

**Guidelines
for Laboratory Accreditation
according to EN ISO 15189**

Hellenic Accreditation System

ESYD G-CLINLAB

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INTRODUCTION

This Guideline refers to procedures required for Accreditation of Medical / Clinical Laboratories that apply, either approved standardized methods (CE IVD), which require verification by the Lab, or laboratory-developed tests (LDTs or else in-house methods) and modified approved methods, which require analytical validation and clinical verification.

The verification of the applied methods for each parameter, under accreditation, consists of the evaluation of specific analytical characteristics, with regard to the suitability of the method for fitness of purpose.

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1. TESTS PERFORMED ON AUTOMATED ANALYZERS

1.1 Quantitative tests

This category includes examinations such as: biochemical, immunochemical, immunological, nephelometric, haematological, etc.

1.1.1 Verification

Verification is performed, either by using commercial control samples (control samples), or by using CRM (Certified Reference Materials), or mixtures obtained by mixing patient samples (pooled samples), at two concentration levels at least, within and above the reference range (normal - abnormal) or within and below the reference range (normal - sub normal), according to the critical medical decision limits of the parameter measured.

Trueness: is calculated by recovery experiments (mixing with control sample or calibrator with different concentrations) and measuring samples of known concentration six (6) times at least, within the same day. The %recovery (R%) and the %error (bias) are calculated respectively. It is supplemented and monitored by participation in proficiency testing schemes.

Repeatability: At least six (6) measurements of the same control sample, divided into aliquots or a pooled sample, divided into aliquots. The measurements should cover the entire duration of the daily operation of the laboratory. A 15 min interval at least, is required between the six measurements. The CV_r% of the measurements is calculated.

Intermediate precision/intra-laboratory reproducibility: At least six (6) measurements of the same control sample under different conditions, e.g. different days and using at least two different batches of the analyte reagents. The results of the internal quality control charts (QC) may also be used. The CV_R% of the measurements is calculated.

Limit of Detection (LOD) and Limit of Quantification (LOQ), are calculated when they are critical for drawing conclusions from the parameter examined. The characteristics are calculated by sextet measurement of a diluted sample near the LOQ stated by the manufacturer, within the same day. Particularly, in the case of immunochemical techniques, imprecision plots (SD versus concentration diagram) could also be used.

1.1.2 Estimation of Uncertainty

The components of the uncertainty budget are estimated as:

Type A: By the standard deviation of at least six (6) measurements under conditions of laboratory reproducibility, at all concentration levels tested during verification and the standard deviation of six (6) measurements of each parameter of the recovery experiments (see Trueness).

Type B: Appraisal of sources of uncertainty for the calibrators used by the automated analyzer. In the case of a calibrator being reconstituted, the contribution of the uncertainty of the volumetric equipment used can also be estimated. Generally, all sources of type B uncertainty are recorded and advice is given in order to restrict their contribution to the final result (equipment, sampling, sample transportation, pre-analytical sample preparation etc.).

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The combined uncertainty is calculated by the law of uncertainty propagation. To assess the suitability of the application of the method by the laboratory, the expanded uncertainty is compared with the values provided by the manufacturer of the device and / or the values mentioned in the literature.

NOTE: The mixing process and the process of calculation of recovery can not be applied in the cases of free forms of parameters, such as fT3, fT4. In order to calculate the accuracy of these parameters during verification, only analysis of control samples and the results of participation in interlaboratory comparison schemes (external quality control) are used.

1.1.3 Quality Assurance

Internal Quality Control

Internal quality control is always performed for all tests and is based on the manufacturer's instructions, methodology, biological and analytical variation.

External Quality Control

Annual participation in appropriate proficiency testing schemes (PTs) is required for all tests included in the laboratory accreditation scope.

For clinical tests applied to matrices apart from peripheral blood (e.g. urine or CSF), at least one participation in a suitable interlaboratory proficiency scheme is required for those matrices, within the four-year accreditation cycle.

In case of calculated parameters (e.g. LDL) participation in a PT scheme is not required provided that there is participation for the parameters used for the calculation, having set an acceptable z-score, ranging from -2 to 2 and within the range of concentrations that the relative equation applies.

1.2 Qualitative methods

This category includes methods with a qualitative result, i.e. detectable or undetectable, positive or negative.

1.2.1 Verification

Verification of qualitative methods is performed, either by using commercial control samples, or by using Certified Reference Materials (CRM), or mixtures obtained by mixing patient samples (pooled samples), at different concentration levels, with regard to the levels of medical decisions.

The verification is achieved by determining the following relevant performance characteristics:

Trueness: At least six (6) negative and six (6) positive samples with a known value should be analysed. Trueness is calculated from the ratio [true positive + true negative] / [total number of samples]. In case the kit contains both a negative and a positive control sample, these could be analyzed in duplicate for six (6) days. In case of semi-quantitative methods with a qualitative final expression, samples with a known value should be analysed (at different concentration levels) and the % error (bias) or the % recovery should be determined.

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Repeatability: A control sample (positive and negative) or a pooled sample (positive and negative), divided into aliquots, should be measured for six (6) times. The measurements should cover the entire duration of the daily operation of the laboratory. Between measurements, a time interval of at least 15 min is required.

Intermediate precision/intra-laboratory reproducibility: For purely qualitative tests, analysis of positive and negative samples by different analysts during six (6) different days is required. In the case of semi-quantitative methods with an ultimate qualitative result, analysis of samples (known or unknown) between different dates is required as well as calculation of the coefficient of variation (CV%) of the measurements. Measurements have to be made at concentration levels with clinical significance. Trueness experiments could also be used.

Limit of detection (LOD): For purely qualitative tests, analysis of serial dilutions of a positive control material is required and the LOD is defined as the concentration level above which the sample is reliably classified as positive (through repeated measurements). In case of semi-quantitative methods with an ultimate qualitative result, standards or low concentration positive samples is required, as well as calculation of the standard deviation (SD) of multiple measurements (e.g. 6). The detection limit is 3.3 times the SD. It may, also, be necessary to determine the Cut Off Value (COV) and the area around it for which the outcome is uncertain (Unreliability Region, from the level with False Positive Rate to level with False Negative Rate).

1.2.2 Estimation of Uncertainty

Qualitative tests belong to the category of tests where strict metrological and statistical calculations of uncertainty cannot be implemented. For semi-quantitative methods which result in a qualitative output the estimation of uncertainty is required (as in § 1.1.2).

1.2.3 Quality Assurance

Internal Quality Control

Internal quality control for the qualitative tests is performed by analyzing positive and negative control samples (controls), before analyzing patient samples. Moreover, in accordance with the quality standards used (e.g. CLSI), these procedures should, where appropriate, be incorporated into the daily laboratory workflow.

External Quality Control

The requirements of § 1.1.3 apply.

NOTE: In the case of accrediting more than one automated analyzers to perform the same tests, documentation of equivalence of results is required with analysis of control samples or real samples, in a wide concentration range and statistical elaboration (t-test and correlation). Also, the analysis of proficiency testing scheme samples should demonstrate the equivalence of analyzers.

2. MICROBIOLOGICAL TESTS

The validation of microbiological test methods should reflect actual test conditions. This may be achieved by using naturally contaminated products or products spiked with a predetermined level of contaminating organisms. The analyst should be aware that the addition of contaminating organisms to a matrix only mimics in a superficial way the presence of the naturally occurring contaminants. However, it is often the best and only solution available. The extent of validation necessary will depend on the method and the application. The laboratory shall validate standard methods applied to matrices not specified in the standard procedure.

The methods used should be appropriate for the tests carried out in the laboratory, according to the requirements of clinical evaluation (community patients, hospital patients, etc.), which are indicated by the manufacturers of analyzers and / or rely on methods established by international scientific organizations.

Beyond the initial confirmation of the correct application of the method, at least once per year, re-evaluation of the efficiency of laboratories to perform specific methods correctly is performed. The annual review of the Laboratory's efficiency is conducted through analysis and systematic evaluation of all data from internal and external quality schemes.

2.1 Quantitative and semi-quantitative tests

2.1.1 Verification

Trueness: Assessment of trueness is achieved by using reference materials and results of participation in external quality assurance schemes.

Repeatability: In order to check repeatability at least six (6) measurements per organism are required, depending on the difficulty and the inherent danger of the microorganism and the substrate in two to three levels of inoculated samples. The standard deviation and coefficient of variation ($CV_r\%$) of measurements is estimated.

Intermediate precision / reproducibility:

First method: Use of two to three levels of inoculated samples (spiked samples). At least ten measurements are made for each sample at different dates (if the sample is stable) or with different operators or different reagents.

Second method: From quality control charts (control charts) over a one year period.

Third method: From factorial experimental design of multiple measurements of the same sample in different experimental conditions. One - way ANOVA application may be used for calculating the SD_R .

The precision of a method is satisfactory if the relative standard deviation (CV%) is less than 10% or less than the permissible limit specified by the relevant literature.

Limit of detection (LOD): The detection limit is determined by examining artificially contaminated samples, which are the product of successive decimal dilutions of the tested microorganism. The initial number of cfu should be known. The samples analyzed by laboratory analysts under reproducibility conditions are at least six (6). The smallest number of microorganisms that can be detected is the detection limit of the method. The number of samples to be analyzed depends on the microorganism and the substrates with a justification for the number by the laboratory.

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2.1.2 Estimation of Uncertainty

The estimation of uncertainty budget is based on reproducibility data and on elements of systematic errors (bias), as determined by the results of proficiency testing schemes. For estimation of the uncertainty, examination of at least ten (10) samples is required.

The desired homogeneity of the sample should be a specific element of evaluation, depending on the biological material, in relation with the type and number of microorganisms it contains. A comprehensible protocol for sample size and processing (suitable / unsuitable sample) should be used for this parameter.

Analysis of 10 different samples (i) (real or spiked) at various levels, in both conditions of reproducibility A and B (e.g. two analysts, different reagent lots etc)
Measurement of the number of microorganisms/ cfuXiA and XiB
Calculating $\log_{10}(XiA)$ and $\log_{10}(XiB)$

2.2. Qualitative tests

2.2.1 Verification

Repeatability / Intermediate precision / laboratory reproducibility: analysis of at least six (6) positive and negative samples per microorganism and substrate is required from the laboratory analysts. The number of samples to be analyzed depends on microorganisms and substrates with a justification for the numbers from the laboratory.

Sensitivity and Specificity: The sensitivity is calculated from the ratio: true positive / total positive results and the specificity from the ratio: true negative results / total negative results.

Limit of detection (LOD): The detection limit of the method is determined by examining artificially contaminated samples, which are the product of successive decimal dilutions of the microorganism examined. The samples analyzed are at least six (6), from the laboratory analysts, under conditions of intralaboratory reproducibility. The smallest number of microorganisms that can be detected is the detection limit of the method. The number of samples to be analyzed depends on the microorganism and the substrates with a justification of the number by the laboratory. The percentage of "positive" results should not deviate from the approved rate of sensitivity of the method, which is derived from the validation studies of the method or the relevant literature.

2.2.2 Quality Assurance

Internal Quality Control

For microbiological tests, Internal Quality Control should include specific reference materials, naturally or artificially contaminated samples. The frequency of these tests is determined according to the type of examination, the frequency of execution and the daily program of the Laboratory.

External Quality Control

Participation should be annually or more frequent, in accordance with the program of the provider of the proficiency testing scheme and for all tests, in an approved

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interlaboratory program (Proficiency Testing) or in the case of absence of an approved interlaboratory program in an interlaboratory comparison scheme, whose provider complies with specific requirements and is evaluated based on these requirements by participants (ESYD PDI).

NOTE: Verification, uncertainty assessment and quality control of microscopy in microbiology (fresh samples of biological fluids and exudates, stained preparations) apply as mentioned in § 5.

3. MOLECULAR TESTS

3.1 Verification of CE IVD qualitative tests

Trueness: Assessment of trueness is achieved by using control samples provided commercially, reference materials, results from interlaboratory schemes and recovery experiments.

In multiparametric methodologies where more than one microorganisms / genes / mutations / polymorphisms are detected, it is not always easy to control all of them (e.g. 32 mutations in CFTR), especially if they are many. However, the laboratory must obtain a satisfactory panel of control samples with e.g. at least the most frequent mutations / polymorphisms detected in the Greek population in order to verify the trueness of the kit used.

Repeatability/Reproducibility: In qualitative molecular methods, repeatability has to be assessed with three (3) measurements of control samples (as the ones mentioned above) and reproducibility with six (6) measurements under different conditions.

Limit of Detection (LOD): In the case of determination of parameters with clinical significance, confirming the Limit of Detection is required and is achieved by analyzing five (5) samples (control or reference material provided by the manufacturer) diluted close to LOD (up to +20% LOD).

3.2 Verification of CE IVD quantitative tests

In addition to the requirements of § 3.1, the calibration curve should be checked three (3) times, by using at least 4 calibration points (in duplicate), if calibrators are available.

3.3 Validation of laboratory-developed internal (in-house) tests

In-house methodologies are validated the same way CE-IVD methodologies are validated by their manufacturers. In the case of accreditation according to ISO 15189, in addition to analytical validation, clinical validation is also required (diagnostic sensitivity and specificity, NPV, PPV, clinical utility).

For Research-use-only tests the laboratory may be accredited according to ISO 17025, without the need for clinical validation.

Requirements regarding the validation of in-house laboratory developed methods are the following:

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Trueness: Assessment of trueness is achieved either by using control samples commercially provided or reference materials, results from proficiency testing schemes and recovery experiments.

Furthermore, trueness is checked by:

- *Method comparison*: For in-house methods, it is required to compare the method with a CE-IVD Kit (or when absent, with another commercial kit or other established methodology) with 40 samples (e.g. 20 negative and 20 positive in qualitative parameters, 10 negative and 30 positive with a broad range of values in quantitative parameters) and appropriate statistical analysis.

In multiparametric methodologies where more than one microorganism / gene / mutation / polymorphism is detected, the laboratory must have a complete panel of control samples in order to validate the accuracy of the method used.

Repeatability/ Intermediate precision/intralaboratory reproducibility: At least ten (10) measurements of control samples in at least two levels (negative / weakly positive, 2-3 x LOD) on different days and using different lots of reagents. The CV% of the measurements is calculated (it can be drawn from control charts within a period of 3 or 6 months).

Limit of Detection (LOD): Validation of LOD is calculated by applying Probit Analysis at five concentration levels of the reference material, around the LOD (each level with 8-10 samples). The verification of LOD should be done with samples at -20% of LOD and +20% of LOD (at least 5 times). For multiparametric methodologies, the process should be repeated for each detected parameter.

Limit of quantification (LOQ) in quantitative methods: the point where a satisfactory CV% (e.g. 20%) is achieved.

Linearity and Measuring Range for quantitative methods: For an in-house Q-PCR methodology able to measure in the range of 10 log units, using at least 7 points (in triplicate) by diluting appropriate reference material is necessary for obtaining the standard curve (n = 5) and performing linearity check (dilutions shall cover at least 5 log units).

Analytical Specificity: check with electrophoresis and DNA Sequencing the obtained PCR product (and T_m in Q-PCR), check for interfering substances that could inhibit or block the measurement (e.g. haemoglobin, heparin, etc.), in Molecular Microbiology check for the presence of genetically-similar organisms or organisms that are often found in the samples analyzed in the laboratory, in Molecular Biology/Genetics additional check for pseudo genes or homologous regions.

3. 4 Estimation of Uncertainty

As in § 1.1.2

3. 5 Quality Assurance

Internal Quality Control

- In conventional / Q-PCR: always use a blank (no DNA), a negative and a positive control (in molecular microbiology and in somatic mutation detection, a weak positive shall be used in place of the positive, e.g. 2-3 x LOD), in Molecular Genetics at least two control samples shall be used: blank and mutant.

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- For high complexity tests (e.g. microarrays) where additional method or DNA isolation controls exist, the laboratory should use one positive or negative control sample either per kit of 20-40 samples or at least once a month, for small number of samples.

External Quality Control

For Molecular Diagnostics laboratories, participation in external quality assessments for each category of tests is done according to the following:

- For initial assessment and at any extension of the scope of accreditation, the laboratory must have successful results of interlaboratory comparisons for all laboratory tests for which accreditation is requested. The laboratory could then make groups according to parameter and technique/equipment and rotate on a yearly basis. Within the four year accreditation cycle, the full scope of accreditation should be covered (matrices/tests/techniques).
- In the molecular detection of pathogens or somatic mutations, external quality control shall be more demanding in order to check the sensitivity of the method (to include rare strains or very dilute samples). In the molecular detection of inherited mutations in genes where multiple mutations exist, external quality control is recommended to include the range of all mutations appearing in the Laboratory Accreditation Scope (and not just specific mutations) or combinations of them.
- After the first accreditation cycle (4 years) and on condition that the laboratory has demonstrated excellent results in all the previous External Quality Assessments, the frequency of interlaboratory comparisons may be reduced (once every 2 years) per group of parameters and/or techniques/equipment, after evaluation of laboratory's performance by ESYD and the consent of the assessment team.

4. FLOW CYTOMETRY

4.1 Quantitative Tests

Two standardized flow cytometry methods exist, both belonging to the calculation of immunologically identified cell populations by flow cytometry (CLSI Former NCCLS H 42 - A the 2nd (vol 27 No 16) :

1. Calculation of lymphocyte subpopulations.
2. Calculation of CD 34 + hematopoietic progenitor cells.

4.1.1 Verification

All the applied methods must be verified on existing equipment in the laboratory premises. The verification is performed by using commercial control samples of fixed whole blood (Control samples) at least at two concentration levels, wherever available. The verification of the methods implemented for each parameter under accreditation, consists of the calculation of the following analytical characteristics:

Trueness: It is evaluated by participation in interlaboratory programs.

Repeatability: At least six (6) measurements of the same control sample. The CV% of the measurements is calculated. Alternatively, three (3) samples may be analyzed, three (3) times each, at respective time intervals.

Intermediate precision / reproducibility : At least six (6) measurements of the same control sample on different days. The CV% of the measurements is calculated (it can be drawn from the results of control charts within 3 or 6 months).

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Limit of Detection (LOD) and Limit of Quantification (LOQ) , wherever it is crucial to draw conclusions from the parameter examined. The parameters are calculated by sextet measurement of a diluted sample at a concentration similar to the within day detection limit stated by the manufacturer.

Determination of reference values : Initially, the values given by the manufacturer are accepted, but it is advisable to check them with the existing healthy population (number of samples 20). In the case of differences, the values found by the laboratory should be used.

4 .1.2 Estimation of Uncertainty

As § 1.1.2

4.1.3 Quality Assurance

It is required to use one sample of internal quality control weekly (fixed blood sample for method 1, an appropriate sample supplied by the manufacturers for method 2). In method 1 all major lymphocyte subpopulations shall be determined (CD 3 +, CD 3 + CD 4 +, CD 3 + CD 8 +, CD 19 +, CD 3 - CD 16/56 +)

Internal Quality Control

Internal Quality control includes control of equipment and control of methods. More specifically, it is required:

A. Daily use (or at each opening of the instrument) of alignment beads (type 1) according to the manufacturer's instructions. The allowable limits have been set by the technician during the initial installation of the instrument, usually for an alignment with CV <2.5%. Storage of corresponding Levy Jennings diagrams on the flow cytometer is required.

B. Weekly use of beads for the confirmation of the repeatability of measurement for each fluorescence (type 2) according to the manufacturer's instructions. Storage of corresponding Levy Jennings diagrams on the flow cytometer is required.

C. Annually (or after each major repair) use of validation beads for instrument alignment and calculation of the response of the instrument to the fluorescence signals with special beads with different fluorescence intensities (output of a linear calibration curve for each fluorescence detector).

D. Control of fluorescence compensation with suitable beads or appropriate cells. It is suggested that the testing is done when setting up a new protocol and in the case of significant change of PMTs and in general of the instrument's settings.

E. At least weekly or for every 20 patient samples use of commercial-fixed blood sample or corresponding commercial control sample for counting CD 34 + cells as an internal quality control sample. Construction of Levy Jennings diagrams is required.

External Quality Control

Participation in appropriate Proficiency Testing Schemes, with at least 4 samples per year for both the above mentioned tests, is required.

4 .2 Qualitative tests

The tests concerning the certification panels of acute leukaemia and lymph proliferative syndromes can be considered as qualitative, since each index is required to be classified as positive or negative.

The requirements of § 1.2 apply.

5. MICROSCOPY

This category includes microscopical haematological, microbiological, cytological and histopathological tests.

5.1 Verification

The verification of the above tests is achieved by determining the diagnostic accuracy and diagnostic reproducibility -repeatability.

Diagnostic accuracy: is determined by specific statistical parameters such as specificity, sensitivity, positive and negative predictive value. These parameters are a measure of the reliability of the diagnosis and may vary per material and per laboratory, but should fall within levels acceptable by the international literature.

The calculation of sensitivity, specificity and the ratio of false-negative cytological results are performed by using the histological examination as the reference method. The calculation of the positive predictive value (PPV), and the negative predictive value of cytology results (NPV) is performed by using the histological examination as the reference method.

Diagnostic Reproducibility-repeatability: It is estimated with random retesting by the same or different doctors of a representative number of samples corresponding to the workload of the laboratory (measurement of inter-observative and intra-observative agreement - κ statistical parameter)

The guidelines of authoritative international scientific societies are also taken into account.

5.2 Estimation of Uncertainty

Microscopy belongs to a category of tests, where strict metrological and statistical calculations of uncertainty can not apply.

The estimation of uncertainty is based on repeatability and reproducibility data and primarily on data of systematic bias as determined by the results of proficiency testing or interlaboratory comparison schemes.

The guidelines of authoritative international scientific societies are also taken into account.

5.3 QUALITY ASSURANCE

Internal Quality Control

The following internal quality control measures are required:

a) Implementation of regular medical Conferences. Periodic meetings of clinicians with personnel from the Laboratories Division, where all clinical, imaging, cytological, histopathological, microscopic and other relevant data are discussed, critically analyzed and correlated.

b) Random rescreening: The laboratory staff reviews a representative number of samples, proportional to the laboratory workload (measurement of inter-observative and intra-observative agreement - κ statistical parameter).

c) Comparison between biopsy and cytological results (calculation of sensitivity, specificity, positive and negative predictive value using ROC curve)

d) comparison of histological-cytological diagnosis with the results of other ancillary diagnostic techniques such as electron microscopy, immunocytochemistry, molecular cytology, image analysis, flow cytometry, cytogenetic tests.

The guidelines of authoritative international scientific societies are also taken into account.

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The participation of the Laboratory in proficiency testing programs should be at least annual, ensuring the participation of all members of the Laboratory.

For the initial evaluation and extension of the Laboratory accreditation Scope, the participation of all the examinations under accreditation is required, while for maintaining the accreditation the Laboratory should cover all the examination under the accreditation scope within the 4-year period.

The guidelines of authoritative international scientific societies are also taken into account.

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6. REFERENCES

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7. USEFUL WEBSITES

ELOT: <http://www.elot.gr/>

EPTIS: <http://www.eptis.bam.de/>

ISO: <http://www.iso.org/iso/home.html>

Eurogentest: <http://www.eurogentest.org/>

IFCC: <http://www.ifcc.org/>

CLSI: <http://www.clsi.org/>

CAP: <http://www.cap.org/apps/cap.portal>