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Medicinske rokavice za enkratno uporabo - 3. del: Zahteve in preskušanje za biološko ovrednotenje

Medical gloves for single use - Part 3: Requirements and testing for biological evaluation

Medizinische Handschuhe zum einmaligen Gebrauch - Teil 3: Anforderungen und Prüfung für die biologische Bewertung

Gants médicaux non réutilisables - Partie 3 : Exigences et essais pour évaluation biologique

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COMITÉ EUROPÉEN DE NORMALISATION
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Foreword

This document (EN 455-3:2015) has been prepared by Technical Committee CEN/TC 205 “Non-active 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of an identical text or by endorsement, at the latest by October 2015 and conflicting national standards shall be withdrawn at the latest by October 2015.

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 455-3:2006.

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.

With respect to EN 455-3:2006 the following changes are:

a) standard was specified to relevant parts of EN ISO 10993 for Biological evaluation of medical devices;

b) normative references revised;

c) EN 980 was replaced by EN ISO 15223-1;

d) subclause 4.2 "chemicals" was specified;

e) subclause 4.4 specified as "powder-free gloves";

f) level "As Low As Reasonably Practicable" (ALARP) removed in the whole standard;

g) subclause 4.6 "labelling" specified;

h) symbol for products containing natural latex (Figure 1) removed;

i) the references in Annex B revised;

j) Correspondence between this European Standard and Directive 89/686/EEC on Personal Protective Equipment made (see Annex ZA).

EN 455 consists of the following parts under the general title "*Medical gloves for single use*":

— *Part 1: Requirements and testing for freedom from holes;*

— *Part 2: Requirements and testing for physical properties;*

— *Part 3: Requirements and testing for biological evaluation;*

— *Part 4: Requirements and testing for shelf life determination.*

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.

Introduction

Adverse reactions to proteins in latex products have been reported over several years in variable rates of prevalence. Additionally, adverse reactions due to chemicals, lubricants, sterilization residues, pyrogens or other residues are described in the scientific literature. Adverse reactions are most often reported due to gloves made from natural rubber latex, but some of the reactions can also be seen due to gloves made from synthetic polymers.

EN ISO 10993 specifies requirements and test methods for biological evaluation of medical devices. However it does not specifically address adverse reactions that can result from the use of medical gloves (e.g, immediate type allergies). These adverse reactions occur to specific allergens that can be present in gloves. Several factors contribute to the risk of reaction:

a) the duration and frequency of skin contact with gloves;

b) the exposure to the allergens through direct contact to mucosa and skin (especially when not intact) and by inhalation of particles;

c) the occlusive nature of the glove/skin interaction during glove use.

This part of EN 455 gives requirements and test methods for evaluation of the biological safety of medical gloves as part of a risk management process, in accordance with EN ISO 10993.

1 Scope

This part of EN 455 specifies requirements for the evaluation of biological safety for medical gloves for single use. It gives requirements for labelling and the disclosure of information relevant to the test methods used.

2 Normative references

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

EN 1041:2008+A1:2013, *Information supplied by the manufacturer of medical devices*

EN ISO 10993-1:2009, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process (ISO 10993-1:2009)*

EN ISO 10993-5:2009, *Biological evaluation of medical devices - Part 5: Tests for in vitro cytotoxicity (ISO 10993-5:2009)*

EN ISO 10993-10:2013, *Biological evaluation of medical devices -Part 10: Tests for irritation and skin sensitization (ISO 10993-10:2010)*

EN ISO 14971:2012, *Medical devices - Application of risk management to medical devices (ISO 14971:2007, Corrected version 2007-10-01)*

EN ISO 15223-1:2012, *Medical devices - Symbols to be used with medical device labels, labelling and information to be supplied - Part 1: General requirements (ISO 15223-1:2012)*

EN ISO 21171:2006, *Medical gloves - Determination of removable surface powder (ISO 21171:2006)*

European Pharmacopoeia, General chapter 2.6.14 Bacterial Endotoxins: publisher EDQM - Council of Europe; 7 allée Kastner, CS 30026, F-67081 Strasbourg; France http://www.edqm.eu/

3 Terms and definitions

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

3.1
chemicals
substances added or formed during any step of the manufacturing process or in storage which may be available in the final product

Note 1 to entry: These can include lubricants, chemical coatings and sterilizing agents. Several chemical ingredients are commonly used during processing of gloves, some of them are known to cause type IV allergic reactions. The type and amount of residual chemicals added and finally present are variable.

3.2
endotoxins
lipo-polysaccharides originating from the outer cell-membrane of Gram-negative bacteria

Note 1 to entry: Endotoxins are one type of pyrogen. Sources of endotoxins can include bacterial contamination of the raw materials, especially the process water used during manufacturing and manual handling of the gloves.

3.3
powder
all water insoluble material on the surface of a glove that is removed by washing under the conditions of the test

[SOURCE: EN ISO 21171:2006, 3.1]

Note 1 to entry: This includes both deliberately added powder and other processing aids or materials accidentally present which may be readily detached from the surface of the glove. For the purpose of this European Standard any glove containing 2 mg or less powder is a powder-free glove and more than 2 mg is a powdered glove (for requirement see 4.4.).

3.4
process limit
highest value likely to be encountered for a validated manufacturing process

3.5
proteins, allergenic
proteins capable of causing a type I allergic reaction

3.6
proteins, leachable
aqueous proteins and peptides extractable from the final product

3.7
pyrogens
substances creating fever in rabbits which can be related to fever and other adverse reactions in humans

4 Requirements

4.1 General

EN ISO 10993-1:2009 describes the general principles governing the biological evaluation of medical devices and shall be used to select the appropriate tests as described in other parts of the series. Based on EN ISO 10993-1:2009 medical gloves are classified as limited contact duration surface devices and require compliance to EN ISO 10993-5:2009 and EN ISO 10993-10:2013.

The classification of medical gloves according to EN ISO 10993-1:2009 should not be confused with the definitions provided in the medical device directives for these products.

A risk management process in accordance with EN ISO 14971:2012 shall be established.

4.2 Chemicals

Gloves shall not be dressed with talcum powder (magnesium silicate).

The manufacturer shall disclose, upon request, a list of chemical ingredients either added during manufacturing or already known to be present in the product such as accelerators, antioxidants and biocides that are known to cause adverse health effects based on current data.

Upon request the manufacturer shall provide evidence of the steps taken to reduce the risk to the end-user of exposure to chemicals used in the manufacturing process which, based on current data, are known to cause adverse health effects.

Manufacturers may only declare the absence of a substance if the substance is not used in any part of the manufacturing process. No compounds shall be used in the manufacture of the product that is known to form a substance that is subject of such a declaration.

4.3 Endotoxins

The manufacturer shall monitor the endotoxin contamination of sterile gloves using the test method specified in 5.1 if the gloves are labelled with 'low endotoxin content'. For such labelled gloves the endotoxin content shall not exceed the limit of 20 endotoxin units per pair of gloves.

4.4 Powder-free gloves

For powder-free gloves the total quantity of powder residues determined according to the test method under 5.2 shall not exceed 2 mg per glove. Any glove containing more than 2 mg powder is a powdered glove.

4.5 Proteins, leachable

The manufacturer shall strive to minimize the leachable protein level.

The manufacturer shall monitor the process limit of leachable protein in the finished gloves containing natural rubber latex by the method specified in 5.3 and described in Annex A. The documentation of these results shall be retained. The results of the test and applied test method shall be made available on request.

NOTE Proteins, allergenic: This European Standard specifies a method measuring a broad approximation for the allergen content, e.g. leachable proteins. There is no direct correlation between leachable proteins and allergen content. Quantitative methods to measure allergenic proteins are, described in Annex B.

4.6 Labelling

In addition to the labelling specified in EN 1041:2008+A1:2013 and the relevant symbols given in EN ISO 15223-1:2012, the following requirements apply:

a) medical gloves containing natural rubber latex shall be labelled on the packaging of at least the smallest packaging unit with the EN ISO 15223-1:2012 symbol for latex (reference number 5.4.5).

The labelling shall include the following or equivalent warning statement together with the symbol (Product) contains natural rubber latex which may cause allergic reactions, including anaphylactic responses;

b) the labelling shall include a prominent indication of whether the glove is powdered or powder-free;

c) sterile powdered gloves shall be labelled with the following or equivalent: 'CAUTION: Surface powder shall be removed aseptically prior to undertaking operative procedures in order to minimize the risk of adverse tissue reactions;

NOTE 1 This caution statement can be given on the inner wrapping.

d) for any medical glove containing natural rubber latex the product labelling shall not include:

   — any term suggesting relative safety, such as low allergenicity, hypoallergenicity or low protein;

   — any unjustified indication of the presence of allergens;

e) if the manufacturer labels the gloves with the protein content, the process limit, measured as specified in 5.3 shall be given.

NOTE 2 This does not allow a protein labelling claim below 50 µg/g. Lower claims are not considered to be reliable given the expected process variation in manufacture and inter-laboratory testing.

5 Test methods

5.1 Endotoxins

Except where non-removable interferences in the Limulus Amoebocyte Lysate (LAL) procedures are present, selection, validation and use of technique shall be as described in the European Pharmacopoeia, Monograph 2.6.14, "Bacterial Endotoxins". The results shall be expressed in endotoxin units (E.U.) per pair of gloves.

NOTE 1 Where non-removable interferences in the LAL procedure are present, the bacterial endotoxin level cannot be accurately measured.

The minimum number of pairs of gloves recommended to be tested in relation to the number of items in the batch are two pairs of gloves for a batch size under thirty, three pairs of gloves for a batch size thirty to one hundred, and 3 % of a batch above size one hundred, up to a maximum of ten pairs of gloves per batch.

The outside surface of a pair of gloves is extracted with 40 ml of endotoxin-free water (Water LAL, European Pharmacopoeia, for not less than 40 min and not more than 60 min at a temperature between 37 °C and 40 °C in a way to ensure that all surfaces come into contact with the extraction medium. The extract is centrifuged, if necessary, for 15 min at 2 000 *g* to remove particles after which the liquid component is decanted and tested for endotoxin immediately afterwards.

NOTE 2 Other methods for the analysis of endotoxins exist and these can be used for routine quality control purposes provided they have been validated and a correlation established against the reference method specified in this European Standard.

5.2 Powder

The test method for the determination of powder residues described in EN ISO 21171:2006, Clauses 7 and 9 shall be used.

5.3 Proteins, leachable

The test method for the analytical determination of leachable protein shall be the modified Lowry method given in Annex A or a suitably validated method which has been correlated against the modified Lowry method.

NOTE 1 An example of a validated analytical method is given in Annex C.

NOTE 2 The immunological methods in Annex B are currently not validated against the modified Lowry method but may be correlated to clinical response data.

6 Test report

The test report shall include at least the following information:

— reference to this part of EN 455;

— the type of gloves and the manufacturing batch code;

— the name and address of the manufacturer or distributor and of the test laboratory, if different;

— the date of the testing performed;

— the description of the test method applied;

— the test results.

Annex A
(normative)

Method for the determination of aqueous extractable proteins in natural rubber gloves using the modified Lowry assay

A.1 Scope

This method is for the determination of the amount of aqueous extractable proteins in gloves for medical use made from natural rubber (NR). It has been validated during inter-laboratory tests. The lower quantification limit is approximately 10 µg protein per g of glove (i.e. 2 µg protein per ml of extract) depending on the glove weight.

Chemicals such as surfactants, accelerators and antioxidants added to the NR latex during the manufacture of the gloves can interfere with the colour development during the determination, some materials may reduce colour development while others can increase it. If the test method yields results that appear erroneous due to interferants, then any validated amino acid analysis method can be used (as an example see the method given in Annex C).

Persons using this method should be familiar with normal laboratory practice.

NOTE This method does not purport to address all of the safety problems, if any, associated with its use. It is the responsibility of the user to establish appropriate safety and health practices and to ensure compliance with any national regulatory conditions.

A.2 Principle

Water soluble proteins are extracted into a buffer solution and then precipitated with acids in the presence of sodium deoxycholate to concentrate them and to separate them from water soluble substances which may interfere with the determination. The precipitated proteins are redissolved in alkali and quantified colorimetrically by a modified Lowry method. The assay is based on the reaction of proteins with copper and Folin reagent in an alkaline medium to give a characteristic blue colour. Spectrophotometric measurements are performed at a fixed wavelength in the range 600 nm to 750 nm.

A.3 Reagents

A.3.1 General

Wherever water is called for, double distilled water or water of equivalent quality should be used. All other reagents should be of analytical quality.

A.3.2 Extractant

A.3.2.1 **N-tris-[Hydroxymethyl]-methyl-2-aminoethanesulfonic acid (TES)**, hemisodium salt.

A.3.2.2 **Extraction buffer**, 0,1 M, prepared by dissolving 24 g TES (A.3.2.1) in 1 l water. Any equivalent buffering system can be used provided the solution has sufficient buffering capacity to hold a pH of 7,4 ± 0,2 in the glove extracts.

Prepare a sufficient quantity for the glove extraction (A.6.2), the preparation of the protein standard solutions (A.6.3.2) and the blank.