BRITISH STANDARD

BS EN
13975:2003

Sampling procedures used for acceptance testing of in vitro diagnostic medical devices — Statistical aspects

The European Standard EN 13975:2003 has the status of a British Standard

ICS 11.100

BSI
British Standards

National foreword

This British Standard is the official English language version of EN 13975:2003.

The UK participation in its preparation was entrusted to Technical Committee CH/212, IVDs, which has the responsibility to:

— aid enquirers to understand the text;

— present to the responsible international/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 Catalogue* under the section entitled "International Standards Correspondence Index", or by using the "Search" facility of the *BSI Electronic Catalogue* or of British Standards Online.

This publication does not purport to include all the necessary provisions of a contract. Users are responsible for its correct application.

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

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 28 March 2003

Summary of pages

This document comprises a front cover, an inside front cover, the EN title page, pages 2 to 12, 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 41510 4

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN 13975

March 2003

ICS 11.100

English version

Sampling procedures used for acceptance testing of in vitro diagnostic medical devices - Statistical aspects

Procédures d'échantillonnage utilisées pour l'acceptation des essais des dispositifs médicaux de diagnostic in vitro - Aspects statistiques

Probenahmeverfahren für die Annahmeprüfung von In-vitro-Diagnostika - Statistische Aspekte

This European Standard was approved by CEN on 14 November 2002.

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 13975:2003) 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 2003, and conflicting national standards shall be withdrawn at the latest by September 2003.

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

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

Annex A is informative.

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, Hungary, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Slovakia, Spain, Sweden, Switzerland and the United Kingdom.

Introduction

This European Standard relates to Annex VI "EC VERIFICATION" of the Directive 98/79/EC of the European Parliament and of the Council of 27 October 1998 on in vitro diagnostic medical devices, setting out requirements for sampling procedures used for acceptance testing of in vitro diagnostic medical devices by a notified body.

In Annex VI three provisions for verification are described:

— Section 5 provides for verification by examination and testing of every finished device;

— Section 6.3 provides for verification based on statistical control by attributes and/or variables;

— Section 2.2 provides for alternative conformity assessment procedures for those situations where statistical verification as specified in Section 6.3 is considered to be not appropriate.

The first provision is not considered in the present standard since the associated sampling plan requires no statistical considerations.

The second provision is applied when sufficient certainty on the result of such verification on finished devices can be gained by a sampling plan established on a statistical basis. For this purpose existing standards on acceptance testing can be applied.

The third provision is addressed in Section 2.2 of Annex VI which states that:

"To the extent that for certain aspects the final testing according to Section 6.3 is not appropriate, adequate in-process testing, monitoring and control methods shall be established by the manufacturer with the approval of the notified body. The provision of Annex IV, Section 5, shall apply accordingly in relation to the above mentioned approved procedures."

Annex IV, Section 5, prescribes surveillance and approval of a manufacturer's quality system.

It is current state of the art that inspection and verification of the finished devices is complementary to process control and final testing performed by the manufacturer. Performance verification is generally performed by measurements on defined control materials or a defined panel of reference specimens (e.g. sera).

Valid conclusions can only be drawn from a limited number of units of the final product, if adequate in-process testing, monitoring and control procedures ensure the homogeneity of the final product batch and its components at the intermediate stage(s) of manufacture as well as the suitability of the process applied. Any sampling plan used for final testing of in vitro diagnostic medical devices is based on statistical considerations. This does not necessarily mean that a large number of units is sampled and tested. In many cases using very small sample sizes (sometimes equal to one unit) can be an acceptable approach, provided that an adequate level of conformity has been demonstrated by other appropriate means.

Following this last approach, this standard can also be used for establishing sampling procedures when annex III or IV or VII is applied.

1 Scope

This European Standard specifies sampling procedure requirements for acceptance testing of finished in vitro diagnostic medical devices, which require EC verification by a notified body.

Two different provisions are addressed:

a) verification by testing attributes and/or variables on a statistical basis;

b) verification by testing a homogeneous batch which has been defined by appropriate means of process validation and in-process control.

This standard specifies requirements and criteria for testing procedures to establish and verify the homogeneity of processes and products. This standard is also applicable for drawing up sampling plans for finished products according to the requirements laid down for manufacturers' product certification and production quality systems.

2 Normative references

This European Standard incorporates by dated or undated reference provisions from other publications. These normative references are cited at the appropriate places in the text and the publications are listed hereafter. For dated references, subsequent amendments to, or revisions of, any of these publications apply to this European Standard only when incorporated in it by amendment or revision. For undated references the latest edition of the publication referred to applies (including amendments).

ISO 2859-1, *Sampling procedures for inspection by attributes — Part 1: Sampling plans indexed by acceptable quality level (AQL) for lot-by-lot inspection.*

ISO 2859-2, *Sampling procedures for inspection by attributes — Part 2: Sampling plans indexed by limiting quality (LQ) for isolated lot inspection.*

ISO 2859-3, *Sampling procedures for inspection by attributes — Part 3: Skip-lot sampling procedures.*

ISO 3951, *Sampling procedures and charts for inspection by variables for percent nonconforming.*

3 Terms and definitions

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

3.1
acceptable quality level
AQL
quality level that for the purpose of sampling inspection of a continuous series of batches is the limit of a satisfactory process average

3.2
acceptance testing
sampling inspection
process of inspecting a sample of the units of product that make up a batch for the purpose of accepting or rejecting the entire batch, as prescribed in the associated pre-established sampling plan

3.3
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]

3.4
batch acceptance
procedure of establishing conformity of a batch with the device specifications

3.5
in vitro diagnostic medical device
IVD MD
any medical device which is a reagent, reagent product, calibrator, control material, kit, instrument, apparatus, equipment or system, whether used alone or in combination, intended by the manufacturer to be used in vitro for the examination of specimens, including blood and tissue donations, derived from the human body, solely or principally for the purpose of providing information concerning a physiological or pathological state, or concerning congenital abnormality, or to determine the safety and compatibility with potential recipients, or to monitor therapeutic measures

[Directive 98/79/EC]

NOTE 1 A specimen receptacle, whether vacuum-type or not, is considered to be an in vitro diagnostic medical device when it is specifically intended by its manufacturer for the primary containment and preservation of specimens derived from the human body for the purpose of in vitro diagnostic examination.

NOTE 2 Products for general laboratory use are not in vitro diagnostic medical devices unless such products, in view of their properties, are specifically intended by their manufacturer to be used for in vitro diagnostic examination.

3.6
inspection by attributes
inspection method whereby the unit of product is classified simply as conforming or nonconforming with respect to a given requirement or set of requirements

3.7
inspection by variables
inspection method whereby a specified quantitative property is measured in a sample of units of product, either components or finished devices, to establish statistically the acceptability of a batch

3.8
limiting quality
LQ
when a batch is considered in isolation, a quality level which for the purposes of sampling inspection is limited to a low probability of acceptance

[ISO 2859-1:1999]

3.9
sample
one or more units of product, either components or finished devices, drawn from a batch without regard to the quality of the units

3.10
sample size
number of units of product in the sample

3.11
sampling plan
plan that indicates the number of units of product, either components or finished devices, from each batch which is to be drawn for inspection and the associated criteria for determining the acceptability of the batch

NOTE A sampling plan either contains or refers to instructions for the sampling strategy.

3.12
sampling strategy
established method for obtaining an adequate sample

EXAMPLE Random selection, stratified, with stated frequency, rational sub-grouping.

3.13
validation
confirmation, through the provision of objective evidence, that the requirements for a specific intended use or application have been fulfilled

[EN ISO 9000:2000]

NOTE 1 Process validation means establishing by objective evidence that a process consistently produces a result or product meeting its predetermined specifications.

NOTE 2 Design validation means establishing by objective evidence that device specifications conform with user needs and intended use(s).

3.14
verification
confirmation, through the provision of objective evidence, that specified requirements have been fulfilled

[EN ISO 9000:2000]

4 Procedures

4.1 General

Sampling procedures used for batch acceptance testing shall be an integral part of the operational quality control strategy for any particular in vitro diagnostic medical device and shall take the nature of that product and possible consequences of nonconformity into account, i.e. ensure a high level of safety and performance according to the state of the art.

Batch acceptance shall be based on, either:

— verification by examination and testing of every unit of product (finished devices);

— statistical verification of a batch of finished devices;

— process control, complemented, where appropriate, by final testing of finished devices;

— an appropriate combination of such quality control measures.

NOTE The sampling procedure for verification and testing of every unit of product requires no statistical considerations and is therefore not elaborated in this standard.

Sampling procedures for batch acceptance, as a part of the operational quality control strategy, shall be properly validated.

Validation shall demonstrate amongst others that:

— the suitability of starting and manufacturing materials is defined by relevant characteristics;

— the variation of ingredients in terms of e.g. amount, concentration or activity lies within specified tolerance limits as shown by appropriate control of processes;

— product homogeneity within specified limits is ensured;

— the manufacturing process has been appropriately defined and is reproducible.

If the manufacturing process is changed to an extent that would affect the specified performances (i.e. essential changes) a supplemental validation shall be performed.

When deviations from defined procedures can affect product homogeneity or significant discrepancies are observed in the course of complaint handling and corrective action, consideration shall be given to tightening the sampling plan.

Whenever sufficient experience on the quality of a product, component or material is obtained, initial sampling procedures may be revised comprising smaller sample sizes or, where appropriate, by expanding the testing intervals. Such a revision shall be justified by demonstrating satisfactory results on a sufficiently large number of (cumulative) samples taken from previous batches, provided that neither the product design nor the manufacturing process(es) and conditions have been essentially modified.

Any number of finished devices required for final testing by manufacturer and notified body shall be sampled in accordance with an established sampling strategy.

4.2 Statistical verification

The manufacturer shall present the manufactured product in the form of homogeneous batches which are subjected to acceptance testing.

The required sampling plan(s) shall be taken from relevant standards such as the ISO 2859 series or ISO 3951. The probability of acceptance and the acceptable quality (either specified as an acceptable quality level or limiting quality according to such standards) shall be specified by the manufacturer.

One or more random samples, as necessary, shall be taken from each batch. The units of product that make up the sample(s) shall be subjected to the appropriate type of inspection, the result of which determines whether the entire batch is accepted or rejected.

If there is any need to adopt a sampling plan which deviates from those given in relevant standards, the following information shall be available and appropriately documented:

— calculating basis: source and underlying distribution;

— resulting operating characteristic presented either as a table or a graph;

— resulting sampling plan: sampling strategy, sample size(s), batch acceptance criteria and the interval of batch sizes for which the plan will be applicable.

4.3 Final testing based on process control

4.3.1 General

When establishing a sampling procedure, the following aspects shall be taken into consideration, where appropriate:

— natural process stability / variability;

— product homogeneity;

NOTE Some processes can be expected to yield homogeneous products e.g. due to fluidity (gases, liquids) or adequate prior mixing operations. Any single aliquot of a suitable size is then considered to be an adequate sample.

— process robustness, i.e. the capability to withstand unintended variation in manufacturing conditions;

— identification of critical process steps and relevant properties of materials, which can influence quality characteristics of finished products;

— nature of the inspection type (destructive or not);

— number and kind of attributes or quantitative characteristics to be tested;

— sampling strategy;

— history of quality of the process and/or (its) product(s);

— required quality level;

— batch size.

The sampling procedures shall be part of a quality control plan for a particular IVD MD. This plan shall be based on process control measures, where appropriate complemented by final testing.

When establishing a sampling procedure for a particular control measure, it shall be taken into account that the confidence in the entire operational quality control strategy is built upon the combined confidence associated with its individual quality measures.

The number of measurements to be made, taking the intended inspection method and sampling strategy into account and thereby the sample size, shall therefore depend on the confidence required for that particular control measure, as a part of the quality control strategy.

4.3.2 Statistical process control (SPC)

Statistical process control is applicable to variables or attributes. The natural variation of the process defines control limits for those process properties. The result of consecutive samples with typical sample sizes of 2 to 5 are checked against these control limits. As long as the mean, range or other appropriate parameters are found within these statistically derived control limits the process will be qualified as "under statistical control".

If these control limits are established within the limits of the quality specification(s) and the process is correctly centred, the process may be called "capable", provided that appropriate process capability assessment techniques are used.

Whenever a process is "under statistical control" and process capability has been established, then the associated quality characteristics shall be considered appropriately controlled.

NOTE For example, mass can be used as an associated quality characteristic for volume.

4.3.3 100 %-verification

100 %-verification procedures shall ensure that:

— one or more properties of a product (or component) which are relevant for its quality are verified on each item during the manufacturing process;

— the failure rate, as specified e.g. as a maximum allowable percentage of nonconforming items, is not exceeded;

— items conforming to specification(s) are strictly separated from nonconforming items.

Whenever these requirements are met, the associated product quality characteristics shall be considered appropriately controlled.

NOTE 100 %-verification is preferably performed by automated testing.

4.3.4 Other types of process control

For process controls other than statistical process control and 100 %-verification, the relevant quality characteristics shall be considered adequately controlled, if the results of such control measures are found to lie within established tolerance limits.

4.3.5 Final testing

If the relevant quality characteristics are considered appropriately controlled, then there is no further need to verify these characteristics on a sample of the components and/or finished devices.

If a finished device is composed of components, each of which has been properly controlled during manufacture, it shall be sufficient to check, in addition to the process controls, the identity or, in certain cases, the proper performance of the finished device.

NOTE Such a performance verification on finished devices is generally performed by evaluating the results obtained with measurements on defined control materials and/or defined panel(s) of reference samples (e.g. sera).

Sampling procedures prescribing a small sample size or even only one unit of product to be taken from each batch of finished devices may be applied only if the product/process specifications at intermediate stages of manufacture are met.

The concept of only one representative unit of product shall be deemed acceptable, if:

— product homogeneity is obvious (e.g. in case of most liquid products derived by aliquoting from a homogeneous bulk solution);

— product homogeneity can be demonstrated by validation results combined with strict adherence to defined materials and process specifications. This includes in-process controls and testing at intermediate stages of manufacture, to be performed on a random basis or periodically or targeted at the most relevant stages of the process (e.g. beginning and end).

Annex A
(informative)

General notes

Given the scope of this standard, it is important to note that:

— It is considered current state of the art to rely on product quality assurance based on a controlled design and development process resulting in a validated design and validated manufacturing process, including adequately qualified and controlled resources as well as starting materials, where appropriate complemented with a specified degree of performance verification on finished devices.

— In combination with an approved quality system, e.g. based on EN 46001, this generally provides a sufficient basis for allowing placing of products on the market and putting them into service, where appropriate after approval by a notified body.

In such a situation, manufacturers therefore predominantly rely on the effective implementation of their quality system and an operational quality control strategy.

The situation where the manufacturer makes use of the EC verification procedure as described in Annex VI of Directive 98/79/EC, i.e. the provision for batch release based on statistical verification by a notified body (Annex VI, section 6), is fundamentally different. In this situation, in principle, no other means are made available to assess conformity with product requirements than offering a particular batch of finished devices for acceptance testing by the notified body.

Such a procedure therefore requires statistical control of products based on inspection by attributes and/or variables, entailing sampling schemes with operational properties which ensure a high level of safety and performance according to the state of the art.

Annex VI (section 2.2) of Directive 98/79/EC recognises that, to the extent that batch acceptance based on statistical verification is, for certain aspects, not considered appropriate (either by the manufacturer or the notified body), this procedure is to be complemented or replaced by other means of batch conformity assessment procedures.

This in effect resembles, or may become identical to, the situation where the manufacturer makes no use of the provision for statistical verification. It should therefore involve adequate (process) control measures and product monitoring to be established by the manufacturer with the approval of the notified body complemented with the approval and surveillance of the manufacturer's quality system by the notified body.

NOTE An example of a product quality which can be difficult or even impossible to verify by testing the finished product(s), but that can be demonstrated by process control and validation of processes, is sterility.

Batch acceptance by a notified body based on acceptance testing (statistical verification) is not to be confused with the requirement for batch release by a notified body for IVD MDs listed in annex II. The latter is based on approval and surveillance of the manufacturer's quality system and evaluation of batch records by a notified body. This may involve the making available of (samples of) batches of finished devices to the notified body, in accordance with pre-agreed conditions and modalities. For this purpose, the sample-size is not to be based on a statistical rationale but depends on the objectives of the notified body, for which a very limited number of units of product may prove to be sufficient.

Annex ZA
(informative)

Clauses of this European Standard addressing requirements 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 requirements of Directive 98/79/EC.

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

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

All clauses of this standard support specifically the requirements included in General Essential Requirement A.3 of Directive 98/79/EC.

Bibliography

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

[2] EN ISO 9000:2000, *Quality management systems – Fundamentals and vocabulary (ISO 9000:2000).*

[3] Directive 98/79/EC of the European Parliament and the Council of 27 October 1998 on in vitro diagnostic medical devices, OJ, 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