SLOVENSKI STANDARD

SIST EN 13975:2003

01-september-2003

Postopki vzorļenja, ki se uporabljajo pri preskusih sprejema in vitro diagnostiļnih pripomoļkov ï Statistiļni vidiki

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

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

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

Ta slovenski standard je istoveten z: **EN 13975:2003**

ICS:

11.100.10	Diagnostiļni preskusni sistemi in vitro	In vitro diagnostic test systems

SIST EN 13975:2003 **en**

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.

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Ref. No. EN 13975:2003 E

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of an identical text or by endorsement, at the latest by September 2003, and conflicting national standards shall be withdrawn at the latest by September 2003.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;