AMERICAN NATIONAL STANDARD

for Ophthalmics –

Laser Systems for Corneal Reshaping

ANSI Z80.11-2007

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Z80.11-2007

American National Standard
for Ophthalmics –

Laser Systems for Corneal Reshaping

Secretariat

Information Technology Industry Council

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American National Standard

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Foreword (This foreword is not part of American National Standard ANSI Z80.11-2007.)

This American National Standard was developed to address the expressed needs of those members of the ophthalmic community who correct the refractive errors of the human eye using laser refractive correction procedures, those who manufacture the lasers systems for corneal reshaping used to perform these procedures, and those who insure the public interest by ensuring that these systems are made in such a way so that they may perform their function in a safe and effective way when used correctly by those skilled in their use.

It must be realized that correcting the refractive error of the human eye with laser corrective surgery is a medical procedure involving not only a laser system for corneal reshaping but also (1) other devices used during surgery, (2) the assessment of the refractive state of the eye prior to surgery, (3) decisions on the best approach to take for treatment that involve not only the judgment of the physician but the desires of the patient, (4) the postsurgical care, and (5) the effects of healing, known and unknown. This standard only addresses the laser system for corneal reshaping and makes no attempt to standardize the procedure itself.

However, in response to a perceived need, informative annexes have been included in the standard to give guidance on types of clinical testing deemed to be adequate to ensure that the entire procedure is safe and effective. It was felt that a service would be performed for those in the field if this information were to be placed in a public document where it would be readily available to all.

While it is true that the outcome of a laser refractive procedure will not prove acceptable if the laser system for corneal reshaping used to perform it is not adequate for the task, it cannot be assumed that a laser system is inadequate if outcomes are not acceptable, as this may be the result of deficiencies in other important parts of the medical procedure. Thus, no claim is made that, if a laser system for corneal reshaping complies with this standard for the tasks it is designed to perform, that surgical procedures performed with the laser will have acceptable outcomes.

This standard was created by a special working group created by the Z80 Subcommittee on Medical Ophthalmic Devices and included experts in the field of laser refractive correction from the clinical, manufacturing and academic areas of the ophthalmic community and by experts from the regulatory agency given oversight in this field in the United States of America.

This standard contains seven annexes. Annexes A and B are normative and are considered part of the standard. Annexes C through G are informative and are not considered part of this standard.

Suggestions for improvement of this standard will be welcome. They should be sent to the Optical Laboratories Association, P.O. Box 2000, Merrifield, VA 22116-2000.

This standard was processed and approved for submittal to ANSI by the Accredited Standards Committee on Ophthalmic Optics, Z80. Committee approval of this standard does not necessarily imply that all committee members voted for its approval. At the time it approved this standard, the Z80 Committee had the following members:

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Quido Cappelli, Vice-Chairman
Robert Rosenberg, O.D., Secretary
Daniel Torgersen, Secretariat

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American National Standard for Ophthalmics –

Laser Systems for Corneal Reshaping

1 Scope and purpose

This standard applies to any laser system whose primary intended use is to alter the shape of the cornea through the removal of corneal tissue, resulting in the improvement of visual performance.

This standard addresses the vocabulary, performance requirements, labeling, and clinical investigations necessary for this type of device.

2 Normative references

The following standards contain provisions that, through reference in this text, constitute provisions of this American National Standard. 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 Z136.1-2000, *Safe Use of Lasers*

ANSI Z136.3-2005, *Safe Use of Lasers in Health Care Facilities*

IEC 60601-1:2001, *Medical Electrical Equipment – Part 1: General Requirements for Safety*

IEC 60601-1-1:2000, *Medical Electrical Equipment – Part 1-1: General Requirements for Safety – Collateral Standard: Safety Requirements for Medical Electrical Systems*

IEC 60601-1-2:1993, *Medical Electrical Equipment – Part 1: General Requirements for Safety – 2. Collateral Standard: Electromagnetic Compatibility – Requirements and Tests*

IEC 60601-1-4:2000, *Medical Electrical Equipment – Part 1-4: General Requirements for Safety – Collateral Standard: Programmable Electrical Medical Systems*

IEC 60601-2-22:1995, *Medical Electrical Equipment – Part 2: Particular Requirements for the Safety of Diagnostic and Therapeutic Laser Equipment*

IEC 60825-1:2001, *Safety of Laser Products – Part 1: Equipment Classification, Requirements and User's Guide*

ISO 8598:1996, *Optics and optical instruments – Focimeters*

ISO 10936-2:2001, *Optics and optical instruments – Operation microscopes – Part 2: Light hazard from operation microscopes used in ocular surgery*

ISO 12100-1:2003; *Safety of machinery – Basic concepts, general principles for design – Part 1: Basic terminology, methodology*

ISO 12100-2:2003; *Safety of machinery – Basic concepts, general principles for design – Part 2: Technical principles*

ISO 13849-1:1999, *Safety of machinery – Safety-related parts of control systems – Part 1: General principles for design*

ISO 13850:1996, *Safety of machinery – Emergency stop – Principles for design*

ISO 13852:1996, *Safety of machinery – Safety distances to prevent danger zones being reached by the upper limbs*

ISO 13853:1996, *Safety of machinery – Safety distances to prevent danger zones being reached by the lower limbs*

ISO 13854:1996, *Safety of machinery – Minimum gaps to avoid crushing of parts of the human body*

ISO 14155-1:2003, *Clinical investigation of medical devices for human subjects – Part 1: General requirements*

ISO 14155-2:2003, *Clinical investigation of medical devices for human subjects – Part 2: Clinical investigation plans*

ISO 14971:2000, *Medical devices – Application risk management to medical devices*

ISO /FDIS 15004-2 *Ophthalmic instruments – Fundamental requirements and test methods – Part 2: Light hazard protection*

American Conference of Governmental Industrial Hygienists (ACGIH), Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices 1999 (American Conference of Governmental Industrial Hygienists, Cincinnati, Ohio, 1999).

U.S. Code of Federal Regulations Title 21, 1040.10, *Laser Products* (21 CFR 1040.10)

U.S. Code of Federal Regulations Title 21, 1040.11, *Special-Purpose Laser Products* (21 CFR 1040.11)

U.S. Code of Federal Regulations Title 21, 812, *Investigation Device Exemptions* (21 CFR 812)

NOTE: Lasers and laser systems that are sold or imported into the U.S. are required to meet the Federal Performance Standard for Laser Products (21 CFR 1040.10 and 1040.11). At the time of this document revision, the Federal Performance Standard for Laser Products is being amended to harmonize with certain requirements of IEC 60825-1 and IEC 60601-2-22. Guidance has been issued to industry concerning conformance with these IEC standards.

3 Definitions

For the purpose of this standard, the definitions given below and in ISO 14155-1, ISO 14155-2, ANSI Z136.1, and ANSI Z136.3 apply.

Physical Terms

3.1 Ablation zone: The entire corneal region covered by laser ablation.

3.2 Active eye tracker: A device that monitors eye position relative to a defined reference position, moves the laser beam position to compensate for fixational eye movements, and maintain constant relative positions of the beam and cornea coordinate systems.

3.3 Alignment: Positioning a laser system for corneal reshaping to a desired location in three dimensions with respect to the eye under treatment.

3.4 Beam-positioning module: a motorized device that rotates or translates the exposed portion of the laser beam on the cornea. This may include an active eyetracker that repeatedly adjusts beam position to compensate for fixational eye movements. The beam-positioning module may be integrated with a beam-shaping module.

3.5 Beam-shaping module: An aperture, mask or other device that allows a predetermined portion of the laser beam to reach the cornea and fashions the ablation pattern. This may include the capability for manual or motorized adjustment of the size and/or shape of the beam. The beam-shaping module may be integrated with a beam-positioning module.

3.6 Broad beam laser: A laser having a beam for which the size and shape of corneal exposure are controlled by variable apertures, masks, or other mechanisms.

3.7 Centration: The process of positioning the origin of the laser coordinate system by the user to align with the intended point on the cornea.

3.8 Corneal ablation: Removal of tissue from the cornea by a laser beam.

3.9 Critical subsystem: A subsystem whose malfunction or failure could result in sight-threatening problems or in functionally significant errors in refractive correction.

3.10 Etch rate: The amount of ablated material that is removed by each laser pulse, expressed either as microns/pulse (ablation depth, usually for broad beam lasers) or microns^3/pulse (ablation volume) usually for small beam scanning lasers.

3.11 Etch rate ratio: A comparison of the etch rate in cornea to the etch rate in an inert substrate (usually PMMA), calculated by dividing the substrate etch rate by the corneal etch rate.

3.12 Excimer laser: A pulsed gas laser having output at discrete wavelengths in the ultraviolet region of the spectrum. The excimer (excited dimer) is formed when the appropriate gas mixture is excited, most commonly in a fast high-voltage discharge.

3.13 Fluence: Energy per unit area of a laser beam.

NOTE: This definition is intended solely for use in this standard.

3.14 Beam homogeneity: The spatial uniformity of the laser beam fluence at the treatment plane.

3.15 Laser system for corneal reshaping: An assembly of electrical, mechanical, and optical components, which includes a laser and software algorithms necessary to alter the shape of the cornea through the removal of corneal tissue.

3.16 Optical zone: The corneal region that receives the full intended refractive treatment.

3.17 Passive eye tracker: A device that monitors eye position relative to a defined reference position and pauses the laser treatment if the error in corneal position exceeds a criterion angle or distance.

3.18 Registration: The process of three-dimensional rotational and translational adjustments that superposes the coordinate systems of the cornea and the laser beam, or equivalently, the cornea and the intended ablation.

3.19 Safety critical software function: Any software function whose failure would produce a hazard.

3.20 Safety-related software requirement: A software requirement that is included in the design to mitigate a specific hazard that is identified in the hazard analysis.

3.21 Scanning laser: A laser having a beam that is smaller than the intended treatment zone and that is moved between successive pulses to cover the entire zone in a predefined sequence of beam positions.

NOTE: This definition differs from that in ANSI Z136.1 and is intended solely for use in this standard.

3.22 Transition zone (blend zone): The corneal region outside the optical zone but inside the ablation zone.

3.23 Treatment area: The sum of the zone of the full intended refractive correction plus the transition zone.

Clinical Terms

3.24 Astigmatism, regular: On-axis refractive error in which the flattest and steepest radii are orthogonal (perpendicular) and every cross-section along the optical axis is an ellipse. Regular astigmatism can be corrected with a cylindrical lens.

3.25 Astigmatism, compound hyperopic: Occurs when both focal lines (far lines) are behind the retina, resulting in a refraction that can be expressed as two plus cylinders (cross cylinder form, e.g., +1.00 x 180° & +2.00 x 90°) or a sphere and a cylinder (spherocylindrical form, e.g., +1.00 DS +1.00 DC x 90°).

3.26 Astigmatism, compound myopic: Occurs when both focal lines (far lines) are in front of the retina, resulting in a refraction that can be expressed as two minus cylinders (cross cylinder form, e.g., -1.00 x 180° & -2.00 x 90°) or a sphere and a cylinder (spherocylindrical form, e.g., -1.00 DS -1.00 DC x 90°).

3.27 Astigmatism, mixed: Occurs when one focal line (far line) is in front of the retina and one focal line (far line) is behind the retina, resulting in a refraction that is myopic in one meridian and hyperopic in the orthogonal meridian. The resulting refraction can be written in cross cylinder form with one positive cylinder and one negative cylinder (e.g., +1.00 x 90° & -1.00 x 180°), in plus spherocylinder form (e.g., -1.00 DC +2.00 DC x 90°), or in minus spherocylinder form (e.g., +1.00 DS -2.00 DC x 180°).

3.28 Astigmatism, simple hyperopic: Occurs when one focal line (far line) is on the foveola and the other focal line (far line) is behind the retina, resulting in a refraction that is plano in one meridian and a plus cylinder in the orthogonal meridian (e.g., 0.00 DS +1.00 DC x 90°).

3.29 Astigmatism, simple myopic: Occurs when one focal line (far line) is on the foveola and the other focal line (far line) is in front of the retina, resulting in a refraction that is plano in one meridian and a minus cylinder in the orthogonal meridian (e.g., 0.00 DS -1.00 DC x 90°).

4 Mechanical, thermal, and environmental requirements

This section applies to the mechanical, thermal, and environmental requirements of the laser.

4.1 Combination of different devices

If the laser system device is intended for use in combination with another instrument, the connecting system shall not impair the specified performance of either instrument. Sufficient objective evidence should be obtained either from testing and/or analysis to demonstrate that the laser system fulfills the requirements of this standard when said other devices are connected.

For coupling with active ophthalmic instruments, the electromagnetic compatibility provisions of IEC 60601-1-2 shall apply.

4.2 Materials

Materials shall meet the safety requirements of IEC 60601-1-1 for medical electrical systems.

4.3 Resistance to transport and storage conditions

After exposure of the laser system in its original packaging to the range of transport and storage conditions, within the temperature and humidity range given below and any other environmental conditions specified in the user instructions, the laser system shall conform to all safety, optical, and mechanical requirements under the environmental conditions specified in the user instructions for clinical use.

Temperature range: -10° C to +55° C.
Humidity range: 10% to 95% relative humidity (noncondensing)

5 Safety requirements

This clause applies to the safety requirements for the laser that are necessary to reduce the associated risks for patients and users.

5.1 Protection against contaminants

Parts of the laser system that are designed to come in contact with the patient or operator shall either be capable of easy disinfection or be protected by a disposable cover.

5.2 Protection against toxins and allergens

Components of the laser system that are designed to come into contact with the patient or operator shall be made of materials that are neither toxic nor known to create significant allergic reactions, when used as intended by the manufacturer.

5.3 Photobiological hazards

For wavelengths of the laser system other than the treatment wavelength from 200 nm to 330 nm, including those created by secondary emission, the total cumulative exposure during one procedure shall be less than 10 mJ/cm^2 effective exposure as spectrally weighted by the UV hazard action spectrum, S(λ), (see Annex A) where the effective exposure, H_{eff}, is calculated by

$$H_{eff} = \sum_{200}^{330} (E_\lambda \cdot t) \cdot S(\lambda) \cdot \Delta\lambda$$

where:

t is the exposure time;

$E_\lambda \cdot t$ is the spectral radiant exposure in J/cm^2 • nm;

$\Delta\lambda$ is the summation interval in nm extending from 200 nm to 330 nm.

The corneal radiant exposure shall be evaluated by averaging highest localized radiation power incident upon a circular area at the corneal plane with a diameter of 1 mm (7.9×10^{-3} cm^2).

5.4 Thermal hazards

The temperature of parts of the laser system held by the operator or accessible to the patient shall not exceed the allowable limits given in IEC 60601-1.

5.5 Mechanical hazards

The laser system shall be designed so that, when used to perform the intended function(s) in conformance with the user instructions, the risk of physical injury when using this instrument is reduced as much as is practicable. Conformance to this requirement shall be achieved by complying to the following standards: ISO 12100-1, ISO 12100-2, ISO 13849-1, ISO 13850, ISO 13852, ISO 13853 and ISO 13854.

5.6 Electrical safety

The manufacturer shall complete testing and certify that the device conforms to IEC 60601-1-1.

5.7 Radiation safety

The manufacturer shall complete testing and certify that the device complies with 21 CFR 1040.10 and 1040.11 (or the equivalent requirements of IEC 60825-1 and IEC 60601-2-22).

5.7.1 Light hazards

Measures shall be taken to ensure that illumination levels that reach the retina (i.e., due to aiming beams, fixation lights, microscope illumination, or secondary radiation from the treatment beam) are held as low as possible. Illumination levels for the operation microscope shall conform to the limits set by ISO 10936-2 and for other illumination sources to the limits for non-exempt instruments set by ISO 15004-2.

5.8 Gas safety (for gas lasers)

For systems using gas (e.g., excimer lasers), the laser system shall have an appropriate means of containment, control, and evacuation of any gases used to perform the intended function(s) in conformance with the user instructions. The gas containment system shall be designed such that the risk of physical injury when using this instrument is reduced as much as is practical.

The use, storage, and maintenance of any gases used to perform the intended function(s) shall conform to applicable environmental and occupational requirements. All pressurized gas bottles used with the product shall be housed in hermetically sealed containment devices or be built into a structure that shall prevent accidental release of toxic and or high pressure gas. If customer access to the fluorinated gas (i.e. customer can change the pre-mix gas bottle) is provided, there shall be a suitable fluorine detector/alarm provided to indicate automatically if the concentration of fluorine exceeds 0.1 ppm, the maximum permissible exposure limit for an eight-hour exposure.

The user instructions shall contain appropriate procedures for ensuring the safety of all personnel in the event of a gas leak.

5.9 Safety in use

The manufacturer of the laser system shall establish a procedure to maintain laser safety in use. ANSI Z136.3 should be consulted for information concerning the requirements of the laser safety program, which is applicable to Class 3B or Class 4 lasers. In brief, these requirements include, but are not limited to, control measures such as written standard operating procedures (ANSI Z136.3, 4.2.1), the establishment of a laser treatment controlled area and nominal hazard zone (ANSI Z136.3, 4.4), the posting of warning signs denoting the laser treatment controlled area (ANSI Z136.3, 4.4.2.1), the establishment of a laser safety and training program for personnel using the laser (ANSI Z136.3, clause 5), and the establishment of a medical surveillance program for personnel using the laser (ANSI Z136.3, Clause 6). It is recommended that the IEC Technical Report (IEC TR 60825-8) also be consulted for guidance on establishing a laser safety program.

The laser manufacturer shall recommend methods to minimize or remove any laser by-products, biological by-products, and odor (referred to as laser-generated airborne contaminants (LGAC)) that are produced as a result of the laser procedure.

5.10 System hazard analysis

A complete system hazard analysis shall be performed on the laser system. ISO 14971 gives general guidance for constructing a proper Hazard Analysis. A complete system hazard analysis, including Fault Tree Analysis (top down) and Failure Modes and Effects Analysis (bottom up) shall be performed on all safety related hardware and software components of the laser system. In addition to the laser system itself, the hazard analysis shall include consideration of faults and effects from interactions between the laser system and accessory devices, the patient, the operator, and the immediate operating environment.

6 Optical requirements

The optical components shall be protected from dust and other environmental contaminants by an appropriate containment system.

6.1 Alignment system

The laser system shall provide a method for the user to view and align the cornea, through the use of microscopes, fixation, aiming or focusing beams, or other appropriate means so that the user may align the eye to the system to within ±0.1 mm of the desired location. The accuracy of the alignment system shall be verified using the method of 9.1 or equivalent.

6.2 Fail safe monitoring

The laser system shall contain an appropriate means of monitoring and displaying the energy output of the system and a warning indicator if the energy values are outside specified acceptable limits. As required by 21 CFR 1040.11, the means for the measurement of the energy may have an error in measurement of no more than 20 percent when calibrated in accordance with the procedure and schedule specified by the manufacturer of the laser system. The location(s) for monitoring energy should be specified. The preferred location is as close to the eye as is practical within the laser system.

6.3 System calibration

The manufacturer shall employ a methodology for verifying the calibration of the laser system using one of the test methods given in Annex B or equivalent. The manufacturer shall perform validation testing to establish a calibration schedule. The calibration schedule shall be derived from estimates of the likely frequency of use of the device.

NOTE: Guidance on developing and characterizing laser ablation beams and treatment patterns may be found in Annex C.

If the laser system is capable of correcting sphero cylindrical refractive errors the cylinder axis shall be aligned to the desired axis for correction to ±2 degrees. This alignment shall be verified using one of the test methods given in 9.2.

7 System control and performance

7.1 Software

The laser system software shall be developed and validated in accordance with IEC 60601-1-4 for high-risk systems.

8 Clinical evaluation

The safety and effectiveness of a laser system for corneal reshaping shall be established through a clinical evaluation if the safety and effectiveness have not been previously established clinically.

This clinical evaluation shall adhere to the general requirements concerning the clinical investigations of medical devices for human patients specified in ISO 14155-1 and ISO 14155-2, and shall include the following particular requirements.

8.1 Clinical investigation plan

The clinical investigation plan shall contain the elements specified in 4.7 of ISO 14155-2, with the following additions.

To minimize the risks associated with the clinical investigation of a new laser system for which there is no prior clinical data, patient enrollment shall occur in stages. Guidance on patient enrollment is included in Annex D, clause D.5.

Guidance on establishing primary endpoints, statistical calculations to determine the sample size, and the recommended study duration is to be found in Annexes D and E.

NOTE: It is recommended that bilateral treatment and retreatment not be implemented until initial safety, effectiveness and stability data have been collected and evaluated by the manufacturer.

8.2 Surgical procedure

A description of any surgical procedures that are to be used in clinical study shall be described in the clinical investigation plan. Any surgical procedures that could affect the evaluation of safety or effectiveness shall be standardized.

8.3 Reporting periods and evaluations

Annex D contains guidance on recommended evaluations and an examination schedule.

The clinical investigation plan shall describe how patient visits between reporting periods (see Annex D for guidance) will be handled in the data analyses (e.g., an interim case report form shall be used and the data reported separately).

8.4 Adverse events

Adverse events and procedures for reporting adverse events shall be specified in the clinical investigation plan.

Guidance regarding reporting of adverse events is provided in Annex D. Reports of serious or unanticipated adverse device effects shall be reported to the sponsor, the United States Food and Drug Administration (FDA), all reviewing Investigational Review Boards (IRB) and participating investigators in accordance with 21 CFR 812.150(a)(1) and 21 CFR 812.150(b)(1). All other adverse events shall be documented in the case reports.

9 Test methods

9.1 Verification of alignment system accuracy

9.1.1 Materials

- Flat transparent plate of known chemical composition and physical dimensions on which is printed or otherwise placed a pattern that may be aligned with the alignment system of laser ablation system (test plate);
- An optical comparator or a profilometer (Sloan Dektak IIA, or equivalent) capable of locating the ablated pattern with respect to the alignment marks;
- A written procedure.

9.1.2 Procedure

- Program the laser system to create a pattern whose position may be easily assessed with respect to the alignment markings on the test plate;
- Place the test plate in the path of the treatment beam in the location where the eye is intended to be placed for treatment;
- Align the laser system centering it on the marked pattern on the test plate using the alignment system used during treatment of eyes;
- Ablate the pattern in the plate;
- Using the optical comparator or profilometer measure the displacement of the ablation pattern from the expected position with respect to the alignment marks that remain visible after ablation;
- Compare the displacement measured to the limits of 6.1.

9.2 Verification of the cylinder axis alignment

9.2.1 Materials

- Flat transparent plate of known chemical composition and physical dimensions on which is printed or otherwise placed a pattern having at least one visible line that may be rotationally aligned using the laser system alignment system, this line being parallel to one edge of the plate, a straight edge at least 50 mm in length;
- Focusing focimeter conforming to ISO 8598;
- An ablation pattern that will create an astigmatic correction with power in the range 2 diopters cylinder to 4 diopters cylinder at a designated axis;
- Written procedure.

9.2.2 Procedure

- Program the laser system to create an ablation pattern;
- Place the test plate in the path of the treatment beam in the location that the eye is intended to be placed for treatment;
- Align the pattern on the test plate to the laser system using the alignment system used during treatment of eyes;
- Ablate the pattern;
- Measure the cylinder axis of the ablated pattern using the focimeter, compare to expected axis and verify that the measured axis is within the tolerance specified in 6.3.

10 Accompanying documents

The laser system shall be accompanied by documents containing information for the physician, information for the patient and instructions for use together with maintenance procedures and their frequency of application.

In particular,r this information shall contain:

- Name and address of manufacturer;
- Trade name / Trademark;
- Model number / Serial Number;
- Additional marking or labels as required by IEC 60601, IEC 60825-1, and 21 CFR 1040.10 and 21 CFR 1040.11;
- Indications for use;
- Contraindications for use;
- Warnings;
- Precautions;
- Any environmental requirements (e.g., room temperature, humidity, air exchange rate) that are necessary for the device to meet its operating specifications;
- Clinical study results (including adverse events).

11 Marking

The laser system shall be permanently marked with at least the following information:

- name of manufacturer and, where appropriate, trademark or tradename;
- address of manufacturer, model and serial number;
- where appropriate, any warnings and/or precautions to be taken;
- additional marking or labels as required by IEC 60601, IEC 60825-1, and 21 CFR 1040.10 and 21 CFR 1040.11.

Annex A

(normative)

Spectral weighting function for ultraviolet radiation hazard analysis

Wavelength nm	**UV radiation hazard function** $S(\lambda)$
200	0.03
205	0.051
210	0.075
215	0.095
220	0.12
225	0.15
230	0.19
235	0.24
240	0.3
245	0.36
250	0.43
254	0.5
255	0.52
260	0.65
265	0.81
270	1
275	0.96
280	0.88
285	0.77
290	0.64
295	0.54
297	0.46
300	0.3
303	0.12

Wavelength nm	**UV radiation hazard function** $S(\lambda)$
305	0.06
308	0.03
310	0.02
313	6.00E-03
315	3.00E-03
316	2.40E-03
317	2.00E-03
318	1.60E-03
319	1.20E-03
320	1.00E-03
322	6.70E-04
323	5.40E-04
325	5.00E-04
328	4.40E-04
330	4.10E-04
333	3.70E-04
335	3.40E-04
340	2.80E-04
345	2.40E-04
350	2.00E-04
355	1.60E-04
360	1.30E-04
365	1.10E-04
370	9.30E-05
375	7.70E-05
380	6.40E-05
385	5.30E-05
390	4.40E-05
395	3.60E-05
400	3.00E-05

Annex B

(normative)

Methods for system calibration

Any one of the methods for laser system calibration given in this annex fulfills the requirements of 6.3.

B.1 Plastic plate ablation and measurement

B.1.1 Materials

- Flat transparent plate of known chemical composition and physical dimensions;
- Focusing focimeter conforming to ISO 8598;
- Profilometer (Sloan Dektak IIA, or equivalent);
- Designated ablation patterns;
- Expected profiles for each pattern with limit bands around each profile;
- Expected refractive power values with specified limits for each ablation;
- Written procedure.

B.1.2 Procedure

- For each pattern, position plate in laser system in an area with no ablation visible;
- Ablate the pattern;
- For patterns with a specified refractive power, measure the power using the focimeter, compare to expected power and verify that the measured power is within the specified limits;
- For all patterns scan the ablated area both vertically and horizontally with the profilometer such that the trace goes through the ablation center;
- Compare the measured profile to the expected profile and verify that all parts of the measured trace fit within the limit band of the expected profile template.

B.2 Laminated calibration plate method

B.2.1 Materials

- Flat plate of known chemical composition and physical dimensions with a series of known thickness layers of differing colors;
- Designated ablation pattern;
- Expected rate of ablation for each pattern;
- Written procedure.

B.2.2 Procedure

- For each pattern, position plate in laser system in an area with no ablation visible;
- Ablate the pattern(s);
- Utilize the color change of the pattern to determine the number of laser pulses necessary to achieve the known depth of ablation;
- Identify the location of the patterns relative to the axis of the surgical microscope and the shape of the pattern(s);
- Compare the location and shape of the ablation pattern(s) and the number of pulses required to achieve the known depth of ablation to expected outcomes, and adjust laser as necessary to achieve them;
- If the laser parameters are changed due to the initial test results, the tests are to be repeated to confirm that the adjustments had the intended effect.

Annex C

(informative)

Characterization of laser ablation beams and treatment patterns

During the development of a laser system for corneal reshaping the characteristics and action of the laser beam and the treatment pattern created by it need to be well understood. Appropriate test models and procedures should be established and testing performed to verify the ablation characteristics of the beam and the effectiveness of the software algorithm to create desired treatment patterns using the beam. This annex gives guidance in accomplishing these tasks.

Models may include ablation and ablation depth measurement in: (1) ex vivo corneas of human cadaver eyes, explanted animal eyes or in vivo animal models; (2) model corneas of plastic or other material with ablation characteristics comparable to those of corneal stromal tissue; and (3) simulated corneas in theoretical mathematical models.

C.1 Ablation characteristics of the beam

The tests of the ablation characteristics of the beam should include measurements or reliable documentation of prior measurements of the following quantities:

(1) Radiant exposure at the calibrated beam energy level for all beam configurations to be used for corneal ablation;
(2) Temporal intensity profile of a single pulse;
(3) Temporal intensity pulse train and related analysis showing variability of pulse energy at the intended treatment pulse frequency over the maximum expected time required for an individual ablation;
(4) *in vitro* testing of ablation depth and/or volume per laser pulse (etch rate) in a specified homogeneous or layered material to be used for beam calibration purposes,
    (i) from ablation threshold to at least the intended operating radiant exposure on a surface perpendicular to the beam direction; and
    (ii) at the calibrated radiant exposure as a function of the angle of beam incidence onto the corneal surface, from normal incidence to the largest deviation from normal incidence that will be encountered in clinical corneal ablations;
(5) *ex vivo* (human cadaver eyes, animal eyes) and/or *in vivo* (live animal models) testing of ablation depth and/or volume per laser pulse in corneal stromal tissue,
    (i) from ablation threshold to at least the intended operating radiant exposure on a surface perpendicular to the beam direction and at the calibrated radiant exposure as a function of the angle of beam incidence onto the corneal surface;
    (ii) from normal incidence to the largest deviation from normal incidence that will be encountered in clinical corneal ablations;
(6) Ratio of etch rate in corneal tissue to test material;
(7) Characterization of the beam intensity profile.

C.2 Mathematical models and simulations

Based on measurements of the ablation depth/volume per shot and beam energy as described in C.1, mathematical models of the ablation characteristics of the beam in corneal stromal tissue and in the selected calibration material should be formulated and incorporated into a simulation program for use in the validation of ablation algorithms designed for the correction of specified refractive errors.

Each specific ablation algorithm should be designed to achieve a target ablation depth map based on theoretical optical principles and other available relevant information, e.g., the biomechanical effects of flap creation and tissue removal and the healing properties of the cornea. The theoretical ablation map for each specific algorithm should be quantitatively and graphically compared to the corresponding simulated ablation map. Satisfactory validation of the simulation program should be achieved when the depth difference between the theoretical shape and the simulated shape does not exceed the depth of a single simulated laser pulse.

C.3 Validation of ablation algorithm software

Verification and validation testing of the laser system ablation algorithm(s) should include characterization of the ablation as described in clause C.1, including the depth and diameter of the optical zone, transition zones, and ablation zone. Ablations should be generated in accordance with clause C.1(4) over a treatment range representative of the intended use of the laser system and be measured using an appropriate methodology with depth resolution and accuracy of at least 1.0 µm and lateral resolution and accuracy of at least 100 µm. The experimentally generated ablation profiles should be compared with the corresponding theoretical and simulated profiles predicted by the laser system software. For the validation to be considered successful, any differences between corresponding measured and simulated ablations should be unsystematic and explainable by measurement error.

Annex D

(informative)

Guidance on clinical study design of refractive procedures that use laser systems for corneal reshaping

D.1 General

Annexes D, E and F provide guidance that will assist manufacturers in designing clinical studies of safety and effectiveness of refractive procedures that use Laser Systems for Corneal Reshaping. Nothing in this informative annex should be taken as standardizing clinical practice. A clinical study should include consideration of all of the elements listed below:

- Study Objectives (D.2)
- Design of the clinical study (D.3)
- Study duration (D.4)
- Enrollment of subjects (D.5)
- Inclusion and exclusion criteria for subject selection (D.6)
  - Inclusion criteria (D.6.1)
  - Exclusion criteria (D.6.2)
- Examination schedule (D.7)
- Evaluations and methodology (D.8)
  - Visual Acuity (D.8.1)
  - Measurement of Intraocular Pressure (D.8.2)
  - Subject Questionnaire (D.8.3)
  - Mesopic Pupil Size (D.8.4)
  - Contrast Sensitivity (D.8.5)
  - Low contrast letter acuity (D.8.6)
  - Specular Microscopy (D.8.7)
- Adverse events (D.9)
- Statistical sample size consideration (Annex E)
- Presentation of results of clinical studies (Annex F)
  - Accountability of Subjects (F.2)
  - Refractive Stability (F.3)
  - Safety (F.4)
  - Effectiveness (F.5)
  - Retreatment (F.6)

D.2 Study objectives

The objectives of the clinical investigation are to determine the safety and effectiveness of refractive procedures that use a Laser System for Corneal Reshaping for which safety and efficacy have not been previously established clinically.

The sample size for the study should be adequate to detect adverse events with an expected rate of 1% or greater. The statistical method recommended to make these calculations is found in clause E.2. Examples of sample size calculations made using these methods are found in E.2.1 and E2.2.

NOTE: If prior clinical data available for the laser system demonstrate an adequate safety profile and the risk analysis can demonstrate that a new indication for use does not raise new safety issues, then the sample size for the study may be selected based on the number of subjects necessary to adequately evaluate the primary effectiveness endpoint. This kind of substudy for a new indication will usually require around 125 eyes.

The claims to be verified include the visual performance of the subject after treatment with the Laser System for Corneal Reshaping and the stability of the refraction. The adverse device effects to be assessed include those described in clause D.9

D.3 Design of the clinical study

The type of clinical investigation recommended is a prospective, single group study. The postoperative performance of the subjects is compared to their preoperative performance.

Each investigator should contribute a minimum of 20 eyes to the study population, but not more than 25% of the eyes in the study.

The surgical procedure used for treating the eyes included in the study needs to be clearly delineated at the beginning of the study. Detailed instructions to the surgeon need to include:

- detailed instructions for configuring the laser system;
- detailed instructions for control of environmental conditions during surgery including humidity and temperature parameters and control;
- specification of auxiliary surgical devices to be used such as microkeratomes;
- specification of preoperation measurements to be taken to develop the treatment plan.

D.4 Study duration

Studies initially should be proposed for 24 months follow-up, with the option to shorten follow-up time if refractive stability, as defined in clause F.3, can be demonstrated earlier. All subjects should be followed through one reporting period for the cohort beyond the time at which they exhibit refractive stability. Any device specific safety and/or effectiveness concerns that might require longer follow-up should be assessed at the time of the protocol design to determine the appropriate study duration.

D.5 Enrollment of subjects

If the laser system has not been used previously to treat human subjects or the treatment data were not obtained in a controlled fashion, the manufacturer should complete a small pilot study (e.g., 20 subjects) to obtain initial evidence of safety and effectiveness. The results from the pilot study subjects may be used to estimate the sample size for the full study.

The manufacturer's study plan needs to show how the study will be phased to complete the total number of required subjects in the prescribed time period. Prior clinical experience with the device should be considered in devising such a plan. A series of stopping points as the trial expands is not necessary, but provisions should be made for interim evaluation of progress at each expansion point.

D.6 Inclusion and exclusion criteria for subject selection

D.6.1 Inclusion criteria

The following inclusion criteria are recommended:

- Meets specified refractive criteria (spherical and cylindrical components);
- Minimum Best Spectacle Corrected Visual Acuity (BSCVA) in each eye;
- Minimum 18 years of age;
- For myopes, Uncorrected Visual Acuity (UCVA) 20/40 or worse in the eye to be operated; for hyperopes, difficulty maintaining UCVA 20/40, as evidenced by need for constant contact lens or spectacle wear;
- Less than 0.75 D spherical equivalent (SE) difference between cycloplegic and manifest refractions;
- Stable refraction (within ±0.5 D), as determined by Manifest Refraction Spherical Equivalent (MRSE) for a minimum of 12 months prior to surgery, verified by consecutive refractions and/or medical records or prescription history;
- In addition, contact lens wearers need to demonstrate a stable refraction (within ±0.5 D), as determined by MRSE on two consecutive exam dates. Stability of the refraction is determined under the following conditions: (a) lenses are not worn for at least 2 weeks (rigid or toric contact lenses) or 3 days (soft contact lenses) prior to the first refraction used to establish stability and through the day of surgery; (b) the two refractions are performed at least 7 days apart;
- For expected residual postoperative cylindrical refractive error of ≥1 D or spherical refractive error of ≥2.0 D, the subject has been given the opportunity to experience his/her best spectacle vision with anticipated correction only and is willing to proceed with the surgery;
- Given written informed consent;
- Willing and able to comply with schedule for follow-up visits.

D.6.2 Exclusion criteria

The following exclusion criteria are recommended:

- Acute or chronic disease or illness that would increase the operative risk or confound the outcomes of the study (e.g., dry eyes, immuno-compromised, connective tissue disease, clinically significant atopic disease, diabetes, etc.);
- Systemic medications that may confound the outcome of the study or increase the risk to the subject, including, but not limited to steroids, antimetabolites, etc.;
- Ocular condition (other than high myopia) that may predispose the subject to future complications, for example:

  - history or evidence of active or inactive of corneal disease (e.g., herpes simplex keratitis, herpes zoster keratitis, recurrent erosion syndrome, corneal dystrophy, etc.);
  - evidence of retinal vascular disease;
  - keratoconus or keratoconus suspect;
  - glaucoma or glaucoma suspect by exam findings and/or family history;
- Previous intraocular or corneal surgery that might confound the outcome of the study or increase the risk to the subject;
- An increased risk for developing strabismus post-treatment (applicable only to treatment of hyperopic refractive errors);
- A known sensitivity to study medications;
- Pregnant, lactating during the course of the study, or has another condition associated with the fluctuation of hormones that could lead to refractive changes.

D.7 Examination schedule

The following reporting periods are recommended:

- Preoperative (Pre-op);
- Operative (OP);
- Day 1 (D1);
- Re-epithelialization (where applicable, e.g., PRK);
- Week 1 (5-9 days) (W1);
- Month 1 (3-5 weeks) (M1);
- Month 3 (10-14 weeks) (M3);
- Month 6 (21-26 weeks) (M6);
- Month 9 (35-43 weeks) (M9);
- Month 12 (11-14 months) (M12);
- Month 24 (23-27 months) (M24).

Table D.1 contains the recommended examination schedule including clinical evaluations to be preformed at each visit.

Table D.1 – Recommended postoperative examination schedule

	Pre-op	OP	D1[1]	W1	M1	M3	M6-M24[12]	Final Exam[2]
Subject information, current medications, complications and adverse events	X	X	X	X	X	X	X	X
Distance UCVA	X			X	X	X	X	X
Distance BSCVA	X			X	X[3]	X[3]	X[3]	X[3]
Manifest Refraction[4]	X			X	X	X	X	X
Cycloplegic Refraction	X							X
Near UCVA	X					X[9]		X
IOP	X				X	X	X	X
Slit Lamp Exam[5]	X		X	X	X	X	X	X
Pupil size[6]	X							X
Dilated Fundus Exam	X							X
Pachymetry, keratometry[7]	X							
Topography[7]	X				X			X
Subject Questionnaire[8]	X						X	X
Contrast Sensitivity[10]	X					X	X	X
Specular Microscopy[11]	X						X	X

Notes for the Examination Schedule

1. The same parameters are to be measured at each examination performed until re-epithelialization occurs (when applicable).
2. The final exam should be conducted at least three months after the time when refractive stability is achieved. All measurements performed at the "Final Examination" must be performed before any enhancements or retreatments.
3. If the visual acuity with spectacle correction is > 2 lines below that obtained preoperatively, a rigid contact lens over refraction should be performed to estimate the best possible corrected visual acuity.
4. Manifest refractions for hyperopia should be conducted using a standard procedure that "pushes plus", i.e., maximizes the hyperopic correction acceptable to the subject.
5. The slit lamp exam should include a complete survey of the anterior segment. The cornea should be examined in detail with specific recordings and gradings (0 to 4+ scale, 0=clear) of the following information: overall corneal clarity, any abnormalities such as corneal infiltrates, opacities in the lamellar bed and density of the scar around the edge of the flap (for LASIK).
6. Pupil size should be assessed under mesopic conditions at the preop exam and final exam.
7. Pachymetry, keratometry, and topography should be assessed on all eyes preoperatively and if needed to assess anomalous results in the postoperative course.
8. The questionnaire should be administered at the preop exam, at the time of the anticipated stability and at the final exam. It should include questions regarding mesopic conditions (including but not limited to night driving). The analysis of study results should attempt to correlate haze to problems identified by subjects under mesopic conditions.
9. Near UCVA needs to be measured at Month 3 only for eyes treated for hyperopia with or without astigmatism.
10. Examination included for subjects enrolled in a contrast sensitivity substudy (see D.8, D.8.5 and E.3.1). Mesopic pupil size should be measured at all contrast sensitivity testing visits.
11. For guidance on substudy see D.8, D.8.7 and E.3.2.
12. The indicated evaluations are recommended to be performed at each of the study visits from Month 6 through Month 24 prior to Final Exam

D.8 Evaluations and methodology

The following examinations should be performed on all study subjects:

- UCVA (distance and near);
- BSCVA (distance and near);
  NOTE: Manufacturers may wish to perform Best Contact Lens Corrected Visual Acuity (BCLVA) on high myopes and high hyperopes to increase the accuracy of preoperative refractions and power calculations.
- Manifest and cycloplegic refractions;
- Subject questionnaire;
- Intraocular pressure;
- Slit lamp exam;
- Dilated fundus exam;
- Mesopic pupil size;
- Pachymetry (preoperatively);
- Topography ;
- Keratometry (preoperatively).

The following evaluations should be performed on a subset of subjects if the indicated relevant safety concerns apply:

- An endothelial cell substudy should be performed: (1) when laser refractive surgery is performed closer than 250 microns to the corneal endothelium; or, (2) the laser parameters (e.g., wavelength and radiant exposure) used are likely to damage the endothelium. The recommended method for determining endothelial cell density is given in D.8.7. Guidance for statistical assessment of the appropriate number of subjects for this substudy is provided in E.3.2

- A contrast sensitivity substudy should be performed: (1) when features of the laser beam or the ablation algorithm raise concerns that the refractive surgery procedure may produce significant visual performance losses not correctable by spectacles; or, (2) when the manufacturer wishes to use contrast sensitivity results to justify softening or deleting precautionary labeling statements that the treatment may impair visual performance under poor lighting conditions. Methods for determining contrast sensitivity are given in D.8.5. Guidance for statistical assessment of the appropriate number of subjects for this substudy is provided in E.3.1

D.8.1 Visual acuity and manifest refraction

Distance and near acuity charts, chart luminance, ambient illumination, testing distances and testing procedures should be standardized for all investigators (see reference [5], Annex G). Reporting of refractions should be standardized across study sites. Manifest refraction should be performed under clinically equivalent conditions for distance and chart luminance.

The following conditions, materials and procedures for acuity testing are recommended:

(a) *Luminance*: A chart background luminance should be selected from 80 – 160 cd/m^2 (85 cd/m^2 recommended) for photopic testing and from 2.5 - 3.5 cd/m^2 (3 cd/m^2 recommended) for mesopic testing. Luminance should be identical for all testing centers.

Chart contrast for normal (high contrast) acuity testing should be 85% or greater.

Ambient illumination 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 in luminance.

(b) *Chart distance*: All distance acuity assessments should be performed with identical charts at all centers at a minimum optical distance of 4 meters. Chart distance should be precisely defined and be identical to that recommended by the chart manufacturer. For distance acuity testing, the best correction to the chart distance should be used. When determining the best distance refraction for treatment, however, the refraction should be adjusted to the refractive correction at infinity (e.g., - 0.25 D for a 4 meter chart distance).

Uncorrected near visual acuity should be tested at an optical distance of 40 cm with a chart calibrated for 40 cm.

For testing at a fixed distance, the chart distance should be precisely defined, i.e., no head movements relative to the chart should be allowed.

(c) *Data recording procedures*

i. All physical and optical testing distances should be recorded.

ii. All corrective lenses should be recorded.

iii. All acuity measurements should be recorded using MAR (Minimum Angle of Resolution in minutes of arc) notation or other notation convertible to MAR. Examples of acceptable notation include:
- logMAR (common logarithm of MAR)
- decimal notation (reciprocal of MAR)
- standard Snellen notation (actual test distance/test distance that would render MAR = 1)

iv. Jaeger notation for near acuity may be used only after a letter size calibration has established the relationship between the Jaeger values and Snellen or MAR values.

D.8.2 Measurement of intraocular pressure

Intraocular pressure should be measured using Goldmann applanation tonometry. Other methods may be used providing the tonometer used meets the requirements of ISO 8612, but the same method should be used throughout the study. Additionally, for high refractive error corrections, effects of thinner corneas on Goldmann applanation readings should be taken into account.

D.8.3 Subject questionnaire

A subject questionnaire should be administered to all subjects. Examples of validated questionnaires are found in Annex G, references [6], [10], and [13].

The questionnaire should include questions regarding glare, halos, double vision, spectacle/contact lens use, and night driving. A scaling system for subjective ratings should be specified. Subjective ratings should be utilized to assess incidence of clinically significant symptoms as well as postoperative change in symptoms from preoperative status.

Postoperative subject's satisfaction with surgery and postoperative frequency of distance correction should be incorporated into the questionnaires.

The results of the subject questionnaire should be stratified by fellow eye status (untreated, treated, treated with other refractive surgery, etc.).

D.8.4 Mesopic pupil size

Mesopic pupil diameters should be measured and recorded with a precision of at least ±0.5 mm. For the mesopic pupil diameters, eye illumination should be identical to that used for mesopic contrast sensitivity testing. It is recommended that pupil measurements be made with an infrared CCD camera or light amplification equipment to increase precision and reliability, and to provide good pupil visibility with dark irises. The pupil measurement device should not block the illumination of the subject's eye.

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.

D.8.5 Contrast sensitivity

If the need to collect contrast sensitivity information is indicated, grating contrast sensitivity is recommended.

D.8.5.1 Grating contrast sensitivity testing

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 bar width). At each spatial frequency, the contrast is varied until the bar pattern is just detectable.

NOTES:
(1) Methods to minimize high frequency artifacts that may affect the data are to blur the outer edges of the grating and to surrounded 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 and Schwartz (1990), (see Annex G, reference [12}).
(2) Since aberrations such as astigmatism, coma and other higher order aberrations are not rotationally symmetric, the ideal sinusoidal optotype would theoretically be rotationally symmetric to avoid any axis dependence on the threshold detection of the target. Other optotypes of one fundamental frequency with equal amplitude at all spatial frequencies and orientations may be used, if available, to address these concerns.

Contrast sensitivity testing should be performed under mesopic conditions. 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 preoperatively and with best spectacle correction postoperatively, but results should be stratified by type of preoperative habitual correction.

The same chart luminance selected from the range of 2.5 – 3.5 cd/m^2 (3 cd/m^2 recommended) should be used at each substudy site and the ambient illumination should be lower than the chart luminance.

To enhance the quality of the contrast sensitivity data, a practice trial should be performed. At the first contrast sensitivity evaluation, a full practice trial (at one spatial frequency) on each eye should be performed. At subsequent evaluations, the practice trial can be limited to one eye and several spatial frequencies. Testing should be performed once and then repeated; the average of these two tests should be used for the data analysis.

The same contrast sensitivity equipment and protocol should be used at each site. The instructions provided by the manufacturer of the equipment for using missing data (i.e., subject unable to see targeted spatial frequency at any available contrast) in the data analysis should be followed.

The subject population should be large enough to detect a 0.15 log unit difference in contrast sensitivity between the preoperative and postoperative levels. (See E.3.1 for sample size calculations.)

Mesopic contrast sensitivity should be measured on all subjects preoperatively, and postoperatively on subjects who experience significant visual symptoms, such as glare, haloes or double vision. In addition, a mesopic contract sensitivity substudy should be performed when indicated. Mesopic pupil size should be measured at all contrast sensitivity visits.

D.8.6 Low contrast letter acuity testing

Visual performance losses related to reading in low illumination conditions and /or low-contrast conditions may be assessed via low-contrast letter acuity testing. It is recommended that such testing be performed as follows:

Illumination conditions: The chart background at each site should have the same luminance selected from the range of 2.5 – 3.5 cd/m^2 (3 cd/m^2 recommended) “white” light. The chosen background luminance level should be the same for all sites in a given study. The room lights should be off.

Chart: The chart should have dark letters with a 10% contrast (Michelson) compared to the background. The letters on the chart should be in a standardized format such as ETDRS, i.e, 5 letters per line, letter sizes change by 0.1 LogMar units per line, with the letters sized for the chosen viewing distance.

Viewing distance: The letters should be presented at a viewing distance of 4 meters or greater with the same viewing distance used for all sites in a given study.

Refractive correction: Testing should be performed with the best correction for viewing distance in place.

Sample size: Sample size determination should be based on published data or a pilot study.

Procedure

(1) Dark adapt for at least 5 minutes;
(2) Test monocularly;
(3) Start patient at the top line of the chart and have them read each letter left to right;
(4) Force patient to continue to "guess" until they miss all the letters on a line;
(5) On a form showing the letters on the chart arranged by lines, circle the last complete line and individual letters correctly identified. Draw a line through all letters incorrectly identified and the first line where no letters were correctly identified;
(6) Record the number of letters correctly identified.

NOTE: When standard light boxes are used to present charts, the mesopic background illumination condition may be achieved by inserting neutral density filters in the light box.

D.8.7 Specular microscopy

To determine endothelial cell density loss, specular microscopy should be performed preoperatively and at Month 3 (or Month 6). Losses may be determined by evaluating the cell counts at Month 3 (or Month 6) in comparison to the preoperative measurements and calculating the difference between the pairs (postop measurement minus preop measurement). The number of subjects should be sufficient to detect endothelial cell density loss of 10% (upper limit of 95% CI $\leq$ 10%).

Specular microscopy images should be taken of the central cornea. Peripheral measurements should be taken if warranted by the ablation pattern. The peripheral locations to be photographed should be specified based on the design and/or pattern of the ablation.

Analyses of specular microscopy data should include the determination of the mean cell density loss over time and a frequency distribution. The mean rate of cell density loss should be calculated via a paired analysis in order to calculate the mean of the differences. A frequency distribution of cell density losses should also be performed. The outcomes should be stratified by coefficient of variation and preoperative contact lens or spectacle wear.

Collection of data: The methods used for the collection and analysis of specular microscopy data are critically important to minimizing the variability associated with these measurements. Common sources of variability in specular microscopy are:

- difficulty in returning to same location on the cornea at each visit;
- poor image quality (less than 100 countable cells);
- technician error;
- improper reader analysis; and
- maintaining equipment calibration/alignment.

There are several ways to reduce this variability. Sponsors should implement as many of these recommendations as possible.

To address differences in location of the image within a given area of the cornea, three acceptable images should be taken at each visit. The mean density from the three images should be used.

Problems due to poor image quality and/or technician error may be avoided by using appropriate equipment and trained, experienced clinical sites. Non-contact specular microscopes are strongly recommended. The same model of specular microscope should be used at each site. Images should be stored on 35 mm slides, half-inch video, or in electronic format. Specular cameras that can record digitized images on disk or to e-mail are preferable for ease of data transfer.

Prior to the beginning of the study, it is recommended that each site take an initial set of images for an evaluation of image quality. Training (or retraining) should be performed as necessary.

A preferred image has:

- distinct cells;
- at least 100 identifiable (countable) cells as a minimum, 150 cells preferred; and
- cells that can be grouped in a uniform area.

To capture a good image, the following are recommended:

- Make sure the subject is comfortable;
- Instruct the subject to blink;
- Instruct subject not to move and to open eyes wide;
- Instruct subject to focus on the fixation light;
- Be patient; and
- If necessary, use the manual setting. (Note that the use of the manual setting may require additional training.)

The use of a reading center is strongly recommended. If the use of a reading center is not possible, the sponsor should establish a protocol for the collection and analysis of images to be used by each participating site. The person responsible for taking and accepting the images should be adequately trained in both specular photography and in the evaluation of the images. If possible, the same trained and certified technician/photographer should be used at each site throughout the study. A back-up technician who is trained should also be available.

The reading center or technician performing the image analysis should be advised of the following recommendations:

- A minimum of 100 cells (ideally 150 cells) in a contiguous area should be counted. The center method for counting cells is recommended.
- The quality of cells in an image is critical. Be aware that the presence of disease can increase variability (e.g., polymegathism/pleomorphism post-contact lens wear, keratoconus). When selecting cells to count, use the area with the fewest distortions (not in shadow, washed-out, or blurred).

A calibration grid may be obtained from the specular microscope manufacturer. The study monitor should check the calibration at each site on a yearly basis.

D.9 Adverse device effects / Adverse events

The following adverse device effects / events, although not an all-inclusive list, should be considered to be reportable, as described in 21 CFR 812.150(b)(1):

- Diffuse lamellar keratitis (Grade 3 or above) (see reference [9] in Annex G);
- Corneal infiltrate or ulcer;
- Any persistent corneal epithelial defect at one month or later;
- Corneal edema at 1 month or later (for LASIK, specify flap or bed);
- Epithelium in the interface with loss of 2 lines (10 letters) or more BSCVA (LASIK only);
- Miscreated flap (lost, incomplete, too thin) (LASIK only);
- Melting of the flap (LASIK only);
- IOP with increase of >10 mm Hg above baseline on two consecutive examinations or an IOP greater than 30 mm Hg on two consecutive examinations;
- Haze beyond 6 months with loss of 2 lines or greater (≥10 letters ETDRS) of BSCVA;
- Decrease in BSCVA of greater than or equal to 2 lines (≥10 letters ETDRS) not due to irregular astigmatism as shown by rigid contact lens refraction at 3 months or later;
- Retinal detachment;
- Retinal vascular accidents;
- Any other vision-threatening event;
- Ocular penetration.

The manufacturer should include in the clinical protocol a list of possible adverse events, including any that apply from the list below. The clinical report forms should include forced-choice listings of these adverse events and allow for the recording of other adverse events not listed.

- Diffuse lamellar keratitis (Grade 2 or less);
- Corneal edema between one week and one month after the procedure;
- Peripheral corneal epithelial defect at one (1) month or later (for LASIK, location of the defect to be identified as on, off, or across the flap);
- Epithelium in the interface (LASIK only);
- Recurrent corneal erosion at one month or later (PRK only);
- Foreign body sensation at 1 month or later;
- Pain at one month or later;
- Ghost/double images in the operative eye;
- Flap is not of the size and shape as initially intended or microkeratome stopped in mid-cut or resultant flap is misaligned (LASIK only).

Adverse events that occur in association with a device that is used in conjunction with the laser system (e.g. microkeratome for LASIK) will be reported separately from those occurring with the laser device.

Annex E

(informative)

Statistical Sample Size Considerations

E.1 Statistical symbols and definitions

Table E.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
$\bar{x}$	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	Alternate hypothesis
α	The probability of falsely rejecting the null hypothesis
β	The probability of falsely accepting the null hypothesis
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 (coverage probability) (1-β)
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 a sample size of n"

Table E.2 provides a convenient list of standard normal quantiles that will be used throughout. A *quantile* is the fraction of a population lying outside the chosen confidence interval.

Table E.2 – Normal Quantiles to Use in Equations

α	$(1-\alpha)$	$z_{1-\alpha}$
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 based on safety estimates

The sample size needed in a study, based on safety estimates, may be determined from an evaluation of the probability of observing adverse events at a rate greater than or equal to an expected rate for a control population but less than or equal to a target rate that is deemed acceptable for the procedure considered. The control population may be an untreated population or it may be a treated population for which an acceptable adverse event rate has been established from historical data. The expected adverse event rate for the control population is generally assumed to be 1%. The adverse event rates observed are expressed as sample proportions.

Using the evaluation of adverse events occurring at an expected rate or greater as the primary safety endpoint, the null hypothesis (H_0) is that the true adverse event sample proportion for the procedure (p_t) is less than or equal to a target value (fixed) proportion (p_c). The alternative hypothesis (H_1) is that the true adverse event sample proportion (p_t) is larger than the control sample proportion (p_c).

$$H_0: p_t \leq p_c$$
$$H_1: p_t > p_c$$

The calculation is based on the use of the binomial distribution, as mathematically described in equation E1 below, to test the null hypothesis that the true adverse event sample proportion is less than or equal to that associated with the control population. The alternative hypothesis would be that the sample proportion of the adverse events is greater than the control.

$$\Pr\{X \geq x \mid n, p\} = \sum_{i=x}^{n} \binom{n}{i} p^i (1-p)^{n-i} \qquad \text{(E1)}$$

Where:

- p is the adverse event sample proportion
- n is the sample size;
- X is the random variable for the observed number of adverse events from the investigation
- x is the observed number of adverse events

To use equation (E1) to find the necessary sample size, n, values are first chosen for α and β. The values typically chosen are $\alpha = 0.05$ and $\beta = 0.20$. Then values are found for n and x such that

$$\Pr\{X \geq x \mid n, p_c\} \leq \alpha$$

and

$$\Pr\{X \geq x \mid n, p_t\} \geq 1 - \beta$$

The smallest value of n that satisfies these two conditions is the minimum sample size needed. The smallest value of x that satisfies these two conditions is the critical value, x_{crit}, i.e., the minimum number of events for rejection of the null hypothesis.

As an example, when the chosen values for the control and target proportions are $p_c = 0.001$ and $p_t = 0.01$, equation (E1) may be used to verify that $x_{crit} = 2$ and $n = 299$ eyes.

If a different primary safety endpoint is chosen, the manufacturer should document the statistical basis for the sample size.

E.2.2 Sample size based on effectiveness estimates using noninferiority hypothesis testing

When the statistical method known as *noninferiority hypothesis testing* is used for studies in which postoperative data to preoperative data of the same subject are compared, the sample size required for paired differences can be determined from the following equation (see reference [8], Annex G):

$$n = \sigma_d^2 \left[\frac{(z_{1-\alpha} + z_{1-\beta})}{\delta + \mu_d} \right]^2 \text{ for } \mu_d > -\delta \qquad \text{(E2)}$$

Where:

μ_d is the mean of the paired differences

σ_d is the standard deviation of the paired differences

δ is the amount that sample mean may be less than μ_d and still have the treatment be considered non-inferior to the pretreatment (control) condition – the noninferiority margin

Table E.1 provides parameter definitions. The paired differences are formed by subtracting the control values from the treatment values. Usually, the mean of the paired differences is assumed to be zero.

Noninferiority hypothesis testing means that the statistical question has been asked "Is the measured result of the tested procedure as effective as the result obtained from some chosen control procedure?" If it is, to within some bound set by δ, the noninferiority margin, then the tested procedure is claimed to be "noninferior" to the control procedure. For instance, in the case of a laser refractive procedure to correct the refraction error of the eye, the measured result of the procedure might be taken to be the acuity for distance vision taken after the procedure and the measured result of the control procedure taken to be the best distance acuity that could be obtained with spectacle correction before the procedure. As can be readily understood, great care must be taken when using non-inferiority hypothesis testing to properly pose the statistical question by using reasonable measures and wisely choosing the value for δ based on them.

The above sample size formula for treatment differences is based on solving the probability statement

$$1-\beta = \Pr[\text{Lower } 100(1-\alpha)\% \text{ Confidence Limit on Difference} > -\delta]$$

for the sample size. For example, noninferiority in a paired comparison of means solves this equation for the sample size:

$$1-\beta = \Pr[lci > -\delta]$$

$$= \Pr[\bar{x}_d - z_{1-\alpha}\frac{\sigma_d}{\sqrt{n}} > -\delta]$$

Where:

$\bar{x}_d$ is the mean of the paired differences

σ_d is the standard deviation for each member of the differences assumed to be the same for both members

The abbreviation, lci, stands for "lower confidence interval." The resulting sample size equations have boundary conditions for the expected values and noninferiority margins. If the boundary conditions are not met, then the probability statement above should be analyzed directly by numerical methods.

Also note that if the noninferiority margin is set to zero, then these sample size formulae simplify into usual sample size formulae for one-sided hypothesis tests. In all cases, the sample size should be rounded up to the next largest integer.

In order to calculate sample size using the above equations, the acceptable difference between means (noninferiority margin), the standard deviation, the power level and the confidence interval must be chosen. Values for these parameters should be chosen based on experience or published literature.

E.3 Clinical substudies

E.3.1 Sample size for a contrast sensitivity study

For a contrast sensitivity study comparing postoperative data to preoperative data for the same subject (paired sample) the sample size is found using the method of E.2.2.

Contrast sensitivity is measured in log units so the values for the standard deviation and non-inferiority margin are given in those units. The standard deviation is given the value 0.4, based on historical evidence. A one-sided upper 95% confidence interval level on the mean paired difference is chosen so that $\alpha = 0.05$ and from Table E.2 it is found that $z_{1-\alpha} = 1.645$. Non-inferiority is taken to mean that the paired difference mean is no less than 0.15 below zero (selected for this example as one half of the clinically significant value of 0.3 log units). So that the non-inferiority margin, δ, equals 0.15 and $\mu_d = 0$. To ensure that this condition may be detected with a probability of 90%, the "power" of the test, Table E.2 gives a value for $z_{1-\beta} = 1.282$.

Using these values in equation (E2)

$$n = \left[\frac{0.4(1.645 + 1.282)}{0.15}\right]^2 = 60.92 \cong 61$$

Therefore, the sample size needed would be 61 subjects.

E.3.2 Sample size for endothelial cell density study

An endothelial cell substudy should be performed: (1) when laser refractive surgery is performed closer than 250 microns to the corneal endothelium; or, (2) when the laser parameters (e.g., wavelength and fluence) used are likely to damage the endothelium. The recommended method for determining endothelial cell density is given in D.8.7.

The change of endothelial cell density over time should be determined by evaluating measurements taken preoperatively and at the Month 6 or Month 12 exam to determine the change (paired difference) in endothelial cell density between the pairs.

For an endothelial cell substudy comparing postoperative data to preoperative data for the same subject (paired sample), the sample size is found using the method of E.2.2.

Endothelial cell decrease is measured in percent so the values for the standard deviation and noninferiority margin are given in those units. The standard deviation is given the value 0.1, based on historical evidence. A one-sided upper 95% confidence interval level on the mean paired difference is chosen so that $\alpha = 0.05$ and from Table E.2 it is found that $z_{1-\alpha} = 1.645$.

Noninferiority is taken to mean that the paired difference mean is no more than 0.035 above zero. So that the noninferiority margin, δ, equals 0.035 and $\mu_d = 0$. To ensure that this condition may be detected with a probability of 90%, the "power" of the test, Table E.2 gives a value for $z_{1-\beta} = 1.282$.

Using these values in equation (E2)

$$n = \left[\frac{0.1(1.645 + 1.282)}{0.035}\right]^2 = 69.9 \cong 70$$

Therefore, the sample size needed would be 70 subjects.

Annex F

(informative)

Presentation of results of clinical studies

F.1 General

This annex contains information on the recommended presentation of results of clinical studies of safety and effectiveness as described in Annex D. The contents of this annex are listed below:

F.1 General
F.2 Accountability of subjects
F.3 Refractive stability
F.4 Safety
F.5 Effectiveness
F.6 Retreatment

F.2 Accountability of subjects

The general requirement for accountability of subjects is given in 6.10 of ISO 14155-1. More specific guidance for subject accountability is provided below.

Table F.1 provides an illustration, in the form of a spread sheet, of the type of data needed when performing an accountability analysis for the clinical investigation and how it is organized for analysis. In this spread sheet two numbers are to be placed in each status box. The first number is the number of subjects in the category of the box (n), i.e., the number of qualifying subjects for that examination period. The second number is the ratio of n/N, expressed as a percent, where N is the total number subjects enrolled in the investigation. The accountability values are found by the special formula given and only one number is placed in those boxes.

Depending upon the clinical investigation, the total number of subjects may or may not be the total number of eyes.

To minimize the uncertainty in the data, the lost to follow-up subjects should comprise less than 10% of the study population after one year and less than 20% of the study population after 2 years.

Table F.1 – Accountability by post-operative visit

Enrolled [1] (N)		Subject Status (n, % (100n/N))			
Visit Interval		1 Month	3 Months	6 Months	12 Months
Available for Analysis[2]					
Active[3]					
Missed Visit[4]	Discontinued[5] Retreatment Other causes				
	Lost to follow-up[6]				
	Missed visit, but seen at a later visit				
	Not seen, but status obtained (e.g. phone)				
%Accountability[7] = Available for Analysis x100 / (Enrolled - Discontinued - Active)					

[1] Enrolled – Total number (N) of subjects enrolled in the investigation.

[2] Available for analysis – Total number of subjects for whom data is available that have reached the postoperative interval being reported.

[3] Active – Total number of subjects that have not yet reached the postoperative interval being reported (not yet eligible for the interval).

[4] Missed visit – Total number of subjects that missed the visit being reported upon. Missed visit group includes the discontinued subgroup, the lost to follow-up subgroup, subgroup of subjects that missed the visit being reported upon but were seen at a later visit and a subgroup of subjects that were not seen but their status was obtained (e.g., by telephone interview).

[5] Discontinued – Total number of subjects that have discontinued the study prior to completion of the prescribed investigational period for any reason (e.g., retreatment, death). This category doesn't include subjects that are lost to follow-up.

[6] Lost to follow-up – Total number of subjects for whom a visit at the prescribed post-operative visit or later has not been obtained and no information is available about them.

[7] Percent Accountability – Total number of subjects available for analysis divided by (the total enrolled less total discontinued less total active).

F.3 Refractive stability

Stability analyses should be performed on the eyes that had every follow-up exam from 1-month up to the stability time point (the Consistent Cohort), as well as on the eyes that had 2 consecutive exams, but not necessarily every follow-up exam. Recommended stability analyses, to be performed for the time intervals between all consecutive pairs of scheduled postoperative refractions, are:

- Percentage of eyes that achieve:
    - a change of less than or equal to 1.00 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
    - a change of less than or equal to 0.50 D of MRSE between two refractions performed at 1 month and 3 months, and between subsequent refractions performed at least 3 months apart;
- Mean overall change and change per month in MRSE between consecutive scheduled visits as determined by a paired analysis;
- Mean ±SD MRSE for the preoperative and each postoperative visit;
- Assessment of cylinder stability for correction of spherocylindrical refractive errors;

NOTE: Refractive stability is generally accepted to have been achieved at the latter of two postoperative refractions performed at least 3 months apart or at 3 months after surgery when compared with the 1-month interval, if all of the following recommended criteria are met:

- At least 95% of the treated eyes have a change ≤1.00 D of MRSE between the two refractions;
- The mean rate of change in MRSE, as determined by a paired analysis, is ≤0.5 D per year (0.04 D/month) over the same time period;
- The mean rate of change of MRSE decreases monotonically over time, with a projected asymptote of zero or a rate of change attributable to normal aging;
- The 95% confidence interval for the mean rate of change includes zero or a rate of change attributable to normal aging; and
- Stability is confirmed at least 3 months after the stability time point by a statistically adequate subgroup.

F.4 Safety

The following analyses are recommended for safety evaluation:

- Percentage of eyes that lose 2 lines or more of BSCVA;
- Percentage of eyes with BSCVA worse than 20/40 (for eyes with BSCVA of 20/20 or better pre-op);
- Percentage of eyes that have an increase of manifest refractive astigmatism of greater than 2.00 D of absolute cylinder as compared to the preoperative refraction;
- Rates of adverse events;
- Contrast sensitivity changes (if substudy was performed) (See clause D.8);
- Endothelial cell density changes (if substudy was performed) (See clause D.8.);

F.5 Effectiveness

The following effectiveness analyses are recommended to be performed at each interval where pertinent variables are collected (see Table D.1).

- Percentage of eyes that achieve predictability[1] (attempted[2] versus achieved[3]) of the MRSE of
  - ±0.50 D
  - ±1.00 D
  - ±2.00 D
- Percentage of eyes that are overcorrected by
  - >1.00 D
  - >2.00 D
- Percentage of eyes that are undercorrected by
  - >1.00 D
  - >2.00 D
- Percentage of eyes targeted for emmetropia that achieve UCVA[4] of
  - 20/40 or better
  - 20/20 or better
- Percentage of eyes not targeted for emmetropia that achieve UCVA[4] of
  - 20/40 or better
  - 20/20 or better
- Percentage of eyes that achieve an UCVA equal to or better than the preoperative BSCVA (for those eyes targeted for emmetropia)
- Change in BSCVA

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[1] Primary predictability analyses for mixed astigmatism should be based on the cylindrical component instead of the MRSE.

[2] Attempted change in MRSE is the difference between the preoperative MRSE and the targeted postoperative MRSE. The targeted refraction is to be documented for each subject.

[3] Achieved change in MRSE is the difference between the preoperative MRSE and the postoperative MRSE.

[4] These analyses should be performed for the overall cohort and repeated for eyes with BSCVA of 20/20 or better preoperatively.

- Accuracy of Sphere (to Target) and Cylinder (to zero) components within:
  - ± 0.50 D
  - ± 1.00 D

These analyses should be performed for the whole cohort as well as stratified by preoperative MRSE subgroups

When spherocylindrical treatments are performed, additional analyses are needed. Such analysis methods may be found in Annex G, reference [4], which contains detailed descriptions and discussions of the analyses it covers, including mathematical definitions of the terms and the methods of calculating key variables.

F.6 Retreatment

All eyes that have undergone retreatment prior to the completion of the prescribed investigational period constitute the Retreatment Cohort. It recommended that the following analyses be performed on the Retreatment Cohort:

- Total percentage of eyes retreated (see clause F.2)
- Percentage of eyes retreated per category (e.g., undercorrection, overcorrection, inability to tolerate symptoms, etc.)
- Safety outcomes prior to retreatment (see clause F.4)
- Safety outcomes after retreatment (see clause F.4)
- Effectiveness outcomes prior to retreatment (see clause F.5)
- Effectiveness outcomes after retreatment (see clause F.5)

Annex G

(informative)

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