ACCREDITATION SCHEME FOR LABORATORIES

Technical Notes MED 002

Specific Criteria for Clinical Chemistry Section

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1. Introduction & Scope

1.1 This document describes the specific requirements for clinical chemistry including automated chemistry, immunoassay, special chemistry, urinalysis as well as point of care testing (POCT) laboratories to be accredited.

1.2 The document shall be read in conjunction with ISO 15189 Medical laboratories – Requirements for quality and competence', SAC-SINGLAS documents, Proficiency Testing Technical Note 001, and other MEDICAL Series Technical Notes published by SAC-SINGLAS.

2. Facilities and Environmental Conditions

2.1 When using hazardous materials (toxic, mutagenic and radioactive), there shall be clear documented procedures describing the appropriate measures taken to protect the personnel and the environment.

3. Laboratory Equipment

3.1 Written procedures should be available for all analysers operations, maintenance and quality control practices. Maintenance and service records should be available for all equipment.

3.2 Training and competency records should be available for all staff using analysers.

3.3 The laboratory shall have a written routine maintenance and function verification schedule for all instruments and equipment including clinical microscopy section.

3.4 Urinalysis – If manual microscopy is used a process should be in place to ensure all technologists are trained and competent with a standardised reporting of elements.

3.5 Automated chemistry analysers – Information on the standardisation of all assays should be available. Haemolysis, lipaemia and icterus may be measured on the analyser for sample quality interpretation. Otherwise a robust manual method must be in place and clear information on their effect on each test available.

3.6 Gamma counters – A radiation manual should be available for the safe handling of radioactive material and waste. Training and competency records including devices monitoring staff exposure to radiation are available (according to local regulations). There is documentation of work area decontamination on each day of use and the effectiveness of the decontamination determined at least once a month. There is a documented calibration practice for the gamma counter. The gamma counter and the performance of radioactive testing is performed in a segregated and identified area.

3.7 Automated image analysers (including immunofluorescence slides, urinalysis, etc) shall be calibrated according to manufacturer's specification. Standardised

training and competency must be available for all staff performing this testing. A comprehensive atlas should be available at all times.

3.8 Laboratory automation system (LAS) modules – this may include centrifuges, bulk loaders, decappers, aliquoters, re-cappers, stockyards, inlet and outlet modules and tracks. All components of the LAS should meet the maintenance and safety requirements of the individual components. Staff training and troubleshooting should also be available and robust.

3.9 Point of care analysers – a procedure for calibration and QC process should be available for all POC analysers/devices. Users (not laboratory personnel) require to have training and competency in place with full documentation.

4. Pre-examination Procedures

4.1 The same general requirements are applicable to all areas of the laboratory under the clinical chemistry umbrella including general chemistry and immunoassays, urinalysis, therapeutic drug monitoring, manual tests, and it covers blood (serum/plasma), urines, fluids and calculi.

4.2 For point of care testing (POCT) the same requirements should be in place as those for general chemistry. POCT is defined as laboratory analytical testing of services within an institution that are performed outside the laboratory in a non-dedicated space.

Examples include bedside and/or ward testing and they will be handled as an additional laboratory section under the direction and authority of the laboratory director. It is recommended that there by centralised coordination of the POCT programme with designated laboratory personnel responsible for validation of devices, monitoring testing procedures and quality control, and coordinating training and competency of personnel performing testing.

4.3 Instructions are available to the patient for samples that require the patient to fast. A clear definition of what fasting means is available.

4.4 Urinalysis

a. Written instructions shall be provided to patients for proper collection of clean voided specimens for random collections.
b. For 24-hour urinalysis, written instructions should be available for patients to safely collect the total urine over 24 hours. Cautionary notice should be provided when preservatives are added to the bottle.

4.5 The laboratory shall have a procedure for stimulation and suppressions tests e.g. glucose tolerance test

4.6 Written instructions should be available regarding sample stability and the type of sample storage that is appropriate prior to arrival of the sample in the laboratory.

5. Examination Procedures

5.1 Performance Verification

5.1.1 A laboratory is required, upon installation, and in routine use, to be able to comply to the minimum specifications determined by the manufacturer and the acceptability criteria of the laboratory.

5.1.2 All tests have to be validated or verified with the extent of this exercise to confirm it is suitable for its intended use.

5.1.3 The performance of tests and analysers have been validated by the manufacturer. Hence, laboratories are only expected to verify their tests on the analysers according to the manufacturer's instructions.

5.1.4 If a methodology or reagents used in the analyser deviate from the manufacturer's instructions, then the validation requires to be conducted as a laboratory developed test (LDT).

5.1.5 Verification will determine if the total analytical error for the tests is within the total allowable error and this can be determined by reviewing imprecision, method bias and sample bias.

5.1.7 Verification must be performed (i) new analyser (for all analysers, even if they are the same model) (ii) replacement of analyser (iii) transfer of test from one identical analyser to another. This includes all POC analysers.

5.1.8 The laboratory shall have detailed documentation of procedure for verification available in the laboratory.

a. Within and between batch/day imprecision – previously analysed patient samples, control samples or other suitable material with known values. Ideal to have same matrix as patient samples. A minimum of 5 replicates of each level run for five days. Alternatively, within one day with multiple replicates, and between day for 10-20 days. The longer period incorporates potential for greater variability and more realistic of patient sampling over time. To cover concentrations of normal and pathological concentrations and clinical decision concentrations. Sample volume, test stability and storage conditions are critical. To calculate SD and %CV and compare to acceptance criteria. Using QC material, the commutability of QC material with patient samples requires to be determined.

b. Inter-instrument comparison – comparison with test results from current instrument and comparison with new instrument. Secondly, comparison with more than one of the same analyser being used in the same laboratory. Differences must be within acceptable limits. At least 40 samples covering the whole analytical range (the linear range). A scatter plot to be used for results obtained from instruments with identical scales and ranges. Linear regression model (least square, Deming or Passing-Bablok). Ideally correlation coefficient >=0.975. Blank-Altman plot should compare two deferent analysers/methods.
    - Inter-instrument comparison of more than one analyser of the same type is required to be performed periodically to ensure that results are comparable when analysers are used interchangeably.

c. Linearity of Measuring range – ability to provide a numerical result of test within measuring range directly proportional to concentration. The concentrations studied should cover the entire analytical range. A minimum of five concentrations in a minimum of two replicates. Acceptability criteria should be defined.

d. Limit of quantitation (LOQ), Limit of detection (LOD), Limit of blank (LOB)
   - LOB is the highest measurement detected for a blank sample. To achieve 20 replicated over multiple days using two blank sample pools.
   - LOD is the lowest amount of the analyte detected with a stated probability. To achieve this two sample pools are required and 20 replicates over multiple days.
   - LOQ is required for immunoassays where detection of low analyte concentrations are critical eg troponin, TSH, PSA. To verify or establish the LOQ, the %CV needs to be determined using samples of concentrations close or below the claimed LOQ. To be acceptable the precision should be <20% for TSH or PSA and <10% for troponin. When LOQ is verified or established the LOD should not be used as the LOQ is more appropriate.

e. If autodilution is available on analysers it requires to be verified. The result of samples with high results are diluted by analyser and compared with an equivalent manual dilution.

f. Carry-over – this may result from a sampling syringe or component of the assay that has been exposed to a previous sample or reagent. The determine effect by performing three replicates of sample containing high concentration of analyte followed by a sample with a low concentration of the analyte in replicates. This only requires to be performed on relevant tests eg HCG, AFP, TSH, etc

g. Interferences (e.g. haemolysis, lipaemia and icterus) shall be assessed. Manufacturers limits may be adopted with rational for adoption and documentation. Action levels and actions need to be documented for each test. To perform interference testing using split sample testing and spiking with the interferent. Spiking material should not exceed 10% of sample volume to prevent matrix changes. An equal volume of diluent and spike should be added to paired samples and assayed in duplicated. The recovery of the spiked sample should be determined. Different analyte concentrations should be tested to determine concentration dependent differences.

h. Clinical concordance for qualitative tests - For qualitative tests eg HbsAg the results can be compared between analysers, however, concordance with clinical presentation is also required.

i. Reference ranges – ranges for interpreting analyte result required to be verified before putting new analyser into service. To verify the manufacturer's range at least 20 normal subjects should be sued and fall within the manufacturers range. To establish a range at least 120 normal subjects are required for statistical significance (male and female). 120 each would be required if there are gender specific ranges in place. Both

parametric or non-parametric statistics can be used, depending on data distribution.

j. Measurement of Uncertainty – see *Technical Guide 4 – A Guide on Measurement Uncertainty in Medical Testing*.

k. Summary Report for each test – name of person carrying out verification, dates of exercise, name and model of analyser(s), analyte details with lot and expiry dates of all reagents, calibrators, QC), summary of data with graphical presentation and analysis, results and conclusion, limitations and precautions if necessary. References.

5.2 There is a written procedure for the laboratory to follow for all analysers and tests, including calibration and quality control procedures

5.3 There is a weekly review or quality control results by the supervisor and a monthly review by the laboratory director or designate.

5.4 All corrective action taken as action to unacceptable results is documented.

5.5 New kits are reagent shall be checked against old reagents to ensure comparable results are generated. A document for acceptability criteria should be in place which contains details for all tests.

5.6 The laboratory shall have a procedure for common interference that may affect the accuracy of results (e.g. haemolysis, lipaemia or icterus). When specific tests are affected they should be tagged with an appropriate comment. This should occur with both automated indices and manual interpretation of sample quality.

5.7 There shall be a defined role for the laboratory in the validation, assessment and quality control of point of care testing.

5.8 Appropriate criteria shall have been developed and should be available for test selection, specimen collection and procession. Procedures should be in place to ensure accurate and reliable tests reporting systems. There shall be appropriate record storage and retrieval systems.

5.9 <u>Therapeutic Drug Monitoring</u>

5.9.1 The same general requirements shall be met in Therapeutic Drug Monitoring as in clinical chemistry. Emphasis should be placed on examining the frequency of assay standardization.

5.5 <u>Experimental Testing</u>

5.5.1 There shall be procedures for experimental testing, including regulation for informed consent and involvement of the medical ethical committee.

5.5.2 Testing shall be performed strictly according to protocols.

5.5.3 If different conditions with respect to routine laboratory procedures exist, they should be made explicit.

5.6 Urinalysis

5.6.1 The procedure manual shall provide the descriptions of urine sediment elements and be available to the bench technologists. It should be reviewed annually by the LD or supervisor to ensure that the technical protocol is complete and current.

5.6.2 The laboratory has a written procedure defining the criteria under which the microscopic examination may be omitted.

6. Ensuring the Validity of Examination Results

6.1 Quality Control

6.1.1 The laboratory should have a QC procedure for all sample types of all tests performed in Clinical Chemistry and POCT. The options for daily QC practices include

(i) Manufacturers QC material
(ii) Third party QC with instrument specific ranges
(iii) Pooled patient sample that require to have the targets and ranges established.

Appropriate storage conditions should be in place to ensure maximum use of a single lot/batch of QC material.

6.1.2 A laboratory procedure should be in place to establish a laboratory QC range prior to the implementation of the QC material when appropriate. The laboratory should not routinely practice 'adopting' the manufacturers range, but using it only as a guide. To note that some manufacturers use ± 3SD in their package insert and not ±SD.

6.1.3 Suitable rules should be put into place for determining acceptability of QC and reviewing trends in QC, e.g. Westgard rules. This should be used to accept or reject a run.

6.1.4 For random access testing the QC's must be acceptable prior to analysis.

6.1.5 If the QC's fail a process must be in place to determine the accuracy of the tests performed just prior to the QC failure.

6.1.6 When a pre-treatment step or extraction process is a component of the assay prior to analysis, the QC materials must also be tested through all of the steps.

6.1.7 Grey-zone QC material should be purchased or prepared that target a low positive range for semi-qualitative assays e.g. Hepatitis, HIV, drugs of abuse.

6.1.8 High sensitive QC material should be purchased or prepared that target the area of low concentration reporting e.g. troponin just above the reference range.

6.1.9 QC material should be available and tested for urines, csf and calculi when relevant.

6.1.10 For some POC devices only an electronic check is available for daily review. In these situations, purchase and periodic analysis of two levels of a suitable QC material must be performed eg weekly, monthly, lot change, shipment change.

6.2 External Quality Assessment

A POC analysers require to participate external quality assessment (EQA) programme. They may be self-evaluated using an EQA material and then a documented self-evaluation with acceptability criterion that is aligned with the external programme.

6.3 General Chemistry

6.3.1 The laboratory shall have a system/programme of internal quality control and participate in proficiency testing.

6.3.2 Criteria against which analytical processes (measurement and also observation) are judged should preferably be based on biological variance.

6.3.3 Internal quality control results should be checked and kept at the bench according to the working procedures.

6.3.4 Internal quality control results, including results from point of care equipment, and proficiency testing results shall be regularly evaluated. Staff meetings and actions taken shall be documented.

6.3.5 There shall be appropriate internal quality control procedures for each testing process, selected on the basis of the analytical quality required. Control specimens (type and frequency) for the various analytical systems shall be carried out to demonstrated on-going system stability.

6.3.6 Where available, appropriate multi-level control specimens shall be used at least daily whenever patient specimens are run. These results shall be documented. Positive and negative controls for qualitative tests shall be run at least once on each day of analysis, based on the manufacturer's instructions. For quantitative tests, control samples at more than one level shall be run at least once each day of analysis.

6.4 Diagnostic Immunology and Serology

6.4.1 Positive and negative controls for qualitative tests shall be run at least once on each day of analysis, based on the manufacturer's recommendations.

6.4.2 For quantitative tests control samples at more than one level shall be run at least once each day of analysis.

6.4.3 New kits and reagents shall be checked against old reagents to ensure comparable reactivity and the results shall be documented.

6.5 Urinalysis

6.5.1 There is a written procedure for the laboratory to follow manufacturer's instructions for quality control, calibration and related functions.

6.5.2 The laboratory has a written procedure for correlation of macroscopic results with microscopic sediment findings.

6.5.3 Review of quality control results at least weekly by section supervisor and monthly by Laboratory Director (LD)/ however named, or designate, shall be documented.

6.5.4 Corrective action taken in response to unacceptable results shall also be recorded.

6.5.5 The elements of a urinalysis vary according to the patient populations served and the needs of clinicians. Urinalysis may include the following: glucose, protein, blood/haemoglobin, leukocyte esterase, nitrite, specific gravity, bilirubin, ketones, pH and urobilinogen. Their utility should be reviewed periodically by the laboratory.

6.5.6 The laboratory shall have a written procedure defining criteria used for assessing morphologic observation among personnel performing urine sediment microscopy.

6.5.7 Controls and Standards

6.5.7.1 a) Reference materials (atlases, charts or photomicrographs) shall be available to assist in the microscopic identification of sediment constituents. Microscopic findings should be correlated with macroscopic results.

b) A protocol for processing quality control materials of known compositions should be available. Controls shall be used regularly to check reactivity and accuracy of the qualitative procedures (protein, glucose, etc.).

c) Control specimens shall be tested in the same manner as patient samples and results of controls should be verified for acceptability before reporting results.

d) Control samples shall be integrated within the routine laboratory workload to be analysed by personnel who routinely test patient samples.

7. Reporting of Results

7.1 For therapeutic drug monitoring, there is an expected therapeutic range provided for the drug and a toxic range is report when relevant.