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American National Standard (DRAFT) **ANSI Z80.35**

American National Standard for Ophthalmics

Extended Depth of Focus Intraocular Lenses

1 Scope and Purpose

This standard applies to intraocular lenses (IOLs) whose function is the correction of aphakia, with extended range of focus above a defined functional visual acuity threshold to provide useful distance and intermediate vision with monotonically decreasing visual acuity from the best distance focal point.

This standard addresses specific requirements for Extended Depth of Focus Intraocular Lenses (EDF IOLs) that are not addressed in the normative references, and include vocabulary, optical properties and test methods, mechanical properties and test methods, labeling, biocompatibility, sterility, shelf-life and transport stability, and clinical investigations necessary for this type of device. As with any standard, alternative validated test methods may be used.

2 Normative references

The following standards contain provisions that, through reference in this text, constitute provisions of this American National Standard. At the time of publication, the editions indicated were valid. All standards are subject to revision, and parties to agreements based on this American National Standard are encouraged to investigate the possibility of applying the most recent editions of the standards indicated below. Members of the IEC and ISO maintain registers of currently valid International Standards.

ANSI Z80.7, American national standard for ophthalmics-intraocular lenses

ISO 10993-2, Biological evaluation of medical devices – Part 2: Animal welfare requirements.

ISO 10993-6, Biological Evaluation of Medical Devices – Part 6: Tests for local effects after implantation

ISO 11979-1, Ophthalmic implants - Intraocular lenses - Part 1: Vocabulary

ISO 11979-2, Ophthalmic implants - Intraocular lenses - Part 2: Optical properties and test methods

ISO 11979-3, Ophthalmic implants - Intraocular lenses - Part 3: Mechanical properties and test methods

ISO 11979-4, Ophthalmic implants - Intraocular lenses - Part 4: Labelling and information

ISO 11979-5, Ophthalmic implants - Intraocular lenses - Part 5: Biocompatibility

ISO 11979-7, Ophthalmic implants - Intraocular lenses - Part 7: Clinical investigations

ISO/DIS 11979-8, Ophthalmic implants - Intraocular lenses - Part 8: Fundamental requirements

ISO/WD 11979-9, Ophthalmic implants - Intraocular lenses - Part 9: Multifocal intraocular lenses

ISO14155-1, Clinical Investigation of Medical Devices Part 1: General Requirements

ISO 14155-2, Clinical Investigation of Medical Devices Part 2: Clinical Investigation Plans

3 Definitions

For the purpose of this standard, the definitions given below and in ISO 11979-1, ISO 14155-1 and ISO 14155-2 apply.

3.1 Monotonically Decreasing**:** Based on an average of all eyes in a clinical defocus curve study (refer to Section B.4.8.2.1 Defocus Curve), “a non-increasing trend of less than or equal to 0.04 logMAR change

between two successive negative optical defocus levels from far through near range of vergence".

4 Physical requirements

4.1 Scope

This section applies to the physical properties of EDF IOLs in the assembled or final form as intended for implantation in the human eye.

4.2 Requirements

The manufacturer shall describe the optical design that provides an extended depth of focus as compared to a monofocal IOL. Optical testing shall be performed over a range that includes the clinical function of the device and intended claim(s).

4.2.1 Tolerances and dimensions

The requirements of ISO 11979-3 shall apply.

5 Optical requirements

5.1 Scope

This section applies to the optical properties and performance requirements of EDF IOLs in their final form, as intended for implantation in the human eye.

The test methods described in this standard are reference methods. Alternative methods that produce equivalent results to those obtained with the reference methods can be used if the manufacturer can demonstrate that the IOLs meet the minimum dioptric power and imaging quality requirements.

5.2 Requirements

Optical testing shall be performed over a range that includes the clinical function of the device and intended claim(s).

5.2.1 Optical characterization

The optical performance of the EDF IOL shall be compared to the optical performance of a monofocal IOL and multifocal IOL that has the same dioptric power for distance vision. The optical performance parameters that shall be compared are;

a) The modulation transfer function (MTF) shall be performed, as specified in Annex A, over an optical vergence range that includes the clinical function of the device and intended claim(s).

b) The depth of focus range.

c) Unwanted optical / visual effects

d) Expected visual acuity at specified defocus values

Details of these performance measurements are given in Annex A.

NOTE 1: The monofocal IOL shall be the parent monofocal IOL or if no parent monofocal IOL is available, then a commercially available monofocal IOL can be used.

NOTE 2: The multifocal IOL shall be a commercially available multifocal IOL.

5.2.2 Dioptric power.

The labeled power for distance vision associated with the EDF IOL is the power for which the EDF IOL creates the best focus. This power shall be determined by one of the methods in ISO 11979-2. When determined by one of these methods, the dioptric power tolerances specified in ISO 11979-2 shall apply.

NOTE 1: Since EDF IOLs will in general have a range of dioptric powers that give essentially the same best focusing quality, typically the value in such a range of best focus powers that is the lowest power is to be taken as the dioptric power of the EDF IOL.

NOTE 2: A value different from the lowest power may be used as the labeled power with adequate justification.

NOTE 3: The tolerances specified in ISO 11979-2 represent the combined manufacturing and measurement tolerances around the nominal power.

5.2.3 Imaging quality.

EDF IOLs shall have imaging quality verified by measuring its MTF per applicable sections of ISO 11979-2. The MTF testing shall be performed for 3 mm diameter aperture.

The manufacturer shall demonstrate that all available labeled powers of an EDF IOL meet far image quality specifications.

MTFs taken with vergences of light entering the model eye from the target of a value found to give best distant focus shall be used to verify far image quality. MTFs taken at a second value at -1.5 D from the best distant focus value, or other validated second focus value shall be used to verify depth of focus.

The manufacturer shall have the option of setting the minimum MTF specification based on either the area under the curve between two spatial frequencies or on the MTF value found at 50 cycles/mm.

The manufacturer shall set the minimum MTF specification by characterizing the EDF IOLs that were successfully used in clinical trials to demonstrate compliance with this standard using the specification method they have chosen.

5.2.4 Spectral Transmittance.
The requirements in 5.2.3 of ANSI Z80.7 shall apply.

6 Mechanical requirements

6.1 Scope

This section applies to the mechanical properties and performance requirements of EDF IOLs in the assembled or final form, as intended for implantation in the human eye.

6.2 Requirements

The requirements in ISO 11979-3 shall apply.

7 Biocompatibility requirements

7.1 Scope

This section applies to the biocompatibility requirements for EDF IOLs in the assembled or final form, as intended for implantation in the human eye.

7.2 General guidelines

Animals shall be cared for in accordance with ISO 10993-2.

Unless otherwise indicated, the materials used in biological testing shall either be the sterile finished EDF IOLs or facsimile materials fabricated and processed in a manner equivalent to that used for the EDF IOLs. The manufacturer shall establish and document equivalency in material and in test sensitivity, where appropriate, for the test sample and the sterile finished EDF IOL.

7.3 Biological test requirements

The requirements in 7.3 of ANSI Z80.7 shall apply with the following additional requirements:

Manufacturers of new IOL materials shall include in their risk analysis an assessment of the potential for material changes such as calcification. The risk analysis shall consider the history of clinical use of the material, and accelerated models to test the long-term stability of the material in an animal model. One non-ocular implantation test to assess the stability of the material is described in ISO 11979-5.

After light microscopy evaluation of the explanted EDF IOLs from the ocular implantation test (ANSI Z80.7 Annex C), half of the samples shall be thoroughly cleaned (if the optical surfaces can be cleaned without being damaged) and then assessed for changes in optical properties in accordance with the requirements in Section 5 of this standard. The other half of the samples shall then be evaluated by SEM/ EDX, where feasible, for surface changes.

NOTE The test or control material used for the ocular implantation test (ANSI Z80.7 Annex C) may be a representative sample of the EDF IOL that has gone through the same fabrication methods as the device to be marketed, has a mass at least equivalent to the finished EDF IOL, and has a size and shape that would allow the required post-retrieval evaluations to be performed, if its use can be justified.

7.4 Physicochemical test requirements

The requirements as specified in ANSI Z80.7 shall apply with the following additional requirements:

Addition:

The dioptric power shall be determined before and after testing if finished EDF IOLs are used in hydrolysis testing. The refractive index shall be determined before and after hydrolysis testing if a facsimile material is used. The dioptric power shall be within the tolerance limits specified in ISO 11979-2 before and after hydrolysis testing or the refractive index change shall be used to determine the resulting power change and this difference shall be within the tolerance limits specified in ISO 11979-2.
A risk analysis shall be performed to determine whether mechanical testing is required of the EDF IOL after the material aging associated with the hydrolytic stability testing specified in ANSI Z80.7 and the photostability testing specified in ANSI Z80.7.

The EDF IOL material shall be assessed for the presence of residual insoluble inorganics in or on the lens arising from the manufacturing materials and process aids. -When residues have been identified, the lens itself shall be evaluated for such residuals. The test methods used for this evaluation shall be identified, validated and justified. Consideration shall be given to methods that use solvents that dissolve the contaminating materials and that have a detection limit of 0.2 μg/lens or 10μg/g. Correlation between these results and the results from biological tests, if any, shall be documented.

8 Sterility/package integrity requirements

8.1 Scope

This section applies to the sterility and integrity of the packaging of the EDF IOL in its final form, as intended for implantation in the human eye.

The EDF IOL shall be provided sterile. Whenever possible, the product shall be terminally sterilized in its final container.

8.2 Requirements

The requirements in Section 8.2 of ANSI Z80.7 shall apply.

9 Shelf-life and transport stability requirements

9.1 Scope

This section applies to the ability of the packaging to protect the EDF IOL from damage during shipping and to maintain the sterility of the device for the duration of its shelf-life.

9.2 Requirements

The requirements in 9.2 of ANSI Z80.7 shall apply.

10 Clinical evaluation

10.1 Scope

This section applies to the clinical performance of the EDF IOL in its final form, as intended for implantation in the human eye.

The general requirements concerning the clinical investigations of medical devices for human subjects specified in ISO 14155-1, ISO 14155-2 and ISO 11979-7 shall apply, together with the following particular requirements.

10.2 Clinical investigation plan

The requirements in ISO 14155-1 and ISO 14155-2 and the monofocal IOL requirements in ISO 11979-7 shall apply. The same type of monofocal IOL as used in the optical characterization evaluations (Section 5.2.1) shall be used as the control lens in the clinical investigation.

10.2.1 EDF IOL as a modification of an approved monofocal parent:

At least 100 subjects in the EDF IOL and at least 100 subjects in the control arm shall be included in a bilateral implantation study and followed up for 6 months postoperatively.

To evaluate depth of focus performance or visual disturbances, a pilot study or a phased approach may be considered. Typically, bilateral implantation of the EDF IOL in 30 subjects may be adequate for a pilot study.

10.2.2 EDF IOL without approved monofocal parent:

In cases where no previously approved monofocal parent exists for the EDF IOL, the study design requirements for demonstrating safety and effectiveness shall also fulfill all basic requirements from ISO 11979-7

10.3 Effectiveness Requirements

The effectiveness of the EDF IOL shall be evaluated. The following criteria shall be met:

- The EDF IOL demonstrates statistical superiority over the control group on mean, monocular distance corrected intermediate visual acuity at 66 cm.

- The EDF IOL demonstrates at least 0.5 D greater monocular photopic distance-corrected depth of focus compared to the monofocal control IOL at 0.2 logMAR visual acuity threshold.

- The median, monocular distance-corrected photopic intermediate visual acuity at 66 cm is at least 0.2 logMAR.

- The mean, monocular best corrected distance acuity for the EDF IOL is statistically non-inferior to the control using a non-inferiority margin of 0.1 logMAR.

Annex B contains suggested detail concerning a clinical investigation.

11 Labeling

The requirements of Annex D shall apply.

Annex A
(normative)

Optical Characterization

A.1 General

The manufacturer shall characterize the optical performance of the EDF IOL, a monofocal IOL of the same distance power and a multifocal IOL of the same distance power, in the manner described below to conform to the requirements of section 5.2.1 *Optical Characterization.*

This characterization includes measurements of the optical performance of the EDF IOL that will assist in predicting performance on clinical endpoints as specified in 10.3.

The monofocal IOL to be used in optical characterization tests shall be the same type as the one used as control group in the EDF IOL clinical trial.

The multifocal IOL to be used in optical characterization tests shall be one that is currently available commercially. When reporting the results of testing with the multifocal IOL, the specific lens model used shall be reported.

In particular, this characterization will assess the optical performance of the EDF IOL and the comparison monofocal IOL and multifocal IOL when used to view objects at different distances.

A.2 Theoretical evaluation

The manufacturer shall perform a theoretical evaluation (e.g., ray trace evaluation) of the optical design demonstrating the additional depth of focus of the EDF IOL compared to a monofocal IOL in an eye model with a physiologically appropriate cornea and white light at 3, and 4.5 mm diameter pupils. Suitable parameters for a physiological cornea are found in Annex C, C.9. Suitable eye models for theoretical evaluation are described in [1, 2, 3]. The appropriate spectral distribution of white light is described in A.6.

The theoretical evaluation shall include calculation of the modulation transfer function of the eye under various entering vergence conditions, the conditions of lens tilt and de-centration specified in A.3.2. Using the calculated modulation transfer function data, the expected performance of the implanted lens during visual acuity testing shall be reported per A.3.3.

A.3 Optical testing

A.3.1 MTF through-focus response testing

Optical performance is tested and compared to that of a monofocal lens and a multifocal lens.
The model eyes specified in Annex C, C.2 are suitable for performing these tests. If model eye type 2, specified in ISO 11979-2, is used, special instructions for its use are found in Annex C, C.8. These tests are to be made with the following additions, allowing for measurements in white light:

a) The light is covering at least the range of visible light, i.e. 380 nm to 700 nm as per A.6
b) Spectral sensitivity of the combination of light source, spectral filter(s), and camera sensitivity shall follow the photopic luminosity V(λ) function for the eye.
c) The model eye having a physiological amount of corneal spherical aberration.

d) The model eye having a physiological amount of chromatic aberration.

The model eyes specified in C.2.1 and C.2.2 fulfill the requirements of c) and d).

Generate the MTF through-focus-response of the IOL with a medium aperture (3.0 mm) and a large aperture (between 4 mm and 5 mm). Focus to maximum MTF at 50 cycles/mm for an object at infinity and then measure MTF at the following defocus positions:

- Range +1.50 D to -2.50 D
- Increment or vergence step
  0.25 D from 0.00 D to ±0.50 D
  0.50 D greater than 0.50 D or less than -0.50 D

NOTE: In addition to using white light to make the above measurements, green light (550 nm) may also be used.

A.3.2 MTF testing with tilt and decentration

The modulation transfer function shall be measured for the case of entering target vergence of 0 D with the lens centered in large diameter (4 mm to 5 mm) pupil aperture, de-centered 1 mm and centered but tilted 5 degrees with respect to the pupil plane.

NOTE: When the IOL is de-centered, the pupil aperture should be of an appropriate diameter to expose only the clear optic of the IOL.

A.3.3 Expected visual acuity

The expected visual acuity, expressed in logMAR units, for a given testing condition shall be found by using the measured modulation transfer function values as found in A.3.1. A value of expected visual acuity shall be reported for each of the test conditions specified in A.3.1 (3.0 mm pupil). An example method for calculating the expected visual acuity using measured modulation transfer function value is given Annex C, C.7.

A.3.4 Depth of focus range

The reported depth of focus value shall be the defocus range for which the expected visual acuity, as found using the method of A.3.3, has the logMAR value 0.2 or better.

A.4 Unwanted optical/visual effect testing

The EDF, monofocal and multifocal lenses shall be tested while in the model eye for the creation of spurious images, such as *halos,* various types of *glare* or secondary images, by examining the image of an extended source of light for concentrations of light other than the expected primary image.

A.4.1. Testing conditions

- Spurious image testing shall be performed in a physiological model eye. An example of such a physiological eye model is provided Annex C, C.2.2.
- The physiological eye model shall include chromatic and spherical aberration.

- The image capture system shall be able to examine the image formed over a visual angle of minimum 1 degree.
- The image capture system shall be able to record over a range of light intensities of at least 4 decades.
- The physical pupil diameter of at least 4.0 mm shall be used, corresponding to an entrance pupil of approximately 4.5 mm.

A.4.2 Light source

The light source shall be an extended light source. The visual angle shall be at least 1 minute, but no larger than 30 minutes in diameter. All tests shall be performed using the same light source. The light source shall be white light as specified in A.3.1 a) and b).

A.4.3. Procedure

The lens shall be centered in the pupil aperture of a physiological model eye.

Images shall be recorded of the distance image of the same lens power for each of the lens models (EDF, monofocal, and multifocal). A medium lens power shall be used (between 19.0D and 22.0D).

Images shall be reported in two ways:

a) As a printed image, using a gamma correction that clearly shows the halo of the multifocal lens. All images shall use the same gamma correction.
b) As a radial light intensity graph, plotting visual angle on the horizontal axis and the logarithmic value of the light intensity on the vertical axis.

Images shall be assessed considering the size and intensity of the spurious image, as well as any intensity irregularities and asymmetries.

NOTE 1: a clearly visible halo of a multifocal lens can be obtained when the pixel value of the halo in an 8-bit greyscale printout is between 100 and 150.

NOTE 2: a dynamic range of 4 decades can be achieved using a 14-bit camera, or by combining images obtained with different shutter times. Other methods may be used as well.

A.5 Determination of distance image plane within the model eye

The distance image plane is defined as the plane within the model eye where the best image of the target forms when the vergence of light from the target, as it enters the model eye is 0 D. However, in the case of EDF-IOLs, where a very good image of a 0 D target forms over an axial range within the model eye, a method is needed to fix a single axial position for the image capture plane. Note that a microscope system for image transfer will have a very short depth of focus so object plane of the camera system is well defined.

The distance image plane will therefore be experimentally found by first insuring that the target vergence is 0 D as it enters the model eye. While using a point target and while observing the image formed by the camera system, the distance between the camera system and the model eye is varied while noting the peak intensity of the captured image. The model eye is moved until the intensity is observed to take a maximum value. Then the camera system is moved away from the model eye until the peak intensity falls to 80% of the maximum peak intensity previous found. This procedure is equivalent to the procedure used in subjective eye refraction of increasing plus spherical power until blur is positively detected. This is done to ensure that there is not an axial position giving good image resolution beyond the selected distance axial position. Finally, the model eye is moved toward camera system until the peak intensity returns

to 95 % of the maximum peak intensity found.

A.6 White light

For the purposes of this Annex *white light* is defined as polychromatic radiation covering at least the range of visible light, i.e. 380 nm to 700 nm, that has a spectral signature similar to that used for illumination of visual acuity targets. An acceptable source of such radiation is a thermal source such as a quartz halogen lamp with a color temperature of at least 2800 K.

Annex B
(informative)

Clinical investigation

B.1 General

In this annex, guidance is given on the design of the clinical investigation to assess the safety and performance of an EDF IOL and in analyzing the data from that investigation.

In most cases, the EDF IOL will be a modification of a previously approved monofocal IOL and a clinical study of bilaterally implanted 100 EDF IOL subjects and a minimum of 100 bilateral control subjects followed for 6 months may be sufficient to assess the safety and performance of the EDF IOL.

In cases where no previously approved monofocal parent exists for the EDF IOL, the studies described below should be integrated into clinical design of a monofocal IOL described in ISO 11979-7 (300 subjects in the investigational lens followed for 1 year) plus an appropriate monofocal control group.

B.1.1 Clinical assessments

All of the monofocal safety and effectiveness assessments specified in ISO 11979-7 should be performed.

The following additional safety and effectiveness assessments should be performed:

- Defocus testing to measure depth of focus
- Uncorrected visual acuity at far and intermediate
- Manifest Refraction
- Best corrected distance visual acuity
- Intermediate visual acuity with best distance correction
- Patient reported outcome (if there is no parent monofocal lens, or if required from risk assessment of the preclinical glare assessment)
- Contrast sensitivity (at distance)
- Letter acuity – 10% contrast (at intermediate)

Additional assessments may be necessary, based upon risk analysis or for unusual designs such as non-rotationally symmetric lenses.

B.2 Objectives of the clinical investigation

The objectives of the clinical investigation are to determine the safety and effectiveness of the EDF IOL. The recommended primary safety assessments and analysis are provided in ISO 11979-7. In addition to the safety analyses recommended in ISO 11979-7 and the rates of adverse events per ISO 11979-7 “grid”, the trial should characterize the rate of adverse events that may be specifically related to the design features of the EDF IOL and any non-grid significant events. In addition, key safety endpoints should include distance contrast sensitivity (mesopic, with and without glare), and best-corrected distance visual acuity (demonstration of non-inferiority compared to an appropriate monofocal control IOL).

Effectiveness should be demonstrated by the effectiveness assessments listed in B.1.1. The sample size for the study should be adequate to detect adverse events with an expected rate of 1% or greater If the EDF IOL has no approved monofocal parent, then 300 evaluable investigational device subjects available at all scheduled visits in the EDF IOL group are needed, and if the EDF IOL is a modification of an approved monofocal IOL, a sample size of 100 device subjects may be sufficient for the clinical assessments.

A control group with a sample size equal to the EDF IOL group used for the additional testing in B.1.1 is also needed.

B.3 Design of the clinical investigation

For an EDF lens without a monofocal parent, there should be an initial phase 1 (approximately 50 subjects) in which unilateral implantation of the control monofocal IOL or the EDF IOL should be done in a randomized manner. In the second phase (balance of subjects), test and control lenses should be bilaterally implanted in separate groups of subjects per ISO 11979-7. The bilateral implantation will permit appropriate evaluation of visual disturbances.

For an EDF lens with a monofocal parent, a prospective, controlled, randomized, masked (subject and examiner), bilaterally implanted, multicenter trial of 100 subjects in EDF group and 100 bilateral subjects in the control group may be appropriate. The adverse events that are common to ISO 11979-7 are compared to the safety and performance endpoints described in ISO 11979-7.

The study is designed to determine the additional depth of focus at a functionally useful acuity level (e.g. 0.2 logMAR) for the EDF IOL compared to the control monofocal IOL with an additional criterion such that the EDF IOL must provide a minimum visual performance at an intermediate distance (66 cm). It is also designed to assess any decrease in best corrected distance visual acuity and contrast sensitivity as a result of the increased depth of focus of the EDF IOL.

The clinical investigative plan should include a description of the methods used to minimize potential for bias (e.g., age-matching, masking, randomization). The protocol should include a thorough description of the methodology used in the defocus testing, including details of instructions given to technicians and subjects that help to minimize bias of the measurement method.

Investigators should implant the same monofocal IOL (parent lens if one exists) into all control eyes. Subjects and examiners should be masked for key test procedures such as visual acuity and manifest refraction.

The clinical investigation plan (CIP) should describe how subject visits in between reporting periods will be reported and analyzed.

The CIP should specify that each investigator should contribute a minimum of 20 investigational subjects to the study population, but not more than 25% of the subjects in the study.

The lost to follow-up subjects should comprise less than 10% of the study population after one year.

B.3.1 Investigation duration

An investigation duration of 1 year should be adequate for EDF IOLs –that have no approved parent. An investigation duration of 6 months is adequate to for EDF IOLs that have an approved parent IOL.

B.3.2 Enrollment of subjects

For a lens without an approved parent monofocal lens, enrollment should be in two phases:

- Phase 1: 50 EDF subjects and 50 control subjects unilaterally implanted.
    - Subjects should complete 6 months follow-up before phase 2 is entered.
- Phase 2: Balance of subjects

For a lens with an approved parent monofocal lens: The study is a single phase investigation with 100 bilaterally implanted subjects followed for 6 months.

B.3.3 Inclusion and exclusion criteria for subject selection

B.3.3.1 Inclusion criteria

The following inclusion criteria are recommended:

- Cataractous lens changes as demonstrated by best corrected visual acuity of 20/40 or worse either with or without a glare source present (e.g., Brightness Acuity Tester) or with significant cataract-related visual symptoms
- Best corrected visual acuity to be better than 20/32 after cataract removal and IOL implantation as estimated by potential acuity meter (PAM) or surgeon estimation.
- ≤ 1.0 D of preoperative keratometric astigmatism
- Clear intraocular media other than cataract
- Given written informed consent by subject
- Subject is willing and able to comply with schedule for follow-up visits
- Subjects should be 22 years or older

B.3.3.2 Exclusion criteria

The following exclusion criteria are recommended:

- systemic disease that could increase the operative risk or confound the outcome
- systemic medications that may confound the outcome or increase the risk to the subject in the opinion of the investigator (tamsulosin hydrochloride (Flomax) or other medications with similar side effects (floppy iris syndrome))
- ocular condition that may predispose for future complications
- previous intraocular or corneal surgery that might confound the outcome of the investigation or increase the risk to the subject
- pregnant, lactating during the course of the investigation, or has another condition with associated fluctuation of hormones that could lead to refractive changes
- Subjects with diagnosed degenerative visual disorders (e.g. macular degeneration or other retinal disorders) that are predicted to cause future acuity loss to 20/30 or worse
- Subjects with conditions that increase the risk of zonular rupture during cataract extraction procedure that may affect the postoperative centration or tilt of the lens
- If preclinical testing or risk analysis indicates potential for substantially increased light scatter over a monofocal lens, then exclude subjects who are expected to require retinal laser treatment;

NOTE: Subjects for whom the surgeon is unable to achieve secure lens placement in the designated location, should be discontinued from the study.

B.3.4 Examination schedule

The following reporting periods are recommended:

- Preoperative
- Operative
- Day 1 (1-2 days postoperative)
- Week 1 (7-14 days postoperative)
- Month 1 (30 - 60 days postoperative)
- Month 6 (120 - 180 days postoperative)
- Month 12 (330 - 420 days postoperative) – If no approved monofocal parent IOL

Table B.1
Recommended Schedule of Procedures

Clinical Evaluation	Illumination	Testing performed	Preop	Op	Day 1	Week 1	Month 1	Month 6	Month 12[1]
Uncorrected Distance Visual Acuity (UCDVA)	Photopic	Monocular Binocular	X		X	X	X	X	X X
Best Corrected Distance Visual Acuity (BCDVA)	Photopic	Monocular Binocular	X			X	X	X	X X
Uncorrected Intermediate Visual Acuity (UCIVA)	Photopic	Monocular Binocular					X	X	X X
Distance-Corrected Intermediate Visual Acuity (DCIVA)	Photopic	Monocular Binocular					X	X	X X
Distance-Corrected Intermediate Low Contrast Acuity (10%)	Photopic	Monocular						X	
Best-Corrected Intermediate Low Contrast Acuity (10%)	Photopic	Monocular						X	
Manifest Refraction	Photopic	N/A	X			X	X	X	X
Pupil Size	Photopic	N/A	X				X	X	X
Pupil Size	Mesopic	N/A					X		X[2]
Dilated Fundus Exam	N/A	N/A	X					X	X
Slit Lamp Exam	N/A	N/A	X		X	X	X	X	X
Intraocular Pressure	N/A	N/A	X		X	X	X	X	X
Lens Stability (Tilt/ Decentration)[3]	N/A	N/A					X	X	X
Keratometry	N/A	N/A	X						
Subject Questionnaire[4]	N/A	N/A					X	X	X
Axial Length	N/A	N/A	X						
Anterior Chamber Depth	N/A	N/A	X						
Gonioscopy	N/A	N/A	X				X[5]	X	X
Far Contrast Sensitivity	Mesopic	Monocular						X	X[6]
Far Contrast Sensitivity	Mesopic with glare	Monocular						X	X[6]
Defocus Curve Test	Photopic	Monocular Binocular						X	

NOTE: Controls to be tested at the same time intervals as study group through 1 year postoperatively.

1 Minimum study duration of 6-months is required. Only EDF IOLs without approved monofocal parent IOL require 12 month study.
2 Mesopic pupil size should be assessed at any visit postop where the subject complains of visual symptoms, as well as the specific visits for contrast sensitivity testing.
3 Lens stability evaluation is performed according to current ISO 11979-7 guidance.
4 Questionnaire is administered if warranted by risk analysis and results of preclinical glare assessment.
5- Gonioscopy should be done at the final visit as determined by risk analysis.
6 Testing is repeated at the 12 months visit in the 12 month study for those subjects in the contrast sensitivity study that had a posterior capsulotomy after the Form 4 visit.

B.4 Clinical tests

Table B.1 contains the recommended examination schedule, and the clinical evaluations to be performed at each visit.

The following examinations are to be performed on all investigational subjects:

- Uncorrected distance visual acuity (UCDVA) [photopic]
- Uncorrected intermediate visual acuity (UCIVA) [photopic]
- Best corrected distance visual acuity (BCDVA) [photopic]
- Distance-corrected intermediate visual acuity (DCIVA) [photopic]
- Low Contrast (10%) Distance Corrected Intermediate Visual Acuity [photopic]
- Low Contrast (10%) Best Corrected Intermediate Visual Acuity [photopic]
- Defocus curves (monocular)
- Manifest refraction
- Subject questionnaire (if required from preclinical glare assessment)
- Subject ocular and visual symptoms (non-directed questions)
- Intraocular pressure
- Slit lamp exam
- Dilated fundus exam
- Evaluation of clarity of fundus image
- Keratometry
- Photopic pupil size
- Mesopic pupil size (all visits for exams with contrast sensitivity assessment, and in eyes with visual symptoms)
- Axial length measurement
- Gonioscopy
- Contrast sensitivity (monocular) – distance

NOTE: If optics of the lens are such that intermediate acuity is strongly dependent on pupil size, then mesopic high contrast distance-corrected intermediate acuity should also be done at 6 months.

B.4.1 Visual acuity and Manifest Refraction

Far and intermediate charts, chart luminance, ambient illumination, testing distances and testing procedures should be standardized for all investigators. Reporting format for refraction results should be standardized across investigational sites.

Distance (far) manifest refraction and the testing distance used should be recorded on the case report forms. With EDF lenses, it is likely that the endpoint of refraction for both sphere and cylinder will not be clear-cut due to the extended depth of focus. The protocol should have a well-defined and detailed standard operating procedure for determining the distance refractive endpoint.

If the distance manifest refraction is done at a testing distance of less than 6 meters or 20 feet, the manifest refraction should be adjusted for infinity. This infinity-adjusted manifest refraction should have a sphere equal to the measured manifest refraction sphere minus 1/(testing distance in meters). (For example, if distance testing is done at 4 meters and the measured manifest refraction is -0.25-0.75X 090, then the infinity-adjusted manifest would be -0.50-0.75X090.) All intermediate testing that is done through the distance correction should be done through this infinity-adjusted manifest refraction (rounded to the nearest 0.25 D).

Intermediate visual acuity testing should be performed at 66 cm (1.5 diopters).

Because of the large number of acuity tests and the likelihood that the treatment effect is small, it is essential to minimize bias due to squinting, blur interpretation, memorization, etc. The protocol should detail how sources of bias will be minimized. It is crucial to eliminate bias due to chart memorization. For this reason it is recommended that acuity testing be done whenever possible using computerized charts with random presentation of letters. If this procedure is not followed, the protocol should explain how memorization will be eliminated.

NOTE: When using a chart at a different test distance than what the chart was designed and calibrated for, all corresponding visual acuity values should be calculated appropriately. For example the 20/40 letter (0.30 logMAR) of a chart developed for 80 cm will be equivalent to 20/50 (0.40 logMAR) at 66 cm viewing distance and 20/80 (0.6 logMAR) at 40 cm viewing distance.

NOTE: When testing using trial frame or phoropter, the subject should be carefully observed for squinting and should be frequently reminded not to squint.

B.4.1.2 Luminance

A specific chart background luminance should be selected ***from 80 - 110 cd/m^2 (***85 cd/m^2 recommended) for photopic testing. Luminance should be similar for all testing centers.

Ambient luminance should be from dim to dark to maximize pupil size. No surface (including reflective surfaces) within the subject's field of view should exceed the chart background luminance.

B.4.1.3 Data recording procedures

- All physical and optical testing distances should be recorded.
- All corrective lenses should be recorded.

B.4.3 Contrast sensitivity

Grating contrast sensitivity tests assess contrast threshold for spatial gratings, i.e., patterns of alternating light and dark parallel bars, as a function of spatial frequency (inverse of bar width). At each spatial frequency, the contrast is varied until the bar pattern is just detectable.

NOTE: Methods to minimize high frequency artifacts that may affect the data are to blur the outer edges of the grating and to surround all edges by a uniform field equal to the grating in space-average luminance. Further information about the problem of sharp edged gratings may be found in Thorn [4].

Contrast sensitivity testing should be performed monocularly, under mesopic and mesopic with glare conditions. Mesopic contrast sensitivity should be measured at spatial frequencies as close as possible to 1.5, 3, 6, and 12 cycles/degree. Subjects should be tested with their best spectacle correction. The same contrast sensitivity equipment and method should be used at each site, per manufacturer's instruction.

NOTE: Photopic with glare contrast sensitivity testing may be performed if warranted by risk analysis due to lens design characteristics. In this case, spatial frequencies, 3, 6, 12, and 18 cycles/degree should be tested.

For mesopic testing, the chart luminance should be 3 cd/m^2 (±0.5 cd/m^2) and the ambient illumination should be lower than the chart luminance. The level of glare should be the minimum necessary to significantly reduce the contrast sensitivity of young adult subjects with normal corneas and normal vision, but the illumination should not be so great as to completely wash out the target in these young, normal subjects. The reduction in contrast sensitivity due to glare in normal subjects should be a mean decrease of about 0.10 log units at 6 cycles/ degree (for grating charts). A small pilot investigation of normal subjects may be necessary to determine an appropriate glare level. Subjects in this pilot study that show an increase in contrast sensitivity performance with glare should be excluded from the analysis to determine the appropriate glare level.

To enhance the quality of the contrast sensitivity data, a practice trial should be performed at each evaluation.

A minimum of 10 minutes should be provided for subject dark adaptation prior to beginning the mesopic contrast testing. Testing should be performed once and then repeated; the average of these two tests should be used for the data analysis. If the two measurements for a spatial frequency differ by two contrast sensitivity patches (i.e. 0.30 log units), then a third measurement should be performed and the average of these three tests should be used for data analysis. The scoring instructions provided by the manufacturer of the equipment are to be followed with the following exception: If a subject is unable to see a targeted spatial frequency at any available contrast (including the contrast of the reference patch), the highest contrast or, equivalently, the lowest contrast score should be given, preceded by the appropriate inequality symbol (< or >) to indicate that the actual sensitivity is below the given value. Prior to any averaging or other statistical calculations, all contrast threshold values should be converted to log contrast sensitivity values (i.e., $\log_{10}(1/C_T)$, where C_T is the threshold contrast value). The number and percentage of subjects who cannot see any contrast should be recorded and tabulated for each spatial frequency to provide a qualitative extent of the bias. Descriptive tables should include a note that the corresponding mean values are biased upward and variability values are biased downward (using < and > symbols). The percentage of subjects who cannot see any contrast level gives a qualitative indication of the extent of the bias. In such cases, statistical comparisons between test and control are not warranted.

NOTE: It should be confirmed that the percentage of subjects with scores of zero is consistent with the equipment manufacturer's population norms at the mesopic luminance. Testing used by the Sponsor should employ contrast test pattern that provides sufficient maximum contrast to minimize the proportion of subjects who are unable to see any of the patterns (including the test patch). Testing utilizing test patterns without a full range of contrast will increase the proportion of subjects unable to see any of the test patterns (including the demonstration patch

B.4.4 Pupil size

Photopic pupil size:

Photopic pupil size is to be measured under the same lighting conditions as the photopic visual acuity measurements. Photopic pupil size for each eye should be measured to the nearest one-half millimeter under standardized testing conditions with the subject instructed to focus at distance.

Mesopic pupil size:

Mesopic pupil size should be measured for all eyes in the investigation with eye illumination identical to that used for mesopic contrast sensitivity testing. The measurements should be made with an infrared or light amplification pupilometer/camera or any other objective method and should be measured with a precision of ± 0.5 mm or better. Contrast sensitivity and pupil measurement should begin only after the eye has had time to fully adapt to the testing conditions (approximately 10 minutes).

It is recommended that pupilometers that allow the fellow eye to be exposed to the room lighting conditions be used to measure pupil size instead of "look-in" pupilometers. A "look-in" pupilometer may require additional calibration to match the room lighting conditions under which visual acuity testing is performed.

Note: For "look-in" contrast sensitivity viewing systems, unless the pupil can be measured while each subject looks into the instrument, the subject's head must be moved from the system to measure pupil size. It is therefore critical that the room lighting be calibrated to be identical to the test lighting inside the "look-in" instrument.

B.4.5 Slit lamp exam

The slit lamp exam should include the measurement of aqueous cell and flare, and the measurement of corneal edema by a standard grading system [5]. It should also include an evaluation for the presence of pupillary irregularities, iris atrophy and pigment dispersion**.** A gonioscopic exam using a consistent grading system at each site should also be performed preoperatively and at any post-operative visits as determined by the risk assessment. Posterior Capsule Opacification (PCO) should be assessed using a standardized grading system described in the protocol. Laser capsulotomy procedures should be performed only when meeting standardized criteria described in the study protocol. Analysis of PCO and laser capsulotomy rates should be done for test and control eyes and the rates compared.

B.4.6 Measurement of intraocular pressure

Intraocular pressure should be measured using Goldmann applanation tonometry or other validated methods. Other methods may be used with a scientific justification, but the same method should be used by all investigators.

B.4.7 Subject symptom assessment

- Subjects should be given a questionnaire to assess symptoms related to the optical characteristics of the EDF IOL, if warranted by preclinical testing or the risk analysis. The mode of questionnaire administration (self- vs. interviewer-administered) and the setting in which the questionnaire is completed should be carefully considered to avoid bias. The questionnaire should include questions regarding intermediate vision, glare, halos, double vision, spectacle/contact lens use, and trouble with night vision (e.g., night driving, etc.). The time of onset after surgery of visual symptoms should also be addressed. The results of the subject questionnaire should be stratified by fellow eye status (untreated, implanted with same EDF IOL, etc.). FDA's Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims [6] should be consulted for further guidance, particularly for evaluating the adequacy of a patient-reported outcome (PRO) instrument as a measure to support device claims.

- In all cases, subject ocular and visual symptoms should be collected at each postoperative visit through use of non-directed questions. For example the subject could be asked, "Are you experiencing any problems with your eyes or vision?" Subjects should be asked whether reported symptoms are mild, moderate, or severe. Responses should be recorded and characterized into distinct groups of symptoms (e.g., halos, glare, ocular pain, ocular dryness, etc.) for reporting purposes.

B.4.8.2.1 Depth of Focus

Defocus curve testing is used to demonstrate the clinical subjective depth of focus performance per the theoretical lens design. This test measures the range of vision provided by the EDF IOL through the measurement of visual acuity for various vergence demands from trial lenses of different powers. A distance visual acuity chart, under standardized test conditions, is used to measure visual acuity through different trial lenses.

Number of subjects and eyes: 100 EDF IOL eyes of 100 subjects and 100 monofocal control eyes of 100 subjects

Test conditions and Equipment

Defocus curve testing should be performed using the phoropter or trial frame and the 100% contrast ETDRS chart at 4 meters. Due to numerous visual acuity measurements in a defocus curve test, it is recommended that acuity testing be done whenever possible using computerized charts with random presentation of letters. If the use of computerized charts is not possible, the Sponsor should explain, in the study protocol, how bias due to memorization of letters will be eliminated.

Testing is done under photopic lighting conditions with a background luminance of the chart ranging from 80 - 110 cd/m2 (85 cd/m2 recommended). Luminance should be identical for all testing centers. Ambient luminance should be from dim to dark to maximize pupil size. No surface (including reflective surfaces) within the subject's field of view should exceed the chart background luminance.

Test Procedures

In general, throughout the test procedure, the subject should be carefully observed for squinting and should be frequently reminded not to squint. The best distance correction/manifest refraction should be used to ensure the subject's vision is optimally corrected for the testing distance. Testing should be performed monocularly and the untested eye should be occluded. To obtain the defocus curve, visual acuity should be measured first with the best distance correction and then subsequently in 0.5 diopter defocus steps between +1.50 D and -2.50 D, except for the region from +0.50 D through -0.50 D, which should be done in 0.25 D steps. Letters should be randomly presented to avoid memorization. The defocus range of +1.50 D to -2.50 D may be modified as applicable based upon lens design and expected depth of focus. The protocol should specify range of lens powers.

NOTE When testing using trial frame or phoropter,the subject should be carefully observed for squinting and should be frequently reminded not to squint.

Analysis:

For the monofocal and EDF IOL, the individual visual acuity data at each defocus level should be averaged and the mean visual acuity is plotted as a line plot with visual acuity (on Y axis) as a function of defocus (X axis).

For the assessment of the magnitude of extended depth of focus provided by the EDF lens and control, an absolute visual acuity of 0.2 logMAR (20/32) should be considered. At this absolute visual acuity level, the depth of focus should be estimated as the dioptric range between zero defocus (or best distance vision) and the point on the negative lens induced defocus curve that crosses the 0.2 logMAR. Figure B.1 provides a hypothetical example of a defocus curve and shows how depth of focus is estimated.

The defocus data should be grouped into three photopic pupil size ranges: ≤ 2.5 mm (small), >2.5 mm to <4.0 mm (medium), and ≥ 4.0 mm (large) to analyze pupil size effects on defocus curve results.

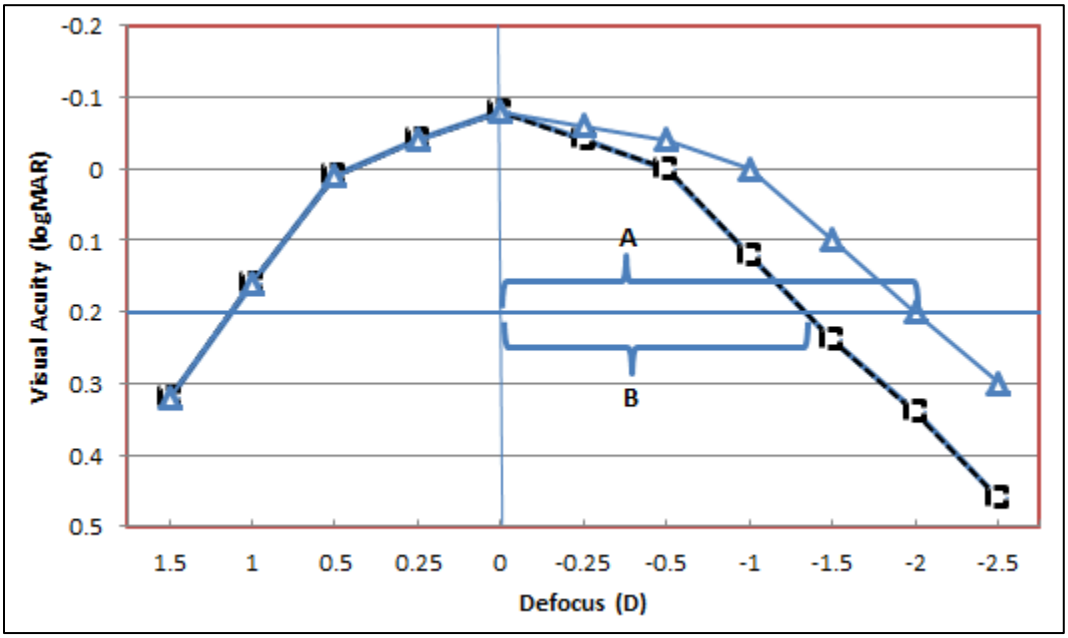

Figure B.1. Hypothetical example of a defocus curve for an EDF lens (solid line, triangle) and monofocal control (dotted line, square). The depth of focus for an absolute visual acuity level of 0.2 log MAR is shown as 'A' for the EDF IOL and as 'B' for the control IOL.

B.5 Investigation Analyses

In addition to the safety and effectiveness analyses described in ISO 11979-7, the following additional analyses are recommended.

B.5.1 Safety analyses

Safety analyses should be performed separately for primary eyes and "all eyes" (including fellow eyes).

- In addition to rates of adverse events per ISO 11979-7 "grid", provide the rate of adverse events that may be specifically related to the EDF IOL design features [e.g., adverse events related to the optical characteristics of the lens] and any non-grid significant events. The rates should be accompanied by 2-sided 95% confidence intervals
- Mean BCDVA: Statistical non-inferiority analysis (compared to monofocal control), with non-inferiority margin of 0.1.
- Log Contrast sensitivity analysis (mesopic with and without glare)
    - Between-group mean difference in log contrast sensitivity with 90% non-parametric confidence interval for each spatial frequency.
    - Provide descriptive statistics for the log contrast sensitivity for each group (mean; standard deviation; median; 0^{th}, 25^{th}, 50^{th}, 75^{th}, and 100^{th} percentiles) and for each spatial frequency.
    - The number and frequency of eyes that can and cannot see the reference pattern for each spatial frequency.

B.5.2 Effectiveness analyses

There should be two co-primary effectiveness endpoints:

- Mean (logMAR) monocular DCIVA under photopic conditions at 66 cm at 6 months
    - Demonstrate statistical superiority over the control [one-sided test using level of significance of 0.025]
    - At least 50% of EDF eyes should achieve DCIVA of logMAR 0.2 or better
- Mean monocular depth of defocus (measure only negative direction from zero) where visual acuity is logMAR 0.2 or better at 6 months
    - The mean difference over control should be at least 0.50 D

The protocol should indicate that all of the above must be met for success on the co-primary effectiveness endpoints.

The following should be considered to be other endpoints analyzed with descriptive statistics only:

- The frequency and proportion of eyes with ocular and visual symptoms collected via a non-directed questionnaire.
- The frequency and proportion of eyes with visual symptoms collected via a patient-reported outcome questionnaire, if warranted by preclinical testing or the risk analysis.
- Distance-corrected low (10%) contrast acuity at intermediate distance (66 cm) by group
- Best corrected low (10%) contrast acuity at intermediate distance (66 cm) by group
    - Also compare mean distance-corrected low contrast acuity in the EDF group to mean best-corrected low-contrast acuity in the monofocal control group
- UCDVA (provide means and compare mean difference between eyes or between groups for bilateral implants)
- Residual refractive error: descriptively compare mean error and mean absolute error
- Monocular uncorrected intermediate visual acuity at 66 cm (descriptive statistics).

Testing of multiple statistical hypotheses should be conducted in such a manner as to keep the study-wise significance level at 0.05

All descriptive statistics for the visual acuity outcomes should be provided for both test and control groups. When appropriate, correlations to pupil diameter are to be performed for selected effectiveness measures (e.g., defocus, etc.). For binocularly implanted subjects, provide similar descriptive statistics as described above for binocular measures of visual acuity.

B.5.3 Accountability analysis

The general requirement for accountability of subjects is given in 6.10 of ISO 14155-1. More specific guidance for subject accountability at each visit in EDF IOL clinical investigations is provided in ISO 11979-7 Annex A.

B.6 Adverse events and adverse device effects

The manufacturer should include in the clinical protocol a list of possible adverse events that may occur in conjunction with the investigational device. In addition to any theoretical adverse events identified by the device risk analysis, the case report forms should include forced-choice listings of specific adverse events listed in ISO 11979-7 and allow for the recording of other adverse events not listed.

Annex C
(informative)

Methods and devices for use in the Optical Characterization of EDF IOLs

C.1 General

Within this annex are found methods and devices that can be successfully used to fulfill the imaging quality verification requirements of 5.2.3 and the optical characterization requirements for EDF IOLs set forth in 5.2.1 and specified in Annex A. Other methods and/or devices that can be shown to successfully perform the tests required by 5.2.3 and by 5.2.1 as specified in Annex A can be used instead of the methods and devices given in this annex if so desired.

C.2 Model eye specifications

The model eye suitable for testing EDF IOLs and comparison monofocal IOLs has the following characteristics

1. A corneal refracting element whose optical characteristics closely match those of the physiological cornea. These characteristics include the power of corneal refracting element when the external media is air and the internal media is the fluid surrounding the tested IOL, the amount of spherical aberration in the wavefront exiting the corneal element into the fluid within the model eye and the dispersion of the material with which the corneal refracting element is made. Suitable parameters specifying a physiological corneal are given in C.9.
2. A means of holding the tested IOL within the model eye while surrounded with a fluid whose properties closely match those of the aqueous humor both with respect to index of refraction and dispersion.
3. A pupil aperture with a specified diameter that can be placed within the model eye anterior to and essentially touching the tested IOL
4. A means of positioning the optical center of tested IOL at a specified lateral position with respect to the pupil aperture
5. A means of tilting the tested IOL with respect to the plane of the pupil aperture a specified angular mount
6. The ability to place the tested IOL at a distance from the principal planes of the corneal refracting surface similar to the distance the IOL would be placed with respect to the corneal vertex when implant within a human eye.
7. A provision to allow the image formed within the model eye with the tested IOL in it to be captured with a digital image capture system.

The designs for model eyes specified in C.2.1 and C.2.2 fulfill these requirements.

C.2.1 Fluid Cell Model Eye

The specifications for a model eye that fulfills the requirements of 5.2.3 and 5.2.1 as specified in Annex A, A.3.1 are given below in Table C.1. This model eye is designated the *fluid cell model eye*. Its construction is illustrated in Figure C.1.

This model eye is similar in design to the ISO 11979-2 model type 2 but the dimensions and spacing of the elements are such that it performs optically in a manner very similar to the physiological model eye, C.2.2. However, it has a fluid cell that is completely separate from the corneal lens and is designed so that the image of test object falls in the air space following the final window of the fluid cell. In design,

this model eye is quite similar to that specified and used by Ohnuma, et. al. 2011 [8], the difference being in the use of thicker glass windows for the fluid cell thus making it possible to use readily available, high optical quality microscope slide glass and a change in the design of the corneal lens so that reduced distance between the corneal refracting surface and the IOL is the same as that found in the physiological eye [7].

Surface number	Surface radius (mm)	Conic constant	Separation space to next surface (mm)	Diameter (mm)	Refractive index (in the material following the surface)_	Material following the surface
1	11.50	0.5	2.79	12.7	1.493	Polymethymetharcrylate (PMMA)
2	∞	0	0.1	12.7	1.000	Air
3	∞	0	1.0	12.7	1.519	Glass microscope slide
4	∞	0	0.5	12.7	1.336	Pupil aperture – 2.1% sucrose/water solution in clear aperture
5	IOL anterior surface radius	various	2.0 (nominal)	IOL size	Index of IOL	Tested IOL
6	IOL posterior radius	various	1.0 (nominal) the distance across the fluid cell is 3.5	12.7	1.336	2.1% sucrose/water solution
7	∞	0	1.0	12.7	1.519	Glass microscope slide
8	∞	0		12.7	1.000	air

Table C.1 Specifications of the fluid cell model eye

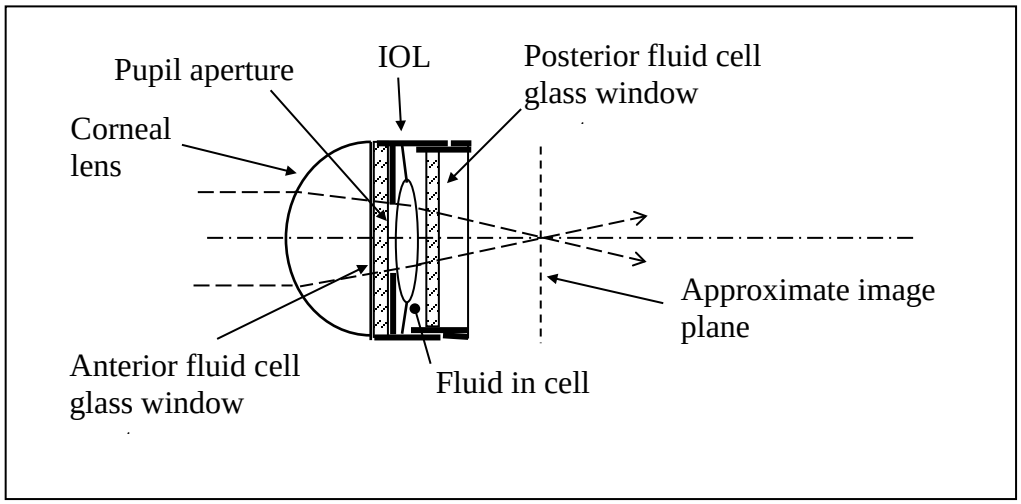

Figure C.1 A cross section of the fluid cell model eye. The fluid cell is shown with a removable posterior window. The cell is shown constructed using thin brass tubes that hold the glass microscope slide windows and make it easy to hold a pupil aperture and the IOL, fill the cell with fluid and close it by inserting the posterior window. Dashed light rays illustrate the creation of a focus in the air space posterior to the model eye where the image is easy to view with a microscope/camera system. Note that proper spacing of the cell is achieved by simply placing the anterior window against the rear surface of the corneal lens.

C.2.2 Physiological model eye

The specifications for a model eye that fulfills the requirements of Annex A, A.3.1 are given below in Table C.2 and is illustrated in Figure C.2. This model eye is designated the *physiological model eye* [7].

Surface number	Surface radius (mm)	Conic constant	Separation space to next surface (mm)	Diameter (mm)	Refractive index(in the material following the surface)	Material
1	7.80	-0.10	0.5	12.7	1.493	Polymethymetharcrylate (PMMA)
2	7.22	0	3.5	12.7	1.336	2.1% sucrose/water solution
3	∞	0	0.5	12.7	1.336	Pupil aperture - 2.1% sucrose/water solution in clear aperture
4	IOL anterior surface radius	various	2.0 (nominal)	Size of IOL	Index of IOL	IOL tested
5	IOL posterior surface radiua	various	20.0	12.7	1.336	2.1% sucrose/water solution
6	∞	0	1.0	12.7	1.519	Glass microscope slide
7	∞	0		12.7	1.000	air

Table C.2 Specifications for the physiological model eye

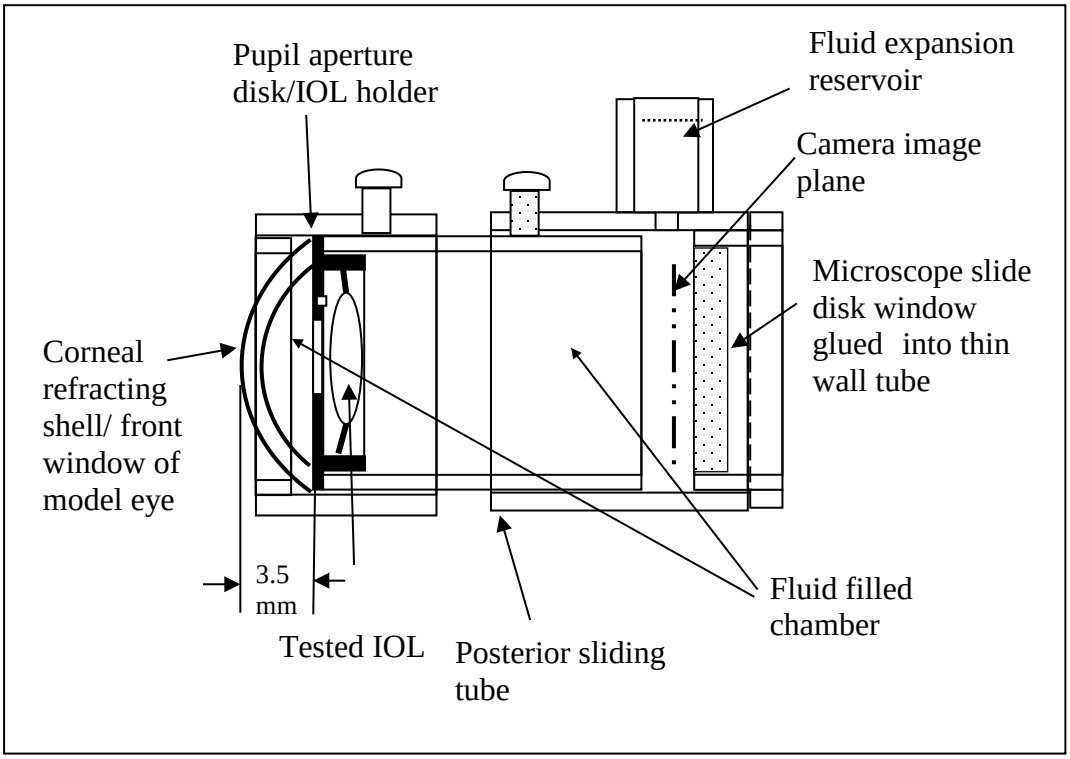

Figure C.2 Illustration of the physiological model eye that will fulfill the specified characteristics of A.3.1. The camera image plane is shown to illustrate it falling within the fluid filled chamber of the model eye. However, its position within the model eye is physically set by moving the model eye with respect to the camera imaging system using the procedure given in A.5.

The pupil aperture disk/IOL holder serves the dual purpose of creating the circular aperture of a size required by 5.2.3 and A.3.1 and holding the IOL correctly centered with respect to the center of the aperture and in the correct axial location within the model eye. Figure C.3 illustrates the design of such a pupil aperture disk/holder. The haptics of a posterior chamber IOL are designed to hold the IOL correctly positioned within the human eye with respect to the pupil and the cornea via peripheral contact with the capsular bag. The pupil aperture disk/IOL holder of this design will hold the IOL under test in a similar way via contact of the haptics with the holder. However, with some IOLs the haptic may not reliably center the IOL with respect to the aperture center and it may be necessary to affix the IOL more permanently in the holder – for instance with glue. When the testing an IOL de-centered by 1 mm with respect the aperture, as required by A.3.2, it will be necessary to affix the IOL in this position within the holder because the haptics will tend to center the IOL if the IOL is left free in the holder.

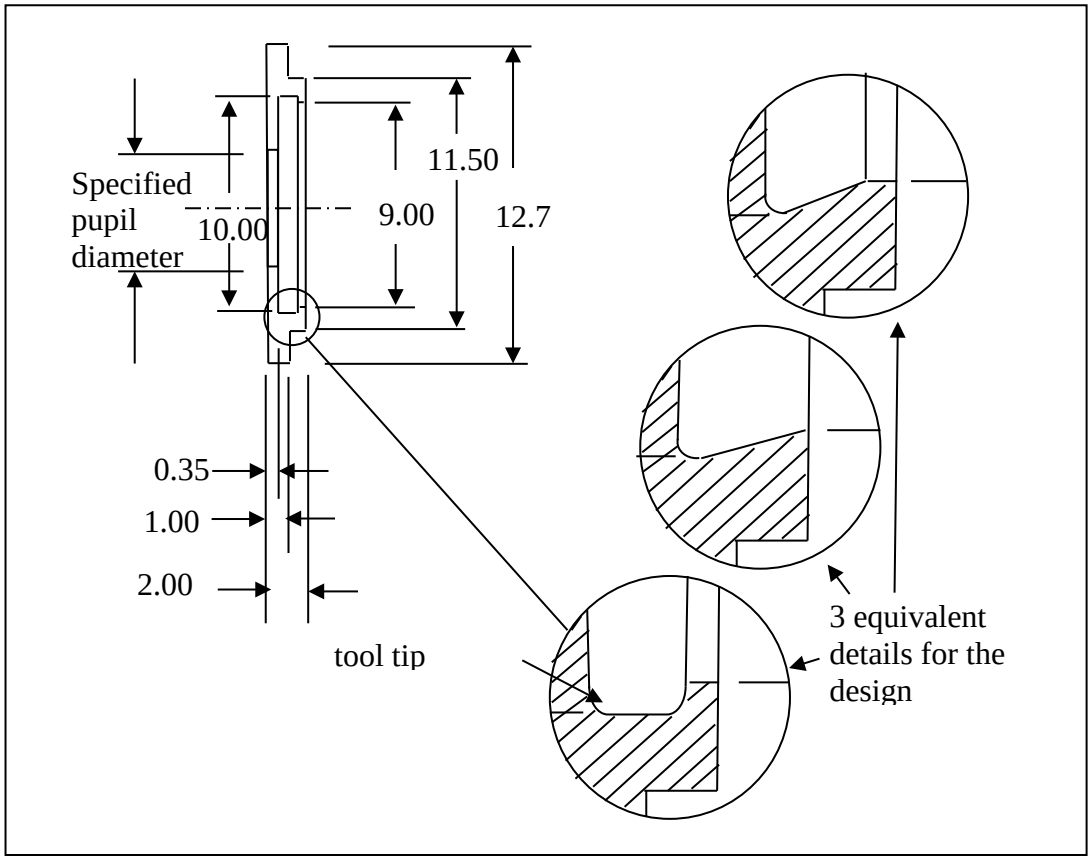

Figure C.3 A design of model eye pupil aperture disk/IOL holder designed to hold a posterior chamber IOL correctly positioned in a model eye of the design of C2.1 or C.2.2 during optical testing.

To fulfill the requirements of A.3.2 the IOL must be held within the model eye tilted by 5 degrees with respect to the optical axis of the testing apparatus while its MTF is measured. This can be accomplished with the model herein specified by slightly lifting one edge of the aperture disk as it is placed in contact with the posterior edge of the corneal shell. This can be done by first affixing a small piece of material to one edge of the disk on the anterior side of the aperture disk and a similar piece diametrically across from it on the posterior side of the disk. Then when the disk is placed into position against the corneal shell and its retainer ring pressed against it, it will automatically tilt the desired amount. For instance, for a tilt of 5° and a disk diameter of 12.7, one edge of the disk must be raised 1.11 mm with respect the diametrically opposed edge. This method to tilt the IOL in a controlled fashion is illustrated in Figure C.4.

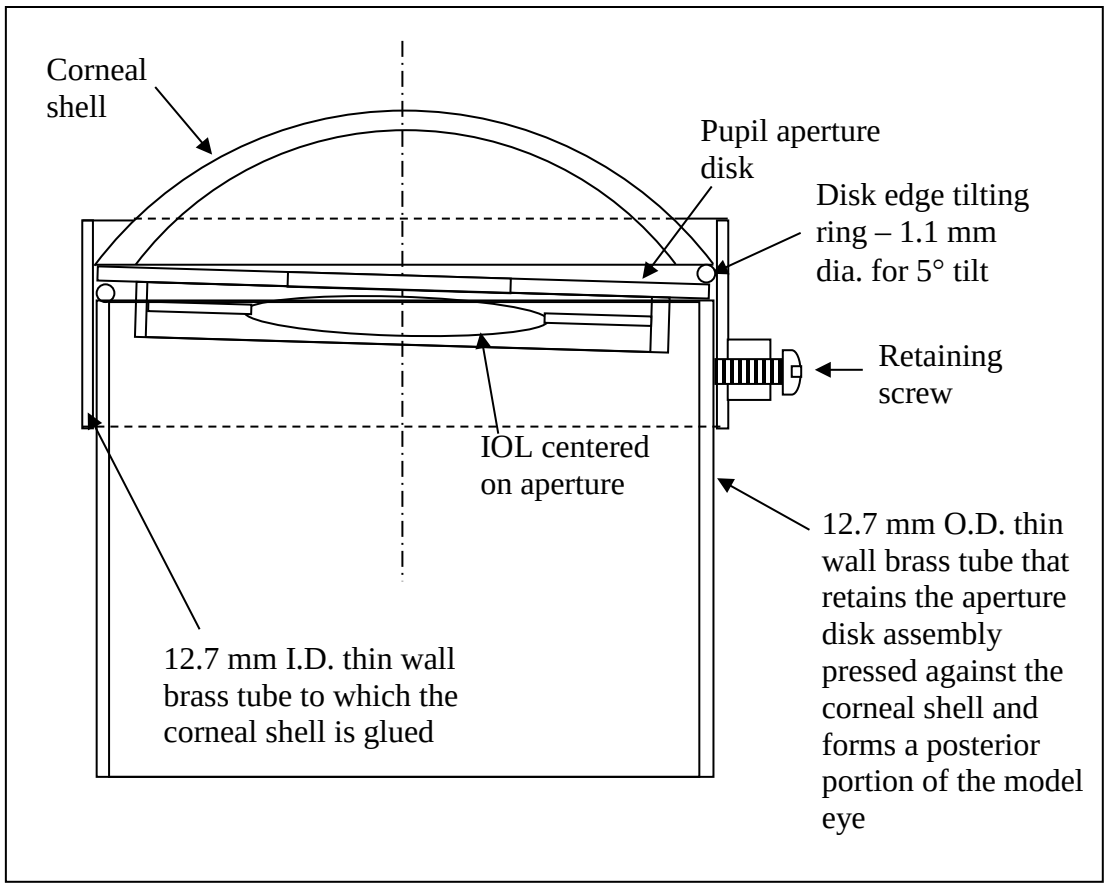

Figure C.4 Illustration of a method to hold an IOL under optical testing within a model eye of the design of C.2.2 at tilt angle of 5°. The same method can be used with the model eye of the design of C.2.1

C.3 Target creation optical system

A target creation optical system that fulfills the requirements of 5.2.3 and Annex A, section A.7 can be constructed through the use of a Badal optometer system with a trans-illuminated target that can be axially moved along the optical axis of the system and is illuminated with a quartz-halogen light source that is diffusely filtered prior to the light passing through the target. A list of components that can be used successfully to make such a system is given below. A source for each component is also given. Equivalent components will also serve.

1) Optical rail at least 50 cm long (Edmond Optics 36" J54-402 or Edmund Optic 500 mm J54-931)
2) 4 carriers for optical rail (Edmond Optics J54-403 or Edmond Optics J54-930)
3) 4 12 mm post holders
4) 4 12 mm posts
5) 2 x,y adjustable 25 mm lens mounts
   NOTE: Be sure that the carriers, post holder, posts and lens carriers all have the same screw thread size.
6) 100 mm achromatic doublet with 25 mm dia. (Edmund Optics J47-641)
7) 10 micron pinhole in 25 mm dia. Holder (Edmund Optics J56-276)
8) 1951 USAF Resolution Target (Edmunds Optics NT53-715)
9) Halogen lamp (Osram 41600 SP)

10) Power supply for lamp

Use of an optometer lens with a100 millimeter focal length is suggested because then a movement of the target with respect to the optometer of 1 millimeter will change the vergence of light from the target in the focal plane of the optometer lens by 0.1 D. This makes measurements of vergence entering the model very easy.

The 0 D vergence position of the target on the measuring scale is found by viewing the target as light exits the optometer lens using a telescope set to image objects at an infinite distance. With the focus of the telescope properly set and while viewing the target through it, the target slide is moved until the target is seen at best focus. This slide location on optical rail is then the O D position from which all other vergence values are measured.

In a similar way, the axial position of the model eye can be adjusted until the front focal plane of the optometer lens is coincident with the corneal vertex of the model eye. Using a mirror so that the model eye can be viewed with the telescope through optometer lens, the model eye is moved until dust placed near the corneal vertex of the model eye is seen in best focus. The corneal vertex then lies in the front focal plane of the optometer lens.

In a Badal optometer system with an optometer lens having a100 millimeter focal length, the 10-micron pinhole subtends an angle of 0.34 arc minutes. If the effective focal length of a human eye is assumed to 17 mm, a 2-micron diameter macular cone subtends 0.40 arc minutes. Thus, such a 10 micron pinhole target can be effectively used to examine the point spread function of created by the model eye/IOL optical system.

To select the group and element of the 1951 USAF Resolution Target to use for measurement of EDF IOL and comparison monofocal IOL depth of focus values, as per A.3.4, it is necessary to first convert the published line pair per millimeter values for the various elements of the target to the width of the bars and then to convert these values to subtended angles in the Badal optometer system. The width of a bar is equal to one half the period of the bar grating, which in turn, is equal to the reciprocal of the line pairs per millimeter value. The subtended angle of a bar created by the Badal system, given in minutes of arc, equal the arc tangent of the width divided by the optometer focal length times 180 divided by pi.

Using these formulas, Element 4 of Group 3 of the 1951 USAF Resolution Target, which has 11.3 line pairs per millimeter, is found to subtend an angle of 1.5211 arc minutes. Therefore, it represents an acuity value of 20/30.4. This is sufficiently close to 20/32 to use as the test target for depth of focus measurements.

C.4 Microscope/camera system

The task of the microscope/camera system is to capture a digital image formed by the model eye/IOL/target system in the retinal plane of the model eye so that it may be analyzed and thus the image characteristics of the IOL evaluated. The resolution of the microscope/camera system must be such that details that can be perceived by the human visual system can be fully examined. The finest resolution of the human eye is set by the size of its finest receptors – the macular cones. The macular cones are on average 2 microns wide. There are available CCD and CMOS cameras with pixels 5.2 microns wide. For such a detector to resolve details that are several microns in width, those details must be magnified by the system. Choosing a magnification of 10 means that in the retinal image plane the effective size of these camera pixels is 0.52 microns and hence 4 would fit onto a macular cone that is 2 microns in width. This sampling density is sufficient to fully assess resolution issues for a given IOL tested in the model

eye.

The following components can be used to create the microscope/camera system fulfilling the above requirements.

1) 10X DIN achromatic microscope objective (Edmund Optics J36-132)
2) DIN objective to camera tube assembly (Edmund Optics J54-868)
3) CCD or CMOS camera (Edmund Optics has an interesting new offering in a compact CMOS camera that is designed to send its bit map images via a USB connection directly to a PC or laptop without the need to have a frame grabber. It is available in either B&W or color. Their EO-1312 would be adequate as the pixel size is 5.2 x 5.2 micron)

A simple but effective way to hold the physiological model eye, C.2.2, with respect to the microscope/camera system to construct a tube, as shown in Figure C.5, that slides over the microscope objective body and into which the posterior end of the model can be inserted. This arrangement allows the model eye to quickly and easily removed from and replace on the microscope/camera when the IOL is changed at the same precise distance between the model eye posterior window and the microscope object plane each time. When using this type of holder, the axial position of the holder tube can be adjusted by placing some dust on the anterior window surface and moving the tube until the dust is in focus as seen by viewing the digital image. Then the microscope/camera system effectively records light intensity pattern that forms within the model eye fluid but just at the window surface.

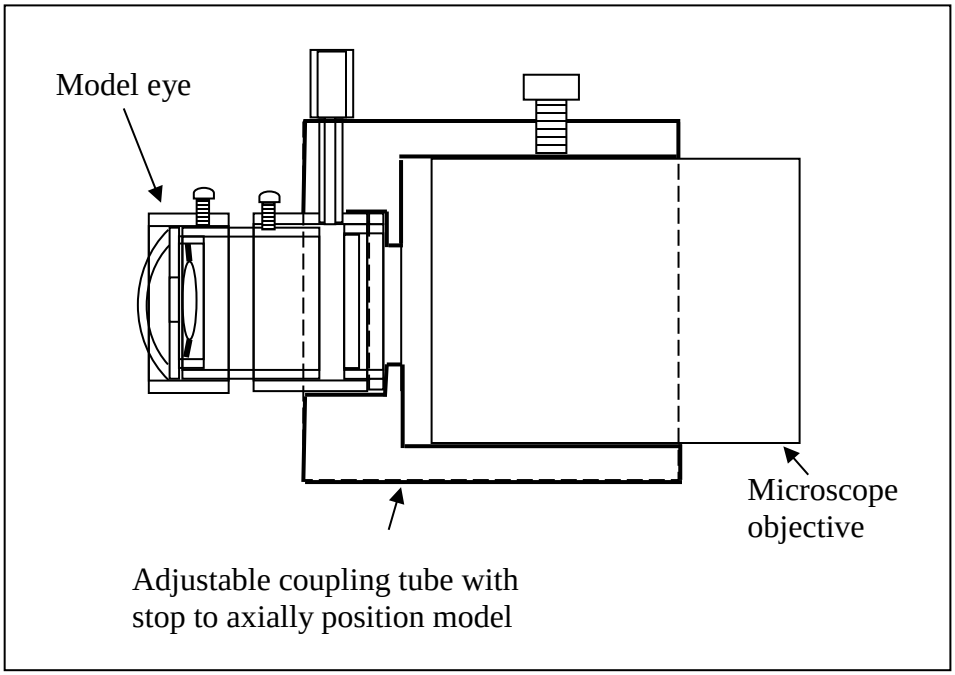

Figure C.5. Holder to attach the physiological model eye to the microscope camera system. Although it is not shown, there is a slot cut in the anterior end of the hold to allow it to slide past the fluid reservoir tubing. This slot also insures that the fluid reservoir is oriented vertically on the top of the model eye during use so that fluid does not drain out of it.

C.5 Modulation transfer function measurement method (MTF)

The 2-dimensional modulation transfer function (MTF) of an optical system is defined as the modulus of the 2-dimensional Fourier transform of its point spread function.

The 2-dimensional MTF of a model eye containing an IOL can therefore be found by capturing the image, in digital form, of a point target created by the test eye and then performing a Fast Fourier Transform (FFT) on this image. If a line target is used, the FFT of the image in the narrow dimension is the 1-dimensional MTF of the model eye/IOL system is the meridian perpendicular to the line target axis. The modulus of these FFTs at the various sampled coordinates in the spatial frequency space of the FFT gives the MTF of the model eye/IOL system at those spatial frequencies.

The captured image of the target with the highest peak intensity, i.e. the image that is in best focus, shall first be examined to ensure that the peak intensity is below saturation value for the image. The gain of the camera system or the intensity of the target illumination is then altered as necessary to ensure that saturation is avoided.

A second method for measuring the MTF of a model eye containing an IOL consists of forming an image of target with an image detail of known angular subtense, α degrees, and counting in the x and y directions how many pixels, n_x and n_y the detail subtends.

The target creation optical system of C.3 and the microscope/camera system of C.4 are appropriate systems for creating necessary targets and capturing the images to be analyzed for both of the MTF measurement methods.

The details for performing both measurement methods are given below

C.5.1 MTF measurement using point or line targets

The diameter of the point target or the width of the line target should subtend no more than 0.35 arc minute. This is to ensure that the size of these targets in the retinal plane are less than the size of retinal cones and so can resolve spatial frequencies that are applicable to the visual system. In the target creation system specified by C.3, use the 10-micron pinhole or a 10-micron wide slit aperture as a target will fulfill this criterion.

Initially set the vergence of light exiting the optometer at 0 D and adjust the model eye containing the IOL so that the front focal plane of the optometer is coincident with the vertex of the model eye cornea. Then axially position the microscope system as specified in C.4 to obtain best-focus of the target as specified in A.5.

The digital image of the pinhole or slit can now be captured at the various entering vergence settings required by 5.2.3 or A.3.1. For each digital image thus captured, the following procedure is used to calculate the MTF.

The captured image of the point target, in digital form, is first to be examined to ensure that the peak intensity is below saturation value for the image with the highest peak intensity, i.e. the image that is in best focus. The gain of the camera system or the intensity of the target illumination is then altered as necessary to ensure that saturation is avoided. If it is chosen to change the target illumination intensity, this should be done using neutral density filters so that the spectrum of the light source is not altered from that which provides *white light* as defined in A.6. If the intensity is varied by varying the power to lamp, the color temperature of the lamp will change and with it the spectrum of the light.

With unsaturated images, a fast Fourier transform (FFT) is made of the digital image of the point target,

i.e. the point spread. The array thus formed constituted the Optical Transfer Function (OTF) of the optical system. The modulus of each complex value in the two-dimensional array thus formed is normalized by dividing it by modulus of the value for an array location corresponding to zero spatial frequency. The values of the two-dimensional array thus formed constitute the measured two-dimensional modulation transfer function.

The incremental spatial difference between the modulation transfer function array values, *dw*, given in units of cycles per degree is calculated using Eq. C.1

$$dw = \frac{f}{Ni \cdot di} \cdot \frac{\pi}{180} \qquad \text{C.1}$$

where

di is the distance between pixel centers in the image
Ni is the number of elements in dimension *i* of the image array
f is the distance between IOL and the image plane, typically approximately 17 mm

The distance between pixel centers in the image equals the distance between pixel centers in the CCD or CMOS camera divided by the magnification of the microscope system. For example, if the distance between the pixel centers in the camera sensor is 5.2 microns and the magnification of the microscope system is 10, then the value of *di* is 0.52 microns.

When a FFT of a digital image is formed, the array of complex values formed does not have the value for 0 spatial frequency at the center of the array. To rearrange the array of values so that the 0 spatial frequency value is that the center of the array a shift operation is performed on the complex array in which the values in the first quadrant are switched with the those in the third quadrant and the values in the second quadrant are switched with those in the fourth quadrant.

The modulus of any complex number is found by taking the square root of the product of the complex number and its complex conjugate.

Once the FFT array has been shifted and converted to an array of normalized modulus value, the spatial frequency of any element of that array is found from the index numbers of the element. Designating the index numbers as *nx* and *ny*, the spatial frequency component values, *wx* and *wy*, for the element with index values *nx* and *ny* are

$$wx = nx \cdot dw = \frac{nx}{Nx} \cdot \frac{f}{di} \cdot \frac{\pi}{180} \qquad \text{C.3}$$

$$wy = ny \cdot dw = \frac{ny}{Ny} \cdot \frac{f}{di} \cdot \frac{\pi}{180} \qquad \text{C.4}$$

The spatial frequency of the element with index values *nx* and *ny* is found using component values as;

$$w(nx, ny) = \sqrt{\left(\frac{nx}{Nx}\right)^2 + \left(\frac{ny}{Ny}\right)^2} \cdot \frac{f}{di} \cdot \frac{\pi}{180} \qquad \text{C.5}$$

The spatial orientation of the element with index values *nx* and *ny* is given by;

$$\theta(nx, ny) = \arctan\left(\frac{ny/Ny}{nx/Nx}\right) \qquad \text{C.6}$$

If a point spread method is used, a fast Fourier transform is made of the digital image of the point target, i.e. the point spread. The modulus of each complex value in the two-dimensional array thus formed is normalized by dividing it by modulus of the value for an array location corresponding to zero spatial frequency. The values of the two-dimensional array thus formed constitute the measured two-dimensional modulation transfer function (MTF).

If a line method is used, a fast Fourier transform is made of the digital image of the line target, i.e. the line spread. The modulus of each complex value in the two-dimensional array thus formed is normalized by dividing it by modulus of the value for an array location corresponding to zero spatial frequency. The values of the two-dimensional array thus formed constitute the measured two-dimensional modulation transfer function (MTF).

C.5.2 MTF measurement using a target with known spatial frequency elements

When the modulation transfer function is found using at target consisting of elements with known spatial frequencies, such as the 1951 U.S. Air Force resolution target, the spatial frequencies of each element in the image of the target created by model eye/IOL system must be found.

The spatial frequency increment, *df*, for a given IOL can be found by forming an image of target with an image detail of known angular subtense, α degrees, and counting in the *x* and *y* directions how many pixels, n_x and n_y the detail subtends. This procedure is be done with the tested IOL in the model eye and the image sensor placed in the axial position specified by A.5. The spatial frequency increment is then given by Eq. C.7

$$df_i = \frac{n_i}{N_i \cdot \alpha_i} \qquad \text{C.7}$$

where;

n_i is the number of pixels subtended in i dimension by the target detail
N_i is the total number pixels in the i dimension of the image
α_i is the known angular subtense of the target detail in the i dimension

A suitable target for use in finding the value of α_i for a given testing situation is a grating pattern of the 1951 U.S. Air Force resolution target, created using a Badal system so that the angular subtense of the chosen pattern as it enters the model eye can be calculated. A pattern of this target is specified in terms of line pairs per millimeter, lp/mm, so the physical distance between the left hand edge of one bar of the grating and the left hand edge of its neighbor is the reciprocal of this value, expressed in millimeters. The angular subtense of the line pair in a Badal system with a optometer focal length f_B, is then given by Eq. C.8

$$\alpha = \arctan\left(\frac{1}{(lp/mm)\cdot f_B}\right) \qquad \text{C.8}$$

When finding the values to use in Eq. C.7 with a 1951 U.S. Airforce Resolution Target pattern, n_i is the

number of image pixels spanning one black line and the white space next to it.

A pattern of the 1951 U.S. Airforce Resolution Target is specified by two integers, designated *Group* and *element*. Both integers run from 1 to 6. The lp/mm value of the pattern (G, element), is given by the equation C.9;

$$lp/mm = 2^{Group+(element-1)/6} \qquad \text{C.9}$$

C.6 Depth of focus measurement method

To measure the depth focus range of an EDF IOL as required by 5.2.1 (b) and as specified in A.3.4, the model eye of C.2.1 or C.2.2, the target creation optical system of C.3 and the microscope/camera system of C.4 can be used in the following.

The target used in the target creation optical system is the 1951 USAF Resolution Target positioned so that the elements of Group 3 image in the center of field of view of the microscope/camera system. For the target creation optical system specified in C.3, Element 4 of Group 3 represents a 20/30.4 acuity target and is the element that will be used in the testing.

With the target thus positioned in the optometer system, the vergence exiting the optometer lens is set to 0 D. Then the model eye is positioned with its corneal vertex located in the focal plane of the optometer lens and positioned with respect to the microscope so that Element 4 of Group 3 is imaged at best focus using the procedure of A.5.

While viewing the image created by the model eye containing the tested IOL of Element 4 of Group 3 on a video monitor fed by the camera, the vergence created by the optometer system is changed to more negative values by moving the target with respect to optometer on the optical rail until it is judged that Element 4 of Group 3 can no longer be resolved.

At this point, the scale position of the target is read. The difference of this reading from the reading at a vergence of 0 D is calculated and converted to a dioptric change. In the target creation system specified in C.2, the change in target position, recorded in millimeters is divided by 10 to convert to a change in of vergence in diopters.

C.7 Expected visual acuity

The expected visual acuity for a given testing condition can be found using the measured modulation transfer function values in equation C.10 [9].

$$VA(\log MAR) = ax^b + c \qquad \text{C.10}$$

where

a = 0.085
b = -1.0
c = -0.21
x = $MTFa$

$$MTFa = \sum_{f=1}^{50/d} \frac{d}{50} MTF(f \cdot d)$$

f is the summation index, an integer that is incremented in value by 1
d is the spatial frequency sampling interval as found in Eq. C.1
$MTF(f \cdot d)$ is the value of modulation transfer function at spatial frequency $(f \cdot d)$

The image resolution, expressed as an achievable acuity logMAR value, for a given test condition, is the value found, using Eq. C.10 using the measured MTF values.

NOTE: The expected visual acuity estimation was derived based on conditions described in [9] such as a i) a specific average human eye, ii) a specific model eye configuration, iii) using thin lens equation for the power of the IOL, iv) assumption that the IOL has the same focusing power in the model eye as in the real eye.

C.8 Use of ISO 11979-2 type 2 model eye

To properly measure the MTF of an IOL for the various entering vergences specified in A.3.1 using the ISO 11979-2 type 2 model eye, the vergence of light entering the model eye cannot be varied as it can with the fluid cell model eye or the physiological model eye. It must remain in collimation and, instead, the camera image plane must be changed from the plane found for distance best-focus by a distance that is a function of the desired change in entering vergence and the distance power of the IOL. Equation C.11 will give the correct moment distance, *dt*, in millimeters for a specified entering vergence, V_{object}, in diopters and for an IOL with a specified distance dioptric power $F_{IOL\text{-}distance}$.

$$dt = 1000\left\{\frac{1}{F_{IOL-\text{distance}} + 48.3 - \left(\frac{42.86 + V_{object}}{0.872 - .003 \cdot V_{object}} - 49.17\right)} - \frac{1}{F_{IOL-\text{distance}} + 48.3}\right\} \qquad \text{C.11}$$

A simpler, approximate formula, that gives values for *dt* that are almost the same of those given by C.11 is ;

$$dt = \frac{1315 \cdot V_{object}}{\left(F_{IOL-\text{distance}} + 48.3\right)^2} \qquad \text{C.12}$$

When using the model eye of C.2.1 to comply with A.3.1, if it is desired to move the camera image plane instead of varying the vergence entering the model eye, C.11 or C.12 can be used to find the proper movement for a given value of V_{object} once the value 48.3 is changed to 49.17.

C.9 Physiological cornea

The following parameters specify a physiological cornea that is considered appropriate for theoretical optical characterization of EDF IOLs and comparison monofocal IOLs. Other corneal designs whose total effective power fall into the range of 41.5 D and 43.5 D, inclusive, when the anterior media is air and

the posterior media is the aqueous humor, whose wavefront entering the anterior chamber of the eye has a spherical aberration close to that of the cornea specified below and whose material is corneal stromal tissue, are also acceptable.

- Anterior surface radius of curvature = 7.8 mm
- Anterior surface conic constant = -0.25
- Anterior surface type = Ellipsoid of revolution
- Central corneal thickness = 0.5 mm
- Posterior surface radius of curvature = 6.4 mm
- Posterior surface conic constant = -0.36
- Posterior surface type = Ellipsoid of revolution
- Index of refraction @ 550 nm = 1.376
- Abbe value = 56

Annex D
(Normative)

Labeling

D.1 Scope

This annex provides recommendations for labeling of EDF IOLs in addition to the requirements stated in clause 11.

D.2 Information to be found on the outer container

Where applicable, the following items should be provided on the outer lens container:

- Name and address of manufacturer
- Trade name
- Model number
- Diopter power
- Lot/serial number
- Overall diameter and optic body diameter (minimum and maximum if non-symmetric)
- Drawing/diagram depicting configuration of the lens
- Anatomical placement
- Expiration date
- “Single Use” statement or symbol
- “Sterile” statement or symbol
- Method of sterilization
- Storage conditions

D.3 Labeling for inner container and/or pouch

The inner container and/or pouch should provide the following information:

- Name of manufacturer
- Model number
- Diopter power
- Lot/serial number
- Overall diameter and optic body diameter (minimum and maximum if non-symmetric)
- The following statements: “Sterile,” “Do not reuse,” “Do not resterilize”

D.4 Physician package insert

The package insert for the implanting physician should include the following information:

- Prescription device statement: “Caution: Federal (USA) law restricts this device to sale by or on the order of a physician.”
- Indications for use
- Contraindications
- Warnings
- Precautions

- Adverse events experienced during the clinical investigation
- A graph of the MTF through focus response of the EDF IOL in the model eye compared to a monofocal IOL.
- Clinical investigation - description of the trial design and results of primary safety and effectiveness evaluations including defocus curves and potential for visual disturbances
- Name and address of manufacturer
- A graph of the spectral transmittance through the EDF IOL
- Instructions for use, including power constant and a statement that only validated folders/ injectors shall be used.

D.5 Patient labeling

Patient labeling is recommended for EDF IOLs and should include the following information, written as closely as possible to an 8th grade reading level.

NOTE: Additional information on patient labeling may be found in "Guidance on Medical Device Patient Labeling; Final Guidance for Industry and FDA Reviewers," FDA, April 2001[10].

- Purpose of the device (indications for use)
- Device description. Include a description of the lens, where in the eye it is placed, and a brief description of how it works. Use of graphics is recommended in describing the lens and/or its action.
- When the device should not be used (contraindications)
- Risks and benefits. Provide the patient with information about the risks and benefits associated with the EDF IOL. This discussion may include information about alternatives and should aid the patient in deciding whether to undergo implantation of the EDF IOL.
- Warnings and precautions
- Expectations of the device and associated procedures: Provide information to the patient as to what to expect before, during, and after implantation of the EDF IOL.
- Adverse events experienced during the clinical investigation
- Clinical investigation results

Annex E
(informative)

Determination of sample sizes for the clinical investigation

E.1 Statistical symbols and definitions

Table D.1 lists the statistical symbols used throughout the following statistical analysis methods and gives their definitions.

Table E.1.
Symbol Definitions

Parameters and statistics in Normal Distribution	
Symbol	**Description**
z	Standard normal variable (units of standard deviations)
μ	population mean
σ	population standard deviation
n	sample size
$\overline{X}$	sample mean
π	population proportion
p	sample proportion
Hypothesis testing symbols	
Symbol	**Description**
H_0	null hypothesis
H_0: $\mu \leq 0$	a logical statement to be read " The null hypothesis is that the mean, μ, is less than or equal to zero"
H_1	alternative hypothesis
α	The probability of falsely rejecting the null hypothesis. This is also referred to as the "significance level" for the hypothesis test.
β	The probability of falsely accepting the null hypothesis
1-α	Confidence interval level
1-β	The statistical 'power" of the hypothesis test.
δ	Non-inferiority margin - The difference between two population means (e.g., before/after; Treatment A/Treatment B) that can be allowed before this difference is believed to be of clinical significance.
$z_{1-\alpha}$	Standard normal quantile. The value of the standard normal variable Z, below which (1-α) of the distribution lies.
$z_{1-\beta}$	Standard normal quantile for power
Φ	Distribution function for standard normal distribution
Pr	probability - generally given numerically as a fraction between 0 and 1 or as a percentage between 0% and 100%
Pr{$X>x \mid n$}	a logical probability statement to be read "the probability that X is greater than x for the condition of sample size n"

The Table E.2 provides a convenient list of standard normal quantiles that will be used throughout.

Table E.2
Normal Quantiles to Use in Equations

α	(1-α)	$z_{1-\alpha}$
0.025	0.975	1.960
0.050	0.950	1.645
0.100	0.900	1.282
0.150	0.850	1.036
0.200	0.800	0.842
0.500	0.500	0.000

E.2 Calculation of necessary sample sizes

E.2.1 Sample size for the primary effectiveness endpoint

***Bilateral implantation (parallel group study design)*:**

Power calculations for a one-sided, two-sample t-test can be used to estimate the number of subjects necessary. Many standard statistical software packages can perform this calculation. The following hypotheses are being tested:

H_0: $\mu_t \geq \mu_c$
H_1: $\mu_t < \mu_c$

, where μ refers to the population mean logMAR of the measured visual acuity endpoint and the subscripts t and c refer to the test and control groups, respectively

Here, as an example, it is assumed that it is important to show that the mean DCIVA is better for test versus control. Further, it is assumed that

- the between-group difference in mean DCIVA is 0.1 logMAR; and
- the common standard deviation is 0.20 logMAR

A control sample size of 100 with test sample size of 100 provides 94% power (1-β) with one-sided significance level (α) of 2.5%.

E.2.2 Sample size based on non-inferiority hypothesis testing

***Bilateral implantation (parallel group study design)*:**

For non-inferiority hypothesis testing for studies that compare test and control eyes of different subjects, the sample size required can be determined from the following equation from Lin, S.C. [11].

$$n = 2\sigma^2\left[\frac{\left(z_{1-\alpha} + z_{1-\beta}\right)}{\left(\mu_t - \mu_c\right) + \delta}\right]^2 \text{ for testing } \begin{cases} H_0 : \mu_t - \mu_c \leq -\delta \\ H_1 : \mu_t - \mu_c > -\delta \end{cases}$$

$$n = 2\sigma^2\left[\frac{\left(z_{1-\alpha} + z_{1-\beta}\right)}{\left(\mu_t - \mu_c\right) - \delta}\right]^2 \text{ for testing} \begin{cases} H_0 : \mu_t - \mu_c \geq +\delta \\ H_1 : \mu_t - \mu_c < +\delta \end{cases}$$

The subscript "t" refers to the test group and the subscript "c" refers to the control group. Usually, the population means for the two groups are assumed equal for power and sample size calculations. If they are not assumed equal, the denominator is constrained to be positive in non-inferiority problems. This assumption increases the sample size as the differences between population means approaches the non-inferiority margin. The assumptions also avoid the extreme condition of having smaller sample size requirements when the denominator becomes more negative.

Here, as an example, it is assumed that it is important to show that the mean BCDVA for the test is not inferior to control with a non-inferiority margin of 0.10 logMAR. Further, it is assumed that

- power $(1 - \beta) = 90\%$ and one-sided significance level (α) of 5%
- the true between-group mean difference (μ_t - μ_c) in BCDVA is 0.02 logMAR
- the common standard deviation is 0.20 logMAR

Solving for the equation:

$$n = 2 \cdot 0.20^2\left[\frac{\left(1.645 + 1.282\right)}{\left(0.02\right) - 0.10}\right]^2 = 107.09 \cong 107$$

Therefore, 107 study eyes and 107 control eyes are needed to provide 90% power (1-β) to show non-inferiority with one-sided significance level (α) of 5%.

E.2.3 Sample size of the EDF IOL arm, based on safety *considerations*

Bilateral implantation (parallel group study design):

The sample size for the study should be adequate to detect any type of adverse event with an expected rate of 1% or greater. The calculation is based on the use of the binomial distribution, as mathematically described in the equation below:

$$\Pr\left\{X = x \mid n, \pi\right\} = \binom{n}{x}\pi^x\left(1 - \pi\right)^{n-x}$$

where:

π is the true adverse event population proportion
n is the number of primary eyes in the EDF IOL arm;
X is the random variable for the observed number of adverse events from the investigation
x is the observed number of adverse events

Calculate the probability that x≥1, given that π =.01 by using:

$$\Pr\left\{X \geq 1 \mid n, \pi\right\} = 1 - \Pr\left\{X = 0 \mid n, \pi\right\}$$

For π =.01, in order for the probability to be at least 95% that you will see one or more events in the study, n (the number of primary eyes in the EDF IOL arm) must be greater than or equal to 299. This figure refers to the number at the conclusion of the study. Enrollment should be adjusted to compensate for anticipated drop out and loss to follow-up.

Annex F
(informative)

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