BRITISH STANDARD

BS EN
13640:2002

Stability testing of in vitro diagnostic reagents

The European Standard EN 13640:2002 has the status of a British Standard

ICS 11.100

National foreword

This British Standard is the official English language version of EN 13640:2002.

The UK participation in its preparation was entrusted to Technical Committee CH/69, In vitro diagnostic systems, which has the responsibility to:

— aid enquirers to understand the text;

— present to the responsible European committee any enquiries on the interpretation, or proposals for change, and keep the UK interests informed;

— monitor related international and European developments and promulgate them in the UK.

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

Cross-references

The British Standards which implement international or European publications referred to in this document may be found in the BSI Standards Catalogue under the section entitled "International Standards Correspondence Index", or by using the "Find" facility of the BSI Standards Electronic Catalogue.

A British Standard does not purport to include all the necessary provisions of a contract. Users of British Standards are responsible for their correct application.

Compliance with a British Standard does not of itself confer immunity from legal obligations.

This British Standard, having been prepared under the direction of the Health and Environment Sector Policy and Strategy Committee, was published under the authority of the Standards Policy and Strategy Committee on 3 May 2002

Summary of pages

This document comprises a front cover, an inside front cover, the EN title page, pages 2 to 10, an inside back cover and a back cover.

The BSI copyright date displayed in this document indicates when the document was last issued.

Amendments issued since publication

Amd. No.	Date	Comments

ISBN 0 580 39653 3

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN 13640

March 2002

ICS 11.100

English version

Stability testing of in vitro diagnostic reagents

Essais de stabilité des réactifs de diagnostic in vitro

Haltbarkeitsprüfung von Reagenzien für in-vitro-diagnostische Untersuchungen

This European Standard was approved by CEN on 27 December 2001.

EUROPEAN COMMITTEE FOR STANDARDIZATION
COMITÉ EUROPÉEN DE NORMALISATION
EUROPÄISCHES KOMITEE FÜR NORMUNG

Management Centre: rue de Stassart, 36 B-1050 Brussels

Foreword

This document EN 13640:2002 has been prepared 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 September 2002, and conflicting national standards shall be withdrawn at the latest by September 2002.

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(s).

For relationship with EU Directive(s), see informative annex ZA, which is an integral part of this document.

Annexes A and ZA are for information only.

This standard includes a Bibliography.

According to the CEN/CENELEC Internal Regulations, the national standards organizations of the following countries are bound to implement this European Standard: Austria, Belgium, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland and the United Kingdom.

1 Scope

This European Standard is applicable to the stability testing of in vitro diagnostic reagents including reagent products, calibrators, control materials and kits, hereinafter called IVD reagents. It specifies general requirements for stability testing and gives specific requirements for real-time testing and accelerated testing when generating stability data in the

– determination of IVD reagent shelf-life including transport stability;

– determination of stability of the IVD reagent in use after the first opening of the primary container (e. g. on-board stability);

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

– verification of stability after IVD reagent modifications that may affect stability.

This standard does not apply to instruments, apparatus, equipment, systems, or specimen receptacles.

2 Terms and definitions

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

2.1
accelerated stability study
stability study designed to increase the rate of chemical or physical degradation of an in vitro diagnostic reagent by using exaggerated conditions with the purpose of predicting the shelf-life

NOTE The design of an accelerated study may include elevated temperature, high humidity, light and vibration.

2.2
batch
lot
defined amount of material, either starting material, intermediate or finished product, which is uniform in its properties and has been produced in one process or series of processes
[EN 375:2001]

2.3
expiry date
date up to which product performance is assured by the manufacturer based on the stability of the IVD reagent
[EN 375:2001]

2.4
in vitro diagnostic reagent
IVD reagent
in vitro diagnostic medical device which is a reagent, reagent product, calibrator, control material or kit

NOTE 1 For the definition of an in vitro diagnostic medical device see Bibliography.

NOTE 2 In some cases a particular IVD reagent, as defined for use in human medicine, may serve also in veterinary medicine.
[EN 375:2001]

2.5
real-time stability testing
exposing the IVD reagent to the conditions anticipated by the manufacturer to which an IVD reagent is exposed during transportation, storage and use, and investigating robustness and stability under these conditions

2.6
shelf life
period until expiry date
[EN 375 : 2001]

2.7
stability
ability of an IVD reagent, when kept under specified conditions, to retain throughout the shelf life its properties and/or performance within limits specified by the manufacturer
[EN 375 : 2001]

3 General requirements

3.1 Protocol

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

– responsibilities;

– clear IVD reagent identification;

– presumed storage conditions;

– objective and purpose of testing;

– information about the samples (e.g. number of batches, amount , container, identification);

– storage conditions recommended for the samples (e.g. frozen, refrigerated, room temperature);

– simulation of transport as appropriate;

– intervals between examinations;

– examinations to be performed at the end of each interval (e. g. procedure and extent of testing);

– stability criteria to be met;

– interpretation of data.

3.2 Final report

A final report shall be prepared to complete each study. This report shall at least include or refer to

– the protocol which was followed;

– the batch(es) involved;

– all testing results obtained;

– summary and conclusions regarding stability.

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

4 Procedures

4.1 General

Stability assessment shall in principle be based on data derived from real-time testing. Depending on the risk associated with the IVD reagent, data derived from accelerated testing as well as experience gained with similar IVD reagents that can reasonably be expected to be comparable as regards their stability profile may also be taken into account. If at the time of placing an IVD reagent onto the market, stability claims are based on such previous data, these data shall be subsequently verified by real-time testing.

Testing may be performed on any IVD reagent batch provided that the manufacturing conditions do not essentially differ from the routine production conditions.

To cover remaining uncertainties, the stability claims shall include an adequate safety margin.

The manufacturer shall consider the need for regular monitoring of the stability of an IVD reagent already placed on the market and, where necessary, establish an appropriate monitoring programme. Examinations at the end of shelf-life can be sufficient for this purpose.

The minimum number of batches to be investigated depending on the objective of testing shall be

– 3 batches for the verification of a new IVD reagent shelf-life (long-term stability);

– 1 batch for transport simulation;

– 1 batch for in-use stability of IVD reagents, for example those which are to be reconstituted or were initially packed under vacuum.

In other cases at least the following number of batches shall be investigated:

– 3 batches for extension of an IVD reagent shelf-life;

– 1 batch for IVD reagent modification.

In any case, at the time of placing the IVD reagent onto the market, all stability claims shall be justified by adequate data, considering the risks associated with the IVD reagent and the potential influence of critical raw materials, where appropriate.

NOTE "Critical" is meant with respect to stability.

4.2 Real-time stability testing

4.2.1 Objectives of real-time stability testing

4.2.1.1 General

Real-time stability testing shall include long-term stability covering the shelf-life, transport simulation and in-use stability.

4.2.1.2 Long-term stability

During long-term stability testing the IVD reagent shall be stored under the conditions recommended by the manufacturer (e. g. temperature, humidity).

Examinations shall be undertaken at specified time intervals as indicated in the protocol. The time intervals shall be chosen to encompass at least the whole of the target shelf life and, if appropriate, continue until significant degradation in the performance of the IVD reagent can be determined. The number of time intervals shall be appropriately chosen so that trends may be discerned from variability of the data.

4.2.1.3 Transport simulation

The simulation of the transport stress shall be based on the knowledge of the transport conditions (e. g. duration of transport, expected temperatures and humidity). Where appropriate, an investigation shall be performed to determine the real transport conditions as a basis for this simulation.

4.2.1.4 In-use stability

The real-time stability testing for the purpose of determining the in-use stability shall reflect the routine conditions of use as specified by the manufacturer.

4.2.2 Procedure

4.2.2.1 Material

There shall be a sufficient amount of the IVD reagent batch to be tested to last for the whole test period. If the IVD reagent is not stored or exposed in the final configuration, in particular in terms of volume and material of the primary container, the manufacturer shall base this decision on an adequate justification.

4.2.2.2 Examinations and assessment

In designing analytical procedures the manufacturer shall consider the variability which may be encountered due to equipment and IVD reagents.

The number of examinations to be performed with an IVD reagent depends on the precision of the test methods used. Assessment of the individual test results shall be based on pre-established stability criteria.

4.3 Accelerated stability testing

4.3.1 Storage conditions and testing intervals

Although other factors may also be of interest (e. g. sensitivity to light, humidity, low temperature), typically IVD reagents are exposed to different elevated temperatures. The manufacturer shall specify these stress conditions and the testing intervals. The test conditions chosen should, where appropriate, demonstrate significant deterioration of the IVD reagent over the testing period in order to allow for a mathematical extrapolation.

4.3.2 Procedure

4.3.2.1 Material

The material under investigation shall be stored under the conditions defined until the accelerated testing programme starts. Sufficient amounts of the material shall then be exposed to the defined stress conditions. Samples shall be removed at the specified times and stored under the defined conditions until analysis. If the IVD reagent is not exposed in the final configuration, in particular in terms of volume and material of the primary container, the manufacturer shall base this decision on an adequate justification.

4.3.2.2 Examinations and assessment

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 on the precision of the test methods used.

4.3.3 Interpretation of results

If the results of accelerated testing are to be used to predict the shelf-life under the recommended storage conditions in the absence of sufficient real-time data, this shall be done on the basis of experience with similar IVD reagents and/or by using the Arrhenius equation or other stated models.

Annex A
(informative)

Procedure for predicting the shelf-life from accelerated stability testing based on the Arrhenius equation

If a prediction of stability for a given storage temperature is intended to be based on the Arrhenius equation, the calculation can be done as follows:

a) For each temperature the decimal log of concentration (*y* axis) is plotted versus time (*x* axis) and the regression equation $y = ax + b$ is calculated.

b) The percentage of the time "zero" value, at which the IVD reagent is no longer acceptable, is calculated on the basis of the defined stability criteria. The result is converted to decimal log concentration.

c) For each temperature in the equation according to a) "*y*" is substituted by decimal log concentration according to b) and the stability time (*x*) is calculated.

d) The times according to c) are converted to decimal log time. Decimal log time (*y* axis) is plotted versus the reciprocal value of the absolute temperature (*x* axis). The regression equation $y = mx + n$ is calculated.

e) Using the equation according to d) the expected stability time can be calculated for a given storage temperature.

Annex ZA
(informative)

Clauses of this European Standard addressing essential requirements or other provisions of EU Directives

This European Standard has been prepared under a mandate given to CEN by the European Commission and the European Free Trade Association, and supports essential requirements of the Directive 98/79/EC.

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

The following clauses of this standard, as detailed in Table ZA.1, are likely to support requirements of the EU Directive 98/79/EC.

Compliance with these clauses of this standard provides one means of conforming with the specific essential requirements of the Directive concerned and associated EFTA regulations.

Table ZA.1 - Correspondence between this European Standard and EU Directive 98/79/EC

Clauses/subclauses of this European Standard	Corresponding essential requirements of Directive 98/79/EC	Qualifying remarks/Notes
4.1	A.3, A.4, A.5	
4.2.1	A.4, A.5, B.8.4 (e), B.8.7 (a)	
4.2.1.2	B.8.4 (e), B.8.7 (a)	
4.2.1.3	A.4, A.5	
4.2.1.4	B.8.7 (c)	

Bibliography

EN 375:2001, *Information supplied by the manufacturer with in vitro diagnostic reagents for professional use.*

Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, OJEC, 1998, No L 331

blank

BSI — British Standards Institution

BSI is the independent national body responsible for preparing British Standards. It presents the UK view on standards in Europe and at the international level. It is incorporated by Royal Charter.

Revisions

British Standards are updated by amendment or revision. Users of British Standards should make sure that they possess the latest amendments or editions.

It is the constant aim of BSI to improve the quality of our products and services. We would be grateful if anyone finding an inaccuracy or ambiguity while using this British Standard would inform the Secretary of the technical committee responsible, the identity of which can be found on the inside front cover. Tel: +44 (0)20 8996 9000. Fax: +44 (0)20 8996 7400.

BSI offers members an individual updating service called PLUS which ensures that subscribers automatically receive the latest editions of standards.

Buying standards

Orders for all BSI, international and foreign standards publications should be addressed to Customer Services. Tel: +44 (0)20 8996 9001. Fax: +44 (0)20 8996 7001. Email: orders@bsi-global.com. Standards are also available from the BSI website at http://www.bsi-global.com.

In response to orders for international standards, it is BSI policy to supply the BSI implementation of those that have been published as British Standards, unless otherwise requested.

Information on standards

BSI provides a wide range of information on national, European and international standards through its Library and its Technical Help to Exporters Service. Various BSI electronic information services are also available which give details on all its products and services. Contact the Information Centre. Tel: +44 (0)20 8996 7111. Fax: +44 (0)20 8996 7048. Email: info@bsi-global.com.

Subscribing members of BSI are kept up to date with standards developments and receive substantial discounts on the purchase price of standards. For details of these and other benefits contact Membership Administration. Tel: +44 (0)20 8996 7002. Fax: +44 (0)20 8996 7001. Email: membership@bsi-global.com.

Information regarding online access to British Standards via British Standards Online can be found at http://www.bsi-global.com/bsonline.

Further information about BSI is available on the BSI website at http://www.bsi-global.com.

Copyright

BSI
389 Chiswick High Road
London
W4 4AL