On 19 September 2014, the current version of the "Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations" was published. It featured an introduction by the German Medical Association.

Revision of the "Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations – Rili-BAEK" (unauthorized translation)

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In November 2007, the previous version of the **Guideline of the German Medical Association on Quality Assurance in Medical Laboratory Examinations – Rili-BAEK** was approved by the Executive Board of the German Medical Association and published in the spring of 2008 in the *Deutsches Ärzteblatt* — the German Medical Association's official international bilingual science journal. At that time, the Guideline comprised Chapter A, Part B1 and Chapter C, D and E, thus specifying basic requirements for quality assurance in medical laboratory examinations and requirements for conducting external quality assurance programmes. In subsequent years, additions were made to the guideline designated Parts B2, B3, B4 and B5. Also, Expert Groups for these respective parts were installed to supervise and further develop the external quality assurance programmes. In 2013, the Expert Groups instituted according to the Rili-BAEK undertook another revision of the entire guideline and prepared a new, linguistically consolidated version. A few additions were made in Chapter A in the definition of terms, and the tables for Parts B1 and B5 were updated. The Executive Board of the German Medical Association decided to publish the consolidated version in its entirety in order to create a quotable text.

Berlin, August 2014

The German Medical Association (BAEK) has been informed of this translation of the Rili-BAEK guideline into English, and it is being done with the chamber's approval. The original publication in the Deutsches Ärzteblatt (German Medical Journal) *remains the basis for a legally compliant application of the Rili-BAEK guideline in Germany.*

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

As per the decision by the Executive Board of the German Medical Association of 04 April 2014 and 20 June 2014.

A Basic requirements for quality assurance in medical laboratory examinations

1 Scope

The guideline regulates quality assurance for medical laboratory examinations in the field of medicine.

The basic requirements described in Chapter A of the guideline are effective for all medical laboratory examinations and specific requirements apply to those as far as for the latter a special Part B has been formulated.

2 Objective

The objective of the system described in the guideline is to ensure the quality of medical laboratory examinations. The guideline aims to ensure, in particular, that:

- Influencing factors and in-vitro effects during the pre-analytical phase are minimised,
- Medical laboratory examinations are conducted properly and factors interfering with the results are identified and minimised, and
- Results are correctly assigned and documented, including the generation of a report.

3 Terminology

The following definitions explain important terms as used in this guideline.

The definitions take into account national and international standards and terminology as well as metrological terminology; however, they have to be used in the context of the guideline, so there may be deviations from the aforementioned terminologies.

Accuracy of measurement

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

Analyte

The component to be determined by an analysis.

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) by one single organisational unit ("medical laboratory") and by appropriately qualified technical personnel. The central laboratory can also be an external laboratory managed by another legal entity/operator.

Control strain

A reference culture or reference strain of microorganisms, viruses and cells which is directly obtained from an approved culture collection or from a national reference laboratory or, if applicable, which is adequately characterised using suitable methods (e.g., characterisation as an external quality assessment programme isolate, by sequencing, by mass spectrometry). When using normative procedures (e.g., sensitivity testing), corresponding normative control strains have to be used.

Deviation of measurement

The difference between a measurement result and the true value of the measurand. To estimate the deviation of measurement, the difference between the measurement result of a control sample and the target value of this control sample is used 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.

Deviations of measurement, maximum permissible

Limits for deviations of measurement as defined by this guideline. If these values are exceeded, the deviations are considered non-conformities and require corrective measures.

Deviation of measurement, random (imprecision)

The difference of a measured value from the mean, which would result from an infinite number of repeated measurements of the same measurand. The imprecision is estimated by 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 scatter of distribution 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 single measurement
- n is the number of individual values used for calculation

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

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

where

- s represents the empirical standard deviation of a random sample
- δ represents the systematic 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 $\bar{x}$, calculated from an appropriate number of repeated measurements, and the target value x_0, e.g.,

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

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

Device, technical

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

Document

A document includes information and its carrier. For example, records, instructions (including quality regulations), method descriptions, specifications, calibration tables, reference ranges, drawings, reports, results, legal provisions or standards.

Equipment

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

Findings

Findings are laboratory results judged by a physician.

Influencing factor

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

In-vitro effects

In-vitro effects influence medical laboratory analyses. They interfere with the measurement procedures and thus lead to changes in the results of the analysis. They do not represent the patient's status.

Laboratory, medical

A medical laboratory as defined by this guideline means, depending on the context,

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

Laboratory examinations, patient near immediate

This includes medical laboratory analyses that are performed directly as single measurements without sample preparation.

An important criterion for these laboratory examinations is the immediate deduction of therapeutic actions from the laboratory analysis performed.

Location

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

Measurand

The particular quantity that is measured.

Measurement

Sum of all actions involved in determining a measurand.

Measurement method

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

Measurement procedure

Complete set of specifically described operations, used in the performance of particular measurements according to a given method.

Organisational unit

This is every 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/measurement devices assigned solely at this unit, and
- the operation of the measuring stations only by the defined personnel.

Performance

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

Pre-analytical phase

Pre-analytical phase include all steps prior to the actual measurement:
- collection of sample material,
- transport and storage of the specimen or sample material,
- assessment of the specimen or sample material,
- preparation of samples (e.g., separation of corpuscular components by centrifugation).

Precision of measurement

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, 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

This 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.

How the results are reported (scale level) is crucial for assigning medical laboratory examinations to Parts B1 or B2.

Quality policy

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

Quantitative examination

This 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).

How the results are reported (scale level) is crucial for assigning medical laboratory examinations to Part B1 or B2.

Reference method

A thoroughly investigated measurement method 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 value obtained using a reference method.

Referral laboratory

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

Report

A combined presentation of laboratory results.

Responsibility of the central laboratory

Responsibility in this case refers to guidance and supervision. With reference to near-patient immediate examinations, "under the responsibility of the central laboratory" means that the central laboratory is monitoring the adherence to the guideline for internal quality assurance of the individual organisational units of the institution. Responsibility does not mean that the control sample measurements and their evaluation are conducted by employees of the central laboratory.

Sample material

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

Sample preparation

This 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 of the sample and volume dosing is not included in this definition. If the collection system contains additives included by the manufacturer, this does also not constitute sample preparation.

Nominal value

Target value determined without using a reference measurement method.

Specimen

Body fluids/material extracted from or excreted by a person to be examined (e.g., venous blood, cerebrospinal fluid, aspirate, tissue, urine, stool), and possible additives, stored in an appropriate container.

Standard deviation, empirical

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

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

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

Target value

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

Trueness of measurement

The closeness of agreement between the mean of the measured values obtained from a control period and the target value.

This is usually quantified numerically using the systematic deviation of measurement, which is inversely correlated with trueness of measurement.

Unit use reagents

These are reagents which are portioned for single measurements and are fully consumed after one analysis.

Validation of a measuring procedure

This is the objective proof that the requirements are met by the measurement method. Objective proof can be done through observation, measurement, testing or other methods.

Validation of a test 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 (i. a. including constellation check of 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 under the control of a professionally qualified person. The responsibility of the management encompasses technical, organisational, administrative functions, training and continuing education as well as consultation.

5.2 Personnel

Medical laboratory examinations must only be performed by personnel who are professionally qualified corresponding to legal regulations, and who are authorised by management.

The number of personnel must be sufficient with regard to the amount of work.

Regular participation in continuing education programmes must be ensured for all staff members. Participation in training and continuing education programmes must be documented.

It must be stipulated and documented who is responsible for the training of new employees or training for new devices and new examination methods and how such training has to be performed.

The realisation of mandatory training and educational sessions has to be 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 can affect the quality of the examination results are to be identified, monitored, regulated and documented for medical laboratory examinations.
5.3.3 Access to rooms and areas, whose condition can impact medical laboratory examinations, and their use are to be established and monitored.
5.3.4 Adequate space for storage and appropriate room conditions are to be ensured in order to maintain the integrity of testing material, stored microorganisms, cells, devices, reagents, 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. The integrity of the data is to be maintained and the data must be safeguarded 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 to regularly monitor the proper functioning of its devices, reagents and analysis systems and it has to implement this procedure. Maintenance has to be performed according to a written schedule.
5.4.3 Records have to be kept for each analysis system and device needed to perform medical laboratory examinations

that can impact on the quality of these medical laboratory examinations.

These records should contain, at a minimum:

(1) Name of system or device
(2) Name of the manufacturer, model and serial number or other form of identification
(3) Date of initial operation
(4) Instructions for use, operating instructions and other information from the manufacturer, or justification, if they are not available
(5) Functional tests
(6) Instrument maintenance intervals and results of conducted controls including date, time and type of inspection and other maintenance work
(7) The nature, dates and times of equipment outage, malfunctions, structural modifications and repairs.

These records have to be kept for 2 years beyond the working life of the equipment and have to be promptly accessible.

5.4.4 Authorised and trained members of staff may only operate devices and analysis systems. Instructions for operating and servicing the equipment have to be kept up-to-date and be accessible to the members of staff in the workplace.

6 Medical laboratory examinations

6.1 Pre-analytical phase

6.1.1 The sender of the specimen to be examined has to be given a list of the laboratory examinations offered by the medical laboratory relevant to their purposes as well as a document stating the details of specimen collection.

6.1.2 The medical laboratory has to provide professionally competent advice regarding the examinations offered, including the examination method to be selected, the type of specimen to be used and the evaluation of results of examinations.

6.1.3 The examination request form submitted by the sender of the material has to contain the following information:

(1) Identification of the patient – including gender and date of birth in the case of age and gender-specific measurands
(2) Identification of the sender 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) Requested examinations and
(5) Clinically relevant patient information required for the requested examination.

6.1.4 Written instructions outlining the correct method of collection and handling of specimens have to be available to the persons responsible. These instructions have to be summarised in the document for collecting the specimen.

6.1.5 The document for collecting the specimen has to specifically contain the following:

(1) The list of the medical laboratory examinations offered, or reference to this
(2) Instructions on:
    (a) Preparing the patient
    (b) Completing the examination request form or filling in an electronic entry mask
    (c) The required information about the patient
    (d) The type and quantity of the specimen to be collected
    (e) The specific time constraints for collecting, storing and transporting the specimen, if required
    (f) Collecting the specimen, with a description of the containers for the specimen and all required additives
    (g) Unmistakably labelling the specimen
    (h) All of the measures that are to be taken between the time the specimen is collected and its arrival at the medical laboratory, and
    (i) The period of time within which further medical laboratory examinations can be requested.
(3) Information and instructions to be provided to the patients regarding preparation measures for collecting the specimen and, if necessary, patient consent forms for collecting the specimen and for performing the medical laboratory examinations and
(4) Patient information regarding the self-collection of the specimen and storage and transportation details of the self-collected specimen.

6.1.6 Criteria have to be established for rejecting medical laboratory examinations.

6.1.7 The submitted specimen and portions thereof have to be clearly assigned to one patient. If this is not fulfilled, the medical laboratory may not process them. The sender of the material has to be notified and the incident has to be documented.

If the specimen cannot be assigned beyond a doubt to one patient and a specimen of the same quality cannot be collected or was collected when the patient was in a critical condition, the medical laboratory shall decide, after consulting with the sender of the specimen, if the requested medical laboratory examinations should nevertheless be performed. The result of the consultation has to be documented.

6.1.8 When the specimen arrives, the medical laboratory has to check whether there is any indication that a

timely delivery has not occurred for the requested medical laboratory examinations or whether the conditions established in the document governing the collection, handling, storage and transport of the specimen were not met. If such indications are identified, the medical laboratory has to decide whether the examinations are to be performed despite this, or whether a new specimen is to be requested. This incident has to be documented.

6.1.9 If necessary, the medical laboratory must have documented procedures in place covering the acceptance, labelling and processing of specimens, and the reporting of medical laboratory examinations that are considered to be urgent.

6.2 Procedures for conducting medical laboratory examinations

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

6.2.2 The medical laboratory may only use validated examinations procedures. It has to document the procedure used for validation and the results obtained.

6.2.3 All medical laboratory examination procedures have to be documented in procedural instructions. These instructions have to be written in such a way that medical laboratory staff can understand them. They have to be available at the workstations at all times.

The manufacturer's instructions for use and additional remarks as appropriate are deemed to be part of the procedural instructions.

Each procedural instruction has to contain the following, where applicable:

(1) Identification of the document
(2) Principle of the procedure used for examination (methods)
(3) Individual steps of the procedure
(4) Calibration procedure as appropriate or as available
(5) Procedure used to calculate the result as appropriate or as available
(6) Required specimen (including details of the type of specimen container and the necessary additives)
(7) Required instruments, reagents, culture media and test systems
(8) Specification of the performance of the examination procedure
(9) Information on possible interference and cross-reactivity
(10) Reference ranges for healthy probands
(11) Objective of the medical laboratory examination (medical indication)
(12) Possible causes of deviating results
(13) Measures to be taken in the case of abnormal results
(14) Safety precautions, and
(15) References.

6.2.4 If the medical laboratory modifies one of its examination procedures so that the results, and thus the interpretation, change in a clinically significant way, the sender of the material has to be informed as soon as possible in written form.

6.3 Post-analytical phase

6.3.1 The results have to be technically validated and, using the available clinical data, medically validated.

The medical laboratory must have procedures in place for releasing the examination results. These should include information about who may authorise the release of reports and whom they may be issued to. The procedures have also to contain a guideline for the immediate issuance of reports to patients.

It has to be documented which persons carried out the technical and medical validation.

6.3.2 The reports have to be easy to read and contain at least the following information:

(1) Date, and if required, time the report was issued
(2) Identification of the patient
(3) Name or other means of identifying the sender of the specimen and, if required, his address; the address of the recipient of the report if not the same as that of the sender
(4) Name of the medical laboratory
(5) Date and time when the specimen arrived at the medical laboratory
(6) Date and time when the specimen was collected, if this information is available and important for interpreting the examination results
(7) Type of specimen
(8) Name of the laboratory examinations and the methods used, if the latter is important 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) Identification 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 has to be stated in the report. As the case may be, the report should state that the results are conditional.

6.3.4 The medical laboratory must have written policies and procedures in place for subsequent amendments to reports. The changes have to be marked with the date, time and name of the person responsible for the changes. The original results have 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 Specimens and samples have 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

7.1 Quality manual

7.1.1 The quality management system and the documentation used in the medical laboratory have to be compiled in a quality manual. This quality manual has to include or make reference to all procedures. Laboratory personnel have to be instructed on the use and practical application of the quality manual and all referenced documents. The quality manual shall be kept up-to-date at all times.

The quality manual must contain the following information where applicable:

(1) Introduction: description of the medical laboratory, its legal status and its main tasks
(2) Objectives and strategies: description of the quality assurance policy
(3) Management: description of their responsibilities and qualifications
(4) Staff:
    (a) Qualifications, briefings, training and continuing education and
    (b) Health protection and safety procedures
(5) Resources and partnerships:
    (a) Rooms
    (b) Equipment
    (c) Environmental conditions
    (d) Partnerships (referral laboratories, external service providers and suppliers)
    (e) Environmental issues
(6) Processes:
    (a) Procedures in accordance with the document for collecting the specimen
    (b) Examination procedures, handling equipment, reagents and other relevant consumables, validation of the examinations procedures
    (c) Ensuring the analytical quality of the examinations procedures through internal and external quality assurance and 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 procedure
    (g) Keeping, storing and archiving records
    (h) Resolving with complaints
    (i) Determining errors and corrective measures
    (j) Preventive measures
    (k) Communication and other interaction especially with patients, medical personnel, referral laboratories, and
    (l) Internal audits.

7.1.2 If the medical laboratory is a part of an organisation which already has a quality management system in place, it is not necessary to have a separate quality manual for the medical laboratory, if the corresponding section in the organisation's quality manual contains requirements similar to the ones contained in this guideline. The same applies to 7.2 and 7.3 below.

7.2 Document control

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

7.3 Resolving complaints

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

7.4 Examinations in referral laboratories

7.4.1 The medical laboratory has to keep a list of all referral laboratories it commissions. 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 sender receives the examniation results and findings from the referral laboratory.
7.4.3 When hiring referral laboratories outside the scope of this guideline, the commissioning medical laboratory has to ensure that the referral laboratory possesses the required competencies and that a similar quality management system is in place.

7.5 Non-conforming examination results

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

Management must specifically ensure that:

(1) Persons responsible for problem resolution are named
(2) The medical significance of the incorrect result is considered and, if necessary, the sender is informed thereof
(3) Examinations are halted and reports are withheld as necessary
(4) Corrective action is taken immediately
(5) Already-released examination results are recalled or the recipient is appropriately informed of the error
(6) There is a designated person responsible for the recalling of the examination results
(7) Causes and corrective measures taken are documented and
(8) The success of any corrective action taken is verified to ensure that all identified non-conformities have been eliminated.

The records documenting the identified non-conformities and the corrective measures have to be kept for 2 years.

8 Internal and external quality assurance

8.1 A control system has to be used for internal quality assurance in the medical laboratory that is in line with the present state-of-the-art in science and technology and the procedures described in Chapter B of this guideline.
8.2 External quality assurance for the medical laboratory has to be performed by participating regularly in external quality assessment programmes in accordance with the procedures described in Chapter B of this guideline.

B Special parts

B1 Quantitative medical laboratory examinations

1 Principles of quality assurance

(1) Part B1 specifies minimum requirements to assess the quality of quantitative results of medical laboratory examinations. These minimum requirements include internal and external quality assurance.
(2) All of the quantitative examinations performed by the medical laboratory 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 device or measuring stations.
(3) In addition, all measurands listed in Table B1a to c of this Part are subject to external quality assurance.
(4) The measurands in Table B1a to c are listed alphabetically based on the type of specimen. The criteria used for including a measurand in the table are, specifically, the frequency of the measurement procedure and its medical relevance according to the current state of science. Deviations of measurements as listed in the table are determined based on medical requirements and current state of analytical technology. Table B1 is continuously updated.
(5) This Part of the guideline does not apply to hemacytometer counting of corpuscular components in body fluids, determination of erythrocyte sedimentation rate and examination of pH test strips.

2 Procedure of quality assurance

2.1 Internal quality assurance

2.1.1 Procedure

(1) Regarding the type and frequency of internal quality assurance the specifications of the manufacturer have to be followed. Irrespective of this, internal quality assurance has to be performed in accordance with (2) to (4).
(2) A single measurement of a control sample has to be performed at the start of the measuring procedure.

(3) On days when a measuring procedure is used to analyse patient samples, a single measurement of a control sample has 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 has to be performed after every intervention to the measuring system.
Interventions into 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. Within the same measuring procedure the control and calibration materials must not be identical.
(6) Control samples have to be used with known target values that are within the measurement interval relevant for medical decisions.
(7) Control samples with target values in at least two different concentration intervals have to be used alternately, if available.

2.1.2 Evaluation of the results of single measurements of control samples

(1) The evaluation of the results of the single measurements of control samples has to be performed without delay as after the results are available. Evaluation is based on the deviations of measurement as listed in Table B1a to c Column 3, or either on the basis of the internal laboratory deviation limits or on the intervals of the manufacturers of the control samples.
(2) If a single measurement of a control sample exceeds the deviation of measurements, the measuring procedure will initially be blocked for further use in measuring specimens from patients. The cause of the failure of performance has to be sought and, if possible, rectified. Taking medical relevance into consideration, the responsible person must decide whether the measuring 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 have to be repeated, or whether the sender has to be notified about already communicated results. The entire process has to be documented.

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

(1) Based on the results from all single measurements of control samples that have led to the release of the measuring procedure or of the patient results, the relative root mean square of the deviation of measurement has to be calculated immediately after the completion of a control period. A control period generally consists of 1 calendar month. If, per control period, there are fewer than 15 results from single measurements of control samples per measurement procedure that have led to the release of a measurement, this period will be extended by 1 month until at least 15 such results are available. The total period of time may not exceed 3 months.
(2) If the relative root mean square of the deviation of measurement for a control sample exceeds the value given in Table B1a to c, Column 3, the examination procedure has to be blocked from further use in measuring patient specimens. The measurement procedure must not be made available for measurements until the functionality of the procedure has been proven through appropriate measures. The entire process has to be documented.
(3) If the value given in Table B1a to c, Column 3 is again exceeded in the subsequent control period for the same control sample, and user-related causes can be excluded, apart from taking the appropriate measures according to (2) the responsible federal authorities have to be informed, if this can be defined as an "incident" according to § 2 of the German Safety Plan for Medical Devices (MPSV).
(4) As to measurands that are not listed in Table B1a to c (2) applies accordingly. Instead of the maximum permissible deviation as listed in Table B1a to c, Column 3, the laboratory's internal Δ_{max} has to be used as established by the laboratory in accordance with 2.1.4. The measurement procedure must not be made available for measurements until the functionality of the procedure has been proven through appropriate measures. The entire process has to be documented.

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

(1) In order to establish internal laboratory deviation limits for single measurements of control samples of measurands not listed in Table B1a to c, one control sample result per day is chosen for a minimum of 15 days, or for a maximum of one control period, for each control sample used. Values are selected based on a pattern, i.e., either the first, the *n*th or the last value

is used in the calculation. Randomly selected control results may also be used.

The limits of deviation 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 pre-evaluation period.

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_{ep}^2 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 deviate from this procedure can also be defined. The reasons and the chosen procedure have to be documented in a transparent way.

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

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

(4) No internal laboratory deviation limits need to be calculated for control samples with a batch life of less than 12 weeks. The interval given by the manufacturer of the control samples have to be applied.

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

(1) Are unit-use reagents and the corresponding measuring systems applied in patient near immediate diagnostic, they have to be checked in accordance with the manufacturer's instructions on quality control. The results have 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 has to be performed 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 measurements of the control samples and any resulting consequences have to be carried out in accordance with Section 2.1.2 (2). For measurands not listed in Table B1, Sentence 1 applies accordingly. The permitted deviation 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 3 months have 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 single measurements of control samples and the consequences in accordance with Section 2.1.2 (2) have to be performed for all control samples.

Sentence 1, applies accordingly for measurands not listed in Table B1. The permitted deviation 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 have to be documented in a structured way by measurand and by type of sample material taking into account the measuring procedure and measuring station. Upon the request of the authority responsible for inspecting adherence to this guideline, the respective documentation has to be presented.

(2) The documentation must include the following:
   (a) Name of the medical laboratory
   (b) Name of the measuring station
   (c) Date and time of the measurement
   (d) Measurand, sample material and unit
   (e) Measuring 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 according to Table B1a to c, Column 3, or the internal laboratory deviation limits or the ranges stated by the manufacturer of the control samples
   (i) Release or lock flag
   (j) Corrective measures 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 should be represented graphically.

(4) All measurement results of the quality assurance must be stored for 5 years together with the respective calculations after the control period and evaluations, as well as 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) Participating in an EQA once a quarter for each measurand listed in Table B1a to c, is obligatory for each site if the medical laboratory provides this examination.

(2) The participant of the EQA examines the EQA samples under routine conditions, and conveys results and information as required by the reference institution. When communicating results, the participant confirms that the analysis was performed in accordance with this guideline, in the participant's laboratory, and under his supervision.

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

(4) If the participant does not receive a certificate for a measurand because one of the participant's results exceeds the authorised limits of error as specified in Table B1a to c, Column 5, the participant is obliged to determine the causes and rectify them if this lies within their responsibility. The entire process has to be documented.

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

Table B1

Explanations on Table B1

Columns 2 to 4 contain requirements for the user in the medical laboratory. Columns 2 and 4 to 6 contain

Table B1a: Measurands in plasma/serum/whole blood.

1	2	3	4			5	6
No.	Measurand	Permissible relative deviation of a single result or the relative root mean square, respectively	Rili-BAEK applicable concentration intervals of columns 3 and 5			Permissible relative deviation in EQA	Type of target value in EQA
			From	To	Unit		
1	Activated partial thromboplastine time (aPTT)	10.5%	20	120	s	18.0%	NV
2	Alanine aminotransferase (ALT or GPT) EC 2.6.1.2	11.5%	30 0.5	300 5.0	U/L µkat/L	21.0%	RMV
3	Albumin	12.5%	20	70	g/L	20.0%	NV
4	Alkaline phosphatase (AP) EC 3.1.3.1	11.0%	20 0.33	600 10	U/L µkat/L	18.0%	NV
5	Alpha fetoprotein (AFP)	17.0%	5	250	kIU/L	24.0%	NV
6	Aspartate aminotransferase (AST or GOT) EC 2.6.1.1	11.5%	20 0.33	400 6.67	U/L µkat/L	21.0%	RMV

(**Table B1a**: Continued)

1 No.	2 Measurand	3 Permissible relative deviation of a single result or the relative root mean square, respectively	4 Rili-BAEK applicable concentration intervals of columns 3 and 5			5 Permissible relative deviation in EQA	6 Type of target value in EQA
			From	To	Unit		
7	Bilirubin (total)	13.0%	>2	30	mg/dL	22.0%	NV
			>34	513	µmol/L		
		22.0%	0.1	≤2	mg/dL		
			1.7	≤34	µmol/L		
8	Ca 15-3	16.0%	10	250	U/ml	24.0%	NV
9	Calcium (total)	6.0%	1	6	mmol/L	10.0%	RMV
10	Calcium (ionised)	7.5%	>1	2.5	mmol/L	15.0%	NV
		14.0%	0.2	≤1	mmol/L	18.0%	
11	Carbamacepine	12.0%	2	20	mg/L	20.0%	NV
12	Carcinoembryonic antigen (CEA)	14.0%	1	200	µg/L	24.0%	NV
13	Chloride	4.5%	70	150	mmol/L	8.0%	RMV
14	Cholesterol (total)	7.0%	50	350	mg/dL	13.0%	RMV
			1.3	9.1	mmol/L		
15	Cortisol	16.0%	>60	500	µg/L	30.0%	RMV
			>166	1380	nmol/L		
		18.5%	20	≤60	µg/L		
			55	≤166	nmol/L		
16	Creatine kinase (CK) EC 2.7.3.2	11.0%	50	1000	U/L	20.0%	RMV
			0.83	16.7	µkat/L		
17	C-reactive protein (CRP)	13.5%	1	120	mg/L	20.0%	NV
18	Digitoxin	15.5%	5	80	µg/L	30.0%	RMV
19	Digoxin	14.0%	>1	5	µg/L	30.0%	RMV
		17.5%	0.5	≤1	µg/L		
20	Erythrocytes	4.0%	1.5	7	10^{12}/L	8.0%	RMV
21	Oestradiol 17-beta	22.0%	10	500	ng/L	35.0%	RMV
			37	1835	pmol/L		
22	Ethanol (clinical toxicologic)	9.0%	>0.6	5	g/L	12.0%	NV
		15.0%	0.2	≤0.6	g/L	21.0%	
23	Ferritin	13.5%	10	600	µg/L	25.0%	NV
24	FSH	14.0%	4	70	U/L	21.0%	NV
25	Gamma glutamyl transferase (γ-GT) EC 2.3.2.2	11.5%	20	300	U/L	21.0%	RMV
			0.33	5	µkat/L		
26	Glucose	11.0%	40	400	mg/dL	15.0%	RMV
			2.2	22	mmol/L		
27	Haematocrit	5.0%	10	60	%	9.0%	NV
			0.1	0.6	l/l		
28	Haemoglobin	4.0%	2	20	g/dL	6.0%	RMV
			1.2	12.4	mmol/L		
29	Haemoglobin A 1c (HbA1c)	10.0%	30	140	mmol/mol Hb	18.0%	RMV
30	Uric acid	7.0%	2	13	mg/dL	13.0%	RMV
			119	773	µmol/L		
31	Urea	10.5%	15	200	mg/dL	20.0%	RMV
			2.5	33	mmol/L		
32	Human chorionic gonadotropin (hCG)	14.0%	>100	1500	IU/L	30.0%	NV
		17.0%	2	≤100	IU/L		
33	Immunoglobulin A	12.0%	0.5	6	g/L	20.0%	NV
34	Immunoglobulin G	10.0%	4	30	g/L	18.0%	NV
35	Immunoglobulin M	13.0%	0.4	5	g/L	26.0%	NV
36	Potassium	4.5%	2	8	mmol/L	8.0%	RMV
37	Creatinine	11.5%	0.5	10	mg/dL	20.0%	RMV
			44	884	µmol/L		

(**Table B1a:** Continued)

1 No.	2 Measurand	3 Permissible relative deviation of a single result or the relative root mean square, respectively	4 Rili-BAEK applicable concentration intervals of columns 3 and 5			5 Permissible relative deviation in EQA	6 Type of target value in EQA
			From	To	Unit		
38	Lactate	11.0%	9	90	mg/dL	18.0%	NV
			1	10	mmol/L		
39	Lactate dehydrogenase (LDH) EC 1.1.1.27	9.0%	100	700	U/L	18.0%	RMV
			1.67	11.7	µkat/L		
40	Leucocytes	6.5%	2	30	10^9/L	18.0%	RMV
41	Lithium	6.0%	0.3	3.5	mmol/L	12.0%	RMV
42	Magnesium	7.5%	0.3	3.5	mmol/l	15.0%	RMV
43	Sodium	3.0%	110	180	mmol/l	5.0%	RMV
44	pCO_2	7.5%	≤35		mmHg	12.0%	NV
		6.5%	>35				
45	pH	0.4%	6.75	7.80		0.80%	RMV
46	Phenobarbital	10.0%	8	80	mg/L	20.0%	NV
47	Phenytoin	11.0%	3	35	mg/L	20.0%	NV
48	Phosphate (inorganic)	9.0%	1	10	mg/dL	16.0%	RMV
			0.3	3.2	mmol/L		
49	pO_2	5.5%	>125	350	mmHg	12.0%	NV
		7.0%	>80	≤125	mmHg	18.0%	
		11.0%	40	≤80	mmHg	18.0%	
50	Progesterone	17.0%	>5.0	35	µg/L	35.0%	RMV
			>16	111	nmol/L		
		22.0%	0.2	≤5.0	µg/L		
			0.6	≤16	nmol/L		
51	Prostate specific antigen (PSA)	15.5%	0.2	50	µg/L	25.0%	NV
52	Protein (total)	6.0%	35	110	g/L	10.0%	RMV
53	Testosterone	20.5%	0.2	20	µg/L	35.0%	RMV
			0.7	69	nmol/L		
54	Theophylline	13.0%	3	40	mg/L	24.0%	RMV
55	Thromboplastin time (Quick)	11.5%	10	120	%	23.0%	NV
56	Thrombocytes	7.5%	>300	700	10^9/L	13.0%	NV
		8.5%	>150	≤300	10^9/L	15.0%	
		13.5%	40	≤150	10^9/L	18.0%	
57	Thyreotropic hormone (TSH)	13.5%	0.1	40	mU/L	24.0%	NV
58	Thyroxine, total (T4)	12.5%	0.5	22	µg/dL	24.0%	RMV
			6.4	283	nmoL/L		
59	Thyroxine, free (fT4)	13.0%	>20	85	ng/L	20.0%	NV
			>26	109	pmol/L		
60	Transferrin	8.0%	0.5	6	g/L	12.0%	NV
61	Triglycerides	9.0%	60	400	mg/dL	16.0%	RMV
			0.68	4.6	mmol/L		
62	Triiodothyronine, total (T3)	15.0%	>1.2	10	µg/L	24.0%	NV
			>1.8	15	nmol/L		
		16.0%	0.2	≤1.2	µg/L		
			0.3	≤1.8	nmol/L		
63	Triiodothyronine, free (fT3)	13.0%	1	25	ng/L	20.0%	NV
			1.5	39	pmol/L		
64	Troponin I	20.0%	0.1	35	µg/L	33.0%	NV
65	Troponin T	16.0%	>1	8	µg/L	33.0%	NV
		21.0%	0.08	≤1	µg/L		
66	Valproic acid	11.5%	20	150	mg/L	20.0%	NV
67	Vancomycin	12.0%	4	100	mg/L	18.0%	NV

RMV, reference method value; NV, nominal value specific to measuring method.

Table B1b: Measurands in urine.

1 No.	2 Measurand	3 Permissible relative deviation of a single result or the relative root mean square, respectively	4 Rili-BAEK applicable concentration intervals of columns 3 and 5			5 Permissible relative deviation in EQA	6 Type of target value in EQA
			From	To	Unit		
1	Albumin	15.0%	1	500	mg/L	26.0%	NV
2	Calcium	8.5%	0.5	6	mmol/L	17.0%	NV
3	Glucose	11.0%	100	4000	mg/L	22.0%	RMV
			0.6	22	mmol/L		
4	Uric acid	13.5%	5	300	mg/L	23.0%	RMV
			30	1784	µmol/L		
5	Urea	13.5%	0.1	20	g/L	21.0%	RMV
			1.7	333	mmol/L		
6	Potassium	8.5%	2	140	mmol/L	15.0%	RMV
7	Creatinine	12.0%	0.01	3	g/L	21.0%	RMV
			0.1	27	mmol/L		
8	Sodium	6.5%	50	200	mmol/L	12.0%	RMV
9	Phosphate (inorganic)	11.5%	30	900	mg/L	20.0%	NV
			1	29	mmol/L		
10	Protein (total)	11.5%	5	10,000	mg/L	24.0%	NV

Table B1c: Measurands in cerebrospinal fluid.

1 No.	2 Measurand	3 Permissible relative deviation of a single result or the relative root mean square, respectively	4 Rili-BAEK applicable concentration intervals of columns 3 and 5			5 Permissible relative deviation in EQA	6 Type of target value in EQA
			From	To	Unit		
1	Albumin	13.5%	20	1000	mg/L	23.0%	NV
2	Glucose	9.5%	20	300	mg/dL	18.0%	RMV
			1.1	17	mmol/L		
3	Immunoglobulin A	15.5%	2	40	mg/L	27.0%	NV
4	Immunoglobulin G	12.0%	15	500	mg/L	20.0%	NV
5	Immunoglobulin M	15.5%	1	30	mg/L	33.0%	NV
6	Lactate	11.5%	10	99	mg/dL	20.0%	NV
			1.1	11	mmol/L		
7	Protein (total)	13.5%	10	2000	mg/L	23.0%	NV

requirements for evaluation the results by reference institutions.

The Rili-BAEK applicable concentration interval is the concentration interval in which the specifications for target values of control samples, stated in Columns 3 and 5, apply.

If the target value of the control sample is outside the given interval, the regulations for non-Table B1 measurand apply. If control samples with lower target values stated in the Rili-BAEK applicable concentration intervals are used, the limits of deviation given for the Rili-BAEK applicable concentration intervals can also be used in evaluation the measurements of these control samples.

B2 Qualitative medical laboratory examinations

1 Principles of quality assurance

(1) Part B2 specifies minimum requirements to assess the quality of qualitative results of medical laboratory examinations. These minimum requirements include internal and external quality assurance.

(2) All of the qualitative examinations performed by the medical laboratory (measurands and nominal characteristic) are subject to internal quality

assurance. If several instruments or measuring stations are used to perform a medical laboratory examination, internal quality assurance has to be performed on each of these instruments or measuring stations.

(3) In addition, all measurands and nominal characteristics listed in Table B2-2 of this Part are subject to external quality assurance.

(4) The measurands in Tables B2-1 and B2-2 are listed alphabetically. The criteria used for including a measurand in the tables are, specifically, the frequency of the measurement procedure and its medical relevance according to the current state of science. Tables B2-1 and B2-2 are continuously updated.

(5) This section of the guideline does not apply to qualitative tissue examinations and to examinations whose internal and external quality assurance requirements are stated in further special Parts B.

2 Procedure of quality assurance

2.1 Internal quality assurance

2.1.1 Procedure

(1) Regarding the type and frequency of internal quality assurance the specifications of the manufacturer have to be followed.
Irrespective of this, internal quality assurance has to be performed:
(a) In accordance with Table B2-1 for the examinations listed therein
(b) Adequately and regularly in accordance with medical necessity and with the required examination frequency of patient specimens, in case the examinations are not listed in Table B2-1.
The requirements of (1) Sentence 2 are considered to be met, if corresponding controls that ensure the accurateness of the results, are integrated within the applied measuring system.

(2) In addition, internal quality assurance has to be performed after every intervention to the examination procedure. Interventions 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. Within the same measuring procedure, control and calibration materials must not be identical.

(4) Control samples have to be used with known results 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 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.

2.1.2 Evaluation of the results

(1) The evaluation of results of control sample measurements has to be performed without delay. The evaluation is performed using the target objectives assigned to the control sample.

(2) If the requirements are not met, the measuring procedure will initially be blocked from further use in measuring specimens from patients. The cause of the failure of performance has to be sought and, if possible, rectified. Taking medical relevance into consideration, the responsible person must decide whether the measuring 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 have to be repeated, or whether the sender has to be notified about already communicated results. The entire process has to be documented.

2.1.3 Documentation

(1) All of the results of the internal quality assurance have to be documented in a structured way by type of the sample material, taking into account the measuring procedure and measuring station or instrument. Upon the request of the authority responsible for inspection adherence to this guideline the respective documentation has to be presented.

(2) The documentation must include the following:
(a) Name of the medical laboratory
(b) Name of the measuring station or device

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.

(c) Date and, where relevant, time of the examination
(d) Examination, sample material, and, if necessary, the unit of measurement
(e) Measuring method
(f) Result of control sample
(g) Target objectives of the control sample
(h) The evaluation
(i) Release or lock flag
(j) Corrective measures taken
(k) Manufacturer, name and lot number of the control sample and
(l) Name/ cipher or signature of the investigator.

(3) The documentation on the performed internal quality assurance has to be stored for 5 years, along with the evaluations as well as the protocols of the measures taken when the target objectives were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) The medical laboratory is required to participate in an external quality assurance for every measurand listed in Table B2-2 in the frequency of participation specified there. In a medical laboratory comprising several sites, each site has to participate for the examinations it provides. 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 examines the EQA samples under routine conditions, and conveys results and information as required by the reference institution. By communicating these results, the participant confirms that the tests were performed in accordance with this guideline, in the participant's laboratory, and under his supervision.

(3) 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 objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them insofar as this lies within the participant's responsibility. The entire procedure is to be documented.

(4) Certificates of both participation and successful participation in the external quality assurance programme have to be kept for 5 years, unless a longer archiving period is stipulated by other regulations.

Table B2-1: Internal quality assurance.

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

Daily, each calendar day on which patient samples are tested; weekly, each calendar week in which patient samples are tested, etc.

Table B2-2: External quality assurance (EQA).

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

B3 Direct detection and characterisation of infectious agents

1 Principles of quality assurance

(1) Part B3 defines the minimum requirements of quality assurance for medical laboratory examinations for the direct detection of medically relevant infectious agents. These requirements include, if applicable, subsequent tests for the characterisation of pathogens (e.g., differentiation, identification, and typing) and their properties relevant for the treatment of infections (e.g., antimicrobial susceptibility testing). These minimum requirements apply to internal and external quality assurance.

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

(3) In addition, all examinations listed in Tables B3-2 and B3-2a are subject to external quality assurance.

(4) The examinations in Tables B3-1, B3-1a, B3-2 and B3-2a have been listed separately according to the

type of pathogen or testing method(s) applied. The criteria used for the listing of an examination in the tables include, specifically, the frequency of the tests applied and their medical relevance according to the current state of the knowledge. The respective tables are continuously updated.

2 Implementation of quality assurance

2.1 Internal quality assurance

2.1.1 Implementation

(1) With respect to the type and frequency of internal quality assurance performance the guidelines of the manufacturer have to be followed. Irrespective of this, internal quality assurance has to be performed with respect to frequency:
   (a) In accordance with Tables B3-1 and B3-1a for the examinations listed therein.
   (b) Sufficiently and regularly 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 Table B3-1.

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

(2) As part of the internal quality assurance, the following should be examined:
   (a) Culture media and supplements
   (b) Cell lines utilised for cell cultures
   (c) Reagents, staining solutions, diagnostic antibodies and antigens
   (d) Methods used for the identification of pathogens and the susceptibility testing
   (e) Equipment and instruments utilised for the respective examination

(3) Furthermore, internal quality assurance has to be performed after every intervention of the examination procedure. Interventions of the examination procedures include:
   (a) Calibration
   (b) Repairs or maintenance of equipment and instruments relevant to the respective examination and
   (c) Alternations of reagent batches.[2]

(4) Control samples must be as similar as possible to the examined patient samples. Within the same measuring procedure, control and calibration materials must not be identical.

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

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

2.1.2 Special guidelines

2.1.2.1 Microscopy

Internal quality assurance for microscopic techniques is specified in Table B3-1.

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

2.1.2.2 Culture procedures

2.1.2.2.1 Non cell culture-based procedures

Internal quality assurance for non cell culture-based methods is specified in Table B3-1. The following regulations also apply:

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

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

(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 be used for a maximum of 1 week only.

2.1.2.2.2 Cell culture-based procedures

Internal quality assurance for cell culture-based methods is specified in Table B3-1. 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) have to be used. That the negative control sample is morphologically normal must be documented.

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

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.

Table B3-1: 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)	No deviation	Daily
Ziehl-Neelsen stain	Characteristic staining of acid-fast bacilli on a control specimen	No deviation	Daily
Giemsa stain	Characteristic staining of erythrocytes and leucocytes in a smear, if applicable, from the patient being tested examined	No deviation	Daily
	pH value of the buffer	6.8–7.2	Weekly
Microscopic detection of pathogens, e.g., parasites	Recognition of characteristic pathogen structures, e.g., using image charts or external quality assurance programme / other preserved specimens (“consensus training”)	A maximum of a 20% deviation (based on the number of specimens assessed)	Annually
Negative contrasting in transmission electron microscopy of viruses	Use of samples with defined viruses/ virus quantities (testing the integrity of the carrier film, its binding properties, negative contrasting and amplification factor) clear detection of the viruses / virus groups	No deviations	With every new lot of film-coated copper mesh
Culture procedures			
Non cell culture-based procedures			
Visual check of solid culture media	Identifying of transport or storage damage, such as impurities, drying out	No deviation	Each package unit in every delivery or all new batches
Checking sterility[a]	No growth	No deviation	Every new batch
Examination of the culture media[b] using control strains or parallel testing comparing earlier batches for		No deviation	When changing batches
- all media	- Formation of characteristic colony morphology		
- solid culture media with incubation periods exceeding 72 hours	- 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)		
- selective media	- Suppression of the growth of non-target organisms		
- indicator media	- Pathogen-typical reactions		
- induction of typical morphologies in fungi	- Formation of the characteristic morphology		

(**Table B3-1:** Continued)

Examination	Objective	Permissible deviation	Frequency
Pathogen identification			
Examination of individual methods for (orientating) pathogen identification with control strains: catalase, oxidase, indole, coagulase, germ tube test, urease	Pathogen-typical reactions	No deviation	Daily
Verification of commercial systems for pathogens identification	Pathogen-typical reactions of control strains	No deviation	When changing lots
Examination of the inoculum purity in commercial systems used in identifying pathogens	Pure culture	No deviation	Each isolate
Susceptibility testing			
Beta-lactamase	Positive and negative controls using control strains	No deviation	Daily
Verification of the susceptibility test	On 20 consecutive work days using appropriate control strains, evaluation of the findings of the pathogen-antibiotic combinations	1 out of 20 findings per pathogen-antibiotic combination outside the permissible tolerance range	Before initial use and when requirements of the current internal quality 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 combination: troubleshooting, correction and, if required, re-verification of the test system	Weekly and when changing batches; for systems used less than once a week: each time the system is used
Inoculum purity	Examination of the inoculum purity	No deviation	Each isolate
Cell culture-based procedures			
Examination of the permissiveness using positive control strains	Detection of the virus-typical cytopathic effect or virus antigen	No deviation	Monthly and when changing batches of cells or for new passage made from cryopreserved cell cultures
Exclusion of viral contamination of cell cultures by running negative controls (non-infected cell control)	No viral contamination	No deviation	Monthly and when changing batches of cells or for new passage made from cryopreserved cell cultures
Virus cultivation: Exclusion of mycoplasma contamination of the cell culture	No mycoplasma contamination	No deviation	Every quarter year and when changing the cell culture batch
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[c] (the extraction control can be identical to the inhibition control)	No deviation	For every sample extraction

(**Table B3-1:** Continued)

Examination	Objective	Permissible deviation	Frequency
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 batch	No deviation	In the case of new reagent batch or newly dissolved reagent
Pathogen-specific nucleic acid detection	Positive and negative control according to 2.1.2.3	No deviation	Each procedure
Sequence-based methods (NAT, FISH and other hybridisation techniques	Checking database of the primer and probe sequences used in each detection method with respect to the declared species specificity	No deviation impacting on the test results	At least once a year or in accordance with provision by the producer
Immunological procedures			
Diagnostic antibodies	Positive and, if applicable, negative control	No deviation	When changing batches
Antigen detection (EIA, ELFA,CLIA and other immunochemical detection methods)	Positive and negative controls	No deviation	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	No deviation	Once per test package
Direct immunofluorescence test (e.g., respiratory viruses, *Legionella, Pneumocystis jirovecii, Giardia lamblia*)	Positive and negative controls	No deviation	Daily
Antigen detection using particle / erythrocyte suspensions for antigen detection (agglutination assays)	Checking function by using known positive and negative control samples	No deviation	Daily

Daily, every calendar day on which patient samples are tested; weekly, every calendar week in which patient samples are tested.

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

[b]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.

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

Table B3-1a: Internal quality assurance when examining nucleic acid concentration in blood/plasma/serum.

1 No.	2 Analyte	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value[a]	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	5000	5,000,000	IU/mL	Each use
2	HBV DNA	-0.5 to +0.5	500	5,000,000	IU/mL	Each use
3	HCV RNA	-0.5 to +0.5	500	5 000,000	IU/mL	Each use
4	HIV-1 RNA	-0.5 to +0.5	500	5,000,000	Copies/mL	Each use

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

(3) The virus dose for cell culture-based neutralisation tests must 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 biology procedures

The internal quality assurance for molecular biology methods is specified in Tables B3-1 and B3-1a. 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, have 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 must be carried out. If available, the concentration of one of the positive control samples should be close to the sensitivity limit of the applied amplification procedure. The negative control sample can be waived for closed, fully mechanised systems. The assessment has to be based on the assigned benchmarks.
(3) For the determination of nucleic acid concentrations, control samples containing known concentrations of nucleic acid or the respective pathogen must be used. These control samples have to be verified with international standards, if available.
(4) Limits of detection must comply with the stipulations listed in Table 3-1a. For specifications not listed in Table 3-1a the following regulation shall apply: the permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value of the quantitative positive control has 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/Ct, crossing point/Cp, cycle quantitative/Cq) has to be established. Likewise, the validity interval for the quantitative positive control must be established and documented.
(5) The base sequence of amplification products must be verified.

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 B3-1. The following regulation also applies: for direct procedures to detect pathogen-derived antigens using fluorescence-marked antibodies: analysis criteria must be established and, when using particle/erythrocyte suspensions as a component of the diagnostic test (e.g., agglutination, lytic reaction), evaluation criteria for the test readout must be defined.

2.1.3 Evaluation of the results

(1) The evaluation of control sample results has to be performed without delay. The evaluation is based on target objectives assigned to the respective control sample.
(2) If the required specifications are not met, the respective analytical technique will be initially excluded from the examination of further patient samples. The cause of performance failure has to be sought and, whenever possible, rectified. Taking medical relevance into consideration, the person in charge must decide whether the analytical technique can be re-authorised or whether further actions have to be taken, e.g., whether all of the examinations preceding and including the control examination have to be repeated, or whether the sender has to be notified

Table B3-2: External quality assurance (EQA).

No.	Examination Bacteria	Frequency	Type of target value in EQA[a]
1	Gram stain	Every half year	NV
2	Cultivation, identification and sensitivity testing of bacteria	Every half year	RLV
3	Cultivation, identification and sensitivity testing of fast growing bacteria and, if applicable, detection of accompanying flora of the urogenital system	Every half year	RLV
4	*Bordetella pertussis*, genome detection	Every half year	NV
5	*Borrelia burgdorferi* sensu lato, genome detection	Every half year	NV
6	*Chlamydia pneumoniae*, genome detection	Every half year	NV
7	*Chlamydia trachomatis*, antigen detection	Every half year	NV
8	*Chlamydia trachomatis*, genome detection	Every half year	NV
9	EHEC/STEC (Shiga toxin), genome detection	Every half year	NV
10	*Helicobacter pylori*, genome detection	Every half year	NV
11	*Legionella pneumophila*, genome detection	Every half year	NV
12	*Listeria monocytogenes*, genome detection	Every half year	NV
13	Methicillin-resistant *Staphylococcus aureus* (MRSA), genome detection	Every half year	NV
14	*Mycoplasma pneumoniae*, genome detection	Every half year	NV
15	*Neisseria gonorrhoeae*, genome detection	Every half year	NV
16	*Salmonella enterica*, genome detection	Every half year	NV
17	*Coxiella burnetii*, genome detection	Every half year	NV
18	*Francisella tularensis*, genome detection	Every half year	NV
	Mycobacteria	Every half year	NV
19	Microscopic detection of mycobacteria	Every half year	NV
20	Cultivation of mycobacteria	Every half year	NV
21	Differentiation of tuberculosis bacteria	Every half year	NV
22	Susceptibility test of Mycobacterium tuberculosis	Every half year	NV
23	Identification of mycobacteria	Every half year	NV
24	Mycobacterium tuberculosis, genome detection	Every half year	NV
	Parasites		
25	Parasites in the blood, microscopic detection	Every half year	RLV
26	Parasites in the stool, microscopic detection	Every half year	RLV
27	*Toxoplasma gondii*, genome detection	Every half year	RLV
	Yeasts		
28	Cultivation and identification of yeasts and hyphomycetes (mycoses of mucosa, organ, systemic or resulting from trauma)	Every half year	RLV
29	Identification of dermatophytes, yeasts and moulds (pathogens causing dermatomycoses and mucosal yeast infections)	Every half year	RLV
30	*Candida*, antigen detection	Every half year	NV
31	*Cryptococcus neoformans*, antigen detection	Every half year	NV
	Viruses		
32	Adenoviruses, genome detection	Every half year	NV
33	Cytomegalovirus, genome detection	Every half year	NV
34	Enteroviruses, genome detection	Every half year	NV
35	Epstein-Barr virus, genome detection	Every half year	NV
36	Hepatitis A virus, genome detection	Every half year	NV
37	Hepatitis B virus, genome detection	Every half year	NV
38	Hepatitis B virus, HBs antigen detection	Every half year	NV
39	Hepatitis B virus, HBe antigen detection	Every half year	NV
40	Hepatitis C virus, genome detection	Every half year	NV
41	Hepatitis C virus genotyping, genome detection	Every calendar year	NV
42	Hepatitis C virus, HCV antigen detection	Every half year	NV
43	Herpes simplex virus type 1 / type 2, genome detection	Every half year	NV
44	HIV-1 (RNA), genome detection	Every half year	NV
45	HIV-1, p24 antigen detection	Every half year	NV
46	Human papillomavirus, genome detection	Every half year	NV
47	Influenza A and B viruses, genome detection	Every half year	NV
48	Influenza A and B viruses, antigen detection	Every half year	NV
49	Parvovirus B19, genome detection	Every half year	NV
50	Respiratory syncytial virus, genome detection	Every half year	NV
51	Respiratory syncytial virus, antigen detection	Every half year	NV
52	Varicella zoster virus, genome detection	Every half year	NV

[a]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).

Table B3-2a: External quality assurance when examining nucleic acid concentration in blood/plasma/serum.

1 No.	2 Analyte	3 Permissible absolute deviation of the logarithmic (base 10) single value from the logarithmic nominal value in EQA	4 Rili-BAEK applicable concentration intervalsof column 3			5 Target value in EQA	6 Frequency of EQA
			From	To	Unit		
1	CMV DNA	-0.8 to +0.8	5000	5,000,000	IU/mL	NV	Every half year
2	HBV DNA	-0.6 to +0.6	500	5,000,000	IU/mL	NV	Every half year
3	HCV RNA	-0.6 to +0.6	500	5,000,000	IU/mL	NV	Every half year
4	HIV-1 RNA	-0.6 to +0.6	500	5,000,000	Copies/mL	NV	Every half year

about results already communicated. The entire process has to be documented.

2.1.4 Documentation

(1) All of the results of the internal quality assurance have to be documented in a structured way according to type of the sample material, taking into account the measurement procedure and site or device. Upon request of the inspection authority charged with control of adherence to this guideline the respective documentation has to be presented.
(2) The documentation must include the following:
   (a) The name of the medical laboratory
   (b) The name of the site or device
   (c) Date and, if relevant, time of the test
   (d) Examination, samples and, if required, the unit of measurement
   (e) Examination method
   (f) Result of the control sample
   (g) Objectives for the control sample
   (h) Evaluation
   (i) Release or lock flag
   (j) Corrective measures 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 stored for a minimum of 5 years, along with the evaluations as well as the protocols of the corrective measures taken when the target objectives were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) The medical laboratory is required to participate in an external quality assurance for every examination listed in Tables B3-2 and B3-2a in the therein specified frequency. In a medical laboratory comprising several sites, each site has to participate for the examinations it provides.
(2) The participant in the external quality assurance programme should examine the EQA samples under routine conditions, and convey results and information as required by the reference institution. By communicating these results, the participant confirms that the examinations were performed in accordance with this guideline, in the participant's laboratory, and under his supervision.
(3) If a participant does not receive a certificate for an examination because one or more of the results do not meet the target objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them insofar as this lies within the participant's responsibility. The entire procedure has to be documented.
(4) Certificates of both participation and successful participation in the external quality assessment programme must be kept for 5 years, unless a longer archiving period is stipulated by other regulations.

B4 Examination of ejaculate

1 Principles of quality assurance

(1) The minimum requirements of quality assurance for the results of ejaculate examinations are specified in Part B4. These minimum requirements include internal and external quality assurance.
(2) Ejaculate examinations, as defined in this guideline, are examinations for sperm concentration, motility and morphology.
(3) All of the ejaculate examinations performed by the medical laboratory are subject to internal and external quality assurance. If a test is performed on multiple devices or at multiple sites, internal quality assurance

has to be performed on each of these instruments or at each of these sites.

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

2 Procedure of quality assurance

2.1 Internal quality assurance

2.1.1 Procedure

(1) All examinations on the spermatozoa with regard to their concentration, motility and morphology have to be performed in duplicate and have to be documented. A minimum of 2×200 sperm have to be counted for this. Diluting or enriching the concentration of the ejaculate and/or the number of counting fields used for counting has to be done on the basis of a preliminary investigation. If the sperm concentration is less than 1–2 sperm per visual field (40-fold lens magnification), the concentration of the sample should be enriched. If there are fewer than 200 sperm per counting net in the counting chamber, the requirement of counting at least 2×200 spermatozoa no longer applies.

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

For testing spermatozoa concentration:

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

where:
in this case $x_{i1}=N_{i1}$ and $x_{i2}=N_{i2}$ are the counting results in the counting chamber halves and $\bar{x}_i=\bar{N}_i$ is the corresponding average from the repeat determination.

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 retested, if possible, and the result evaluated.

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

For testing the morphology and motility of spermatozoa:

The normal or abnormal spermatozoa have to be quantified in terms of morphology. The progressively motile, locally motile or non-motile spermatozoa are to be quantified in terms of motility.

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

where:
in this case $x_{i1}=p_{i1}$ and $x_{i2}=p_{i2}$ represent the percentage of the corresponding spermatozoa and $\bar{x}_i=\bar{p}_i$ represents the corresponding average of the repeat determination; N=number of the 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 retested and the result evaluated. If deviations recur, the cause is to be sought and, if possible, rectified. The entire process has to be documented.

2.1.2 Calculating and evaluating the average of the differences from the repeat determinations at the end of a control period

(1) A control period generally comprises of 1 calendar month. If there are more than 50 released pairs of values after a calendar month, the average $\overline{(x_1-x_2)}$ has 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 have 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 has to be performed based on the validation rule (formula):

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

If the absolute value of this average exceeds the right term of the inequality (formula), the testing procedure has

to be blocked from being used for measuring patient specimens. The measuring procedure cannot be released until the functionality of the procedure has been established through suitable measures. The entire process has to be documented.

2.1.3 Documentation

(1) All of the results of the internal quality assurance have to be documented in a structured way by type of the sample material, taking into account the measuring procedure and measuring station or device. Upon the request of the authority responsible for inspection of adherence to this guideline the respective documentation has to be presented
(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, specimen, unit of measurement
  (e) Examination methods (counting chamber used, dyeing technique)
  (f) Examination results including the single values of the repeat determinations
  (g) Evaluation in accordance with the corresponding formula
  (h) Release or lock flag
  (i) Corrective measures taken, and
  (j) Name/cipher or signature of the investigator
(3) The documentation on the performed internal quality assurance has to be stored for 5 years, along with the evaluations as well as the protocols of the measures taken when the target objectives were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) Every location of the medical laboratory has to participate once every half-year in an EQA to examine concentration, morphology and motility if the medical laboratory provides this examination.
(2) The participant in the external quality assessment programme examines the EQA samples under routine conditions and conveys results and information as required by the reference institution. By communicating the results, the participant confirms that the examinations were performed in accordance with this guideline, in the participant's laboratory, and under their supervision.
(3) 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 objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them, if this lies within the participant's responsibility. The entire procedure has to be documented.
(4) Certificates of both participation and successful participation in the external quality assessment programme have to be kept for 5 years, unless a longer archiving period is stipulated by other regulations.

B5 Molecular-genetic and cytogenetic medical laboratory examinations

1 Principles of quality assurance

(1) Part B5 specifies minimum requirements to assess the quality of molecular-genetic and cytogenetic medical laboratory examinations. These minimum requirements include internal and external quality assurance.
(2) Molecular-genetic and cytogenetic medical laboratory examinations, as defined in this Part of the guideline, are all medical laboratory examinations on the human genome and transcriptome aiming to detect known sequence variants, identify unknown variants, and establish the structure or copy number of genomic segments or to detect epigenetic modifications of genomic segments. They include molecular karyotyping using array analysis (e.g., array CGH, SNP arrays).
  Cytogenetic medical laboratory examinations, as defined in this Part of the guideline, include all medical laboratory examinations of postnatal cytogenetic diagnostics, prenatal cytogenetic diagnostics and cytogenetic diagnosis of tumours.
  (a) Postnatal cytogenetic diagnostics, as defined in this guideline, is the cytogenetic investigation of a blood sample, tissue sample, cytologic smear or a cell culture from a body tissue after birth.
  (b) Prenatal cytogenetic diagnostics, as defined in this guideline, is the cytogenetic investigation of amniotic cells, chorionic villi or foetal lymphocytes.
  (c) Cytogenetic diagnosis of a tumor, as defined in this guideline, is the analysis of neoplastic cells. This includes the analysis of cells from bone marrow, blood, lymph nodes and other tissues.

Cytogenetic medical laboratory examinations in the areas of postnatal cytogenetic diagnostics, prenatal cytogenetic diagnostics and cytogenetic diagnosis of tumours include the application of conventional molecular cytogenetics [ISH, usually fluorescence *in situ* hybridisation (FISH)].

(3) All of the molecular-genetic and cytogenetic examinations performed by the medical laboratory (measurands and nominal characteristics) 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 at each of these instruments or measuring stations.

(4) In addition, all of the examinations listed in Column 7 of Table B5-1 and the quantities listed in Table B5-2b are subject to external quality assurance. For molecular genetic examinations that are not listed in Table B5-1 Column 7, external quality assurance has to be performed in the form of participation in an external quality assessment programme that examines the method used, if such an external quality assessment programme is offered. The requirements of Part B5, Sentence 2 are deemed to be met when the applied methodology has been included in an external quality assessment programme listed in Table B5-1 and participation has occurred.

(5) The examinations and quantities are divided into molecular-genetic and cytogenetic examinations in Tables B5-1, B5-2a and B5-2b. They are included in the tables based on the frequency of their testing and their medical significance in accordance with the current state of science. The tables are continuously updated.

2 Procedure of quality assurance

2.1 Internal quality assurance

2.1.1 Procedure

1. General

(1) The manufacturer's requirements have to be observed regarding type and frequency of the internal quality assurance performed.
Irrespective of this, internal quality assurance has to be performed in terms of frequency:
(a) According to Tables B5-1 and B5-2a for the examinations or quantities individually listed therein
(b) Regularly and adequately according to medical necessity and testing frequency of patient samples if the examinations are not listed in Tables B5-1 and B5-2a.
The requirements of (1) Sentence 1 may be waived if suitable controls are integrated into the applied analysis system that ensures the accuracy of the results.

(2) Additionally, internal quality assurance has to be performed after there has been an intervention to the examination procedure.
Interventions 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 for the results of the medical laboratory examination, and
(d) Changing reagent lots.[3]

2. Molecular-genetic medical laboratory examinations

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

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

(3) Where nucleic acid amplification procedures are used for examining, control samples capable of detecting contaminations must be used.

(4) In the case of array analyses, known control parameters must be used to ensure that, at minimum, the requirements of the manufacturers have been met for the analysis.

3. Cytogenetic medical laboratory examination

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

3 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 of reagents.

2.1.2 Evaluation of results

2.1.2.1 For molecular-genetic medical laboratory examinations based on control sample examinations

(1) The control sample examination and/or the control measurand have to be evaluated as soon as the results are available. The assessment is done based on the target objectives.

(2) If the requirements are not met, the examination procedure will initially be blocked from further use in examining patient specimens. The cause of the failure of performance has to be sought and, if possible, rectified. Taking medical relevance into consideration, the responsible person must decide whether the examination procedure method can be re-authorised or whether further measures must be taken, e.g., whether all of the examinations preceding the control sample and including the control examination have to be repeated or whether the sender needs to be notified about already communicated results. The entire process has to be documented.

2.1.2.2 For cytogenetic medical laboratory examinations based on the quantities

The quality of each patient sample has, where appropriate, to be tested according to the quantities listed in Table B5-2a. If one of the quantities exceeds the limits given in Column 4 of Table B5-2a, the person responsible has to decide whether the patient sample should be re-examined. If the limit is also exceeded when the examination is repeated, the cause must be sought and, if possible, rectified. Based on medical relevance, the person responsible has to decide whether test results can still be obtained using this sample and, with corresponding comments in the findings, be used.

2.1.3 Assessing the results of cytogenetic examination based on quantities at the end of a control period

A control period generally comprises 1 calendar month.

If more than 50 approved results of patient samples are obtained after the period of a calendar month, the medical laboratory has to calculate the relative percentage, by which the limits given in Column 4 of Table B5-2a are exceeded.

If less than 50 approved results of patient samples are available, the period of time has to be extended by 1-month intervals until at least 50 of the same results are obtained. The total time period is not allowed to exceed 3 months.

If the limits given in Column 4 of Table B5-2a are exceeded, the examination procedure has to be initially blocked for testing further patient samples. The examination procedure cannot be released until the functionality of the procedure has been established through suitable measures. If it is likely that less than 50 results of patient samples will be released within a 3-month period, it is not necessary to calculate the relative percentage of violation of limits as specified in Sentence 1. If, in this case of low testing numbers, the limits set forth in Column 3 of Table B5-2a are exceeded five times in 3 months, action has to be taken as specified in Sentences 4 and 5.

The entire process has to be documented.

2.1.4 Documentation

(1) All of the results of the internal quality assurance have to be documented in a structured way by type of the sample material, taking into account the measuring procedure and measuring station or device. Upon the request of the authority responsible for inspection adherence to this guideline the respective documentation has to be presented.

(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) Result of control sample or quantity
- (g) Specification of the control sample or quantity
- (h) The evaluation
- (i) Release or lock flag
- (j) Corrective measures taken
- (k) Manufacturer, name and lot number of the control sample, as far as applicable, and
- (l) Name/cipher or signature of the investigator.

(3) The documentation on the performed internal quality assurance has to be stored for 5 years, along with the evaluations as well as the protocols of the measures taken when the target objectives were not met, unless longer archiving periods are stipulated by other regulations.

2.2 External quality assurance (EQA)

(1) The medical laboratory is required to participate in an external quality assurance for every examination or quantity listed in Tables B5-1 Column 7 and B5-2b in the frequency of participation specified there. In a

Tables B5

Table B5-1: Internal and external quality assurance of molecular genetic examination.

No.		Gene trivial name(s)	Gene HGNC name	Molecular-genetic category/ies of the genetic changes[a]	Frequency of the internal quality assurance or the evaluation of the control variable	Frequency of participation in external quality assurance programme
1	Alpha1-antitrypsin	*AAT, PI1*	*SERPINA1*	MUT/SNP	Weekly	6-monthly
2	Apolipoprotein B 100	*APOB*	*APOB*	MUT/SNP	Weekly	6-monthly
3	Apolipoprotein E	*APOE*	*APOE*	MUT/SNP	Weekly	6-monthly
4	Cytochrome p450 2C9 (CYP2C9)	*CYP2C9*	*CYP2C9*	MUT/SNP	Weekly	6-monthly
5	Cytochrome p450 2C19 (CYP2C19)	*CYP2C19*	*CYP2C19*	MUT/SNP	Weekly	6-monthly
6	Cytochrome p450 2D6 (CYP2D6)	*CYP2D6*	*CYP2D 6*	MUT/SNP, IN/DEL, CNV	Weekly	6-monthly
7	Factor V (Leiden)	*FV-Leiden*	*F5*	MUT/SNP	Weekly	6-monthly
8	Hereditary haemochromatosis	*HLA-H*	*HFE*	MUT/SNP	Weekly	6-monthly
9	HLA-B27	*HLA-B*	*HLA-B*	MUT/SNP	Weekly	6-monthly
10	Lactase-phlorizin hydrolase	*LPH*	*LCT*	MUT/SNP	Weekly	6-monthly
11	Methylenetetrahydrofolate reductase	*MTHFR*	*MTHFR*	MUT/SNP	Weekly	6-monthly
12	Plasminogen activator inhibitor I	*PAI1*	*SERPINE1*	IN/DEL	Weekly	6-monthly
13	Prothrombine	*FII*	*F2*	MUT/SNP	Weekly	6-monthly
14	Thiopurine S-methyltransferase	*TPMT*	*TPMT*	MUT/SNP	Weekly	6-monthly
15	Uridyl glucuronyl transferase-1A	*UGT1*	*UGT1A1*	IN/DEL	Weekly	6-monthly
16	Vitamin K epoxide reductase	*VKORC1*	*VKORC-1*	MUT/SNP	Weekly	6-monthly
17	Cystic fibrosis, mucoviscidosis	*CFTR*	*CFTR*	MUT/SNP IN/DEL, CNV	Weekly	Annually
18	Familial breast/ovarian cancer (BRCA)	*BRCA1, BRCA2*	*BRCA1 BRCA2*	MUT/SNP, IN/DEL, CNV	Weekly	Annually
19	21-Hydroxylase deficiency (congenital adrenal hyperplasia)	*P450-C21*	*CYP21A2*	MUT/SNP IN/DEL CNV	Weekly	Annually
20	Duchenne and Becker muscular dystrophy	*Dystrophine*	*DMD*	CNV, MUT/SNP, IN/DEL	Weekly	Annually
21	Fragile X syndrome	*FRAXA*	*FMR1*	EXP	Weekly	Annually
22	Severe hearing impairment	*Connexin 26*	*GJB2*	MUT/SNP, IN/DEL	Weekly	Annually
23	Hereditary nonpolyposis colorectal cancer	*HNPCC*	*MSH2, MLH1*	MUT/SNP, IN/DEL, CNV	Weekly	Annually
24	Huntington's disease	*Huntington*	*HTT*	EXP	Weekly	Annually
25	Prader-Willi and Angelman syndrome	*Chr. 15q11-q13*	*ANCR*	CNV, METH	Weekly	Annually
26	Spinal muscle atrophy	*SMA*	*SMN1*	CNV	Weekly	Annually
27	Wilson's disease	*ATPase*	*ATP7B*	MUT/SNP, IN/DEL	Weekly	Annually
28	Y chromosome, microdeletions	*Azoospermia factor*	*AZF*	CNV	Weekly	Annually

Daily, every calendar day on which patient samples are tested; weekly, every calendar week in which patient samples are tested, etc.

[a]Due to genetic heterogeneity, "molecular genetic categories" are – by definition of the placeholder concept – listed as classifiers of genetic alterations:

Point mutation and/or single nucleotide polymorphism (MUT/SNP), insertion/deletion (IN/DEL), changes in the copy number of a genomic segment or a genomic sub-segment (CNV), repeat expansion (EXP), methylation defect (METH).

medical laboratory comprising several sites, each site has to participate for the examination it provides.

(2) The participant in the external quality assessment programme examines the EQA samples under routine conditions and conveys results and information as required by the reference institution. By communicating the results, the participant confirms that the tests were performed in accordance with this guideline, in the participant's laboratory, and under their supervision.

(3) 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 objectives of the respective reference institute, the participant is obligated to determine the causes and rectify them, if this lies within the participant's responsibility. The entire procedure has to be documented.

(4) Certificates of both participation and successful participation in the external quality assessment programme have to be kept for 5 years, unless a longer archiving period is stipulated by other regulations.

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

(3) The Advisory Board may commission external experts.

(4) The Advisory Board is made up of representatives from the following institutions:
   (a) Three representatives from the relevant medical scientific societies
   (b) The chairs of the Expert Groups listed in Chapter 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 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 for the members shall be borne by the delegating institutions.

(6) The Advisory Board shall issue for itself and the Expert Groups by procedural rules in accordance with Part D of this guideline.

D Expert Groups

(1) There shall be an Expert Group for each Part B.

(2) The composition of the Expert Group and their tasks shall be set forth in the special D Parts.

(3) 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 be borne by the delegating institutions.

D1 Expert Group "Quantitative Medical Laboratory Examinations"

(1) The Expert Group "Quantitative Medical Laboratory Examinations" shall be established at the German Medical Association and have the following tasks:
   (a) Advising the German Medical Association in all questions pertaining to Parts B1 and E1

Table B5-2a: Cytogenetic examination – internal quality assurance.

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

Table B5-2b: Cytogenetic examination – external quality assurance.

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

[a]Nominal chromosome number, e.g., 45, X (Turner syndrome); 46, XX (normal female); 47, XXY (Klinefelter syndrome).

(b) Establishing the pass modalities for the external quality assurance programmes
(c) Dealing with questions pertaining to the application of Parts B1 and E1
(d) Collecting, assessing and formulating suggestions for updating Parts B1 and E1

(2) The members of this Expert Group are recommended by the institutions listed in (3) below, and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are

permitted. The Expert Group shall elect a chairman from among its members. The members of the Expert Group may be represented by proxy with approval of the chairman.

The Expert Group may commission external experts.

(3) Members of the Expert Group include:
   (a) Three representatives from relevant medical scientific societies
   (b) A representative from the German Medical Association
   (c) A representative from the National Association of Statutory Health Insurance Physicians
   (d) A representative from the German Hospital Federation
   (e) A representative from the German Association of Medical Technologists and Analysts
   (f) A representative from a competent industrial association
   (g) Two state representatives, and
   (h) A representative from the Physikalisch-Technische Bundesanstalt (PTB)

D2 Expert Group "Qualitative Medical Laboratory Examinations"

(1) The Expert Group "Qualitative Medical Laboratory Examinations" shall be established at the German Medical Association and have the following tasks:
   (a) Advising the German Medical Association in all questions pertaining to Parts B2 and E2
   (b) Establishing the pass modalities for the external quality assurance programmes
   (c) Dealing with questions pertaining to the application of Parts B2 and E2
   (d) Collecting, assessing and formulating suggestions for updating Parts B2 and E2

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

The Expert Group may commission external experts.

(3) Members of this Expert Group include:
   (a) Five representatives from relevant medical scientific societies
   (b) A representative from the German Medical Association
   (c) A representative from the National Association of Statutory Health Insurance Physicians
   (d) A representative from the German Hospital Federation
   (e) A representative from the German Association of Medical Technologists and Analysts
   (f) A representative from a competent industrial association
   (g) Two state representatives
   (h) A representative from the Physikalisch-Technische Bundesanstalt (PTB)

D3 Expert Group "Direct Detection and Characterisation of Infectious Agents"

(1) The Expert Group "Quality assurance for Medical Laboratory Examinations for Direct Detection and Characterisation of Infectious Agents" shall be established at the German Medical Association and have the following tasks:
   (a) Advising the German Medical Association in all questions pertaining to Parts B3 and E3
   (b) Establishing the pass modalities for the external quality assurance programmes
   (c) Dealing with questions in the application of Parts B3 and E3,
   (d) Collecting, assessing and formulating suggestions for updating Parts B3 and E3.

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

The Expert Group may commission external experts.

(3) Members of the Expert Group include:
   (a) Five representatives from relevant medical scientific societies
   (b) A representative from the German Medical Association
   (c) A representative from the National Association of Statutory Health Insurance Physicians

(d) A representative from the German Hospital Federation
(e) A representative from the German Association of Technologists and Analysts
(f) A representative from a competent industrial association
(g) A state representative, and
(h) A representative from the Physikalisch-Technische Bundesanstalt (PTB), the Robert Koch-Institute (RKI), the Paul-Ehrlich-Institute (PEI) and the Federal Institute for Drugs and Medical Devices (BfArM), respectively.

D4 Expert Group "Examination of ejaculate"

(1) The Expert Group "Examination of ejaculate" shall be established at the German Medical Association and have the following tasks:
(a) Advising the German Medical Association in all questions pertaining to Parts B4 and E4
(b) Establishing the pass modalities for the external quality assurance programmes
(c) Dealing with questions pertaining to the application of Parts B4 and E4
(d) Collecting, assessing and formulating suggestions for updating Parts B4 and E4.
(2) The members of this Expert Group are recommended by the institutions listed in (3) below, and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The Expert Group shall elect a chairman from among its members. The members of the Expert Group may be represented by proxy with approval of the chairman.
The Expert Group may commission external experts.
(3) The Expert Group includes:
(a) Five representatives from relevant medical scientific societies
(b) A representative from the German Medical Association
(c) A representative from the National Association of Statutory Health Insurance Physicians
(d) A representative from the German Hospital Federation
(e) A representative from the German Association of Medical Technologists and Analysts
(f) A representative from a competent industrial association
(g) A state representative
(h) A representative from the Physikalisch-Technische Bundesanstalt (PTB)

D5 Expert Group "Molecular-genetic and Cytogenetic Medical Laboratory Examination"

(1) The Expert Group "Molecular-genetic and Cytogenetic Medical Laboratory Examination" shall be established at the German Medical Association and have the following tasks:
(a) Advising the German Medical Association in all questions pertaining to Parts B5 and E5
(b) Establishing the pass modalities for the external quality assurance programmes
(c) Dealing with questions pertaining to the application of Parts B5 and E5
(d) Collecting, assessing and formulating suggestions for updating Parts B5 and E5.
(2) The members of this Expert Group are recommended by the institutions listed in (3) below, and are appointed by the Executive Board of the German Medical Association for a period of 4 years. Extraordinary appointments during the current term shall remain in effect until the end of the term. Re-appointments are permitted. The Expert Group shall elect a chairman from among its members. The members of the Expert Group may be represented by proxy with approval of the chairman.
The Expert Group may commission external experts.
(3) Members of this Expert Group include:
(a) Three representatives from relevant medical scientific societies
(b) A representative from the German Medical Association
(c) A representative from the National Association of Statutory Health Insurance Physicians
(d) A representative from the German Hospital Federation
(e) A representative from the German Association of Medical Technologists and Analysts
(f) A representative from a competent industrial association
(g) A state representative
(h) A representative from the Physikalisch-Technische Bundesanstalt (PTB)

(i) A representative from the Robert Koch-Institute (RKI)

E General requirements for reference institutions conducting external quality assurance programmes

(1) External quality assurance programmes are conducted by reference institutions. These reference institutions are appointed by the German Medical Association for a period of 5 years. The appointment requires the following requirements to be met:
   (a) The reference institution has proven that it maintains a quality management system, exhibits reliability and expertise, is able to provide personnel with the expertise necessary for running the reference institution, and can raise the funds needed for the necessary rooms, technical equipment and on-going operations
   (b) The reference institution must have at its disposal a sufficient number of reference laboratories or laboratories for determination of nominal values that are qualified to conduct the work at hand
   (c) The reference institution or its supporting organisation must prove that it is willing and capable of compensating for any loss that may result from an activity performed in accordance with this guideline
   (d) The reference institution must be fully independent of the persons responsible for first placing medical products in the market in line with Part 5 of the German Medical Devices Act (MPG).

   The appointment can be repealed if the requirements are no longer fulfilled in their entirety.
(2) The reference institutions are each specifically responsible for:
   (a) Announcing, organising and properly executing the 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 determination of nominal values
   (e) Taking further measures if problems with the external quality assurance programme samples arise, and involving the affected manufacturer if necessary.
(3) The special requirements of the external quality assurance programme organisations and of the external quality assurance programmes are regulated in the special Part E 1 and following.

E1 Special requirements for external quality assurance programme of quantitative medical laboratory examinations

1 Obligations of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of external quality assurance programmes are offered for all of the measurands listed in Table B1a-c so that every medical laboratory can participate in at least one external quality assurance programme per quarter. They may only deviate from this if they can prove that there is an insufficient amount of suitable external quality assurance programme samples.
(2) The reference institutions announce for 1 year in advance the external quality assurance programmes that they will conduct for the measurands in accordance with (1). This announcement includes:
   (a) The deadline for registration for participation in the external quality assurance programmes
   (b) The respective date of sample shipment and the deadline for sending back the results
   (c) The measurands involved in the external quality assurance programme, if necessary, with details on the measurement procedure
   (d) Type of specimen, and the sample volumes of the liquid or reconstituted external quality assurance programme samples.
(3) The reference institutions select the external quality assurance programme samples and check their suitability. The suitability of the selected external quality assurance programme samples for those measurands, whose evaluation is carried out on the basis of reference method values, needs to be checked prior to their use in the external quality assurance programmes under routine conditions and using a routine measurement procedure

(4) The reference institutions charge suitable reference laboratories with the determination of the reference method values of samples for external quality assurance as long as this is required according to Table 1a to c of Part B1. The reference laboratories are deemed suitable if they are accredited calibration laboratories in accordance with DIN EN ISO/IEC 17025 and DIN EN ISO 15195. This only applies to measurands where an accreditation is offered by an accreditation body. Only those 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. Moreover, the leader of a reference laboratory must have special expertise and experience in the area of the reference measurement methods and be capable of examining new methods.

(5) For every external quality assurance programme, the reference institutions commission each participant to examine at least two external quality assurance programme samples with varying concentrations or activities of the measurands.

(6) The reference institutions send the external quality assurance programme samples to each external quality assurance programme participant with information on handling the samples and conveying their measurement results.

(7) Reference institutions shall only analyse measurement results that were submitted by the external quality assurance programme participant before the set deadline.

(8) A certificate showing the submission date of the external quality assurance programme has to be issued to every external quality assurance programme participant giving the information which of his results from the examinations of these measurands are within the admissible evaluation limits. In addition, a participation certificate has to be issued for all measurands where participation in an external quality assurance programme occurred. The certificate and participation certificate shall be sent to the participants no later than four weeks before the next external quality assurance programme.

External quality assurance programme participants are also to be informed of:

(a) Target values and evaluation limits of the external quality assurance programme samples
(b) The position and measures of scattering of the measurement results of all participants and the measurement procedures used
(c) Number of participants, as appropriate, listed according to measurement procedure.

The certificate is valid for 6 months.

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

(10) Further details for conducting external quality assurance programmes and analysing external quality assurance programme test results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target values

(1) After consulting with its competent committees and after formal consultation of the parties concerned, the German Medical Association establishes and announces the type of target value has to be used for the measurands. Reference methods have to be used, where possible, when determining the target values in control samples.

(2) The reference institutions establish the test plans for determining the target values of the external quality assurance programme samples, commission the reference laboratories, analyse the measurement results and merge these into a target value.

(3) The reference institutions must store the documentation used in determining the target values for a period of at least 5 years beginning from when they were used in the external quality assurance programmes.

2.1 Determining reference method values

(1) The reference laboratory commissioned by the reference institution uses a reference method to determine the reference method value for a measurand.

(2) The reference method values for external quality assurance programme 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 the nominal values

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

3 Assessing the external quality assurance programme results

(1) Assessment is performed based on column 5 in Table B1a-c.

(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target value, i.e., a deviation which influences the pass rate, the reference institutions must research the cause and, if possible, rectify this in co-operation with the affected manufacturer of the external quality assurance programme sample or with experts. They are to check whether, in such a case, extending the pass limits or changing the target value would allow for a proper assessment. They decide whether the results have to be analysed according to the acceptance limits listed in column 5 or according to the modified pass limits, or whether the external quality assurance programme has to be repeated for this measurand.
The process has to be substantiated and documented. The participants of the external quality assurance programme participants and the Expert Group at the German Medical Association in accordance with Part D1 have to be informed.

E2 Special requirements for external quality assurance programme of qualitative medical laboratory examination

1 Obligations of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of external quality assurance programmes are offered for all of the examinations listed in Table B2-2 so that every medical laboratory can participate at the intervals stipulated in Table B2-2. They may only deviate from this if they can prove that there is an insufficient amount of suitable external quality assurance programme samples.

(2) The reference institutions announce for 1 year in advance, the external quality assurance programmes that they will conduct for the examinations in accordance with (1). This announcement includes:
   (a) The deadline for registrations for participation in the external quality assurance programmes
   (b) The respective date of sample shipment and the deadline for sending back the results
   (c) The examinations involved in the external quality assurance programme, if necessary, with details on the examination procedure
   (d) Type of specimen, the sample volumes of the liquid or reconstituted external quality assurance programme samples.

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

(4) For every external quality assurance programme, the reference institutions commission each participant to examine at least two external quality assurance programme samples.

(5) The reference institutions send the external quality assurance programme samples to each external quality assurance programme participant with information on handling the samples and conveying their measurement results.

(6) Reference institutions shall only analyse examination results that were submitted by the external quality assurance programme participant before the set deadline.

(7) A certificate showing the submission date of the external quality assurance programme has to be issued to every external quality assurance programme participant giving the information which of his results from the examinations are within the admissible evaluation limits. In addition, a participation certificate has to be issued for all examinations where participation in an external quality assurance programme occurred. The certificate and participation certificate shall be sent to the participants no later than four weeks before the next external quality assurance programme date.
External quality assurance programme participants are also to be informed of:
   (a) Target results and, if applicable, evaluation limits of the external quality assurance programme samples

(b) Position and distribution of the examination results of all participants, and the examination procedures used
(c) Number of participants, as appropriate, listed according to examination procedure.

The certificate is valid for double the interval given in Table B2-2

(8) If the reference institution establishes that participants frequently are not receiving a certificate for an examination with reagents or devices from a particular manufacturer, and if the cause for this cannot be traced to the medical laboratories taking part in the external quality assurance programme or the reference institution, the appropriate federal authorities have to be notified if this can be defined as an "incident" according to Section 2 of Germany's Medical Devices Safety Plan Ordinance.
(9) Further details for conducting external quality assurance programmes and analysing external quality assurance programme results are set forth in the implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining the target results

(1) After consulting with its competent committees and after formal consultation of the parties concerned, the German Medical Association establishes and announces the type of target result to be used for the examinations. Reference methods have to be used, where possible, when determining the target values in control samples.
(2) The reference institutions establish the examination plans for determining the target values of the external quality assurance programme samples, commission the reference laboratories, analyse the results and merge these into a target result.
(3) The reference institutions must store the documentation used in determining the target results for a period of at least 5 years starting from when they were used in the external quality assurance programmes.

3 Assessing the external quality assurance programme results

(1) Assessment is performed based on the target results. The assessment criteria must be fulfilled for all samples. The external quality assurance programme organisations have to inform the participants of the assessment criteria.
(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target result, i.e., a deviation which influences the pass rate, the reference institutions must search for the cause and, if possible, to rectify this in co-operation with the affected manufacturer of the external quality assessment programme sample, the manufacturers of the respective examination systems or with experts. They have to check whether, in such a case, changing the target result would allow for a proper assessment. They decide whether the external quality assurance programme has to be repeated for this measurand.
This process has 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 Part D2.

E3 Special requirements for external quality assurance programme of medical laboratory detection and characterisation of infectious agents

1 Obligations of the reference institutions

(1) Each of the reference institutions ensure that a sufficient number of external quality assurance programmes are offered for the examinations listed in Tables B3-2 and B3-2a so that every medical laboratory can participate at the intervals stipulated in Tables B3-2 and B3-2a. They may only deviate from this if they can prove that there is an insufficient amount of suitable external quality assessment programme samples.
(2) The reference institutions announce for 1 year in advance the external quality assurance programmes that they will conduct for the examinations in accordance with (1). This announcement includes:
(a) The deadline for registrations for participation in the external quality assurance programmes
(b) The respective date of sample shipment and the deadline for sending back the results
(c) The examinations involved in the external quality assurance programme, if necessary, with details on the examination procedure

(d) Type of specimen, the sample volumes of the liquid or reconstituted external quality assurance programme samples
(e) Pass modalities.

(3) The reference institutions select the external quality assurance programme samples and check their suitability. The suitability of the selected external quality assurance programme samples needs prior to their use in the external quality assurance programme be checked under routine conditions using routine examination procedures.

(4) For every external quality assurance programme, the reference institutions commission each participant to examine at least two external quality assurance programme samples.

(5) The reference institutions send the external quality assurance programme samples to each external quality assurance programme participant with information on handling the samples and conveying their measurement results.

(6) Reference institutions shall only analyse examination results that were submitted by the external quality assurance programme participant before the set deadline.

(7) A certificate showing the submission date of the external quality assurance programme submission date has to be issued to every external quality assurance programme participant giving the information which of his results from the examinations of these measurands are within the admissible evaluation limits. In addition, a participation certificate has to be issued for all examinations where participation in an external quality assurance programme occurred. The certificate and participation certificate shall be sent to the participants no later than 4 weeks before the next external quality assurance programme date.

External quality assurance programme participants are also to be informed of:

(a) Target results and, where necessary, evaluation limits of the external quality assurance programme samples
(b) Position and distribution of the examination results of all participants and the examination procedures used
(c) Number of participants, as appropriate, listed according to examination procedure.

The certificate is valid for double the interval listed in Tables B3-2 and B3-2a.

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

(9) Further details for conducting external quality assurance programmes and analysing external quality assurance programme results are set forth in implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target results

(1) After consultation with its competent committees, and after formal consultation of the parties concerned, the German Medical Association establishes and announces the type of target result to be used for the examinations and how the target results have to be determined. Reference methods have to be used whenever possible to determine target results in control samples.

(2) The reference institutions establish the test plans for determining the target results of the external quality assurance programme samples, commission the reference and normal value laboratories, analyse the results and merge these into a target result.

(3) The reference institutions must store the documentation used in determining the target results for a period of at least 5 years starting from when they were used in the external quality assurance programmes.

3 Assessing the external quality assurance programme results

(1) Analysis is performed using the target results. The assessment criteria must be fulfilled for all samples. The external quality assurance programme organisations are to inform the participants of assessment criteria.

(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target results, 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 affected manufacturer of the external quality assurance programme sample,

the manufacturers of the respective test systems, or with other experts. They have to check whether, in such a case, changing the target result would allow for a proper assessment. They decide whether the external quality assurance programme is to be repeated for this examination.

This 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 Part D3.

E4 Special requirements for external quality assurance programme of ejaculate examinations

1 Obligations of the reference institutions

(1) Each of the reference institutions ensures that a sufficient number of external quality assurance programmes are offered for all listed examinations, so that every medical laboratory can participate in at least one external quality assurance programme per half year. They may only deviate from this if they can prove that there is an unsufficient amount of suitable external quality assurance programme samples.

(2) The external quality assurance programme is comprised of an examination for sperm concentration, sperm motility and sperm morphology.

(3) The reference institutions announce for 1 year in advance, the external quality assurance programmes that they will conduct for the examinations in accordance with (2). This announcement includes:
   (a) The deadline for registration for participation in the external quality assurance programmes
   (b) The respective date of control material shipment and the deadline for sending back the results
   (c) The examinations included in the external quality assurance programme, if necessary, with details on the measuring procedure
   (d) The type of external quality assurance programme material, the sample volumes of the liquid or reconstituted external quality assurance programme materials.

(4) The reference institutions select the external quality assurance programme materials and check their suitability. The suitability of the selected external quality assurance programme samples needs to be checked prior to their use in the external quality assurance programme under routine conditions and using routine examination procedures.

(5) For every external quality assurance programme, the reference institutions commission each participant to examine at least two sets of external quality assurance programme materials.

(6) The reference institutions send the external quality assurance programme materials to each external quality assurance programme participant with instructions on handling the material and conveying their measurement results.

(7) Reference institutions shall only analyse measurement results that have been submitted by the external quality assurance programme participant before the set deadline.

(8) A certificate showing external quality assurance programme submission date has to be issued to every external quality assurance programme giving the information which of his results are within the admissible evaluation limits. In addition, a participation certificate has to be issued for all examinations where participation in an external quality assurance programme occurred. The certificate and participation certificate shall be sent to the participants no later than four weeks before the next external quality assurance programme date.

   External quality assurance programme participants are also to be informed of:
   (a) The target results and evaluation limits of the external quality assurance programme materials
   (b) Position and distribution of the measurement results of all participants and the examination procedures used
   (c) Number of participants, as appropriate, listed according to the measurement procedure.

   The certificate is valid for 12 months.

(9) If the reference institution establishes that participants frequently are not receiving a certificate for specific measurement procedure and if the cause for this cannot be traced to the medical laboratory taking part in the external quality assurance programme or the reference institution, the appropriate federal authorities have to be notified if this can be defined as an “incident” according to Section 2 of Germany’s Medical Devices Safety Plan Ordinance.

(10) Further details for conducting external quality assurance programmes and analysing external quality assurance programme results are set forth in the implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining target results

(1) After consultation with its competent committees, and after formal consultation of the parties concerned, the German Medical Association establishes and announces the type of target values to be used for the examinations and how the target results have to be determined. Reference methods have to be used whenever possible to determine target results in control samples. Target results are calculated from the respective external quality assurance programmes as an arithmetic average or mean.

(2) The reference institutions establish the test plans for determining the target results of the external quality assurance programme samples, commission the reference laboratories, analyse the results and merge these into a target result.

(3) The reference institutions must store the documentation used in determining the target results for a period of at least 5 years starting from when they were used in the external quality assurance programmes.

3 Assessing the external quality assurance programme results

(1) Assessment is performed based on target results. The assessment criteria must be fulfilled for all samples. The external quality assurance programme organisations have to inform the participants of the assessment criteria.

(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target result, 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 experts. They have to check whether, in such a case, extending the pass limits or changing the target result would allow for a proper assessment. They decide whether the results have to be analysed using the previously determined nominal values or using modified evaluation limits, or whether the external quality assurance programme has to be repeated for this measurand. This process has to be substantiated and documented. The participants of the external quality assurance programme and the Expert Group at the German Medical Association have to be informed in accordance with Part D4.

E5 Special requirements for external quality assurance programme of molecular-genetic and cytogenetic medical laboratory examination

1 Obligations of the reference institutions

(1) Each of the reference institutions is to ensure that a sufficient number of external quality assurance programmes are offered for all the examinations or quantities listed in Table B 5-1 Column 7 or Table B5-2b and for methodical external quality assurance programmes, so that every medical laboratory can participate at the intervals stipulated in Table B5-1 Column 7 or Table B5-2b. They may only deviate from this if they can prove that there is an unsufficient amount of suitable external quality assurance programme samples.

(2) The reference institutions announce for 1 year in advance the external quality assurance programmes that they will conduct for the examination in accordance with (1). This announcement includes:
   (a) The deadline for registrations for participation in the external quality assurance programmes
   (b) The respective date of sample shipment and the deadline for sending back the results
   (c) The examinations included in the external quality assurance programme, if necessary, with details on the examination procedure
   (d) Type of specimen, the sample volumes of the liquid or reconstituted examination samples.

(3) The reference institutions select the external quality assurance programme samples and check their suitability. The suitability of the selected external quality assurance programme samples for those examinations, whose evaluation is carried out on the basis of reference method values, needs to be checked prior to their use in the external quality assurance programmes under routine conditions using routine measurement procedures.

(4) For every external quality assurance programme, the reference institutions commission each participant to examine at least two external quality assurance programme samples.

(5) The reference institutions send the external quality assurance programme samples to each external quality assurance programme participant with information on handling the samples and conveying their measurement results.

(6) Reference institutions shall only analyse examination results that were submitted by the external quality assurance programme participant before the set deadline.

(7) A certificate showing the submission date of the external quality assurance programme has to be issued to every external quality assurance programme participant giving the information which of his results are within the admissible evaluation limits. In addition, a participation certificate has to be issued for all examinations where participation in an external quality assurance programme occurred. The certificate and participation certificate shall be sent to the participants no later than four weeks before the next external quality assurance programme date.

External quality assurance programme participants have also to be informed of:

(a) The target results and, if applicable, evaluation limits of the external quality assurance programme samples
(b) Position and distribution of the examination results of all participants and the examination procedures used
(c) Number of participants, as appropriate, listed according to examination procedure.

The certificate is valid for double the interval listed in Table B5-1 Column 7 and Table B5-2b.

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

(9) Further details for conducting external quality assurance programmes and analysing external quality assurance programme results are set forth in the implementation regulations. These are published by the German Medical Association and by the reference institutions.

2 Determining the target results

(1) After consultation with its competent committees, and after formal consultation of the parties concerned, the German Medical Association establishes and announces the type of target values to be used for the examinations and how the target results have to be determined. Reference methods have to be used whenever possible to determine target results in control samples.

(2) The reference institutions establish the examination plans for determining the target results of the external quality assurance programme samples, commission the reference laboratories, analyse the results and merge these into a target result.

(3) The reference institutions must store the documentation used in determining the target results for a period of at least 5 years starting from when they were used in the external quality assurance programmes.

3 Assessing the external quality assurance programme results

(1) Assessment is based on the target results. The assessment criteria have to be fulfilled for all samples. The external quality assurance programme organisations have to inform the participants of the assessment criteria.

(2) If the entire population or method-dependent subpopulations of the participants' results show a considerable deviation to the target result, 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 affected manufacturer of the external quality assurance programme sample or with experts. They have to check whether, in such a case, changing the target result would allow for a proper assessment. They decide whether the external quality assurance programme has to be repeated for this measurand.

This process has 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 Part D5.

F Temporary regulations

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

G Entry into force

The amendments to this guideline, established on 11 April 2014, shall come into force with the publishing of the *Deutsches Ärzteblatt*.

Amendments to Table B1a-c shall come into force on 1 January 2015.

The "Guideline for Quality assurance in Microbiology" dated 10 January 1992 (*Deutsches Ärzteblatt* 1992; 89: Issue 7) shall become ineffective on 1 June 2015.

Effective as of June 2014.