Please note:

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Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations

In accordance with a resolution passed by the Executive Board of the German Medical Association at its meeting on 11 September 2026.

A Basic requirements for quality assurance in medical laboratory examinations

1 Scope

This guideline sets out the basic requirements for quality management and quality assurance for medical laboratory examinations in the field of medicine.
Part A of the guideline specifies the basic requirements for structural and process quality which apply to all medical laboratory examinations. The sections in Part B contain the specific requirements pertaining to the quality of the results.

2 Objective

The objective of this guideline is to ensure, and constantly improve the quality of medical laboratory examinations, and to keep risks for patients and users to a minimum. It aims to ensure, in particular, that:

- influencing and interfering factors are minimised during the pre-analytical phase,
- medical laboratory examinations are conducted properly and factors influencing and interfering the results are identified and minimised and
- results are correctly assigned and documented, and a report is generated in compliance with information security and data protection regulations.

3 Terminology

The following definitions clarify important terms as used in this guideline.
The definitions take into account national and international standards as well as metrological terminology; however, as they are used in the context of the guideline, there may be deviations from the aforementioned terminologies.

Accuracy
The closeness of agreement between the mean of the measured values obtained within a control period and the target value. This is usually quantified numerically using the systematic deviation of measurement, which is inversely proportional to the accuracy.

Analyte

(see “Measurand”)

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

Central laboratory
Central laboratory means that the medical laboratory examinations are usually performed for the entire institution (e.g., hospital) in one single organisational unit “medical laboratory” by appropriately qualified technical personnel. The central laboratory can also be an external laboratory managed by another legal entity/operator.

Control sample
Sample with target values provided.

Control strain
A reference culture or reference strain of microorganism, virus or cell-lines which is directly obtained from an approved culture collection or from a national reference laboratory or, where applicable, which is adequately characterised using suitable methods (e.g., characterisation of an isolate by an EQA, by sequencing or mass spectrometry). Normative procedures (e.g., sensitivity testing) require the use of corresponding normative control strains.

Deviation of measurement
The difference between a measurement result and the true value of the measurand. The difference between the measurement result of a control sample and the target value of this control sample is used to estimate the deviation of measurement as part of quality assurance of medical laboratory examinations.
The relative deviation of measurement is calculated by dividing the deviation of measurement by the target value.

Deviation of measurement, random (imprecision)
The difference of a measured value from the mean that would result from an infinite number of repeated measurements of the same measurand. The imprecision is estimated by calculating the difference between the value of the single measurement and the arithmetic mean of the measured values.

Deviation of measurement, root mean square of the
The root mean square of the deviation of measurement is a measure of the scatter of the measured values around the (conventional) true value of the measurand (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 deviation of measurement
x_0 represents the true value of the measurand; here, the target value of the control sample
x_i represents the value of the single measurement
n is the number of individual values used for calculation

The following mathematical relationship exists between the root mean square of the measurement deviation, the systematic measurement deviation and the empirical standard deviation of a 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 deviation of measurement

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

Deviation of measurement, systematic (inaccuracy)

This is the arithmetic mean which would result from an infinite number of repeated measurements of the same measurand, minus the true value of the measurand. The systematic deviation of measurement *δ* of a measurement procedure is estimated by taking the difference between the arithmetic mean $\overline{x}$, calculated from an appropriate number of repeated measurements, and the target value x_0, e.g.,

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

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

Device

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

Documentation, documented information

This refers to linked information and its storage media (digital or analogue), for example, records, instructions (including quality regulations), flow charts, method descriptions, specifications, calibration tables, reference ranges, drawings, reports, findings, legal provisions or standards.

Documentation may also involve the use of process-oriented quality management programmes.

Equipment

Equipment includes, but is not limited to, devices, reagents, control samples, reference materials, consumables and analytical systems.

Error limits

The maximum permissible limits for measurement deviations as defined by this guideline. Should these limits be exceeded, the deviations are considered errors and require corrective measures.

Examination, medical laboratory

An in-vitro diagnostic procedure used for obtaining values from sample material.

Finding

Findings are laboratory examination results assessed by a physician.

HIL index

For blood tests, the test results can provide relevant and objectively verifiable information regarding the interfering factors hemolysis, icterus, and lipemia (HIL index).

Influencing factors

Influencing factors affect the patients being examined. They influence the composition of the specimen as a result of illness or defects or other biological phenomena. They reflect the patient's status.

Instruction
Instructions are defined procedures for carrying out specific operations. Instructions include, for example, standard operating procedures, documents, videos and apps. Instructions must be clear and comprehensible for the medical laboratory staff.

Interfering factors
Interfering factors influence medical laboratory examinations. They interfere with the examination procedures and thus lead to a distortion of the results of the examination. They do not represent the patient's status.

Laboratory, medical
Depending on the context, a medical laboratory as defined by this guideline as follows

- spatial definition: a room, a part of a room or multiple rooms in which medical laboratory examinations are performed,
- personnel definition: a person under whose responsibility medical laboratory examinations are performed,
- organisational definition: a functional or organisational unit in which medical laboratory examinations are performed.

Laboratory examinations, patient-near immediate
Patient-near immediate laboratory examinations are defined as medical laboratory examinations that are performed directly as single measurements without sample preparation. A major criterion for patient-near immediate laboratory examinations is the ability to make instant decisions about further diagnosis or treatment based on the results of the laboratory examination.

Location
The geographical location (postal address) of a company or an institution where medical laboratory examinations are performed.

Mean, robust
Expected value for the population mean estimated using a robust method. A robust method is insensitive to outliers.

Measurand
Defined variable that is to be measured.

Measurement
Sum of all actions involved in determining a measurand.

Measurement method
General description of the logical sequence of actions for performing measurements.

Measurement procedure
Complete set of specifically described operations used to perform particular measurements according to a given method.

Minimal difference (MD)
The smallest distance between a measurement result and a cut-off at which they can be denoted as being different. The MD is calculated from the standard deviation (SD):
MD = 1,65 x SD.

NAAT
Nucleic acid amplification technique, e.g., polymerase chain reaction (PCR), including systems with isothermal amplification and sole signal amplification, e.g., branched DNA (bDNA).

NAAT systems, closed (e.g., for detection of pathogen-specific nucleic acid)

Systems (e.g., unit-use test cartridges) that already contain all the necessary reagents, including individual ready-to-use packs for sample preparation into which no further external reagents can be introduced or can enter the system after the sample material has been added. Furthermore, the system cannot be opened throughout the process chain so that the risk of contamination and/or the release of amplificates is eliminated.

Nominal value
Target value determined without using a reference measurement procedure.

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

- a defined group of users (doctors, nurses),
- a pool of measuring stations and/or measuring devices assigned solely to this unit and
- measuring stations that can only be operated by designated personnel.

Peer review
Critical (self-)assessment of medical care in consultation with colleagues which uses a structured process to continuously improve the quality and safety of patient care.

Performance of a measurement method
The following criteria are used to describe the performance of a measurement method: analytical sensitivity, analytical specificity, measurement precision, accuracy expressed in terms of systematic deviation of measurement, reproducibility expressed as random deviation of measurement, repeatability, measuring interval, theoretical and practical limits of detection, and linearity.

Pre-analytical phase
The pre-analytical phase includes all steps prior to the actual measurement; in particular the

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

Precision
In the context of this guideline, precision refers to reproducibility. It expresses the extent of the reciprocal convergence of the results of repetitive measurements of the same measurand when performed under varying measurement conditions (e.g., laboratory personnel, test, time, reagent deterioration). The extent of 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 related to precision.

Qualitative examination
A qualitative laboratory examination is used to determine a qualitative characteristic. A characteristic is qualitative when its values are assigned to a scale on which no intervals are defined (topological scale).
Nominal characteristics are qualitative characteristics whose values are not ordinally related (nominal scale): e.g., detectable, not detectable.
Ordinal characteristics are qualitative characteristics whose values are ordinally related (ordinal scale): e.g., titre level, + to +++, indication of a range of values, pH value on a test strip.
Medical laboratory examinations are assigned to Part B 1 or Part B 2 based on how the results are reported (scale level).

Quality assurance, risk-based
A quality assurance concept which ensures the laboratory runs a sufficient number of control samples for a given measurand/examination, taking into account e.g., the relevance of test results, testing frequency, the respective positive or negative rates and, where applicable, the performance of further test procedures. Risk-based quality assurance also includes suitable measures for detecting irregularities in the test system as well as preventive measures to minimise negative effects. The risk assessment of a specific examination must be documented.

Quality policy
The overall intentions and objectives of a medical laboratory with regard to quality, as formally expressed by the laboratory management.

Quantitative examination
A quantitative laboratory examination is used to determine a quantitative characteristic. A characteristic is quantitative when its values are assigned to a scale on which intervals are defined (metric or cardinal scale).
Medical laboratory examinations are assigned to Part B 1 or Part B 2 based on how the results are reported (scale level).

Reference measurement procedure
A thoroughly investigated measurement procedure whose results have an uncertainty of measurement commensurate with its intended use, such as in assessing the trueness of other measurement procedures used for the same measurand and for the characterisation of reference materials.

Reference method value
A target value obtained using a reference method.

Referral laboratory
A medical laboratory under the control of another legal entity and/or economic operator, to which the specimen or sample material is submitted for examination.

Report
Reports are summarized presentations of laboratory examination results.

Responsibility of the central laboratory
Responsibility in this case refers to guidance and supervision. In the context of patient-near immediate laboratory examinations, “under the responsibility of the central laboratory” means that the central laboratory monitors whether the individual organisational units of an institution adhere to the guideline with respect to internal quality assurance.
Responsibility does not mean that the control samples are measured and evaluated by employees of the central laboratory.

Risk management
Risk management is used to handle potential risks and to avoid and prevent errors and adverse events.

Sample material
The specimen used for the medical laboratory examination, with or without prior sample preparation.

Sample preparation
Sample preparation includes all changes made to the material to be examined prior to loading it into the measuring device or instrument by the person collecting the sample or by the person carrying out the measurement. Pipetting/volume dosing is not considered sample preparation

in the sense of this definition. If the collection system contains additives included by the manufacturer, this also does not constitute sample preparation.

Specimen
The body fluid/material (e.g., venous blood, cerebrospinal fluid, aspirate, tissue, urine, stool) taken from or excreted by a person for examination purposes, including any additives, which is stored in an appropriate container.

Standard deviation, empirical
The empirical standard deviation of a random sample is a measure of the distribution of the results around the mean. It is calculated by taking the square root of the mean of the (estimated) random measurement deviations, i.e.,

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

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

Target value
The target value of a control sample as determined and declared by the manufacturer or as determined by a reference institution.

Trueness of measurement
This is the closeness of agreement between the result of a measurement and the true value of the measurand. The trueness of measurement of a measurand cannot be given as a numerical value; but it has to be provided qualitatively, such as “sufficient” or “insufficient”.

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

Validation of a measurement procedure
This is the objective proof that the determined requirements are met by a measurement procedure. Objective proof can be obtained through observation, measurement, testing or other methods.

Validation of an examination result
This consists of the technical validation (assessment of the analytical quality) and medical validation (plausibility), including, where applicable, an analysis of conformity with an orientation diagnosis made by the requestor (including a constellation check of the results).

4 Structure

4.1 Identification
Institutions in which medical laboratory examinations are conducted must be legally identifiable.

4.2 Organisation
The responsibility, duties and competence of the staff performing medical laboratory examinations must be clearly defined and documented.

5 Resources

5.1 Management
The medical laboratory must be managed by a professionally qualified person.

Management responsibilities encompass technical, organisational, administrative activities, training and continuing education as well as consultation. Quality management also falls under the responsibility of management.

5.2 Personnel

Medical laboratory examinations may only be performed by personnel who are professionally qualified in accordance with legal regulations, and who are authorised to do so by management.

A sufficient number of staff must be available to carry out the medical laboratory examinations as well as to conduct quality management and, if necessary, to provide reserve capacities in the context of emergency care.

Staff members are required to participate in regular meetings, specialised training and continuing education. Participation in training and continuing education programmes must be documented.

The training of new staff and the familiarisation of staff with new analytical systems and laboratory medical examination procedures must be regulated and documented.

5.3 Rooms and environmental conditions

5.3.1 Rooms are to be available for medical laboratory examinations where the intended work can be performed without an adverse effect on the quality of the medical laboratory examinations and on the health and safety of the staff and the patients.

5.3.2 Environmental conditions that affect the quality of the examination results are to be identified, monitored, regulated and documented.

5.3.3 Access to and use of rooms and areas whose condition can impact medical laboratory examinations must 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 specimens, stored microorganisms, cells, devices, reagents, laboratory materials, records, reports and other documents. Measures are to be taken to safeguard against unauthorised access.

5.3.5 Provisions are to be made which guarantee the prompt availability of data. In order to ensure information security and data protection, data integrity is to be maintained and the data must be protected against unauthorised access.

5.4 Equipment

5.4.1 The medical laboratory must have the equipment necessary to perform its tasks. The requirements of the guideline also apply to equipment that is used by the medical laboratory but not under its responsibility.

5.4.2 The medical laboratory must have a procedure in place to regularly monitor the proper functioning of its devices, reagents and analysis systems and this procedure must be implemented. Maintenance is to be performed and documented based on defined specifications.

5.4.3 Documentation is to be retained for every analysis system and device that is needed to perform medical laboratory examinations and which can impact the quality of these medical laboratory examinations. This documentation must contain, but is not limited to:

(1) name of system or device,
(2) name of the manufacturer, model and serial number or other form of identification,
(3) date of commissioning,
(4) instructions for use, operating instructions and other information from the manufacturer, or justification, if these are not available,
(5) functional tests,
(6) maintenance requirements including date, time and type of inspection that has been carried out,

(7) the nature, date and time of equipment outages, malfunctions, structural modifications and repairs.
These records must be retained for two years beyond the working life of the equipment and must be promptly accessible.

5.4.4 Only authorised and trained members of staff may operate devices and analysis systems. Instructions for operating and servicing the equipment must be kept up-to-date and accessible to members of staff in their workplace.

6 Medical laboratory examinations

6.1 Pre-analytical phase

6.1.1 A complete list of the relevant laboratory examinations offered by the medical laboratory must be accessible to the submitter.

6.1.2 The medical laboratory must provide professionally competent advice regarding the examinations it offers, especially with regard to the selection of medical laboratory examination, the type of specimen, and the evaluation of the examination results.

6.1.3 The examination request form submitted by the submitter must contain the following information:

(1) identity of the patient – including sex and date of birth in the case of age-specific and sex-specific measurands,
(2) identity of the submitter of the material and the recipient of the report if not the same,
(3) type of specimen and, if relevant, the anatomical site of collection and time of collection,
(4) the examinations that have been ordered and
(5) clinically relevant patient information.

6.1.4 Instructions outlining the correct method for collection, handling and transporting specimens must be available to the persons responsible for this.
The instructions for collecting the specimen must contain, at minimum, the following:

(1) the list of the medical laboratory examinations offered, or reference to this,
(2) instructions on:
  a) preparing the patient,
  b) ordering the examination,
  c) the information required about the patient,
  d) the type and quantity of the specimen to be collected,
  e) collecting the specimen, with a description of the specimen containers and all required additives,
  f) special conditions for collecting, handling, storing and transporting the specimen, if applicable,
  g) unequivocal labelling the specimen and
  h) the actions to be taken between the time the specimen is collected and its arrival at the medical laboratory,
(3) criteria for requesting additional medical laboratory examinations,
(4) information and instructions to be provided to the patients regarding instructions for collecting the specimen and, if necessary, patient consent forms for collecting the specimen and for performing the medical laboratory examinations,
(5) information for the patient regarding the self-collection of the specimen as well as for handling, storing and transporting it.

6.1.5 The medical laboratory must have instructions for receiving, labelling and processing the specimen for laboratory medical examinations.

6.1.6 Criteria are to be defined for rejecting medical laboratory examinations. Rejections are to be documented.

6.1.7 The submitted specimen and portions thereof must be clearly assigned to one patient. If this is not possible, the specimen may not be processed. The submitter of the material is to be notified accordingly. The procedure 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 has to decide, after consulting with the sender of the specimen, whether the requested medical laboratory examinations should nevertheless be performed. The result of the consultation is to be documented.

6.1.8 On specimen arrival the medical laboratory must check whether there is any indication that:

(1) the conditions defined in the instructions for obtaining the specimen have not been complied with, or

(2) delivery was untimely for the requested medical laboratory examinations, or

(3) the requested examination cannot be carried out.

If such indications exist, the medical laboratory must decide, on the basis of established criteria, whether the examination should nevertheless be performed, or whether a new specimen should be requested.
The procedure is to be documented.

6.1.9 Special processes may need to be defined for time-critical medical laboratory examinations.

6.1.10 Specifications for minimising influencing and interfering factors – in accordance with the state of the art in science and technology – can be found in Part B of this guideline.

6.2 Procedures for conducting medical laboratory examinations

6.2.1 The medical laboratory may only use examination procedures that meet medical requirements.

6.2.2 The medical laboratory may only use validated examination procedures. It must document the procedure used for validation and the results that were obtained.

6.2.3 All medical laboratory examination procedures must be documented and be available at the workstations at all times.
This documentation is to include the manufacturer's instructions for use and, where necessary, additional remarks.
The documentation is to contain the following, where applicable:

(1) identification of the examination procedure,

(2) aim of the medical laboratory examination (medical indication),

(3) principle of the examination procedure (method),

(4) individual steps of the procedure (process),

(5) calibration procedure,

(6) procedure used to calculate the result,

(7) required specimen taking into account the pre-analytical phase (including container and the necessary additives),

(8) required instruments, reagents, culture media and test systems,

(9) specification of the performance of the examination procedure,

(10) information on possible interference factors, interference and cross-reactivity,

(11) reference ranges for healthy subjects, therapeutic ranges, decision limits or other indications for interpreting the examination results,

(12) process to be taken in the case of abnormal results,

(13) safety precautions and

(14) references.

6.2.4 If the medical laboratory modifies an examination procedure so that the results, and thus the interpretation, change in a clinically significant way, this procedure must be validated and the sender of the material is to be informed as soon as possible.

6.3 Post-analytical phase

6.3.1 Results must be technically validated and, using the available clinical data, medically validated.

Instructions on releasing the examination results must be available. These must include information about who may authorise the release of reports and how and to whom these reports may be issued. The instructions must also contain requirements for the direct issuance of reports to patients.

Which person carried out the technical and medical validation is to be documented.

6.3.2 Reports must be easy to read and contain, at minimum, the following information:

(1) date, and - if required - time the report was issued,
(2) identity of the patient,
(3) name or other means of identifying the submitter of the specimen and, if required, the address; the address of the recipient of the report if not the same as that of the submitter,
(4) name of the medical laboratory,
(5) date and time when the specimen arrived at the medical laboratory,
(6) date and time specimen collection if this information is available and relevant for interpreting the results,
(7) type of specimen
(8) name of the laboratory examinations and the methods used if the latter is relevant for interpreting the examination results,
(9) examination results and corresponding units as necessary,
(10) reference intervals or other remarks for interpreting the examination results and
(11) identity of the person responsible for releasing the report.

6.3.3 If there is a possibility that the examination result was affected by the condition of the specimen, this must be stated in the report. Where necessary, the report shall state that the results are conditional.

6.3.4 The medical laboratory must have instructions 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 must have procedures in place for immediately notifying a physician (or other clinical personnel responsible for patient care) if examination results exceed “alarming” or “critical” limits. This includes reports from referral laboratories.

6.3.6 When evaluating quantitative analysis results, the medical laboratory is to retain data on measurement uncertainty and makes this available on request. The minimum difference (MD) is a useful tool for describing measurement uncertainty.

6.3.7 Specimens and sample materials are to be stored in such a way that enables repeat or additional medical laboratory examinations to be performed over a period of time as established by the medical laboratory.

7 Quality management system

Quality management means that organisation and work processes are defined and regularly reviewed alongside the achieved results.

7.1 Documenting quality management

7.1.1 Quality management documentation must describe every relevant process. All employees must be instructed in how to use and implement the quality management documentation. This documentation must be continuously kept up to date.

It must contain the following information, if applicable:

(1) description of the medical laboratory, its legal status and its main tasks,
(2) objectives and strategies: Description of the quality assurance policy, risk management and measures to enhance the laboratory and improve quality,
(3) management: description of the responsibilities and qualifications,

(4) staff:
   a) qualifications, familiarisations, training, continuing education and meetings
   b) health and safety procedures,
(5) resources:
   a) rooms,
   b) facilities and equipment,
   c) environmental conditions,
(6) partnerships (referral laboratories, external service providers and suppliers),
(7) environmental issues,
(8) processes: instructions for
   a) collecting the specimen,
   b) examination procedures, handling equipment, reagents and other relevant consumables, validation of the examination procedures,
   c) ensuring the analytical quality of the examination procedures through internal and external quality assurance as well as regular discussions about the results of the quality assurance,
   d) post-analytical procedures and generating and transmitting reports,
   e) technical and medical validation of the examination results,
   f) document control
   g) generating, storing and archiving records,
   h) resolving complaints,
   i) determining errors and corrective actions,
   j) preventive actions,
   k) communication and co-operation with patients, medical personnel and partners,
   l) internal audits or peer reviews,
   m) information security and data protection.

7.1.2 If the medical laboratory is a part of an organisation that has a quality management system in place, reference can be made to the corresponding documents of this organisation.
The same applies to 7.2 and 7.3 below.

7.2 Document control

The medical laboratory is to define, document and maintain procedures for the control of all quality assurance documentation (internal and external). Each version of this documentation must be stored for future reference. Management must establish the retention period, taking legal requirements into consideration.
It must be ensured that only the current version of the documentation is accessible at the place where it is being used.

7.3 Complaint management

The medical laboratory is to establish and implement a procedure for documenting and handling complaints. Records of the complaints as well as the investigative, preventive and corrective actions taken by the medical laboratory, are to be drawn up and retained.

7.4 Examinations in referral laboratories

7.4.1 The medical laboratory must keep a list of all referral laboratories it commissioned by it. All medical laboratory examinations sent to a referral laboratory must be documented.

7.4.2 The commissioning medical laboratory is responsible for ensuring that the original submitter receives the examination results and findings from the referral laboratory.

7.4.3 When commissioning referral laboratories outside the scope of this guideline, the commissioning medical laboratory must ensure that the referral laboratory possesses

the required competencies and that an equivalent quality management system is in place.

7.5 Error management

The medical laboratory is to define and apply procedures for corrective and preventative measures for defective processes.

In the case of erroneous examination results, management must specifically ensure that:

(1) persons are designated as responsible for resolving issues,
(2) the medical significance of the erroneous result is considered and, if necessary, the sender is informed thereof,
(3) examinations are halted and reports are withheld as necessary,
(4) corrective actions are taken immediately,
(5) examination results that have been already released are recalled or the recipient is appropriately informed of the error,
(6) the party responsible for the recalling of the examination results is established,
(7) causes and corrective actions are documented and
(8) the success of any corrective action is verified to ensure that all identified non-conformities have been rectified.

The records documenting the identified non-conformities and the corrective actions are to be retained for two years.

8 Internal and external quality assurance

8.1 Internal quality assurance is to be conducted in medical laboratories using a control system that is in line with the present state-of-the-art in science and technology and the procedures described in the sections of Part B of this guideline.

8.2 The medical laboratory undertakes external quality assurance for by participating regularly in external quality assurance programmes in accordance with the procedures described in the sections of Part B of this guideline.

B Special Parts

B 1 Quantitative medical laboratory examinations

1 Principles of quality assurance

(1) Part B1 specifies minimum requirements for the quality assurance of results of quantitative medical laboratory examinations. These minimum requirements include internal and external quality assurance.
(2) All examinations performed by the medical laboratory in accordance with (1) are subject to internal quality assurance. If several devices or measuring stations are used to perform a medical laboratory examination, internal quality assurance is to be performed on each of these devices or measuring systems.
(3) Table B 1-1 contains the specifications and explanations for the pre-analytical phase of the sample material to be used – in order to minimise influencing and interfering factors – as well as the specific transport conditions.
(4) In addition, the measurands listed in Table B 1-2 a to d of this Part are subject to external quality assurance unless exempted.
(5) The measurands in Table B 1-2 a to d are listed alphabetically and according type of specimen. The criteria used for including a measurand in the table are, specifically, the frequency of the examination procedure and its medical relevance according to the current state of science. The deviations of measurements listed in the table are determined based on medical requirements and the current state of analytical technology. This Table is updated on a continuous basis.

(6) This Part of the guideline does not apply to the chamber counting of corpuscular components in body fluids, the determination of erythrocyte sedimentation rate, or the use of pH test strips.

2 Quality assurance procedure

2.1 Internal quality assurance

2.1.1 Procedure

(1) The specifications of the manufacturer are to be followed with regard to the type and frequency of the internal quality assurance. Irrespective of this, internal quality assurance is to be performed in accordance with (2) to (4).

(2) A single measurement of a control sample is to be performed at the start of the measurement procedure.

(3) On days when a measurement procedure is used to analyse patient samples, a single measurement of a control sample is to be performed at least twice within a 24-hour period and, at the latest, after 16 hours.

(4) In addition, a single measurement of a control sample is to be performed after every intervention to the measuring system.
Interventions to the measuring system are:
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 results of the medical laboratory examination and
d) changing reagent lots.

(5) The control samples must be as similar as possible to the patient samples being examined. The control material and calibration material used in the measurement procedure may not be identical.

(6) Control samples are to be used that have known target values that are within the measurement intervals relevant for medical decisions.

(7) Control samples with target values in at least two different concentrations are to be used on an alternating basis, if available.

2.1.2 Evaluating the results of single measurements of control samples

(1) The results of the single control sample measurements are to be evaluated without delay as soon as these results are available. Evaluation is based on the error limits as listed in in Column 3 of Table B1-2 a to d, or otherwise on the basis of the internal laboratory error limits or on the intervals of the manufacturers of the control samples. If the manufacturers' error limits are smaller than the permissible deviation listed in Column 3 of Table B 1-2 a to d, the manufacturers' error limits shall apply.

(2) If a single measurement of a control sample exceeds the error limit, the measurement procedure will initially be barred for further use in with patient specimens. The cause of the deviation is to be sought and, if possible, rectified. Taking into account the medical relevance, the person in charge must decide whether the examination procedure can be re-authorised or whether further measures must be taken, e.g., whether all of the examinations preceding and including the control examination are to be repeated, or whether the submitter are to be notified about results that have already been submitted. The entire process must be documented.

2.1.3 Calculating and evaluating the root mean square of the deviation of measurement after a control period ends

(1) The relative root mean square of the deviation of measurement must be calculated immediately after a control period ends from the results of all single control sample measurements that have led to the release of the measurement procedure or of the patient results. A control period generally consists of one calendar month. If, in one

control period, there are fewer than 15 results from single control sample measurements per measurement procedure that have led to the release of a measurement, this period will be extended by one month until at least 15 such results are available. The total period of time may not exceed three months.

(2) If the relative root mean square of the deviation of measurement for a control sample exceeds the value listed in Column 3 of Table B 1-2 a to d, the examination procedure is to be barred from further use in measuring patient sample material. The measurement procedure may not be approved for further measurements until the functionality of the procedure has been proven through appropriate actions. The entire process must be documented.

(3) If the value listed in Column 3 of Table B 1-2 a to d is again exceeded in the subsequent control period for the same control sample, and user-related causes can be excluded, appropriate actions are to be taken in accordance with (2) and the responsible federal authorities must be informed if this can be defined as an "incident" according to Section 2 of the Medical Device User Notification and Information Ordinance (MPAMIV).

(4) Paragraph (2) shall apply accordingly to measurands that are not listed in Table B 1-2 a to d. The laboratory's internal Δ_{max}, as established by the laboratory in accordance with 2.1.4 must be used instead of the maximum permissible deviation listed in Column 3 of Table B 1-2 a to d. The measurement procedure may not be made available for measurements until the functionality of the procedure has been proven through appropriate measures. The entire process is to be documented.

2.1.4 Establishing internal laboratory error limits for measurands not listed in Table B1

(1) In order to establish internal laboratory error limits for single control sample measurements of measurands not listed in Table B 1-2 a to d, one control sample result is chosen selected per day for a minimum of 15 days, or for a maximum of one control period, for each control sample used. Values are selected methodically, i.e., either the first, the nth or the last value. Randomly selected control results may also be used.

The error limits 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 internal laboratory deviation limits

s_{ep}, empirical standard deviation of the control sample measurements used in the calculations during the evaluation period (*ep*)

δ_{ep}, systematic deviation of measurement of the control sample measurements used in the calculations during the evaluation period (*ep*)

For simplification purposes, variance s^2_{ep} is not corrected with (n-1)/n.

To calculate relative internal laboratory deviation limits, Δ_{max} is to be divided by the target value x_0.

In justified cases, an internal laboratory deviation limit that deviates from this procedure can also be defined. The reasons and the chosen procedure are to be documented in a transparent way.

(2) The acceptability limits of the manufacturer of the control samples are to be used while the laboratory is establishing its own internal laboratory error limits.

(3) The internal laboratory error limits must be within the interval provided by the manufacturer of the control sample.

(4) No internal laboratory error limits need to be calculated for control samples with a shelf life of less than twelve weeks. The interval provided by the manufacturer of the control samples shall apply.

2.1.5 Patient-near immediate laboratory examinations with unit-use reagents

(1) When unit-use reagents and the corresponding measuring systems are used in patient-near immediate laboratory examinations, these must be examined 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 (2), (3) and (4 letter a) may be waived if electronic/physical standards are used daily, or where there is another form of integrated testing of the device's functionality that prevents the output of erroneous results. In such cases a single measurement of a control sample is to be taken at least once a week if the procedure is used during that calendar week to test patient specimens.

In the case of devices that do not use electronic/physical standards, or where there is no other form of integrated testing of the device's functionality to prevent the output of erroneous measuring results, only the regulations set forth in (2) and (4 letter a) of Section 2.1.1 shall be waived.

(3) The evaluation of the single control sample measurements and the consequences to be drawn therefrom must be in accordance with Section 2.1.2.

Sentence 1, shall apply accordingly for measurands not listed in the Tables B 1-2 a to d. The permitted error limits are those stated by the manufacturer of the control samples.

(4) Calculation and evaluation of the root mean square of the error of measurement according to Section 2.1.3 are omitted as well as a graphic illustration, as required in Section 2.1.7 (3).

2.1.6 Measurands with low examination frequencies

(1) Measurands 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, if available, on the days on which the patient samples are examined.

(2) The evaluation of the single measurements of the control samples and the consequences therefrom in accordance with Section 2.1.2 shall be carried out for all control samples. Sentence 1 shall apply accordingly for measurands not listed in the Tables B 1-2 a to d. The permitted error limits are those stated by the manufacturer of the control samples.

(3) Calculation and evaluation of the root mean square of the error of measurement according to Section 2.1.3 are omitted as well as a graphic illustration, as required in Section 2.1.7 (3).

2.1.7 Documentation

(1) All results of the internal quality assurance must be documented in a structured way according to the measurand and type of sample material, taking into account the measurement procedure and measuring system. The documentation must be presented upon request to the body responsible for ensuring compliance with this guideline.

(2) The documentation must include the following:

a) name of the medical laboratory,
b) name of the measuring system,
c) date and time of the measurement,
d) measurand, sample material and units,
e) measurement method,
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 evaluation in accordance with Column 3 of Table B1-2 a to d, or the internal laboratory error limits or the ranges stated by the manufacturer of the control samples,
i) release or blocking notice,
j) corrective actions taken,
k) manufacturer, name and lot number of the control sample and
l) name/cipher or signature of the investigator.

(3) In addition, the measured values of the control samples shall be represented graphically.

(4) All measurement results of the quality assurance must be retained for five years together with the calculations made after the control period ends, as well as the evaluations and the protocols on actions taken when limits of deviation were exceeded, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) Every location must participate in an EQA once a quarter for every measurand listed in Tables B 1-2 a to d, for which criteria are defined in Columns 5 and 6, for all examinations performed.

(2) The participant of the EQA shall examine the EQA samples under routine conditions and submit the results and information as required by the reference institution. By submitting the results, the participant confirms that the analysis was performed in accordance with this guideline, in the participant's laboratory, and under the participant's supervision.

(3) The obligations pursuant to (1) do not apply to examinations with unit-use reagents as part of patient-near immediate laboratory examination in:
a) hospitals, if the central laboratory is responsible for internal quality assurance and also determines the measurand itself,
b) doctors' offices and medical services without a central laboratory. Here, participation in EQAs is recommended.

(4) If the participant does not receive a certificate for a measurand because one of the participant's results exceeds the authorised error limits as specified in Column 5 of Table B1-2 a to d, the participant is obliged to determine the causes and rectify them if this lies within the participant's responsibility. The entire process is to be documented.

(5) The EQA participation certificate and the acquired EQA certificates must be retained for a period of five years unless longer periods of time are stipulated by other regulations.

Table B 1-1 – Specifications on specimen

1 No.	2 Measurand	3 Specimen to be used	4 Requirements for the pre-analytical phase	5 Annotation
1	Glucose	Plasma or whole blood (as part of the patient-near immediate laboratory examinations, if applicable, with proper anticoagulants)	If plasma separation or measurement does not occur within 15 minutes, in exceptional cases, but no later than 30 minutes, blood collection tubes with suitable glycolysis inhibition shall be used.	Without glycolysis inhibition, glucose values will be falsely low. The use of serum is unsuitable.
2	Potassium	Heparin-plasma or whole blood (as part of the patient-near immediate laboratory examinations, if applicable, with proper anticoagulants) are to be preferred	The separation of the cellular components must be carried out as soon as possible.	A deviation in potassium levels from the in vivo plasma levels occurs in particular 1) through delayed separation of cellular components, through

				hemolysis, and through the modulation of the membrane-bound, temperature-dependent sodium-potassium ATPase 2) when using serum, due to the release of potassium from platelets during in vitro coagulation

Notes on the Tables B 1-2 a to d:
In the tables below, the preferred units are shown in bold. This notation is intended to provide quick guidance and indicates that the unit in bold is the preferred notation according to the Rili-BAEK. Where other units are listed in the table, they represent acceptable but not preferred notations.

In Germany, the lowercase "l" is typically used for the unit of volume "liter". In the international context, however, it is customary to capitalize the letter "L" to avoid confusion with the numeral "1". It has been decided that the Rili-BAEK will use the German spelling with a lowercase "l".

Table B 1-2 a
Explanations for Table B 1-2 a below
Columns 2 to 4 list the requirements for use in the medical laboratories. Columns 2 and 4 to 6 list the requirements for the evaluation of the results by reference institutions.
The Rili-BAEK applicable concentration range is the concentration interval in which the specifications for the target values of control samples stated in Columns 3 and 5 shall apply.
If the target value of the control sample lies outside this interval, the regulations for measurands not listed in Table B 1-2 a shall apply. If control samples with target values under the Rili-BAEK-applicable concentration ranges are used, the error limits for this ranges can also be used to evaluate the measurements of these control samples.
RMV = reference method value
NV = nominal value specific to the measurement method.

Table B 1-2a – Measurands in plasma/serum/whole blood

1 **No.**	**2** **Measurand**	**3** **Permissible relative deviation of the single measurement of the control sample or the relative root mean square of the deviation of measurement**	**4** **Rili-BAEK applicable concentration intervals for Columns 3 and 5**			**5** **Permissible relative deviation in the EQA**	**6** **Type of EQA target value**
			From	**To**	**Unit**		
1	1,25-OH2-Vitamin D	±25.0 %	24 10	384 160	**pmol/L** ng/L	-	-
2	25-OH-Vitamin D	±25.0 %	12.5 5	300 120	**nmol/L** µg/L	-	-
3	ACE	±23.0 %	10 0.16	200 3.33	**U/L** µkat/L	-	-
4	Activated partial thromboplastin time (aPTT)	±10.5 %	20	120	s	±18.0 %	NV
5	Alanine aminotransferase	±11.5 %	30 0.5	300 5.0	U/L µkat/L	±21.0 %	RMV

	(ALT or GPT) EC 2.6.1.2						
6	Albumin	±12.5 %	20	70	g/L	±20.0 %	NV
7	Aldosterone (only in plasma)	±25.0 %	5	1,000	ng/L	-	-
8	Alkaline phosphatase (AP) EC 3.1.3.1	±11.0 %	20 0.33	600 10	U/L µkat/L	±18.0 %	NV
9	Alpha-amylase	±7.0 %	20 0.33	1,000 16.7	U/L µkat/L	-	-
10	Alpha fetoprotein (AFP)	±17.0 %	5	250	kU/L	±24.0 %	NV
11	ApoA1	±10.0 %	0.5 50	2.5 250	**g/L** mg/dL	±15.0 %	NV
12	ApoB	±10.0 %	0.4 40	2.0 200	**g/L** mg/dL	±15.0 %	NV
13	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
14	Bilirubin (total)	±13.0 % ±22.0 %	>34 >2 1.7 0.1	513 30 ≤34 ≤2	**µmol/L** mg/dL **µmol/L** mg/dL	±22.0 %	NV
15	BNP	±15.0 %	20 20	5,000 5,000	**ng/L** pg/mL	-	-
16	Ca 15-3	±16.0 %	10	250	kU/L	±24.0 %	NV
17	CA 19-9	±20.0 %	5	500	kU/L	-	-
18	CA 125	±16.0 %	10	1,000	kU/L	-	-
19	Calcium (total)	±6.0 %	1	6	mmol/L	±10.0 %	RMV
20	Calcium (ionised)	±7.5 % ±14.0 %	>1 0.2	2.5 ≤1	mmol/L mmol/L	±15.0 % ±18.0 %	NV
21	Carbamazepine	±12.0 %	2	20	mg/L	±20.0 %	NV
22	Carcinoembryonic antigen (CEA)	±14.0 %	1	200	µg/L	±24.0 %	NV
23	CDT	±25.0 %	0.5	10	%	-	-
24	Chloride	±4.5 %	70	150	mmol/L	±8.0 %	RMV
25	Cholesterol (total)	±7.0 %	1.3 50	9.1 350	**mmol/L** mg/dL	±13.0 %	RMV
26	Cortisol	±16.0 % ±18.5 %	>166 >60 55 20	1,380 500 ≤166 ≤60	**nmol/L** µg/L **nmol/L** µg/L	±30.0 %	RMV
27	C-reactive protein (CRP)	±13.5 %	1	120	mg/L	±20.0 %	NV
28	Creatine kinase (CK) EC 2.7.3.2	±11.0 %	50 0.83	1,000 16.7	U/L µkat/L	±20.0 %	RMV
29	Cyclosporine A	±25.0 %	20 20	1,500 1,500	**µg/L** ng/mL	-	-
30	Cystatin C	±13.0 %	0,3	6	mg/L	-	-
31	D-Dimer	±20.0 %	0.1	5	mg/L	-	-
32	Digitoxin	±15.5 %	5	80	µg/L	±30.0 %	RMV
33	Erythrocytes	±4.0 %	1.5	7	10^{12}/L	±8.0 %	RMV
34	Estradiol 17-beta	±22.0 %	37 10	1,835 500	**pmol/L** ng/L	±35.0 %	RMV
35	Ethanol (clinical toxicological)	±9.0 % ±15.0 %	>0.6 0.2	5 ≤0.6	g/L g/L	±12.0 % ±21.0 %	NV

	Ethanol in whole blood (clinical toxicological) Ethanol in plasma/serum (clinical toxicological)	±9.0 % ±15.0 % ±9.0 % ±15.0 %	>0.57 0.19 >0.49 0.16	4,73 ≤0.57 4.06 <0.49	‰ ‰ ‰ ‰	±12.0 % ±21.0 % ±12.0 % ±21.0 %	NV NV
36	Ferritin	±13.5 %	10	600	µg/L	±25.0 %	NV
37	Fibrinogen	±20.0 %	0.5	10	g/L	-	-
38	Folic acid	±25.0 %	2.27 1	90.8 40	**nmol/L** ng/mL	-	-
39	FSH	±14.0 %	4	70	U/L	±21.0 %	NV
40	Gamma glutamyl transferase (γ-GT) EC 2.3.2.2	±11.5 %	20 0.33	300 5	U/L µkat/L	±21.0 %	RMV
41	Gentamicin	±25.0 %	0.5 0.5	15 15	**mg/L** µg/mL	-	-
42	Glucose (see also Table B 1-1)	±5.0 %	2.2 40	22 400	**mmol/L** mg/dL	±8.0 %	RMV
43	Haematocrit	±5.0 %	0.1 10	0.6 60	**L/L** %	±9.0 %	NV
44	Haemoglobin	±4.0 %	1.2 2	12.4 20	**mmol/L** g/dL	±6.0 %	RMV
45	Haemoglobin A 1c (HbA1c)	±3.0 %	30	140	mmol/molHb	±8.0 %	RMV
46	Haptoglobin **larger** 1g/L Haptoglobin **smaller** 1g/L	±10.0 % ±20.0 %	>1 0.05	6 1.0	g/L g/L	- -	- -
47	Uric acid	±7.0 %	119 2	773 13	**µmol/L** mg/dL	±13.0 %	RMV
48	Urea	±10.5 %	2.5 15	33.3 200	**mmol/L** mg/dL	±20.0 %	RMV
49	HDL-C	±13 %	0.26 10	3.1 120	**mmol/L** mg/dL	-	-
50	Human chorionic gonadotropin (hCG)	±14.0 % ±17.0 %	>100 2	1,500 ≤100	U/L U/L	±30.0 %	NV
51	Immunoglobulin A (IgA)	±12.0 %	0.5	6	g/L	±20.0 %	NV
52	Immunoglobulin E (IgE, total)	±20.0 %	0.1 0.1	1,000 1,000	**kU/L** U/mL	-	-
53	Immunoglobulin G (IgG)	±10.0 %	4	30	g/L	±18.0 %	NV
54	Immunoglobulin M (IgM)	±13.0%	0.4	5	g/L	±26.0 %	NV
55	Interleukin 6 (IL-6)	±18.0 %	3 3	2,000 2,000	ng/L pg/mL	-	-
56	Potassium (see also Table B 1-1)	±4.5 %	2	8	mmol/L	±8.0 %	RMV
57	Creatinine	±11.5 %	44 0.5	884 10	**µmol/L** mg/dL	±20.0 %	RMV
58	Lactate	±11.0 %	1 9	10 90	**mmol/L** mg/dL	±18.0 %	NV
59	Lactate dehydrogenase (LDH) EC 1.1.1.27	±9.0 %	100 1.67	700 11.7	**U/L** µkat/L	±18.0 %	RMV
60	LDL-C	±9.0 %	0.78 30	7.8 300	**mmol/L** mg/dL	-	-
61	Leucocytes	±6.5 %	2	30	10^9/L	±18.0 %	RMV
62	LH	±15.0 %	0.2	150	U/L	-	-
63	Lipase	±11.0 %	20	1,000	**U/L**	-	-

			0.33	16.7	µkat/L		
64	Lithium	±6.0 %	0.3	3.5	mmol/L	±12.0 %	RMV
65	Magnesium	±7.5 %	0.3	3.5	mmol/L	±15.0 %	RMV
66	Methotrexate	±25.0 %	0.05	10	µmol/L	-	-
67	Sodium	±3.0 %	110	180	mmol/L	±5.0 %	RMV
68	NT-proBNP	±15.0 %	30 30	10,000 10,000	**ng/L** pg/mL	-	-
69	pCO2 (SI conform unit) pCO2 (conventional unit)	±7.5 % ±6.5 % ±7.5 % ±6.5 %	≤4,67 >4,67 ≤35 >35		**kPA** **kPA** mmHg	±12.0 % ±12.0 % ±12.0 % ±12.0 %	NV NV
70	pH	±0.4 %	6.75	7.80		±0.80 %	NV
71	Phenobarbital	±10.0 %	8	80	mg/L	±20.0 %	NV
72	Phenytoin	±11.0 %	3	35	mg/L	±20.0 %	NV
73	Phosphate (inorganic)	±9.0 %	0.3 1	3.2 10	**mmol/L** mg/dL	±16.0 %	NV
74	pO_2 (SI conform unit) pO_2 (conventional unit)	±5,5 % ±7,0 % ±11,0 % ±5.5 % ±7.0 % ±11.0 %	>16.66 >10.66 5.33 >125 >80 40	 350 ≤125 ≤ 80	**kPA** **kPA** **kPA** mmHg mmHg mmHg	±12.0 % ±18.0 % ±18.0 % ±12.0 % ±18.0 % ±18.0 %	NV
75	Procalcitonin	±18.0 %	0.1	60	ng/mL	-	-
76	Progesterone	±17.0 % ±22.0 %	>16 >5.0 0.6 0.2	111 35 16 ≤5.0	**nmol/L** µg/L **nmol/L** µg/L	±35.0 %	RMV
77	Prostate specific antigen (PSA)	±15.5 %	0.2	50	µg/L	±25.0 %	NV
78	PSA, free	±20.0 %	<30 <30		**µg/L** ng/ml		
79	Protein (total)	±6.0 %	35	110	g/L	±10.0 %	RMV
80	Prothrombin time	±11.5 %	10	120	%	±23.0 %	NV
81	Renin	±25.0 %	1	300	ng/L	-	-
82	Reticulocytes automated measurement	±25.0 %	20 20	400 400	**109 cells/L** cells/nL	-	-
83	Tacrolimus	±25.0 %	1	50	**µg/L**	-	-
84	Testosterone	±20.5 %	0.7 0.2	69 20	**nmol/L** µg/L	±35.0 %	RMV
85	Theophylline	±13.0 %	3	40	mg/L	±24.0 %	RMV
86	Thrombocytes	±7.5 % ±8.5 % ±13.5 %	>300 >150 40	700 ≤300 ≤150	**10^9/L** **10^9/L** **10^9/L**	±13.0 % ±15.0 % ±18.0 %	NV
87	Thyreotropic hormone (TSH)	±13.5 %	0.1	40	mU/L	±24.0 %	NV
88	Thyroxine, free (fT4)	±13.0 %	>26 >20	109 85	**pmol/L** ng/L	±20.0 %	NV
89	Transferrin	±8.0 %	0.5	6	g/L	±12.0 %	NV
90	Triglycerides	±9.0 %	0.68 60	4.6 400	**mmol/L** mg/dL	±16.0 %	RMV
91	Triiodothyronine, free (fT3)	±13.0 %	1.5 1	39 25	**pmol/L** ng/L	±20.0 %	NV
92	Troponin, cardiac	±20.0 %	10	3,000	ng/L	±33.0 %	NV
93	Valproic acid	±11.5 %	20	150	mg/L	±20.0 %	NV
94	Vancomycin	±12.0 %	4	100	mg/L	±18.0 %	NV
95	Vitamin B12	±25.0 %	36.9 50	1,107 1,500	**pmol/L** pg/mL	-	-

Table B 1-2 b – Measurands in urine

1 No.	2 Measurand	3 Permissible relative deviation of the single measurement of the control sample or the relative root mean square of the deviation of measurement	4 Rili-BAEK-applicable concentration intervals for Columns 3 and 5			5 Permissible relative deviation in the EQA	6 Type of EQA target value
			From	To	Unit		
1	Albumin	±15.0 %	0.001 1	0.5 500	**g/L** mg/L	±26.0 %	NV
2	Calcium	±8.5 %	0.5	6	mmol/L	±17.0 %	NV
3	Glucose	±5.0 %	0.6 100	22 4,000	**mmol/L** mg/L	±8.0 %*	RMV
4	Uric acid	±13.5 %	30 5	1,784 300	**µmol/L** mg/L	±23.0 %	RMV
5	Urea	±13.5 %	1.7 0.1	333 20	mmol/L g/L	±21.0 %	RMV
6	Potassium	±8.5 %	2	140	mmol/L	±15.0 %	RMV
7	Creatinine	±12.0 %	0.1 0.01	27 3	**mmol/L** g/L	±21.0 %	RMV
8	Sodium	±6.5 %	50	200	mmol/L	±12.0 %	RMV
9	Phosphate (inorganic)	±11.5 %	1 30	29 900	**mmol/L** mg/L	±20.0 %	NV
10	Protein (total)	±11.5 %	0.005 5	10 10,000	**g/L** mg/L	±24.0 %	NV

Table B 1-2 c – Measurands in cerebrospinal fluid

1 No.	2 Measurand	3 Permissible relative deviation of the single measurement of the control sample or the relative root mean square of the deviation of measurement	4 Rili-BAEK-applicable concentration intervals for Columns 3 and 5			5 Permissible relative deviation in the EQA	6 Type of EQA target value
			From	To	Unit		
1	Albumin	±13.5 %*	20	2,000	mg/L	±23.0 %	NV
2	Glucose	±5,0 %	1.1 20	17 300	**mmol/L** mg/dL	±8.0 %*	RMV
3	Immunoglobulin A (IgA)	±15.5 %*	0.5	80	mg/L	±25.0 %*	NV
4	Immunoglobulin G (IgG)	±12.0 %*	15	500	mg/L	±20.0 %*	NV
5	Immunoglobulin M (IgM)	±15.5 %*	0.2	60	mg/L	±33.0 %*	NV
6	Lactate	±11.5 %	1.1 10	11 99	**mmol/L** mg/dL	±20.0 %	NV
7	Protein (total)	±13.5 %	0.05 50	4 4,000	**g/L** mg/L	±20.0 %	NV
Specifications for cerebrospinal fluid/plasma ratios and cerebrospinal fluid/serum ratios							
8	Albumin ratio	±15.0 %	1	150		±20.0 %	NV
9	IgA ratio	±20.0 %	0.2	75		±30.0 %	NV
10	IgG ratio	±15.0 %	0.5	100		±20.0 %	NV
11	IgM ratio	±20.0 %	0.1	50		±35.0 %	NV

* If no cerebrospinal fluid/plasma or serum pairs with known nominal values are available, the cerebrospinal fluid/plasma or serum ratios must be calculated from the nominal values of the individual controls for cerebrospinal fluid and plasma or serum.

Table B 1-2 d – Measurands in dried blood

1 No.	2 Measurand	3 Permissible relative deviation of the single measurement of the control sample or the relative root mean square of the deviation of measurement	4 Rili-BAEK-applicable concentration intervals for Columns 3 and 5			5 Permissible relative deviation in the EQA	6 Type of EQA target value
			From	To	Unit		
1	17-OH-Progesterone	±20 %	15	120	nmol/L	±30 %	NV
2	IRT	±20 %	30	180	µg/L	±30 %	NV
3	PAP	±20 %	1	6.3	µg/L	±30 %	NV
4	TSH	±20 %	8	60	mU/L	±30 %	NV

B 2 Qualitative medical laboratory examinations

1 Principles of quality assurance

(1) Part B 2 specifies minimum requirements for the quality assurance of the results of qualitative medical laboratory examinations. These minimum requirements include internal and external quality assurance.

(2) All examinations performed by the medical laboratory in accordance with (1) are subject to internal quality assurance. If several devices or measuring stations are used to perform a medical laboratory examination, internal quality assurance is to be performed on each of these devices or measuring stations.

(3) In addition, the measurands and nominal characteristics listed in Table B 2-2 of this Part are subject to external quality assurance.

(4) The measurands in Tables B 2-1 and B 2-2 are listed alphabetically. The criteria used for including a measurand in the tables are, specifically, the frequency of the examination procedure and its medical relevance according to the current state of science. The tables are updated on a continuous basis.

(5) This Part of the guideline does not apply to qualitative tissue examinations and to examinations whose internal and external quality assurance requirements are stated in other sections of Part B.

2 Quality assurance procedure

2.1 Internal quality assurance

2.1.1 Procedure

(1) The specifications of the manufacturer are to be followed with regard to the type and frequency of the internal quality assurance.
Irrespective of this, internal quality assurance must be performed:
a) in accordance with Table B 2-1 for the examinations listed therein,
b) on an adequate and regular basis in accordance with medical necessity and with the required examination frequency of patient specimens, if the examinations are not listed in Table B 2-1.
The requirements of (1) Sentence 2 are considered to be met if corresponding controls that ensure the accuracy of the results are integrated into the applied measuring system.

(2) In addition, internal quality assurance is to be performed after every interruption to the examination procedure. Interruptions to the examination 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 medical laboratory examination and
d) changing reagent lots[1]

(3) The control samples must be as similar as possible to the patient samples being examined. The control material and calibration material used in the examination procedure must not be identical.

(4) Control samples with known results are to be used that are within the measurement interval relevant for making medical decisions.

(5) When unit-use reagents and their corresponding measuring systems are used in patient-near immediate laboratory examination, the requirements of (1) Sentence 2 and (2) Sentence 2 (a) do not need to be met as long as process control measures indicating the display of erroneous examination results are integrated into the test. If the manufacturer has not provided specifications, or if the manufacturer has not specified that positive and/or negative control samples are required, the laboratory must establish the frequency of positive and/or negative control samples based on criteria tailored to the specific procedure (risk-based quality assurance). The frequency and results of these control samples must be documented.

2.1.2 Evaluating the results

(1) The results of the control sample examinations are to be evaluated without delay as soon as the result/results are available. The evaluation is performed using the target values assigned to the control sample.

(2) If the requirements are not met, the examination procedure will initially be barred from further use with samples from patients. The cause of the failure is to be sought and, if possible, rectified. Taking medical relevance into consideration, the person in charge must decide whether the examination procedure can be re-authorised or whether further actions must be taken, e.g., whether all of the examinations prior to and including the control examination are to be repeated, or whether the submitter is to be notified about results that have previously been submitted. The entire process is to be documented.

2.1.3 Documentation

(1) All results of the internal quality assurance must be documented in a structured way according to the type of sample material, taking into account the examination procedure and measuring station or device. The documentation is to be presented upon request to the body responsible for ensuring compliance with this guideline.

(2) The documentation must include the following:
a) name of the medical laboratory,
b) name of the measuring station or device,
c) date and, where relevant, time of the examination,
d) examination, sample material, and, if necessary, the unit of measurement,
e) examination method,
f) measured value of the control sample,
g) target value of the control sample,
h) the evaluation,
i) release or blocking notice,
j) corrective actions taken,
k) manufacturer, name and lot number of the control sample and
l) name/cipher or signature of the investigator.

[1] This also includes changes to the composition of the reagents, such as the production of dilutions or, in the case of in-house production, the reiterated preparation of reagents.

(3) The documentation on the performed internal quality assurance must be retained for five years along with the evaluations as well as the protocols of the actions taken when the target values were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) Every location must participate in an EQA for every examination listed in Table B 2-2 in accordance with the frequency stated therein if the medical laboratory examination is provided by the location. Participation is mandatory for the examinations listed in the table regardless of whether the examination result is quantitatively or qualitatively stated in the report or in the findings.

(2) The participant in the external quality assessment programme shall examine the EQA samples under routine conditions and submit the results and information as required by the reference institution. By submitting these results, the participant confirms that the examinations were performed in accordance with this guideline, in the participant's laboratory, and under the participant's supervision.

(3) If the participant does not receive a certificate for an examination because one or more of the participant's results do not meet the target values of the respective reference institute, the participant is obliged to determine the causes and rectify them insofar as this lies within the participant's responsibility. The entire procedure is to be documented.

(4) The EQA participation certificate and the acquired EQA certificates are to be retained for a period of five years unless longer periods of time are stipulated by other regulations.

Table B 2-1 – Internal quality assurance

No.	Measurand/Examination	Frequency of controls
1	6-Acetylmorphine	Daily
2	ABO features	Weekly
3	Amphetamines	Daily
4	Anti-glomerular basement membrane	Daily
5	Anti-mitochondrial antibodies (M2) (AMA)	Daily
6	Barbiturates	Daily
7	Benzodiazepines	Daily
8	*Borrelia burgdorferi*, antibodies against	Daily
9	Buprenorphine	Daily
10	*Candida albicans*, antibodies against	Daily
11	Cannabinoids	Daily
12	Chromatographic analysis with identification of the active substance (STA)	Daily
13	Cocaine and metabolites	Daily
14	Cytomegalovirus (CMV), antibodies against	Daily
15	Direct Coombs test	Weekly
16	dsDNA, autoantibodies against	Daily
17	*Echinococcus*, antibodies against	Daily
18	Electrophoresis with immunoreaction	Monthly
19	*Entamoeba histolytica*, antibodies against	Daily
20	Epstein-Barr virus (EBV), antibodies against	Daily
21	Erythrocyte antigens, antibodies against (Coombs test)	Daily
22	Extractable nuclear antigens, autoantibodies against	Daily
23	Smooth muscle, autoantibodies against	Daily
24	HBc antigen, antibodies against	Daily
25	HBs antigen, antibodies against	Daily
26	Hepatitis A virus, antibodies against	Daily
27	Hepatitis C virus, antibodies against	Daily
28	Herpes simplex virus (HSV), IgG antibodies against	Daily
29	HIV, antibodies against	Daily

30	iFOBT, immunological faecal occult blood test	Weekly
31	IgE antibodies, allergen-specific single allergen test Method-specific control in a rotating procedure with a leading allergen	Weekly
32	Immune complexes, circulating	Daily
33	Kell antigen	Weekly
34	Nuclei (ANA), autoantibodies against	Daily
35	Measles virus, antibodies against	Daily
36	Methadone and metabolites	Daily
37	Methaqualone	Daily
38	Mitochondria (AMA), autoantibodies against	Daily
39	Mumps virus, antibodies against	Daily
40	Opiates	Daily
41	Parvovirus B19, antibodies against	Daily
42	Phencyclidine	Daily
43	Plasmodium, antibodies against	Daily
44	Rhesus type	Weekly
45	Rheumatoid factor (RF)	Daily
46	Ribonucleoprotein (RNP), autoantibodies against	Daily
47	Rubella virus, antibodies against	Daily
48	*Schistosoma*, antibodies against	Daily
49	Scl-70 antigen, autoantibodies against	Daily
50	Sm antigen, autoantibodies against	Daily
51	SS-A antigen, autoantibodies against	Daily
52	SS-B antigen, autoantibodies against	Daily
53	Streptococcal desoxyribonuclease, antibodies against	Daily
54	Streptolysin O, antibodies against	Daily
55	*Toxoplasma gondii*, antibodies against	Daily
56	Transglutanimase, antibodies against	Daily
57	*Treponema pallidum*, antibodies against	Daily
58	Tricyclic anti-depressives	Daily
59	*Varicella zoster* virus, antibodies against	Daily
60	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 (EQA)

No.	Measurand/Examination	Frequency of participation
1	ABO features	Quarterly
2	Anti-glomerular basement membrane	6-monthly
3	Anti-mitochondrial antibodies (M2) (AMA)	6-monthly
4	*Borrelia burgdorferi*, antibodies against	6-monthly
5	*Candida albicans*, antibodies against	6-monthly
6	Cannabinoids	Quarterly
7	CD4 T cells	6-monthly
8	CD8 T cells	6-monthly
9	Chromatographic analysis with identification of the active substance (STA)	6-monthly
10	Cocaine and metabolites	Quarterly
11	Cytomegalovirus (CMV), antibodies against	6-monthly
12	Differential, blood smear	Quarterly
13	Direct Coombs test	Quarterly
14	dsDNA, autoantibodies against	6-monthly
15	*Echinococcus*, antibodies against	Annually
16	*Entamoeba histolytica*, antibodies against	Annually
17	Epstein-Barr virus (EBV), antibodies against	6-monthly
18	Erythrocyte antigens, antibodies against (Coombs test)	Quarterly
19	HBc antigen, antibodies against	6-monthly
20	HBs antigen, antibodies against	6-monthly
21	Hepatitis A virus, antibodies against	6-monthly
22	Hepatitis C virus, antibodies against	6-monthly

23	Herpes simplex virus (HSV), IgG antibodies against	6-monthly
24	HIV, antibodies against	6-monthly
25	iFOBT, immunological faecal occult blood test	Annually
26	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	6-monthly
27	Immunoglobulins, oligoclonal (oligoclonal bands)	6-monthly
28	Kell antigen	Quarterly
29	Nuclei (ANA), autoantibodies against	6-monthly
30	Measles virus, antibodies against	6-monthly
31	Methadone and metabolites	Quarterly
32	Mumps virus, antibodies against	6-monthly
33	Opiates	Quarterly
34	Parvovirus B19, antibodies against	6-monthly
35	*Plasmodium*, antibodies against	Annually
36	Rhesus type	Quarterly
37	Rheumatoid factor r (RF)	Quarterly
38	Rubella virus, antibodies against	6-monthly
39	*Schistosoma*, antibodies against	Annually
40	Streptococci desoxyribonuclease, antibodies against	6-monthly
41	Streptolysin O, antibodies against	6-monthly
42	*Toxoplasma gondii*, antibodies against	6-monthly
43	Transglutanimase, antibodies against	
44	*Treponema pallidum*, antibodies against	6-monthly
45	Tricyclic antidepressives	Quarterly
46	Urine sediment	Annually
47	*Varicella zoster* virus, antibodies against	6-monthly
48	Cytoplasmic components of neutrophil granulocytes (C-ANCA, P-ANCA), autoantibodies against	6-monthly

B 3 Direct detection and characterisation of infectious agents

1 Principles of quality assurance

(1) Part B 3 specifies the minimum requirements for the quality assurance of the results of medical laboratory examinations used to directly detect of medically relevant infectious agents. These minimum requirements can include subsequent examinations for the characterisation of pathogens (e.g., differentiation, identification, and typing) and their properties relevant for the treatment of infections (e.g., susceptibility testing to anti-infective agents). These minimum requirements apply to internal and external quality assurance.

(2) All examinations performed by the medical laboratory in accordance with (1) are subject to internal quality assurance. If multiple instruments or measuring stations are used for an examination, internal quality assurance is to be performed on each of these devices or measuring stations.

(3) In addition, the examinations listed in Tables B 3-2 and B 3-2 a are subject to external quality assurance.

(4) The examinations in Tables B 3-1, B 3-1 a, B 3-2 and B 3-2 a are listed separately according to the type of pathogen or testing method(s) used. The criteria used for including an examination in the tables are, specifically, the frequency of the examination and its medical relevance according to the current state of science. The respective tables are updated on a continuous basis.

2 Quality assurance procedure

2.1 Internal quality assurance

2.1.1 Procedure

(1) The specifications of the manufacturer are to be followed with regard to the type and frequency of the internal quality assurance. Irrespective of this, internal quality assurance is to be performed
   a) in accordance with Tables B 3-1 and B 3-1 a for the examinations listed therein,
   b) on an adequate and regular basis in accordance with the medical necessity and the frequency of examinations required for the analysis of patient samples, if the examinations are not listed in the Tables B 3-1 and B 3-1 a.

   The requirements of (1) Sentence 2 are considered to be met if corresponding controls that ensure the accuracy of the results are integrated in the applied analysis system.

(2) The following must be examined as part of the internal quality assurance:
   a) culture media and supplements,
   b) cell lines utilised for cell culture procedures,
   c) reagents, staining solutions, diagnostic antibodies and antigens,
   d) methods used for identifying of pathogens and for the susceptibility testing,
   e) equipment and instruments utilised for the respective examination.

(3) Furthermore, internal quality assurance is to be performed after every intervention to the examination procedure. Interventions to the examination procedures include:
   a) calibration,
   b) repairs or maintenance of equipment and instruments relevant to the respective examination,
   c) events that could interfere with the integrity of relevant components of the measurement procedure and
   d) a change in reagent lots[2].

(4) Control samples must be as similar as possible to the examined patient samples. The control and calibration materials used in the examination must not be identical.

(5) Control samples with known results are to be used unless otherwise stated.

(6) Statistics are to be kept and evaluated with respect to the frequency of the pathogens detected and their susceptibility to anti-infective agents.

2.1.2 Special specifications

2.1.2.1 Microscopy

Internal quality assurance for microscopic techniques is specified in Table B 3-1.

Additionally, suitable specimens (e.g., durable specimens, preserved parasites) or illustrative materials (e.g., image charts, atlases) must be available in sufficient quantities to be used as reference, comparison and teaching materials.

2.1.2.2 Culture-based procedures

2.1.2.2.1 Non-cell culture-based procedures

Internal quality assurance for non-cell culture-based procedures is specified in Table B 3-1. The following regulations also apply:

(1) Appropriately prepared and, if applicable, cryopreserved control strains are to be used for control purposes.

(2) The laboratory must specify the rules and standards used for susceptibility testing. Susceptibility tests may only be performed on pure cultures. Thus, the inoculum must always undergo a purity check. Susceptibility tests for orientation with non-standardised inocula (e.g., from blood cultures) are to be repeated on a standardised basis.

[2] This also includes changes to the composition of the reagents, such as the production of dilutions or, in the case of in-house production, the reiterated preparation of reagents.

(3) Stock cultures must be prepared from reference cultures at least once a month for the susceptibility testing. Test cultures prepared from stock cultures may only be used for a maximum of one week.

2.1.2.2.2 Cell culture-based procedures

Internal quality assurance for cell culture-based methods is specified in Table B 3-1. The following regulations also apply:

(1) Appropriately prepared and, if applicable, cryopreserved control strains (positive control sample) and a non-infected culture control (negative control sample) are to be used. It must be checked whether the negative control sample used is morphologically normal. The result must be documented.

(2) Sub-cultures generated for the enrichment of pathogens from low initial quantities within patient samples are to be documented.

(3) The virus dosage for cell culture-based neutralisation tests is to be determined and documented using a TCID50 assay or a comparable procedure.

(4) Sensitive and non-sensitive control strains must be used as positive and negative control samples for phenotypic resistance testing. The extent of inhibition by the antiviral control substance must be documented.

2.1.2.3 Molecular biological procedures

The internal quality assurance for molecular biological methods is specified in Tables B 3-1 and B 3-1 a. The following regulations also apply:

(1) The procedures for the isolation of nucleic acids, adjusted to the properties of the respective pathogens and specimens to be tested, are to be reviewed on a regular basis.

(2) At least one positive and one negative control sample must be used and, if applicable, inhibition controls[3] must be carried out. If available, the concentration of one of the positive control samples shall 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 based on the assigned target values.

(3) When determining nucleic acid concentrations, control samples containing known concentrations of nucleic acid or the respective pathogen must be used. These control samples are to be verified with international standards, if available.

(4) The following quality controls are to be carried out on sequence-based NAT systems which are operated continuously during the day and in which there is an internal process control (internal control/internal quantification standard):
   a) For qualitative tests: at least one positive and one negative control sample each working day before the start of testing or in parallel.
   b) For quantitative tests: at least one positive and one negative control each working day before the start of testing or in parallel, and at least one positive control within 24 hours and, at the latest, after 16 hours. If available, control samples with target values in at least two different concentration ranges shall be used in alternation on a regular basis.

(5) In the case of closed test systems (e.g., cartridge systems) for the qualitative or quantitative detection of pathogen-specific nucleic acid, the need to use additional control samples for each test may be waived – in deviation from Paragraphs 1 to 3 – if enough process controls are integrated into the process to ensure the functionality of the reagents, including extraction, purification, amplification and inhibition. In the absence of any specifications by the manufacturer, or if no positive and/or no negative control sample is deemed necessary by the manufacturer, the laboratory must justifiably determine the frequency of positive and/or negative control samples through

[3] Waiving inhibition controls requires justification

specifications adapted to the respective procedure (risk-based quality assurance). The frequency and result of these control samples is to be documented. When such systems are used for qualitative nucleic acid detection, the positive control shall be a maximum of 2 log levels (base 10) above the lower detection limit. For quantitative nucleic acid detection, two controls with known concentrations from the upper and lower range of quantification are to be used respectively. Deviations from the target value must not exceed ± 0.5 log (base 10). In the case of multiplex analyses, care must be taken to ensure that the positive control samples represent all pathogens detectable by the system over the course of 12 months (risk-based quality assurance). The frequency and results of these control samples must be documented. It must also be ensured that, in the case of analysis equipment with several test stations, all modules are used at a similar frequency (unless specified by the device).

(6) Limits of detection must comply with the stipulations listed in Table 3-1 a. For specifications not listed in Table 3-1 a the following regulation applies: the permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value of the quantitative positive control is to be established internally in the laboratory and documented, or alternatively, for real time PCR, the permissible absolute deviation of the number of cycles from the nominal value (cycle threshold/C_t, crossing point/C_p, cycle quantitative/C_q) is to be established. Likewise, the area of validity for the quantitative positive control must be established and documented.

(7) The identity of amplification products must be verified using sequence-specific procedures.

2.1.2.4 Immunological examinations to directly detect pathogens

Internal quality assurance for immunological examinations for the direct detection of pathogens is specified in Table B 3-1. The following also applies: analysis criteria must be established for direct procedures to detect pathogen-derived antigens using fluorophore-marked antibodies and evaluation criteria for the test readout must be defined when using particle/erythrocyte suspensions as a component of the diagnostic test (e.g., agglutination, lytic reaction).

2.1.3 Evaluating the results

(1) The control sample result/results are to be evaluated without delay. The evaluation is based on target values assigned to the respective control sample.

(2) If the required specifications are not met, the respective examination procedure will be initially barred from examining further patient samples. The cause of the performance failure is to be sought and, whenever possible, rectified. Taking medical relevance into consideration, the person in charge must decide whether the examination procedure can be re-authorised or whether further actions are to be taken, e.g., whether all of the examinations prior and including the control examination have to be repeated, or whether the sender has to be notified about results already submitted. The entire process is to be documented.

2.1.4 Documentation

(1) All results of the internal quality assurance are to be documented in a structured way according to the type of the sample material taking into account the examination procedure and measuring station or device. The documentation is to be presented upon request to the body responsible for ensuring compliance with this guideline.

(2) The documentation must include the following:

a) the name of the medical laboratory,
b) the name of the measuring station or device,
c) date and, if relevant, time of the examination,
d) examination, sample material and, if required, the unit of measurement,
e) examination method,

f) result of the control sample,
g) objectives for the control sample,
h) the evaluation,
i) release or blocking notice,
j) corrective actions taken,
k) manufacturer, name and batch number of the control sample as appropriate and
l) name/cipher or signature of the investigator.

(3) The documentation on the performed internal quality assurance must be retained for a minimum of five years along with the evaluations as well as the protocols of the corrective actions taken when target values were not met, unless longer archiving periods are stipulated by other regulations.

2.2. External quality assurance (EQA)

(1) Every location must participate in an EQA for every examination listed in Tables B 3-2 and B 3-2 a in accordance with the frequency stated therein if the medical laboratory examination is provided by the location.

(2) The participant in the external quality assurance programme shall examine the EQA samples under routine conditions and submit the results and information as required by the reference institution. By submitting the results, the participant confirms that the examinations were performed in accordance with this guideline, in the participant's laboratory, and under the participant's supervision.

(3) If the participant does not receive a certificate for an examination because one or more of the results do not meet the target values of the respective reference institute, the participant is obliged to determine the causes and rectify them if this lies within the participant's responsibility. The entire procedure is to be documented.

(4) The EQA participation certificate and the acquired EQA certificates are to be retained for a period of five years unless longer periods of time are stipulated by other regulations.

Table B 3-1 – Internal quality assurance

Examination	Objective	Permissible deviation	Frequency
Microscopy			
Gram stain	Characteristic staining of gram-negative and gram-positive bacteria on a control specimen (e.g., tongue swab)	None	Daily
Ziehl-Neelsen stain	Characteristic staining of acid-fast bacilli on a control specimen	None	Daily
Giemsa stain	Characteristic staining of erythrocytes and leucocytes in a smear, if applicable, from the specimen being tested pH value of the buffer	None 6.8–7.2	Daily Weekly
Microscopic detection of pathogens, e.g., parasites	Identification of characteristic pathogen structures e.g., using image charts or external quality assurance programme/other preserved specimens ("consensus training")	A maximum 20 % deviation (based on the number of specimens assessed)	Annually
Negative contrasting in the 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	None	With every new lot of film-coated copper mesh
Culture procedures			

Non-cell culture-based procedures			
Visual check of solid culture media	Detection of transport or storage damage, such as impurities, drying out	None	Each package unit in every delivery and all new lots
Checking sterility[4]	No growth	None	When changing lots
Examination of the culture media[5] using control strains or parallel testing with comparison to earlier batches for: - all media - solid culture media with incubation periods exceeding 72 hours - selective media - indicator media - induction of typical morphologies in fungi	 - Formation of 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 reaction - Formation of the characteristic morphology	None	When changing lots
Pathogen identification			
Examination of individual methods for (orientating) pathogen identification with control strains: catalase, oxidase, indole, coagulase, germ tube test, urease	Pathogen-typical reactions	None	Daily
Verification of commercial systems for pathogens identification	Pathogen-typical reactions of control strains	None	When changing lots
Examination of the inoculum purity in commercial systems used in identifying pathogens	Pure culture	None	At each isolate
Susceptibility testing			
Beta-lactamase	Positive and negative controls using control strains	None	daily
Verification of the susceptibility test	Evaluation of the findings of the pathogen-antibiotic combinations on 20 consecutive working days using appropriate control strains.	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 assurance are not met
On-going internal quality assurance of the susceptibility test	Compliance with tolerance ranges for the normative control strains	If deviation occurs more than twice for a pathogen-antibiotic	Weekly and when changing lots; for systems used less than once a week:

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

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

		combination: troubleshooting, correction and re-verification of the test system, if required	each time the system is used
Inoculum purity	Examination of the inoculum purity	No deviation	For each isolate
Cell culture-based procedures			
Examination of the permissiveness using positive control strains	Detection of the virus-typical cytopathic effect or virus antigen	None	Monthly and when changing lots of cells or for a new passage made from cryopreserved cell cultures
Ruling out viral contamination of cell cultures by running negative controls (non-infected cell control)	no viral contamination	None	Monthly and when changing lots of cells or for a new passage made from cryopreserved cell cultures
Virus cultivation: Ruling out of mycoplasma contamination of the cell culture	no mycoplasma contamination	None	Every quarter year and when changing the cell culture lot
Molecular biological procedures			
Nucleic acid isolation	Extraction control by nucleic acid analysis of an afflicted target sequence added to or occurring in a test specimen[6] (the extraction control can be identical to the inhibition control)	None	For every sample extraction
Reaction components	Conformity testing of the reagents (primers, polymerase, nucleotides and probes) by nucleic acid/signal amplification of the target sequence with old and new reagent lot	None	In the case of new reagent lot or newly dissolved reagent
Pathogen-specific nucleic acid detection	Positive and negative control according to 2.1.2.3	None	For each procedure
Closed test systems (e.g., cartridge systems) for detecting pathogen-specific nucleic acid	Positive and negative control according to 2.1.2.3	None	a) when changing lots, b) for every reagent delivery (if special requirements are placed on transport by the manufacturer, e.g., continuous cooling), c) when equipment is

[6] Extraction control, and possibly, inhibition control do not have to be performed if there are validation data on the efficient nucleic acid extraction from the relevant target organism for closed, mechanised systems.

			used by another organisational unit, d) as determined by the laboratory on the basis of risk-based quality assurance
Sequence-based methods (NAT, FISH and other hybridisation techniques)	Database comparison of the primer and probe sequences used in each detection method with respect to the declared species specificity	None impacting test results	At least once a year or in accordance manufacturer specifications
Immunological procedures			
Diagnostic antibodies	Positive and, if applicable, negative control	None	When changing lots
Antigen detection (EIA, ELFA, CLIA and other immunochemical detection methods)	Positive and negative controls	None	Daily
Antigen detection using diagnostic rapid tests (e.g., immunochromatographic tests) with integrated function controls (e.g., stool pathogens)	Positive and, if applicable, negative control	None	Once per test package
Direct immunofluorescence test (e.g., respiratory viruses, *legionella, pneumocystis jirovecii, Giardia lamblia*)	Positive and negative controls	None	Daily
Antigen detection using particle / erythrocyte suspensions for antigen detection (agglutination assays)	Checking function by using known positive and negative control samples	None	Daily

daily = every calendar day on which patient samples are tested, weekly = every calendar week in which patient samples are tested.

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

1 No.	2 Measurand	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value[7]	4 Rili-BAEK applicable concentration intervals of Column 3			5 Frequency of control examination
			From	To	Unit	
1	CMV DNA	-0.5 to +0.5	5 000	5 000 000	IU/mL	each use[8]
2	HBV DNA	-0.5 to +0.5	500	5 000 000	IU/mL	each use[8]
3	HCV RNA	-0.5 to +0.5	500	5 000 000	IU/mL	each use[8]
4	HIV-1 RNA	-0.5 to +0.5	500	5 000 000	Copies/mL	each use[8]

Table B 3-2 – External quality assurance (EQA)

[7] Alternatively a control sample can be used that has a designated target interval with a maximum span of one $\log_{10}$ step.
[8] Except with closed test systems – see B 3 - 2.1.2.3 (5)

No.	Examination	Frequency	Type of target value in EQA[9]
	Bacteria		
1	Gram stain	6-monthly	NV
2	Cultivation, identification and sensitivity testing of bacteria	6-monthly	RLV
3	Cultivation, identification and sensitivity testing of fast growing bacteria and, if applicable, detection of accompanying flora of the urogenital system	6-monthly	RLV
4	*Bordetella pertussis*, genome detection	6-monthly	NV
5	*Borrelia burgdorferi* sensu lato, genome detection	6-monthly	NV
6	*Chlamydia pneumoniae*, genome detection	6-monthly	NV
7	*Chlamydia trachomatis*, antigen detection	6-monthly	NV
8	*Chlamydia trachomatis*, genome detection	6-monthly	NV
9	*Clostridium* [Clostridioides] difficile toxin gene, genome detection	6-monthly	NV
10	EHEC/STEC (Shiga toxin), genome detection	6-monthly	NV
11	*Helicobacter pylori*, genome detection	6-monthly	NV
12	*Legionella pneumophila*, genome detection	6-monthly	NV
13	*Listeria monocytogenes*, genome detection	6-monthly	NV
14	Methicillin-resistant Staphylococcus aureus (MRSA), genome detection	6-monthly	NV
15	*Mycoplasma pneumoniae*, genome detection	6-monthly	NV
16	*Neisseria gonorrhoeae*, genome detection	6-monthly	NV
17	*Salmonella enterica*, genome detection	6-monthly	NV
18	*Coxiella burnetii*, genome detection	6-monthly	NV
19	*Francisella tularensis*, genome detection	6-monthly	NV
	Mycobacteria		
20	Microscopic detection of mycobacteria	6-monthly	NV
21	Cultivation of mycobacteria	6-monthly	NV
22	Differentiation of tuberculosis bacteria	6-monthly	NV
23	Susceptibility test of Mycobacterium tuberculosis	6-monthly	NV
24	Identification of mycobacteria	6-monthly	NV
25	Mycobacterium tuberculosis, genome detection	6-monthly	NV
	Parasites		
26	Parasites in the blood, microscopic detection	6-monthly	RLV
27	Parasites in the stool, microscopic detection	6-monthly	RLV
28	*Toxoplasma gondii*, genome detection	6-monthly	RLV
	Fungi		
29	Cultivation and identification of as (opportunistic) pathogens causing organ, mucosal, systemic, or wound mycoses, as well as typical contaminants in the corresponding specimens	6-monthly	RLV
30	Identification of fungi as causative agents of dermatomycoses and fungal infections of the mucous membranes adjacent to the skin, as well as typical contaminants in the corresponding specimens	6-monthly	RLV
31	*Candida*, antigen detection	6-monthly	NV
32	*Cryptococcus neoformans*, antigen detection	6-monthly	NV
33	Dermatophytes, genome detection*	6-monthly	RLV
	Viruses		
34	Adenoviruses, genome detection	6-monthly	NV
35	Cytomegalovirus, genome detection	6-monthly	NV
36	Enteroviruses, genome detection	6-monthly	NV
37	Epstein Barr virus, genome detection	6-monthly	NV
38	Hepatitis A virus, genome detection	6-monthly	NV
39	Hepatitis B virus, genome detection	6-monthly	NV
40	Hepatitis B virus, HBs antigen detection	6-monthly	NV
41	Hepatitis B virus, HBe antigen detection	6-monthly	NV
42	Hepatitis C virus, genome detection	6-monthly	NV
43	Hepatitis C virus genotyping, genome detection	Annually	NV
44	Hepatitis C virus, HCV antigen detection	6-monthly	NV

[9] RLV = reference laboratory value: the target values of the external quality assurance programme are calculated by reference laboratories as the arithmetic average or median (if applicable); NV = nominal value: the target values are calculated from the results of the external quality assurance programme as the arithmetic average or median (as appropriate).

45	Hepatitis E virus, genome detection	6-monthly	NV
46	Herpes simplex virus type 1 / type 2, genome detection	6-monthly	NV
47	HIV-1 (RNA), genome detection	6-monthly	NV
48	HIV-1, p24 antigen detection	6-monthly	NV
49	Human papillomavirus, genome detection	6-monthly	NV
50	Influenza A and B viruses, genome detection	6-monthly	NV
51	Influenza A and B viruses, antigen detection	6-monthly	NV
52	Measles virus, genome detection	6-monthly	NV
53	Mumps virus, genome detection	6-monthly	NV
54	Norovirus, genome detection	6-monthly	NV
55	Parvovirus B19, genome detection	6-monthly	NV
56	Respiratory syncytial virus, genome detection	6-monthly	NV
57	Respiratory syncytial virus, antigen detection	6-monthly	NV
58	Rubella virus, genome detection	6-monthly	NV
59	SARS-CoV-2, genome detection*	6-monthly	NV
60	*Varicella zoster* virus, genome detection	6-monthly	NV
61	West Nile virus, genome detection	6-monthly	NV

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

1 No.	2 Measurand	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value in EQA	4 Rili-BAEK applicable concentration intervals for Column 3			5 EQA target value	6 EQA frequency
			From	To	Unit		
1	CMV DNA	-0.8 to +0.8	5,000	5,000,000	IU/mL	NV	6-monthly
2	HBV DNA	-0.6 to +0.6	500	5,000,000	IU/mL	NV	6-monthly
3	HCV RNA	-0.6 to +0.6	500	5,000,000	IU/mL	NV	6-monthly
4	HIV-1 RNA	-0.6 to +0.6	500	5,000,000	copies/mL	NV	6-monthly

B4 Examination of ejaculate

1 Principles of quality assurance

(1) Part B 4 specifies minimum requirements for quality assurance for the results of ejaculate examinations. These minimum requirements include internal and external quality assurance.

(2) Ejaculate examinations, as defined in this guideline, are examinations assessing sperm concentration, motility and morphology.

(3) All ejaculate examinations performed by the medical laboratory are subject to internal and external quality assurance. If several devices or measuring stations are used to perform a medical laboratory examination, internal quality assurance is to be performed on each of these devices or at each of these measuring stations.

(4) All examinations listed in (2) are also subject to external quality assurance.

(5) All participating laboratories are brought to determine the consensus value and establish the target ranges. The only exception is participating laboratories that use computer-assisted or AI-based analysis methods for ejaculate examinations.

2 Quality assurance procedure

2.1 Internal quality assurance

2.1.1 Procedure

(1) All examinations assessing the concentration, motility and morphology of the spermatozoamust be performed in duplicate and must be documented. A minimum of 2x200 sperm must 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 examination. If the sperm concentration is less than 1-2 sperm per visual field (40-fold lens magnification), the ejaculate should be centrifuged and the sediment analysed. If there are fewer than 200 sperm per defined counting field in the counting chamber, the requirement of counting at least 2x200 spermatozoa no longer applies.

(2) The absolute value of the difference $|x_{i1}-x_{i2}|$ and the arithmetic average $\overline{x}_i = (x_{i1}+x_{i2})/2$ are to be calculated for each of the repeat determinations.

2.1.2 Evaluating the differences of repeat determinations

The evaluation must be carried out as soon as the results of the repeat determination, done according to (1), are available. The following test rules (formulae) are to be used:

When examining spermatozoa concentration:

$$| x_{i1} - x_{i2} | \leq 1.96 \cdot \sqrt{2 \cdot \overline{x}_1}$$

where:

in this case $x_{i1}=N_{i1}$ and $x_{i2}=N_{i2}$ are the sperm counts in the counting chamber halves and $\overline{x}_1 = \overline{N}_i$ is the corresponding average from the repeat determination.

Note: 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 examination may not be released. The patient specimen is to be re-examined, if possible, and the result evaluated.

If deviations recur, the cause is to be sought and, if possible, rectified. The entire process must be documented.

When examining the morphology and motility of spermatozoa:

Normal or abnormal spermatozoa are to be quantified when assessing morphology. Progressively motile, locally motile or non-motile spermatozoa are to be quantified when assessing motility.

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

where:

in this case $x_{i1}=p_{i1}$ and $x_{i2}=p_{i2}$ represent the percentage of the corresponding spermatozoa and $\overline{x}_i = \overline{p}_i$ represents the corresponding average of the repeat determination;

N=number of the differentiated spermatozoa.

Note: 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 examination may not be released. The patient specimen is to be re-examined 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 evaluating the average of the differences from the repeat determinations after a control period ends

(1) A control period generally comprises one calendar month. If there are more than 50 released pairs of values 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 examination procedure must be barred from being used for measuring patient specimens. The measurement procedure cannot be released until the functionality of the procedure has been established through suitable actions. The entire process must be documented.

2.1.4 Documentation

(1) All results of the internal quality assurance are to be documented in a structured way according to the type of sample material, taking into account the examination procedure and measuring station or device. The respective documentation is to be presented upon request to the body responsible for ensuring compliance with this guideline.

(2) The documentation must include the following:

a) the name of the medical laboratory,
b) the name of the measuring station,
c) the period of evaluation,
d) examination, sample material, unit of measurement,
e) examination methods (counting chamber used, staining technique),
f) examination results including the single values of the repeat determinations,
g) evaluation in accordance with the corresponding formula,
h) release or blocking notice,
i) corrective actions taken and
j) name/cipher or signature of the investigator.

(3) The documentation on the performed internal quality assurance must be retained for five years along with the evaluations as well as the protocols of the actions taken when the target values were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) Participation in an EQA is mandatory once every half-year for every location of the medical laboratory that performs concentration, morphology and motility examinations.

(2) The participant in the external quality assessment programme shall examine the EQA samples under routine conditions and submits the results and information as required by the reference institution. By submitting the results, the participant confirms that the examinations were performed in accordance with this guideline, in the participant's laboratory and under the participant's supervision.

(3) If the participant does not receive a certificate for an examination because one or more of the participant's results do not meet the target values of the respective reference institute, the participant is obliged to determine the causes and rectify them if this lies within the participant's scope of responsibility. The entire procedure is to be documented.

(4) The EQA participation certificate and the acquired EQA certificates are to be retained for a period of five years unless longer periods of time are stipulated by other regulations.

B 5 Molecular genetic and cytogenetic medical laboratory examinations

1 Principles of quality assurance

(1) Part B 5 specifies minimum requirements for the quality assurance of the results of molecular genetic and cytogenetic medical laboratory examinations. These minimum requirements include internal and external quality assurance as well as special requirements for carrying out certain measurement procedures.

In general, molecular genetic and cytogenetic medical laboratory examinations are divided into postnatal, prenatal and tumour genetic diagnostics and have the following specimen requirements:

a) A postnatal laboratory medical examination, as defined in this guideline, is the molecular genetic or cytogenetic examination of a blood sample, tissue sample, cell swab or cell culture from body tissue after birth.

b) A prenatal laboratory medical examination, as defined in this guideline, is the molecular genetic or cytogenetic examination of fetal tissues such as amniotic cells, chorionic villi, fetal lymphocytes, isolated fetal cells or nucleic acids from maternal blood.

c) A tumour genetic laboratory medical examination as defined in this guideline is the molecular genetic or cytogenetic examination of neoplastic tissue, bone marrow, circulating tumour cells and cell-free nucleic acids.

(2) Molecular genetic and cytogenetic medical laboratory examinations, as defined in this Part of the guideline, are all examinations on the human genome and transcriptome whose purpose is to detect known sequence variants, identify unknown variants, investigate the structure or copy number of genomic segments or detect epigenetic modifications of genomic segments.

Cytogenetic medical laboratory examinations, as defined in this Part of the guideline, include all examinations used for postnatal cytogenetic diagnostics, prenatal cytogenetic diagnostics and for the cytogenetic diagnosis of tumours. These methods include molecular cytogenetics (ISH, usually fluorescence in situ hybridisation [FISH]) and molecular karyotyping using chromosomal microarray analysis (CMA) or Massively Parallel Sequencing (MPS).

(3) All molecular genetic and cytogenetic examinations performed by the medical laboratory are subject to internal quality assurance. If an examination is performed on multiple instruments or at multiple measurement stations, internal quality assurance has to be performed on each of these instruments or measuring stations.

(4) In addition, all examinations listed in the Tables in Part B 5 are subject to external quality assurance. Participation in an EQA programme is mandatory at every laboratory for each of the above-mentioned examinations in accordance with the frequency listed in the tables, provided that this examination is conducted at the location. If the laboratory only offers examinations whose methodology is not already verified by participation in an EQA programme in accordance with the tables in Part B 5, external quality assurance must take place by participating in an EQA programme that verifies the methodology used.

An EQA programme as defined in this guideline is an interlaboratory test offered by reference institutions in accordance with Part E of this guideline.

(5) The examinations and requirements on internal and external quality assurance are listed in the tables in Part B 5. Inclusion in the tables is based on the frequency of the examination and its medical significance in accordance with the current state of scientific knowledge. The tables are updated on a continuous basis.

2 Pre-analytical phase

For information on pre-analytical influencing factors and requirements for cytogenetic and molecular genetic analyses, please refer to Table B 5-1.

Table B 5-1 – Specifications on specimen to be used

No.	Kind of diagnostics / examination	Standard material / improper material	Additional specifications	Specifications for transport
1	Prenatal cytogenetic diagnostics	Amniotic cells in amniotic fluid, chorionic villi in physiological saline (e.g., 0.9% NaCl), or commercially available cell culture medium		Samples should be transported at room temperature whenever possible. Avoid freezing the sample. Transport the sample to the laboratory within three days, if possible.
2	Postnatal cytogenetic diagnostics	Heparinised peripheral blood (HEP blood)		Samples should be transported at room temperature whenever possible. Avoid freezing the sample. Transport the sample to the laboratory within three days, if possible.
3	Molecular Karyotyping (Array Diagnostics)	EDTA blood		Samples should be transported at room temperature.
4	Postnatal moleculargenetic diagnostics	EDTA blood	Can be stored at room temperature for several days.	Samples should be transported at room temperature.
5	Examination of ctDNA	Plasma (EDTA or with stabilisers), the use of serum is unsuitable	Double centrifugation of blood samples is recommended Prompt separation for EDTA plasma tubes (max. 6 hours) For stabiliser tubes, the manufacturer's instructions regarding transport and storage (time, temperature) must be followed	Gentle Blood Collection and Transport Storage and pre-analytical processing under validated conditions Freeze only after separating the plasma
6	Rhesus NIPT and Aneuploidy NIPT	According to the test manufacturer		

3 Validation – special requirements for conducting certain examinations

(1) Validation of molecular and cytogenetic measurement procedures in accordance with Part A 6.2.2 encompasses the entire measurement procedure including, if required, any subsequent bioinformatic analysis.

(2) The performance of the bioinformatics pipeline must be validated for all variant types to be reported, regardless of whether in-house, freely available, or commercial software is used. If software solutions that have already been validated by the manufacturer (CE marking) are used, the scope of validation may be reduced accordingly. To evaluate

the performance of the bioinformatics pipeline with respect to a specific variant type, internal or external reference materials must be used. In this context, a separate validation must be performed for each variant type with regard to analytical sensitivity and, where applicable, the method-specific limit of detection (LOD). Limitations of the method used, such as uncovered or unanalyzable regions (dark regions), pseudogenes, and method-related limitations, must be identified.

(3) Measurement procedures used for circulating tumor DNA (ctDNA) from cell-free body fluids need to be able to detect a variant allele frequency (VAF) of at least 0.5%. The method-specific limit of detection (LOD) for the result must be stated in the report. The quantitative reporting range must have a coefficient of variation of less than 25%.

(4) For molecular genetic examinations that obtain quantitative results, the performance of a measurement procedure must be determined and documented for each measurand and, in the case of high-throughput methods, for relevant measurands (at minimum for the markers listed in Tables B 5-3 and B 5-4). A limit of blank (LOB), limit of detection (LOD) and limit of quantification (LOQ) must be determined.

4 Quality assurance procedure

4.1 Internal quality assurance procedure

4.1.1 General

(1) The specifications of the manufacturer are to be followed with regard to type and frequency of the internal quality assurance performed.

(2) Irrespective of this, internal quality assurance must be performed at a frequency that is:

a) in accordance with the tables in Part B 5 for the examinations or test parameters individually listed therein,

b) regularly and adequately according to medical necessity and testing frequency of patient samples if the examinations are not listed in the tables of Part B 5,

c) at least once a week, if patient samples are examined using this measurement procedure during this calendar week.

(3) Additionally, internal quality assurance must be performed after there has been an intervention to the examination procedure.

Interventions to the examination procedure include:

a) calibration by the user,

b) repair or maintenance work on devices relevant for the results of the medical laboratory examination,

c) a change in reagent lots[10].

Paragraphs (2) and (3) are deemed to be fulfilled if process controls are integrated into the measurement procedure which ensure its functionality.

4.1.2. Molecular genetic medical laboratory examinations

(1) The control samples must be as similar as possible to the patient sample material being examined. The control and calibration material used in the examination procedure must not be identical.

(2) Control samples with known results must be used. When examining for known sequence variations, the control samples must represent the known alleles or allelic ranges of the known sequence variants, structure variants, or copy number of genomic segments, if available.

(3) If no control samples are available, due to the rarity of the molecular genetic alteration to be detected, or if it is not feasible to process such samples, a procedural control must be in place that encompasses suitable actions.

[10] This also includes changes to the composition of the reagent, such as the production of dilutions or, in the case of in-house production, the reiterated preparation of reagents.

(4) For examinations using nucleic amplification procedures, actions must be in place that are capable of detecting contaminations.

(5) When analysing circulating tumor DNA (ctDNA), the sample-specific limit of detection LOD must be determined for each examination based on the total amount of cell-free DNA (cfDNA). For quantitative methods, the proportion of the variant allele frequency (VAF) to all alleles must be determined for each identified sequence variation.

(6) To ensure data quality, quality and performance parameters (average coverage, read depth11, number of variants per variant type, contamination) must be continuously monitored and, if possible, stored in a database. All variants located within the genomic regions considered for interpretation should be annotated. Identified variants should be stored in an in-house, laboratory-specific database and used for annotation to identify pipeline- or device-specific artifacts.

(7) The following requirements must be met when determining variants (variant calling) in oncology- or haematology-related matters: Variants with a VAF < 1% must not be defined solely by increasing the read depth. In this instance additional measures for error suppression, such as so-called unique molecular identifiers (UMIs), are required. Variants with a VAF ≥ 1 % may be determined if they are contained in at least three unduplicated reads. If this is not possible, variants can only be determined from a VAF ≥ 5 % with a proportion of mutant reads ≥ 5 % of the average coverage.

(8) The quality of molecular genetic examinations listed in Tables B 5–6 (NIPT) is assessed based on the fetal fraction, to the extent that the method permits. With the rolling-circle amplification-based method, the minimum number of counts must be taken into account instead. If the minimum criteria for continuous quality assurance are not met, no report may be prepared for this sample.

(9) The quality of molecular genetic examinations in Table B 5-7 must be assessed for each patient sample, where applicable, using the test parameters listed in this table. If one of the test parameters exceeds the limits specified in Table B 5-6, the person in charge must decide whether the examination should be repeated. If the limit is exceeded even after the examination is repeated, the cause must be sought and, if possible, rectified. Concerning the medical relevance, the person in charge must decide whether examination results can nevertheless be evaluated from the sample and included in the report, accompanied by appropriate comments.

4.1.3. Cytogenetic medical laboratory examination

The test parameters (banding resolution, the number of chromosomal overlaps in the metaphase, their degree of greyscales and their hybridisation efficiency) must be determined and documented in accordance with Table B 5-8 for all reported cytogenetic examination results.

4.2 Evaluating results

4.2.1. Evaluating the results of molecular genetic laboratory control samples and test parameters

(1) An evaluation of the control sample examination and/or of the test parameter-based internal control process is to be conducted as soon as the results are available. The assessment is done based on the target values.

(2) If the requirements are not met, the measurement procedure is barred from further use in examining patient specimens until the cause of the failure of performance is determined and rectified. Taking medical relevance into consideration, the person in charge must decide whether the measurement procedure can be re-authorised or whether further actions must be taken, e.g., whether all of the examinations up to and including the control sample examination have to be repeated or whether the submitters

need to be notified with regard to already submitted results. The entire process is to be documented.

4.2.2 Evaluating the results of cytogenetic medical laboratory examinations based on the test parameter

(1) The quality of the cytogenetic medical laboratory examinations of each patient sample is, where applicable, to be evaluated using the test parameters listed in Table B 5-8. If one of the test parameters exceeds the limits listed in Column 4 of Table B 5-8, the person in charge must decide whether the examination should be repeated. If the limit is also exceeded after the examination has been repeated, the cause must be determined and, if possible, rectified. Taking the medical relevance into account, the person in charge must decide whether test results can still be obtained using this sample and included in the report, accompanied by appropriate comments.

(2) A retrospective evaluation of the test parameters takes place after a control period ends. A control period generally comprises one calendar month. If more than 50 approved results from patient samples have been obtained after the period of one calendar month, the medical laboratory must calculate the relative percentage by which the limits listed in Column 4 of Table B 5-8 have been exceeded.

If fewer than 50 patient sample results have been released, the period of time must be extended by one-month intervals until at least 50 such results have been obtained. The total period of time may not exceed three months.

If the limits listed in Column 4 of Table B 5-8 are exceeded, the examination procedure must be barred from examining further patient samples. The examination procedure cannot be re-approved until the functionality of the procedure has been established by suitable actions.

If it is likely that fewer than 50 patient sample results of will be released within a three-month period, it is not necessary to calculate the relative percentage of limit violations as listed in Column 4. If, in the case of low testing numbers, the limits listed in Column 3 of Table B 5-8 are exceeded five times in three months, measured must be taken as specified in (4) and (5). The entire process is to be documented.

4.2.3 Documentation

(1) All results of the internal quality assurance are to be documented in a structured way according to type of sample material, taking into account the examination procedure and measuring station or device. The documentation is to be presented upon request of the body responsible for ensuring compliance with this guideline.

(2) The documentation must include the following:

a) Name of the medical laboratory,
b) name of the measuring station or device,
c) date and, if relevant, time of the examination,
d) examination, sample material, and, if necessary, the unit of measurement,
e) examination method,
f) result of the control sample or test parameter, including device- and software-generated internal procedural controls of the specimen (e.g. Phred score),
g) specification of the control sample or test parameter,
h) the evaluation,
i) release or blocking notice,
j) corrective actions taken,
k) manufacturer, name and lot number of the control sample, where applicable and
l) name/cipher or signature of the investigator.

(3) The documentation on the performed internal quality assurance must be retained for five years along with the evaluations as well as the protocols of the actions taken when

target values were not met, unless longer retention periods are prescribed by other regulations.

4.2.4 Postanalytics

Along with the physician's evaluation in the report the results of genetic testing must include:

(1) Information as per Part A 6.3.2,
(2) the medical indication for a genetic examination,
(3) for chromosome analysis:
    a. specification of the banding technique, band resolution and the karyotype in accordance with the current ISCN,
(4) for a molecular cytogenetic analysis (FISH)
    a. Information about the DNA probe used (chromosomal location, locus, product name, manufacturer)
(5) for molecular karyotyping:
    a. specification of the genome build used, genomic localisation in accordance with the specifications of the current ISCN,
(6) for molecular genetic analysis:
    a. the genes or gene segments examined, including the size of the flanking intronic regions (exon-intron junctions),
    b. the nomenclature used,
    c. the specification of the variants using an acknowledged nomenclature:
        1. all disease-causing and probable disease-causing variants,
        2. unclear variants, if connected to the disease,
    d. the software used for the data analysis (name and version) and the genome used as a reference for the variant comparison (calling),
    e. evaluated technical data, if these are relevant for the assessment of the result in the findings,
    f. when high-throughput sequencing is used, quality metrics for the analysis, such as the sensitivity and precision determined using reference material, the LOD (if applicable) for the analysed variant types, and the average coverage, must be appropriately noted in the report. Limitations of the analysis must also be addressed. All clinically relevant areas specified in the examination order for which the sequencing depth is insufficient for the reported LOD must be identified and, if necessary, made available.

4.3 External quality assurance (EQA)

(1) The participant in the external quality assessment programme shall examine the EQA samples under routine conditions and submit the results and information as required by the reference institution. By submitting the results, the participant confirms that the tests were performed in accordance with this guideline, in the participant’s laboratory, and under the participant’s supervision.
(2) If a participant does not receive a certificate for an examination because one or more of the participant’s results do not meet the target values of the respective reference institute, the participant is obliged to determine the causes and rectify them if this lies within the participant’s scope of responsibility. The entire procedure is to be documented.
(3) The EQA participation certificate and the acquired EQA certificates are to be retained for a period of five years unless longer retention periods are stipulated by other regulations.

Table B 5-2 – Internal and external quality assurance of molecular genetic examinations

No.		Gene	Molecular genetic	Frequency of the internal	Frequency of participation in

		HGNC name	category(ies) of the genetic changes*	quality assurance	an EQA programme
1	Alpha1-Antitrypsin	*SERPINA1*	SNV	Weekly	6-monthly
2	Antithrombin	*SERPINC1*	SNV	Weekly	6-monthly
3	Apolipoprotein B 100	*APOB*	SNV	Weekly	6-monthly
4	Apolipoprotein E	*APOE*	SNV	Weekly	6-monthly
5	Cytochrome p450 2C9 (CYP2C9)	*CYP2C9*	SNV	Weekly	6-monthly
6	Cytochrome p450 2C19 (CYP2C19)	*CYP2C19*	SNV	Weekly	6-monthly
7	Cytochrome p450 2D6 (CYP2D6)	*CYP2D6*	SNV, INDEL, CNV	Weekly	6-monthly
8	Dihydropyrimidin Dehydrogenase	*DPYD*	SNV	Weekly	6-monthly
9	Factor V (Leiden)	*F5*	SNV	Weekly	6-monthly
10	Hereditary haemochromatosis	*HFE*	SNV	Weekly	6-monthly
11	HLA-B*27	*HLA-B*	SNV	Weekly	6-monthly
12	HLA-B*57:01	*HLA-B*	SNV	Weekly	6-monthly
13	Lactase-phlorizin hydrolase	*LCT*	SNV	Weekly	6-monthly
14	Methylenetetrahydrofolate reductase	*MTHFR*	SNV	Weekly	6-monthly
15	Prothrombine	*F2*	SNV	Weekly	6-monthly
16	Thiopurine S-methyltransferase	*TPMT*	SNV	Weekly	6-monthly
17	Uridyl glucuronyl transferase-1A	*UGT1A1*	INDEL	Weekly	6-monthly
18	Angiotensin Converting Enzyme Apolipoprotein	*ACE*	INDEL	Weekly	6-monthly
19	C-C motif chemokine receptor 5	*CCR5*	DEL	Weekly	6-monthly
20	Cystic fibrosis, mucoviscidosis	*CFTR*	SNV, INDEL, CNV	Weekly	Annually
21	Familial breast/ovarian cancer (BRCA)	*BRCA1, BRCA2*	SNV, INDEL, CNV	Weekly	Annually
22	21-Hydroxylase deficiency (congenital adrenal hyperplasia)	*CYP21A2*	SNV, INDEL, CNV	Weekly	Annually
23	Duchenne and Becker muscular dystrophy	*DMD*	SNV, CNV, INDEL	Weekly	Annually
24	Fragile X syndrome	*FMR1*	EXP	Weekly	Annually
25	Severe hearing impairment	*GJB2*	SNV, INDEL, CNV	Weekly	Annually
26	Hereditary nonpolyposis colorectal cancer	*MSH2, MLH1, MSH6, PMS2*	SNV, INDEL, CNV	Weekly	Annually
27	Huntington's disease	*HTT*	EXP	Weekly	Annually
28	Prader-Willi syndrome	*SNRPN*	CNV, METH	Weekly	Annually
29	Spinal muscle atrophy	*SMN1, SMN2*	CNV	Weekly	Annually
30	Wilson's disease	*ATP7B*	SNV, INDEL	Weekly	Annually
31	Y chromosome, microdeletions	*AZF region*	CNV	Weekly	Annually

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: Single nucleotide variants (**SNV**), insertion/deletion < 50 bp (**INDEL**), changes in the copy number of a genomic segment or a genomic sub-segment (from 50 bp) (**CNV**), repeat expansion (**EXP**), methylation defect (**METH**).

Table B 5-3 – Internal and external quality assurance of molecular genetic ctDNA examinations of solid tumours

No.	Gene HGNC name	Molecular genetic category/ies of the genetic changes	Measurand (variant allele frequency, VAF)	Requirements for the method, minimum verification limit/VAF	Frequency of participation in an EQA programme
1	BRAF	SNV	V600 variants	0.5 %	6-monthly
2	EGFR	SNV	T790M variant	0.5 %	6-monthly
3	KRAS	SNV	Codon 12 variants Codon 13 variants Codon 61 variants	0.5 %	6-monthly
4	NRAS	SNV	Codon 61 variants	0.5 %	6-monthly
5	ESR1*	SNV	Hotspot variants E380Q variant Codon-L536 variants Codon-Y537 variants D538G variant	0.5 %	6-monthly
6	PIK3CA*	SNV	Hotspot variants E542K variant E545K variant Codon-H1047 variants	0.5 %	6-monthly

Internal quality assurance is carried out using the examination parameters defined under 3.1.2 and for each use.

*= Provided that detection is primarily performed using digital PCR and, in the event of a negative result, a reflex analysis is conducted using MPS on ctDNA, the quality requirements for MPS are governed by Table B 5-7.

Table B 5-4 – Internal and external quality assurance of targeted molecular genetic, quantitative examinations for haemato-oncological diseases

No.	Tran-script	Molecular genetic category (ies) of genetic modifica-tions	Permissible absolute deviation of the logarithm-mised (base 10) individual value from the logarithm-mised target value	Permissible deviation of the logarithm-mised (base 10) values from the logarithm-mised target value in the external quality assessment	Require-ments for the method: Minimu m detectio n limit using a control gene	Frequen-cy of internal quality assur-ance	Type of target value for the EQA	Frequency of participatio n in an EQA programme
1	BCR::A BL1	Expression	± 0,8 log (base 10) of the nominal value	± 1,0 log (base 10) of the nominal value	10^{-5*}	With every use	Nominal value	6-monthly
4	PML::R ARA	Expression	± 0,8 log (base 10) of the nominal value	± 1,0 log (base 10) of the nominal value	10^{-4}	With every use	Nominal value	6-monthly

*specification of the measured value using the International Scale (IS)

Table B 5-5 – Internal and external quality assurance of targeted molecular genetic examinations for haemato-oncological diseases in initial and relapse diagnostics

No.	Gene HGNC name/ transcript	Molecular genetic category(ies) of genetic modifications	Requirements for the method: Minimum detection limit/VAF	Frequency of participation in an EQA programme
1	BCR::ABL1	Gene fusion	5 %	6-monthly
2	PML::RARA	Gene fusion	5 %	6-monthly
3	ABL1	Variant	5 %	6-monthly
4	JAK2	V617F variant	5 %	6-monthly
5	JAK2	Exon-12 variant	5 %	6-monthly
6	KIT	D816V variant	0.1 %	6-monthly
7	FIP1L1::PDGFRA	Gene fusion	5 %	6-monthly

8	FLT3	Internal tandem duplication (ITD)	5 %	6-monthly
9	TP53	Variant	5 %	6-monthly
10	BRAF	V600 variant	5 %	6-monthly

Internal quality assurance is carried out on the basis of the principles defined under 3.1.2, (1) to (4) and for each use.

Table B 5-6 – Internal and external quality assurance of molecular genetic cffDNA** tests for the nominal determination of aneuploidy* and fetal sex (non-invasive prenatal test - NIPT)

Test parameter	Continuous quality assurance Specification	Retrospective quality assurance Specification	Frequency of quality assurance
Internal quality assurance			
Fetal fraction (FF), e.g., in sequencing- or array-based methods	≥2% FF in the single sample	At most 5% of the single samples with FF <4%	Weekly
Counts cfDNA*** in Rolling-Circle-Amplification method	>100,000 counts in the single sample	At most 5 % of the single samples with <150,000 counts	Weekly
Achievable result ("call")		At most 5% of the single samples “no call”	Weekly
External quality assurance	**Permissible relative deviation in the EQA**		
Nominal determination of fetal sex and aneuploidy*	None		6-monthly

*aneuploidy: indication of trisomy 13, 18 or 21
**cell-free fetal DNA
***cell free DNA

Table B 5-7 – Internal and external quality assurance for high-throughput/massiv parallel sequencing (MPS) for the report of variants

Area of application	Molecular genetic category(ies) genetic changes	Required minimm read depth of reported variants	Frequency of participation in an EQA programme
Molecular analysis of constitutional changes	SNV, INDEL, CNV	20 (heterozygous, homozygous)	Annually
Molecular analysis of haemato-oncological changes	SNV, INDEL	300 (variants with VAF of 1 %)*	Annually
Molecular analysis of solid tumours	SNV, INDEL	60 (variants with VAF of 5 %)*	Annually
Molecular analysis of circulating tumour DNA (ctDNA)	SNV, INDEL	600 (variants with VAF of 0.5 %)*#	Annually

*If a known variant is available, deviations from these requirements may be permitted during the process.
To detect variants with a lower VAF, the read depth must be increased accordingly.

Internal quality assurance is conducted based on the test parameters defined in section 3.1.2.
Participation in an external quality assurance programme for MPS does not replace participation in the specific EQA schemes listed in Tables B 5-2, B 5-3 and B 5-5.

Table B 5-8 – Cytogenetic examination – internal quality assurance

	Quantity		Continuous quality assurance requirements	Retrospective quality assurance requirements
Postnatal analyses				
Lymphocytes	Banding resolution		At least 400 bphs	A maximum of 5% of the samples with banding resolution <400 bphs
	Number of overlapping points in the case of <400 bphs		At most 12 per metaphase	A maximum of 5% of the samples >12

	Number of overlapping points in the case of ≥400 bphs	At most 20 per metaphase	A maximum of 5% of the samples >20
	Degree of grey scales	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 <400 bphs	At most 12 per metaphase	A maximum of 5% of the samples >12
	Number of overlapping points in the case of ≥ 400 bphs	At most 20 per metaphase	A maximum of 5% of the samples >20
	Degree of grey scales	At least 3	A maximum of 5% of the samples <3
FISH diagnostics			
FISH (metaphase, constitutional)	Hybridisation efficiency	Per batch	A maximum of 10% of metaphases without signals from the control probe
FISH (interphase, constitutional)	Hybridisation efficiency	Per batch	A maximum of 10% of the interphase cores without signals from the control probe
FISH (interphase, somatic)	Hybridisation efficiency	Per batch	A maximum of 10% of the interphase cores without signals from the control probe
Molecular karyotyping			
CMA or MPS	The manufacturers' specifications for internal quality assurance shall be met	Per batch	A maximum of 5% of the methods do not meet the targets

bphs = "band per haploid set"

Table B 5-9 Cytogenetic examinations – external quality assurance

	Quantity	**Requirement**	**Participation in EQA**
Postnatal analyses			
	Nominal chromosome number*	No deviation	Annually
Lymphocytes	Banding resolution	None of the samples <400 bphs	Annually
	Number of overlapping points in the case of <400 bphs	None of the samples >12	Annually
	Number of overlapping points in the case of ≥400 bphs	None of the samples >20	Annually
	Degree of grey scales	None of the samples <3	Annually
Prenatal analyses			
	Nominal chromosome number*	No deviation	Annually
Amniotic cells	Banding resolution	None of the samples <400 bphs	Annually
Chorionic villus cells	Banding resolution	None of samples <300 bphs	Annually
Amniotic and chorionic villus cells	Number of overlapping points in the case of <400 bphs	None of samples >12	Annually
	Number of overlapping points in the case of >400 bphs	None of samples >20	Annually
	Degree of grey scales	None of samples <3	Annually
FISH diagnostics			

FISH (metaphase, constitutional)	Qualitative and quantitative verification of the target value	No deviation	Annually
FISH (interphase, constitutional)	Qualitative and quantitative verification of the target value	No deviation	Annually
FISH (interphase, somatic)	Qualitative and quantitative verification of the target value	No deviation	Annually
Molecular karyotyping			
CMA or MPS	Qualitative and quantitative verification of the target value	No deviation	Annually

* **Nominal** chromosome number e.g., **45**,X (Turner syndrome), **46**,XX (normal female), **47**,XXY (Klinefelter syndrome)
bphs = "band per haploid set"

C Advisory Board

(1) An Advisory Board “Quality Assurance in Medical Laboratory Examination” shall be established at the German Medical Association that shall primarily perform the following duties:
   a) Advising the German Medical Association in all aspects of this guideline
   b) Dealing with questions pertaining to the application of this guideline
   c) Collecting, assessing and formulating suggestions for updating this guideline.

(2) The members of the Advisory Board shall be recommended by the institutions listed under (4) below and be 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 Advisory Board shall elect a chairperson from among its members. The members of the Advisory Board may be represented by proxy, with approval of the chairperson.

(3) The Advisory Board may commission external experts.

(4) The Advisory Board is made up of representatives from the following institutions:
   a) representatives of the competent scientific medical societies,
   b) the chairs of the Expert Groups listed in each Part 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 a 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 (BfArM) and
   k) a representative from the Physikalisch-Technische Bundesanstalt (PTB)

(5) The Advisory Board shall have as permanent guest: One representative from each of the reference institutions in accordance with Part E of this guideline.

(6) The business of the Advisory Board shall be administrated by the German Medical Association. The German Medical Association shall bear the costs for conducting the Advisory Board meetings. The participation costs incurred by the members shall be borne by the delegating institutions. The regulations of the BAEK committees shall apply.

(7) The Advisory Board shall issue for itself and the Expert Groups by-laws in accordance with Part D of this guideline.

D Expert Groups

(1) An Expert Group shall be appointed for each Part B.

(2) The Expert Groups shall have the following duties:
   a) Advising the German Medical Association in all questions pertaining to Parts B and E within their respective field of competence,
   b) Dealing with questions pertaining to the application of these Parts,
   c) Collecting, assessing and formulating suggestions for updating these Parts,
   d) Establishing the pass modalities for the external quality assurance schemes.

(3) The composition of the Expert Groups is set forth in Table D.

(4) The members of the Expert Group are recommended by the institutions listed in Table D 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 Group shall elect a chair from among its members. The members of the Expert Group may be represented by proxy with approval of the chair. The Expert Group may commission external experts.

(5) The Expert Groups shall have as permanent guests: One representative from each of the reference institutions in accordance with Part E of this guideline.

(6) The business of the Expert Groups shall be administrated by the German Medical Association. The German Medical Association shall bear the costs for conducting the Expert Group meetings. Participation costs incurred by the members shall borne by the delegating institutions. The regulations of the BAEK committees shall apply.

Table D: Composition of the Expert Groups

	Expert Group D 1 "Quantitative Medical Laboratory Examinations"	**Expert Group D 2 "Qualitative Medical Laboratory Examinations"**	**Expert Group D 3 "Direct Detection and Characterisation of Infectious Agents"**	**Expert Group D 4 "Examination of Ejaculate"**	**Expert Group D 5 "Molecular genetic and Cytogenetic Medical Laboratory Examinations"**
Competent scientific medical societies	x	x	x	x	x
German Medical Association	x	x	x	x	x
National Association of Statutory Health Insurance Physicians	x	x	x	x	x
German Hospital Federation	x	x	x	x	x
German Association of Medical Technologists and Analysts	x	x	x	x	x
Competent industrial association	x	x	x	x	x
Federal states	x	x	x	x	x

	Expert Group D 1 **"Quantitative Medical Laboratory Examinations"**	**Expert Group D 2** **"Qualitative Medical Laboratory Examinations"**	**Expert Group D 3** **"Direct Detection and Characterisation of Infectious Agents"**	**Expert Group D 4** **"Examination of Ejaculate"**	**Expert Group D 5** **"Molecular genetic and Cytogenetic Medical Laboratory Examinations"**
Physikalisch Technische Bundesanstalt	x	x	x	x	x
Robert Koch Institute	-	-	x	-	x

E Reference institutions

E 1 General requirements for reference institutions conducting external quality assurance programmes

(1) a) External quality assurance programmes are carried out by reference institutions

b) The reference institutions must fulfil the general and special requirements listed under E 1 and E 2.

c) Proof must be provided by means of accreditation in accordance with DIN EN ISO 17043 which can be applied for at the Deutsche Akkreditierungsstelle GmbH (DAkkS). The proof must also document the requirements to be fulfilled by reference institutions in accordance with Rili-BAEK.

(2) General requirements

a) The reference institution has proven through ISO 17043 accreditation 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 on-going operations.

b) The reference institution must have at its disposal a sufficient number of reference laboratories or laboratories for the determination of nominal values which are qualified to conduct the work at hand.

c) The reference institution or its supporting organisation must be fully independent of the persons responsible for first placing medical products on the market in accordance with Art. 2 No. 23, 25 and 26 IVDR.

d) The reference institution or its supporting organisation must be independent of the marketing of in-vitro diagnostics or the provision of laboratory medical services.

e) The reference institution has to ensure that all EQA certificates and EQA participation certificates have been authorised by a qualified physician.

(3) The reference institutions are each specifically responsible for:

a) announcing, organising and properly executing the external quality assurance programmes in accordance with this guideline, and for the timely assessment and publication of the results,

b) appointing the external quality assurance programme leaders,

c) selecting and reviewing the suitability of the external quality assurance programme material,

d) determining the target values of the control samples used in external quality assurance in conjunction with reference laboratories and laboratories for the determination of nominal values,

e) taking further actions if problems with the EQA samples arise and, where applicable, involving the affected manufacturer.

(4) The special requirements of the EQA programmes and the organisations conducting the external quality assurance programmes set forth in the Part E 2.

E 2 Special requirements for reference institutions

1 Obligations of the reference institutions

(1) The reference institutions shall ensure that a sufficient number of external quality assurance programmes are offered for all of the measurands/examinations listed in the tables so that every medical laboratory can participate in at least one external quality assurance programme at the frequencies listed in the respective tables.
They may only deviate from this if they can prove that there is an insufficient amount of suitable EQA samples/materials.

(2) The reference institutions shall announce one year in advance the external quality assurance programmes for the examinations pursuant to (1). This announcement shall include:
- a) The deadline for registering to participate in the external quality assurance programmes
- b) The respective date of sample/material shipment or provision, and the deadline for sending back the results
- c) The measurands/examinations included in the external quality assurance programme with details on the measurement/examination procedure, where applicable.
- d) The Type of sample material, the sample volumes of the liquid or reconstituted EQA samples, or type of material.

(3) The reference institutions shall select the EQA samples/materials and check their suitability.
The suitability of the selected EQA samples for those measurands/examinations whose evaluation is carried out on the basis of reference method values needs to be determined prior to their use in the external quality assurance programmes under routine conditions and using a routine measurement procedure.

(3.1) Specific requirements for Part B 1
The reference institutions shall operate their own calibration laboratories to determine the reference method values for the samples used in external quality assurance programmes if this is required by the tables in Part B 1. In exceptional cases, suitable calibration laboratories can be commissioned. The calibration laboratories are deemed suitable if they are accredited in accordance with DIN EN ISO/IEC 17025 and DIN EN ISO 15195 and if they are listed with the Joint Committee for Traceability in Laboratory Medicine (JCTLM) for at least 20 entries from the tables in Part B 1. Only accreditation bodies that are included in the Multilateral Agreement on the Mutual Acceptance of Calibration Certificates of the European Co-operation for Accreditation (EA) may be used.

(4) For every external quality assurance programme, the reference institutions shall commission each participant to examine at least two EQA samples/materials. As a rule, the EQA samples/materials shall be dispatched with different target values.

(5) The reference institutions shall provide or send the EQA samples/materials to each participant of the EQA accompanied by information on how to handle the samples/materials, including clinical information, where applicable, and how to submit the measurement/examination results.

(6) Reference institutions shall only analyse measurement/examination results that were submitted by the participant of the EQA before the set deadline.

(7) Every participant of the EQA is to be issued a certificate showing the submission date of the external quality assurance programme and stating which measurand/examination results correspond to the target values. In addition, every

participant of an external quality assurance programme is to be issued a participation certificate for all measurands/examinations. The certificate and participation certificate are to be sent to the participants no later than eight weeks after the deadline to submit results of the external quality assurance programme.

Participants of the EQA are also to be informed of:

a) target values of the EQA samples/materials
b) for quantitative target values, or where applicable, the position, distribution and measurement results for all participants and, if applicable, for the measurement/examination procedure used by the participant
c) number of participants, where appropriate, listed according to measurement/examination procedure. Certificates are valid for six months or double the time interval listed in the tables.

(8) If the reference institution finds that participants frequently are not being granted a certificate for measurements/examinations that use reagents or devices from a particular manufacturer and if the cause for this cannot be traced to the medical laboratories taking part in the external quality assurance programme or the reference institution, the appropriate federal authorities are to be notified if it can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.

(9) Further details on conducting external quality assurance programmes and analysing the results of external quality assurance programmes are set forth in implementation regulations. These are published by the reference institutions.

2 Determining target values

(1) After consulting with its competent committees and after formal consultation with the relevant parties concerned, the German Medical Association shall establish and announce which target value to use for the measurement/examinations and how target values are determined. Reference measurement procedures are to be used, where possible, when determining the target values in EQA samples.

(2) The reference institutions shall establish the test plans for determining the target values of the EQA samples/materials, commission the reference laboratories and/or target value laboratories, analyse the measurement results and merge these into a target value.

(3) The reference institutions must retain the documentation on determining the target values for a period of at least five years beginning from when they were used in the external quality assurance programmes.

Specific requirements for Part B 1

2.1 Determining reference method values

(1) The calibration laboratory commissioned by the reference institution shall use a reference measurement procedure to determine the reference method value for a measurand.

(2) The reference method values for EQA samples must be available before the start of the external quality assurance programme. Exceptions are permitted in special cases (e.g., very limited shelf life of the control sample).

2.2 Determining nominal values

The nominal values depend on the measurement method and are calculated from the external quality assurance programmes as a robust mean or as a median.

3 Assessing the results of external quality assurance programmes

(1) Assessment is performed based on target values. The assessment criteria shall be communicated by the reference institutions to the participants if these criteria are not listed in the tables.

(2) If the entire population or method-related sub-populations 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 co-operation with the manufacturer of the EQA sample, the manufacturers of the respective test systems, or experts. They are to check whether, in such a case, increasing the pass limits or changing the target values would allow for a proper assessment.

They shall decide whether the results are to be analysed according to the target value or according to the modified pass limits, or whether the external quality assurance programme is to be repeated for this measurand/examination. The process is to be substantiated and documented. The participants of the external quality assurance programme and the Expert Group at the German Medical Association are to be informed in accordance with Parts B 1 to B 5. The reference institutions shall report annually to the German Medical Association on their activities in the previous calendar year.

F Temporary regulations

The revised requirements set forth in this directive must be met no later than two years after their publication in the Deutsches Ärzteblatt.

G Entry into force

This directive, adopted on 11 September 2026, shall come into force upon publication in the Deutsches Ärzteblatt.