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Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications

Implants ophtalmiques — Lentilles intraoculaires — Directives relatives à l'évaluation de la nécessité d'investigation clinique pour les modifications de conception des lentilles intraoculaires

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Foreword

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The procedures used to develop this document and those intended for its further maintenance are described in the ISO/IEC Directives, Part 1. In particular the different approval criteria needed for the different types of ISO documents should be noted. This document was drafted in accordance with the editorial rules of the ISO/IEC Directives, Part 2 (see www.iso.org/directives).

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

This second edition cancels and replaces the first edition (ISO/TR 22979:2006), which has been technically revised.

Ophthalmic implants — Intraocular lenses — Guidance on assessment of the need for clinical investigation of intraocular lens design modifications

1 Scope

This document provides guidance on the application of all parts of the ISO 11979 series of International Standards for intraocular lenses (IOLs).[1–9] It addresses factors to be considered in the risk management process of modifications to anterior and posterior chamber IOLs in accordance with ISO 14971.[11] It also suggests methods of data analysis and interpretation that can be used to determine the need for a clinical investigation and its design.

2 Normative references

The following documents are referred to in the text in such a way that some or all of their content constitutes requirements 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 11979-1, *Ophthalmic implants — Intraocular lenses — Part 1: Vocabulary*

3 Terms and definitions

For the purposes of this document, the terms and definitions given in ISO 11979-1 and the following apply.

ISO and IEC maintain terminological databases for use in standardization at the following addresses:

— IEC Electropedia: available at http://www.electropedia.org/

— ISO Online browsing platform: available at http://www.iso.org/obp

NOTE The terms listed are related to Annex B.

3.1
open-loop IOL
IOL model which contains two loops, each loop having one end attached to the body of the IOL and the other end free

3.2
closed-loop IOL
IOL model, which contains two loops, each loop having both ends attached to the body of the optic

3.3
hybrid open-loop/closed-loop IOL
IOL model which contains two loops, with one loop having one end attached to the body of the IOL and the other end free, and the other loop having both ends attached to the body of the IOL

4 Modifications to parent models

4.1 General

IOLs, that are modifications of a parent IOL, have different requirements for clinical investigations depending on the risk associated with the modifications and depending on their location in the eye.

This document provides considerations for the risk assessment to determine the clinical investigation effort that is needed based on the level of modification which is defined in 4.2.

ISO 13485[10] provides requirements for the design and development of medical devices, which are applicable to intraocular lenses including modifications of existing models. The risk assessment and design evaluation are part of the risk management in the design control process in accordance with ISO 14971, and can be used as input for the clinical evaluation. ISO 14971 describes sources for data and information for estimating risks. To determine and evaluate the hazards associated with the modification of IOL models, the manufacturer can additionally use the following sources:

a) clinical data;

b) literature study of equivalent features of similar IOL models. The literature can be general published and unpublished reports, proprietary evaluations and post-market surveillance reports;

c) physical model-eyes, laboratory bench testing or numerical/computational models, which have been verified and validated for evaluation of optical and mechanical behaviour;

d) usability and human factor engineering data resulting from the application of IEC 62366-1[12] or ANSI/AAMI HE75[13] such as the use of error risk analysis, formative and summative evaluation results, including studies to evaluate surgical manipulation and delivery of the IOL in the eye.

Modifications to the delivery system are subject to the design control process in accordance with ISO 13485 and factors that pertain to the interaction of IOL and delivery system, as described in ISO 11979-3, and user interaction during surgery are to be considered in a risk assessment.

4.2 Modification levels

4.2.1 General

Design modifications to parent model IOLs are classified as Level A, B or C. The classification depends on the safety and performance risks that are identified. Examples of risks associated with design modifications are provided in Annex A.

4.2.2 Level A modifications

Level A modifications of a parent model are those for which all safety and performance questions can be adequately addressed without clinical investigation. The modified model is essentially equivalent to the parent model(s). All risks resulting from risk assessment to the modification are adequately addressed by existing clinical evidence. The residual risk will have to be outweighed by the benefits.

4.2.3 Level B modifications

Level B modifications of a parent model are those that raise safety and/or performance risks that can be adequately addressed with a limited clinical investigation of a justified number of subjects followed up for a justified period.

NOTE Typically 100 subjects followed up for 4 months to 6 months. The statistical precision of a 100-subject investigation to detect differences from the safety and performance end points (SPE) ratings is provided in ISO 11979-7.

4.2.4 Level C modifications

Level C modifications are modifications that raise safety and/or performance risks that can only be addressed with a full clinical investigation as defined in ISO 11979-7 and ISO 11979-10.

4.2.5 Clinical investigation with multiple IOL models

More than one IOL model can be studied in the same investigation and with the same study end points if supported by a risk assessment and provided these models are Level A modifications of one another. If the intent is that data from the various models are to be pooled, a justification from the manufacturer is required per study end point to demonstrate that the design differences between models will affect neither investigation outcomes nor investigation execution nor interfere with the application of statistically sound test design techniques such as randomization and masking.

5 Considerations for the assignment of modification level

5.1 General

The process of assignment of a modification level is illustrated in Figure A.1. A risk assessment of the model modifications is performed, especially considering any safety and performance changes due to the differential design aspects compared with the parent models. Multiple parent models can be considered in the evaluation given the premise that the modifications are related to these parent model(s).

The assigned modification level depends on the additional potential hazards or hazardous situations, their probability of occurrence and the probability that they will lead to harm, as well as the severity of the harm(s) compared with that of the parent model. For additional guidance, see ISO 14971.

Overall, the risk assessment would weigh the risk/performance impact and benefit to determine modification Level A, B or C. Examples of potential Level A modifications to parent models are provided in Annex A. A plurality of modifications may change the level assignment. If there is insufficient data to assess the risk of plurality of modifications, as compared with parent IOLs, a suitable clinical investigation should be performed.

5.2 Risk assessment

In the risk assessment, the hazards and hazardous situations that are related to the modification(s) relative to the parent model will be considered. By assigning modification Level A, B or C, the clinical performance relative to the parent model is addressed. Table A.5 includes examples of potential hazards and harms that may be associated with the modification and that can be included in the risk assessment. Table A.5 also includes references to test methods described in the ISO 11979 series, which can be considered to assess the potential risks. The risk assessment addresses all changes made to the product and includes changes of labelling, packaging and package inserts.

5.3 Special considerations

5.3.1 Phakic lenses

Phakic lenses require additional considerations in the risk assessment to determine the modification level because of the proximity of other tissue compared with aphakic anterior and posterior chamber lenses. The clinical requirements are outlined in ISO 11979-10.

5.3.2 Anterior chamber lenses

Additional hazards may arise from the potential direct IOL-tissue interaction, static or dynamic, which needs to be evaluated including the risk of rotation, displacement, aqueous flow and corneal damage. The clearance analysis described in ISO 11979-3 can be used to assess the clearance to the cornea.

5.3.3 Posterior chamber lenses intended for implantation in the sulcus

Posterior chamber lenses implanted in the sulcus have more potential interaction with surrounding tissue than lenses implanted in the capsular bag. Examples of potential tissue interaction effects are pigment dispersion and changes to the ciliary body.

6 Modifications of optical design features

6.1 Optical design changes

Optical bench testing of imaging quality, as defined in ISO 11979-2, is performed and analysed to compare the modified IOL model and parent IOL model(s).

Interchanging optics or combining two or more optical design concepts (spherical, aspheric, monofocal, toric, multifocal and/or accommodative optics) may be considered Level A modifications if the optical designs have been evaluated in parent IOL models. The risk assessment is conducted to evaluate any new risk when interchanging optical designs and includes the following:

a) the potentially increased misalignment of the IOL optic (i.e. tilt, decentration and rotation) due to the parent IOL body and haptic designs. The analysis includes comparison of clinical study reports of centration and mechanical differences in IOL design;

b) evaluation of the potential for changes in the predictability and stability of post-operative refraction and, if applicable, changes in the stability and magnitude of the accommodative amplitude at the point of stabilization;

c) when combining two or more approved optical concepts, all clauses applicable to these concepts and their interaction are considered.

Examples of Level A and B modifications are listed in Annex A.

6.2 Multifocal lenses (MIOL)

When the modification of the multifocal parent design is a change of the fundamental technology creating the multiple dioptric powers, e.g. diffraction versus refraction, this modification is potentially a Level B or Level C modification depending on the risk assessment. A change to a multifocal design that can be verified and compared with a parent multifocal may be considered a Level A modification if it does not increase the risk profile. However, if the modification increases the risk profile, for example adding risks of visual disturbances, the change is potentially a Level B or Level C modification. If the material of the modified model IOL is different from the material of the multifocal parent IOL with respect to optical material characteristics, in particular refractive index and dispersion, this is potentially a Level B or Level C modification.

6.3 Toric lenses (TIOL)

Refer to ISO 11979-7 and ISO 11979-10 for evaluation of modifications of the mechanical design platform, in particular with respect to rotational stability. Changes in mechanical design affecting the axial and rotational stability are potentially Level B or Level C modifications.

6.4 Accommodating lenses (AIOL)

Any change in optic design (single and multi-optic lenses) or haptic design is reviewed for potential impact on the accommodative power of the IOL and optical performance, as defined in ISO 11979-2 and ISO 11979-7, of the IOL at far power configuration and configurations associated with the designed range of accommodation in 0,5 D increments. The risks associated with interaction with surrounding tissue due to the accommodative action need to be evaluated to classify the modification level of a model change. Any characteristic of the parent lens optics and material that may have an impact on the accommodative performance of the approved AIOL is considered in the risk assessment.

7 Modifications to the mechanical design

7.1 General

Evaluation of modifications of the mechanical design considers the impact of the modification on the mechanical interaction with ocular tissue, consequences for the surgical handling, interaction with delivery systems, refractive outcomes, visual outcomes including visual disturbances and any potential biological response. Examples of modifications to the mechanical design and the biological response are:

a) changes in the vault height, sagitta, axial displacement under compression may affect the refraction stability and axial position of the IOL;

b) changes in the compression force and contact angle may damage the capsular bag and the zonular fibres with the effect of tilt and decentration, and may change the shape of the capsular bag with the consequences of capsular striae and optical disturbances and posterior capsule opacification.

Any modification to the mechanical design of anterior chamber IOLs is considered a Level B modification.

7.2 Mechanical analysis

The data from the compression force, compression force decay and angle of contact, tested in accordance with ISO 11979-3, is used to assess the difference in mechanical behaviour between the modified IOL model and potential parent IOL model(s). The methods for assessment of the differences in compression force (decay) and angle of contact between a modified IOL model and one or more parent IOL models are described in Annex B. These methods can be used to determine whether a modified posterior chamber IOL is a Level A modification of one or more parent IOL models included in the analysis.

8 Modifications to material

8.1 Interchanging IOL materials

Interchanging IOL materials may be considered Level A modifications if the materials and designs have each been evaluated in a parent IOL. The risk assessment is conducted to evaluate any new risk when interchanging IOL materials in particular when interchanging material from one-piece, three-piece or plate lens design.

8.2 New materials

If the material of the modified IOL model is different from the material of the parent IOL model(s), a clinical investigation is considered depending on the risk assessment. If the change in material is a change in polymeric structure, and there is no experience for use of this polymer in the eye, typically a full clinical investigation is performed.

Annex A
(informative)

Examples of modifications to a parent IOL model

A.1 General

Modifications to an IOL that has undergone a clinical investigation can be classified in one of three categories depending on the level of modification: Level A, Level B or Level C. This annex provides typical examples of potential Level A and B modifications with additional criteria where applicable.

The examples in this annex do not apply to phakic IOLs or iris fixation lenses.

The applicability column indicates the type of IOL that the modification is applicable to:

a) P designates non-plate posterior chamber IOLs, for in the capsular bag implantation;

b) A designates anterior chamber IOLs;

c) S designates IOLs for sulcus implantation;

d) PL designates posterior chamber IOLs made from flexible materials that are of a one-piece plate design.

A.2 Potential Level A modification examples

Examples of potential Level A modifications are listed in Tables A.1 and A.2. If the risk assessment brings forward new risks or results in increased risks from individual or multiple changes over the parent models(s), the classification of modification level should be reconsidered.

Table A.1 — Change in optic design

Modification	Applicability
Change in dioptric power range Whereby any power of the IOL model is in the range that the manufacturer makes available.	P/A/PL/S
Change of dioptric power increments Inclusion or deletion of power steps inside the range of the power steps of the parent model e.g. the current power steps are 5,0 D, 6,0 D, 7,0 D, etc., are modified to 5,0 D, 5,5 D, 6,0 D, 6,5 D, 7,0 D, etc.	P/A/PL/S
Change in cylinder power range (TIOL) Where any cylinder power ≥1,0 D of the IOL model is within the range of manufacturer's available cylinder power range.	P/A/PL/S
Change in addition power (MIOL) Whereby any addition power of the IOL is within the range of manufacturer's available addition powers, that the manufacturer makes available for parent models with identical optical principles to accomplish the multifocality and the same optical specifications.	P/A/PL/S

Table A.1 *(continued)*

Modification	Applicability
Change to axis indicator marks of TIOL Provided that the markings remain compatible with a vision evaluation system.	P/A/PL/S
Change in spherical aberration level Whereby the spherical aberration remains within the range of that the manufacturer makes available.	P/A/PL/S
The application of a multifocal optic design of one parent model to the optic of another parent model Whereby optical design, optical specifications, material and technology to accomplish the multifocality of the IOL are identical to the parent model(s).	P/A/PL/S

Table A.2 — Change in mechanical design

Modification	Applicability	Mechanical data analysis
Changes in haptic features Changes such as the addition of notches or the addition of eyelets or rounded ends to loops.	P/S	No
Change in overall diameter Changes within the previously clinically investigated overall diameter range.	P/S	Yes
Change in haptic thickness or width	P/S	Yes
Change in haptic configuration (shape)	P/S	Yes
Change in optic or body size Changes in body circumference design or optic size if the length is not less than 5,0 mm along any meridian (e.g. going from circular to an ovoid body) and not greater then 7,5 mm along any meridian.	P/S	No
Change of clear optic Any obstruction that interferes with the performance of the optic, provided that the clear optic diameter is greater than 4,25 mm.	P/S	No

A.3 Potential Level B modification examples

Examples of potential Level B modifications are listed in Tables A.3 and A.4. If the risk assessment brings forward new risks, the classification of modification level should be reconsidered.

Table A.3 — Change in optic design

Modification	Applicability
Change in addition power outside the range of addition power made available by the manufacturer through the MIOL parent lenses Whereby any addition power of the IOL follows the identical optical principles as the parent model(s) to accomplish the multifocality and the same optical specifications as the parent model(s).	P/A/PL/S

Table A.4 — Change in mechanical design

Modification	Applicability	Mechanical data analysis
Change in haptic configuration Including change in overall diameter, haptic thickness or width, when not meeting the Level A criteria mechanically. If the change in haptic configuration of the modified lens appears to have the potential to cause different or greatly increased safety concerns as compared with the parent model(s), it is considered to be a Level C modification.	P	Yes
Change in haptic configuration Including change in overall diameter, haptic thickness or width, when not meeting the Level A criteria mechanically. Given the more complex behaviour of the plate design lens compared with open loop design lenses, plate design lenses are evaluated at dimensional extremes to demonstrate stability under expected conditions.	PL	Yes

A.4 Considerations for characteristics to compare when evaluating a design modification

Table A.5 provides examples of product characteristics or performance parameters, associated characteristics, and parts of ISO 11979, which can be used to identify potential differences between the modified model and the parent model with respect to performance or safety. These characteristics and parameters can be considered when identifying potential harms and hazardous situations.

Table A.5 — Examples of risks potentially associated with modification of IOL characteristics

Modification	Hazardous situation	Potential harm	Type of modification	ISO 11979 reference
Extension of dioptric power range or cylinder range.	Contact with ocular tissue: cornea, iris and pupil, ciliary body, capsular bag and zonular fibres.	Damage to the ocular tissue: cornea, iris and pupil, ciliary body, capsular bag and zonular fibres.	Design	ISO 11979-3: Vault height Sagitta Axial displacement under compression Clearance analysis Recovery of properties following simulated surgical manipulation.
	IOL delivery results in permanent deformation of the IOL.	Refractive error, loss of contrast and visual acuity.		
	Changed delivery characteristics, i.e. increased delivery forces resulting in damage to the optic and haptics.	Loss of contrast and visual acuity. Damage to ocular tissue.		
	Design changes leading to changes in optical performance such as changed spherical aberration.	Loss of contrast and visual acuity.		
	Change in rotation stability for TIOL lens models.	Residual cylinder.		
	Tilt and decentration due to the capsular bag shape or damage to the capsular bag and zonular fibres.	Loss of contrast and visual acuity.		

Table A.5 *(continued)*

Modification	Hazardous situation	Potential harm	Type of modification	ISO 11979 reference
Change in haptic design, such as a change in overall diameter and haptic width or thickness, leading to a change in mechanical characteristics.	Tilt and decentration due to the capsular bag shape or damage to the capsular bag and zonular fibres.	Loss of contrast and visual acuity. Capsular rupture leading to vitreous loss, retinal detachment and possible blindness.	Design	ISO 11979-3 Annex B
	Decreased function of optical features.	Loss of contrast and visual acuity.		
	Striae.	Visual disturbances		
	Damage to ciliary body and aqueous-blood barrier.	Inflammation.		
	Change in tilt and decentration due sensitivity of the design.	Loss of contrast and visual acuity.	Design	ISO 11979-3 ISO 11979-2
	Change in axial IOL location stability and/or rotational stability.	Refractive error Residual cylinder (TIOL).	Design; Optical	ISO 11979-3 ISO 11979-7
Optic shape factor.	Optical performance due to changing aberration.	Loss of contrast and visual acuity.	Design; Optical	ISO 11979-2 ISO 11979-3
	Surface reflection (plano-convex).	Visual disturbance.		
Change in MTF sensitivity to decentration and tilt.	Poor optical performance.	Loss of contrast and visual acuity.	Design; Optical	ISO 11979-2
Change in clear optic.	Reflections from non-optical features as positioning holes.	Visual disturbances.	Design	ISO 11979-3
Change in optical edge design.	Reflected light produces ghost images on the retina.	Visual disturbances.	Design	No standard test available.
	Reduced barrier for LEC migration.	Posterior capsule opacification.		
Change in material and/or its surface characteristics.	Surface evokes inflammatory reaction	Inflammation.	Biocompatibility.	ISO 11979-5
	Reduced adherence of posterior capsule to the posterior IOL surface.	Posterior capsule opacification.		
	Reduced biocompatibility of the materials.	Inflammation and toxic effects.		

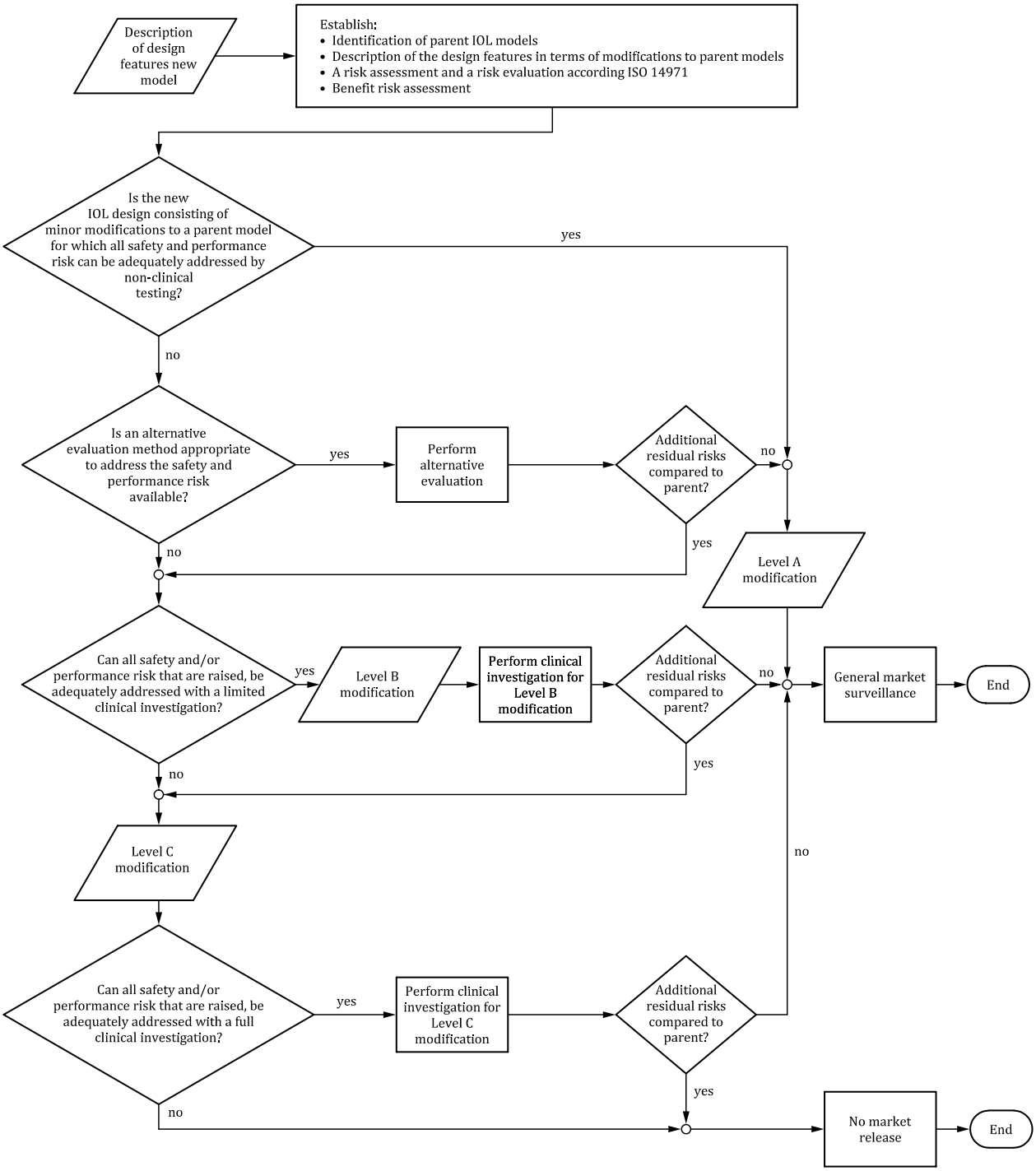


Figure A.1 — Method for assigning a modification level and associated actions

Annex B
(informative)

Mechanical data analysis

B.1 Principle

The methods in this Annex apply to two-looped lens models only. Mechanical data, i.e. compression force, compression force after decay and angle of contact, can be used to assess whether a modified IOL is a Level A modification of a parent IOL, as described in Annex A.

For lenses with open haptics (loop style) the mechanical analysis is applicable. For other style haptics like plate style or hybrid, other type of analysis may be more useful to assess the interaction with the surrounding tissue.

B.2 Mechanical comparison methods

B.2.1 General

For comparisons between a modified model and a single parent model, which is either currently undergoing a clinical investigation or has completed a clinical investigation, the manufacturer demonstrates that the mechanical properties of the modified lens are not significantly different from those of the parent model.

For comparisons between a modified model and multiple parent models, the manufacturer demonstrates that the mechanical properties of the modified lens are not significantly different from the range of properties associated with the parent models.

The analysis between the modified model and the manufacturer's parent model(s) includes the following comparisons:

a) compression force divided by angle of contact per loop;

b) compression force after decay divided by angle of contact per loop.

For each test needed for the analysis, the lens is evaluated at 10,0 mm compressed diameter if the modified lens is only for capsular bag fixation, at 11,0 mm if it is only for ciliary sulcus fixation or at both diameters if intended for both capsular bag and ciliary sulcus fixation.

B.2.2 Restrictions

B.2.2.1 The method of comparison with a single parent model includes the following restrictions:

a) a model of either the open-loop, closed-loop or hybrid open/closed-loop types is only compared with the same type of model;

b) for models of the open-loop or closed-loop type having dissimilar loops, each loop is assessed separately, and then each loop on the modified model is compared with the corresponding loop on the parent model that it most closely resembles.

B.2.2.2 The method of comparison with multiple parents includes the following restrictions:

a) an open-loop model or the open loop of a hybrid open-loop/closed-loop model is only compared with the properties associated with open-loop parent models;

b) a closed-loop model or the closed loop of a hybrid open-loop/closed-loop model is only compared with the properties associated with closed-loop parent models;

c) for models of the open-loop or closed-loop type having dissimilar loops (and therefore different angles of contact), each loop is compared separately with the appropriate (i.e. open-loop or closed-loop) graph of properties associated with the parent models.

B.2.3 Calculations

The manufacturer determines the force necessary to compress the parent model and the modified model to the applicable overall diameter(s) (see ISO 11979-3 for the test method). The mean force value, F, and the standard deviation, σ, are determined for the parent model and the modified model for the applicable overall diameters.

The force spread value, f, in the formulae is set equal to 20 % of the mean force value (0,2 F) or to the standard deviation, σ, provided that σ is lower than 0,2 F.

From this data, the upper force boundaries, UFB_p, and lower force boundaries, LFB_p, are calculated using Formulae (B.1) to (B.6) for the parent model:

when $F_p \geq 1\,100 \times 10^{-5}$ N:

$$UFB_p = F_p + f_p \tag{B.1}$$

when $800 \times 10^{-5} < F_p < 1\,100 \times 10^{-5}$ N:

$$UFB_p = F_p + 3\,f_p - [(F_p - 800 \times 10^{-5}) / 150 \times 10^{-5}]\,f_p \tag{B.2}$$

when $F_p \leq 800 \times 10^{-5}$ N:

$$UFB_p = F_p + 3\,f_p \tag{B.3}$$

when $F_p \geq 150 \times 10^{-5}$ N:

$$LFB_p = F_p - 3\,f_p \tag{B.4}$$

when $50 \times 10^{-5} < F_p < 150 \times 10^{-5}$ N:

$$LFB_p = F_p - (F_p / 50 \times 10^{-5})\,f_p \tag{B.5}$$

when $F_p \leq 50 \times 10^{-5}$ N:

$$LFB_p = F_p - f_p \tag{B.6}$$

The upper force boundaries, UFB_m, and lower force boundaries, LFB_m, are calculated using the Formulae (B.7) and (B.8) for the modified model:

$$UFB_m = F_m + f_m \tag{B.7}$$

$$LFB_m = F_m - f_m \tag{B.8}$$

B.2.4 Background of the calculations

The compression force values 150×10^{-5} N and 800×10^{-5} N represent the lower and upper boundaries, respectively, containing most of the IOL models that have demonstrated acceptable clinical performance. Since much less is known about the clinical performance of IOL models outside these boundaries, a

more conservative approach has been taken with parent models with loop flexibilities outside these boundaries to minimize the difference between the parent and the modified model. The formulae above accomplish this in the following manner for the parent models:

a) by using 3 f_p only with parent models that have mean compression force values between 150×10^{-5} N and 800×10^{-5} N;

b) by decreasing the multiplier of f_p used in the LFB_p formula with parent models that have mean compression force values below 150×10^{-5} N in a continuous manner until it equals 1 at a mean compression force value of 50×10^{-5} N;

c) by using f_p with parent models that have mean compression force values below 50×10^{-5} N;

d) by decreasing the multiplier of f_p used in the UFB_p formula with parent models that have mean compression force values above 800×10^{-5} N in a continuous manner until it equals 1 at a mean compression force value of $1\,100 \times 10^{-5}$ N;

e) by using f_p with parent models that have mean compression force values above $1\,100 \times 10^{-5}$ N.

B.2.5 Analysis of a single parent comparison

The manufacturer determines the angle of contact *AC* associated with the loops of the parent model and the modified model when the lenses are compressed to the required overall diameter(s); see ISO 11979-3. The *UFB* and the *LFB* divided by the mean *AC* at the compressed overall diameter(s) determine the range of force values per degree of *AC* associated with the parent lens and the modified lens at the compressed diameter(s).

For the modified lens to be considered a Level A modification of the parent model, the following criteria apply:

a) the mean AC_m associated with the loops of the modified model at the applicable compressed overall diameter(s) is within ±40 % of the mean AC_p associated with the loops on the parent model at each of the compressed overall diameters;

b) some part of the range defined by the UFB_m/AC_m and the LFB_m/AC_m for the modified lens overlaps the range defined by the UFB_p/AC_p and the LFB_p/AC_p for the parent model at each of the compressed overall diameters, both initially and after decay.

Example 1 and Example 2 in B.3 illustrate hypothetical results using this method of analysis to demonstrate that a modified lens is a Level A modification of the parent lens.

B.2.6 Analysis of a multiple parent comparison

The manufacturer determines the angle of contact, *AC*, associated with the loops of the parent models and the modified model when the lenses are compressed to the required overall diameter(s); see ISO 11979-3 for method.

Then for each parent model, the manufacturer graphs the force values as a function of loop *AC* for each overall diameter and condition.

For hybrid open-loop/closed-loop parent models, the properties are separated into their open-loop and their closed-loop components and the data are added to the corresponding graph.

For the modified lens to be considered a Level A modification of the parent models, part of the force range for the modified model falls within the boundary ranges defined by the force characteristics of any two of the manufacturer's parent models that are separated by not more than 30° of *AC* for the loop type in question. It is not necessary that the same two parent models be used for the comparisons under all of the test conditions.

Example 3 in B.3 illustrates hypothetical results using this method of analysis to demonstrate that a modified lens is a Level A modification of the multiple parent lens models.

B.3 Examples

B.3.1 Example 1: Single parent comparison (IOLs with symmetrical loops)

Example 1 discusses the testing necessary to demonstrate the Level A relationship between two open-loop models with symmetrical loops. The manufacturer, in this example, has designed a new model (Model 5) by modifying a parent IOL model (Model 2), with modified C haptics and an overall diameter of 12 mm, by increasing the overall diameter from 12,0 mm to 14,0 mm and by modifying the shape of the loop to a different form of modified C-loop. To determine if Model 5 is a Level A modification of Model 2, the manufacturer has evaluated the mechanical characteristics of the new model.

The manufacturer has taken a minimum of 10 samples of each of the models and has determined the compression force necessary to compress each model to an overall diameter of 10 mm. The mean force values, F, and the standard deviations, σ, were determined. From these data, the upper force boundaries *UFB* and lower force boundaries *LFB* were calculated according to the formulae and procedure in B.2, in which the force spread values, f, were set equal to the standard deviations, σ.

The *AC* associated with each loop when the lens was compressed to 10 mm was measured and the mean value was determined. Next, the *UFB* and *LFB* were divided by the mean *AC*. These values determine the range of force values per degree of *AC* associated with a lens when compressed to 10 mm overall diameter.

The procedures described above were repeated for an overall compression diameter of 11 mm and for 10 mm and 11 mm after decay. Table B.1 and B.2 show the data associated with the two hypothetical models.

Table B.1 — Mechanical data for Model 2

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	300×10^{-5} N	180×10^{-5} N	130×10^{-5} N	80×10^{-5} N
σ	45×10^{-5} N	20×10^{-5} N	20×10^{-5} N	12×10^{-5} N
UFB	435×10^{-5} N	240×10^{-5} N	190×10^{-5} N	116×10^{-5} N
LFB	165×10^{-5} N	120×10^{-5} N	78×10^{-5} [a]	61×10^{-5}[a]
AC	60°	42°	62°	44°
UFB/AC	7,3	5,7	3,1	2,6
LFB/AC	2,8	2,9	1,3	1,4

[a] $F < 150 \times 10^{-5}$ N, therefore $LFB = F_p - (F_p/50 \times 10^{-5})\ \sigma_p$ was used.

Table B.2 — Mechanical data for Model 5 (modification of Model 2)

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	450×10^{-5} N	250×10^{-5} N	220×10^{-5} N	120×10^{-5} N
σ	70×10^{-5} N	55×10^{-5} N	30×10^{-5} N	20×10^{-5} N
UFB	520×10^{-5} N	300×10^{-5}[a]	250×10^{-5} N	140×10^{-5} N
LFB	380×10^{-5} N	200×10^{-5} N[a]	190×10^{-5} N	100×10^{-5} N
AC	70°	52°	74°	55°
UFB/AC	7,5	5,8	3,4	2,6
LFB/AC	5,4	3,8	2,6	1,8

[a] $\sigma > 0{,}2\ F$, therefore f was set equal to $0{,}2\ F$.

Based on these data, the proposed Model 5 was compared with parent Model 2. The following comparisons form the elements necessary to conclude that Model 5 is a Level A modification of Model 2:

a) the mean AC_m for Model 5, 70° (10 mm) and 52° (11 mm), is within 40 % of the mean AC_p for Model 2, i.e. 60° (10 mm) and 42° (11 mm);

b) the LFB/AC_m to UFB/AC_m range for Model 5 overlaps the range defined by the UFB/AC_p and the LFB/AC_p for Model 2 at all four test conditions: 10 mm and 11 mm compressed overall diameters and 10 mm and 11 mm compressed overall diameters after decay.

Therefore, Model 5 does not need to undergo a clinical investigation, provided it is otherwise in compliance with all relevant parts of ISO 11979.

If Model 2 is undergoing a clinical investigation, this analysis can be used to determine that Model 5 is a Level A modification of Model 2 and can therefore be added to its clinical investigation.

NOTE The same testing is performed to demonstrate the Level A relationship between two closed-loop models with symmetrical loops.

B.3.2 Example 2: Single parent comparison (IOLs with asymmetrical loops)

Example 2 discusses the testing necessary to demonstrate the Level A relationship between two open-loop models with asymmetrical loops, two closed-loop models with asymmetrical loops or two hybrid open-loop/closed-loop models.

The manufacturer, in this example, has modified a hybrid closed-loop/open-loop parent model, Model 6, by changing the configuration of both the open-loop and the closed-loop, and reducing the overall diameter of the model from 14 mm to 12,5 mm. The new model is designated Model 7. In cases like this, in which a model possesses asymmetrical loops, the mechanical characteristics have to be determined for each loop separately. The characteristics of the closed loops of Models 6 and 7 are first compared, and then the characteristics of the open loops of Models 6 and 7 are compared.

Table B.3 and Table B.4 provide the mechanical characteristics of the closed loops on Models 6 and 7, respectively.

Table B.3 — Mechanical data for the closed loop on Model 6

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	900×10^{-5} N	750×10^{-5} N	450×10^{-5} N	375×10^{-5} N
σ	110×10^{-5} N	100×10^{-5} N	80×10^{-5} N	60×10^{-5} N
UFB	$1\,157 \times 10^{-5}$ N[a]	$1\,050 \times 10^{-5}$ N	690×10^{-5} N	555×10^{-5} N
LFB	570×10^{-5} N	450×10^{-5} N	210×10^{-5} N	195×10^{-5} N
AC	65°	64°	66°	65°
UFB/AC	18	16	11	8,5
LFB/AC	8,8	7	3,2	3

[a] $F_p > 800 \times 10^{-5}$ N, therefore $UFB_p = F_p + 3\,\sigma_p - [(F_p - 800 \times 10^{-5}) / 150 \times 10^{-5}]\,\sigma_p$ was used.

Table B.4 — Mechanical data for the closed loop on Model 7

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	700×10^{-5} N	600×10^{-5} N	350×10^{-5} N	250×10^{-5} N
σ	100×10^{-5} N	70×10^{-5} N	50×10^{-5} N	25×10^{-5} N
UFB	800×10^{-5} N	670×10^{-5} N	400×10^{-5} N	275×10^{-5} N
LFB	600×10^{-5} N	530×10^{-5} N	300×10^{-5} N	225×10^{-5} N
AC	50°	48°	51°	49°
UFB/AC	16	14	7,8	5,6
LFB/AC	12	11	5,9	4,6

Table B.5 and Table B.6 provide the mechanical characteristics of the open-loops on Models 6 and 7, respectively.

Table B.5 — Test data for the open loop on Model 6

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	900×10^{-5} N	750×10^{-5} N	450×10^{-5} N	375×10^{-5} N
σ	110×10^{-5} N	100×10^{-5} N	80×10^{-5} N	60×10^{-5} N
UFB	$1\,157 \times 10^{-5}$ N[a]	$1\,050 \times 10^{-5}$ N	690×10^{-5} N	555×10^{-5} N
LFB	570×10^{-5} N	450×10^{-5} N	210×10^{-5} N	195×10^{-5} N
AC	40°	35°	41°	36°
UFB/AC	29	30	17	15
LFB/AC	14	13	5,1	5,4

[a] $F_p > 800 \times 10^{-5}$ N, therefore $UFB_p = F_p + 3\,\sigma_p - [(F_p - 800 \times 10^{-5})/150 \times 10^{-5}]\,\sigma_p$ was used.

Table B.6 — Test data for the open loop on Model 7

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	700×10^{-5} N	600×10^{-5} N	350×10^{-5} N	250×10^{-5} N
σ	100×10^{-5} N	70×10^{-5} N	50×10^{-5} N	25×10^{-5} N
UFB	800×10^{-5} N	670×10^{-5} N	400×10^{-5} N	275×10^{-5} N
LFB	600×10^{-5} N	530×10^{-5} N	300×10^{-5} N	225×10^{-5} N
AC	46°	41°	47°	42°
UFB/AC	17	16	8,5	6,6
LFB/AC	13	13	6,4	5,4

It is noted that for Tables B.3 to B.6, the force value necessary to compress the open-loop and closed-loop of each model are, of course, identical (see Tables B.3 and B.5; Tables B.4 and B.6). This is because for the measurement both the haptics of the IOL are compressed between anvils and the force measured is exerted by both haptics.

The force boundaries for the parent model in Tables B.3 and B.5 were derived using 3*f*, except in the cases where $F > 800 \times 10^{-5}$ N. The force boundaries for the modified model in Tables B.4 and B.6 were derived using force spread value *f*. For the parent model and the modified model, the force spread value *f* was set equal to the standard deviation, σ.

Based upon the following analysis of the data, it can be concluded that new Model 7 is a Level A modification of parent Model 6:

a) the mean AC_m for new Model 7, 50° (10 mm) and 48° (11 mm) is within 40 % of the mean AC_p for parent Model 6, 65° (10 mm) and 64° (11 mm) for the closed loops;

b) the mean AC_m for new Model 7, 46° (10 mm) and 41° (11 mm) is within 40 % of the mean AC_p for parent Model 6, 40° (10 mm) and 35° (11 mm) for the open loops;

c) the LFB/AC_m to UFB/AC_m range for Model 7 overlaps the range defined by the UFB/AC_p and the LFB/AC_p for Model 6 at all of the test conditions: 10 mm and 11 mm compressed overall diameters, and 10 mm and 11 mm compressed overall diameters after decay, for both the open-loop and closed-loop comparisons.

B.3.3 Example 3: Multiple parents

The manufacturer has four open-loop posterior chamber parent models, which are indicated for both ciliary sulcus and capsular bag fixation:

a) model 1: C-loop (14,0 mm overall diameter);

b) model 2: modified C-loop (12,0 mm overall diameter);

c) model 3: J-loop (13,5 mm overall diameter);

d) model 4: modified J-loop (13,0 mm overall diameter).

All relevant models of the manufacturer's lens product range are considered. Tables B.7 to B.10 list the mechanical data associated with the four hypothetical models. The manufacturer constructs graphs of the compression properties associated with these four hypothetical parent models (see Figures B.1 to B.4). The force spread value is set equal to the standard deviation, σ, for each model.

The data associated with the four parent models at 10 mm constrained overall diameter is listed in Table B.7. Figure B.1 shows the bar chart derived from those data.

Table B.7 — Mechanical data for Models 1 to 4 at 10 mm

Parameter	Model			
	1	2	3	4
F	90×10^{-5} N	300×10^{-5} N	500×10^{-5} N	250×10^{-5} N
σ	25×10^{-5} N	45×10^{-5} N	75×10^{-5} N	40×10^{-5} N
UFB	144×10^{-5} N[a]	435×10^{-5} N	725×10^{-5} N	370×10^{-5} N
LFB	58×10^{-5} N[a,b]	165×10^{-5} N	275×10^{-5} N	130×10^{-5} N
AC	50°	60°	20°	22°
UFB/AC	2,9	7,3	36	17
LFB/AC	1,2	2,8	14	5,9

[a] $\sigma > 0{,}2\ F$, therefore f was restricted to 0,2 *F*.

[b] $F < 150 \times 10^{-5}$ N, therefore $LFB = F_p - (F_p/50 \times 10^{-5})\ \sigma_p$ was used.

Table B.8 lists the data associated with the four parent models at 11 mm constrained overall diameter and Figure B.2 shows the bar chart derived from those data.

Table B.8 — Mechanical data for Models 1 to 4 at 11 mm

Parameter	Model			
	1	2	3	4
F	80×10^{-5} N	180×10^{-5} N	450×10^{-5} N	200×10^{-5} N
σ	16×10^{-5} N	20×10^{-5} N	50×10^{-5} N	25×10^{-5} N
UFB	128×10^{-5} N	240×10^{-5} N	600×10^{-5} N	275×10^{-5} N
LFB	54×10^{-5} N[a]	120×10^{-5} N	300×10^{-5} N	125×10^{-5} N
AC	40°	42°	23°	22°
UFB/AC	3,2	5,7	26	12
LFB/AC	1,4	2,9	13	5,7

[a] $F < 150 \times 10^{-5}$ N, therefore $LFB = F_p - (F_p/50 \times 10^{-5})\ \sigma_p$ was used.

Table B.9 lists the data associated with the four parent models at 10 mm constrained overall diameter after decay and Figure B.3 shows the bar chart derived from those data.

Table B.9 — Mechanical data for Models 1 to 4 at 10 mm after decay

Parameter	Model			
	1	2	3	4
F	50×10^{-5} N	130×10^{-5} N	240×10^{-5} N	120×10^{-5} N
σ	12×10^{-5} N	20×10^{-5} N	30×10^{-5} N	20×10^{-5} N
UFB	80×10^{-5} N[a]	190×10^{-5} N	330×10^{-5} N	180×10^{-5} N
LFB	40×10^{-5} N[a,b]	78×10^{-5} N[b]	150×10^{-5} N	72×10^{-5} N[b]
AC	52°	62°	22°	24°
UFB/AC	1,5	3,1	15	7,5
LFB/AC	0,8	1,3	6,8	3,0

[a] $\sigma > 0{,}2\ F$, therefore σ was restricted to $0{,}2\ F$.

[b] $F < 150 \times 10^{-5}$ N, therefore $LFB = F^p - (F^p/50 \times 10^{-5})\sigma_p$ was used.

Table B.10 lists the data associated with the four parent models at 11 mm constrained overall diameter after decay and Figure B.4 shows the bar chart derived from those data.

Table B.10 — Mechanical data for Models 1 to 4 at 11 mm after decay

Parameter	Model			
	1	2	3	4
F	45×10^{-5} N	80×10^{-5} N	200×10^{-5} N	90×10^{-5} N
σ	10×10^{-5} N	12×10^{-5} N	25×10^{-5} N	15×10^{-5} N
UFB	72×10^{-5} N [a]	116×10^{-5} N	275×10^{-5} N	135×10^{-5} N
LFB	37×10^{-5} N [a, b]	61×10^{-5} N [c]	125×10^{-5} N	63×10^{-5} N [c]
AC	42°	44°	25°	24°
UFB/AC	1,7	2,6	11	5,6
LFB/AC	0,9	1,4	5	2,6

[a] $\sigma > 0{,}2\ F$, therefore σ was restricted to $0{,}2\ F$.

[b] $F < 50 \times 10^{-5}$ N, therefore $LFB = F_p - \sigma_p$ was used.

[c] $F < 150 \times 10^{-5}$ N, therefore $LFB = F_p - (F_p/50 \times 10^{-5})\ \sigma_p$ was used.

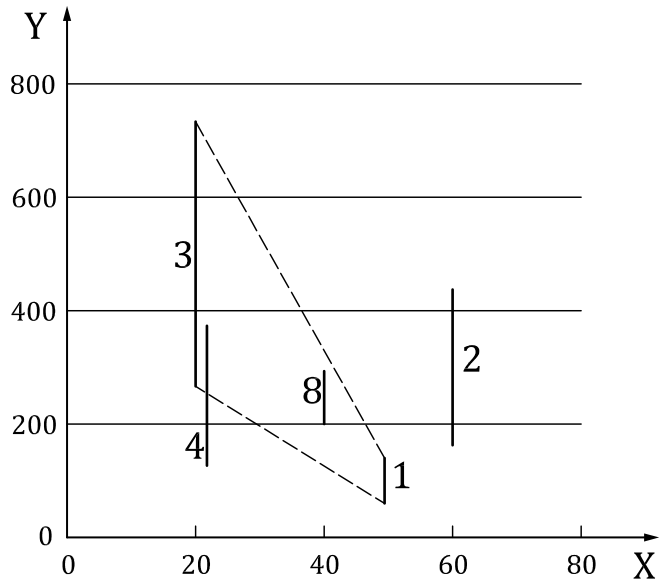
In this example, the manufacturer has modified one of the open-loop parent models and designated it Model 8. The modified model differs from its parent model in loop configuration and overall diameter. To determine if Model 8 is a Level A modification, its compression properties were determined and found

as given in Table B.11. As always, the force spread value f (here set equal to the standard deviation, σ) from the mean was used to define the force boundaries for this modified model.

Table B.11 — Mechanical data for new Model 8

Parameter	Compressed diameter			
	10 mm	11 mm	10 mm after decay	11 mm after decay
F	250×10^{-5} N	220×10^{-5} N	120×10^{-5} N	100×10^{-5} N
σ	40×10^{-5} N	30×10^{-5} N	20×10^{-5} N	15×10^{-5} N
UFB	290×10^{-5} N	250×10^{-5} N	140×10^{-5} N	115×10^{-5} N
LFB	210×10^{-5} N	190×10^{-5} N	100×10^{-5} N	85×10^{-5} N
AC	40°	32°	42°	34°

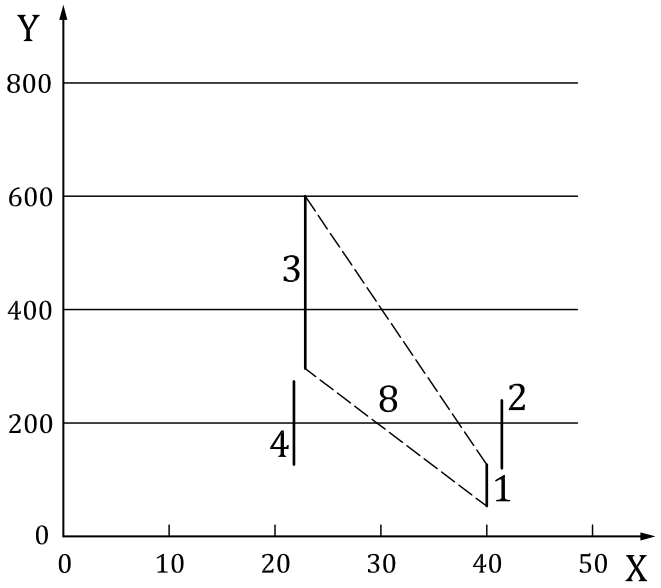
The data in Table B.11 for Model 8 are incorporated in Figures B.1 to B.4, from which it can be concluded that Model 8 is a Level A modification of the manufacturer's open-loop parent models and therefore does not have to undergo a clinical evaluation. This conclusion is based on the following elements. The force ranges for Model 8 overlap the boundary ranges associated with two parent models which are no more than 30° of *AC* different from each other under all the test conditions (at 10 mm and 11 mm, and at 10 mm and 11 mm after decay).



Key

X	angle of contact, degrees	Y	force, 10^{-5} N
1	Model 1	4	Model 4
2	Model 2	8	Model 8
3	Model 3		

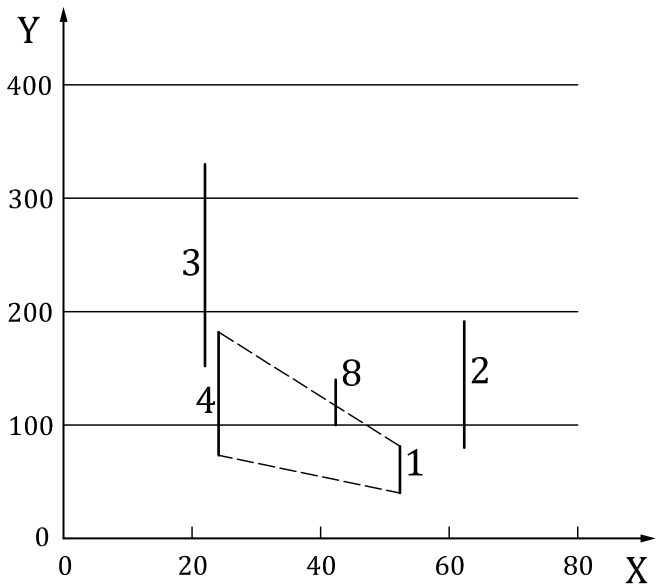
Figure B.1 — *F*/*AC* range for Models 1 to 4 at 10 mm of Example 3



Key

X	angle of contact, degrees	Y	force, 10^{-5} N
1	Model 1	4	Model 4
2	Model 2	8	Model 8
3	Model 3		

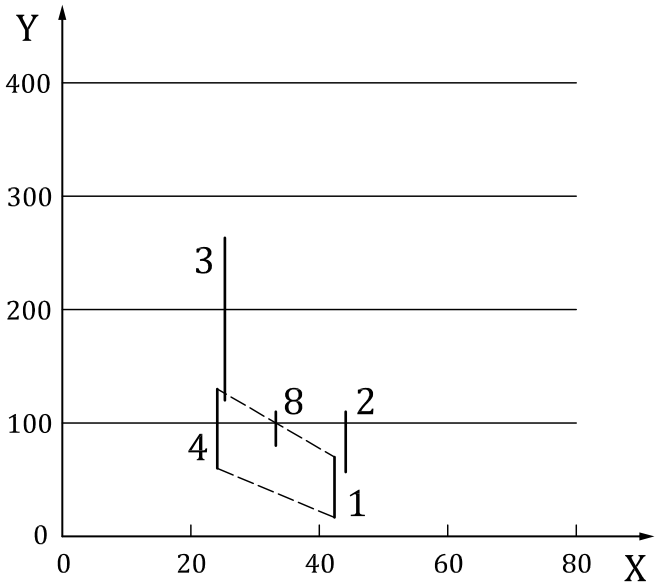
Figure B.2 — *F/AC* range for Models 1 to 4 at 11 mm of Example 3



Key

X	angle of contact, degrees	Y	force, 10^{-5} N
1	Model 1	4	Model 4
2	Model 2	8	Model 8
3	Model 3		

Figure B.3 — *F/AC* range for Models 1 to 4 at 10 mm, after decay of Example 3



Key

X	angle of contact, degrees	Y	force, 10^{-5} N
1	Model 1	4	Model 4
2	Model 2	8	Model 8
3	Model 3		

Figure B.4 — *F/AC* range for Models 1 to 4 at 11 mm after decay of Example 3

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1) ISO 11979-7 is under revision to incorporate multifocal intraocular lenses, at which point ISO 11979-9 will be withdrawn.

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