BS EN ISO 23640:2013

In vitro diagnostic medical devices — Evaluation of stability of in vitro diagnostic reagents

National foreword

This British Standard is the UK implementation of EN ISO 23640:2013. It supersedes BS EN ISO 23640:2011 which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs.

A list of organizations represented on this committee can be obtained on request to its secretary.

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In vitro diagnostic medical devices - Evaluation of stability of in vitro diagnostic reagents (ISO 23640:2011)

Dispositifs médicaux de diagnostic in vitro - Évaluation de la stabilité des réactifs de diagnostic in vitro (ISO 23640:2011)

In-vitro-Diagnostika - Haltbarkeitsprüfung von Reagenzien für in-vitro-diagnostische Untersuchungen (ISO 23640:2011)

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Contents

Foreword

The text of ISO 23640:2011 has been prepared by Technical Committee ISO/TC 212 “Clinical laboratory testing and in vitro diagnostic test systems” of the International Organization for Standardization (ISO) and has been taken over as EN ISO 23640:2013 by Technical Committee CEN/TC 140 “In vitro diagnostic medical devices” the secretariat of which is held by DIN.

This European Standard shall be given the status of a national standard, either by publication of an identical text or by endorsement, at the latest by August 2013, and conflicting national standards shall be withdrawn at the latest by August 2013.

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

This document supersedes EN ISO 23640:2011.

This document has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of EU Directive.

For relationship with EU Directive, see informative Annex ZA, which is an integral part of this document.

According to the CEN-CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, Former Yugoslav Republic of Macedonia, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey and the United Kingdom.

Endorsement notice

The text of ISO 23640:2011 has been approved by CEN as EN ISO 23640:2013 without any modification.

Annex ZA
(informative)

Relationship between this European Standard and the Essential Requirements of EU Directive 98/79/EC

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association to provide one means of conforming to Essential Requirements of the New Approach Directive 98/79/EC on *in vitro* diagnostic medical devices.

Once this standard is cited in the Official Journal of the European Union under that Directive and has been implemented as a national standard in at least one Member State, compliance with the normative clauses of this standard given in Table ZA.1 confers, within the limits of the scope of this standard, a presumption of conformity with the corresponding Essential Requirements of that Directive and associated EFTA regulations.

Table ZA.1 — Correspondence between this European Standard and Directive 98/79/EC on *in vitro* diagnostic medical devices

Clauses/subclauses of this European Standard	Essential Requirements of the Directive 98/79/EC	Qualifying remarks/Notes
4.1, 4.2, 4.3, 5.1, 5.2, 5.3	A.4	

WARNING — Other requirements and other EU Directives may be applicable to the product(s) falling within the scope of this standard.

Introduction

One important aspect of the development and manufacture of *in vitro* diagnostic (IVD) medical device reagents is initially designing the stability of a product, then determining and verifying the expiry date of the product that is placed on the market. To determine shelf life, transport stability, and in-use stability, the manufacturer performs an evaluation. In order to provide this important information to the customer, the manufacturer identifies critical factors that might influence stability of the IVD reagent and carefully evaluates these characteristics. Stability of the IVD reagent affects the performance of the device and therefore has an impact on patient results.

It is the manufacturer's responsibility to determine and monitor stability of IVD reagents to ensure that performance characteristics of the product are maintained. This is best accomplished by developing a stability evaluation protocol, and producing valid data and analysis to establish appropriate shelf life, transport limitations and in-use stability information, which are then provided to the customers.

The basis for this ISO standard is EN 13640, *Stability testing of* in vitro *diagnostic reagents*[2].

INTERNATIONAL STANDARD ISO 23640:2011(E)

In vitro diagnostic medical devices — Evaluation of stability of *in vitro* diagnostic reagents

1 Scope

This International Standard is applicable to the stability evaluation of *in vitro* diagnostic medical devices, including reagents, calibrators, control materials, diluents, buffers and reagent kits, hereinafter called IVD reagents. This International Standard can also be applied to specimen collection devices that contain substances used to preserve samples or to initiate reactions for further processing of the sample in the collection device.

This International Standard specifies general requirements for stability evaluation and gives specific requirements for real time and accelerated stability evaluation when generating data in:

— the establishment of IVD reagent shelf life, including transport conditions suitable to ensure that product specifications are maintained;

— the establishment of stability of the IVD reagent in use after the first opening of the primary container;

EXAMPLE On-board stability, stability after reconstitution, open vial/bottle stability.

— the monitoring of stability of IVD reagents already placed on the market;

— the verification of stability specifications after modifications of the IVD reagent that might affect stability.

This International Standard is not applicable to instruments, apparatus, equipment, systems or specimen receptacles, or the sample subject to examination.

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

3 Terms and definitions

For the purposes of this document, the following terms and definitions apply.

3.1
accelerated stability evaluation
study designed to increase the rate of chemical and/or physical degradation, or change, of an IVD reagent by using stress environmental conditions to predict shelf life

NOTE The design of an accelerated stability evaluation can include extreme conditions of temperature, humidity, light or vibration.

3.2
Arrhenius plot
mathematical function that describes the approximate relationship between the rate constant of a chemical reaction and the temperature and energy of activation

[CLSI EP25-A]

3.3
batch
lot
defined amount of material that is uniform in its properties and has been produced in one process or series of processes

[ISO 18113-1:2009, definition 3.5]

3.4
batch code
lot number
distinctive set of numbers and/or letters that specifically identifies a batch and permits its manufacturing, packaging, labelling and distribution history to be traced

[ISO 18113-1:2009, definition 3.6]

3.5
expiry date
expiration date
upper limit of the time interval during which the performance characteristics of a material stored under specified conditions can be assured

NOTE Expiry dates are assigned to IVD reagents, calibrators, control materials and other components by the manufacturer based on experimentally determined stability properties.

[ISO 18113-1:2009, definition 3.17]

3.6
IVD medical device
***in vitro* diagnostic medical device**
device, used alone or in combination, intended by the manufacturer for the *in vitro* examination of specimens derived from the human body solely or principally to provide information for diagnostic, monitoring or compatibility purposes, which can include reagents, calibrators, control materials, specimen receptacles, software, and related instruments or apparatus or other articles

[ISO 18113-1:2009, definition 3.27]

3.7
IVD reagent
***in vitro* diagnostic reagent**
chemical, biological or immunological components, solutions or preparations intended by the manufacturer to be used as an IVD medical device

[ISO 18113-1:2009, definition 3.28]

3.8
real time stability evaluation
study designed to establish or verify the shelf life of the IVD reagent when exposed to the conditions specified by the manufacturer

NOTE Conditions that can affect stability of an IVD reagent include temperature, transport conditions, vibration, light, humidity.

3.9
shelf life
period of time until the expiry date, during which an IVD reagent, in its original packaging, maintains its stability under the storage conditions specified by the manufacturer

NOTE **Stability** (3.10) and **expiry date** (3.5) are related concepts.

[ISO 18113-1:2009, definition 3.66]

3.10
stability
ability of an IVD medical device to maintain its performance characteristics within the limits specified by the manufacturer

NOTE 1 Stability applies to:

— IVD reagents, calibrators and controls, when stored, transported and used in the conditions specified by the manufacturer;

— reconstituted lyophilized materials, working solutions and materials removed from sealed containers (when prepared, used and stored according to the manufacturer's instructions for use).

NOTE 2 Stability of an IVD reagent or measuring system is normally quantified with respect to time:

— in terms of the duration of a time interval over which a metrological property changes by a stated amount;

— in terms of the change of a property over a stated time interval.

[ISO 18113-1:2009, definition 3.68]

3.11
verification
provision of objective evidence that a given item fulfils specified requirements

EXAMPLE 1 Confirmation that a given material as claimed is homogeneous for the quantity value and measurement procedure concerned.

EXAMPLE 2 Confirmation that performance properties or requirements of a measuring system are achieved within the specified expiry date.

EXAMPLE 3 Confirmation that the magnitude and direction of a consistent change over time from initial determination will conform to the stated specification throughout the claimed stability of the IVD reagent.

EXAMPLE 4 Confirmation that a target measurement uncertainty can be met.

NOTE 1 The item can be a process, measurement procedure, material or compound examination or measuring system response.

NOTE 2 The specified requirements can be, for example, that a manufacturer's claims or specifications are met.

NOTE 3 Adapted from ISO 18113-1:2009, definition 3.73.

4 General requirements

4.1 General principles

Stability claims shall be justified by adequate data, considering the risks associated with the use of the IVD reagent, and with consideration of components that might be labile.

Data from accelerated stability studies and/or experience gained with IVD reagents that can reasonably be expected to be comparable with regard to their stability characteristics may be taken into account for establishing initial expiry dating. Experience with similar reagents and the risk associated with the use of the device should be used to establish the basis for initial expiry dating. If, at the time of placing an IVD reagent onto the market, stability claims are based on such previous data, the claim shall be verified with real time study data.

The evaluation shall be performed on IVD reagents manufactured under conditions that are essentially equivalent to routine production conditions. If this is not the case, or if the IVD reagent is not stored in the final configuration, the manufacturer shall provide justification for the stability claims.

The manufacturer shall establish whether there is a need for a stability monitoring programme and establish one where necessary. Evaluation at the end of shelf life can be sufficient for this purpose.

Subsequent product or manufacturing process modifications shall be reviewed to determine whether changes in the stability programme are necessary.

4.2 Protocol

Conclusions on IVD reagent stability shall be based on data that are generated in accordance with a pre-established protocol that includes:

— responsibilities;

— clear IVD reagent identification;

— use conditions;

EXAMPLE 1 Considering variation in environmental factors, including the worst case.

— objective and purpose of the evaluation;

— information about the reagent samples;

EXAMPLE 2 Numbers of batches, amount, container, identification of the source, and concentrations.

— potential influence of critical components;

NOTE "Critical" is meant with respect to stability.

— storage conditions recommended for the reagent samples;

EXAMPLE 3 Between 2 °C and 8 °C, less than 20 °C.

— simulation of transport;

— intervals between examination time points;

— examinations to be performed at the end of each interval;

EXAMPLE 4 Procedure and extent of examinations.

— the number of examinations to be performed with an IVD reagent, which depends on the precision of the test methods used (considering the variability which might be encountered due to equipment and IVD reagents);

— the duration of the stability study protocol, which might include an additional confidence margin beyond the targeted stability claim;

— description of the data analysis;

EXAMPLE 5 References to any statistical techniques and conditions for accepting or rejecting a data point.

— acceptance criteria to be met;

— interpretation of data.

The protocol shall be part of the technical documentation related to the IVD reagent.

4.3 Stability reports

Stability reports shall be prepared in order to document the study, or studies.

EXAMPLE Interim and final reports.

Reports shall, at a minimum, include or refer to:

— the protocol which was followed;

— the batch(es) involved;

— all results obtained;

— analysis of data;

— acceptance criteria with pass/fail determination;

— conclusions regarding stability.

Reports shall be maintained as part of the technical documentation related to the IVD reagent.

5 Procedures

5.1 General

5.1.1 Purpose

Procedures shall be performed to evaluate and verify the stability claims of the IVD reagent.

NOTE CLSI EP25-A[3] contains information regarding conditions and procedures that can be useful to the design and conduct of stability evaluation studies.

5.1.2 Examinations

Examinations shall be performed according to the procedures described in the protocol. The number of examinations to be performed with an IVD reagent representing a specific storage condition and time depends upon the precision of the methods used.

Examinations shall be undertaken at specified time points as indicated in the protocol. The time intervals shall be chosen to cover, as a minimum, the whole of the target shelf life. The number of time points should be appropriately chosen so that trends can be distinguished from the variability of the data.

There shall be a sufficient amount of the IVD reagent sample to be examined to last for the entire evaluation period and for any re-examination.

Stability evaluation conditions of the IVD reagent that differ from the final configuration shall be justified in the risk assessment (see ISO 14971 for guidance on risk management for IVD medical devices).

EXAMPLE Differences in reagent volumes or conducted in materials that differ from the primary reagent container.

5.1.3 Number of batches to be examined

The minimum number of batches to be examined shall depend on the objective of the evaluation as follows:

— 3 batches for the evaluation of a new IVD reagent shelf life (real time stability);

— 3 batches for the extension of an IVD reagent shelf life;

— 1 batch for transport simulation;

— 1 batch for in-use stability of the IVD reagent;

— 1 batch for an IVD reagent modification, if the risk assessment for the IVD reagent in accordance with ISO 14971 indicates that stability evaluation is required.

Using fewer than the number of batches required shall be justified in the risk assessment of the IVD reagent, in accordance with ISO 14971.

5.2 Real time stability evaluation

5.2.1 Shelf life

During shelf life evaluation the IVD reagent shall be stored under the conditions stated by the manufacturer.

NOTE Specifications can be determined by the capabilities of the equipment being used in the examination or the conditions in which the product is expected to be stored.

EXAMPLE Refrigerators used for reagent storage in laboratories generally claim that control temperature is between 2 °C to 8 °C. The shelf life evaluation should not include temperatures below 2 °C or above 8 °C.

5.2.2 Stability during transport

The manufacturer shall verify that the specified transport conditions will not affect the IVD reagent expiry date.

If transport conditions are simulated, then the protocol design shall be based on the knowledge of the transport conditions. If not already known, an investigation shall be performed to determine the real transport conditions as a basis for this simulation.

EXAMPLE Duration of transport, expected temperatures, humidity.

5.2.3 In-use stability

The in-use stability shall reflect the routine conditions of use.

EXAMPLE On-board stability, reconstitution, and open vial/bottle stability.

5.3 Accelerated stability evaluation

5.3.1 General

Accelerated stability evaluation shall be acceptable as the basis for establishing initial expiry dating for product introduction.

NOTE 1 For some reagents, accelerated stability evaluations might not be appropriate.

NOTE 2 See CLSI EP25-A[3] for information regarding accelerated stability evaluation procedures.

5.3.2 Procedure

The material under investigation shall be stored under the conditions described in the information supplied by the manufacturer until the examination begins. Material included in the accelerated stability evaluation shall then be exposed to the defined stress conditions. Samples shall be removed at the specified times and examined or returned to the storage conditions, as described in the information supplied by the manufacturer, until the examination proceeds according to established protocol.

5.3.3 Analysis of data

Analysis of accelerated stability data shall be conducted according to the protocol.

EXAMPLE Arrhenius plot, non-linear modelling.

5.3.4 Evaluations and conclusions

Establish the expiry date based on data analysis, interpretation and pre-established acceptance criteria.

Bibliography

[1] ISO 18113-1:2009, In vitro *diagnostic medical devices — Information supplied by the manufacturer (labelling) — Part 1: Terms, definitions and general requirements*

[2] EN 13640, *Stability testing of* in vitro *diagnostic reagents*

[3] CLSI EP25-A, *Evaluation of Stability of* In Vitro *Diagnostic Reagents*; Approved Guideline, CLSI, Wayne, PA, 2009

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