BS EN ISO 9394:2012

BSI Standards Publication

Ophthalmic optics — Contact lenses and contact lens care products — Determination of biocompatibility by ocular study with rabbit eyes

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National foreword

This British Standard is the UK implementation of EN ISO 9394:2012. It supersedes BS EN ISO 9394:1998, which is withdrawn.

The UK participation in its preparation was entrusted to Technical Committee CH/172/9, Contact lenses and contact lens care products.

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

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Published by BSI Standards Limited 2012.

ISBN 978 0 580 74794 6

ICS 11.040.70

Compliance with a British Standard cannot confer immunity from legal obligations.

This British Standard was published under the authority of the Standards Policy and Strategy Committee on 31 October 2012.

Amendments issued since publication

Date	Text affected

EUROPEAN STANDARD

NORME EUROPÉENNE

EUROPÄISCHE NORM

EN ISO 9394

October 2012

ICS 11.040.70

Supersedes EN ISO 9394:1998

English Version

Ophthalmic optics - Contact lenses and contact lens care products - Determination of biocompatibility by ocular study with rabbit eyes (ISO 9394:2012)

Optique ophtalmique - Lentilles de contact et produits d'entretien pour lentilles de contact - Détermination de la biocompatibilité par évaluation de la tolérance oculaire chez le lapin (ISO 9394:2012)

Augenoptik - Kontaktlinsen und Kontaktlinsenpflegemittel - Bestimmung der Biokompatibilität durch Erprobung am Kaninchenauge (ISO 9394:2012)

This European Standard was approved by CEN on 30 September 2012.

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Ref. No. EN ISO 9394:2012: E

Foreword

This document (EN ISO 9394:2012) has been prepared by Technical Committee ISO/TC 172 "Optics and photonics" in collaboration with Technical Committee CEN/TC 170 “Ophthalmic optics” 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of an identical text or by endorsement, at the latest by April 2013, and conflicting national standards shall be withdrawn at the latest by April 2013.

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Endorsement notice

The text of ISO 9394:2012 has been approved by CEN as a EN ISO 9394:2012 without any modification.

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Foreword

ISO (the International Organization for Standardization) is a worldwide federation of national standards bodies (ISO member bodies). The work of preparing International Standards is normally carried out through ISO technical committees. Each member body interested in a subject for which a technical committee has been established has the right to be represented on that committee. International organizations, governmental and non-governmental, in liaison with ISO, also take part in the work. ISO collaborates closely with the International Electrotechnical Commission (IEC) on all matters of electrotechnical standardization.

International Standards are drafted in accordance with the rules given in the ISO/IEC Directives, Part 2.

The main task of technical committees is to prepare International Standards. Draft International Standards adopted by the technical committees are circulated to the member bodies for voting. Publication as an International Standard requires approval by at least 75 % of the member bodies casting a vote.

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ISO 9394 was prepared by Technical Committee ISO/TC 172, *Optics and photonics*, Subcommittee SC 7, *Ophthalmic optics and instruments*.

This third edition cancels and replaces the second edition (ISO 9394:1998), which has been technically revised.

Introduction

The ocular tissue of the rabbit is traditionally used to evaluate the irritant properties of materials which come in contact with ocular tissue.

The use of the device under evaluation is governed by the nature, degree, duration, frequency and conditions of exposure of humans to the device in normal intended use.

It is incumbent upon the investigator to conduct such evaluations using good scientific laboratory practices, complying with regulations related to animal welfare and the general principles set forth in the normative references.

ISO 10993-1 is the basic horizontal International Standard for biological evaluation of medical devices, and serves as a framework for planning biological evaluation tests.

ISO 10993-10 assesses possible contact hazards from device-released chemicals that may produce skin and mucosal irritation, eye irritation and delayed contact sensitization.

Usage tests for specific devices are defined in vertical standards. This International Standard describes one of several specific usage tests for contact lenses and contact lens care products.

The existence of this International Standard does not imply that rabbit-eye testing is a requirement in the determination of biocompatibility of contact lenses and contact lens care products, nor that this test is sufficient by itself to determine the biocompatibility of contact lenses and contact lens care products. Taking into consideration animal welfare requirements (ISO 10993-2), it is recommended that this *in vivo* test be carried out after obtaining data of *in vitro* toxicological testing such as that described in ISO 10993-5.

Care should be taken when extrapolating the test results to the human eye.

INTERNATIONAL STANDARD **ISO 9394:2012(E)**

Ophthalmic optics — Contact lenses and contact lens care products — Determination of biocompatibility by ocular study with rabbit eyes

1 Scope

This International Standard specifies an *in vivo* method of test to assess the ocular safety of both novel contact lens material and contact lens care products. The test assesses the degree of irritation to the ocular tissue produced by the device under test. The test method is described in application to rabbit eyes.

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 10993-1, *Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process*

ISO 10993-2, *Biological evaluation of medical devices — Part 2: Animal welfare requirements*

ISO 10993-10, *Biological evaluation of medical devices — Part 10: Tests for irritation and skin sensitization*

ISO 18369-1, *Ophthalmic optics — Contact lenses — Part 1: Vocabulary, classification system and recommendations for labelling specifications*

ISO/IEC 17025, *General requirements for the competence of testing and calibration laboratories*

OECD 1997, *OECD Principles of Good Laboratory Practice, No.1*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 18369-1 apply.

4 General requirements

The general principles for biological evaluation and categorization of medical devices given in ISO 10993-1 shall apply. The study shall be performed in accordance with ISO/IEC 17025 and Good Laboratory Practice (GLP) (OECD, Principles of Good Laboratory Practice, No.1).

Tests for irritation and sensitization of contact lenses and contact lens care products shall be carried out in accordance with ISO 10993-10.

The assessment of the results shall be carried out by appropriately experienced and competent personnel.

5 Animals and husbandry

5.1 New Zealand white strain rabbits (male, female or mixed sexes) or equivalent albino rabbits shall be used to test each type of contact lens or lens care product. They shall be healthy young adults from a single strain

from a single recognized source weighing > 2,5 kg. They shall have eyes free from clinically significant ocular irritation or corneal retention of fluorescein stain.

A minimum number of three rabbits shall be used, however a number of six is recommended to ensure an acceptable level of precision of the test results. If less than six rabbits are used, then the quantity shall be justified.

If control articles are included in the evaluation, use the contra-lateral eye or an additional group of animals with the same number of animals chosen as before for each control article. For contact lens care products, the control group should use the same type of contact lens which has not been treated with the test product.

Positive controls shall not be used.

NOTE In this context, “control article“ should be interpreted as being a device with defined safety and performance characteristics.

5.2 The animal welfare requirements set out in ISO 10993-2 shall be met.

5.3 The animals shall be housed individually and have free access to commercially pelted rabbit feed and tap water. Group housing is not feasible in this test since any lens found expulsed from the eye shall be matched to the specific rabbit which wore the lens and re-inserted into the same eye.

5.4 Each animal shall be identified by one of the following:

a) a numbered ear tag;

b) a tattoo;

c) a microchip; or

d) a permanent ink marking.

The animals shall be acclimatized to the laboratory conditions for at least five days prior to testing.

5.5 The nictitating membrane should not be removed from the rabbits’ eyes, and the eyelids should not be sutured during lens wear. Any deviations shall be justified and documented in the test report.

NOTE The albino rabbit eye is free of pigment, easily examined and has historically been used for ocular irritation studies.

All appropriate regulatory requirements governing the care and use of animals shall be followed.

5.6 During daily treatment, the rabbits shall be minimally restrained.

6 Reagents/materials

6.1 **Sodium fluorescein**, as specified by an appropriate pharmacopoeia.

NOTE Attention should be made to the degree of staining and the concentration of fluorescein administered to the eye (e.g. 3 µl of 1 % fluorescein in saline solution).

6.2 **Contact lens care products**, as recommended by the manufacturers.

6.3 **Contact lenses**, as recommended by the manufacturer.

7 Apparatus

7.1 **Slit lamp microscope**, with appropriate filters.

7.2 **Magnifying glass**, of minimum magnification 6×.

7.3 **Balance or weighing machine**, capable of weighing up to 5 kg to an accuracy of 100 g.

8 Test specimens

8.1 Lens parameters

Contact lenses shall be sufficiently thick to represent either

a) reasonable human use extremes; or

b) the extreme of the manufacturer's product line.

The contact lens selected shall produce a good fit to a rabbit eye.

NOTE This is necessary to minimize physical irritation and expulsion. In the case where this thickness does not allow a good fit of the contact lens, a contact lens of the greatest thickness which allows a good fit should be used.

Contact lens parameters shall be documented in the final report.

8.2 Preparation and storage

If contact lens care products are to be used in the evaluation, lenses shall be prepared, cleaned, disinfected, stored and rinsed according to the lens manufacturer's instructions using contact lens care products (6.2). If a lens falls out during the daily treatment period, it shall be rinsed with rinsing solution (6.2) and re-inserted into the rabbit's eye from which it has fallen out.

NOTE 1 Sufficient additional lenses should be treated using at least one complete daily lens care treatment to replace any lenses that are damaged or lost during the lens-wear day.

NOTE 2 Hydrogel lenses which cannot be immediately reinserted because of drying should be swapped for a similar lens which has been treated in line with the manufacturer's recommendations. Hydrogel lenses which have dried out may be re-used once cleaned and/or rehydrated.

Before insertion, contact lenses should be checked for particulate matter, physical damage and, during hydrogel lens use, for lens inversion. While inserting contact lenses, rabbits shall be observed for reactions different to that during the insertion of a control lens. Such reactions shall be recorded.

Contact lenses shall not be intermixed between rabbits in the same treatment group.

If applicable, lens storage cases shall not be intermixed between treatment groups.

For evaluation of contact lens care products, for example multipurpose solutions, testing with representative conventional and silicone hydrogel lenses should be conducted with the lens care product. The choice of lenses should be justified.

9 Test procedure

9.1 Preliminary examination of animals

9.1.1 The preliminary examination may not be made longer than 24 h before commencement of the test.

9.1.2 Using the balance (7.3), weigh the rabbits and record the mass.

9.1.3 Visually examine both eyes of each rabbit using the slit lamp (7.1) and fluorescein stain (6.1), and record the state of the eyes using the McDonald-Shadduck scoring system (see Annex A).

If either eye shows any abnormality, then replace the rabbit.

9.2 Insertion and removal of test lens

9.2.1 Treat the test lens in accordance with 8.2.

9.2.2 Insert the test lens in one eye of the rabbit; the eye should be free from fluorescein at the time of lens insertion. The test lens may be inserted in either eye, although it is recommended that within a test laboratory all testing be carried out on the same side. The contra-lateral eye serves as either a treated or an untreated control.

NOTE In the case of hydrogel lenses, the lid may be loosely taped near the outer canthus to prevent expulsion of the lens.

9.2.3 On days 1 to 21, after 7 h to 8 h, remove the test lens from the rabbit's eye. After removal, lenses shall be cared for as described in 8.2.

NOTE Designate the first day of lens wear as day 1.

9.2.4 If, during the course of the day's wearing, a lens requires reinsertion or replacement, this fact shall be recorded. It is recommended that the presence of the lens in the rabbit's eye is checked regularly, e.g. hourly.

NOTE An appropriate contact lens rewetting solution can be used to hydrate the contact lens and aid in retention of the contact lens during lens wear. The use of such a solution shall be recorded.

9.2.5 When the contact lens rewetting solution is the test article, the solution shall be applied during lens wear as defined in the test protocol.

9.2.6 Whenever relevant, record any change in the appearance of the contact lens.

9.2.7 Repeat 9.2.1 to 9.2.6 on a daily basis.

9.2.8 On day 22, after 4 h to 8 h, remove the test lens from the rabbit's eye.

NOTE The lens may be retained for further examination by the manufacturer.

9.3 Examination of the rabbit's eye

9.3.1 On days 1 to 7, 9 to 14 and 16 to 21, just prior to lens removal, visually examine both eyes of each rabbit and record the state of the eyes using the Draize scoring system (see Annex B).

Additional visual examinations of the eyes may be conducted, e.g. twice daily, so that if a reaction is found, an early endpoint can be instituted. It is recommended to also record the behaviour of the rabbits. Scratching or pawing at the lens would be an early sign that it is irritant.

9.3.2 On days 8, 15 and 22 after lens removal, visually examine both eyes of each rabbit using the slit lamp (7.1) and fluorescein stain (6.1) and record the state of the eyes using the McDonald-Shadduck scoring system (see Annex A).

NOTE Specific days for interim slit lamp examinations may be changed to accommodate the scheduling of the study activities, but slit lamp examinations should be conducted at 7 days ± 1 day intervals.

9.4 Weighing of animals

On day 22, using the balance (7.3), weigh the rabbits and record the mass.

9.5 Histological examination

9.5.1 On day 22, after the lens has been removed and the clinical examination has been completed, the animal should be humanely killed.

9.5.2 Excise the eyes and adnexa and preserve in a suitable fixation solution (e.g.10 % neutral buffered formalin, Zenker's acetic fixative or Davidson's solution).

9.5.3 Embed the eye and adnexa in paraffin wax.

9.5.4 Section the cornea, conjunctivae, iris and lens of each eye and stain for microscopic evaluation.

Evaluation of the rabbit's eyes and examination of histological sections shall be conducted by appropriately experienced and competent personnel.

9.5.5 Examine the histological sections and record the findings.

9.6 Corneal metabolism

If appropriate, determine effects on corneal metabolism using appropriate chemical or physical methods, taking into account the current state of the art.

NOTE If corneal metabolism is to be evaluated, data from a minimum of three rabbits should be provided for each test and control group.

10 Assessment of results

10.1 The overall assessment of the test results shall be carried out by appropriately experienced and competent personnel, taking into consideration all information in the test report.

10.2 If the appropriately experienced and competent personnel considers the results to be either inconclusive or invalid, consideration shall be given to repeating the test.

10.3 The results of the assessment shall be recorded in the test report.

11 Test report

The study report shall include at least the following information:

a) name and address of the testing facility;

b) name of the person(s) who conducted the test;

c) statement of compliance to appropriate good laboratory practices;

d) name and complete description of test/control article(s);

e) description of test animal (species, source, age, sex, body weight and number of animals);

f) justifications and descriptions of test method;

g) test results including statistical methods, if applied:

   — body mass;

   — clinical observations;

- — lens retention (where applicable);
- — macroscopic observations;
- — microscopic observations;
- — detailed description of all histopathological findings;
- — corneal metabolism (if applicable);
- — any other relevant data necessary for assessment of test results;

h) assessment of results;

i) study summary and conclusion.

Annex A
(normative)

McDonald-Shadduck score system — Slit lamp

A.1 Conjunctival congestion

0 = Normal. May appear blanched to reddish pink without perilimbal injection (except at 12:00 and 6:00 o'clock positions) with vessels of the palpebral and bulbar conjunctiva easily observed.

+1 = A flushed, reddish colour predominantly confined to the palpebral conjunctiva with some perilimbal injection but primarily confined to the lower and upper parts of the eye from the 4:00 to 7:00 and 11:00 to 1:00 o'clock positions.

+2 = Bright red colour of the palpebral conjunctiva with accompanying perilimbal injection covering at least 75 % of the circumference of the perilimbal region.

+3 = Dark, beefy red colour with congestion of both the bulbar and the palpebral conjunctiva along with pronounced perilimbal injection and the presence of petechia on the conjunctiva. The petechia generally predominate along the nictating membrane.

A.2 Conjunctival swelling

0 = Normal or no swelling of the conjunctival tissue.

+1 = Swelling above normal without eversion of the lids (can be easily ascertained by noting that the upper and lower eyelids are positioned as in the normal eye). Swelling generally starts in the lower cul-de-sac near the inner canthus, which needs slit-lamp examination.

+2 = Swelling with misalignment of the normal approximation of the lower and upper eyelids; primarily confined to the upper eyelid so that in the initial stages the misapproximation of the eyelids begins by partial eversion of the upper eyelid. In this stage, swelling is confined generally to the upper eyelid, although it exists in the lower cul-de-sac (observed best with the slit-lamp).

+3 = Definite swelling with partial eversion of the upper and lower eyelids essentially equivalent. This can be easily ascertained by looking at the animal head-on and noticing the positioning of the eyelids; if the eye margins do not meet, eversion has occurred.

+4 = Eversion of the upper eyelid is pronounced with less pronounced eversion of the lower eyelid. It is difficult to retract the lids and observe the perilimbal region.

A.3 Conjunctival discharge

Discharge is defined as a whitish, grey precipitate, which should not be confused with the small amount of clear, inspissated, mucoid material that can be formed in the medial canthus of a substantial number of rabbit eyes.

0 = Normal. No discharge.

+1 = Discharge above normal and present on the inner portion of the eye but not on the lids or hairs of the eyelids. One can ignore the small amount that is in the inner and outer canthus.

+2 = Discharge is abundant, easily observed, and has collected on the lids and around the hairs of the eyelids.

+3 = Discharge has been flowing over the eyelids so as to wet the hairs substantially on the skin around the eye.

A.4 Aqueous flare

The intensity of the Tyndall phenomenon is scored by comparing the normal Tyndall effect observed when the slit-lamp beam passes through the lens with that seen in the anterior chamber. The presence of aqueous flare is presumptive evidence of breakdown of the blood-aqueous barrier.

0 = The absence of visible light beam light in the anterior chamber (no Tyndall effect).

+1 = The Tyndall effect is barely discernible. The intensity of the light beam in the anterior chamber is less than the intensity of the slit beam as it passes through the lens.

+2 = The Tyndall beam in the anterior chamber is easily discernible and is equal in intensity to the slit beam as it passes through the lens.

+3 = The Tyndall beam in the anterior chamber is easily discernible; its intensity is greater than the intensity of the slit beam as it passes through the lens.

A.5 Iris involvement

In the following definitions the primary, secondary and tertiary vessels are utilized as an aid to determining a subjective ocular score for iris involvement. The assumption is made that the greater the hyperaemia of the vessels and the more the secondary and tertiary vessels are involved, the greater the intensity of iris involvement.

0 = Normal iris without any hyperaemia of the iris vessels. Occasionally around the 12:00 to 1:00 o'clock position near the pupillary border and the 6:00 and 7:00 o'clock position near the pupillary border there is a small area around 1 mm to 3 mm in diameter in which both the secondary and tertiary vessels are slightly hyperaemic.

+1 = Minimal injection of secondary vessels but not tertiary. Generally, it is uniform, but may be of greater intensity at the 1:00 or 6:00 o'clock position. If it is confined to the 1:00 or 6:00 o'clock position, the tertiary vessels must be substantially hyperaemic.

+2 = Minimal injection of tertiary vessels and minimal to moderate injection of the secondary vessels.

+3 = Moderate injection of the secondary and tertiary vessels with slight swelling of the iris stroma (this gives the iris surface a slightly rugose appearance, which is usually most prominent near the 3:00 and 9:00 o'clock positions).

+4 = Marked injection of the secondary and tertiary vessels with marked swelling of the iris stroma. The iris appears rugose; may be accompanied by haemorrhage (hyphaema) in the anterior chamber.

A.6 Cornea

The scoring scheme measures the severity of corneal cloudiness and the area of the cornea involved. Severity of corneal cloudiness is graded as follows:

0 = Normal cornea. Appears with the slit-lamp as having a bright grey line on the epithelial surface and a bright grey line on the endothelial surface with a marble-like grey appearance of the stroma.

+1 = Some loss of transparency. Only the anterior half of the stroma is involved as observed with an optical section of the slit-lamp. The underlying structures are clearly visible with diffuse illumination, although some cloudiness can be readily apparent with diffuse illumination.

+2 = Moderate loss of transparency. In addition to involving the anterior stroma, the cloudiness extends all the way to the endothelium. The stroma has lost its marble-like appearance and is homogeneously white. With diffuse illumination, underlying structures are clearly visible.

+3 = Involvement of the entire thickness of the stroma. With optical section, the endothelial surface is still visible. However, with diffuse illumination the underlying structures are just barely visible (to the extent that the observer is still able to grade flare, iritis, observe for pupillary response and note lenticular changes).

+4 = Involvement of the entire thickness of the stroma. With the optical section, cannot clearly visualize the endothelium. With diffuse illumination, the underlying structures cannot be seen. Cloudiness removes the capability for judging and grading aqueous flare, iritis, lenticular changes and pupillary response.

The surface area of the cornea relative to the area of cloudiness is divided into five grades from 0 to + 4.

0 = Normal cornea with no area of cloudiness.

+1 = 1 % to 25 % area of stromal cloudiness.

+2 = 26 % to 50 % area of stromal cloudiness.

+3 = 51 % to 75 % area of stromal cloudiness.

+4 = 76 % to 100 % area of stromal cloudiness.

Pannus is vascularization or the penetration of new blood vessels into the corneal stroma. The vessels are derived from the limbal vascular loops. Pannus is divided into three grades.

0 = No pannus.

+1 = Vascularization is present but vessels have not invaded the entire corneal circumference. Where localized vessel invasion has occurred, they have not penetrated beyond 2 mm.

+2 = Vessels have invaded 2 mm or more around the entire corneal circumference.

The use of fluorescein is a valuable aid in defining epithelial damage. The area of staining can be judged on a 0 to +4 scale using the same terminology as for corneal cloudiness.

0 = Absence of fluorescein staining.

+1 = Slight fluorescein staining confined to a small focus. With diffuse illumination the underlying structures are easily visible (the outline of the pupillary margin is as if there were no fluorescein staining).

+2 = Moderate fluorescein staining confined to a small focus. With diffuse illumination the underlying structures are clearly visible, although there is some loss of detail.

+3 = Marked fluorescein staining. Staining may involve a larger portion of the cornea. With diffuse illumination the underlying structures are barely visible but are not completely obliterated.

+4 = Extreme fluorescein staining. With diffuse illumination the underlying structures cannot be observed.

The lens should be evaluated routinely during ocular evaluations and graded as either N (normal) or A (abnormal). The presence of lenticular opacities should be described and the location noted as defined below:

Anterior capsule

Anterior subcapsule

Anterior cortical

Nuclear

Posterior cortical

Posterior subcapsule

Posterior capsule

Annex B
(normative)

Draize scale for scoring ocular lesions

B.1 Cornea

(A)	Opacity-degree of density (area most dense taken for reading)	
	No opacity	0
	Scattered or diffuse area, details of iris clearly visible	1
	Easily discernible translucent areas, details of iris slightly obscured	2
	Opalescent areas, no details of iris visible, size of pupil barely discernible	3
	Opaque, iris invisible	4
(B)	Area of cornea involved	
	One quarter (or less) but not zero	1
	Greater than one quarter, but less than half	2
	Greater than half, but less than three quarters	3
	Greater than three quarters, up to the whole area	4
Score equals A x B x 5		Maximum = 80

B.2 Iris

(A)	Values	
	Normal	0
	Folds above normal, congestion, swelling, circumcorneal injection (any or all of these or combination of any thereof) iris still reacting to light (sluggish reaction is positive)	1
	No reaction to light, haemorrhage, gross destruction (any or all of these)	2
Score equals A x 5		Maximum = 10

B.3 Conjunctivae

(A)	Redness (refer to palpebral and bulbar conjunctivae excluding cornea and iris)	
	Vessels normal	0
	Vessels definitely injected above normal	1
	More diffuse, deeper crimson red, individual vessels not easily discernible	2
	Diffuse beefy red	3

(B)	Chemosis	
	No swelling	0
	Any swelling above normal (includes nictitating membrane)	1
	Obvious swelling with partial eversion of lids	2
	Swelling with lids about half closed	3
	Swelling with lids half closed to completely closed	4
(C)	Discharge	
	No discharge	0
	Any amount different from normal (does not include small amounts observed in inner canthus of normal animals)	1
	Discharge with moistening of the lids and hairs adjacent to lids	2
	Discharge with moistening of the lids and hairs, and considerable area around the eye	3

Score equals (A + B + C) x 2 Maximum = 20

B.4 Maximum total score

The maximum total score is the sum of all scores obtained for the cornea, iris and conjunctivae. Total maximum score possible = 110 per eye.

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