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Clinical laboratory medicine — *In vitro* diagnostic medical devices — Validation of user quality control procedures by the manufacturer

Laboratoires d'analyses de biologie médicale — Dispositifs médicaux de diagnostic in vitro — Validation des recommandations du fabricant pour la maîtrise de la qualité par l'utilisateur

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Foreword

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International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

Attention is drawn to the possibility that some of the elements of this document may be the subject of patent rights. ISO shall not be held responsible for identifying any or all such patent rights.

ISO 15198 was prepared by Technical Committee ISO/TC 212, *Clinical laboratory testing and* in vitro *diagnostic test systems.*

Introduction

Manufacturers of IVD medical devices often include quality control (QC) procedures in their instructions for use. These quality control procedures are intended to provide users with assurance that the device is performing within specifications, and therefore the results are suitable for their intended diagnostic use. For some devices, QC procedures can be an essential risk control measure. Depending on the design of the device, these quality control procedures can help users ensure the quality of results by:

a) verifying the suitability of analytical systems (sample, reagents, instruments, and/or users);

b) monitoring the precision and trueness of measurement results;

c) preventing false-negative and false-positive results;

d) identifying fault conditions that could lead to inaccurate results; and/or

e) troubleshooting problems that require corrective action.

In addition, manufacturers often design IVD medical devices with the ability to detect potential failures and alert users to take corrective action. Such internal control systems could potentially reduce or even eliminate the need for users to run quality control samples to monitor the performance of the device.

This International Standard is written for manufacturers of *in vitro* diagnostic (IVD) medical devices as part of their design control and risk management programs. It will also enable manufacturers to provide validated quality control procedures for users in clinical diagnostic laboratories.

This International Standard describes how manufacturers can validate quality control procedures for their devices. Validation ensures that quality control procedures will perform as intended by the manufacturers and that manufacturers' recommendations fit the needs of particular devices, such as discrete systems, products with built-in electronic controls, and products with “on board” chemical and/or biological controls. Information about the validated quality control procedures increases user's understanding of devices' overall quality assurance requirements so that informed choices regarding suitable control procedures can be made.

Although laboratory directors have the ultimate responsibility for determining appropriate quality control procedures for their laboratories, manufacturers of IVD medical devices are responsible for providing adequate information to users about performance of devices as well as a means to control risks and to verify performance within specifications. Thus, in practice, quality control is a shared responsibility of IVD medical device manufacturers and users.

No single quality control procedure can cover all IVD medical devices, neither now, nor in the future, since the devices may differ fundamentally in design, technology, function and intended use. Quality control practices that developed over the years have provided laboratories with some degree of assurance that results are valid. Although widely accepted by laboratories, government agencies and accrediting organizations, these practices originated when laboratory analyses were performed manually and laboratories prepared their own reagents. They may not always be optimal for current IVD medical devices. Therefore, when quality control procedures are required, the manufacturer has the responsibility to design and validate quality control procedures appropriate for the device.

Quality system standards for medical device manufacturers have also evolved over time. Design control and risk management requirements, for example, are included in ISO 13485:2003 as well as in most contemporary regulatory schemes. Design controls require a risk analysis of the design, and, prior to introduction to the marketplace, require that the design be validated with respect to user requirements and intended use. Quality control procedures in the instructions for use should be viewed as an integral part of the design of an IVD medical device; and thus are subject to design validation requirements.

Clinical laboratory medicine — *In vitro* diagnostic medical devices — Validation of user quality control procedures by the manufacturer

1 Scope

This International Standard describes a process for manufacturers of *in vitro* diagnostic medical devices to validate quality control procedures they recommend to their users. These quality control procedures are intended to provide users with assurance that device performance is consistent with its intended use and the manufacturers' claims. This International Standard applies to all *in vitro* diagnostic medical devices.

2 Normative references

The following referenced documents are indispensable for the application of this document. For dated references, only the edition cited applies. For undated references, the latest edition of the referenced document (including any amendments) applies.

ISO 3534-1, *Statistics — Vocabulary and symbols — Part 1: Probability and general statistical terms*

ISO 5725-1, *Accuracy (trueness and precision) of measurement methods and results — Part 1: General principles and definitions*

ISO 13485:2003, *Medical devices — Quality management systems — Requirements for regulatory purposes*

ISO 14971, *Medical devices — Application of risk management to medical devices*

International vocabulary of basic and general terms in metrology (VIM). BIPM, IEC, IFCC, ISO, IUPAC, IUPAP, OIML, 2nd ed.

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 3534-1, ISO 5725-1, ISO 13485, ISO 14971, the VIM and the following apply. For the convenience of the user, some of the terms and definitions have been reproduced below.

3.1
accuracy
closeness of agreement between a test result and the accepted reference value

[ISO 3534-1]

NOTE The term accuracy, when applied to a set of test results, involves a combination of random error components and a common systematic error or **bias** (3.2) component. See the VIM.

3.2
bias
difference between the expectation of the test results and an accepted reference value

[ISO 5725-1]

3.3
commutability of a material
ability of a material to yield the same numerical relationships between results of measurements by a given set of measurement procedures, purporting to measure the same quantity, as those between the expectations of the relationship obtained when the same procedures are applied to other relevant types of materials

[ISO 15194]

3.4
control material
substance, material or article used to verify the performance characteristics of an *in vitro* diagnostic medical device

[EN 375]

3.5
control procedure
activities at the point of use to monitor the performance of an IVD medical device

NOTE 1 In the IVD medical device industry and in many laboratories that use IVD medical devices, these activities are commonly referred to as quality control.

NOTE 2 Quality control may monitor all or part of the measurement procedure, from the collection of samples to reporting the result of the measurement.

3.6
examination
set of operations having the object of determining the value of a property

NOTE In the IVD medical device industry and in many laboratories that use IVD medical devices, examination of an analyte in a biological sample is commonly referred to as a test, assay or analysis.

3.7
examination procedure
set of operations, described specifically, used in the performance of examinations according to a given method

NOTE In the IVD medical device industry and in many laboratories that use IVD medical devices, an examination procedure for an analyte in a biological sample is commonly referred to as an analytical method, analytical procedure or test procedure.

3.8
information supplied by the manufacturer with the medical device
all written, printed, or graphic matter on a medical device or any of its containers or wrappers, or accompanying a medical device, relating to the identification, technical description and use of the medical device, but excluding shipping documentation and promotional material

NOTE 1 Adapted from EN 1041.

NOTE 2 In some countries, information supplied by the manufacturer is called “labelling”.

3.9
instructions for use
information supplied by the manufacturer with an *in vitro* diagnostic medical device concerning the safe and proper use of the reagent or the safe and correct operation, maintenance and basic troubleshooting of the instrument

NOTE Adapted from EN 375 and EN 591.

3.10
intermediate precision
precision under conditions intermediate between **reproducibility conditions** (3.20) and **repeatability conditions** (3.18)

NOTE The concept of intermediate levels of precision is described in ISO 5725-3.

3.11
intermediate precision conditions
conditions where independent test results are obtained with the same method on identical test items in the same laboratory or location, but where other variables such as operators, equipment, calibration, environmental conditions and/or time intervals differ

NOTE Intended to measure precision in conditions leading to variability representative of actual use. Quantitative measures of intermediate precision depend on the stipulated conditions.

3.12
lot batch
one or more components or finished devices that consist of a simple type, model, class, size, composition or software version that are manufactured under essentially the same conditions and that are intended to have uniform characteristics and quality within specified limits

3.13
manufacturer
natural or legal person with responsibility for the design, manufacture, packaging, or labelling of a medical device, assembling a system, or adapting a medical device before it is placed on the market and/or put into service, regardless of whether these operations are carried out by that person himself or on his behalf by a third party

NOTE Provisions of national or regional regulations may apply to the definition of manufacturer.

[ISO 14971]

3.14
precision of measurement
closeness of agreement between independent test results obtained under stipulated conditions

[ISO 3534-1]

NOTE 1 The degree of precision is expressed numerically by the statistical measures of imprecision of measurements, such as standard deviation and coefficient of variation, that are inversely related to precision. Quantitative measures of precision depend on the stipulated conditions.

NOTE 2 Precision of a given measurement procedure is subdivided according to the specified precision conditions. Particular sets of extreme conditions are termed **repeatability** (3.17) and **reproducibility** (3.19).

3.15
procedure
specified way to carry out an activity or a process

[ISO 9000:2000, definition 3.4.5]

3.16
qualification
process to demonstrate the ability to fulfil specified requirements

NOTE The term “qualified” is used to designate the corresponding status.

[ISO 9000]

3.17
repeatability
precision under **repeatability conditions** (3.18)

[ISO 3534-1]

3.18
repeatability conditions
conditions where independent test results are obtained with the same method on identical test items in the same laboratory (or location) by the same operator using the same equipment within short intervals of time

[ISO 3534-1]

NOTE Essentially unchanged conditions, intended to represent conditions resulting in minimum variability of test results.

3.19
reproducibility
precision under **reproducibility conditions** (3.20)

[ISO 3534-1]

3.20
reproducibility conditions
conditions where test results are obtained with the same method on identical test items in different laboratories (or locations) with different operators using different equipment

[ISO 3534-1]

NOTE Completely changed conditions, intended to represent conditions resulting in maximum variability of test results.

3.21
risk analysis
systematic use of available information to identify hazards and to estimate the risk

[ISO/IEC Guide 51:1999, definition 3.10]

3.22
sample
one or more parts taken from a population and intended to provide information on the population

3.23
traceability
property of the result of a measurement or the value of a standard whereby it can be related to stated references, usually national or International Standards, through an unbroken chain of comparisons all having stated uncertainties

[VIM:1993, 6.10]

3.24
trueness
closeness of agreement between the average value obtained from large series of test results and an accepted reference value

[ISO 3534-1]

NOTE The measure of trueness is usually expressed in terms of **bias** (3.2).

3.25
validation
confirmation, through provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

NOTE The term “validated” is used to designate the corresponding status.

[ISO 9000:2000]

3.26
verification
confirmation, through provision of objective evidence, that specified requirements have been fulfilled

NOTE The term “verified” is used to designate the corresponding status.

[ISO 9000:2000]

4 Quality control procedures

4.1 General

If a manufacturer of an IVD medical device recommends a quality control procedure for the user to monitor device performance, the manufacturer shall describe in the instructions for use all requirements and all actions to be taken by the user (e.g. acceptable control materials, frequency of examination of control materials, means to establish criteria for assessing the validity of the measurement procedure, and guidance for actions to be taken upon observing unacceptable quality control data).

In addition, the manufacturer shall provide sufficient information for the user to understand the basis for the recommendations. Based on the manufacturer's recommended quality control procedures, a user can establish a comprehensive quality control system for the specific setting in which the device is used.

NOTE The user has the ultimate responsibility to choose the appropriate quality control procedures in accordance with applicable regulations.

4.2 Risk analysis

The manufacturer shall conduct a risk analysis during the design and development of the device. The requirements of ISO 14971 shall apply.

The risk analysis method chosen shall consider the intended use of the device and user requirements. The risk analysis shall identify sources of variability and potential hazards that are not mitigated by the design of the device or by manufacturing process controls.

Identified risks that cannot be eliminated by design shall be minimized by protective measures, including manufacturers' recommended quality control procedures.

The quality control procedures shall include a method of detection (e.g. quality control material, electronic monitoring system, or on-board chemical control) and acceptability criteria that will determine when a critical failure occurs, or recommend a means to determine the acceptability criteria.

Limitations of the quality control procedure shall be identified and described in the instructions for use.

4.3 Performance evaluation studies

Results from internal and external evaluation studies shall be considered when developing the quality control procedures. Evaluation data used for this purpose shall, to the extent possible, reflect the user environments and types of samples associated with the intended use of the device.

5 Validation of quality control procedures

5.1 General

The purpose of validating quality control procedures is to provide assurance that they are capable of detecting results that fail to meet performance specifications.

NOTE Performance specifications (e.g. accuracy, precision, trueness, specificity, sensitivity, claims) are given in the instructions for use.

5.2 Applicability

This International Standard applies to IVD medical devices being placed on the market for the first time and modifications of existing IVD medical devices that represent significant design changes.

Based on the results of the risk analysis, the manufacturer shall determine if quality control validation is required.

Quality control procedures shall be validated if the risk analysis determines that failure of the quality control system would constitute a hazard to patients (e.g. from reporting inaccurate results) or if quality control procedures are recommended as a protective measure to reduce the risk to an acceptable level.

For existing IVD medical devices, conventional statistical quality control procedures (e.g. as described in NCCLS C24) are considered adequate unless evidence from risk-monitoring activities indicates the quality control procedures are essential for maintaining risk at an acceptable level. In such cases, the quality control procedures shall be validated.

5.3 Validation

5.3.1 Validation planning

During the design of an IVD medical device, if it is determined that quality control procedures require validation, the manufacturer shall develop a validation plan for the recommended quality control procedures. The quality control validation shall be conducted within the manufacturer's design control and risk management systems. The requirements of ISO 13485:2003, 4.4.8, and ISO 14971 shall apply.

The validation plan shall consider the outputs from the risk analyses conducted during the design and development of the device and any relevant experience with the device. This includes consideration of all identified conditions with the potential to cause a critical failure, as well as the effects of the failure.

5.3.2 Validation responsibility

The manufacturer shall assign responsibilities for the validation to qualified personnel, taking into consideration that input from individuals with different scientific and engineering backgrounds may be necessary for different types of products or for different types of validation needs or phases (planning, protocols, execution, review, etc.). The names and qualifications of personnel responsible for planning and executing the validation shall be documented.

5.3.3 Validation protocol

Validation studies shall be designed to demonstrate the effectiveness of the recommended quality control procedures.

The protocol should include actual and/or simulated challenges from error conditions identified in the risk analysis that the quality control system is intended to detect, as appropriate.

NOTE Demonstration that a statistical control procedure will detect results that exceed predetermined limits does not require induction of actual failure modes. Validation may be based on statistical evaluation of the simulated effects of imprecision and/or bias on actual performance data obtained in routine operating mode. See references [13], [19] and [21] to [26].

Quality control validation studies may be included in performance evaluations conducted as part of the design validation.

Study designs, statistical analysis methods and acceptance criteria shall be established prior to data collection. Statistical methods, simulation models and sample size calculations shall be justified. Rationale for the acceptance criteria (e.g. relationship to user requirements) shall be described. These elements of the plan shall be documented in a validation protocol, which shall be reviewed and approved according to the manufacturer's design validation procedures.

5.4 Validation studies

The validation protocol shall be executed as written by qualified personnel. Equipment and instrumentation shall be qualified prior to initiation of validation studies. Software and analytical test methods shall be validated prior to use.

Experimental observations and data shall be recorded and retained according to established procedures. The recordkeeping requirements of ISO 13485:2003 shall apply.

Protocol deviations shall be justified and approved in advance. Any validation failures shall be investigated and dispositioned according to the manufacturer's design validation procedures.

5.5 Validation report

The results of the validation studies, as well as a description of quality control procedures, validation methods, materials used, pertinent experimental details and individuals performing the validation, shall be documented in a validation report.

The report shall provide a synopsis of validation objectives and data and shall show that all acceptance criteria have been met.

Any protocol deviations, nonconformance and validation failures shall be discussed and justified.

The report shall be approved according to the manufacturer's design validation procedures and shall be retained as part of the manufacturer's risk management file.

5.6 Revalidation

The requirements of ISO 13485:2003, 4.4.8, shall apply.

Performance of quality control procedures shall be monitored. The manufacturer shall periodically evaluate the adequacy of recommended quality control procedures.

The manufacturer shall consider the need to revalidate the quality control procedures periodically, as well as when changes are made to the design of the device, or to validated quality control procedures, when investigating reports of adverse events (e.g. incidents and malfunctions that represent a risk of serious harm), or when indicated by the CAPA system. The results of these evaluations shall be documented.

6 Recommendations to users

The validated quality control procedures shall include, when applicable:

a) type of error that the quality control procedure is intended to detect;

b) control materials that may be used;

c) recommended analyte concentrations;

d) guidelines for determining acceptability criteria (control limits);

e) known limitations of the quality control procedure.

Local, national or regional requirements may apply.

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