Translated from Deutsches Ärzteblatt, Vol. 98, No. 42, 19 October 2001, pp. A 2747 to A 2759

PUBLISHER'S NOTICES

GERMAN MEDICAL ASSOCIATION

Announcements

German Medical Association Directive on Quality Assurance of Quantitative Laboratory Tests for Medical Purposes

– Resolution of the German Medical Association Board of August 24, 2001 –

Preamble

(1) This directive relates to quality assurance of quantitative laboratory tests for medical purposes in the healing arts.

Its contents comprise a necessary element of comprehensive quality management in medical laboratories.

(2) This directive has been written in consultation with the German Institute for Physics and Engineering and in cooperation with the competent societies for specialized branches of medicine with the calibration authorities, and with the competent industrial association.

(3) This "Directive of the German Medical Association on Quality Assurance of Laboratory Tests for Medical Purposes" supersedes the "Directives of the German Medical Association on Quality Assurance in Medical Laboratories" adopted by resolutions of the German Medical Association Board on January 16, 1987, and October 16, 1987, as well as the "Supplement Adopted by Resolutions of the German Medical Association Board" on December 7, 1996, and December 17, 1993, and the "Transition Regulations" issued for the foregoing directives on December 15, 1989, January 10, 1992, and December 17, 1993.

0 General

(1) Minimum quality-assurance requirements are defined in this directive, especially regarding measurement accuracy in quantitative laboratory analyses for medical purposes.

Internal and external quality-assurance results are assessed by means of error limits (permissible maximum measurement deviations). Additional procedures are recommended for control and assessment of accuracy, such as the use of additional control samples in different concentration ranges.

(2) The internal and external quality-assurance measures set forth in this directive are applicable for all measurable quantities listed in Attachment 1.

(3) The main criteria for recording a measurable quantity in Attachment 1 are the frequency of the test and its medical importance according to the state of the art in science.

(4) The definition of error limits in Attachment 1 is determined by medical necessity, taking into consideration the state of the art in analysis.

(5) The measurable quantities and the error limits will be adapted as necessary to the acknowledged state of the art in medical science and analysis, and Attachment 1 will be updated accordingly.

(6) It is recommended that quality-assurance measures confirming to this directive also be applied to measurable quantities not listed in Attachment 1, unless such measures would conflict with other directives of the German Medical Association or other regulations.

(7) This directive is to be used by all persons who perform quantitative laboratory tests for medical purposes.

1 Terminology

The most important terms used in this directive are defined in this section. Each definition takes into consideration national and international standards as well as the terminology of metrology. Nevertheless, these definitions are intended for consistency within this directive, and so deviations from the standard terminologies may occur.

1.1 Analysis series

A sequence of determinations of the same measurable quantity performed with the same measuring instrument and the same calibration under identical conditions. The shortest series

consists of a single sample. In automated analysis instruments, in which human intervention does not take place during the measurement process, an analysis series consists of the determination of measurable quantities within a period not to exceed one work shift.

1.2 Analysis procedure

The totality of all described activities undertaken in performing a measurement in conformance with a predetermined measurement method.

1.3 Expectation value of measured values

The mean value of a probability distribution of the measured values that are derived from one given method of conducting an analysis or measurement procedure. The expectation value of several measured results can be estimated by their arithmetic mean, and the value becomes more accurate with an increasing number of such results. The difference between the expectation value and the accepted reference value is known as the systematic measurement deviation (from the accepted reference value).

1.4 Control cycle

This is usually defined as a period of one month. If fewer than 15 values have been collected per control cycle, the period is extended by one month at a time until 15 values have been obtained. The total period is not permitted to exceed three months.

1.5 Measurement deviation of a single control-sample measurement

The deviation of the measured result of a control sample from the accepted reference value. It is calculated by adding the deviation of the measured result from the expectation value (random measurement deviation) and the deviation of the expectation value from the accepted reference value (systematic measurement deviation).

1.6 Measurement accuracy

The closeness of agreement between the measured result and a true value of the measurable quantity.

The accuracy of a measurement is related both to the trueness of a measurement and to measurement precision.

Accuracy with respect to a measurable quantity cannot be expressed as a numerical value, but must be in the form of descriptions such as “adequate” or “inadequate.”

An estimate of the reciprocal of the accuracy of a measurement is the “deviation,” which is defined as “measured value minus true value.”

1.7 Measurable quantity

This designates the property being determined in a given analysis. The description of a measurable quantity includes the following elements:

System: Material being examined, in which the analyte indicated by the measurable quantity is found (such as serum/plasma, liquor, urine, whole blood).

Analyte: the component to be determined by analysis.

Type of quantity: the quantity (such as mass concentration or molar concentration) suitable for describing the property to be determined.

The value of the measurable quantity is represented by the product of numerical value × the unit.

Unit: unit of the International System of Units (SI), or units defined elsewhere (such as “International Units”) for certain measurable quantities for which SI units are not usable.

1.8 Measurement method

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

1.9 Reference measurement procedures

Carefully studied analysis procedures with results that have a measurement uncertainty that corresponds to their planned use, such as assessment of the trueness of other analysis procedures for the same measurable quantity and characterization of reference materials.

1.10 Measurement uncertainty

A parameter, associated with the measured result, that characterizes the dispersion of the values that can be associated with the measurable quantity.

1.11 Precision

Closeness of agreement between independent measured results obtained under stipulated conditions.

The degree of precision is usually expressed by the statistical measure of the imprecision of measurements such as “standard deviation” and “relative standard deviation” (coefficient of variation), which are inversely related to precision.

The “precision” of a given analysis procedure is subdivided according to the cited precision conditions. “Repeatability” relates essentially to constant conditions, and is often referred to as “within-run precision.” The “between-run precision” reflects the variations of one or more of the factors that normally occur within a laboratory. Such factors can be time, calibration, investigator, or measuring instrument.

1.12 Trueness

Closeness of agreement between the average obtained from a large series of measured results and a true value.

It is usually expressed numerically by the systematic measurement deviation, which is inversely related to the trueness.

1.13 Traceability

A property of a measured result to be related to an exactly defined reference point (generally an international or national standard) through an unbroken chain of comparison measurements with specified measurement uncertainties.

1.14 Systematic measurement deviation (bias)

When several measured results exist, the difference between the expectation value and the accepted reference value is an estimate of the systematic measurement deviation (from the accepted reference value), and it is used to evaluate the trueness of the measurement.

1.15 True value

Value that agrees with the definition of a special quantity under consideration.

Remark: This value would be obtained by an ideal measurement.

1.16 Accepted reference value

Accepted reference value is used as a collective term for subsequent values attributed to control samples for quality assurance of laboratory tests for medical purposes:

(a) Reference-method value

Value determined with a reference measurement procedure.

A reference-method value as defined in this directive is traceable to SI units or conforms with other international agreements or accepted rules for quality-assurance statistics. It expresses the measurement uncertainty for specified confidence limits.

(b) Procedure-dependent theoretical value

Value that is determined with an analysis procedure deviating from a reference measurement procedure and that can exhibit a measurement deviation from the reference-method value or other procedure-dependent theoretical value as an artifact of the analysis procedure.

1.17 Random measurement deviation (imprecision)

The random measurement deviation is estimated by the deviation of the measured result from the mean value. If several measured results exist, their standard deviation (or their relative standard deviation) is used to evaluate the precision of the measurement. The number of measurements, the arithmetic mean, and the experimental characteristic-run (within between-run series, between work shifts, between laboratories) must be reported.

2 Principles of quality assurance of quantitative analyses

The basic program of internal and external quality assurance illustrated in this directive has the following features:

2.1 Internal quality assurance

(1) Inclusion of all measurable quantities listed in Attachment 1 of this directive in internal quality assurance. If several measuring stations are used for determination of a measurable quantity, internal quality assurance shall be undertaken for each measuring station.

(2) Check of measurement accuracy of the analysis procedure by keeping written records of the measurement deviation of each single measured result of the control sample from the accepted reference value and assessing such deviation before release of results of the associated analysis series.

(3) Assessment of random measurement deviations (imprecision) at the end of a control cycle.

(4) Assessment of the systematic measurement deviations (bias) at the end of a control cycle.

(5) Only control samples with predetermined accepted reference values shall be used.

2.2 External quality assurance

(1) Inclusion of all measurable quantities listed in Attachment 1 of this directive in external quality assurance.

(2) External quality assurance by means of comparison measurements (round-robin tests) supports the objective monitoring of the quality of results of quantitative laboratory tests for medical purposes and shall supplement internal quality assurance.

2.3 Control-sample system

(1) The tasks listed in 2.1 and 2.2 can be satisfied by the quality-assurance system described in 3. For this purpose, written records must be kept of the measured results of control

samples included in analysis series with samples to be tested and determined together with them, and such results must be assessed.

(2) In external quality assurance, the reference institutions shall be permitted to use only the types of accepted reference values defined by the German Medical Association and published in the *Deutsches Ärzteblatt* [*German Medical Gazette*].

(3) The control samples shall be as similar in composition as possible to the samples to be tested, particularly in their matrix.

(4) Preparing different concentrations by diluting these samples is not permitted.

(5) Control samples and calibration materials shall not be permitted to be identical in the same analysis procedure.

3 Performance of quality assurance

3.1 Internal quality assurance

3.1.1 Principles

(1) Internal statistical quality assurance in the laboratory shall be achieved with a control-sample system. The following aspects shall be evaluated:

– the measurement deviation of the single control-sample measurements from the accepted reference value,

– the random measurement deviation of the results for control samples after the end of a control cycle as a measure of precision,

– the systematic measurement deviation of the results for control samples after the end of a control cycle as a measure of trueness.

(2) Insofar as they are available, control samples with accepted reference values in the measurement range relevant for medical decisions shall be used for single control-sample measurements.

(3) The random measurement deviation and the systematic measurement deviation shall be calculated by selecting, per analysis series, one control-sample measured value, which in each

case can be the first, the x-th or the last, but must be based on the same selection method. Selection according to statistical random principles shall also be permissible.

(4) Internal quality assurance shall be performed openly, or, in other words, with known accepted reference values. Control samples shall be included in each analysis series. Before release of the measured results of the patient samples, the measured results of control samples shall be evaluated according to the requirements in 3.1.2 and 3.3. After the end of a control cycle, the standard deviations and the systematic measurement deviations of the control-sample measurements shall be assessed by means of the error limits listed in Attachment 1 (see 3.1.3 and 3.1.4).

3.1.2 Performance and assessment of the single control-sample measurement

(1) At least one control sample shall be measured in each analysis series. From one analysis series to another, the control samples shall be used in different concentration ranges, provided at least 15 analysis series are performed within 3 months for each control sample. Otherwise, subject to the special regulation put forth in 3.3.1 of this directive, the switch between different concentration ranges shall be made only from one control cycle to another.

(2) The single control-sample measurement shall first be assessed on the basis of the laboratory's internal error limits; however, the maximum permissible deviations listed in Attachment 1, column 7, may not be exceeded.

(3) The internal laboratory error limits for the single control-sample measurement shall be determined by selecting, for each control sample used, 20 control-sample measured values from 20 consecutive work shifts, based rigorously on the same selection method of the first, x-th or last in each case. Selection according to statistical random principles shall also be permissible. The arithmetic mean value as well as the coefficient of variation and 3 times the standard deviation shall then be calculated from the results. The absolute deviation of the mean value from the accepted reference value must be smaller than or equal to the maximum permissible bias indicated in Attachment 1, column 6, while the coefficient of variation and the standard deviation must be smaller than or equal to the maximum permissible imprecision given in Attachment 1, column 5.

(4) The following data shall be entered in a control chart:

– the arithmetic mean value determined by the laboratory,

– the mean value plus and mean value minus 3 times the standard deviation as the internal error limits of the laboratory (internal 3s spread of the laboratory),

– the additional control-sample measured values performed as described in paragraph (1).

All single control-sample results shall be documented in addition to the control chart.

The documentation must contain:

– Laboratory identification

– Measuring station identification

– Date and time of the measurement

– Measurable quantity (system, analyte, type of quantity), unit

– Analysis procedure

– Control-sample measured value

– Accepted reference value of the control sample

– The relative or absolute deviation from the accepted reference value, and the assessment according to Attachment 1, column 7

– Manufacturer's identification and batch number of the control material

– Name and signature of the investigator.

(5) Only the values listed in Attachment 1, column 7 shall be valid for the determination period of the laboratory's internal error limits.

(6) If a single control-sample measured value of an analysis series exceeds the internal 3s spread of the laboratory, or if its absolute deviation from the accepted reference value in the control sample is larger than the maximum permissible deviation indicated in Attachment 1, column 7, the reason must first be sought. Keeping in mind medical relevance, the responsible person shall be required to decide whether measures must be taken, whether the entire test series, including the control measurement, is to be repeated, or whether the results can nevertheless be released in their entirety or in part. The entire process shall be documented.

3.1.3 Determination and assessment of the random measurement deviation (evaluation of precision)

(1) From the results of the measurements of the control sample accompanying each analysis series in accordance with 3.1.2 (1), the random measurement deviation shall be determined immediately after the end of a control cycle (see 3.3 for exceptions). The standard deviation or the relative standard deviation (coefficient of variation) shall be calculated as a measure of the random measurement deviation.

(2) If the standard deviation or the relative standard deviation (coefficient of variation) for a control sample exceeds the absolute or percentage value obtained from Attachment 1, column 5, the reason must be clarified and eliminated. Written records shall be kept of the entire process.

(3) If the assessment limits according to paragraph (2) are exceeded once again in the next control cycle for this same control sample, further analysis of patient samples with this analysis procedure shall not be permitted until the precision requirements according to Attachment 1 are met. Written records shall be kept of the measures taken.

3.1.4 Determination and assessment of the systematic measurement deviation (evaluation of trueness)

(1) For each of the control samples used and corresponding to different concentration ranges, the systematic measurement deviation shall be determined, from the results of all measurements, at the end of a control cycle (see 3.3 for exceptions). The difference between the arithmetic mean value and accepted reference value shall be calculated as the measure for the systematic measurement deviation.

(2) The absolute systematic measurement deviation shall not be permitted to be larger than the maximum permissible systematic measurement deviation according to Attachment 1, column 6. If this requirement is not satisfied, the reason must be clarified and eliminated. Written records shall be kept of the entire process.

(3) If the maximum permissible systematic measurement deviation is exceeded once again in the next control cycle for this same control sample, further analysis of patient samples

with this analysis procedure shall not be permitted until the requirements of precision according to Attachment 1 are met. Written records shall be kept of the measures taken.

3.1.5 Documentation

All quality-assurance results, including the data from 3.1.2 paragraph (4), shall be documented, broken down according to measurable quantities, measurement methods, and measuring stations. Electronic data media shall also be permissible. Printouts of the quality-assurance records shall be submitted upon request of the authority/organization in charge of auditing compliance with this directive. All measured results of quality assurance shall be retained for 5 years, together with the corresponding calculations after the control cycles (arithmetic mean, standard deviation, difference between mean value and accepted reference value) and both the assessments as well as the written records of the measures taken when error limits were exceeded, unless longer retention periods are stipulated by other requirements.

3.2 External quality assurance (round-robin tests)

(1) The round-robin tests for external quality assurance stipulated with this directive shall be performed by the reference institutions according to 4.1.

(2) The results shall be assessed on the basis of accepted reference values according to 2.3, paragraph (2), and the error limits shall be assessed according to Attachment 1, column 7, in conformance with 3.2.2, paragraph (10).

3.2.1 Obligations of the round-robin test participants

(1) A round-robin test participant shall enroll in a reference institution (round-robin test organizer) appointed by the German Medical Association for a period of one year in each case. Participation in one round-robin test per quarter for each measurable quantity listed in Attachment 1 shall be obligatory.

(2) The round-robin test participant shall perform the analyses of the round-robin test samples under routine conditions and shall enter the measured results and the measurement methods used in each case on the form provided for this purpose. The participant shall confirm

with his or her signature that the analyses were performed in accordance with this directive in his or her laboratory and under his or her supervision.

(3) If a participant does not receive a certificate for a measurable quantity because one of his or her measured results has exceeded the maximum permissible deviation (see 3.2.2, paragraph (9)), he or she shall be obligated to clarify and eliminate the reasons.

(4) The person responsible for laboratory tests for medical purposes shall be obligated to submit the certificates of participation and round-robin test certificates to the responsible medical association if, because of contractual medical regulations, he or she has not delivered them to the responsible health-insurance unit.

3.2.2 Duties of the reference institution and of the round-robin test director

(1) The reference institution as described in Section 4.1 shall offer a sufficient number of round-robin tests for all measurable quantities cited in Attachment 1 of this directive so that participation in at least one round-robin test per quarter is possible. Exemptions from this requirement are permitted only if a sufficient number of suitable round-robin test samples is demonstrably not available.

(2) The reference institution shall announce each round-robin test plans for the measurable quantities in Attachment 1 one year in advance. In these announcements, the reference institution shall disclose:

1. The enrollment deadlines for participation in the round-robin tests,

2. The respective dates of sample shipment and of receipt of samples by the participants, and last date for mailing the results chart,

3. The measurable quantities included in the round-robin test, with indication of the measurement method, if necessary,

4. Sample material, and sample volume of the liquid or reconstituted round-robin test samples.

(3) The reference institution shall select the round-robin test samples and shall check their suitability. The suitability of the selected round-robin test samples for those measurable quantities to be assessed on the basis of reference-method values must be checked under routine conditions with routine analysis procedures before inclusion in round-robin tests.

(4) Reference-method values for round-robin test samples must be on hand before the round-robin test is begun. Exceptions shall be permitted for special reasons, such as very limited stability of the control samples. Procedure-dependent theoretical values may be determined before the beginning of the round-robin tests or derived from the results of the round-robin tests by statistical methods, in accordance with acknowledged rules of the quality-assurance statistics. The notice described in paragraph (8) shall indicate which theoretical values were determined from round-robin test results.

(5) For each round-robin test, the round-robin test director shall ensure that each participant tests at least two round-robin test samples with different concentrations or activities of the analyte.

(6) The reference institution shall send each round-robin test participant the round-robin test samples with procedure instructions and a form for entering the analysis results.

(7) All measured results mailed by the round-robin test participant within the set period shall be evaluated in the reference institution.

(8) A certificate of participation shall be delivered to each round-robin test participant, in the form of a notice that contains at least:

1. Accepted reference values and assessment limits of the round-robin test samples,
2. Mean values and dispersion parameters of the measured results of all participants,
3. Number of participants.

(9) For each measurable quantity for which the analysis results of all round-robin test results submitted were within the associated assessment limits, a certificate confirming that no fault was found shall be issued to each round-robin test participant. The certificate shall be valid throughout the entire territory of the Federal Republic of Germany. The certificate shall have a validity period of 6 months from the date of issue.

(10) Assessment limits according to paragraph (9) shall be the accepted reference value plus or minus the error limits indicated in Attachment 1, column 7. If the results of the participants exhibit a substantial shift of the median from the accepted reference value, especially compared with previous round-robin tests, the round-robin test director shall be required to clarify the reason. He or she should examine whether, taking into consideration the results of previous round-robin tests, expansion of the assessment limits of the accepted reference values

up to one third of the error limits of Attachment 1, column 7 will permit objective assessment of the results. Thereupon, he or she shall decide whether the results will be assessed on the basis of the regular or expanded assessment limits or whether the round-robin test must be repeated. The reason and justification shall be documented. The participants shall be informed of the decision. The accepted reference values determined by the reference institution shall be indicated.

(11) The reference institution shall be required to ensure data protection.

3.3 Exempting regulations for internal and external quality assurance

3.3.1 Quality assurance for low analysis frequencies

(1) For measurable quantities with fewer than 15 analysis series in three months, single control-sample measurements shall be performed only in internal quality assurance. In other words, quality assurance according to 3.1.3 and 3.1.4 shall not be performed. Notwithstanding 3.1.2, paragraph (1), at least two control samples with different concentration ranges shall be analyzed in each series. The deviation of the results of the single control-sample measurements from the accepted reference value shall be assessed in accordance with 3.1.2, paragraph (2). Determination of internal laboratory errors per 3.1.2, paragraph (3), shall be waived.

(2) Subject to paragraph (3), the measured results of the patient samples may be released only when the deviation of the single control-sample measurement, calculated according to 3.1.2, paragraph (2), from the respective accepted reference value does not exceed the error limits indicated in Attachment 1, column 7 in either of the two control samples.

(3) If a measured result of one of the two control materials exceeds the error limits, the reason must be clarified. Thereafter, the responsible person shall be required to decide whether the entire test series, including the control measurement, must be repeated, or the results can be released in their entirety or in part. Written records shall be kept of the entire process.

(4) The obligation to participate in round-robin tests per 3.2 of this directive shall remain in force.

(5) Paragraphs (1) to (4) shall not apply to immediate diagnoses with the patient present.

3.3.2 Quality assurance of laboratory tests for medical purposes for immediate diagnoses with the patient present in practices of private physicians and in medical services lacking a central laboratory

(1) Measuring instruments used in immediate diagnoses near the patient shall be operated in accordance with the manufacturer's instructions and, if so provided, shall be checked at least one time in daily use against a physical and/or electronic standard.

(2) At least one time per week in which patient samples are tested, a control sample must be measured and evaluated in accordance with Attachment 1, column 7. Control samples in different concentration ranges shall be used alternately if medically practical.

(3) Written records must be kept of the results of the single control-sample measurements.

The written record shall contain: type of measuring instrument, serial number, date and time of the measurements, identification of the control sample (such as manufacturer's identification, batch number), measurable quantity (system, analyte, type of quantity), unit, control-sample measured value, accepted reference value of the control sample, relative or absolute deviation from the accepted reference value, assessment per Attachment 1, column 7, and name and signature of the investigator. Otherwise, the requirements per 3.1.5 shall be applicable regarding documentation.

(4) If, for a single control-sample measured value, the absolute deviation of the control sample from the accepted reference value is larger than the maximum permissible deviation indicated in Attachment 1, column 7, the cause must be eliminated. The entire process, including the necessary repeat measurements, must be documented.

(5) If the prerequisites of (1) to (4) are met, the obligation to participate in round-robin tests according to 3.2 of these directives shall be waived.

(6) The regulations of 3.3.2 shall be applicable only for measuring instruments intended exclusively for single-sample measurements or used only for single-sample measurements.

3.3.3 Quality assurance of laboratory tests for medical purposes for immediate diagnoses with the patient present in hospitals and in other facilities having a central laboratory

(1) Measuring instruments used in immediate diagnoses near the patient shall be operated in accordance with the manufacturer's instructions and, if so provided, shall be checked at least one time in daily use against a physical and/or electronic standard.

(2) At least one time per week in which patient samples are tested, a control sample must be measured and evaluated in accordance with Attachment 1, column 7. Control samples in different concentration ranges shall be used alternately if medically practical.

(3) Written records must be kept of the results of the single control-sample measurements. The written record shall contain: type of measuring instrument, serial number, date and time of the measurements, identification of the control sample (such as manufacturer's identification, batch number), measurable quantity (system, analyte, type of quantity), unit, control-sample measured value, accepted reference value of the control sample, relative or absolute deviation from the accepted reference value, assessment per Attachment 1, column 7, and name and signature of the investigator. Otherwise, the requirements per 3.1.5 shall be applicable regarding documentation.

(4) If, for a single control-sample measured value, the absolute deviation of the control sample from the accepted reference value is larger than the maximum permissible deviation indicated in Attachment 1, column 7, the cause must be eliminated. The entire process, including the necessary repeat measurements, must be documented.

(5) Every organization unit (such as an intensive-care station) performing immediate diagnoses with the patient present must participate in round-robin tests according to 3.2 of these directives for external quality control

This obligation shall be waived if the internal quality assurance for immediate diagnoses with the patient present is performed under the supervision of the central laboratory.

(6) The regulations of 3.3.3 shall be applicable only for measuring instruments intended exclusively for single-sample measurements or used only for single-sample measurements.

3.3.4 Counting of corpuscular constituents using a counting chamber

This directive has no application to counting of corpuscular constituents in body fluids using a counting chamber.

4. Organizational regulations for external quality assurance (round-robin tests)

4.1 Reference institutions

(1) The reference institutions must be appointed by the German Medical Association. For appointment, the following prerequisites must be met:

1. The reference institution or its sponsor must demonstrate that it is willing and able to provide the expert staff necessary for operation of the reference institution and to contribute the necessary means for the required premises, technical facilities, and day-to-day operation.

2. The reference institution must possess reference laboratories that meet the requirements cited in 4.2.

3. The reference institution or its sponsor must demonstrate that it or its sponsor is willing and able to compensate for damages that may arise due to the activity of the reference institution.

4. The reference institution must be independent of manufacturers or importers of reagents, calibration materials, control samples, and instruments.

The appointment shall be revoked if these prerequisites are no longer met.

(2) The reference institutions shall have authority for

– determining accepted reference values for the control samples for external quality assurance. In this connection, the reference institutions shall cooperate with reference and theoretical-value laboratories;

– announcing, organizing, and objectively conducting the round-robin tests in conformance with this directive and for punctually evaluating the results;

– naming round-robin test directors.

4.2 Reference laboratories

(1) On the basis of orders from the reference institutions named by the German Medical Association, the reference laboratories shall determine the reference-method values of control materials for external quality assurance.

(2) The director of a reference laboratory must have particularly extensive professional knowledge and experience in the field of the reference methods and be capable of examining new methods. He or she must be authenticated by scientific publications, including in the discipline of methods development.

(3) The suitability of a reference laboratory shall be demonstrated by accreditation as a calibration laboratory according to ISO 17025 or as a reference-measuring laboratory according to ISO 15195. This shall be applicable only for measurable quantities for which accreditation is offered by an accreditation agency. Accreditation agencies are considered to be those approved under the Multilateral Agreement on the Mutual Acceptance of Calibration Certificates of the European Cooperation for Accreditation (EA).

(4) Reference laboratories shall be appointed by the German Medical Association. The appointment shall be made for a term of 4 years in each case, at the suggestion of a reference institution in cooperation with professionally competent academic societies for specialized branches of medicine. The appointment shall be revoked if the prerequisites are no longer met.

(5) Advertising of activity in connection with the determination of reference-method values shall be prohibited.

4.3 Theoretical-value laboratories

(1) The director of a theoretical-value laboratory must have particularly extensive professional knowledge and experience. The theoretical-value laboratories shall be functionally independent and active in service to hospitals.

(2) Theoretical-value laboratories must possess all facilities and procedures by which the reliability of the analysis results they obtained in connection with determination of theoretical values can be ensured. For this purpose, the following attributes shall be necessary:

1. An extensive statistical quality-assurance system.
2. The ability to compare methods.

3. Proof that comparison measurements with other theoretical-value laboratories are conducted regularly under the supervision of a reference institution.

(3) Theoretical-value laboratories shall be appointed by the German Medical Association. The appointment shall be made for a term of 4 years in each case, at the suggestion of a reference institution in cooperation with the professionally competent academic societies for specialized branches of medicine. The appointment shall be revoked if the prerequisites are no longer met.

(4) Advertising of activity in connection with the determination of theoretical values shall be prohibited.

4.4 Determination of accepted reference values

(1) Reference-measurement procedures shall be used whenever available for determination of accepted reference values in control samples. If suitable reference-measurement procedures are not available, it shall be permissible, during a transition phase, to determine accepted reference values of control samples with procedure-dependent theoretical-value methods. The German Medical Association shall decide which of the two types of accepted reference value is to be employed after deliberations in the committees established for the various specializations and after hearing the groups interested in the measurable quantities included in Attachment 1. A time limit may be imposed for the use of procedure-dependent theoretical-value methods.

(2) Reference-measurement procedures shall be developed and/or reviewed under supervision of the academic societies for specialized branches of medicine or approved or recommended by them. They shall be published by the German Medical Association.

(3) Establishment of the protocols for determination of the accepted reference values of round-robin test samples, commissioning of reference and theoretical-value laboratories, and evaluation of the measured results and condensing them to a accepted reference value, shall be entrusted to the reference institutions.

(4) Upon request, the reference institution shall send the following information to the manufacturer or importer of the control samples and to the laboratories participating in establishment of accepted reference values:

1. Measurable quantity

2. Reference-method value or theoretical value

3. Measurement uncertainty for a 95% confidence limit or an appropriate range in the case of theoretical values

4. Participating reference laboratories and theoretical-value laboratories.

(5) The responsibility for the trueness of the reference-method values at the time of their determination shall lie with the reference institution.

(6) The reference institutions must retain the documentation on determination of the accepted reference values for a period of at least five years.

(7) Procedure-dependent theoretical values for the measurable quantities listed in Attachment 1 in round-robin test samples shall be determined by the reference institutions on the basis of measured results obtained by theoretical-value laboratories, or shall be derived from the round-robin test results with statistical procedures in accordance with acknowledged rules of quality-assurance statistics. The manufacturer or importer of the control samples shall be entitled to make suggestions as to the selection of theoretical-value laboratories.

(8) For determinations of theoretical values, the reference institutions shall be entitled to rely on a laboratory of the manufacturer or importer of the respective control sample, provided that such laboratory and its director satisfy the criteria – except for paragraph (1), sentence 2 – listed in 4.3.

(9) Determination of procedure-dependent theoretical values in the theoretical-value laboratory must take place under well defined conditions.

(10) As a rule, five theoretical-value laboratories shall be used for each combination of measurable quantity and analysis principle, although fewer—but at least three—such laboratories, including those defined in paragraph (8), may be used in justified exceptions (such as newly introduced or obsolescent procedures).

(11) To define the theoretical value, the reference institution shall undertake a review of the measured results sent to it by the theoretical-value laboratories. Elimination of “outliers” shall be permissible only with statistical procedures according to accepted rules of quality-assurance statistics.

(12) The theoretical value shall be defined in two steps:

1. Definition of a suitable range (theoretical range) in which 95% of the measured results of the theoretical-value laboratories or the round-robin test results lie for the respective analysis procedure.

2. Definition of the procedure-dependent theoretical value from measured results lying within the 95% range as

– arithmetic mean value or

– median.

4.5 Organizations in other member countries of the European Union

Accepted reference values determined by reference institutions, reference laboratories, and theoretical-value laboratories in other member countries of the European Union shall be equivalent to the accepted reference values determined by reference institutions described in 4.1, reference laboratories described in 4.2, and theoretical-value laboratories described in 4.3, provided the cited organizations

– satisfy the prerequisites for appointment defined in these sections or guarantee a comparable scientific and technical level and comparable independence,

– are approved by a professionally competent independent agency of the member country in question and,

– for determination of the accepted reference values, have employed procedures defined in this directive or procedures of equal or better reliability.

5 Implementing regulations

The German Medical Association shall decide on performance, exempting, and special regulations necessary for implementation of this directive after deliberations in the committees it has established. These regulations shall be published in the *Deutsches Ärzteblatt* [*German Medical Gazette*].

6 Advisory Board for Quality Assurance of Laboratory Tests for Medical Purposes

(1) An Advisory Board for "Quality Assurance of Laboratory Tests for Medical Purposes" shall be established in the German Medical Association, with the following duties:

- Advising the German Medical Association in all questions concerning this directive
- Clarifying questions of interpretation in application of this directive
- Collecting and assessing suggestions about updating this directive.

(2) The members of the Advisory Board shall be appointed for terms of 4 years by the Board of the German Medical Association. Appointments to fill positions vacated in the current term shall be valid until the end of such term. Reappointments shall be permissible. The Advisory Board shall elect a chairperson from among its members. The members of the Advisory Board shall be entitled to have another person represent them, subject to consent of the chairperson. The Advisory Board shall be entitled to call in experts.

(3) The Advisory Board shall be made up of:

- Three representatives from professionally competent academic societies for specialized branches of medicine
- One representative from the German Institute for Physics and Engineering
- One representative from the calibration authorities of the *Länder* [German states]
- One representative from the competent industry association
- Two further representatives named by the chairperson of the German Medical Association.

(4) Business operations for this Advisory Board shall be managed by the German Medical Association.

7 Duties of the German Medical Association

In implementing this directive and its attachments – by arrangement with the German Institute for Physics and Engineering and in cooperation with the calibration authorities and in coordination with the professionally competent specialized academic societies – the German Medical Association shall handle the following duties:

(1) Drawing up and updating the list of measurable quantities subject to quality assurance according to this directive, in conformance with the criteria mentioned in 0, paragraph (3), as well as defining and, if necessary, adapting the maximum permissible measurement deviations in conformance with the criteria mentioned in 0, paragraph (4) – Attachment 1. Attachment 1 shall be a binding part of the directive. It shall be published together with the directive in the *Deutsches Ärzteblatt* [*German Medical Gazette*]. Changes to Attachment 1 shall also be published in the *Deutsches Ärzteblatt*.

(2) Drawing up and publishing the regulations per 5.

(3) Deciding and publishing the types of accepted reference values per 4.4, paragraph (1).

(4) Publishing recommended reference measurement procedures per 4.4, paragraph (2).

In implementing this directive, the German Medical Association shall also handle the following duties:

(1) Appointing the reference institutions per 4.1.

(2) Appointing the reference laboratories per 4.2.

(3) Appointing the theoretical-value laboratories per 4.3.

(4) Appointing the members of the "Advisory Board for Quality Assurance of Laboratory Tests for Medical Purposes" and managing its business operations per 6.

(5) Managing the supervision of the reference institutions.

(6) Maintaining the list of appointments according to paragraphs (1) to (3).

(7) Maintaining the list of published announcements according to sentence 1, paragraphs (2), (3) and (4).

8 Transition regulations

(1) Until December 6, 2003, it shall be permissible, for internal quality assurance, to meet the requirements of Section 2 of the directives of the German Medical Association, which will remain valid until the effective date of the present directive (see paragraph 3 of the Preamble), instead of 2.1 and 3.1 of the present directive. In these cases, Attachment 1 of the directives of the German Medical Association, which will remain valid until the effective date of the present directive (see paragraph 3 of the Preamble), shall also be applied.

(2) The appointments of round-robin test directors, reference institutions, reference laboratories, and theoretical-value laboratories made before the effective date of the present directive shall remain valid until December 31, 2004 at the latest.

(3) Effective until December 31, 2004, the German Medical Association shall be permitted to appoint reference and theoretical-value laboratories per Sections 3.2 paragraph (5) and 3.3.1 paragraph (3) of the directives of the German Medical Association, which will remain valid until the effective date of the present directive (see paragraph 3 of the Preamble).

9 Effective date

This directive shall become effective on January 1, 2002, concurrent with the effective date of the 2nd Medical Products Amending Act.

Attachment 1a

Measurable quantities in serum/plasma

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
1	Albumin	Mass concentration	RMW	6%	11%	23%	
2	Aldosterone	Molar concentration Mass concentration	RMW	10% 30 pmol/l	25% 75 pmol/l	45% 135 pmol/l	≥ 300 pmol/l < 300 pmol/l
3	Alkaline phosphatase (AP) ES 3.1.3.1	Enzyme activity concentration	RMW/SW	7%	7%	21%	
4	Bilirubin (total)	Molar concentration Mass concentration	RMW/SW	7% 0.1 mg/dl	12% 0.2 mg/dl	26% 0.4 mg/dl	≥ 1.5 mg/d/l < 1.5 mg/dl
5	Calcium (total)	Molar concentration	RMW	3%	5%	11%	
6	Carbamazepine	Mass concentration	SW	7%	7%	21%	
7	Chloride	Molar concentration	RMW	2%	4%	8%	
8	Cholesterol (total)	Molar concentration Mass concentration	RMW	3%	7%	13%	
9	Cholinesterase (CHE) EC 3.1.1.8	Enzyme activity concentration	SW	6%	6%	18%	
10	Cortisol	Molar concentration Mass concentration	RMW	8% 16 nmol/l	18% 36 nmol/l	34% 68 nmol/l	≥ 200 nmol/l < 200 nmol/l
11	Creatine kinase (CK) EC 2.7.3.2	Enzyme activity concentration	RMW	5% 2.5 U/l	10% 5 U/l	20% 10 U/l	≥ 50 U/l < 50 U/l
12	CRP (C-reactive protein)	Mass concentration	RMW/SW	5%	14%	24%	
13	Digitoxin	Mass concentration	RMW	8% 1.2 µg/l	12% 1.8 µg/l	28% 4.2 µg/l	≥ 15 µg/l < 15 µg/l
14	Digoxin	Mass concentration	RMW	8% 0.12 µg/l	18% 0.27 µg/l	34% 0.5 µg/l	≥ 1.5 µg/l < 1.5 µg/l
15	Iron	Molar concentration Mass concentration	SW	4%	4%	12%	
16	Protein fractions (electrophoresis) – albumin – gamma globulin	 Mass ratio Mass ratio	SW	 3.3% 8%	 3.3% 8%	 10% 24%	
17	Estradiol, 17-beta	Molar concentration Mass concentration	RMW	12% 36 pmol/l	22% 66 pmol/l	46% 138 pmol/l	≥ 300 pmol/l < 300 pmol/l
18	Ethanol (clinical toxicological)	Mass concentration Mass ratio	SW	3% 0.03 g/l	3% 0.03 g/l	9% 0.09 g/l	≥ 1.0 g/l < 1.0 g/l
19	Ferritin	Mass concentration	SW	8%	8%	24%	

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.

Attachment 1a

Measurable quantities in serum/plasma *(continued)*

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
20	Alpha-fetoprotein (AFP)	Mass concentration International units	SW	8%	8%	24%	
21	Gamma-glutamyl-transferase (gamma GT) EC 2.3.2.2	Enzyme activity concentration	RMW/SW	6% 2.4 U/l	11% 4.4 U/l	23% 9.2 U/l	≥ 40 U/l < 40 U/l
22	(Total) protein	Mass concentration	RMW	3%	5%	11%	
23	Glucose	Molar concentration Mass concentration	RMW	4% 2.4 mg/dl	7% 4.2 mg/dl	15% 9 mg/dl	≥ 60 mg/dl < 60 mg/dl
24	Glutamic-oxaloacetic transaminase (GOT or AST) EC 2.6.1.1	Enzyme activity concentration	RMW/SW	6% 2.4 U/l	11% 4.4 U/l	23% 9 U/l	≥ 40 U/l < 40 U/l
25	Glutamic-pyruvic transaminase (GPT or ALT) EC 2.6.1.2	Enzyme activity concentration	RMW/SW	6% 2.4 U/l	11% 4.4 U/l	23% 9 U/l	≥ 40 U/l < 40 U/l
26	Uric acid	Molar concentration Mass concentration	RMW	4%	6%	14%	
27	Urea	Molar concentration Mass concentration	RMW/SW	7%	12%	26%	
28	Human chorionic gonadotropin (hCG)	International units	SW	12% 0.6 mU/ml	12% 0.6 mU/ml	36% 1.8 mU/ml	≥ 5 mU/ml < 5 mU/ml
29	Immunoglobulin A	Mass concentration	RMW/SW	7%	12%	26%	
30	Immunoglobulin G	Mass concentration	RMW/SW	5%	8%	18%	
31	Immunoglobulin M	Mass concentration	RMW/SW	7%	12%	26%	
32	Potassium	Molar concentration	RMW	2.7%	3.7%	9.1%	
33	Creatinine	Molar concentration Mass concentration	RMW	5% 0.06 mg/dl	9% 0.11 mg/dl	19% 0.2 mg/dl	≥ 1.5 mg/dl < 1.5 mg/dl
34	Lactate	Molar concentration Mass concentration	SW	6%	6%	18%	
35	Lactate dehydrogenase (LDH) EC 1.11.1.27	Enzyme activity concentration	RMW	5%	10%	20%	
36	Lithium	Molar concentration	RMW	3% 0.03 mmol/l	6% 0.06 mmol/l	12% 0.12 mmol/l	≥ 1.0 mmol/l < 1.0 mmol/l
37	Magnesium	Molar concentration	RMW	4% 0.032 mmol/l	7% 0.056 mmol/l	15% 0.12 mmol/l	≥ 0.8 mmol/l < 0.8 mmol/l
38	Sodium	Molar concentration	RMW	1.5%	2%	5%	

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.

Attachment 1a

Measurable quantities in serum/plasma *(continued)*

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
39	aPTT (activated partial thromboplastin time)	Coagulation time	SW	6%	6%	18%	
40	Phenobarbital	Molar concentration Mass concentration	RMW/SW	7%	7%	21%	
41	Phenytoin	Molar concentration Mass concentration	SW	8%	8%	24%	
42	Phosphate	Molar concentration Mass concentration	RMW	5%	8%	18%	
43	Primidone	Molar concentration	SW	8%	8%	24%	
44	Progesterone	Molar concentration	RMW	12% 0.48 nmol/l	21% 0.84 nmol/l	45% 1.8 nmol/l	≥ 4.0 nmol/l < 4.0 nmol/l
45	Prostate-specific antigen (PSA)	Mass concentration	SW	10%	10%	30%	
46	Testosterone	Molar concentration Mass concentration	RMW	10% 0.5 nmol/l	20% 1.0 nmol/l	40% 2.0 nmol/l	≥ 5.0 nmol/l < 5.0 nmol/l
47	Theophylline	Molar concentration Mass concentration	RMW	8%	14%	30%	
48	Thyroxine (total, T4)	Molar concentration Mass concentration	RMW	8% 6.4 nmol/l	14% 11.2 nmol/l	30% 24 nmol/l	≥ 80 nmol/l < 80 nmol/l
49	Thyroid stimulating hormone (TSH)	International units	SW	6%	6%	18%	
50	Triiodothyronine (total, T3)	Molar concentration Mass concentration	SW	8%	8%	24%	
51	Triglycerides (total glycerine)	Molar concentration Mass concentration	RMW	4%	10%	18%	
52	Thromboplastin time (Quick)	Relative coagulation time, INR	SW	8%	8%	24%	
53	Valproic acid	Molar concentration Mass concentration	SW	8%	8%	24%	

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.

Attachment 1b

Measurable quantities in spinal fluid

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
1	Albumin	Mass concentration	SW	8% 0.24 mg/dl	8% 0.24 mg/dl	24% 0.72 mg/dl	≥ 3 mg/dl < 3 mg/dl
2	(Total) protein	Mass concentration	SW	10% 1 mg/dl	10% 1 mg/dl	30% 3 mg/dl	≥ 10 mg/dl < 10 mg/dl
3	Glucose	Mass concentration Molar concentration	RMW	5% 5 mg/dl	5% 5 mg/dl	15% 15 mg/dl	≥ 100 mg/dl < 100 mg/dl
4	Immunoglobulin A	Mass concentration	SW	15% 0.09 mg/dl	15% 0.09 mg/dl	45% 0.27 mg/dl	≥ 0.6 mg/dl < 0.6 mg/dl
5	Immunoglobulin G	Mass concentration	SW	10% 0.3 mg/dl	10% 0.3 mg/dl	30% 0.9 mg/dl	≥ 3 mg/dl < 3 mg/dl
6	Immunoglobulin M	Mass concentration	SW	15% 0.09 mg/dl	15% 0.09 mg/dl	45% 0.27 mg/dl	≥ 0.6 mg/dl < 0.6 mg/dl
7	Lactate	Mass concentration Molar concentration	SW	6% 1.8 mg/dl	6% 1.8 mg/dl	18% 5.4 mg/dl	≥ 30 mg/dl < 30 mg/dl

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.

Attachment 1c

Measurable quantities in urine

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
1	Albumin	Mass concentration	SW	10% 0.3 mg/dl	10% 0.3 mg/dl	30% 0.9 mg/dl	≥ 3 mg/dl < 3 mg/dl
2	Calcium	Molar concentration	SW	5% 0.1 mmol/l	5% 0.1 mmol/l	15% 0.3 mmol/l	≥ 2 mmol/l < 2 mmol/l
3	Chloride	Molar concentration	RMW	4%	6%	14%	
4	(Total) protein	Mass concentration	SW	8% 8 mg/dl	8% 8 mg/dl	24% 24 mg/dl	≥ 100 mg/dl < 100 mg/dl
5	Glucose	Molar concentration Mass concentration	RMW	6% 6 mg/dl	10% 10 mg/dl	22% 22 mg/dl	≥ 100 mg/dl < 100 mg/dl
6	Uric acid	Molar concentration Mass concentration	RMW	7%	12%	26%	
7	Urea	Molar concentration	RMW/SW	5%	7%	17%	
8	Potassium	Molar concentration	RMW	5%	7%	17%	
9	Creatinine	Molar concentration Mass concentration	RMW/SW	7%	10%	24%	
10	Magnesium	Molar concentration	RMW/SW	6% 0.06 mmol/l	8% 0.08 mmol/l	20% 0.2 mmol/l	≥ 1 mmol/l < 1 mmol/l
11	Sodium	Molar concentration	RMW	3% 2.4 mmol/l	5% 4 mmol/l	11% 8.8 mmol/l	≥ 80 mmol/l < 80 mmol/l
12	Phosphate (inorganic)	Molar concentration	SW	6%	6%	18%	

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.

Attachment 1d

Measurable quantities in whole blood

1	2	3	4	5	6	7	8
No.	Analyte	Type of quantity	Accepted reference value[1]	Maximum permissible imprecision	Maximum permissible bias	Maximum permissible deviation of the single value	Measurement range
1	Blood gases/pH						
1a	pH	Negative logarithm of the hydrogen ion activity	SW	0.02	0.02	0.06	
1b	pO2	Partial pressure	SW	4% 4 mm Hg	4% 4 mm Hg	12% 12 mm Hg	≥ 100 mm Hg < 100 mm Hg
1c	pCO2	Partial pressure	SW	4%	4%	12%	
2	Calcium (ionized)	Molar concentration	SW	5% 0.05 mmol/l	5% 0.05 mmol/l	15% 0.15 mmol/l	≥ 1 mmol/l < 1 mmol/l
3	Digitoxin	Mass concentration	RMW	8% 1.2 µg/l	12% 1.8 µg/l	28% 4.2 µg/l	≥ 15 µg/l < 15 µg/l
4	Digoxin	Mass concentration	RMW	8% 0.12 µg/l	18% 0.27 µg/l	34% 0.51 µg/l	≥ 1.5 µg/l < 1.5 µg/l
5	Erythrocytes	Cell concentration	RMW	3%	4%	10%	
6	Ethanol (clinical toxicological)	Mass concentration Mass ratio	SW	3% 0.03 g/l	3% 0.03 g/l	9% 0.09 g/l	≥ 1.0 g/l < 1.0 g/l
7	Glucose	Molar concentration Mass concentration	RMW	4% 2.4 mg/dl	7% 4.2 mg/dl	15% 9 mg/dl	≥ 60 mg/dl < 60 mg/dl
8	Hematocrit	Volume ratio	SW	3%	3%	9%	
9	Hemoglobin	Mass concentration	RMW	2%	2%	6%	
10	Hemoglobin A 1	Mass ratio	SW	7%	7%	21%	
11	Hemoglobin A 1c	Mass ratio	RMW	6%	12%	24%	
12	Urea	Molar concentration Mass concentration	RMW/SW	7%	7%	21%	
13	Potassium	Molar concentration	RMW	2.7%	3.7%	9.1%	
14	Leukocytes	Cell concentration	SW	6% 120/µl	6% 120/µl	18% 360/µl	≥ 2000/µg < 2000/µg
15	Sodium	Molar concentration	RMW	1.5%	2%	5%	
16	Theophylline	Molar concentration Mass concentration	RMW	8%	14%	30%	
17	Thrombocytes	Cell concentration	SW	7% 2800/µl	7% 2800/µl	21% 8400/µl	≥ 40,000/µl < 40,000/µl

[1] RMW = reference-method value, SW = procedure-dependent theoretical value. The type of accepted reference value indicated here is stipulated for performance of external quality assurance.