Guidelines of the German Medical Association on quality assurance in medical laboratory testing

Abstract

The Richtlinie der Bundesärztekammer zur Qualitätssicherung laboratoriumsmedizinischer Untersuchungen (Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations – Rili-BAEK) has been completed and published in a revised version in 2014 (Deutsches Ärzteblatt, Jg. 111, Heft 38, 19. September 2014, A1583-A1618).

The development of quality management regulations for medical laboratories in Germany already started in 1971 with the publication of the first "Guidelines of the German Medical Association for Statistical Quality Control and Proficiency Testing in the Field of Medical Science" (Richtlinien der Bundesärztekammer zur Durchführung der statistischen Qualitätskontrolle und von Ringversuchen im Bereich der Heilkunde; Deutsches Ärzteblatt 1971, 30, 2228ff.) These guidelines were afterwards modified and developed further in the years 1971, 1988, 2002, and finally in 2008. All these guidelines including the one implemented in 2008 primarily focused on the assessment of process quality through internal and external quality control. Historically, parameters with chemical and biochemical measurands and methods from serum and plasma were addressed first, but over time, the regulations also tackled aspects of necessary technical capabilities and the prerequisites for high quality of analytic results in medical laboratories. In a further step, quality regulations for the analysis of other sample materials such as whole blood, CSF, sperm, and urine were included. Finally most other important areas of laboratory medicine like immune hematology, the whole field of microbiology with direct and indirect detection of pathogens and molecular biology including moleculargenetic and cytogenetic examination were integrated in the currently implied in the guidelines of 2014.

The newest version of the Guideline implemented in 2014, which is now mandatory in Germany for all laboratories performing medical laboratory examinations of human specimens, for the first time realizes a total quality management effort for medical laboratories according to current national and international standards including the quality of analytical and structural processes. Therefore, today medical laboratories have to lay open all parts of their analytical processes including the structure of the pre-analytic, analytic and post-analytic phases. Moreover, the Guideline also covers analytical methods for which so far no minimum quality standards have been defined before. This makes the current Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations an important step forward towards a significant improvement of quality in laboratory medicine.

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Extended title

Guidelines of the German Medical Association on quality assurance in medical laboratory testing

in accordance with the resolution passed by the Executive Board of the German Medical Association on 23 November 2007, published in Deutsches Ärzteblatt, 105 (7), 15 February 2008, pages A 341-355 [1]

most recently modified/amended by resolution of the Executive Board of the German Medical Association on 10-11 April 2014, published in Deutsches Ärzteblatt 111 (38), 19 September 2014, pages A 1583-1618 [2].

A Basic requirements for quality assurance in medical laboratory testing

1 Scope

These guidelines regulate quality assurance for medical laboratory testing in the field of medicine.
The basic requirements described in Section A of the guidelines shall apply to all medical laboratory testing, as shall the specific requirements for which a special Part B is has been provided.

2 Objective

The objective of the system described in these guidelines is to ensure quality of the testing conducted in medical laboratories. These guidelines seek to ensure, in particular, that:

- Influencing factors and interference factors during the pre-analytical phase are minimised
- Medical laboratory testing is conducted properly and factors interfering with the results are identified and minimised
- Results are correctly categorised and documented and a report is generated.

3 Terminology

Important terminology is defined below as it is used in these guidelines.
The definitions take into account national and international standards and terminology used in metrology; however, they are to be seen in context with these guidelines, so that there may be deviations from the aforementioned terminologies.

Accuracy

The degree of agreement between the mean of the measured values obtained from a control period and the target value.
This is usually quantified numerically using the systematic error of measurement, which is inversely correlated with accuracy.

Analyte

The constituent to be determined by the analysis.

Audit

Systematic, documented procedure to determine the extent to which established audit criteria have been met.

Central laboratory

Central laboratory means that the medical laboratory analyses are usually performed for the entire institution (e.g. hospital) by one single organizational unit ("medical laboratory") and by appropriately qualified technical personnel. The central laboratory can be an external laboratory managed by another legal entity/operator.

Control strain

A reference culture or reference strain of microorganisms, viruses and cells which is directly obtained from an approved culture collection or from a national reference laboratory or, where appropriate, which is adequately characterised using suitable methods (e.g. characterisation as a round robin testing isolate, through sequencing, through mass spectrometry). When using normative processes (e.g. sensitivity testing), corresponding normative control strains are to be used.

Device

Technical object or technical apparatus used to process, analyse or manufacture something.

Document

Document includes information and storage media. For example, records, instructions (including quality regulations), method descriptions, specifications, calibration tables, reference ranges, drawings, reports, findings, legal provisions or standards.

Effectiveness

The effectiveness of a measurement method is described by the criteria of analytical sensitivity, analytical specificity, measurement precision, accuracy expressed in terms of systematic error of measurement, reproducibility expressed as random error, repeatability, measuring range, theoretical and practical limits of detection, and linearity.

Equipment

Equipment includes devices, reagents, control samples, reference materials, consumables and analysis systems.

Error limits

Deviation limits of measurements as defined by these guidelines. If these values are exceeded, the deviations are considered errors and require corrective measures.

Error of measurement, random (imprecision)

The difference of a measured value from the mean, the (arithmetic) mean being calculated from an indefinite number of repeated measurements of the same meas-

ured parameter. The random error of measurement is approximated by the difference between the value of the single measurement and the arithmetic mean of the measured values.

Error of measurement, root mean square of the

The root mean square of the error of measurement is the degree of variance of the measured values from the (conventional) true value of the measured parameter (here, the target value of the control sample). It is calculated using the formula

$$\Delta = \sqrt{\frac{1}{n}\sum_{i=1}^{n}(x_i - x_0)^2}$$

where
Δ represents the root mean square of the error of measurement
x_0 represents the true value of the measured parameter; here, the target value of the control sample
x_i represents the value of single measurement
n is the number of individual measurements used for calculation

The root mean square of the error of measurement is mathematically related to the systematic error of measurement and the empirical standard deviation of a random sample

$$\Delta = \sqrt{\frac{n-1}{n}\,s^2 + \delta^2}$$

where
s represents the empirical standard deviation of a random sample
δ represents the systematic error of measurement

The relative root mean square of the error of measurement is calculated by dividing Δ by the target value x_0.

Error of measurement, systematic (inaccuracy)

Arithmetic mean, which is calculated from an arbitrary number of repeated measurements of a parameter, minus the true value of the measured parameter. The systematic error of measurement δ of a measurement method is estimated by taking the difference between the arithmetic mean $\bar{x}$, calculated from an appropriate number of repeated measurements, and the target value x_0, e.g.

$$\delta = \bar{x} - x_0$$

The relative systematic error of measurement is calculated by dividing δ by the target value x_0.

Influencing factors

Influencing factors are unique to the patient being examined. These are changes in the composition of bodily fluids as a result of illness or defects (diagnostically relevant) or other biological phenomena (diagnostically irrelevant). They reflect the conditions within the patient.

Interfering factors

Interfering factors have an effect on medical laboratory analyses. They interfere with the measurement methods and thus lead to changes in the results of the analysis. They do not represent the patient's status.

Laboratory, medical

A medical laboratory as defined by these guidelines means, depending on the context,

- a room, a part of a room or multiple rooms, in which medical laboratory testing is performed (spatial definition)
- a person under whose responsibility medical laboratory testing is performed (personnel definition)
- a functional or organisational unit (organisational definition).

Laboratory testing, point of care

Point-of-care laboratory testing includes medical laboratory analyses which can be performed directly as single measurements without sample preparation.
An important criterion for point-of-care laboratory testing is the immediate communication of therapeutic recommendations based on the laboratory analysis.

Location

Location is the geographic location (postal address) of a company or an institution where medical laboratory testing is performed.

Measurement

Sum of all actions involved in determining a measured value.

Measurement error

The difference between a measured value and the true value of the measured parameter. To estimate the error of measurement, the difference between the measured value of a control sample and the target value of this control sample is used as part of quality assurance of medical laboratory testing.
The relative error of measurement is calculated by dividing the error of measurement by the target value.

Measurement method

General description of the logical steps of action required to perform a measurement.

Measurement parameter

The particular parameter that is to be measured.

Measurement procedure

All of the detailed actions involved in performing particular measurements according to an approved measurement method.

Organisational unit

An organisational unit is every distinct section of a medical institution (e.g. the central laboratory or another subunit of the hospital) where medical laboratory testing is performed. It is characterised by:

- a designated range of users (doctors, nurses),
- a range of workstations/measurement devices assigned solely to this unit and
- operation of the workstations only by the designated users.

Pre-analytics

Pre-analytics include all steps prior to the actual measurement:

- collection of sample material
- transport and storage of the specimen or sample material
- assessment of the specimen or sample material
- preparation of samples (i.e. separation of corpuscular components by centrifugation).

Precision

In the context of these guidelines, precision refers to reproducibility. It expresses the extent of the reciprocal approximation of measurement values of consecutive measurements of the same measurement parameter when performed under varying measurement conditions (e.g. technician running the test, time, reagent deterioration). Precision is usually quantified by the statistical measures of the imprecision of measurements “standard deviation” and “relative standard deviation (coefficient of variation)” which are inversely proportional to precision.

Precision of measurement

Degree of agreement between the measured value and the true value of the measurement parameter. The precision of measurement of a measurement parameter cannot be given as a numerical value; rather it has to be provided qualitatively, such as “sufficient” or “insufficient”.

Qualitative analysis

A qualitative medical laboratory analysis is used to determine a qualitative property. A property is qualitative when its values are assigned to a scale that does not contain distinct units (topological scale).
Nominal properties are qualitative properties whose values are not ordinally related (nominal scale): e.g. detectable, not detectable.
Ordinal properties are qualitative properties whose values are ordinally related (ordinal scale): e.g. titre level, + to +++, indication of a range of values, pH value on a test strip.
Crucial for assigning a medical laboratory analysis to parts B1 or B2 is how the results are reported (scale of measurement).

Quality management

Comprehensive objectives and goals of a medical laboratory regarding quality, as formally expressed by management.

Quantitative analysis

Quantitative medical laboratory analysis is used to determine a quantitative property. A property is quantitative when its values are assigned to a scale that contains distinct units (metric or cardinal scale).
Crucial for assigning a medical laboratory analysis to parts B1 or B2 is how the results are reported (scale of measurement).
Reference measurement methods
Accurately tested measurement method whose results have a measurement uncertainty suitable for the intended use, such as for the evaluation of the accuracy of other measurement methods for the same measurement parameter, or for the characterisation of reference material.

Reference method value

A value measured using a reference measurement method.

Referral laboratory

A medical laboratory under the control of another legal entity/operator to which the specimen or sample material is transferred for testing.

Report

Summary of the findings.

Responsibility of the central laboratory

Responsibility in this case refers to guidance and supervision. With reference to point-of-care laboratory testing, “under the responsibility of the central laboratory” means that the central laboratory is monitoring the adherence to the guidelines for internal quality assurance of the individual organisational units of the institution. Responsibility does not mean that the control sample measure-

ments and their evaluation is conducted by employees of the central laboratory.

Results

Results are medically validated findings.

Sample material

The specimen used for the medical laboratory test, with or without prior sample preparation.

Sample preparation

Sample preparation includes any processes by the person collecting the sample or the person performing the test which alter the sample material prior to loading the sample into the measuring system or the analysis procedure. According to these guidelines, pipetting or adjusting the volume is not considered sample preparation. Similarly, if the collection system contains additives included by the manufacturer, this does not constitute sample preparation.

Set value

Target value determined without using a reference measurement method.

Specimen

Bodily fluids/material extracted from or excreted by a patient for analysis (e.g. venous blood, cerebrospinal fluid, aspirate, tissue, urine, stool), and possible additives, stored in an appropriate container.

Standard deviation, empirical

The empirical standard deviation of a random sample is a measure of the distribution of the measured values in relation to their mean. It is calculated by taking the square of the mean of the (estimated) random errors of measurement, meaning

$$s = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}(x_i - \bar{x})^2}$$

The coefficient of variation (CV) is obtained by dividing s by the mean $\bar{x}$.

Target value

The value of a control sample as declared by the manufacturer or by a reference institution.

Unit-of-use-reagents

Unit-of-use-reagents are reagents which are portioned for single measurements and are fully consumed after one analysis.

Validation of a measuring procedure

Objective verification that the requirements are met by the measurement method. Objective verifications can be done through observation, measurement, testing or other methods.

Validation of a testing result

Technical validation (assessment of the analytical quality), medical validation (plausibility), including, where applicable, an analysis of conformity with an orientation diagnosis made by the requestor (including conformation test).

4 Structure

4.1 Identification

Institutions in which medical laboratory testing is conducted must be legally identifiable.

4.2 Organisation

The body responsible and accountable for the execution of medical laboratory testing and the tasks must be clearly defined and documented in a comprehensible manner.

5 Resources

5.1 Management

The medical laboratory must be under the control of qualified management personnel. The management is responsible for professional, organisational and administrative tasks, training and further education, and consultation.

5.2 Personnel

Medical laboratory testing may only be performed by personnel qualified in accordance with legal regulations who are authorised to do so by Management.
There is to be a sufficient number of employees to cope with the volume of work.
Employees are to receive regular briefings and training sessions related to the specific field. These briefings and training sessions are to be documented.
New employee orientation and the introduction of employees to new analysis systems and medical laboratory testing procedures are to be regulated and documented identifying how and by whom they are to be performed.

Mandatory briefings and training sessions are to be documented.

5.3 Rooms and environmental conditions

5.3.1 Rooms are to be available for medical laboratory testing where the intended work can be performed without an adverse effect on the quality of the medical laboratory testing and the health and safety of the employees and the patients.
5.3.2 Environmental conditions that can affect the quality of the test results are to be identified, monitored, regulated and documented for medical laboratory testing.
5.3.3 Access and use of rooms and areas, whose condition can impact medical laboratory testing, are to be established and monitored.
5.3.4 Adequate space for storage and appropriate room conditions are to be ensured in order to maintain the integrity of testing material, stored microorganisms, cells, devices, reagents, lab materials, records, reports and other documents. Measures are to be taken to safeguard against unauthorized access.
5.3.5 Provisions are to be made which guarantee the timely availability of data. The integrity of the data is to be maintained and the data must be safeguarded against unauthorized access.

5.4 Equipment

5.4.1 The medical laboratory is to have the equipment necessary to perform its tasks. The requirements of these guidelines also apply to equipment that is used by the medical laboratory but not under its responsibility.
5.4.2 The medical laboratory is to have a procedure to regularly monitor the proper functioning of its devices, reagents and analysis systems and it is to implement this procedure. Maintenance is to be performed according to a written schedule.
5.4.3 Records are to be kept for each analysis system and device needed to perform medical laboratory testing which can impact the quality of this medical laboratory testing.
These records are to contain, at minimum:
(1) Name of system or device
(2) Name of the manufacturer, model and serial number or other form of identification
(3) Date of initial operation
(4) Instructions for use, operating instructions and other information from the manufacturer, or justification for why they are not available
(5) Functional test
(6) Maintenance deadlines and findings including date, time and type of inspection and other maintenance work
(7) Equipment outage, malfunctions, structural modifications and repairs showing date and time.
These records are to be kept for two years beyond the working life of the equipment and are to be easily accessible.

5.4.4 The devices and analysis systems may only be operated by authorised and trained members of staff. Instructions for operating and servicing the equipment are to be kept up-to-date and be accessible to the employees in the workplace.

6 Medical laboratory testing

6.1 Pre-analytical phase

6.1.1 The provider of the material to be tested is to be given a list of the laboratory analyses offered by the medical laboratory relevant to their purposes as well as a document stating the details of sample collection.
6.1.2 The medical laboratory is to provide professional advice regarding the analyses offered, including the test method to be selected, the type of specimen to be used and the assessment of test results.
6.1.3 The testing request form submitted by the provider of the material is to contain the following information:
(1) Identification of the patient – including gender and birthdate in the case of age and gender-specific measurement parameters
(2) Identification of the provider of the material and the recipient of the report if not identical
(3) Type of specimen and – if relevant – the anatomical site of collection and time of collection
(4) Requested tests
(5) Clinically relevant patient information required for the requested analysis.
6.1.4 Written instructions outlining the proper collection and handling of specimens are to be available to the persons responsible. These instructions are to be summarised in the document for collecting the specimen.
6.1.5 The document for collecting the specimen is to specifically contain the following:
(1) The list of the medical laboratory tests offered, or reference to this
(2) Instructions on
a) preparing the patient
b) completing the test application or the electronic request form
c) the required information about the patient
d) the type and quantity of the specimen to be collected
e) the specific time constraints for collecting, storing and transporting the specimen, if required
f) collecting the specimen, with a description of the containers for the specimen and all required additives
g) distinctively labelling the specimen
h) all of the measures that are to be taken between the time the specimen is collected and its arrival at the medical laboratory
(i) the period of time within which further medical laboratory tests can be requested
(3) Patient information and instructions regarding preparation measures for collecting the specimen and, if necessary, patient consent forms for collecting the specimen and for performing the medical laboratory tests

(4) Patient information regarding the self-collection of specimen and for the storage and transport of the self-collected specimen.
6.1.6 Criteria are to be established for rejecting medical laboratory tests.
6.1.7 The submitted specimen and portions thereof are to be clearly assigned to one patient. If this is not possible, they may not be processed by the medical laboratory. The provider of the material is to be notified and the incident is to be documented. If the specimen cannot be assigned beyond a doubt to one patient and a specimen of the same quality cannot be collected or was collected when the patient was in a critical condition, the medical laboratory shall decide, after consulting with the sender of the test material, if the requested medical laboratory tests should nevertheless be performed.
6.1.8 When the specimen arrives, the medical laboratory is to check whether there is any indication that a timely delivery has not occurred for the requested medical laboratory tests or whether the conditions established in the document governing the collection, handling, storage and transport of the specimen were not met. If such indications are identified, the medical laboratory is to decide whether the tests are to be performed despite this, or whether a new specimen is to be requested. This incident is to be documented.
6.1.9 If necessary, the medical laboratory is to have documented procedures in place covering the acceptance, labelling and processing of specimens, and the reporting of medical laboratory tests that are considered to be urgent.

6.2 Procedures for conducting medical laboratory tests

6.2.1 The medical laboratory may only use testing procedures that meet medical requirements.
6.2.2 The medical laboratory may only use validated testing procedures. It is to document the procedure used for validation and the results obtained.
6.2.3 All medical laboratory testing procedures are to be documented in procedural instructions. These instructions are to be written in such a way that they can be understood by medical laboratory staff. They are to be available at the workstations at all times.
The manufacturer's instructions for use and additional remarks as appropriate are deemed to be part of the procedural instructions.
Each procedural instruction is to contain the following – where applicable:
(1) Identification of the document
(2) Testing principle of the procedure used (methods)
(3) Individual steps of the procedure
(4) Calibration procedure as appropriate or as available
(5) Procedure used to calculate the result as appropriate or as available
(6) Required specimen (including the specimen container and the necessary additives)
(7) Required instruments, reagents, culture media and test systems
(8) Specification of the effectiveness off the testing procedure
(9) Information on possible interference and cross-reactivity
(10) Reference ranges for healthy patients
(11) Objective of the medical laboratory test (medical indication)
(12) Possible causes of deviating results
(13) Measures to be taken in the case of abnormal results
(14) Safety precautions
(15) Literature references.
6.2.4 If the medical laboratory modifies one of its analytical procedures so that the results, and thus the interpretation, change in a clinically significant way, the sender of the material is to be informed as soon as possible in writing.

6.3 Post-analytical phase

6.3.1 The results are to be technically validated and, taking into account the available clinical data, medically validated.
The medical laboratory is to have procedures in place for releasing the test results. These should include information about who may authorise the release of these results and who they may be issued to. The procedures are also to contain guidelines for the immediate issuance of reports to patients.
There must be documentation on which persons carried out the technical and medical validation.
6.3.2 The reports are to be easy to read and to contain at least the following information:
(1) Date – and if required – time the report was issued
(2) Identification of the patient
(3) Name or other means of identifying the sender of the material and – if required – their address; the address of the recipient of the report if not identical to that of the provider
(4) Name of the medical laboratory
(5) Date and time when the specimen arrived at the medical laboratory
(6) Date and time when the specimen was collected, if this information is available and important for interpreting the test results
(7) Type of specimen
(8) Name of the laboratory tests and the methods used, if the latter is important for interpreting the test results
(9) Test results and corresponding units as necessary
(10) Reference ranges or other remarks for interpreting the test results
(11) Identification of the person responsible for releasing the report.
6.3.3 If there is a possibility that the test result was affected by the condition of the specimen, this is to be stated in the report. If required, the report should state that the results are conditional.

6.3.4 The medical laboratory is to have written policies and procedures in place for subsequent amendments to reports. The changes are to be marked with the date, time and name of the person responsible for the changes. The original results are to remain accessible.
6.3.5 The medical laboratory is to have procedures in place for immediately notifying a physician (or other clinical personnel responsible for patient care) if test results exceed "alarming" or "critical" limits. This includes reports from referral laboratories.
6.3.6 Specimens and samples are to be stored in such a way that enables repeat or additional medical laboratory testing to be performed over a period of time established by the medical laboratory.

7 Quality management system

7.1 Quality management manual

7.1.1 The quality management system and the documentation used in the medical laboratory are to be compiled in a quality management manual. This quality management manual is to include or make reference to all procedures. Laboratory personnel are to be instructed on the use and practical application of the quality management manual and all referenced documents. The quality manual shall be kept up-to-date at all times.
The quality management manual must contain the following where applicable:
(1) Introduction: Description of the medical laboratory, its legal status and its main tasks
(2) Objectives and strategies: Description of the quality assurance policy
(3) Management: Description of their responsibilities and qualifications
(4) Employees:
a) Qualifications, briefings, training and further education
b) Health and safety
(5) Resources and partnerships:
a) Rooms
b) Equipment
c) Environmental conditions
d) Partnerships (referral laboratories, external service providers and suppliers)
e) Environmental issues
(6) Processes:
a) Procedures in accordance with the document for collecting the specimen
b) Testing procedures, handling equipment, reagents and other relevant consumables, validation of the testing procedures
c) Ensuring the analytical quality of the testing procedures through internal and external quality assurance and regular discussions about the results of the quality assurance
d) Post-analytical procedures and drawing up and communicating reports
e) Technical validation and medical validation of the test results
f) Document control procedure
g) Keeping, storing and archiving records
h) Dealing with complaints
i) Determining errors and corrective measures
j) Preventative measures
k) Communication and other interaction especially with patients, medical personnel, referral laboratories
l) Internal audits.
7.1.2 If the medical laboratory is a part of an organisation which already has a quality management system in place, it is not necessary to have a separate quality manual for the medical laboratory provided the corresponding section in the organisation's quality management manual contains requirements similar to the ones contained in these guidelines. The same applies to Sections 7.2 and 7.3 below.

7.2 Document handling

The medical laboratory is to define, document and maintain procedures for the handling of all quality assurance documents and information (internal and external). A copy of each version of these documents is to be stored for future reference. Management is to establish the archive period, taking legal requirements into consideration. A procedure is to be introduced which guarantees that only the current version of the documents is accessible at the place where they are being used.

7.3 Resolving complaints

The medical laboratory is to establish and implement a procedure for the documentation and handling of complaints. Records documenting the complaints and the investigation, as well as prevention and corrective measures taken by the medical laboratory, are to be kept and maintained.

7.4 Tests in referral laboratories

7.4.1 The medical laboratory is to keep a list of all referral laboratories it commissions. All medical laboratory tests sent to a referral laboratory must be documented.
7.4.2 The commissioning medical laboratory is responsible for ensuring that the original provider of the testing material receives the test results and findings from the referral laboratory.
7.4.3 When hiring referral laboratories outside the scope of these guidelines, the commissioning medical laboratory is to ensure that the referral laboratory possesses the required competencies and that a similar quality management system is in place.

7.5 Nonconformities

The medical laboratory is to define and apply a procedure for corrective measures for non-conforming test results.

Management staff must specifically ensure that:
(1) Personnel responsible for problem resolution are named
(2) The medical significance of the incorrect result is considered and, if necessary, the sender of the testing material is informed thereof
(3) Tests are halted and reports are withheld as necessary
(4) Corrective action is taken immediately
(5) Already-released test results are recalled or the recipient is appropriately informed of the error
(6) The person responsible for the recalling of the test results is designated
(7) Causes and the corrective measures are documented
(8) The success of any corrective action taken is verified in order to ensure that all identified nonconformities have been eliminated.
The records documenting the identified nonconformities and the corrective measures are to be kept for 2 years.

8 Internal and external quality assurance

8.1 A control system is to be used for internal quality assurance in the medical laboratory which is in line with the present state-of-the-art in science and technology and the procedures described in the B Sections of these guidelines.
8.2 External quality assurance for the medical laboratory is to be performed by participating regularly in round robin tests in accordance with the procedures described in B Sections of these guidelines.

B Special guidelines

B 1 Quantitative medical laboratory testing

1 Principles of quality assurance

(1) Section B1 specifies the minimum requirements that are needed to assess the quality of the quantitative results of medical laboratory tests. These minimum requirements include internal and external quality assurance.
(2) All of the quantitative tests performed by the medical laboratory are subject to internal quality assurance. If several instruments or workstations are used to perform a test, internal quality assurance is to be performed on each of these instruments or workstations.
(3) In addition, all measurement parameters listed in Table B 1a–c of this section are subject to external quality assurance.
(4) The measurement parameters in Table B 1a–c are listed alphabetically based on the type of specimen. The criteria used for including a measurement parameter in the table are, specifically, the frequency of the test and its medical significance based on current scientific knowledge. Error limits, as listed in the table are determined based on medical requirements and current state of analytical technology. Table is continuously updated.
(5) These guidelines do not apply to chamber counting of corpuscular elements of bodily fluids, determining the blood sedimentation rate or analysing pH test strips.

2 Quality assurance procedures

2.1 Internal quality assurance

2.1.1 Procedures

(1) The specifications of the manufacturer are to be observed with regard to the type and frequency of internal quality assurance. Irrespective of this, internal quality assurance is to be performed in accordance with Paragraphs (2) and (4).
(2) A single measurement of the control sample is to be performed at the start of the measuring procedure.
(3) On days when a measuring procedure is used to analyse patient samples, a single measurement of a control sample is to be taken at least twice within a 24 hour period and, at the latest, within 16 hours.
(4) Further, a single measurement of the control sample is to be taken after every disruption to the measuring system.
Disruptions to the measuring system include:
a) Restarting the device after it has been switched off completely
b) Calibration by the user
c) Repair or maintenance work on devices relevant for the test results
d) Changing reagent lots
(5) The control samples must be as similar to the patient samples as possible. The control and calibration materials used in a measuring procedure may not be identical.
Control samples are to be used with known target values that are within the measurement ranges relevant for medical decisions.
If available, control samples with target values in at least two different concentration ranges are to be used alternately.

2.1.2 Evaluating the results of single measurements of control samples

(1) The results of the single measurements of the control samples are to be analysed as soon as the results are available. Analysis is based on the limits of error as listed in Table B 1a–c Column 3, otherwise on the basis of the laboratory's internal limits of error or on the ranges given by the producers of the control samples.
(2) If the single measurement of the control sample exceeds the error limit, the measuring procedure shall be blocked for further use in measuring specimens from patients. The reason for the deviation is to be sought and, if possible, rectifying measures are to be taken. Keeping medical relevance in mind, the authorised person must decide whether or not to re-authorise use of the testing procedure or whether further measures are to be taken, e.g. whether all of the tests preceding the control sample,

including the control measurement, need to be repeated, or whether the sender needs to be informed about results that have already been reported.

2.1.3 Calculating and analysing the root mean square of the error of measurement at the end of a control period

(1) The relative root mean square of the error of measurement is to be calculated immediately upon completion of a control period, using the results of all of the single measurements of the control samples that have led to the release of the measurement procedure or the patient findings. A control period generally consists of one calendar month. If, per control period, there are fewer than 15 results from single measurements of control samples per measurement procedure that have led to the release of a measurement, this period shall be extended by one month until at least 15 such results are produced. The total period of time may not exceed three months.
(2) If the relative root mean square value of the error of measurement for a control sample exceeds the value given in Table B 1a–c, Column 3, the analytical procedure is to be blocked from further use in measuring patient specimens. The analytical procedure cannot be re-authorised for further measurements until the functionality of the procedure has been re-established through suitable measures. The entire process is to be documented.
(3) If the value given in Table B 1a–c, Column 3 is again exceeded in a subsequent control period for the same control sample, and user-related causes can be excluded, measures are to be taken as stated in Paragraph (2) and the federal authorities are to be informed, if this can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.
(4) Paragraph (2) also applies to measurement parameters not listed in Table B 1a–c. Instead of the maximum permissible deviation as listed in Table B 1a–c, Column 3, the laboratory's internal Δ_{max} shall be used as established in accordance with 2.1.4. The measuring procedure cannot be re-authorised until the functionality of the procedure is re-established through suitable measures. The entire process is to be documented.

2.1.4 Determining the internal error limits for measurement parameters not listed in Table B1

(1) In order to establish internal laboratory limits of error for the single measurement of control samples of measurement parameters not listed in Table B 1a–c, one control sample value per day is chosen for a minimum of 15 days, or for a maximum of one control period, for each control sample used. Values are selected based on a pattern, i.e. either the first, the *n*th or the last value is used in the calculation. Randomly selected values may also be used.
The limits of error are then calculated from the target value x_0 plus or minus Δ_{max}. The following formula is used to calculate Δ_{max}:

$$\Delta_{max} = \sqrt{k^2 * s_{ep}^2 + \delta_{ep}^2}\ ,$$

where:

k=3, coverage factor for calculating the laboratory's internal limit of error
s_{ep}, empirical standard deviation of the control sample measurements used in the calculations during the evaluation period (*ep*)
δ_{ep}, systematic error of measurement of the control sample measurements used in the calculations during the evaluation period (*ep*)

For simplification purposes, variance δ_{ep}^2 is not corrected with (n-1)/n.
To calculate relative laboratory internal error limits, Δ_{max} is to be divided by the target value x_0.
In justified cases a laboratory-internal error limit that differs with this procedure can also be defined. The reasons and the chosen procedure are to be documented in a transparent way.
(2) The acceptability ranges of the producer of the control samples are to be used while the laboratory is establishing its own limits of error.
(3) The laboratory's internal limits of error must be within the range provided by the producer of the control sample.
(4) No internal laboratory limits of error need to be calculated for control samples with a shelf-life of less than twelve weeks. The ranges given by the producer of the controlsamples are to be used.

2.1.5 Point-of-care laboratory testing with unit-of-use reagents

(1) Before unit-of-use reagents and the corresponding measuring systems are used in point-of-care testing, they are to be tested in accordance with the manufacturer's instructions on quality control. The results are to be documented.
(2) The provisions set forth in Section 2.1.1 Paragraphs 2, 3 and 4a may be waived when electronic/physical standards are used daily, or where there is another form of integrated testing of the device's functionality that prevents erroneous measuring results. In such cases a single measurement of a control sample is to be performed at least once a week if the procedure is to be used during that calendar week to test patient specimens. In the case of devices which do not use electronic/physical standards, or where there is no other form of integrated testing of the device's functionality to prevent erroneous measuring results, only the regulations set forth in Paragraphs 2 and 4a of Section 2.1.1 shall be waived.
(3) The analysis of the single measurements of the control samples and any resulting actions are to be done in accordance with Section 2.1.2 Paragraph (2). For measurement parameters not listed in Table B 1, Sentence 1 applies accordingly. The permitted limits of error are those stated by the manufacturer of the control samples.
(4) The square root mean of the error of measurement need not be calculated and analysed in accordance with

2.1.3 and a graphic illustration, as required in 2.1.7 Paragraph (3), is not necessary.

2.1.6 Measurement parameters with low testing frequencies

(1) Measurement parameters that are likely to be analysed on fewer than 15 days in three months are to be verified by at least two control samples with target values in different concentration ranges on the days on which the patient samples are tested.
(2) The single measurements of the control samples and the consequent actions taken in accordance with 2.1.2 Paragraph (2) are to be analysed for all control samples. Sentence 1 applies accordingly for measurement parameters not listed in Table B1. The error limits specified by the manufacturer of the control sample are to be used.
(3) The square root mean of the error of measurement need not be calculated and analysed in accordance with 2.1.3 and a graphic illustration, as required in 2.1.7 Paragraph (3), is not necessary.

2.1.7 Documentation

(1) All of the results of the internal quality assurance are to be documented based on the measurement parameter and type of sample material, taking into account the measuring procedure and measuring station. The authority tasked with overseeing guideline compliance is to be shown this documentation upon request.
(2) The documentation is to contain
a) The name of the medical laboratory
b) The name of the measuring station
c) Date and time of the measurement
d) Analyte, sample material, unit
e) Measuring procedure
f) Measured value of the control sample
g) Target value of the control sample
h) The relative or absolute deviation from the target value and the analysis done in accordance with Table B 1a–c, Column 3, or the limits of error established internally by the laboratory or the ranges indicated by the producer of the control samples
i) Notice of the procedure's authorisation or restriction
j) Corrective measures taken
k) Manufacturer, name and lot number of the control sample
l) Name/initials or signature of the tester
(3) The measured values of the control samples are also to be represented graphically.
(4) All measurement results of the quality assurance are to be stored for five years after the control cycles and analyses, together with the corresponding calculations and the reports on measures taken when limits of error are exceeded, if other regulations do not stipulate longer archiving periods.

2.2 External quality assurance (round robin tests)

(1) Every location must participate in a round robin test once a quarter for every measurement parameter listed in Table B 1a–c, if the medical laboratory provides this test there.
(2) The participant of the round robin test analyses the round robin test samples under routine conditions, and communicates results and information as required by the reference institution. When communicating results, the participant confirms that the analysis was performed in accordance with these guidelines, in the participant's laboratory, and under their supervision.
(3) The obligations pursuant to Paragraph 1 do not apply to tests with unit-of-use reagents as part of point-of-care laboratory testing in:
a) doctors' offices and medical services without a central laboratory
b) hospitals, if the central laboratory is responsible for internal quality assurance and determines the measurement parameter itself.
(4) If the participant does not receive a certificate for a measurement parameter because one of the participant's results exceeds the authorised limits of error as specified in Table B 1a–c, Column 5, the participant is obligated to determine the causes and rectify them if this lies within their responsibility. The entire procedure is to be documented.
(5) The round robin participation certificate and the acquired round robin certificates are to be retained for a period of five years unless longer periods of time are stipulated by other regulations.

Remarks on Table B1

Table B 1, Columns 2 to 4 contain the requirements for the user in the medical laboratory. Columns 2 and 4 to 6 contain the requirements for analysing the results by reference institutions.
Range of validity is the range in which the target values of the control samples should lie, for which the specifications in columns 3 and 5 shall apply.
If the target value of the control sample is outside the given range, the regulations for non-Table B 1 measurement parameters shall apply. If control samples with lower target values than in the range of validity are to be used, the limits of error established for the range of validity can also be used in analysing the measurements of the control samples.

RMV = Reference method value
SV = Set value specific to measuring method.

Table B 1a: Analytes in plasma/serum/whole blood

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
1	Activated partial thromboplastine time (aPTT)	10.5%	20	120	s	18.0%	SV
2	Alanine aminotransferase (ALT or GPT) EC 2.6.1.2	11.5%	30 0.5	300 5.0	U/l µkat/l	21.0%	RMV
3	Albumin	12.5%	20	70	g/l	20.0%	SV
4	Alkaline phosphatase (AP) EC 3.1.3.1	11.0%	20 0.33	600 10	U/l µkat/l	18.0%	SV
5	Alpha fetoprotein (AFP)	17.0%	5	250	kIU/l	24.0%	SV
6	Aspartate aminotransferase (AST or GOT) EC 2.6.1.1	11.5%	20 0.33	400 6.67	U/l µkat/l	21.0%	RMV
7	Bilirubin (total)	13.0%	> 2 > 34	30 513	mg/dl µmol/l	22.0%	SV
		22.0%	0.1 1.7	≤ 2 ≤ 34	mg/dl µmol/l		
8	Ca 15-3	16.0%	10	250	U/ml	24.0%	
9	Calcium (total)	6.0%	1	6	mmol/l	10.0%	RMV
10	Calcium (ionised)	7.5% 14.0%	> 1 0.2	2.5 ≤ 1	mmol/l mmol/l	15.0% 18.0%	SV
11	Carbamacepine	12.0%	2	20	mg/l	20.0%	SV
12	Carcinoembryonic antigen (CEA)	14.0%	1	200	µg/l	24.0%	SV
13	Chloride	4.5%	70	150	mmol/l	8.0%	RMV
14	Cholesterol (total)	7.0%	50 1.3	350 9.1	mg/dl mmol/l	13.0%	RMV
15	Cortisol	16.0%	> 60 > 166	500 1380	µg/l nmol/l	30.0%	RMV
		18.5%	20 55	≤ 60 ≤ 166	µg/l nmol/l		
16	Creatine kinase (CK) EC 2.7.3.2	11.0%	50 0.83	1000 16.7	U/l µkat/l	20.0%	RMV
17	C-reactive protein (CRP)	13.5%	1	120	mg/l	20.0%	SV
18	Digitoxin	15.5%	5	80	µg/l	30.0%	RMV

(Continued)

Table B 1a: Analytes in plasma/serum/whole blood

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
19	Digoxin	14.0%	> 1	5	µg/l	30.0%	RMV
		17.5%	0.5	≤ 1	µg/l		
20	Erythrocytes	4.0%	1.5	7	10^{12}/l	8.0%	RMV
21	Estradiol 17-beta	22.0%	10 37	500 1835	ng/l pmol/l	35.0%	RMV
22	Ethanol (clinical toxicology)	9.0%	> 0.6	5	g/l	12.0%	SV
		15.0%	0.2	≤ 0.6	g/l	21.0%	
23	Ferritin	13.5%	10	600	µg/l	25.0%	SV
24	FSH	14%	4	70	U/l	21.0%	
25	Gamma glutamyl transferase (γ-GT) EC 2.3.2.2	11.5%	20 0.33	300 5	U/l µkat/l	21.0%	RMV
26	Glucose	11.0%	40 2.2	400 22	mg/dl mmol/l	15.0%	RMV
27	Haematocrit	5.0%	10 0.1	60 0.6	% l/l	9.0%	SV
28	Haemoglobin	4.0%	2 1.2	20 12.4	g/dl mmol/l	6.0%	RMV
29	Haemoglobin A 1 c (HbA1 c)	10.0%	30	140	mmol/mol Hb	18.0%	RMV
30	Uric acid	7.0%	2 119	13 773	mg/dl µmol/l	13.0%	RMV
31	Urea	10.5%	15 2.5	200 33	mg/dl mmol/l	20.0%	RMV
32	Human chorionic gonadotropin (hCG)	14.0%	>100	1500	IU/l	30.0%	SV
		17.0%	2	≤ 100	IU/l		
33	Immunoglobulin A	12.0%	0.5	6	g/l	20.0%	SV
34	Immunoglobulin G	10.0%	4	30	g/l	18.0%	SV
35	Immunoglobulin M	13.0%	0.4	5	g/l	26.0%	SV
36	Potassium	4.5%	2	8	mmol/l	8.0%	RMV

(Continued)

Table B 1a: Analytes in plasma/serum/whole blood

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
37	Creatinine	11.5%	0.5 44	10 884	mg/dl µmol/l	20.0%	RMV
38	Lactate	11.0%	9 1	90 10	mg/dl mmol/l	18.0%	SV
39	Lactate dehydrogenase (LDH) EC 1.1.1.27	9.0%	100 1.67	700 11.7	U/l µkat/l	18.0%	RMV
40	Leucocytes	6.5%	2	30	10^9/l	18.0%	RMV
41	Lithium	6.0%	0.3	3.5	mmol/l	12.0%	RMV
42	Magnesium	7.5%	0.3	3.5	mmol/l	15.0%	RMV
43	Sodium	3.0%	110	180	mmol/l	5.0%	RMV
44	pCO_2	7.5% 6.5%	≤ 35 ≥35		mmHg	12.0% 12.0%	SV
45	pH	0.4%	6.75	7.80		0.80%	RMV
46	Phenobarbital	10.0%	8	80	mg/l	20.0%	SV
47	Phenytoin	11.0%	3	35	mg/l	20.0%	SV
48	Phosphate (inorganic)	9.0%	1 0.3	10 3.2	mg/dl mmol/l	16.0%	RMV
49	pO_2	5.5%	> 125	350	mmHg	12.0%	SV
		7.0%	> 80	≤125	mmHg	18.0%	
		11.0%	40	≤ 80	mmHg	18.0%	
50	Progesterone	17.0%	>5.0 > 16	35 111	µg/l nmol/l	35.0%	RMV
		22.0%	0.2 0.6	≤ 5.0 ≤ 16	µg/l nmol/l		
51	Prostate specific antigen (PSA)	15.5%	0.2	50	µg/l	25.0%	SV
52	Protein (total)	6.0%	35	110	g/l	10.0%	RMV
53	Testosterone	20.5%	0.2 0.7	20 69	µg/l nmol/l	35.0%	RMV
54	Theophylline	13.0%	3	40	mg/l	24.0%	RMV
55	Thromboplastin time (Quick)	11.5%	10	120	%	23.0%	SV

(Continued)

Table B 1a: Analytes in plasma/serum/whole blood

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
56	Thrombocytes	7.5%	> 300	700	10^9/l	13.0%	SV
		8.5%	> 150	≤300	10^9/l	15.0%	
		13.5%	40	≤150	10^9/l	18.0%	
57	Thyreotropic hormone (TSH)	13.5%	0.1	40	mU/l	24.0%	SV
58	Thyroxine, total (T4)	12.5%	0.5	22	µg/dl	24.0%	RMV
			6.4	283	nmol/l		
59	Thyroxine, free (fT4)	13.0%	> 20	85	ng/l	20.0%	SV
			> 26	109	pmol/l		
		15.0%	2	≤ 20	ng/l		
			2.6	≤ 26	pmol/l		
60	Transferrin	8%	0.5	6	g/l	12.0%	SV
61	Triglycerides	9.0%	60	400	mg/dl	16.0%	RMV
			0.68	4.6	mmol/l		
62	Triiodothyronine, total (T3)	15.0%	> 1.2	10	µg/l	24.0%	SV
			> 1.8	15	nmol/l		
		16.0%	0.2	≤ 1.2	µg/l		
			0.3	≤ 1.8	nmol/l		
63	Triiodothyronine, free (fT3)	13%	1	25	ng/l	20.0%	SV
			1.5	39	pmol/l		
64	Troponin I	20.0%	0.1	35	µg/l	33.0%	SV
65	Troponin T	16.0%	> 1	8	µg/l	33.0%	SV
		21.0%	0.08	≤ 1	µg/l		
66	Valproic acid	11.5%	20	150	mg/l	20.0%	SV
67	Vancomycin	12.0%	4	100	mg/l	18.0%	SV

Table B 1b: Analytes in urine

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
1	Albumin	15.0%	1	500	mg/l	26.0%	SV
2	Calcium	8.5%	0.5	6	mmol/l	17.0%	SV
3	Glucose	11.0%	100 0.6	4000 22	mg/l mmol/l	22.0%	RMV
4	Uric acid	13.5%	5 30	300 1784	mg/l µmol/l	23.0%	RMV
5	Urea	13.5%	0.1 1.7	20 333	g/l mmol/l	21.0%	RMV
6	Potassium	8.5%	2	140	mmol/l	15.0%	RMV
7	Creatinine	12.0%	0.01 0.1	3 27	g/l mmol/l	21.%	RMV
8	Sodium	6.5%	50	200	mmol/l	12.0%	RMV
9	Phosphate (inorganic)	11.5%	30 1	900 29	mg/l mmol/l	20.0%	SV
10	Protein (total)	11.5%	5	1000	mg/l	24.0%	SV

Table B 1c: Analytes in cerebrospinal fluid

1 No.	2 Analyte	3 Acceptable relative deviation of the single value or the relative root mean square	4 Range of validity of columns 3 to 5			5 Acceptable relative deviation in a round robin test	6 Type of target value in a round robin test
			From	To	Unit		
1	Albumin	13.5%	20	1000	mg/l	23.%	SV
2	Glucose	9.5%	20 1.1	300 17	mg/dl mmol/l	18.0%	RMV
3	Immunoglobulin A	15.5%	2	40	mg/l	27.0%	SV
4	Immunoglobulin G	12.0%	15	500	mg/l	20.0%	SV
5	Immunoglobulin M	15.5%	1	30	mg/l	33.0%	SV
6	Lactate	11.5%	10 1.1	99 11	mg/dl mmol/l	20.0%	SV
7	Protein (total)	13.5%	10	2000	mg/l	23.0%	SV

B 2 Qualitative medical laboratory testing

1 Principles of quality assurance

(1) Section B2 lists the minimum requirements that are needed to assess the quality of the quantitative results of medical laboratory tests. These minimum requirements include both internal and external quality assurance.
(2) All of the qualitative tests performed by the medical laboratory (measurement parameters and nominal features) are subject to internal quality assurance. If several instruments or workstations are used for a test, quality assurance is to be performed on each of these instruments or workstations.
(3) In addition, all measurement parameters listed in Table B 2-2 of this section and all nominal characteristics are subject to external quality assurance.
(4) The measurement parameters are listed alphabetically in Tables B 2-1 and B 2-2. A test is included in the Tables based on the frequency of the test and its medical relevance according to the current state of science. Tables B 2-1 and B 2-2 are continuously updated.
(5) This section of the guidelines does not apply to qualitative tissue tests and to tests whose special internal and external quality assurance requirements are stated in parts of Section B.

2 Quality assurance procedures

2.1 Internal quality assurance

2.1.1 Procedures

(1) The manufacturer's requirements are to be observed with regards to type and frequency of internal quality assurance.
Independently of this, internal quality assurance is to be performed in terms of frequency:

a) In accordance with Table B 2-1 for the tests listed therein
b) Adequately and regularly as consistent with medical necessity and with the required testing frequency of patient samples, if the tests are not listed in Table B 2-1.

The requirements of Paragraph (1) Sentence 2 are considered to be met if corresponding controls, which ensure the accurateness of the results, are integrated with the applied analysis system.
(2) In addition, internal quality assurance is to be performed after disruptions to the testing procedure. Disruptions to the testing procedure include:

a) Restarting the device after it has been switched off completely
b) Calibration by the user
c) Repair or maintenance work on devices relevant to the test results
d) Changing reagent lots *[This also includes changes to the composition of the reagents, such as the production of dilutions or, in the case of in-house production, repeated preparation of reagents.]*

(3) The control samples must be as similar to the patient samples being investigated as possible. Identical control and calibration material may not be used in the same testing procedure.
(4) Control samples are to be used which have a known result that is within the measurement ranges relevant for making medical decisions.
(5) When unit-of-use reagents and their corresponding analytical systems are used in point-of-care laboratory testing, the requirements of Paragraph (1) Sentence 2 and Paragraph (2) Sentence 2 (a) do not need to be met if process control measures, which show the output of erroneous test results, are integrated in the test.

2.1.2 Analysing the results

(1) The test results of the controls are to be assessed as soon as the results are available. The assessment is performed using the target objectives assigned to the control sample.
(2) If the requirements are not met, the testing procedure is to be removed from further use in testing patient samples. The cause of the failure of performance is to be sought and, if possible, rectified. Taking medical relevance into consideration, the responsible person must decide whether the testing procedure can be re-authorised or whether further measures must be taken, e.g. whether all of the tests preceding and including the control test are to be repeated, or whether the sender is to be notified about already communicated results. The entire process is to be documented.

2.1.3 Documentation

(1) All of the findings of the internal quality assurance are to be documented and categorised according to test and type of control sample, taking into account the testing procedure and workstation or instrument. The authority tasked with overseeing guideline compliance is to be shown this documentation upon request.
(2) The documentation must contain

a) Name of the medical laboratory
b) Name of the workstation or analysis system
c) Date and, as appropriate, time of the test
d) Test, sample material, and, if necessary, the unit
e) Testing method
f) Control sample result
g) Target objectives of the control sample
h) The assessment
i) Notice of the procedure's authorisation or restriction
j) Corrective measures taken
k) Producer, name and lot number of the control sample
l) Name/initials or signature of the tester

(3) Records documenting that internal quality assurance has been performed are to be stored for five years, along with the evaluations and reports on the measures taken

Table B 2-1: Internal quality assurance

No.	Measurement parameter/Test	Frequency of the control test
1.	6-Acetylmorphine	daily
2.	ABO characteristics	weekly
3.	Amphetamines	daily
4.	Barbiturates	daily
5.	Benzodiazepines	daily
6.	Borrelia burgdorferi, antibodies against	daily
7.	Buprenorphine	daily
8.	Candida albicans, antibodies against	daily
9.	Cannabinoides	daily
10.	Chromatographic analysis with identification of the active substance (STA)	daily
11.	Cocaine and metabolites	daily
12.	Direct Coombs test	weekly
13.	dsDNA, autoantibodies against	daily
14.	Echinococcus, antibodies against	daily
15.	Electrophoresis with immunoreaction	monthly
16.	Entamoeba histolytica, antibodies against	daily
17.	Erythrocyte antigens, antibodies against (Coombs test)	daily
18.	Extractable nuclear antigens, autoantibodies against	daily
19.	Smooth muscle, autoantibodies against	daily
20.	Glutaminase, antibodies against	daily
21.	HBc antigen, antibodies against	daily
22.	HBe antigen, antibodies against	daily
23.	HBs antigen, antibodies against	daily
24.	Hepatitis A virus, antibodies against	daily
25.	Hepatitis C virus, antibodies against	daily
26.	HIV, antibodies against	daily
27.	IgE antibodies, allergen-specific single allergen test Method-specific control in a rotating procedure with a chief allergen	weekly
28.	Immune complexes, circulating	daily
29.	Nuclei (ANA), autoantibodies against	daily
30.	Methadone and metabolites	daily
31.	Methaqualone	daily
32.	Mitochondria (AMA), autoantibodies against	daily
33.	Opiates	daily
34.	Phencyclidine	daily
35.	Plasmodium, antibodies against	daily
36.	Rhesus type	weekly
37.	Rheumatoid factor (RF)	daily
38.	Ribonucleoprotein (RNP), autoantibodies against	daily
39.	Rubella virus, antibodies against	daily
40.	Schistosoma, antibodies against	daily
41.	Scl-70 antigen, autoantibodies against	daily
42.	Sm antigen, autoantibodies against	daily
43.	SS-A antigen, autoantibodies against	daily
44.	SS-B antigen, autoantibodies against	daily
45.	Streptococcal desoxyribonuclease, antibodies against	daily
46.	Streptolysin O, antibodies against	daily
47.	Toxoplasma gondii, antibodies against	daily
48.	Treponema pallidum, antibodies against	daily
49.	Tricyclic anti-depressives	daily
50.	Cytoplasmic components of neutrophil granulocytes (C-ANCA, P-ANCA), autoantibodies against	daily

	Daily = each calendar day on which patient samples are tested Weekly = each calendar week in which patient samples are tested etc.	

Table B 2-2: External quality assurance (round robin tests)

No.	Measurement parameter/Test	Participation frequency / once per
1.	ABO characteristics	Quarter
2.	Borrelia burgdorferi, antibodies against	Half year
3.	Candida albicans, antibodies against	Half year
4.	Cannabinoide	Quarter
5.	CD4 T cells	Half year
6.	CD8 T cells	Half year
7.	Chromatographic analysis with identification of the active substance (STA)	Half year
8.	Cocaine and metabolites	Quarter
9.	Differential, blood smear	Quarter
10.	Direct Coombs test	Quarter
11.	dsDNA, autoantibodies against	Half year
12.	Echinococcus, antibodies against	Calendar year
13.	Entamoeba histolytica, antibodies against	Calendar year
14.	Erythrocyte antigens, antibodies against (Coombs test)	Quarter
15.	Glutaminase, antibodies against	Half year
16.	HBc antigen, antibodies against	Half year
17.	HBe antigen, antibodies against	Half year
18.	HBs antigen, antibodies against	Half year
19.	Hepatitis A virus, antibodies against	Half year
20.	Hepatitis C virus, antibodies against	Half year
21.	HIV, antibodies against	Half year
22.	IgE antibodies, allergen-specific single allergen test Method-specific control on a rotational basis with 6 chief allergens from the following groups: a) seasonal inhaled allergen, b) year-round inhaled allergen, c) food allergen, d) insect poison allergen	Half year
23.	Immunoglobulins, oligoclonal (oligoclonal bands)	Half year
24.	Nuclei (ANA), autoantibodies against	Half year
25.	Methadone and metabolites	Quarter
26.	Opiates	Quarter
27.	Plasmodium, antibodies against	Calendar year
28.	Rhesus type	Quarter
29.	Rheumatoid factor r (RF)	Quarter
30.	Rubella virus, antibodies against	Half year
31.	Schistosoma, antibodies against	Calendar year
32.	Streptococci desoxyribonuclease, antibodies against	Half year
33.	Streptolysin O, antibodies against	Half year
34.	Toxoplasma gondii, antibodies against	Half year
35.	Treponema pallidum, antibodies against	Half year
36.	Tricyclic antidepressives	Quarter
37.	Urine sediment	Calendar year
38.	Cytoplasmic components of neutrophil granulocytes (C-ANCA, P-ANCA), autoantibodies against	Half year

when the target objectives were not met, if other regulations do not stipulate longer archiving periods.

2.2 External quality assurance (round robin tests)

(1) Every location must participate in a round robin test for every test listed in Table B 2-2, based on the rate of frequency specified therein, if the medical laboratory there provides this test. Participation is mandatory for the tests listed in the table regardless of whether the test result was quantitatively or qualitatively stated in the report or in the findings.
(2) The round robin test participant examines the samples under routine conditions, and conveys results and information as required by the reference institution. By communicating these results, the participant confirms that the tests were performed in accordance with these guidelines, in the participant's laboratory, and under their supervision.
(3) If a participant does not receive a certificate because one or more of the participant's results do not correspond to the target objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them insofar as this lies within the participant's responsibility. The entire procedure is to be documented.
(4) Certificates attesting to the participation in the round robin test, and the round robin test certificates awarded, are to be kept for five years if a longer archiving period is not stipulated by other regulations.

B3 Direct detection and characterisation of infectious agents

1 Principles of quality assurance

(1) Section B 3 defines the minimum requirements of quality assurance for medical laboratory testing that directly detects medically relevant infectious agents. These also include, as necessary, subsequent tests for characterising infectious agents (e.g. differentiation, identification, standardisation of types) and their properties relevant to treating infections (e.g. testing sensitivity to anti-infectives). These minimum requirements apply to internal and external quality assurance.
(2) All of the tests performed by the medical laboratory in accordance with Paragraph (1) are subject to internal quality assurance. If multiple instruments or workstations are used for a test, internal quality assurance is to be performed on each of these instruments or workstations.
(3) Furthermore all tests listed in Tables B 3-2 and B 3-2a are subject to external quality assurance.
(4) The tests in Tables B 3-1, B 3-1a, B 3-2 and B 3-2a have been listed according to the type of pathogen or the type of method applied. A test is included in these tables based on the frequency of the test and its medical relevance according to the current state of science. The tables are continuously updated.

2 Quality assurance procedures

2.1 Internal quality assurance

2.1.1 Procedures

(1) The manufacturer's requirements are to be observed with regard to type and frequency of the internal quality assurance procedures. Independent of this, internal quality assurance is performed in terms of frequency:
a) In accordance with Table B 3-1 and B 3-1a for the tests listed there
b) Adequately and regularly as consistent with medical necessity and with the required testing frequency of patient samples, if the tests are not listed in Table B 3-1 and Table 3-1a.
The requirements of Paragraph (1) Sentence 2 are considered to be met if corresponding controls which ensure the accurateness of the results are integrated in the applied analysis system.
(2) The following are to be investigated as part of the internal quality assurance procedures:
a) Culture media and supplements
b) Cell lines for cell culture processes
c) Reagents, staining solutions, diagnostic antibodies and antigens
d) Systems used to identify pathogens and test sensitivity
e) Result-relevant equipment and instruments used for this
(3) Furthermore, internal quality assurance is to be performed after disruptions to the testing procedure. Disruptions to the testing procedure include:
a) Calibration
b) Repairs or maintenance on test result-relevant equipment
c) Changing of reagent lots *[This also includes changes to the composition of the reagents, such as the production of dilutions or, in the case of in-house production, repeated preparation of reagents]*.
(4) Control samples must be as similar as possible to the patient samples being tested. Control material and calibration material may not be identical in the same testing procedure.
(5) Control samples with known results are to be used unless stipulated otherwise below.
(6) Statistics are to be kept and analysed regarding the frequency of detected pathogens and their sensitivity to anti-infectives.

2.1.2 Special requirements

2.1.2.1 Microscopic methods

Internal quality assurance for microscopic methods is specified in Table B 3-1. Additionally, suitable specimens (e.g. permanent specimens, preserved parasites) or visual materials (e.g. image charts, atlases) must be

Table B 3-1: Internal quality assurance

Test	Requirement	Permissible deviation	Frequency
Microscopic method			
Gram stains	Characteristic staining of gram-negative and gram-positive bacteria on a control specimen (e.g. tongue swab)	No deviation	Daily
Ziehl-Neelsen stains	Characteristic staining of an acid-proof swab on a control specimen	No deviation	Daily
Giemsa stains	Characteristic staining of erythrocytes and leucocytes in a smear, if necessary, from the patient being tested pH value of the buffer	No deviation 6.8 – 7.2	Daily Weekly
Microscopic pathogen detection, e.g. parasites	Detection of characteristic pathogen structures e.g. using image charts or round robin/other permanent specimens ("consensus straining")	A maximum of a 20% deviation (based on the number of specimens assessed)	Annually
Negative contrasting in transmission electron microscopy of viruses	Use of samples with defined viruses / virus quantities (testing the integrity of the carrier film, its binding properties, negative contrasting and amplification factor) clear detection of the viruses / virus groups	No deviations	With every new lot of film-coated copper mesh
Culture tests			
Non-cell-culture-based methods			
Visual check of solid culture media	Identifying transport or storage damage, such as impurities, drying out	No deviation	Every package unit in every delivery or when new lot is used
Checking sterility[1]	No growth	No deviation	When changing lots
Examination of the culture media[2] using test cultures or parallel testing comparing earlier lots for - all media - solid culture media with incubation periods exceeding 72 hours - selective media - indicator media - induction of typical morphologies in yeasts	 - Formation of the characteristic colony morphology - Detection of sufficient moisture by pre-incubating for at least 3 days and through growth of a suitable control strain after subsequent inoculation (e.g. Sabouraud agar to detect dermatophytes) - Suppression of the growth of non-target organisms - Pathogen-typical reactions - Formation of characteristic morphology	No deviation	When changing lots

(Continued)

Table B 3-1: Internal quality assurance

Test	Requirement	Permissible deviation	Frequency
Pathogen identification			
Examination of individual methods of (orientating) pathogen identification with control strains: catalase, oxidase, indole, coagulase, germ tube test, urease	Pathogen-typical reactions	No deviation	Daily
Verification of commercial systems for identifying pathogens	Pathogen-typical reactions of control strains	No deviation	When changing lots
Examination of the inoculum purity in commercial systems used in identifying pathogens	Pure culture	No deviation	With each isolate
Sensitivity testing			
Beta-lactamase	Positive and negative controls with control strains	No deviation	Daily
Verification of the sensitivity test	Over 20 consecutive work days using appropriate control strains, evaluation of the findings of the pathogen-antibiotic combinations	1 out of 20 findings per pathogen-antibiotic combination outside the permissible tolerance range	Before initial use and when requirements of the current internal quality control are not met
Ongoing internal quality control of the sensitivity test	Compliance with tolerance ranges for the normative control strains	If deviation occurs more than twice for a pathogen-antibiotic combination: look for, rectify and, if required, re-verify the test system	Weekly and when changing lots; for systems used less than once a week: every time the system is used
Test for purity	Examination of the inoculum purity	No deviation	For every isolate
Cell-culture-based methods			
Examination of the permissiveness using positive control strains	Detection of the virus-typical cytopathic effect or virus antigen	No deviation	Monthly and when changing lots of cells or for new passage made from cryopreserved cell cultures
Confirmation that there is no viral contamination of cell cultures by running negative controls (non-infected cell control)	Free of viral contamination	No deviation	Monthly and when changing lots of cells or for new passage made from cryopreserved cell cultures
Virus cultivation: confirming there is no mycoplasma contamination of the cell culture	Free of mycoplasma	No deviation	Every quarter year and when changing the cell culture lot

(Continued)

Table B 3-1: Internal quality assurance

Test	Requirement	Permissible deviation	Frequency
Molecular biological methods			
Nucleic acid isolation	Extraction control through nucleic acid analysis of an afflicted target sequence[3] or target sequence occurring in a test specimen (the extraction control can be identical to the inhibition control)	No deviation	For every sample extraction
Reaction components	Conformity testing of the reagents (primers, polymerase, nucleotides and probes) through nucleic acid/signal amplification of the target sequence with old and new reagent lot	No deviation	In the case of new reagent lot or newly dissolved reagent
Pathogen-specific nucleic acid detection	Positive and negative control in line with 2.1.2.3	No deviation	With each procedure
Sequence-based methods (NAT, FISH and other hybridisation techniques	Checking database of the primer and probe sequences used with this detection method with respect to the declared species specificity	No deviation that impacts the test results	At least once a year or in accordance with provision by the producer
Immunological methods			
Diagnostic antibodies	Positive and, if applicable, negative control	No deviation	When changing lots
Antigen detections (EIA, ELFA, CLIA and other immunochemical detections)	Positive and negative control	No deviation	Daily
Antigen detection using rapid tests (e.g. immunochromatographic tests) with integrated function controls (e.g. stool pathogens)	Positive and, if applicable, negative control	No deviation	Once per test package
Direct immunofluorescence test (e.g. respiratory viruses, legionella, pneumocystis jirovecii, Giardia lamblia)	Positive and negative control	No deviation	Daily
Particle / erythrocyte suspensions for antigen detection (agglutination assays)	Checking function by using known positive and negative control samples	No deviation	Daily

	Daily = every calendar day on which patient samples are tested Weekly = every calendar week in which patient samples are tested etc.	

[1] In the case of commercial culture media, this inspection can be documented by a corresponding batch certificate from the manufacturer.

[2] Growth promotion, colony morphology and biochemical reactivity are tested using the same control strains where possible. Compliance with the specifications required for culture media (e.g. growth promotion, colony morphology, if required, biochemical reactivity) can also be tested by regularly sub-cultivating the control strains needed for internal quality control.

[3] If there is validating data on the efficient nucleic acid extraction from the relevant target organism for closed, mechanised systems, an extraction control, and possibly, an inhibition control do not have to be done.

Table B 3-1a: Internal quality assurance when analysing nucleic acid concentration in blood/plasma/serum

1 No.	2 Analyte	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic set value[1]	4 Range of validity of column 3			5 Frequency of control test
			From	To	Unit	
1	CMV DNA	-0.5 to +0.5	5,000	5,000,000	IU/mL	With each use
2	HBV DNA	-0.5 to +0.5	500	5,000,000	IU/mL	With each use
3	HCV RNA	-0.5 to +0.5	500	5,000,000	IU/mL	With each use
4	HIV-1 RNA	-0.5 to +0.5	500	5,000,000	Copies/mL	With each use

[1] Alternatively a control can be used that has a designated target range with a maximum span of one $\log_{10}$ step.

available in sufficient quantities to be used as reference, comparison and teaching materials.

2.1.2.2 Culture tests

2.1.2.2.1 Non-cell-culture-based methods

Internal quality assurance for non-cell-culture-based methods is specified in Table B 3-1. The following also apply:
(1) Appropriately prepared control strains are to be used for control purposes, and cryopreserved where required.
(2) The laboratory must identify the set of rules to be used in the sensitivity test. Sensitivity tests may only be conclusively assessed if pure cultures are available. Therefore the inoculum must always undergo a purity check. Sensitivity tests of an orientative nature with non-standardised inocula (e.g. from blood cultures) are to be repeated on a standardised basis.
(3) Test cultures are to be produced from reference stock cultures at least once a month for the sensitivity test. Cultures made from test cultures may only be used for a maximum of one week.

2.1.2.2.2 Cell-culture-based methods

Internal quality assurance for cell-culture-based methods is specified in Table B 3-1. The following also applies:
(1) Appropriately prepared and, as appropriate, cryopreserved control strains (positive control sample) and a non-infected cell control (negative control sample) are to be used. It must be documented that the negative control sample used is morphologically normal.
(2) Sub-cultivation to increase the concentration of low amounts of pathogens from patient samples is to be documented.
(3) In the case of neutralisation testing based on cell cultures, the virus dosage is to be determined and documented using a $TCID_{50}$ assay or similar procedure.
(4) Sensitive and non-sensitive control strains are to be used as positive and negative control samples in phenotypic resistance testing. The degree of inhibition by the antiviral control substance is to be documented.

2.1.2.3 Molecular biology tests

Internal quality assurance for molecular biology tests is specified in Tables B 3-1 and B 3-1a. The following also applies:
(1) The procedure for nucleic acid isolation, adjusted for the properties of the pathogens and specimens, is to be reviewed on a regular basis.
(2) At least one positive and one negative control sample are to be used and, if necessary, inhibition controls are to be carried out. If available, the concentration of one of the positive control samples should be close to the sensitivity limit of the applied amplification procedure. The negative control sample can be waived for closed, fully mechanised systems. The assessment is to be performed based on the assigned target objectives.
(3) When determining nucleic acid concentrations, control samples with known nucleic acid or pathogen concentrations are to be used. These control samples are to be verified with international standards, if available.
(4) Limits are to be observed for the requirements listed in Table B 3-1a. For requirements not listed in Table B 3-1a the following shall apply:
The permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic set value of the quantitative positive control is to be established internally in the laboratory and is to be documented, or alternatively, for real time PCRs, the permissible absolute deviation of the number of cycles from the set value (cycle threshold/C_t, crossing point/C_p, cycle quantitative/C_q) is to be established. Likewise, the range of validity for the quantitative positive control must be established and documented.
(5) The sequence identity of amplification products is to be verified.

2.1.2.4 Immunological tests to directly detect pathogens

Internal quality assurance for immunological tests that directly detect pathogens is specified in Table B 3-1. The following also applies: In the case of direct testing to detect pathogen-antigens with fluorescence-marked antibodies, analysis criteria are to be established and, when

using particle/erythrocyte suspensions as a component of the diagnostic test (e.g. agglutination, lytic reaction), criteria are to be defined for this reading.

2.1.3 Evaluating the results

(1) The test results of the controls are to be analysed as soon as the results are available. Analysis is based on the target objectives.
(2) If the objectives have not been met, the testing procedure is to be removed from use in testing of other patient specimens. The cause of the non-compliance is to be researched and rectified if possible. Based on medical relevance, the person responsible must decide whether the testing method can be re-authorised and whether further measures need to be taken, e.g. whether all of the tests preceding the control sample, including the control test, are to be repeated or whether the sender needs to be informed because results have already been communicated. The entire process is to be documented.

2.1.4 Documentation

(1) All of the findings of the internal quality assurance are to be documented and listed according to test and type of sample material, taking into account the testing procedure and the workstation or instrument. The authority tasked with overseeing guideline compliance is to be shown this documentation upon request.
(2) The documentation must contain:

a) The name of the medical laboratory
b) The name of the workstation or testing device
c) Date and, if relevant, time of the test
d) Test, samples and, if required, unit
e) Testing method
f) Result of the inspection
g) Requirements for the inspection
h) Assessment
i) Notice of test's authorisation or restriction
j) Corrective measures taken
k) Producer, name and lot number of the control sample, as appropriate
l) Name/initials or signature of the tester.

(3) Records documenting that internal quality assurance has been performed are to be stored for five years, along with the assessments and reports on measures taken if targets have not been met, unless a longer archiving period is stipulated by other regulations.

2.2. External quality assurance (round robin tests)

(1) Every location must participate in a round robin test for every test listed in Tables B 3-2 and B 3-2a based on the rate of frequency specified therein, if the medical laboratory there provides this test.
(2) The round robin test participant examines the samples under routine conditions and conveys the results and the information required by the reference institution. By communicating the results, the participant confirms that the analysis was performed in accordance with these guidelines, in the participant's laboratory, and under their supervision.
(3) If a participant does not receive a certificate because one or more of the participant's results does not correspond with the target objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them, if this lies within their responsibility. The entire procedure is to be documented.
(4) Certificates attesting to the participation in the round robin test, and the round robin certificates awarded, are to be kept for five years if a longer archiving period is not stipulated by other regulations.

Table B 3-2: External quality assurance (round robin tests)

No.	Test	Frequency	Type of target value in round robin test[1]
	Bacteria		
1.	Gram stain	Every half year	SV
2.	Cultivation, identification and sensitivity testing of bacteria	Every half year	RLV
3.	Cultivation, identification and sensitivity testing of fast growing bacteria and, if applicable, detection of accompanying flora of the urogenital system	Every half year	RLV
4.	*Bordetella pertussis*, genome detection	Every half year	SV
5.	*Borrelia burgdorferi* sensu lato, genome detection	Every half year	SV
6.	*Chlamydia pneumoniae*, genome detection	Every half year	SV
7.	*Chlamydia trachomatis*, antigen detection	Every half year	SV
8.	*Chlamydia trachomatis*, genome detection	Every half year	SV
9.	EHEC/STEC (Shiga toxin), genome detection	Every half year	SV
10.	*Helicobacter pylori*, genome detection	Every half year	SV
11.	*Legionella pneumophila*, genome detection	Every half year	SV
12.	*Listeria monocytogenes*, genome detection	Every half year	SV
13.	Methicillin-resistant *Staphylococcus aureus* (MRSA), genome detection	Every half year	SV
14.	*Mycoplasma pneumoniae*, genome detection	Every half year	SV
15.	*Neisseria gonorrhoeae*, genome detection	Every half year	SV
16.	*Salmonella enterica*, genome detection	Every half year	SV
17.	*Coxiella burnetii*, genome detection	Every half year	SV
18.	*Francisella tularensis*, genome detection	Every half year	SV
	Mycobacteria	Every half year	SV
19.	Microscopic detection of mycobacteria	Every half year	SV
20.	Cultivation of mycobacteria	Every half year	SV
21.	Differentiation of tuberculosis bacteria	Every half year	SV
22.	Sensitivity test of tuberculosis bacteria	Every half year	SV
23.	Identification of mycobacteria	Every half year	SV
24.	Tuberculosis bacteria, genome detection	Every half year	SV
	Parasites		
25.	Parasites in the blood, microscopic detection	Every half year	RLV
26.	Parasites in the stool, microscopic detection	Every half year	RLV
27.	*Toxoplasma gondii*, genome detection	Every half year	RLV
	Yeasts		
28.	Cultivation and identification of yeasts and hyphomycetes (pathogen of mucosal mycosis, organ mycosis, systemic mycosis or mycosis resulting from trauma)	Every half year	RLV
29.	Identification of dermatophytes, yeasts and moulds (pathogens of dermatomycoses and mucosal yeast infections)	Every half year	RLV
30.	*Candida*, antigen detection	Every half year	SV
31.	*Cryptococcus neoformans*, antigen detection	Every half year	SV
	Viruses		
32.	Adenoviruses, genome detection	Every half year	SV
33.	Cytomegalovirus, genome detection	Every half year	SV
34.	Enteroviruses, genome detection	Every half year	SV
35.	Epstein Barr virus, genome detection	Every half year	SV

(Continued)

Table B 3-2: External quality assurance (round robin tests)

No.	Test	Frequency	Type of target value in round robin test[1]
36.	Hepatitis A virus, genome detection	Every half year	SV
37.	Hepatitis B virus, genome detection	Every half year	SV
38.	Hepatitis B virus, HBs antigen detection	Every half year	SV
39.	Hepatitis B virus, HBe antigen detection	Every half year	SV
40.	Hepatitis C virus, genome detection	Every half year	SV
41.	Hepatitis C virus genotyping, genome detection	Every calendar year	SV
42.	Hepatitis C virus, HCV antigen detection	Every half year	SV
43.	Herpes simplex virus type 1 / type 2, genome detection	Every half year	SV
44.	HIV-1 (RNA), genome detection	Every half year	SV
45.	HIV-1, p24 antigen detection	Every half year	SV
46.	Human papillomavirus, genome detection	Every half year	SV
47.	Influenza A and B viruses, genome detection	Every half year	SV
48.	Influenza A and B viruses, antigen detection	Every half year	SV
49.	Parvovirus B19, genome detection	Every half year	SV
50.	Respiratory syncytial virus, genome detection	Every half year	SV
51.	Respiratory syncytial virus, antigen detection	Every half year	SV
52.	Varicella zoster virus, genome detection	Every half year	SV

[1] RLV = Reference Laboratory Value: the target values of the round robin test are calculated by reference laboratories as the arithmetic average or median (if applicable).
SV = Set Value: The target values are calculated from the results of the round robin test as the arithmetic average or median (as appropriate).

Table B 3-2a: External quality assurance when analysing nucleic acid concentration in blood/plasma/serum

1 No.	2 Analyte	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic set value in round robin tests	4 Range of validity of column 3			5 Target value in a round robin test	6 Frequency of the round robin test
			From	To	Unit		
1	CMV DNA	-0.8 to +0.8	5,000	5,000,000	IU/mL	SV	Every half year
2	HBV DNA	-0.6 to +0.6	500	5,000,000	IU/mL	SV	Every half year
3	HCV RNA	-0.6 to +0.6	500	5,000,000	IU/mL	SV	Every half year
4	HIV-1 RNA	-0.6 to +0.6	500	5,000,000	Copies/mL	SV	Every half year

B 4 Sperm analysis

1 Principles of quality assurance

(1) The minimum requirements of quality assurance for the findings of sperm analyses are specified in Section B 4. These minimum requirements include internal and external quality assurance.
(2) Sperm analyses, as defined in these guidelines, are tests for sperm concentration, motility and morphology.
(3) All of the sperm analyses performed by the medical laboratory are subject to internal and external quality assurance. If a test is performed on multiple instruments or at multiple work stations, internal quality assurance is to be performed on each of these instruments or at each of these work stations.
(4) All of the tests listed in Paragraph (2) are also subject to external quality assurance.

2 Quality assurance procedures

2.1 Internal quality assurance

2.1.1 Procedures

(1) All tests on the spermatozoa with regard to their concentration, motility and morphology are to be performed in duplicate and are to be documented.

A minimum of 2 x 200 sperm are to be counted for this. Diluting or enriching the concentration of the ejaculate and/or the number of counting fields used for counting is to be done on the basis of a preliminary investigation. If the sperm concentration is less than 1–2 sperm per visual field (40-fold lens magnification), the concentration of the sample should be enriched. If there are fewer than 200 sperm per counting net in the counting chamber, the requirement of counting at least 2 x 200 spermatozoa no longer applies.
(2) The absolute value of the difference $|x_{i1}-x_{i2}|$ and the arithmetic average $\bar{x}_i = (x_{i1}-x_{i2})/2$ are to be calculated for each of the repeat determinations.

2.1.2 Analysing the differences between repeat determinations

The analysis is to be performed immediately after obtaining the results of the respective repeat determination in line with Paragraph (1) on the basis of the following validation rules (formulas)

For testing spermatozoa concentration:

$$|x_{i1} - x_{i2}| \leq 1.96 \cdot \sqrt{2 \cdot \bar{x}_i}$$

where:
in this case $X_{i1}=N_{i1}$ and $X_{i2}=N_{i2}$ are the counting results in the counting chamber halves and $\bar{x}_i = \bar{N}_i$ is the corresponding average from the repeat determination.
Remark: The validation rule above assumes a Poisson distribution for the counting results and a confidence level of 95%.
If the absolute value of the difference of the repeat determination exceeds the right term of the inequality (formula), the result of this test may not be released. The patient specimen is to be retested, if possible, and the result evaluated.
If deviations recur, the cause is to be sought and, if possible, rectified. The entire process is to be documented.

For testing the morphology and motility of spermatozoa:
The normal or abnormal spermatozoa are to be quantified in terms of morphology, and the progressively motile, locally motile or non-motile spermatozoa are to be quantified in terms of motility.

$$|x_{i1} - x_{i2}| \leq 1.96 \cdot \sqrt{2\bar{x}_i(100 - \bar{x}_i)/N}$$

where:
in this case $x_{i1}=p_{i1}$ and $x_{i2}=p_{i2}$ represent the percentage of the corresponding spermatozoa and $\bar{x}_i = \bar{p}_i$ represents the corresponding average of the repeat determination; N = number of the different spermatozoa.
Remark: The validation rule above assumes a binomial distribution for the relative counting result and a confidence level of 95%.
If the absolute value of the difference of the repeat determination exceeds the right term of the inequality (formula), the result of this test may not be released. The patient specimen is to be retested and the result evaluated. If deviations recur, the cause is to be sought and, if possible, rectified. The entire process is to be documented.

2.1.3 Calculating and analysing the average of the differences from the repeat determinations at the end of a control period

(1) A control period generally comprises one calendar month.
If there are more than 50 released pairs of variates after a calendar month, the average $\overline{(x_1 - x_2)}$ is to be calculated from this according to the formula

$$\overline{(x_1 - x_2)} = \frac{1}{n}\sum_{i=1}^{n}(x_{i1} - x_{i2})$$

as well as the standard deviation

$$s(x_{i1} - x_{i2}) = \sqrt{\frac{1}{n-1}\sum_{i=1}^{n}((x_{i1} - x_{i2}) - (x_1 - x_2))^2}$$

where n = the number of released pairs of values. Either the concentrations or the relative percentage of the properties for morphology and motility of each repeat determination are to be entered for the values x_{i1} and x_{i2}.
If in the prescribed period of time there are fewer than 50 released pairs of values, the period of time is to be extended until 50 pairs of values are achieved.
(2) Analysis is to be performed based on the validation rule (formula):

$$|\overline{x_1 - x_2}| \leq 1.96 \cdot \frac{s(x_{i1} - x_{i2})}{\sqrt{n}}$$

If the absolute value of this average exceeds the right term of the inequality (formula), the testing procedure is to be blocked from being used for measuring patient specimens. The measuring procedure cannot be released for measuring until the functionality of the procedure has been established through suitable measures. The entire process is to be documented.

2.1.4 Documentation

(1) All of the findings of the internal quality assurance are to be documented and categorised according to tests and based on the testing procedure and workstation or instrument. The authority tasked with overseeing guideline compliance is to be shown this documentation upon request.
(2) The documentation must contain
a) The name of the medical laboratory
b) The name of the measuring station
c) The period of analysis
d) Test, specimen, unit
e) Testing methods (counting chamber used, dyeing technique)

f) Test results including the individual values of the repeat determinations
g) Evaluation in accordance with the corresponding formula
h) Notice of the test's authorisation or restriction
i) Corrective measures taken
j) Name/initials or signature of the tester

(3) The documentation on the internal quality assurance is to be stored for five years along with the corresponding analyses and the reports on the measures taken in the case of non-conformance with the target values unless other regulations require longer archiving periods.

2.2 External quality assurance (round robin tests)

(1) Every location is to participate once every half-year in a round robin test to analyse concentration, morphology and motility if the medical laboratory there provides this test.
(2) The round robin test participant examines the samples under routine conditions and conveys results and information as required by the reference institution. By communicating the results, the participant confirms that the analysis was performed in accordance with these guidelines, in the participant's laboratory, and under the participant's supervision.
(3) If a participant does not receive a certificate for a test because one or more results do not conform to the target values predetermined by the respective reference institute, the participant is obligated to clarify the causes and to rectify them if this lies within their responsibility. The entire procedure is to be documented
(4) The round robin participation certificates and the round robin test certificates are to be kept for five years unless other regulations require longer archiving periods.

B 5 Molecular-genetic and cytogenetic medical laboratory tests

1 Principles of quality assurance

(1) The minimum requirements of quality assurance for the findings of molecular-genetic and cytogenetic medical laboratory tests are specified in Section B 5. These minimum requirements include internal and external quality assurance.
(2) Molecular-genetic and cytogenetic medical laboratory tests, as defined in this section of the guidelines, are all medical laboratory tests on the human genome and transcriptome whose aim is to detect known sequence variants, identify unknown variants, establish the structure or copy number of genomic segments or to detect epigenetic modifications of genomic segments. They include molecular caryotyping using array analysis (e.g. array CGH, SNP arrays).
Cytogenetic medical laboratory tests, as defined in this section of the guidelines, include all medical laboratory tests of postnatal cytogenetic diagnostics, prenatal cytogenetic diagnostics and cytogenetic diagnosis of cancer.

a) Postnatal cytogenetic diagnostics, as defined in these guidelines, is the cytogenetic investigation of a blood sample, tissue sample, cytologic smear or a cell culture from a body tissue after birth.
b) Prenatal cytogenetic diagnostics, as defined in these guidelines, is the cytogenetic investigation of amniotic cells, chorionic villi or foetal lymphocytes.
c) Cytogenetic diagnosis of cancer, as defined in these guidelines, is the analysis of neoplastic cells. This includes the analysis of cells from bone marrow, blood, lymph nodes and other tissues.

Cytogenetic medical laboratory tests in the areas of postnatal cytogenetic diagnostics, prenatal cytogenetic diagnostics and cytogenetic diagnosis of cancer include the application of conventional molecular cytogenetics (ISH, usually fluorescence *in situ* hybridisation (FISH)).
(3) All of the molecular-genetic and cytogenetic tests performed by the medical laboratory (measurement parameters and nominal properties) are subject to internal quality assurance. If a test is performed on multiple devices or at multiple workstations, internal quality assurance is to be performed at each of these devices or workstations.
(4) In addition, all of the tests listed in Column 7 of Table B 5-1 and the test statistics listed in Table B 5-2b are subject to external quality assurance. For molecular genetic tests that are not listed in Table B 5-1 Column 7, external quality assurance is to be performed in the form of participation in a round robin test that examines the method used, if such a round robin test is offered. The requirements of Sentence 2 are deemed to be met when the applied methodology has been included in a round robin test listed in Table B 5-1 and participation has occurred.
(5) The tests and test statistics are divided into molecular-genetic and cytogenetic tests in Tables B 5-1, B 5-2a and B 5-2b. They are included in the tables based on the frequency of the test and its medical significance in accordance with the current state of science. The tables are continuously updated.

2 Quality assurance procedures

2.1 Internal quality assurance

2.1.1 Implementation

1. General

(1) The manufacture's requirements are to be observed with regard to the type and frequency of the internal quality assurance performed.
Irrespective of this, internal quality assurance is to be performed in terms of frequency:

Table B 5-1: Internal and external quality assurance of molecular genetic testing

No.		Gene trivial name(s)	Gene HGNC name	Molecular genetic category/ies of the genetic changes *	Frequency of the internal quality assurance or the analysis of the control parameter	Frequency of participation in round robin tests / once per
1	Alpha1-Antitrypsin	*AAT, PI1*	*SERPINA1*	MUT/SNP	Weekly	Half-year
2	Apolipoprotein B 100	*APOB*	*APOB*	MUT/SNP	Weekly	Half year
3	Apolipoprotein E	*APOE*	*APOE*	MUT/SNP	Weekly	Half year
4	Cytochrome p450 2C9 (CYP2C9)	*CYP2C9*	*CYP2C9*	MUT/SNP	Weekly	Half year
5	Cytochrome p450 2C19 (CYP2C19)	*CYP2C19*	*CYP2C19*	MUT/SNP	Weekly	Half year
6	Cytochrome p450 2D6 (CYP2D6)	*CYP2D6*	*CYP2D 6*	MUT/SNP, IN/DEL, CNV	Weekly	Half year
7	Factor V (Leiden)	*FV-Leiden*	*F5*	MUT/SNP	Weekly	Half year
8	Hereditary haemochromatosis	*HLA-H*	*HFE*	MUT/SNP	Weekly	Half year
9	HLA-B27	*HLA-B*	*HLA-B*	MUT/SNP	Weekly	Half year
10	Lactase-phlorizin hydrolase	*LPH*	*LCT*	MUT/SNP	Weekly	Half year
11	Methylenetetrahydrofolate reductase	*MTHFR*	*MTHFR*	MUT/SNP	Weekly	Half year
12	Plasminogen activator inhibitor I	*PAI1*	*SERPINE1*	IN/DEL	Weekly	Half year
13	Prothrombine	*FII*	*F2*	MUT/SNP	Weekly	Half year
14	Thiopurine S-methyltransferase	*TPMT*	*TPMT*	MUT/SNP	Weekly	Half year
15	Uridyl glucuronyl transferase-1A	*UGT1*	*UGT1A1*	IN/DEL	Weekly	Half year
16	Vitamin K epoxide reductase	*VKORC1*	*VKORC-1*	MUT/SNP	Weekly	Half year
17	Cystic fibrosis, mucoviscidosis	*CFTR*	*CFTR*	MUT/SNP IN/DEL, CNV	Weekly	Calendar year
18	Familial breast/ovarian cancer (BRCA)	*BRCA1, BRCA2*	*BRCA1 BRCA2*	MUT/SNP, IN/DEL, CNV	Weekly	Calendar year
19	21-Hydroxylase deficiency (congenital adrenal hyperplasia)	*P450-C21*	*CYP21 A2*	MUT/SNP IN/DEL CNV	Weekly	Calendar year
20	Duchenne and Becker muscular dystrophy	*Dystrophine*	*DMD*	CNV, MUT/SNP, IN/DEL,	Weekly	Calendar year
21	Fragile X syndrome	*FRAXA*	*FMR1*	EXP	Weekly	Calendar year
22	Severe hearing impairment	*Connexin 26*	*GJB2*	MUT/SNP, IN/DEL	Weekly	Calendar year
23	Hereditary nonpolyposis colorectal cancer	*HNPCC*	*MSH2, MLH1*	MUT/SNP, IN/DEL, CNV	Weekly	Calendar year
24	Huntington's disease	*Huntingtin*	*HTT*	EXP	Weekly	Calendar year
25	Prader-Willi and Angelman syndrome	*Chr. 15q11-q13*	*ANCR*	CNV, METH	Weekly	Calendar year
26	Spinal muscle atrophy	*SMA*	*SMN1*	CNV	Weekly	Calendar year
27	Wilson's disease	*ATPase*	*ATP7B*	MUT/SNP, IN/DEL	Weekly	Calendar year
28	Y chromosome, microdeletions	*Azoospermia factor*	*AZF*	CNV	Weekly	Calendar year

	Daily = every calendar day on which patient samples are tested Weekly = every calendar week in which patient samples are tested etc.	

* Due to genetic heterogeneity, "molecular genetic categories" are – by definition of the placeholder concept – listed as classifiers of genetic alterations: Point mutation and/or single nucleotide polymorphism (**MUT/SNP**), insertion/deletion (**IN/DEL**), changes in the copy number of a genomic segment or a genomic sub-segment (**CNV**), repeat expansion (**EXP**), methylation defect (**METH**)

a) In line with Tables B 5-1 and B 5-2a for the tests or test statistics individually listed therein
b) Regularly and adequately according to medical necessity and testing frequency of patient samples if the tests are not listed in Tables B 5-1 and B 5-2a.

The requirements of Paragraph (1) Sentence 1 are deemed to be met if suitable controls are integrated into the applied analysis system which ensures the accuracy of the results.
(2) Additionally, internal quality assurance is to be performed after there has been a disruption to the testing procedure.
A disruption to the testing procedure includes:

a) A restart after the device has been shut off completely
b) Calibration by the user
c) Repair or maintenance work on equipment relevant for testing
d) Reagent charge replacement *[This includes changes to reagent composition, for example the production of dilutions or, in the case of in-house production, the re-preparation of reagents.]*

2. Molecular genetic medical laboratory testing

(1) Control samples must be as similar to the patient specimen being tested as possible. The control and calibration material may not be identical in the same testing procedure.
(2) Control samples with known results are to be used. Control samples, if available, are to represent the known alleles or allelic ranges when detecting known sequence variants, variants of structure, or copy number of genomic segments.
(3) In the case of tests using nucleic acid amplification procedures, controls are to be used that are able to detect contamination.
(4) In the case of array analyses, known control parameters must be used to ensure that, at minimum, the requirements of the manufacturers have been met for the analysis.

3. Cytogenetic medical laboratory testing

All preparations made from patient specimens must, if applicable, be tested in terms of their banding resolution, the number of overlaps, their degree of lightness and their hybridisation efficiency. The results are to be documented.

2.1.2 Analysing the results

2.1.2.1 For molecular-genetic medical laboratory tests based on control sample testing

(1) The control sample tests and/or the control parameters are to be analysed as soon as the results are available. The analysis is done based on the target objectives.
(2) If the objectives have not been met, the testing procedure is to be blocked from being used in testing other patient specimens. The cause of the non-fulfilment is to be looked for and, if possible, rectified. Based on medical relevance, the person responsible must decide whether the testing method can be re-authorised and whether further measures need to be taken, e.g. whether all of the tests preceding the control sample, including the control test, are to be repeated or whether the sender needs to be informed because results have already been communicated. The entire process is to be documented.

2.1.2.2 For cytogenetic medical laboratory tests based on the test statistic

The quality of each patient sample is, where appropriate, to be tested according to the test statistics listed in Table B 5-2a. If one of the test statistics exceeds the limits given in Column 4 of Table B 5-2a, the person responsible is to decide whether the patient sample should be re-tested. If the limit is also exceeded when the test is repeated, the cause must be sought and, if possible, rectified. Based on medical relevance, the person responsible is to decide whether test results can still be collected using this sample and, with corresponding comments in the findings, be applied.

2.1.3 Analysing the results of cytogenetic testing based on test statistics at the end of a control period

A control period generally comprises one calendar month. If there are more than 50 approved results of patient samples after a calendar month, the medical laboratory is to calculate the relative percentage by which the limits given in Column 4 of Table B 5-2a are exceeded.
If there are fewer than 50 released results of patient samples, the period of time is to be extended by one month intervals until at least 50 of the same results are obtained. The total period of time may not exceed three months.
If the limits given in Column 4 of Table B 5-2a are exceeded, the testing procedure is to be blocked for testing further patient samples. The testing procedure cannot be re-released until the reliability of the procedure has been established by suitable means. If it is likely that less than 50 results of patient samples will be released in three months, it is not necessary to calculate the relative percentage of exceedance as per Sentence 1. If, in this case of low testing numbers, the limits set forth in Column 3 of Table B 5-2a are exceeded five times in three months, action is to be taken as specified in Sentences 4 and 5.
The entire process is to be documented.

2.1.4 Documentation

(1) All of the findings of the internal quality assurance are to be documented according to type of specimen, taking the testing procedure and workstation into consideration.

Table B 5-2a: Cytogenetic testing – internal quality assurance

	Test statistic	Continuous quality assurance Requirements	Retrospective quality assurance Requirements
Postnatal analyses			
Lymphocytes	Banding resolution	At least 400 bphs	A max. of 5% of the samples with banding resolution < 400 bphs
	Number of overlapping points in the case of bphs < 400	At most 12 per metaphase	A maximum of 5% of the samples > 12
	Number of overlapping points in the case of bphs ≥ 400	At most 20 per metaphase	A maximum of 5% of the samples > 20
	Degree of lightness	At least 3	A maximum of 5% of the samples < 3
Prenatal analyses			
Amniotic cells	Banding resolution	At least 400 bphs	A maximum of 5% of the samples < 400 bphs
Chorionic villus cells	Banding resolution	At least 300 bphs	A maximum of 5% of the samples < 300 bphs
Amniotic and chorionic villus cells	Number of overlapping points at bphs < 400	At most 12 per metaphase	A maximum of 5% of the samples > 12
	Number of overlapping points in the case of bphs ≥ 400	At most 20 per metaphase	A maximum of 5% of the samples > 20
	Degree of lightness	At least 3	A maximum of 5% of the samples < 3
FISH (Interphase) constitutional and tumour cytogenetics	Hybridisation efficiency	N/A	A maximum of 10% without signals of the control probe

The authority tasked with checking compliance with these guidelines is to be shown this documentation upon request.

(2) The documentation must contain – if relevant:

a) The name of the medical laboratory
b) The name of the workstation or testing device
c) Date and, if important, time of the test
d) Test, specimen, if required, unit
e) Testing method
f) Results of the control or test statistic
g) Requirements for the control or test statistic
h) The assessment
i) Notice of the test's authorisation or restriction
j) Corrective measures taken
k) Producer, name and lot number of the control sample, as appropriate
l) Name/initials or signature of the tester.

(3) Documentation of internal quality assurance is to be stored for five years along with the assessments and the records of the measures taken when requirements were not met, if a longer archiving period is not stipulated by other regulations.

2.2 External quality assurance (round robin tests)

(1) Every location is to participate in a round robin test for every test or test statistic listed in Table B 5-1 Column 7 and B 5-2b based on the frequency rate specified therein, if the medical laboratory there provides this test.

(2) The round robin test participant examines the round robin test samples under routine conditions and conveys results and information as required by the reference institution. By communicating the results, the participant confirms that the tests were performed in accordance with these guidelines, in the participant's laboratory, and under their supervision.

(3) If a participant does not receive a certificate because one or more of his results does not correspond with the target objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them if this lies within his responsibility. The entire procedure is to be documented.

(4) Certificates attesting to the participation in the round robin test, and the round robin certificates awarded, are to be kept for five years if a longer archiving period is not stipulated by other regulations.

Table B 5-2b: Cytogenetic testing – external quality assurance

	Test statistic	Parameter	Participation in a round robin test once per
Postnatal analyses			
Lymphocytes	Nominal chromosome number*	No deviation	Calendar year
	Banding resolution	None of the samples < 400 bphs	Calendar year
	Number of overlapping points in the case of bphs < 400	None of the samples > 12	Calendar year
	Number of overlapping points in the case of bphs ≥ 400	None of the samples > 20	Calendar year
	Degree of lightness	None of the samples < 3	Calendar year
Prenatal analyses	Nominal chromosome number*	No deviation	Calendar year
Amniotic cells	Banding resolution	None of the samples < 400 bphs	Calendar year
Chorionic villus cells	Banding resolution	None of samples < 300 bphs	Calendar year
Amniotic and chorionic villus cells	Number of overlapping points in the case of bphs < 400	None of samples > 12	Calendar year
	Number of overlapping points in the case of bphs > 400	None of samples > 20	Calendar year
	Degree of lightness	None of samples < 3	Calendar year
FISH (Interphase) constitutional and tumour cytogenetics	Hybridisation efficiency	None of samples > 10% without signal of the control probe	Calendar year
Molecular cytogenetics (OligoArray)	DLRS value	None of samples > 0.4	Calendar year

*__nominal__ chromosome number e.g. **45**.X (Turner syndrome), **46**,XX (normal female), **47**, XXY (Klinefelter syndrome)

C Advisory Committee

(1) An advisory committee "Quality Assurance in Medical Laboratory Testing" shall be established at the German Medical Association which shall primarily perform the following duties:

a) Advising the German Medical Association in all aspects of these guidelines

b) Responding to questions pertaining to the application of these guidelines

c) Collecting, assessing and formulating suggestions for updating these guidelines.

(2) The members of the Advisory Committee shall be recommended by the institutions listed under (4) and appointed by the Executive Board of the German Medical Association, for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The Advisory Committee shall elect a chairman from among its members. The members of the Advisory Committee may be represented by proxy with approval of the chairman.

(3) The Advisory Committee may commission experts.

(4) The Advisory Committee is made up of representatives from the following institutions:

a) Three representatives from the competent scientific and medical societies

b) The chairs of the Expert Committees listed in Section B

c) A representative from the German Medical Association

d) A representative from the National Association of Statutory Health Insurance Physicians

e) A representative from the German Hospital Federation

f) A representative from the German Association of Medical Technologists and Analysts
g) A representative from the competent industrial association
h) Three state representatives
i) A representative from the German Federal Ministry for Health
j) A representative from the Federal Institute for Drugs and Medical Devices
k) A representative from the Federal Institute of Physics and Metrology

(5) The business of the Advisory Committee shall be administrated by the German Medical Association. The German Medical Association shall bear the costs for conducting the Advisory Committee meetings. The participation costs for the members shall be borne by the delegating institutions.
(6) The Advisory Committee shall issue for itself and the expert committees bylaws in accordance with Section D of these guidelines.

D Expert Committees

(1) There shall be an expert committee for each Section B.
(2) The composition of the expert committees and their tasks shall be set forth in the special D sections.
(3) The business of the expert committees shall be administrated by the German Medical Association. The German Medical Association shall bear the costs for conducting the expert committee meetings. Participation costs incurred by the members shall be borne by the delegating institutions.
(4) The expert committees shall work in accordance with the bylaws issued by the Advisory Committee.

D 1 Expert Committee "Quantitative Medical Laboratory Testing"

(1) The expert committee "Quantitative Medical Laboratory Testing" shall be established at the German Medical Association and have the following tasks:
a) Advising the German Medical Association in all questions pertaining to Sections B 1 and E 1
b) Establishing the acceptance modalities for the round robin tests
c) Responding to questions pertaining to the application of Sections B 1 and E 1
d) Collecting, assessing and formulating suggestions for updating Sections B1 and E 1

(2) The members of this expert committee are recommended by the institutions listed in Paragraph (3) and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The expert committee shall elect a chairman from among its members. The members of the expert committee may be represented by proxy with approval of the chairman.
The expert committee may commission experts.
(3) Members of the expert committee include:
a) Three representatives from the competent scientific and medical societies
b) A representative from the German Medical Association
c) A representative from the National Association of Statutory Health Insurance Physicians
d)A representative of the German Hospital Association
e) A representative from the German Association of Medical Technologists and Analysts
f) A representative from the competent industrial association
g) Two state representatives
h) A representative from the Federal Institute of Physics and Metrology

D 2 Expert Committee "Qualitative Medical Laboratory Testing"

(1) The expert committee "Qualitative Medical Laboratory Testing" shall be established at the German Medical Association and have the following tasks:
a) Advising the German Medical Association in all questions pertaining to Sections B 2 and E 2
b) Establishing the acceptance modalities for the round robin tests
c) Responding to questions pertaining to the application of Sections B 2 and E 2
d) Collecting, assessing and formulating suggestions for updating Sections B2 and E2

(2) The members of this expert committee are recommended by the institutions listed in Paragraph (3) and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The expert committee shall elect a chairman from among its members. The members of the expert committee may be represented by proxy with approval of the chairman.
The expert committee may commission experts.
(3) Members of this expert committee include:
a) Five representatives from the competent scientific and medical societies
b) A representative from the German Medical Association
c) A representative from the National Association of Statutory Health Insurance Physicians
d) A representative from the German Hospital Federation
e) A representative from the German Association of Technical Assistants in Medicine
f) A representative from the competent industrial association
g) Two state representatives
h) A representative from the Federal Institute of Physics and Metrology

D 3 Expert Committee "Direct Detection and Characterisation of Infectious Agents"

(1) The expert committee "Quality Assurance for Medical Laboratory Testing for Direct Detection and Characterisation of Infectious Agents" shall be established at the German Medical Association and have the following tasks:

a) Advising the German Medical Association in all questions pertaining to Sections B 3 and E 3

b) Establishing the acceptance modalities for the round robin tests

c) Responding to questions in the application of Sections B 3 and E 3,

d) Collecting, assessing and formulating suggestions for updating Sections B 3 and E 3.

(2) The members of this expert committee are recommended by the institutions listed in Paragraph (3) and are appointed by the Executive Board of the German Medical Association for a period of four years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The expert committee shall elect a chairman from among its members. The members of the expert committee may be represented by proxy with approval of the chairman.
The expert committee may commission experts.

(3) Members of the expert committee include:

a) Five representatives from the competent scientific and medical societies

b) A representative from the German Medical Association

c) A representative from the National Association of Statutory Health Insurance Physicians

d) A representative from the German Hospital Federation

e) A representative from the German Association of Technologists and Analysts

f) A representative from the competent industrial association

g) A state representative

h) One representative from PTB, RKI, PEI and BfArM respectively

D 4 Expert Committee "Sperm Analysis"

(1) The expert committee "Sperm Analysis" shall be established at the German Medical Association and have the following tasks:

a) Advising the German Medical Association in all questions pertaining to Sections B 4 and E 4

b) Establishing the acceptance modalities for the round robin tests

c) Responding to questions pertaining to the application of Sections B 4 and E 4

d) Collecting, assessing and formulating suggestions for updating Sections B 4 and E 4.

(2) The members of this expert committee are recommended by the institutions listed in Paragraph (3) and are appointed by the Executive Board of the German Medical Association for a period of four years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The expert committee shall elect a chairman from among its members. The members of the expert committee may be represented by proxy with approval of the chairman.
The expert committee may commission experts.

(3) The expert committee includes:

a) Five representatives from the competent scientific and medical societies

b) A representative from the German Medical Association

c) A representative from the National Association of Statutory Health Insurance Physicians

d) A representative from the German Hospital Federation

e) A representative from the German Association of Technologists and Analysts

f) A representative from the competent industrial association

g) A state representative

h) A representative from the Federal Institute of Physics and Metrology

D 5 Expert Committee "Molecular-genetic and Cytogenetic Medical Laboratory Testing"

(1) The expert committee "Molecular-genetic and Cytogenetic Medical Laboratory Testing" shall be established at the German Medical Association and have the following tasks:

a) Advising the German Medical Association in all questions pertaining to Sections B 5 and E 5

b) Establishing the acceptance modalities for the round robin tests

c) Responding to questions pertaining to the application of Sections B 5 and E 5

d) Collecting, assessing and formulating suggestions for updating Sections B 5 and E 5.

(2) The members of this expert committee are recommended by the institutions listed in Paragraph (3) and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The expert committee shall elect a chairman from among its members. The members of the expert committee may be represented by proxy with approval of the chairman.
The expert committee may commission experts.

(3) Members of this expert committee include:

a) Three representatives from the competent scientific and medical societies

b) A representative from the German Medical Association

c) A representative from the National Association of Statutory Health Insurance Physicians
d) A representative from the German Hospital Federation
e) A representative from the German Association of Technologists and Analysts
f) A representative from the competent industrial association
g) A state representative
h) A representative from the Federal Institute of Physics and Metrology
i) A representative from the Robert Koch Institute

E General requirements for reference institutions conducting round robin tests

(1) Round robin tests are conducted by reference institutions. These reference institutions are appointed by the German Medical Association for a period of five years. The appointment requires the following requirements to be met:

a) The reference institution has proven that it maintains a quality management system, exhibits reliability and expertise, is able to provide personnel with the expertise necessary for running the reference institution, and can raise the funds needed for the necessary rooms, technical equipment and ongoing operations.
b) The reference institution must have at its disposal a sufficient number of reference laboratories that are qualified to conduct the work at hand.
c) The reference institution or its sponsor must prove that it is willing and capable of compensating for any loss that may result from an activity performed in accordance with these guidelines.
d) The reference institution must be fully independent of the persons responsible for placing medical devices on the market in line with Section 5 of the German Medical Devices Act (MPG).

The appointment can be repealed if the requirements are no longer fulfilled in their entirety.
(2) The reference institutions are each specifically responsible for:

a) Announcing, organising and properly executing the round robin tests in accordance with these guidelines, and for the timely assessment and publication of the findings.
b) Appointing the round robin test leaders
c) Selecting and reviewing the suitability of the round robin testing material
d) Determining the target values of the control samples used in external quality assurance in conjunction with reference laboratories
e) Taking further measures if problems with the round robin test samples arise, and involving the affected manufacturer if necessary.

(3) The special requirements of the round robin testing organisations and of the round robin tests are regulated in the special Section E 1.

E 1 Special requirements for round robin testing of quantitative medical laboratory tests

1 Duties of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of round robin tests are provided for all of the measurement parameters listed in Table B1 a-c so that every medical laboratory can participate in at least one round robin test per quarter. Exceptions may only be made if it can be documented that there is an insufficient amount of suitable round robin test samples.
(2)The reference institutions shall announce for one year in advance the round robin tests that they will conduct for the measurement parameters as per Paragraph (1). This announcement includes:

a) The deadline for applying to participate in the round robin tests
b) The date of sample shipment and the deadline for sending back the results
c) The measurement parameters involved in the round robin test, as appropriate, with details on the analytical procedure
d) Type of sample material, and the sample volumes of the liquid or reconstituted round robin test samples.

(3) The reference institutions select the round robin test samples and check their suitability. The suitability of the selected round robin test samples for those measurement parameters, which are analysed based on reference method values, must be checked under routine conditions using routine analytical procedures before they can be used in the round robin tests.
(4) The reference institutions charge suitable reference laboratories with the responsibility to determine the reference method values of round robin test samples for external quality assurance, if this is required in Table B 1 a-c of Section B 1 of these guidelines. The reference laboratories are deemed suitable if they are accredited calibration laboratories in accordance with DIN EN/IEC 17025 and DIN EN ISO 15195. This only applies to measurement parameters where an accreditation is offered by an accreditation body. Only those accreditation bodies which are included in the Multilateral Agreement on the Mutual Acceptance of Calibration Certificates of the European Co-operation for Accreditation (EA) may be used. Moreover the leader of a reference laboratory must have special expertise and experience in the area of the reference measuring methods and be capable of testing new methods.
(5) For every round robin test, the reference institutions commission each participant to analyse at least two round robin test samples with varying concentrations or to analyse the activities of the measurement parameters.

(6) The reference institutions send the round robin test samples to each round robin test participant with information on handling the samples and conveying their test results.
(7) Reference institutions only analyse measurement results which were submitted by the round robin test participant before the set deadline.
(8) A certificate showing the submission date of the round robin test is to be issued to each round robin test participant whose testing results are within the permitted evaluation limits. In addition, a participation certificate is to be issued for all analytes for which a round robin test was conducted. Certificate and participation certificate are to be sent to the participants no later than four weeks before the next round robin test.
Round robin test participants are also to be informed of:

a) Target values and evaluation limits of the round robin test samples
b) Mean value and standard deviation of the measurement results of all participants and the measuring procedures used
c) Number of participants, as appropriate, listed according to measurement procedure.

The certificate is valid for 6 months.
(9) If the reference institution establishes that participants generally are not receiving a certificate for a measurement parameter with reagents or devices from a particular manufacturer and if the cause for this cannot be traced to the medical laboratory taking part in the round robin test or the reference institution, the appropriate federal authorities are to be notified if this can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.
(10) Further provisions for conducting round robin tests and analysing round robin test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target values

(1) After consulting with its competent committees and the parties affected, the German Medical Association establishes and announces which type of target value is to be used for the measurement parameters. Reference measurement procedures are to be used, where possible, when determining the target values in control samples.
(2) The reference institutions establish the test plans for determining the target values of the round robin test samples, commission the reference laboratories, and analyse the measurement results, consolidating these into a target value.
(3) The reference institutions must store the documentation used in determining the target values for a period of at least five years beginning from when they were used in the round robin tests.

2.1 Determining reference method values

(1) The reference laboratory commissioned by the reference institution uses a reference measuring method to calculate the reference method value for a measurement parameter.
(2) The reference method values for round robin test samples must be available before the start of the round robin test. Exceptions are permitted in special cases (e.g. very limited shelf life of the control sample).

2.2 Determining the set values

The set values depend on the measuring method and are calculated from the round robin tests as an arithmetic average or as a median.

3 Analysing the round robin test results

(1) Analysis is performed based on column 5 in Table B 1 a–c .
(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target value, i.e. a deviation which influences the pass rate, the reference institutions must research the cause and, if possible, rectify this in co-operation with the affected manufacturer of the round robin test sample or with experts. They are to check whether, in such a case, extending the acceptance limits or changing the target value would allow for an acceptable result. They decide whether the results are to be analysed according to the acceptance limits listed in Column 5 or according to the modified acceptance limits, or whether the round robin test is to be repeated for this measurement parameter.
The process is to be substantiated and documented. The round robin test participants and the expert committee at the German Medical Association are to be informed in accordance with Section B 1.

E 2 Special requirements for round robin testing of qualitative medical laboratory tests

1 Obligations of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of round robin tests can be offered for all of the tests listed in Table B 2-2 so that every medical laboratory can participant at the intervals stipulated in Table B 2-2. Exceptions can only be made when there is an insufficient number of round robin test samples available.
(2) The reference institutions announce, one year in advance, the round robin tests that they will conduct for the tests as per Paragraph (1). This announcement includes:

a) The deadline for applying to participate in the round robin tests
b) The date of sample shipment and the deadline for returning the results
c) The tests involved in the round robin test, with requisite details on the testing procedure
d) Type of sample material, the sample volumes of the liquid or reconstituted round robin test samples.

(3) The reference institutions select the round robin test samples and check their suitability. The suitability of the selected round robin test samples for these tests, which are analysed based on reference method values, must be checked under routine conditions using routine analytical procedures before they can be used in the round robin tests.
(4) For every round robin test, the reference institutions commission each participant to analyse at least two round robin test samples.
(5) The reference institutions send the round robin test samples to each round robin test participant with information on handling the samples and conveying their measuring results.
(6) Reference institutions only analyse testing results which were submitted by the round robin test participant before the set deadline.
(7) A certificate showing the submission date of the round robin test is to be issued to every round robin test participant whose test results concur with the target results or are within the permitted evaluation limits. Furthermore, a participation certificate is to be issued for all tests where participation in a round robin test occurred. Certificate and participation certificate are to be sent to the participants no later than four weeks before the next round robin test.
Round robin test participants are also to be informed of:
a) Target results and, if applicable, evaluation limits of the round robin test samples.
b) Mean value of the test results for all participants, and the testing procedures used.
c) Number of participants, as appropriate, listed according to testing procedure.

The certificate is valid for double the interval given in Table B 2-2.
(8) If the reference institution establishes that participants generally are not receiving certificates for a test with reagents or devices from a particular manufacturer, and if the cause for this cannot be traced to the medical laboratories' participation in the round robin test or the reference institution, the appropriate federal authorities are to be notified if this can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.
(9) Further provisions for conducting round robin tests and analysing round robin test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining the target results

(1) After consulting with its competent committees and the parties affected, the German Medical Association establishes and announces the type of target result to be used in the test. Reference test procedures are to be used, where possible, when determining the target results in control samples.
(2) The reference institutions establish the test plans for determining the target results of the round robin test samples, commission the reference laboratories, and analyse the results, consolidating these into a target value.
(3) The reference institutions must store the documentation used in determining the target values for a period of at least five years starting from when they were used in the round robin tests.

3 Analysing the round robin test results

(1) Analysis is performed based on the target results. The evaluation criteria must be fulfilled for all samples. The participants are to be notified of the evaluation criteria by the round robin test organisations.
(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target value, i.e. a deviation which influences the pass rate, the reference institutions must search for the cause and, if possible, to rectify this in cooperation with the affected manufacturer of the respective test systems or with experts. They are to check whether, in such a case, changing the target result would allow for an acceptable result or whether the round robin test is to be repeated for this measurement parameter. This process is to be substantiated and documented. The participants of the round robin test and the expert committee at the German Medical Association are to be informed in line with Section D 2.

E 3 Special requirements for round robin testing of medical laboratory detection and characterisation of infectious agents

1 Obligations of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of round robin tests are offered for the tests listed in Tables B 3 - 2 and B 3 - 2a so that every medical laboratory can participate at the intervals specified in Tables B 3-2 and B 3-2a. Exceptions can only be made when there is an insufficient amount of round robin test samples available.
(2) The reference institutions announce for one year in advance the round robin tests that they will conduct for the tests as per Paragraph (1). This announcement includes:

a) The deadline for applying to participate in the round robin tests
b) The date of sample shipment and the deadline for sending back the results
c) The tests involved in the round robin test, if necessary, with details on the analytical procedure
d) Type of sample material, the sample volumes of the liquid or reconstituted round robin test samples
e) Acceptance modalities.

(3) The reference institutions select the round robin test samples and check their suitability. The suitability of the selected round robin test samples must be checked under routine conditions using routine analytical procedures before they can be used in the round robin tests.
(4) For every round robin test, the reference institutions commission each participant to analyse at least two round robin test samples.
(5) The reference institutions send the round robin test samples to each round robin test participant with information on handling the samples and conveying their results.
(6) Reference institutions only analyse test results which were submitted by the round robin test participant before the set deadline.
(7) A certificate showing the round robin test submission date is to be issued to every round robin test participant whose test results concur with the target results or are within the permitted evaluation limits. Furthermore, a participation certificate is to be issued for all tests where participation in a round robin test occurred. Certificate and participation certificate are to be sent to the participants no later than four weeks before the next round robin testing date.
Round robin test participants are also to be informed of:

a) Target results and, where necessary, evaluation limits of the round robin test samples
b) The mean value of the test results of all participants and the testing procedures used.
c) Number of participants, as appropriate, listed according to test procedure.

The certificate is valid for double the interval listed in Tables B 3-2 and B 3-2a.
(8) If the reference institution establishes that participants generally are not receiving a certificate for tests with reagents or devices from a particular manufacturer and if the cause for this cannot be traced to the medical laboratories taking part in the round robin test or the reference institution, the appropriate federal authorities are to be notified if this can be defined as an “incident” according to Section 2 of Germany’s Medical Devices Safety Plan Ordinance.
(9) Further provisions for conducting round robin tests and analysing round robin test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target results

(1) After consultation is carried out in its competent committees, and after listening to the parties affected, the German Medical Association establishes and announces the type of target result to be used in the tests and how the target values are to be determined. Reference testing procedures are to be used whenever possible to determine target results in control samples.
(2) The reference institutions establish the test plans for determining the target results of the round robin test samples, commission the reference laboratories, analyse the results, and consolidate these into a target value.
(3) The reference institutions must store the documentation used in determining the target results for a period of at least five years starting from when they were used in the round robin tests.

3 Analysing the round robin test results

(1) Analysis is performed using the target results. The assessment criteria must be fulfilled for every sample. The round robin testing organisations are to inform the participants of assessment criteria.
(2) If the entire population or method-dependent subpopulations of the participants’ results show a considerable deviation to the target value, i.e. a deviation which influences the pass rate, the reference institutions must search for the cause and, if possible, rectify this in cooperation with the affected manufacturer of the round robin test sample, the manufacturers of the respective test systems, or with other experts. They are to review whether, in such a case, changing the target result would allow for an acceptable result. They decide whether the round robin test is to be repeated for this test.
This process is to be substantiated and documented. The participants of the round robin test and the expert committee at the German Medical Association are to be informed in line with Section D 3.

E 4 Special requirements for round robin testing of sperm analyses

1 Obligations of the reference institutions

(1) Each of the reference institutions ensures that a sufficient number of round robin tests are provided for all listed tests, so that every medical laboratory can participate in at least one round robin test per half year. Exceptions can only be made when there is an insufficient amount of round robin test material available.
(2) The round robin test is comprised of a test for sperm concentration, sperm motility and sperm morphology.
(3) The reference institutions are to announce, one year in advance, the round robin tests that they will conduct as per Paragraph (1). This announcement includes

a) The deadline for applying to participate in the round robin tests
b) The date of control material shipment and the deadline for sending back the results
c) The measurement parameters included in the round robin test, if necessary, with details on the measuring procedure
d) The type of round robin test material, the sample volumes of the liquid or reconstituted round robin testing materials.

(4) The reference institutions select the round robin testing materials and check their suitability. The suitability of the selected round robin test samples is to be tested under routine conditions using routine testing procedures before being used in the round robin test.
(5) For each round robin test, the reference institutions commission each participant to analyse at least two sets of round robin testing materials.
(6) The reference institutions send the round robin testing materials to each round robin test participant with instructions on handling the material and conveying their test results.
(7) Reference institutions shall only analyse measurement results that have been submitted by the round robin test participant before the set deadline.
(8) A certificate showing the round robin test submission date is to be issued to every round robin test participant whose test results concur with the target results or are within the permitted evaluation limits. Furthermore, a participation certificate is to be issued for all tests where participation in a round robin test occurred. Certificate and participation certificate are to be sent to the participants no later than four weeks before the next round robin testing date.
Round robin test participants are also to be informed of:
a) The target values and evaluation limits of the round robin test materials
b) Mean value and standard deviation of the measurement results of all participants and the procedures used
c) The number of participants, where appropriate, listed according to the measurement procedure.

Certificates are valid for 12 months.
(9) If the reference institution establishes that participants generally are not receiving a certificate for specific measurement procedure and if the cause for this cannot be traced to the medical laboratory taking part in the round robin test or the reference institution, the appropriate federal authorities are to be notified if this can be defined as an “incident” according to Section 2 of Germany’s Medical Devices Safety Plan Ordinance.
(10) Further provisions for conducting round robin tests and analysing round robin test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target results

(1) After consultation is carried out in its competent committees, and after listening to the parties affected, the German Medical Association establishes and announces the type of target result to be used in the tests and how the target values are to be determined. Reference testing procedures are to be used whenever possible to determine target results in control samples. Target values are calculated from the respective round robin tests as an arithmetic average or mean.
(2) The reference institutions establish the test plans for determining the target results of the round robin test samples, commission the reference laboratories, analyse the results, and consolidate these into a target value.
(3) The reference institutions must store the documentation used in determining the target values for a period of at least five years starting from when they were used in the round robin tests.

3 Analysing the round robin test results

(1) Analysis is conducted based on target results. The assessment criteria must be fulfilled by all samples. The reference institutions are to inform the participants of the assessment criteria.
(2) If the entire population or method-dependent subpopulations of the participants’ results show a considerable deviation to the target value, i.e. a deviation which influences the pass rate, the reference institutions must search for the cause and, if possible, rectify this in cooperation with experts. They are to review whether, in such a case, extending the acceptance limits or changing the target value would allow for an acceptable result. They decide whether the results are to be analysed using the previously determined set values or using modified evaluation limits, or whether the round robin test is to be repeated. This process is to be substantiated and documented. The participants of the round robin test and the expert committee at the German Medical Association are to be informed in line with Section D 4.

E 5 Special requirements for round robin testing of molecular-genetic and cytogenetic medical laboratory testing

1 Obligations of the reference institutions

(1) Each of the reference institutions is to ensure that a sufficient number of round robin tests are offered for all the tests or test statistics listed in Table B 5-1 Column 7 or Table B 5-2b, and for methodical round robin tests so that every medical laboratory can participate at the intervals given in Table B 5-1 Column 7 or Table B 5-2b. Exceptions can only be made when there are an insufficient number of round robin test samples available.

(2) The reference institutions announce for one year in advance the round robin tests they have planned in accordance with Paragraph (1). This announcement includes

a) The deadline for applying to participate in the round robin tests

b) The date of sample shipment and the deadline for sending back the results

c) The tests included in the round robin test, if necessary, with details on the testing procedure

d) Type of sample material, the sample volumes of the liquid or reconstituted test samples.

(3) The reference institutions select the round robin test samples and check their suitability. The suitability of the selected round robin test samples for those tests, which are analysed on the basis of reference method results, must be checked under routine conditions using routine analytical procedures before they can be used in the round robin tests.

(4) For every round robin test the reference institutions commission, each participant is to analyse at least two round robin test samples.

(5) The reference institutions send the round robin test samples to each round robin test participant with information on handling the samples and conveying their test results.

(6) Reference institutions shall only analyse test results which were sent off by the round robin test participant before the set deadline.

(7) A certificate showing the round robin test submission date is to be issued to every round robin test participant whose test results concur with the target results or are within the permitted evaluation limits. Furthermore, a participation certificate is to be issued for all tests where participation in a round robin test occurred. Certificate and participation certificate are to be sent to the participants no later than four weeks before the next round robin testing date.

Round robin test participants are also to be informed of:

a) The target results and, where appropriate, evaluation limits of the round robin test samples

b) The mean value of the test results of all participants and the procedures used

c) Number of participants, as appropriate, listed according to test procedure.

The certificate is valid for double the interval listed in Table B 5-1 Column 7 and Table B 5-2b.

(8) If the reference institution establishes that participants generally are not receiving a certificate for a measurement parameter with reagents or devices from a particular manufacturer, and if the cause for this cannot be traced to the medical laboratories taking part in the round robin test or the reference institution, the appropriate federal authorities are to be notified if this can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.

(9) Further provisions for conducting round robin tests and analysing round robin test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining the target results

(1) After consultation is carried out in its competent committees, and after listening to the parties affected, the German Medical Association establishes and announces the type of target result to be used in the tests and how the target values are to be determined. Reference testing procedures are to be used whenever possible to determine target results in control samples..

(2) The reference institutions establish the test plans for determining the target results of the round robin test samples, commission the reference laboratories, and analyse the results, consolidating these into a target result.

(3) The reference institutions must store the documentation used in determining the target values for a period of at least five years starting from when they were used in the round robin tests.

3 Analysing the round robin test results

(1) Analysis is based on the target results. The evaluation criteria is to be fulfilled for all samples. The round robin testing organisations are to notify the participants of the evaluation criteria.

(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation from the target value, i.e. a deviation which influences the pass rate, the reference institutions must search for the cause and, if possible, rectify this in cooperation with the affected manufacturer of the round robin test sample or with experts. They are to review whether, in such a case, changing the target result would allow for an acceptable result or whether the round robin test is to be repeated for this measurement parameter. This process is to be substantiated and documented. The participants of the round robin test and the expert committee at the German Medical Association are to be informed in line with Section D 5.

F Temporary regulations

The requirements set forth in Section B3 are to be fulfilled by 31 May 2015.

G Entry into force

The amendments to these guidelines, established on 11 April 2014, shall enter into force with the publishing of the Deutsches Ärzteblatt.

Amendments to Table B1 a to c shall enter into force on 1 January 2015.

The "Guidelines for Quality Assurance in Microbiology" dated 10 January 1992 (Deutsches Ärzteblatt 89 (1992) Issue 7) shall become ineffective on 1 April 2015.

Effective as of June 2014

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