compounds.

Evidence of Compliance:
- Written policy defining appropriate use of standards/calibrators for TLC AND
- Records showing use of appropriate standards/calibrators with each plate

REFERENCES

CBG.14700  Daily QC - TLC  Phase II
Negative and appropriate positive controls are extracted and run through the entire procedure.

NOTE: Appropriate positive controls must include compounds that test the extraction, chromatographic range of the TLC plate, and the staining/development system. Negative and positive controls (when available) must be extracted and carried through the entire procedure with each plate or card.

Evidence of Compliance:
- Written QC procedure defining QC requirements appropriate to the complexity of the test system AND
- QC records at defined frequency

REFERENCES
1) Department of Health and Human Services, Centers for Medicare and Medicaid Services. Medicare, Medicaid and CLIA programs; CLIA fee collection; correction and final rule. Fed Register. 2003(Jan 24): [42CFR493.1256(d)]

CBG.14800  Solvent Mixtures  Phase II
Solvent mixtures are prepared fresh as needed.
NOTE: If a mixture of solvents is used, certain components will evaporate with time faster than others. This leads to poor extraction or reproducibility of migration rates. If a commercial kit is used, the manufacturer’s instructions should be followed.

Evidence of Compliance:
✓ Written procedure for preparation of solvent mixture

GAS CHROMATOGRAPHY (GC)

Inspector Instructions:

- Sampling of GC policies and procedures
- Sampling of control, calibration/standards records
- Sampling of column verification records

- How does your laboratory evaluate potential carryover?
- How have you determined the limit of detection and the AMR?

CBG.14900 Calibration and Calibration Verification Phase II

Appropriate calibration or calibration verification is performed on each day of patient testing or more frequently if required by the manufacturer's instructions.

NOTE: For qualitative assays, an appropriate calibrator should be run at normal and abnormal levels. For quantitative assays, a multipoint calibration may be required if the measurement has a non-linear response. For some assays, a level near the assay's limit of detection (LOD) or at critical decision point(s) is needed. For measurement systems that have a linear response verified by periodic multipoint calibration verification and AMR verification protocols, a calibration procedure that uses a single calibrator at an appropriate concentration is acceptable. Analyses based on a single point calibration must be controlled by appropriate quality control samples. In addition, inclusion of a negative control (reagent blank) is good laboratory practice.

Evidence of Compliance:
✓ Written procedure for calibration/calibration verification AND
✓ Records of calibration/calibration verification

REFERENCES

CBG.15000 Quality Control - GC Phase II

Appropriate controls are extracted and run through the entire procedure.

NOTE: Controls used in GC procedures must evaluate as much of the complete testing process as is technically feasible. The control process includes any pre-treatment, pre-purification or extraction steps, unless non-pretreated control material is inappropriate. For qualitative assays, the negative and positive controls should be at concentrations that meaningfully confirm performance below and above the decision threshold for the analyte. For quantitative assays, appropriate controls must include at least one normal sample, and at least one sample reflecting
For some assays, an additional control concentration may be useful to confirm performance near the assay's LOD*, LOQ** or cut-off, if appropriate, or at a concentration consistent with highly abnormal levels that test the AMR.

*LOD - limit of detection  
**LOQ - limit of quantitation

Evidence of Compliance:
✓ Written procedure defining QC requirements for each test system AND
✓ QC records at defined frequency

REFERENCES

CBG.15100 Sample Run Order Phase II

A record of sample run order is maintained for review.

NOTE: Run list must include blanks, standards, controls and patients included in each run and be stored with the results of each batch run.

CBG.15200 Chromatographic Characteristics/Column Performance Phase II

There is a procedure for review and approval of chromatographic characteristics and column performance of each run before results are released.

NOTE: Checks should record testing variables such as flow rate of carrier gas and amount of sample injected and indications of error including split peaks, doublets, and tailing.

CBG.15300 Carryover Detection Phase II

There is a procedure for detection and evaluation of potential carryover.

NOTE: No matter what type of injection is used, the procedure must address criteria for the evaluation of potential carryover from a preceding elevated (high concentration) sample to the following sample in each analytical batch analysis.

Evidence of Compliance:
✓ Records of reassessment of samples with potential carryover

REFERENCES
2) Society of Forensic Toxicologists/American Academy of Forensic Sciences. Forensic Toxicology Laboratory Guidelines. 2002; 8.2.8:13

CBG.15400 Column Verification Phase II

New columns are verified for performance before use.

Evidence of Compliance:
✓ Written procedure for column verification AND
✓ Records of column verification

CBG.15500 Instrument Operation Phase II
There are written procedures for operation and calibration of GC equipment.

CBG.15700 Gas Leakage

A written procedure specifies the checking of gas lines and connections for leaks every time tubing or a connection has been manipulated.

Evidence of Compliance:
✓ Records of gas line checks

CBG.15800 Reagent Grade

Reagents, solvents and gases of appropriate grade are used.

Evidence of Compliance:
✓ Written procedure detailing appropriate grade for materials used

CBG.15900 Limit of Detection/AMR

There are records that the limit of detection (sensitivity) and the AMR for quantitative methods have been determined for each procedure.

REFERENCES

HIGH PERFORMANCE LIQUID CHROMATOGRAPHY (HPLC)

Inspector Instructions:

- Sampling of HPLC policies and procedures
- Sampling of control, calibration/standards records
- Sampling of column verification records

- How does your laboratory evaluate potential carryover?
- How have you determined the limit of detection and the AMR?

**REVISED** 04/21/2014

CBG.16000 Calibration and Calibration Verification

Appropriate calibration or calibration verification is performed on each day of patient testing or following the manufacturer's instructions.

NOTE: For qualitative assays, an appropriate calibrator should be run at normal and abnormal levels. For quantitative assays, a multipoint calibration may be required if the measurement has a non-linear response. For some assays, a level near the assay's limit of detection (LOD) or at critical decision point(s) is needed. For measurement systems that have a linear response verified by periodic multipoint calibration verification and AMR verification protocols, a calibration procedure that uses a single calibrator at an appropriate concentration is acceptable. Analyses based on a single point calibration must be controlled by appropriate quality control samples.
Quality control materials in the appropriate concentration range may be used for calibration verification, providing that the linear response is verified by periodic multipoint calibration verification and AMR verification.

In addition, inclusion of a negative control (reagent blank) is good laboratory practice.

**Evidence of Compliance:**
- Written procedure for calibration/calibration verification AND
- Records of calibration/calibration verification

**REFERENCES**

**CBG.16100** Quality Control - HPLC

Appropriate controls are extracted and run through the entire procedure.

**NOTE:** Controls used in HPLC procedures must evaluate as much of the complete testing process as is technically feasible. The control process includes any pre-treatment, pre-purification or extraction steps, unless non-pretreated control material is inappropriate. For qualitative assays, the negative and positive controls should be at concentrations that meaningfully confirm performance below and above the decision threshold for the analyte. For quantitative assays, appropriate controls must include at least one normal sample, and at least one sample reflecting a disease range. For some assays, an additional control concentration may be useful to confirm performance near the assay's LOD*, LOQ** or cut-off, if appropriate, or at a concentration consistent with highly abnormal levels that test the AMR.

*LOD - limit of detection
**LOQ - limit of quantitation

**Evidence of Compliance:**
- Written procedure defining QC requirements for test systems used AND
- QC records at defined frequency

**REFERENCES**

**CBG.16200** Sample Run Order

A record of sample run order is maintained for review.

**NOTE:** Run list must include blanks, standards, controls and patients included in each run and be stored with the results of each batch run.

**CBG.16300** Chromatographic Characteristics/Column Performance

Chromatographic characteristics and column performance are reviewed and approved for each run before results are released.

**CBG.16400** Column Verification

New columns are verified for performance before use.

**Evidence of Compliance:**
- Written procedure for column verification AND
- Records of column verification

**CBG.16500** Reagent Grade
Reagents and solvents are of appropriate grade.

Evidence of Compliance:
✓ Written procedure detailing appropriate grade for materials used

CBG.16600 Instrument Operation

There are written procedures for operation and calibration of HPLC equipment.

CBG.16700 Carryover Detection

There is a procedure for the detection and evaluation of potential carryover.

NOTE: No matter what type of injection is used, the procedure must address criteria for the evaluation of potential carryover from a preceding elevated (high concentration) sample to the following sample in each analytical batch analysis.

Evidence of Compliance:
✓ Records for reassessment of samples with potential carryover

REFERENCES
2) Society of Forensic Toxicologists/American Academy of Forensic Sciences. Forensic Toxicology Laboratory Guidelines. 2002; 8.2.8:13

CBG.16900 Limit of Detection/AMR

There are records that the limit of detection (sensitivity) and the AMR for quantitative methods have been determined for each procedure.

INSPECTOR INSTRUCTIONS:
- Sampling of MS policies and procedures
- Identification criteria compliance

• How does your laboratory identify possible ion-suppression?

CBG.17000 Instrument Operation

There are written procedures for operation and calibration of the mass spectrometer.

CBG.17100 Mass Spectrometer Tuning

Single stage mass spectrometers are tuned each day of patient/client testing, or according to manufacturer's recommendations, and tune records are maintained.
NOTE: Acceptable tolerance limits for tune parameters must be defined, and tune records maintained.

CBG.17200 Tandem Mass Spectrometer - QC

Tandem mass spectrometers are tuned according to manufacturer's recommendations and tuning records are maintained.

NOTE: Tandem mass spectrometers require tuning at the time of maintenance that requires shutdown of the vacuum system.

CBG.17300 Identification Criteria

The identification criteria for single stage mass spectrometry (i.e. GC/MS, LC/MS) are in compliance with recommendations.

NOTE: One acceptable criterion for compound identification by GC/MS using ion ratios is that the unknown result must have ion ratios within a predefined tolerance limit. This limit should be supported by either literature references or through experimental means. Such ion ratio tolerance limits may differ based on the technique applied (e.g. GC/MS versus LC/MS) as well as the analyte(s) being determined (e.g. compounds with mainly ions of low abundance); thus, a defined limit to cover all methods and analytes cannot be given.

Identification using ion ratios typically requires the use of at least two ion ratios. However, one ion ratio of two characteristic ions may be acceptable if there are only a few characteristic ratios AND if there are other identifying characteristics, e.g. retention time. The internal standard's identification should be monitored with at least one ion ratio. An acceptable criterion for compound identification using total spectra is that the unknown result must have a "spectral match" quality or fit that is within the defined limits that the laboratory has set and validated. Ion ratios determined from total spectra analysis are an acceptable identification method, and should fulfill the same criteria as given above for ion ratio identification.

Laboratories using mass spectrometric methods for quantitative purposes based on total ion current measurements (without ion ratios) should have ancillary information and assay characteristics that validate this process, e.g. known compound of interest, retention times, potential interferences by endogenous compounds or other drugs/metabolites, etc.

Evidence of Compliance:
✓ QC and test records

CBG.17400 Identification Criteria

The identification criteria for tandem mass spectrometry (MS/MS) are validated and recorded.

NOTE: In tandem mass spectrometry using multiple reaction monitoring (MRM) there is at least one transition monitored for the internal standard and another for the analyte.

Evidence of Compliance:
✓ QC and test records

CBG.17500 Ion-Suppression-Matrix Blank

To detect ion suppression during LC/MS and MS/MS test development and validation, there is a record of monitoring the total ion current intensity during analysis of an extracted matrix blank.
NOTE: Signal suppression is a common pitfall of methods based on rapid chromatographic separation. The achievement of a stable baseline signal at the end of signal acquisition should also be recorded.

REFERENCES

CBG.17600 Ion Suppression-Patient Sample

To recognize the occurrence of ion suppression during the LC/MS and MS/MS analysis of patient samples, there is a record of an acceptable range of signal intensity of the ion transition(s) selected to monitor each internal standard added to patient samples.

NOTE: Routine monitoring of the signal intensity of internal standard(s) is an effective way to recognize signal suppression in a single patient sample, due to unexpected interfering components of the matrix.

COLORIMETERS, SPECTROPHOTOMETERS, AND FLUORIMETERS

Inspector Instructions:

- Sampling of colorimeter/spectrophotometer policies and procedures
- How does your laboratory verify calibration curves?

CBG.17700 Absorbance/Linearity

Absorbance and/or fluorescence linearity is checked and recorded at least annually or as often as specified by the manufacturer, with filters or standard solutions.

Evidence of Compliance:
✓ Records of absorbance and linearity checks at required frequency

CBG.17800 Wavelength Calibration

Spectrophotometer (including ELISA plate readers) wavelength calibration is checked at least annually or as often as specified by the manufacturer, with appropriate solutions, filters or emission line source lamps, and the results recorded.

NOTE: Some spectrophotometer designs, e.g. diode array, have no moving parts that can alter wavelength accuracy and do not require routine verification. The manufacturer's instructions must be followed.

Evidence of Compliance:
✓ Records of wavelength calibration checks at required frequency

CBG.17900 Stray Light

Phase II
Stray light is checked at least annually with extinction filters or appropriate solutions, if required by the instrument manufacturer.

Evidence of Compliance:
✓ Records of stray light checks, as applicable

### REVISITED 07/28/2015
CBG.18000 Calibration Curves

For procedures using calibration curves, all the curves are rerun at defined intervals and/or verified after servicing or recalibration of instruments.

**NOTE:** Calibration curves must be run following manufacturer's instructions, at minimum, and as defined in laboratory procedure.

Evidence of Compliance:
✓ Records of calibration curve rerun and/or verification at defined frequency

REFERENCES

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## ELECTROPHORESIS

**Inspector Instructions:**

- Sampling of electrophoresis policies and procedures
- Sampling of electrophoresis QC logs
- Electrophoretic patterns (appropriate separations)

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**CBG.18025 Daily QC - Electrophoresis**

Suitable control samples are run and reviewed with each batch of patient samples for all electrophoresis procedures for which controls are available.

Evidence of Compliance:
✓ Records of electrophoresis QC

**CBG.18050 Electrophoresis Separations**

Electrophoretic separations are satisfactory.

**CBG.18075 Acceptable Limits - Controls**

Acceptable limits are set for controls of procedures where the electrophoretic bands are quantified.

Evidence of Compliance:
✓ Records of defined acceptable limits for control range verification of each lot
RADIOIMMUNOASSAYS

Inspector Instructions:

- Sampling of radioimmunoassay policies and procedures
- Sampling of calibration records
- Sampling of background radioactivity records

CBG.18080  Gamma Counter Calibration  Phase II

Gamma counters and/or scintillation counters are calibrated, results recorded and compared to previous values each day of use.

Evidence of Compliance:
✓ Written procedure for calibration

CBG.18085  Background Radioactivity  Phase II

The background radioactivity is determined each day of use, including the background in each well of a multi-well counter, with defined upper limits of acceptability.

Evidence of Compliance:
✓ Records of background radioactivity determinations at defined frequency

CBG.18090  Counting Times  Phase II

Counting times for quantitative procedures are sufficiently long for statistical accuracy and precision.

Evidence of Compliance:
✓ Written procedure defining counting times for each quantitative assay

GLASSWARE

Inspector Instructions:

- Pipette verification procedure
- Sampling of pipette/dilutor checks

What is your laboratory’s course of action prior to using non-certified thermometers and non-certified volumetric glassware?
Glass volumetric flasks are of certified accuracy (Class A, National Institute of Standards and Technology (NIST) Standard or equivalent) or if non-certified volumetric glassware is used, all items are validated for accuracy of calibration before initial use.

Evidence of Compliance:
✓ Glassware marked Class A OR NIST certificate OR validation study of accuracy for non-certified glassware

CBG.18600 Pipette Accuracy Phase II

Glass volumetric pipettes are of certified accuracy (Class A); or they are checked by gravimetric, colorimetric, or some other validation procedure before initial use.

NOTE: The following Table shows the American Society for Testing and Materials' calibration (accuracy) specifications for Class A volumetric pipettes:

Reconstitution of lyophilized calibrators, controls, or proficiency testing materials, or any other tasks requiring accurate volumetric measurement, must be performed only with measuring devices of Class A accuracy, or those for which accuracy has been defined and deemed acceptable for the intended use.

If initial calibration is performed by the manufacturer or other outside facility, sufficient information must be provided to justify acceptance of the pipette’s calibration based on the laboratory’s written specifications of acceptable bias and imprecision. The outside facility must also provide a record of the technique used to check calibration and ship the pipette in a manner that protects it from damage in transit.

<table>
<thead>
<tr>
<th>Nominal Capacity (mL)</th>
<th>Variation (± mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 - 2</td>
<td>0.006</td>
</tr>
<tr>
<td>3 - 7</td>
<td>0.01</td>
</tr>
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<td>40 - 50</td>
<td>0.05</td>
</tr>
<tr>
<td>100</td>
<td>0.08</td>
</tr>
</tbody>
</table>

Evidence of Compliance:
✓ Validation study of accuracy for non-certified pipettes

REFERENCES
5) Johnson B. Calibration to dye for: Artel’s new pipette calibration system. Scientist. 1999;13(12):14

**REVISED** 07/28/2015

CBG.18700 Pipette Accuracy - Non Class A Phase II

Non-class A pipettes that are used for quantitative dispensing of material are checked for accuracy and reproducibility at defined intervals (at least annually), and results recorded.

NOTE: Pipette checks must be performed following manufacturer’s instructions, at minimum, and as defined in laboratory procedure. Such checks are most simply done gravimetrically. This consists of transferring a number of measured samples of water from the pipette to a balance.
Each weight is recorded, the weights are converted to volumes, and then means (for accuracy), and SD/CV (for imprecision) are calculated. Alternative approaches include spectrophotometry or (less frequently) the use of radioactive isotopes, and commercial kits are available from a number of vendors. Computer software is useful where there are many pipettes, and provides convenient records.

REFERENCES

CBG.18800 Measuring Devices

The use of less precise measuring devices such as serological plastic pipettes and graduated cylinders are limited to situations where the accuracy and precision of calibrated glass pipettes are not required.

NOTE: In contrast with the more stringent accuracy requirements of glass pipettes, ASTM requirements for plastic pipettes are ± 3% of the stated volume. The procedure manual should specify when the use of non-class A measuring devices is permissible.

REFERENCES

PIPETTES - FIXED VOLUME, ADJUSTABLE AND/OR MICROPIPETTES

Pipettes and diluting devices of all types must be checked for accuracy and reproducibility before being placed in service and at least annually thereafter.

Inspector Instructions:

- Pipette calibration procedure
- Sampling of pipette/dilutor checks

- How are you assured your automatic pipetting systems exhibit no carryover effects?

CBG.18900 Pipette Accuracy

There is a written procedure defining how pipettes used for quantitative dispensing are checked for accuracy of calibration and reproducibility (gravimetric, colorimetric, volumetric or other verification procedure) before being placed in service initially, and results recorded.
NOTE: Pipettes (fixed volume, adjustable volume, micropipettes, and analytic instruments with integral automatic pipettors) must be checked for calibration accuracy and imprecision either by volumetric, colorimetric, gravimetric, or other means before being placed in service initially, and results recorded. The initial calibration may be performed by the manufacturer or other outside facility, but in such cases the laboratory must have records from the manufacturer or other facility that include the technique used to check calibration, the method of shipment to prevent damage in transit, and the bias and imprecision of the pipette(s). The bias and imprecision must meet the specifications established by the laboratory.

REFERENCES

**REVISED** 07/28/2015

CBG.19000 Pipette Accuracy

Pipette used for quantitative dispensing are checked for accuracy and reproducibility (gravimetric, colorimetric, volumetric or other verification procedure) at defined intervals (at least annually), and results recorded.

NOTE: Pipette checks must be performed following manufacturer's instructions, at minimum, and as defined in laboratory procedure.

For analytic instruments with integral automatic pipettors, the accuracy and precision of the pipetting system should be checked at least annually, unless that is not practical for the end-user laboratory. Manufacturers' recommendations should be followed.

REFERENCES

CBG.19100 Pipette Carryover

The laboratory evaluates its automatic pipetting systems for carryover.

NOTE: The laboratory must have written procedures for evaluating whether carryover effects are present. This requirement applies to both stand-alone pipette systems and to sample pipettes integrated with analytic instruments.

In practice, carryover is a problem only for analytes with a wide clinical range of analyte concentration, such that a minute degree of carry-over could have significant clinical implications. An example may include certain enzyme immunoassays. The laboratory should select representative examples of such analytes for carryover studies.

Evaluation for carryover is not required for automatic pipettes that use disposable tips.

One suggested method to study carryover is to run known high patient samples, followed by known low samples to see if the results of the low-level material are affected. If carryover is detected, the laboratory must determine the analyte concentration above which subsequent samples may be affected, and define this value in the procedure. Results of each analytical run...
must be reviewed to ensure that no results exceed this level. If results that exceed the defined level are detected, then the appropriate course of action must be defined (repeat analysis of subsequent samples, for example).

Carryover studies must be performed, as applicable, as part of the initial evaluation of an instrument. (The laboratory may use the data from carryover studies performed by instrument manufacturers, as appropriate.) Carryover studies should be repeated after major maintenance or repair of the pipetting assembly of the instrument.

Evidence of Compliance:
✓ Records of carryover studies at defined frequency

REFERENCES

ANALYTICAL BALANCES

Inspector Instructions:

- Sampling of balance service records
- Sampling of balance accuracy check records

- Analytical balances (mounting)
- Standard weights (maintained, appropriate class)

CBG.19700 Balance Maintenance Phase I

Balances are cleaned, serviced and checked at least annually only by qualified service personnel (i.e. service contract or as needed).

Evidence of Compliance:
✓ Records of balance maintenance

CBG.19800 Balance Mounting Phase I

Analytical balances are mounted such that vibrations do not interfere with readings.

**REVISED** 07/28/2015

CBG.19900 Analytical Balance Accuracy Phase II

Standard weights of the appropriate ANSI/ASTM Class are available and used for verifying accuracy of analytical balances at defined intervals, with records maintained.

NOTE: The verification of accuracy of the analytical balance must be performed on a regular schedule to ensure accurate creation of analytical calibrators and/or weighed-in controls from standard materials, as well as when gravimetrically checking the accuracy of pipettes.

Accuracy must be verified at least every six months if used for weighing materials to make standard solutions for method calibration. Accuracy must be verified at the time of installation and whenever a balance is moved. Acceptable ranges must be defined.
External verification of accuracy requires the appropriate class of ASTM specification weights. ASTM Class 1 weights are appropriate for calibrating high precision analytical balances (0.01 to 0.1 mg limit of precision). ASTM Class 2 weights are appropriate for calibrating precision top-loading balances (0.001 to 0.01 g precision). ASTM Class 3 weights are appropriate for calibrating moderate precision balances, (0.01 to 0.1 g precision).

Evidence of Compliance:
✓ Written procedure defining criteria for the use of standard weights for accuracy checks of analytical balances

REFERENCES

CBG.20100  Weight Maintenance  Phase II

Weights are well-maintained (clean, in a covered container, not corroded) and appropriate lifting or handling devices are available.

NOTE: Weights must be well-maintained (covered when not in use, not corroded) and only be handled by devices that will not allow residual contaminants to remain on the masses. Certified masses will only meet their specifications if maintained in pristine condition.

CBG.20110  Specimen Collection Instructions  Phase II

Instructions for the proper collection, handling, transport, and submission of newborn screening specimens are provided to locations submitting specimens for analysis.

NOTE: It is acceptable for this information to be electronically available to users rather than in paper format. Instructions must describe the proper application and drying of blood spots and submission of patient information needed for interpretation of the data. The collection instructions must be in compliance with the current edition of the CLSI Standard NBS01, Blood Collection on Filter Paper for Newborn Screening Programs, and state or local regulations for collection of specimens.

REFERENCES
1) CLSI Standard NBS01-A6. Blood Collection on Filter Paper for Newborn Screening Programs; Approved Standard, Sixth Edition. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 2500, Wayne, Pennsylvania 19087-1898, USA

**REVISED** 07/28/2015

CBG.20120  Specimen Quality Monitoring  Phase II

There is a written procedure for the monitoring of specimen quality, completeness of patient records, and transportation time for specimens submitted for newborn screening.

NOTE: The patient records submitted with newborn screening specimens must include information for patient identification and proper interpretation of the data including all required elements defined in the most recent edition of CLSI Standard NBS01. If problems with specimen
quality or missing collection information are identified, the laboratory must record appropriate corrective actions that lead to continuous quality improvement.

Specimens should be transported after they are dry and no later than 24 hours after collection or following the instructions provided by the designated newborn screening laboratory. Delays in specimen transportation from the collection facility to the testing laboratory may compromise the integrity of the specimen and results. Ultimately, the delay could critically impact the newborn.

Evidence of Compliance:
✓ Records of monitoring for poor quality specimens, incomplete collection information submitted, and specimen transport problems AND
✓ Records of communications with clients that submit specimens with quality issues

CBG.20130 Consent Procedure
Phase II

In cases where an indication of consent is required on the newborn screening collection device, either for collection or for later use (research), there is a procedure for review and action to ensure appropriate use of the specimen.

NOTE: Records must demonstrate that this procedure is followed.

CBG.20140 Out-of-Range/Invalid Results
Phase II

There is a procedure for reporting positive (out of range) or invalid results to the submitting location and other appropriate entities to allow for patient follow-up within a timeframe appropriate to ensure maximum health benefit.

NOTE: Positive results include those results that are outside of the expected range of testing results established for a particular condition. Invalid results include situations where the laboratory is unable to complete the screening process due to an unsuitable specimen, test, or incomplete information. The findings must be communicated in a manner consistent with the urgency of the intervention needed. For situations requiring repeat screening or confirmatory testing, the laboratory must clearly communicate the timing of the actions to be taken.

Results must be reported to the submitting location within seven days of specimen receipt and within three days for specimens received for tests requiring additional action (e.g. invalid or positive). The records must indicate when results were reported and who received the results. In cases where the testing laboratory is responsible for ensuring that a replacement specimen has been received and analyzed, appropriate records must attest to specimen receipt, testing and result reporting.

CBG.20150 Results Reporting
Phase II

Newborn screening results are reported to the submitting location and include all required result reporting elements from the Laboratory General Checklist.

**REVISED** 07/28/2015
CBG.20160 Follow-up Procedures
Phase I

In cases where the testing laboratory is responsible for testing and follow-up (including patient tracking), all follow-up procedures are “closed loops” consistent with the CLSI Guideline NBS02, Newborn Screening Follow-up, or appropriate local policy.

NOTE: The laboratory’s written procedures should include:
1. Cases requiring notification
2. Roles and responsibilities of all individuals in the follow up system, as appropriate (laboratory staff, physicians, and birthing centers)
3. Method and timing of notifications (e.g. phone call, fax or letter)
4. Monitoring of follow-up to track the actions taken until resolution - specimen monitoring, follow-up calls/letters, nurse visits, etc.
5. Case Resolution - follow-up actions, including the extent of actions required before closing a case without resolution or lost to follow up

The procedures must follow local laws and regulations. "Lost to follow up" occurs when a notification cannot be made.

REFERENCES
1) Clinical and Laboratory Standards Institute. Newborn Screening Follow-up; CLSI Guideline NBS02-A2. Clinical and Laboratory Standards Institute, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898, USA

HEMOGLOBIN SEPARATION

This section is intended for laboratories that are performing screening tests on newborns from whole blood heel stick specimens collected on filter paper for the routine screening for abnormal hemoglobin variants.

Inspector Instructions:

- Sampling of abnormal hemoglobin policies and procedures
- Sampling of patient reports (confirmatory testing, comments)
- Sampling of QC records
- Hemoglobin separation patterns (appropriate separations and controls)
- Examine a sampling of medium (media) used to identify hemoglobin variants including alkaline/acid electrophoresis, isoelectric focusing, HPLC or other method
- What is your course of action when the primary screening method appears to show Hb S?
- What is your course of action when the primary Hb screening method shows Hb variants migrating in nonA/nonS positions?

**NEW** 04/21/2014

CBG.20165 Hb S Primary Screen

Phase II

For samples that have screening results demonstrating the presence of a hemoglobin consistent with Hb S and suggesting a possible clinically significant condition, reporting of the screening results includes a recommendation that confirmatory testing be performed.

NOTE: For primary definitive diagnosis screening by electrophoresis or other separation methods, all samples with hemoglobins migrating in the “S” positions or peak must be tested for sickling hemoglobin(s). Known sickling and non-sickling controls both must be included with each run of patient specimens tested.

Evidence of Compliance:
✓ Written policy for follow-up when Hb S appears in the primary screen

REFERENCES
**NEW** 04/21/2014

**Daily QC - Hgb Separation**

**Phase II**

Controls containing at least three known major hemoglobins, including Hb F and both a sickling and a nonsickling hemoglobin (e.g. A, F and S) are applied with the patient specimen(s) and separations are satisfactory.

**Evidence of Compliance:**
- Written procedure defining QC requirements for hemoglobin separation **AND**
- QC records reflecting the use of appropriate controls **AND**
- Data, tracings, or other appropriate testing results (e.g. photographs, gels, cards with banding patterns) demonstrate appropriate controls and separation

**REFERENCES**

**NEW** 04/21/2014

**Clinical Biochemical Genetics Checklist**

**Phase II**

All samples with hemoglobin variants not appearing to be Hb A, Hb F, or Hb S by the separation procedure in use, are reported with a recommendation to obtain confirmatory testing consistent with local screening program recommendations.

**NOTE:** The laboratory must have a defined procedure for the reporting of abnormal hemoglobin variants, developed in consultation with hematology advisors. The procedure must address the confirmatory testing recommendations, if confirmatory testing is not performed on-site.
Evidence of Compliance:
✓ Written policy defining criteria for further identification of hemoglobin variants AND
✓ Patient reports and records reflecting adherence to laboratory reporting procedures

REFERENCES

PERSONNEL

Inspector Instructions:

- Records of education and experience

CBG.20200   Bench Testing Supervision

The person in charge of bench testing/section supervisor in clinical biochemical genetics has education equivalent to an associate’s degree (or beyond) and at least 4 years experience (one of which must be in clinical biochemical genetics) under a qualified section director.

Evidence of Compliance:
✓ Records of qualifications including degree or transcript, current license (if required) and work history in related field

LABORATORY SAFETY

The inspector should review relevant requirements from the Safety section of the Laboratory General checklist, to assure that the clinical biochemical genetics laboratory is in compliance. Please elaborate upon the location and the details of each deficiency in the Inspector’s Summation Report.
RADIATION SAFETY

Inspector Instructions:

- Sampling of radiation safety policies and procedures
- Sampling of radiation area surveys/wipe tests records
- Sampling of radioactive waste disposal records
- Sampling of personnel records of radionuclide training

- Radionuclide storage areas (properly shielded)
- Appropriate signage where radioactive materials are used/stored

- Does your laboratory have representation at radiation safety committee meetings?
- How does your laboratory check the effectiveness of workbench decontamination?

CBG.20300  Radiation Safety Manual

There is an up-to-date radiation safety manual that includes sections on decontamination and radioactive waste.

NOTE: For US laboratories, this is required by the Nuclear Regulatory Commission (NRC).

REFERENCES

CBG.20400  Workspace Decontamination

Workbenches and sinks are decontaminated each day of use, and the effectiveness tested at least monthly.

NOTE: If the laboratory uses only Iodine-125, either a wipe test or a portable scintillation probe can be used.

Evidence of Compliance:
✓ Records of daily workbench/sink decontamination AND
✓ Records of monthly effectiveness tests

REFERENCES

CBG.20500  Radionuclides Handling

There are written policies regarding the authorization or restriction of personnel handling radionuclides.
NOTE: These policies should be incorporated into the department's radiation safety manual.

CBG.20600 Radionuclide Leak

There are written procedures for notification if a damaged or leaking radionuclide shipment is received.

NOTE: Procedures must include inspection, monitoring of shipments, and instructions for notification, if leakage or damage is noted in a radionuclide shipment.

Evidence of Compliance:
✓ Records of inspections and notifications

REFERENCES
2) Department of Transportation, Research and Special Programs Administration. Hazardous materials table, special provisions, hazardous materials communications, emergency response information and training requirements. *Fed Register*. 2003 (Oct 1) [49CFR172.403, 600, 602, 604]

CBG.20700 Radionuclide Storage

Radionuclide storage and decay areas are properly shielded, if required for specific isotopic materials.

NOTE: Radionuclide storage and decay areas must be properly shielded, if required for specific isotopic materials, to avoid excessive exposure to personnel and interference with counting procedures.

Evidence of Compliance:
✓ Written procedure defining shielding requirements for radionuclide storage and decay areas

CBG.20800 Radiation Surveys

There are regular radiation area surveys and wipe tests, with records maintained.

NOTE: Routine radiation surveys and wipe tests to determine exposure rates and detect contamination must be performed and recorded at defined frequencies.

Evidence of Compliance:
✓ Written procedure for radiation survey and wipe tests to determine exposure rated and detect contamination

CBG.20900 Radioactive Material Sign

All areas or rooms where radioactive materials are being used or stored are posted to indicate the presence of radioactive materials.

NOTE: For US laboratories, all areas or rooms where radioactive materials are being used or stored must be posted to indicate the presence of radioactive materials, consistent with 10CFR20, Appendix C.

REFERENCES

CBG.21000 Radionuclide Training

Personnel receive training in decontamination routines and in the safe handling and proper disposal of radionuclides (wastes, syringes, needles, and sponges) with records maintained.
Radioactive Waste

Radioactive waste is stored separately, under required conditions, and appropriately discarded, with records maintained.

NOTE: For US laboratories, NRC regulations specify that separate areas be established for the receipt of radioactive waste and that these areas be properly shielded to reduce radiation levels below those maximum permissible limits specified in 10CFR20.

Evidence of Compliance:
✓ Written procedure defining criteria for proper storage and disposal of radioactive waste

REFERENCES

Safety Committee Representation

There are records indicating that a laboratory representative is a member of and/or attends institutional radiation safety committee meetings regularly.

NOTE: Independent laboratories must have a radiation safety officer who fulfills the functions of an institutional radiation safety committee.

Evidence of Compliance:
✓ Records of laboratory participation in institutional Safety Committee meeting OR participation in other appropriate group responsible for radiation safety