

FDA Guidelines for Multifocal Intraocular Lens IDE Studies and PMAs

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U.S DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Center for Devices and Radiological Health

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I. Introduction

A. Background

Artificial intraocular lenses (IOLs) are now used to replace the natural crystalline lens in nearly all cataract removal procedures performed in the United States. The technology for manufacturing IOLs is mature and the regulatory requirements for materials, design, optical performance, clinical performance and labeling are well established in 21 CFR 812 and 814, and in guidance documents issued by the Food and Drug Administration (FDA) Division of Ophthalmic Devices (DOD). Reference materials may be obtained from the Division of Small Manufacturers Assistance (DSMA).

New IOL designs that provide more than one focal distance (multifocal IOLs) are now being developed. The optical properties of these new IOLs raise new questions regarding safety and effectiveness that require special preclinical and clinical testing beyond that needed for monofocal IOLs. Because a multifocal IOL produces no single plane where all the light is in focus, the optical quality of the best-focused retinal image is necessarily worse than that of a monofocal IOL of similar design. The degree to which this loss of image quality affects visual performance and safety depends on many factors, such as IOL design, pupil size, lighting conditions, visual task, etc.

Multifocal IOLs are an optional treatment for pseudophakic presbyopia, a condition for which reversible, lower-risk alternatives (e.g. bifocal spectacles and contact lenses) are available. Also, it is currently difficult to predict before implantation how specific patients will tolerate the visual limitations imposed by multifocal IOLs.

As a result of the above considerations, FDA has determined that additional preclinical and clinical tests beyond those required for monofocal IOLs are necessary to evaluate the safety and efficacy of multifocal IOLs. The purpose of this document is to describe these additional requirements and to provide guidance to sponsors of multifocal IOL premarket studies. This document replaces all previous guidance documents related to multifocal IOLs. Appendix A lists significant changes in the order that they appear in this document.

B. Scope and Terminology

This guidance document applies to investigational device exemption (IDE) and premarket approval (PMA) applications for all multifocal IOLs. It assumes that sponsors will develop multifocal IOLs from previously approved monofocal analogs. All regulations and guidelines that are applicable to monofocal IOLs are also applicable to multifocal IOLs unless explicitly excluded by this document. These regulations and guidelines should therefore be considered to be included by reference into this document. If no previously approved monofocal parent IOL exists, sponsors should refer to IOL standards such as ANSI Z80.7 (1994) and ISO/DIS 11979 for

guidance on pre-clinical testing for monofocal IOLs and contact ODE/DOD for clarification on additional requirements.

Forms 1-5 in this document refer to the five clinical case report forms for postoperative follow-up visits required of each subject in the study. The minimum number of case report forms at each reporting period should be equivalent to at least the minimum sample size for the study. The “core” subject group is defined to be the entire population of enrolled subjects, whereas the “cohort” group is defined as the subpopulation of subjects seen at each form. Form 5 is needed only for subjects who have a posterior capsulotomy at Form 4 or later. The recommended time periods for each form are as follows:

Case Report Form 0: Pre-operative/Operative reporting

Case Report Form 1: Post-operative reporting 1 or 2 days post-operatively

Case Report Form 2: Post-operative reporting 7 - 14 days post-operatively

Case Report Form 3: Post-operative reporting 30 - 60 days post-operatively

Case Report Form 4: Post-operative reporting 120 - 180 days post-operatively

Case Report Form 5: Post-operative reporting 330 - 420 days post-operatively

II. Preclinical Engineering Requirements

A. Optical Design Validation

The following is a list of the optical data that should be included in the IDE and PMA submissions:

- 1.** Engineering drawings and a detailed description of the optical design.
- 2.** Detailed theoretical explanation of how the design will function optically.
- 3.** Theoretical evaluation of the optical design in terms of:
 - a.** the percentage of light energy going to the near and distance image planes as a function of aperture from 1.5 - 6.0 mm (graph should be provided); and,
 - b.** the percentage of light energy going to the near and distance image planes as a function of aperture from 1.5 - 6.0 mm when the lens is decentered 0.5, 1.0, and 2.0 mm (3 graphs should be provided). Any unrefracted light at the larger apertures should be included in the total light energy when determining the percentage going to each of the image planes from each of the zones.
- 4.** Evaluation of the lens to confirm that the actual performance of the manufactured lens is equivalent to its theoretical performance. The following testing should be performed on the manufactured lenses:

a. Modulation transfer function (MTF) testing

MTF curves should be generated for each of the following conditions at 2, 3, and 5 mm apertures for each image plane:

- i.** on-axis
- ii.** decentered (e.g. 0.5, 1.0 mm)
- iii.** tilted (e.g. 5°, 10°)

Appropriate amounts of decentration and tilt should be determined individually for each lens design.

Note: In each case, the performance should be compared to that of a high quality monofocal lens. Testing in an eye model (ISO 11979-2) or water cell (ANSI Z80.7) rather than in air is recommended to give a more realistic assessment of the performance of the multifocal lens.

b. MTF through-focus-response testing

The MTF through-focus-response of the lens should be determined. Testing in an eye model or water cell is recommended. Results should be presented in a format similar to that shown in Appendix B.

c. Soft materials/MTF testing

With soft optic materials, the optical effects of potential deformations of the optic by the compression of the haptics or by the folding process (if the lens is to be folded) need to be determined. On-axis MTF testing with a 3 mm aperture should be performed at each image plane to evaluate the effect(s).

B. Optical Quality Control Procedures

Multifocal optical quality control procedures should be used to evaluate and control the performance of the lens at frequencies other than the resolution limit, including the entire range of transmitted spatial frequencies if necessary.

Sponsors who intend to make continuous depth of field claims for their multifocal lenses (range of 20/40 or better vision) should employ quality control procedures that specifically evaluate and control the depth of focus of the lens (e.g., by MTF through-focus-response testing).

All IDE and PMA applications and supplements requesting evaluation of new multifocal IOL models should include quality control procedures containing the following elements:

1. At least 1 mid/low spatial frequency (e.g., 25% of the diffraction limited cut-off frequency) should be evaluated in addition to the threshold frequency currently evaluated with the standard monofocal optical bench set-up.
2. Methods for monitoring the optical quality of multifocal IOLs must be accurate and highly reproducible, with minimal measurement uncertainty. Low contrast methods that utilize human observers probably will have difficulty meeting this requirement. Sponsors who intend to utilize a subjective method should validate the accuracy and reproducibility of their method with multiple observers, with a single observer over time, and with optics of a wide range of quality and power, against the results obtained from an objective method such as modulation transfer function (MTF) testing.
3. Every multifocal IOL produced should be inspected. Sponsors requesting a waiver of this requirement should provide strong arguments regarding the consistency of their manufacturing process along with the results of validation testing which demonstrate the intra-lot and inter-lot optical consistency of their finished product.
4. Each IOL's performance should be evaluated along at least two orientations, e.g., vertical and horizontal. An acceptable IOL should meet the release specification for both orientations.
5. Release specifications for optical performance should be based on the quality inherent in the population of lenses used for the design validation measurements described previously. Sponsors should determine their release specifications from an evaluation of the quality of their production. The mean performance of the multifocal IOL minus two standard deviations may be used to determine the release specification at each spatial frequency. To prevent the release of IOLs with excessive deviations from the theoretical design, the release specification should be no less than 75% of the mean value at the specified spatial frequency. It may be necessary to have a different release specification for each combination of test aperture and focus. Additionally, because of the decrease in optical performance as the IOL power increases, it may be necessary to have different release specifications for higher power IOLs.
6. The test apertures and focus that are used for optical quality control procedures should be based on the sponsor's multifocal IOL design.

Sponsors should include in the IDE application a detailed description of the proposed optical quality control method, along with a description of the equipment to be used and the results of all validation testing.

III. Clinical Trial

The general design of multifocal clinical studies should be similar to that of monofocal studies, i.e. a large clinical trial using historical (FDA grid) controls, with substudies to examine specific issues. In addition to historical controls, active matched monofocal controls are recommended for specific studies as noted in Appendix C.

A. Staged Phase-In of Clinical Study

FDA believes that, in most cases, a staged phase-in of the subject population during the investigational study is necessary: Ten subjects should be followed to Form 3 before these clinical data are submitted to FDA in order to expand to a total of 50 subjects.

The first 50 subjects should be followed through Form 4 before requesting FDA approval for expansion to the full core population. When at least 300 case report forms have been collected at each of the first four forms (1 - 4), a PMA application may be submitted. Subjects should be followed for a minimum of 4 to 6 months; if a posterior capsulotomy is performed at Form 4 or later, the subject should be examined at Form 5. Less than 10% of subjects should be lost to follow-up.

The sponsor may provide a justification which includes pre-clinical data comparing the optical performance of their design to previously approved designs to support a modification of the recommended phase-in.

FDA expects that 420 subjects will normally be adequate to complete the study. Each investigator in the clinical study should enroll enough subjects to contribute between 25 and 40 cohort subjects for the PMA (Koch et al., "Statistical Consideration in the Design, Analysis, and Interpretation of Comparative Clinical Studies;" Drug Information Journal Vol. 18, pp. 131-51, 1984). Control subjects should be enrolled for subjects whose fellow eyes are not appropriate controls and for substudies requiring subjects with bilateral multifocal implants (see Section III.C.4. for information on bilateral implants.)

Given the unique safety and efficacy concerns associated with multifocal IOLs and given that PMA approved monofocal IOLs are available, modified core investigations will generally not be allowed until a substantive review of the safety and efficacy data has been performed.

B. Statistical Design of Clinical Studies

In any investigational plan, sponsors should prospectively provide the number of investigators proposed and a statistical justification for the investigator/subject ratio. In addition, the statistical formulation used for the combinability of the data from each investigator should be presented. These proposals may vary between studies, depending upon each sponsor's investigational plan. In multifocal IOL studies, various factors (e.g., the clinical substudies being performed on a portion of the investigational population; the staged phase-in, etc.) may influence sponsors' proposals.

As per Koch et al. (ibid.), the number of investigators in a reasonable study design might be four to ten, each evaluating a sufficiently large, yet reasonable number (say >25, preferably <40) of subjects per investigator. For the first 50 subjects in the staged phase-in of multifocal IOL studies, FDA recommends 2 investigators. The clinical safety and effectiveness data should be evaluated separately for each investigator before data are pooled. If a significant difference is found between investigators, then clinical data should not be pooled.

C. Subjects

1. Inclusion Criteria (see Labeling, section IV.A.)

Multifocal IOL sponsors should comply with all inclusion criteria required for monofocal IOLs. They should also comply with the following inclusion criteria or justify their omission:

- a.** Best corrected visual acuity projected (by PAM testing or other reliable potential acuity test procedure) to be better than 20/100 after cataract removal and IOL implantation.
- b.** Sponsors should provide and justify the maximum projected postoperative astigmatism to be allowed in their studies. FDA recommends an approximate maximum value of ≤ 1 diopter.
- c.** Clear intraocular media other than cataract.

2. Exclusion Criteria (see Labeling, section IV.A)

Multifocal IOL sponsors should comply with all exclusion criteria required for monofocal IOLs. They should also comply with the following exclusion criteria or justify their omission:

- a.** Subjects whose best corrected visual acuity is projected (by PAM testing or other reliable potential acuity test procedure) to be 20/100 or worse after cataract removal and IOL implantation should be excluded from the multifocal IOL study.
- b.** Subjects with diagnosed degenerative visual disorders (e.g., macular degeneration or other retinal disorders) that are predicted to cause future acuity losses to a level of 20/100 or worse should normally be excluded from the study. Acuity loss necessarily increases the depth of focus because the blur circle of a defocused image point must exceed the retinal resolution limit in order to degrade the perceived image. Subjects whose limited acuity gives them a depth of focus comparable to that of a multifocal IOL cannot expect to benefit from multifocal lenses, and therefore should not be considered for multifocal implants.
- c.** Some multifocal IOL designs may interfere with the proper focusing of therapeutic retinal laser beams. Subjects who may reasonably be expected to require retinal laser treatments at any time (e.g., diabetics, subjects with macular edema, retinal holes or peripheral retinal degenerations, sickle cell disease or other hemoglobinopathy, and vasculitides potentially affecting the retina, such as systemic lupus erythematosus) should therefore be excluded from the study unless their future treatment is not expected to be compromised by the multifocal IOL.
- d.** Projected postoperative astigmatism consistent with the astigmatism inclusion criterion (see section III.C.1.b above) or irregular optical aberration

(e.g., irregular corneal astigmatism or optical distortion from vitreal refractive changes).

- e. Zonule rupture during the cataract extraction procedure which may affect the postoperative centration or tilt of the lens.

3. Control populations

One control population that can be considered is a multifocal IOL subject's fellow eye, when the fellow eye already contains a monofocal IOL. Because some subjects may not consent to implantation of a multifocal lens in one eye and a monofocal lens in the other, and because some monofocal fellow eyes may not meet the inclusion criteria for the study, a separate control group of prospective monofocal IOL subjects may need to be enrolled. The monofocal IOL control subjects should be randomly selected from the monofocal IOL population. FDA does not require masked control studies; however, we will consider well-controlled masked study proposals. Such proposals should provide a risk/benefit analysis of performing the masked study.

Studies that include both fellow eye controls and separate subject controls will need to adjust statistical analyses to account for the correlation between the two eyes of a single subject. Two possible procedures for making these adjustments are described in: Muñoz et al., *Biometrics* 42:653, 1986; and Katz et al., *Invest. Ophthalmol Vis. Sci.* 35:2461, 1994.

It is expected that the following multifocal clinical data will need to be compared to control subject data:

- a. Visual Acuity
- b. Posterior Capsulotomy Rates
- c. Visual Field
- d. Fundus Photography
- e. Contrast Sensitivity
- f. Low-Visibility Driving Performance

4. Bilateral Implants

Sponsors' protocols should not allow bilateral multifocal IOL implantation in the first 50 subjects. A protocol waiver to perform a bilateral implantation in a particular subject from the first 50 requires approval from both the FDA and the institutional review board.

After the first 50 subjects, bilateral implantation of the multifocal IOL may be added to the clinical protocol if justifiable by the clinical results obtained in the first 50 subjects. The sponsor should propose a minimum time interval between surgeries and obtain IRB approval for bilateral multifocal IOL surgery. The

following information should be provided to obtain IDE approval for implantation of bilateral multifocal IOLs:

- a.** The sponsor agrees to follow the second eye under multifocal core reporting provisions, and agrees to obtain the reason for the second implant in a letter from the investigator.
- b.** The sponsor agrees that the second-eye multifocal IOL implant will not be included in the cohort population in the planned PMA, and that the second eye data will be reported in a separate clinical analysis.
- c.** The sponsor agrees to provide semiannual reports to the IDE which provide the preoperative and postoperative clinical results of the bilateral subjects, including all data on the reasons for the second-eye bifocal implantation.
- d.** The sponsor agrees to conduct binocular studies of visual acuity and contrast sensitivity/low-contrast acuity for all bilateral multifocal subjects and control subjects to be enrolled in the driving performance substudy (see Section III.H.), following the protocols specified in Sections III.E.2. and III.G.4. The testing should be performed when the second eye reaches Form 4. If a posterior capsulotomy must be performed after the binocular testing but before the driving substudy, the binocular testing should be repeated after vision stabilizes following the surgery.
- e.** The sponsor provides an addendum to the Informed Consent Document that specifically addresses the risks associated with bilateral multifocal IOL implantation.

Sponsors are reminded that bilateral multifocal subjects are preferred for the clinical substudy on driving performance (see Section III.H.), and that if any unilateral subjects are used they should be paired with unilateral controls, they should perform all driving performance tests with the fellow eye covered and their data should be analyzed separately. The number of subjects should be determined by validation studies.

D. Informed Consent Document

Sponsors should prepare an informed consent document in compliance with 21 CFR Part 50, that also includes but is not limited to the following information about multifocal IOLs:

- 1.** The multifocal lens optic is significantly different from IOLs currently available; it has theoretically lower optical quality, but the impact of the lower optical quality on visual perception and performance is not fully understood.
- 2.** The multifocal optic presents the possibility of vision problems, including objectionable vision quality under certain lighting conditions, hazy images, halos, and ghost imaging of near and far objects.
- 3.** Future surgery may be required to remove the multifocal IOL because of the potential vision problems.

4. Additional monofocal or bifocal refractive correction with spectacles or contact lenses may be required even after receiving an intraocular lens with a multifocal optic.
5. The multifocal lens may interfere with the diagnosis and treatment of possible future retinal disorders by making it more difficult to view the fundus or deliver laser therapy.

E. Clinical Data

Note: These data should be collected in addition to those collected for monofocal IOLs.

1. Pupil Size

Photopic pupil diameters should be measured at the preop visit and at least one postop visit after Form 1, and recorded with a precision of at least ± 0.5 mm. Eye illumination should be identical to that used for photopic acuity testing. FDA recommends pupil measurement with an infrared CCD camera to increase precision and reliability, to avoid shielding the pupil from light, and to provide good pupil visibility with dark irises. The pupil size data will be needed for selecting and stratifying subjects for the defocus curve, contrast sensitivity/low contrast acuity and driving performance substudies.

2. Visual Acuity

Distance and near best corrected visual acuities should be measured for all subjects at all forms; uncorrected distance, uncorrected near and distance-corrected near acuities should be measured at Form 4. Distance and near acuity charts, chart illumination, ambient illumination, testing distances and testing procedures should be standardized for all investigators. If multiple IOL add powers are included in the study, the sponsor should provide information regarding the optimum mean near distance associated with each add power.

FDA recommends the following conditions, materials and procedures for acuity testing:

a. Chart Design

- i. Printed (not projected) black-on-white chart with letter contrast $\geq 80\%$
- ii. Minimum size range 20/12 – 20/200 (0.6' – 10' MAR)
- iii. Logarithmic letter size progression (0.1 log unit steps over entire range)
- iv. Letter spacing \geq letter width and proportional to letter size
- v. Line spacing \geq line height and proportional to letter size

vi. Same number of letters on each line (at least 5 letters/line)

b. Illumination

- i.** Chart background illuminance 85 cd/m² (80 – 320 cd/m² acceptable range). Illuminance should be identical for all testing centers within an IDE study.
- ii.** 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.

c. Chart Distance

- i.** For uncorrected far acuity testing, FDA recommends a 4 meter chart distance with a +0.25 diopter trial lens added to correct the optical distance to infinity. For corrected far acuity testing, dioptric power should be computed relative to optical infinity.
- ii.** For near acuity testing, near-acuity charts may be used at a distance coinciding with the near focal plane of the lens, provided that the angular sizes of the optotypes are calibrated for the distance used. The chart distance should be precisely defined, i.e. no head movements relative to the charts are allowed. For wall- or stand-mounted charts, the subject's head position relative to the chart should be fixed by a chin and forehead rest. Hand-held charts should be mounted on a spacing rod connected to a head rest.

d. 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 notation (minimum angle of resolution in minutes of arc) 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.

e. Testing Procedure and Scoring Method

- i.** Subjects should be strongly encouraged to guess at all letters in a line if more than 1 correct response was given in the previous line.
- ii.** Tests should be scored by giving equal logMAR credit for each letter read. For example, assuming 0.1 log size step per line and 5 letters per line, each correct letter adds 0.02 logMAR to the total score. The total logMAR score can then be converted to an equivalent notation if desired.

3. Posterior Capsulotomy

Each form (1 through 4) should record whether a capsulotomy has been performed since the last visit and if so, the size of the capsulotomy. If a capsulotomy is performed at Form 4 or later, the subject should be evaluated at Form 5.

4. Lens Stability

- a. Amount of decentration-** Forms 1 through 4 (or 5 if required)
- b. Investigator assessment of lens tilt-** Forms 1 through 4 (or 5 if required)

5. Subject Survey

Investigators should survey all core subjects at Forms 2 or 3 and 4 to determine their impressions of the quality of their monocular and binocular vision. All survey forms should allow space for comments that are not addressed by the specific questions. Subjects (especially those with only one multifocal lens) should be instructed to compare left eye vs. right eye vision and monocular vs. binocular vision by briefly covering one eye with a hand or other occluder.

- a.** Subjects should be asked to describe the quality of their near and distance vision at indoor, outdoor (daylight) and night/dark situations. They should also be asked how the vision compares to the vision from their fellow eye if their fellow eye has a natural or monofocal lens.
- b.** Subjects should be asked specifically to state whether or not they have observed flare/glare, halo, near or distance distortion, near or distance blurring, diplopia (specify whether monocular or binocular complaint), night vision problems, or color disturbances. Subjects should describe the conditions under which they experience any problem.
- c.** Subjects should be asked whether, if given the opportunity, they would again elect to be implanted with a multifocal IOL.

F. Additional Clinical Data Analysis in the PMA

1. Visual Acuity

Data in IDE and PMA visual acuity tables should be grouped with the closest individual acuity chart line, specifically 20/12 (if represented), 20/15, 20/20, 20/25, 20/32 and 20/40.

2. Near Visual Acuity

Additional analysis of the near visual acuity data should be performed when near VA measurements are performed at distances other than the test distance at which the near acuity chart was designed. The acuity value should be converted by the sponsor to minutes of arc in order to standardize the acuity measurement for different test distances. The final adjusted values should be reported.

3. Refraction

Provide spherocylindrical over-refraction at distance, and any additional near over-refraction if required. If more than one add power was investigated, the over-refraction data should be stratified by add power.

4. Astigmatism

Break out and analyze visual acuity data for subjects with astigmatism separately.

5. Neural Acuity Loss

Subjects with macular degeneration or other retinal or postretinal disorders affecting acuity preoperatively should not be included in the multifocal study. (Potential acuity measurements should be taken). If diagnosed after implantation, break out visual acuity data separately for subjects with such disorders. Include preoperative visual acuity in this separate analysis.

6. Posterior Capsulotomy

Break out and analyze visual acuity data from the subjects undergoing capsulotomy separately. Data should be stratified by capsulotomy size.

7. Lens Stability

Provide in a single table the incidence of all secondary surgeries due to lens instability and other reports of lens instability (e.g., decentration, tilt). Depending upon data, further analysis of this data by visual acuity results may be recommended.

8. Subject Survey

Besides summarizing the results of the survey, provide detailed analysis of reports of glare, halos, multiple images, etc. as data warrant.

9. Visual Acuity and Refraction Data

FDA has found it useful for sponsors to use the table in Appendix D, as a format for presentation of visual acuity and refraction data. We suggest presentation of the data in this way in all IDE clinical progress reports, and in PMA applications.

Depending upon the specific information being provided in an application, sponsors should determine whether the table should also be used for specialized data presentation of particular subject subpopulations (e.g., using the format for presentation of visual acuity and refraction data of all bilateral multifocal IOLs).

G. Clinical Substudies

All clinical substudy subjects should be best case, with as many as possible selected from the first 50 subjects to complete their Form 4 follow-up examinations. Best case subjects are defined as those subjects with no pre-operative pathology.

1. Visual Fields

- a.** Number of Subjects: 20 multifocal eyes, 20 age-matched monofocal control eyes (fellow eye controls preferred).
- b.** All investigators should use the same type of projection-type automated static perimeter, in order to standardize conditions.
- c.** Central and peripheral thresholds should be determined in a 60-degree radius field with no fewer than 100 points. Stimulus size and duration should be standardized for all subjects (size I, duration 0.2 sec. recommended).

2. Defocus Curves

The purpose of this substudy is to determine whether the defocus curves agree with the theoretical lens performance and to determine the optimum near distance for future near visual acuity testing.

- a.** Three best-fit defocus curves should be generated, at small (≤ 2.5 mm), medium (>2.5 and <4.0 mm) and large (≥ 4.0 mm) pupil sizes.
- b.** Number of subjects: At least 10 multifocal eyes and 10 age-matched monofocal control eyes for each pupil size group (fellow eye controls preferred).
- c.** A defocus curve should be obtained by using the best corrected distance refraction and then defocusing the subject in 0.5 diopter increments with spherical minus trial lenses. The image should continue to be defocused up to -5 diopters (or more if the visual acuity is still above 20/40 at this point). In regions of the curve where there are sharp peaks of increased acuity above 20/40, that region should be better resolved by defocusing in 0.25 diopter increments.
- d.** The results of the pupil size evaluation which was part of the contrast sensitivity testing could be used to direct the sponsor to the subjects to be

used for this testing (30 different subjects may be used; i.e., more than one defocus curve need not be generated on any one subject). If possible, the sponsor should use subjects who fall in the small, medium or large pupil categories without the need to use either high or low light levels to generate the defocus curves.

3. Fundus Photography Evaluation

- a.** At Form 4, fundus photographs from subjects with a multifocal IOL in one eye and a monofocal IOL in the fellow eye should be visually compared to determine whether there is a clinically significant loss of contrast in the photographs from the multifocal IOL eye relative to the monofocal IOL eye. In order to minimize artifacts arising from subjective investigator biases, FDA recommends the following procedures.
 - i.** Photograph at least five subjects per site at three or more sites.
 - ii.** Mask (i.e. hide the identities of the multifocal and monofocal eyes in each subject from the reader) and pool the photographs from all sites.
 - iii.** All investigators should read the masked left eye/right eye photograph pairs.
- b.** If an appropriate subject becomes available during the course of the study, the photographs after fluorescein angiography should be evaluated to determine if there is a clinically significant loss in contrast in the photograph from the multifocal IOL eye (the control in this case would be the photograph from any monofocal IOL eye after fluorescein angiography).

4. Contrast Sensitivity

As defined by current ophthalmic and optometric practice, clinical contrast sensitivity testing includes both grating contrast sensitivity and low-contrast letter acuity, even though the two types of test differ substantially in appearance, procedure and theoretical interpretation. 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. Low-contrast letter acuity tests, on the other hand, assess letter acuity as a function of chart contrast.

Grating contrast sensitivity and low-contrast letter acuity tests yield data that are similar in many respects, but theoretically are best suited to answer different types of questions. Contrast sensitivity should be more useful for comparison to objective MTF data, whereas low-contrast acuity should be more useful for evaluation of visual performance measures. However, additional data are needed to answer these questions empirically.

FDA will accept the completion of either the grating contrast sensitivity or low-contrast letter acuity substudy. However, sponsors should be aware that if a high correlation can be established between either type of data and visual performance

in driving, driving substudies (see Section III.H.) may not be required in future post-approval Level B studies. It therefore may be to the sponsor's advantage to complete both substudies in order to increase the chance of substituting clinical or preclinical test data for future driving substudies.

a. Basic protocol information

i. Schedule

- Form 4
- Form 5 - repeat test only for subjects who have had posterior capsulotomies at the Form 4 visit or later.

ii. Pupil size

- The performance of most current multifocal IOL designs depends on pupil size. Sponsors should test this dependence by stratifying their contrast sensitivity and low-contrast acuity test results by pupil size in the PMA. Data should be tabulated and/or graphed in 0.5 mm pupil size ranges.
- Sponsors who have designed their lenses to perform independently of pupil size should also stratify their subjects by pupil size in order to verify clinically the theoretical performance.

iii. Subjects

- 25 best case subjects for each of the three pupil size groups (<2.5, >2.5 and <4.0, ≥4.0 mm diameter) are recommended for the PMA for the contrast sensitivity and/or low-contrast acuity testing. FDA recommends testing all best-case subjects until adequate substudy enrollment is achieved. Recruitment should be completed as early in the study as possible.
- FDA believes the simplest way to minimize selection bias is to test sequentially-enrolled subjects that meet the best case criteria. We recognize that there are other methods in which selection bias may be minimized, and will review such proposals under the IDE application. These proposals may include limiting testing to specific centers. It is important to target best case subjects who already have a monofocal IOL in their fellow eye for the contrast sensitivity and/or low-contrast acuity testing, since these subjects also can be tested as part of the control population.

iv. Lighting conditions

- Both distance and near testing should be conducted at the same photopic chart luminance level specified for the standard acuity testing. Additional distance testing should be conducted at a mesopic level of about 3 cd/m² chart background luminance. The mesopic light

level is expected to be more comparable to the low visibility driving substudy (Section III.H) than the higher photopic levels used in clinical tests.

- Ambient illumination for both the photopic and mesopic non-glare conditions should be comparable to the chart illumination, but no surface (including reflective surfaces) within the subject's field of view should exceed the chart background in luminance.
- All testing should be repeated in the presence of a localized parafoveal glare source. The glare source may be a narrow ring or an array of two or more small spots concentrically positioned around the test target. The glare source should be located 0.5° or less from the edge of the test target. The luminance of the glare source should be at least 100 times greater than the average luminance of the test target.
- All light levels for both photopic and mesopic conditions, including ambient illumination, chart luminance and glare source luminance should be standardized across all investigators and sites. Pilot studies to validate the proposed testing conditions are highly recommended.

v. Optical Blur

Testing should be repeated without any refractive correction and with the subject corrected to best visual acuity for the testing distance, to evaluate the effect of optical blur in reducing the contrast sensitivity/low contrast acuity at high spatial frequencies.

vi. Reproducibility

A small subpopulation of the original contrast sensitivity and/or low-contrast acuity subjects should be retested within a week of the original test to confirm the reproducibility of the original measurements. Reproducibility of results will depend on environmental conditions (lighting), as well as other factors. The number of subjects retested will depend on the variability of the results.

b. Sinusoidal Grating Contrast Sensitivity

Contrast sensitivity testing should be monocular, and should be conducted with sine-wave grating targets accurately produced on a reflective chart or a high-resolution CRT screen. Testing should be repeated for the test eye and control eye of each subject.

FDA recommends grating tests with the following features in order to minimize artifacts in the contrast sensitivity data: All gratings should be surrounded by a uniform field equal to the grating in space-averaged luminance. The outer borders of the grating stimuli should be blurred enough to eliminate high-frequency artifacts.

i. Distance target contrast sensitivity testing

A minimum of three points on the subject's contrast sensitivity curve should be defined. The three data points should be between the typical peak contrast sensitivity point on the curve and the high-frequency threshold (Snellen) point (and may include these points), and should be evenly distributed throughout as much of this range as the chosen test system allows.

ii. Near target contrast sensitivity testing

A minimum of three points on the subject's contrast sensitivity curve should be defined. See description above. The targets used for the distant target testing may be used for the near testing by over-refracting the subject with the negative power lens necessary to focus the reading image plane upon the retina. This will produce a virtual image of the target at the near distance defined by the diverging lens. The necessary negative power can be determined from the defocus substudy. The investigator may over-refract from that standard negative power, if necessary, to maximize the acuity. The amount of over-refraction should be recorded.

c. Low Contrast Letter Acuity

Low-contrast acuity testing should be monocular, and, except for the contrast and ambient illumination parameters, should be conducted according to the acuity testing recommendations stipulated above in Section III.E.2. Testing should be repeated for the test eye and control eye of each subject.

i. Distance target low-contrast acuity testing

A minimum of two contrast levels, one below 10% and one between 20% and 50%, should be tested in addition to the high-contrast acuity measure already obtained. If the largest chart letters are unreadable at the lowest contrast level for any of the substudy subjects, the chart may be magnified by reducing the physical chart distance and using corrective lenses to maintain the original optical distance.

ii. Near target low-contrast acuity testing

A minimum of two contrast levels should be defined, as described above. The targets used for the distance target testing may be used for the near testing by over-refracting the subject with the negative power lens necessary to focus the reading image plane upon the retina. This will produce a virtual image of the target at the near distance defined by the diverging lens. The necessary negative power can be determined from the defocus substudy. The investigator may over-refract from that standard negative power, if necessary, to maximize the acuity. The amount of over-refraction should be recorded.

H. Low-Visibility Driving Performance Substudy

In order to assess the affect that implanted multifocal IOLs have on the safe and efficient completion of everyday tasks, FDA strongly recommends that sponsors demonstrate that their multifocal IOLs do not adversely affect the visual performance of subjects that receive them. Sponsors may meet this requirement by conducting a clinical substudy to evaluate the effects of their multifocal IOLs on visual performance while driving under low visibility environmental conditions such as inclement weather, night driving and central headlight glare. Both simulated driving and field driving proposals will be considered, as well as any alternate proposals for assessing visual performance. The purpose of the driving substudy is to determine whether the visual performance of subjects with implanted multifocal IOLs is significantly impaired as compared to the performance of subjects with monofocal IOL implants. The recommended driving protocol was developed with input from the Ophthalmic Devices Advisory Panel and the IOL industry.

1. Subjects

- a.** Sponsors should assess the performance of at least two populations of subjects: a test population with bilateral multifocal implants and a control population with bilateral monofocal implants. Control subjects with natural crystalline lenses or one monofocal implant and one natural crystalline lens may be included in the main control population only if their natural lenses are free of cataract and the visual performance of the eyes with natural and monofocal lenses is shown to be equivalent for all testing conditions in the substudy.
- b.** Sponsors should match test and control populations as much as possible in terms of age, gender, driving experience, left/right eye dominance and spectacle use, and the subjects should not be using any medications that affect visual or motor performance. Both test and control populations should include sufficient numbers of male and female subjects for gender-specific analysis.
- c.** All candidates for the driving substudy should undergo the following clinical testing regimen as part of the qualification process:
 - i.** Binocular visual acuity testing according to the protocol described in Section III.E.2.
 - ii.** Binocular grating contrast sensitivity and low-contrast letter acuity testing according to the protocol described in Section III.G.4.
- d.** The substudy should include enough subjects to detect a 25% performance difference, averaged over test conditions, between the test and control populations at a statistical significance level of 5%. Sponsors should provide realistic estimates of within-subject and between-subject variability for each type of response measure to justify their proposed sample sizes. Data for the variability estimates should be obtained in preliminary validation studies (see Section III.H.5 below) if they are not available from other sources.

- e. All subject populations should be made up of best-case subjects with no observable capsular haze or with a capsulotomy opening large enough not to interfere significantly with visual performance under low light conditions. Best-corrected distance visual acuity must be 20/30 or better for all eyes. Sponsors should assess each subject's retinal/neural function to make certain it is normal and therefore not the factor causing poor clinical performance. If the relative visual function of the multifocal and monofocal driving substudy subjects differs significantly (as assessed by visual acuity, contrast sensitivity and low-contrast acuity data), the sponsor will need to address the differences in the data analysis.

2. Study Design

- a. Sponsors should propose a study that compares the visual performance of the test and control populations at driving tasks that may be affected by the optical limitations of their multifocal IOL. The study may utilize either simulated or real driving environments, but it should conform to the FDA guidelines described herein and it should accurately portray real-world luminance, contrast and spatial resolution levels for the environmental conditions being tested. The simulated or real speed of the test vehicle should be the maximum safe speed for normal drivers for the conditions tested. Except for reduced visibility viewing conditions (see below), the maximum safe speed will be considered to be the normal legal speed limit for the surrounding environment (e.g., freeway, 55 mph; urban, 35 mph). The sponsor should attempt to keep the vehicle speeds comparable for test and control subjects. The following two types of tasks should be included in the protocol:

i. Reading traffic signs

Target signs should include examples of positive contrast (e.g., white on green) and negative contrast (e.g., black on white), and should range in complexity from simple warning signs to informational signs containing messages of several words. Sign size and general appearance should conform to legal restrictions and standard practice for the type of roadway used. Response measures should include recognition distances, percent of recognition responses correct, and visual angle corresponding to the recognition distance.

ii. Detecting road hazards

Realistic hazard objects should be placed at various distances and positions in the path, or potentially intersecting the path, of the subject. The set of hazard objects must include a representative range of sizes and contrasts. The hazard objects may all be stationary, but FDA prefers that at least some of them move from the periphery toward a possible collision point. Response measures should include the detection distance and the visual angle from the road center at the moment of detection.

- b. Environmental lighting conditions for the sign reading and hazard detection tasks should include:

- i.** Night driving with vehicle headlight lighting only
 - ii.** Night driving with combined vehicle headlight and standard roadway lighting (optional)
 - iii.** Twilight driving conditions with no artificial lighting or with vehicle headlight lighting only (optional)
- c.** For each of these lighting conditions, testing must be repeated for each of the following viewing conditions:
- i.** Clear viewing conditions
 - ii.** Inclement weather conditions (e.g., simulated fog or windshield condensation). Conditions should reduce normal visual acuity by a significant and repeatable amount, but small enough to permit the measurement of a large range of abnormal responses.
 - iii.** Central headlight glare conditions. The glare source should consist of automobile headlights or equivalent light sources positioned within 15 deg of target signs and hazard objects.
- d.** Before the main study can be approved, sponsors should provide evidence, either in publications, preexisting unpublished data or preliminary validation studies, that the proposed protocol will yield valid data, free of apparatus-induced artifacts and representative of real-world visual performance for the environmental conditions tested.
- e.** The testing for the driving substudy should be performed at the form 4 timeframe of the second eye or thereafter.

3. Apparatus

The FDA can accept any apparatus configuration for the driving substudy that produces a realistic driving environment, and provides spatial resolution, visual field coverage, luminance range and contrast range sufficient to ensure that apparatus limitations will not affect any visual performance measurements. Extensive interactive features are not required as long as provisions are made to allow the subject to respond quickly and precisely to relevant visual stimuli. Some configurations that are potentially acceptable are:

- a.** High-end video-based driving simulators
- b.** Simulated driving environments based on the projection of prerecorded movie film segments
- c.** Field trials using actual vehicles and driving courses

4. Response Procedures and Measurement Methods

Sponsor should submit monofocal/multifocal comparisons of detection distance for sign and hazard detection tasks and text size as well as recognition distance for sign recognition tasks. Because the subject is always moving with respect to the target, it is necessary to record the precise moment of detection or recognition so the distance from the subject's eyes to the target can be determined. Pressing a button and stepping on a brake pedal are examples of acceptable response methods. Voice responses for initial detection or recognition time are generally not acceptable unless the time of the onset of the response is accurately (i.e., electronically) recorded, or unless the entire delay between response onset and recording can be accurately estimated. To reduce variability, FDA suggests that reaction times for suprathreshold versions of the detection tasks be measured for each subject, and used to compensate for the response delays in the detection and recognition data. For sign recognition measurements in which an initial mechanical response is followed by a verbal report, the display (in simulation studies) should also be frozen or blanked immediately after the initial response so the subject will not be able to continue to look at the looming sign before reporting its contents. This requirement to avoid sign looming after recognition may be difficult to implement in field trials, and it effectively precludes allowing the subject to have actual control of the test vehicle.

5. Validation Studies

FDA recommends that all driving performance substudies be preceded by a pilot study in which adult subjects with normal vision run through the entire proposed protocol. The pilot study subjects should be comparable in age to the youngest group of subjects in the driving performance substudy. This pilot study has two major purposes: The first is to determine whether all testing procedures and data recording procedures are safe, workable and subject-friendly. The second is to obtain baseline measures of within-subject and between-subject response variability that can then be used to estimate the minimum numbers of subjects needed for the control and test populations of the main study.

a. Simulation Studies

Driving simulation studies should be preceded by a validation study, using young adult subjects with normal vision, to establish the ability of the simulator to duplicate real driving conditions sufficiently well to provide equivalent performance data. The validation study should include the following three components:

- i.** The screen resolution should be greater than the visual resolution of the subjects for all sign recognition measurements in the study. Otherwise, the quality of the simulator display image will sometimes determine the recognition threshold rather than the quality of the retinal image formed by the IOL, and real differences in sign reading performance between monofocal and multifocal eyes may be obscured. To guarantee that this does not happen, simulated signs at the limits of normal legibility should be evaluated for legibility under magnification (or at a closer distance) and the contrast of the critical details should be measured photometrically. If a

sign does not become easily legible under magnification, or if the contrast of critical details within the text (e.g., the contrast between a point on a letter “E” and a point between two of the horizontal strokes) falls substantially below the overall contrast between the text and its surround, the reading data for that sign and condition should be deleted from the study.

- ii.** Driving hazards may be stationary or may come from any direction. Sponsors may try to duplicate these conditions by moving some hazard stimuli toward the road from the right or the left. The validation study should include a test to make sure that the field of view of the simulator display is wide enough to allow first detection by the subject’s peripheral retina. If the field of view is too small, it will bias observations of the effect of multifocal IOLs on the detection of laterally-moving hazards that are normally visible anywhere within 30-40 degrees of fixation.

Note: The spatial resolution requirements are less stringent for hazard detection than for sign recognition. If the field of view for sign recognition is too small for hazard detection, it is therefore acceptable to magnify the display, either optically or by moving the subject closer, at the expense of resolution.

- iii.** The validation study should include evidence, if necessary acquired through direct comparisons of real and simulated driving situations, that the range of available luminances in the simulator display is comparable to that of the actual environment to be simulated. In all cases where the primary simulator display is a CRT screen, some form of auxiliary lighting is recommended to simulate glare from automobile headlights. If the simulator cannot mimic the actual luminance range encountered, normal subjects should show equivalent visual performance in comparable real and simulated environments.

If the components of the validation study as described above show inadequacies in simulator resolution or luminance range, sponsors may attempt to find alternate stimulus conditions that will further reduce visibility enough to bring normal performance into line with the simulator display limitations. The parameters for any such alternate conditions would have to undergo the relevant validation procedures stated above.

b. Field Studies

Studies employing real vehicles on a real driving course should be preceded by a validation study, using young adult subjects with normal vision, to establish appropriate testing conditions and procedures, and to develop valid and precise data collection methods. The validation study should include the following elements:

- i.** Calibration of all target sizes, distances from start of course, distances from roadway center, luminance levels and contrasts.
- ii.** Calibration of all significant time-distance relationships on the course.

- iii.** Validation of procedures to control and monitor vehicle speed and position both within and between runs. The study should demonstrate that these procedures are both precise and accurate enough not to affect the detection and recognition distance measures.
- iv.** Validation of all subject response procedures and response recording procedures.

6. Data Analysis

- a.** Sponsors should derive and clearly describe algorithms to convert subject response times to detection and recognition distances, and sign-reading responses to percent of signs recognized.
- b.** Sponsors should provide engineering analyses wherever possible to determine if the detection and recognition distances determined by their studies are adequate for safe and effective vehicle control at speeds up to and including the legal speed limits for the conditions tested.
- c.** Sponsors should employ standard statistical analyses to determine the size and statistical significance of any differences between test and control population data. Where a number of different hypotheses are being tested in parallel, multiple comparison techniques should be used as appropriate to correct significance values for the possibility of finding “significant” effects by chance.

IV. Labeling

At this time, this section is incomplete.

A. IDE Labeling

The package of an investigational multifocal IOL must bear a label containing the name and place of business of the manufacturer, packer or distributor, and the following statement: "CAUTION - Investigational Device. Limited by Federal (or United States) law to investigational use." The base and add optical powers of the IOL should also be stated on the outer package labeling. These labels, or other labeling, should also contain all relevant information on:

- 1.** Device description
- 2.** Indications
- 3.** Warnings
- 4.** Precautions
- 5.** Complications
- 6.** Subject inclusion/exclusion criteria

- a. Astigmatism
 - b. Pupil size
 - c. Fellow eye status
 - d. Refractive error
7. Directions for use
 8. Instructions on the calculation of lens power
 9. Patient registration instructions
 10. Expiration date
 11. Return goods and resterilization policy

B. PMA Labeling

PMA labeling for multifocal IOLs should follow the same general format as that for monofocal IOLs. Labeling should provide the following information:

1. Brief Device Description
2. Indications
3. Contraindications
4. Warnings
5. Precautions
6. Adverse Reactions
7. Summary of safety and effectiveness as established by clinical trials. This summary should include but not be limited to the following data:
 - a. Distance and near visual acuity
 - b. Test results for clinical substudies:
 - i. Visual fields
 - ii. Defocus curves
 - iii. Fundus photography evaluation
 - iv. Contrast sensitivity and/or low contrast acuity

- c.** Test results for driving substudy
 - d.** Distances at which all distance and near visual testing was performed
 - e.** Complications
 - f.** Adverse events
 - g.** Frequency of spectacle use
 - h.** Visual symptoms reported by patients
- 8.** Detailed Device Description
 - 9.** Directions for Use
 - 10.** Calculation of Lens Power
 - 11.** Patient registration instructions
 - 12.** Instructions for reporting of potentially sight-threatening complications
 - 13.** Instructions on how the IOL is supplied
 - 14.** Expiration date
 - 15.** Returned goods policy
 - 16.** Bibliography

Sections of the labeling will contain information derived from prior experience with monofocal intraocular lenses as well as information specific to the multifocal IOL. These two types of information should be clearly delineated. Examples of sections where both types of information will occur include: indications, precautions and warnings.

Curves for the centered performance and a table listing the percentage of light energy going to the near and distance image planes with the 2, 3, and 5 mm apertures should be provided in the IDE and PMA labeling. In the case of designs that have a small aspheric contribution to the total theoretical light energy going to an image plane at a specified aperture, the percentage of refracted/diffracted light should be reported in the table with a plus sign (e.g., 20+%). The table should be footnoted to explain that the plus sign indicates the aspheric contribution. In the case of designs where most or all of the light energy going to an image plane is from an aspheric surface, the sponsor should include in the table the range of dioptric power associated with each aperture, as well as the total percentage of energy going to that range of power. For example, the entry for the 3 mm aperture at the near plane would be reported as 15% (0 - 2 diopters add).

The PMA labeling should include best-fit defocus curves for small, medium and large pupil sizes obtained from the clinical substudy data.

A patient information booklet should also be prepared for distribution after PMA approval to potential multifocal IOL recipients. This booklet should explain in simple English that multifocal IOLs involve optical trade-offs between multiple focal planes and reduced acuity and contrast, and whether spectacle dependence will be eliminated or substantially reduced. The patient booklet should further explain the effect the multifocal optic is likely to have on daily tasks, including those adversely influenced by the reduced contrast afforded by the multifocal optic.

V. Design Modifications

A. Modifications that Will Not Affect Multifocal Optic Performance

Sponsors who wish to make changes in the design of a multifocal IOL or add new models of the same design after the start of an IDE study should submit a request to FDA for approval. FDA will generally approve a change if the modified design incorporates an IOL characteristic previously PMA approved for the same sponsor, and if the sponsor can demonstrate that the change will have no effect on the multifocal properties (i.e., the MTF performance) of the IOL. If FDA judges the proposed change to affect multifocal performance, the modified IOL will be considered a new design requiring a new study. If the change does not affect multifocal performance but does affect other IOL attributes such as safety or stability, approval will be unlikely since the purpose of the study is solely to evaluate the multifocal design, and all other parameters should therefore be held constant for the duration of the study. For this reason, FDA believes that multifocal IOL studies should be conducted using only one class of optic material (e.g. PMMA, silicone or hydrogel).

Some examples of multifocal IOL modifications (PMA approved characteristics) that usually may be added to an ongoing IDE study or to a PMA are:

- 1.** PMA approved haptic material
- 2.** PMA approved optic material (if of the same class of materials as the parent model)
- 3.** PMA approved optic shape factor
- 4.** PMA approved haptic configuration

The sponsor should demonstrate that the MTF performance of the parent model and the modified model are equivalent by testing at least 10 randomly selected samples of the parent and modified model. The separation between the two curves at any point should not be greater than 0.05 modulation units when the two models are tested in a water cell with the lenses constrained in the mount to an overall diameter of 10 mm.

These changes may be requested at any time during an IDE clinical study. The application for a change should fully justify why the change is needed and provide evidence that the change will have no significant effects on multifocal performance or

adverse effects on safety. If approval is granted, the study may then continue with the modified multifocal IOL without repeating phase I or increasing the total number of core subjects. Upon completion of the study, a comparative analysis of data from the original and modified lenses may be necessary to confirm their functional equivalence.

B. Multiple Add Powers

Sponsors may include more than one near add power in their investigation in order to achieve consistent near focal plane performance with different eye geometries. The add powers to be included should be stated in the IDE application. If sponsors wish to add new powers after the start of the clinical investigation, they should submit an IDE Supplement and wait for FDA approval before incorporating the new powers into the study. The clinical data should be stratified by add power in the PMA. Guidance to physicians on add power selection should be provided in the IDE protocol and subsequently in the PMA labeling.

C. Modified Multifocal Designs

Changes that are sufficiently fundamental to significantly change the product's essential function are considered equivalent to designing a new product requiring a new IDE. One example of such a change in a multifocal IOL is a qualitative redesign of the multifocal optical geometry, such as adding an additional focal plane or changing from a discrete zone design to a diffractive design.

Significant changes that affect the multifocal optical performance will normally be considered only after PMA approval. If such changes are intended to replace the original design, the original design should be discontinued, and the ongoing IDE study should be stopped.

D. Modifications after PMA Approval

Sponsors may also request design changes in multifocal IOLs that have already been given PMA approval or received a substantive review of the clinical data. If a change is comparable to one that would have been approvable during the clinical study, it can usually be approved without additional clinical validation. More significant design changes, analogous to "Level B" changes for monofocal IOLs, may also be approved after satisfactory completion of a limited clinical (Level B) study.

Changes that should not be applied for until after a substantive review of the clinical data of the initial multifocal design include changes of shape, size or material that either have not previously been PMA approved, or that have been PMA approved but are expected to significantly affect the fit, stability or mechanical performance of the implanted IOL. Examples are:

- 1.** Changes in haptic design or material to one that previously has received PMA approval but that differs in mechanical properties or performance from the initial multifocal lens design, when these differences may affect the multifocal optical performance.

2. Changes in optic material to a previously approved material in a general material class different from the original multifocal lens. (For these purposes, polymethylmethacrylates, silicones, and hydrogels would be in different material classes.)

Major changes to a PMA approved multifocal IOL design (but not the multifocal optical geometry) should be qualified through a separate limited clinical investigation. The investigation should enroll a maximum cohort of 150 subjects, at least 75 of which are “best case” subjects. All subjects should be followed through Form 4. Sample size requirements for the clinical substudies and driving substudy are the same as those associated with a full IDE clinical study; i.e. 20 best case subjects for perimetry, 15 best case subjects for fundus photography, 10 best case subjects for each of the three pupil size groups for defocus curves, and 25 best case subjects per pupil size group for contrast sensitivity and/or low-contrast acuity. If fewer than the desired number of best case subjects is available in any pupil size category, then the maximum number of available best case subjects should be tested. In addition, a low visibility driving performance substudy should be performed only if the contrast sensitivity and/or low-contrast acuity results are worse than those of the original PMA study, or if the correlation between the clinical and driving results in the original study was too low to allow reliable performance predications from the clinical data.

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APPENDIX A

Significant Changes from Previous Multifocal IOL Guidelines

This document replaces four previous documents: an original multifocal guidance document dated June 13, 1990, two brief updates on optical quality control testing dated January 4, 1991 and March 4, 1991, and a more extensive update adding driving performance and binocular vision substudies dated February 16, 1993. The previous documents have been substantially reorganized, combined and updated based primarily upon comments received at the January 26, 1995 Ophthalmic Devices Panel meeting as well as separate comments received from multifocal IOL sponsors. This section sequentially lists significant changes in the order that they appear in the current document.

1. Introduction

An Introduction section has been added, with subsections on Background and Scope and Terminology.

2. Optical Design Validation

MTF testing is now recommended only at one decentration distance and at one tilt angle. The decentration and tilt parameters are to be determined individually for each lens design.

3. Optical Quality Control Procedures

The deadline is past for the upgrading of quality control procedures that was discussed in the two 1991 guidance update documents. All references to this upgrade have therefore been removed and the section has been thoroughly revised.

4. Staged Phase-In of Clinical Study

The size of the main study has been reduced to 420 core subjects and a minimum of 300 cohort subjects. No modified core studies will be allowed, and no Level B studies may be started prior to a substantive review of the clinical design. Standard follow-up now stops at Form 4. Additional follow-up to Form 5 is recommended only if a capsulotomy is done at Form 4 or later. The report forms have been redefined to be consistent with the ISO/DIS 11979-7 IOL clinical standard.

5. Inclusion/Exclusion Criteria

The exclusion criteria have been generalized to subjects with any condition that is predicted to produce a substantially below normal visual acuity, either immediately after implantation or later.

6. Informed Consent

The informed consent document should now include the information that the multifocal lens may interfere with the diagnosis and treatment of possible future retinal disorders by making it more difficult to view the fundus or deliver laser therapy.

7. Clinical Data

a. Visual Acuity

Recommended conditions for acuity testing are spelled out in detail, and are consistent with standard operating procedures agreed upon at the 1994 Eye Care Technology Forum. Testing at multiple light levels is no longer required.

b. Subject Survey

Recommendations are added for instructing subjects on methods for self-evaluation of monocular vision.

c. Defocus Curves

Only one light level instead of three is now recommended for defocus curves. Different pupil sizes may be obtained through natural variations across subjects rather than by varying light adaptation level.

d. Contrast Sensitivity Studies

Procedures for sinusoidal grating contrast sensitivity and low-contrast letter acuity are described separately. The contrast sensitivity reproducibility study has been moved into the contrast sensitivity section, where it logically belongs, and a similar reproducibility study is specified for low-contrast acuity. Testing should now be performed at both photopic and mesopic light levels to facilitate comparison with driving performance substudy data.

e. Low Visibility Driving Performance

Guidelines for driving performance studies were first drafted on February 16, 1993. The text of these guidelines has now been extensively rewritten and reorganized. Below are listed specific content changes, ordered sequentially with respect to the original document, with paragraph references included where appropriate:

i. Paragraph 3: A unilateral multifocal subject sample is no longer required and the properties of the control population are described in more detail. Test and control subjects should now be matched with regard to spectacle use and eye dominance. Recommendations for sample size are more explicit.

ii. Paragraph 4: No lane tracking task is now required.

- iii. Paragraph 5, item 1: The requirements for testing under dark conditions with standard roadway lighting and under twilight conditions have been made optional. The recommendations for inclement weather testing have been operationalized in terms of the required contrast sensitivity loss in control subjects, and acceptable examples of simulated fog or windshield condensation are suggested.
- iv. Paragraph 6: More detail is provided about glare source recommendations. The recommendation for an engineering analysis has been moved to a new section on Data Analysis.
- v. Paragraph 10: Enclosure A, “Additional Safety Concerns Related to Driving Simulation Studies” is not included in the revised guidance document.
- vi. New sections on Apparatus, Response Procedures and Measurement Methods, Validation Studies, and Data Analysis have been added.

8. Labeling

A new section on labeling has been added.

9. Design Modifications

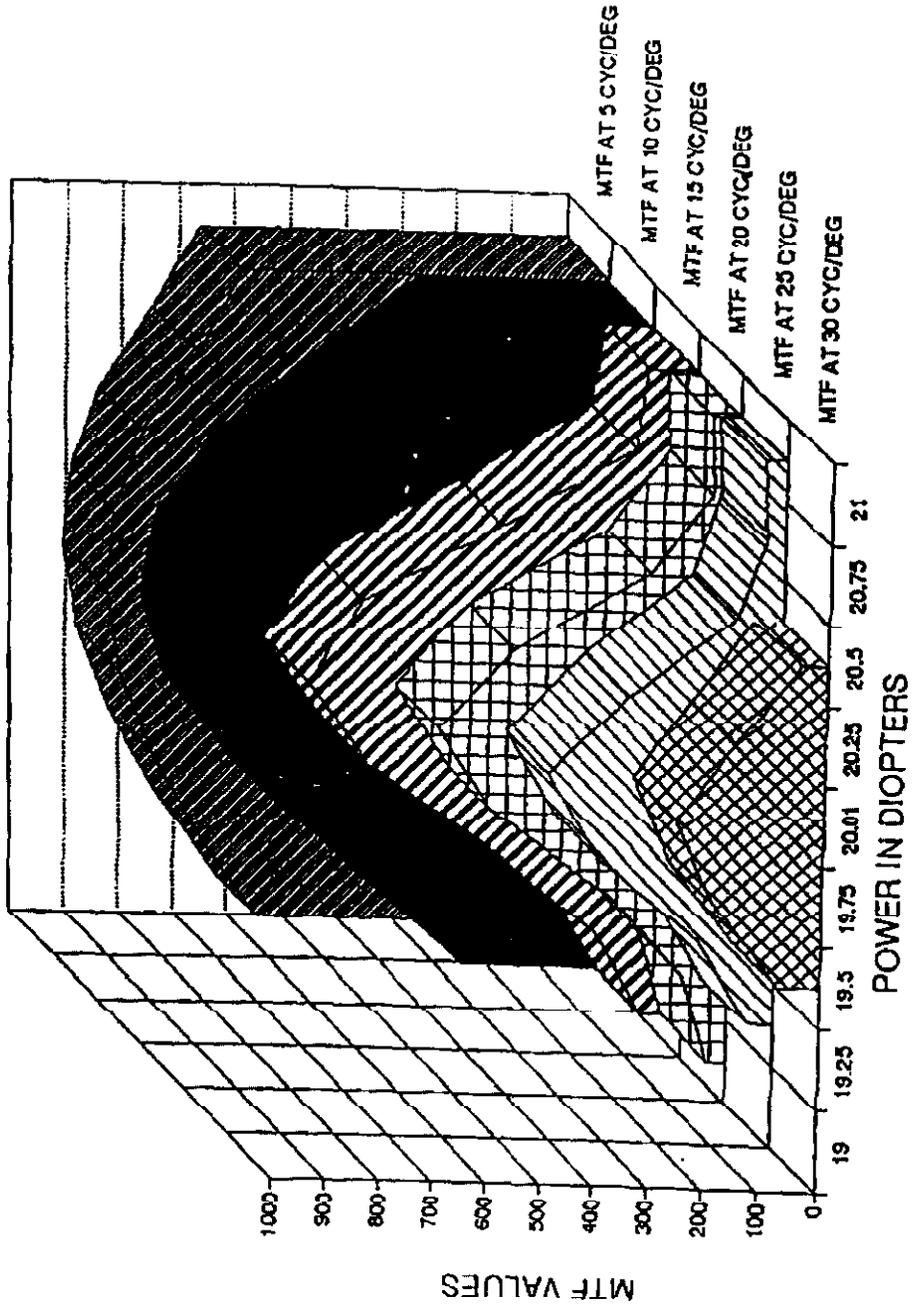
Level B studies are allowed only after a substantive review of the clinical data. New requirements for the size of Level B studies are described. The requirements for approval of changes are revised.

10. Bibliography

A bibliography of publications on multifocal IOLs and related topics has been added.

APPENDIX B

THROUGH FOCUS RESPONSE ANALYSIS 20.0 MONOFOCAL



APPENDIX C

FULL INVESTIGATION

MULTIFOCAL LEVEL B STUDY

TEST	FORMS	SUBJECTS ¹	FORMS	SUBJECTS ¹
Visual Acuity (Distance/Near)				
Corrected	1,2,3,4	300	1,2,3,4	150
Uncorrected Distance	4	300	4	150
Uncorrected Near	4	300	4	150
Distance-Corrected Near	4	300	4	150
Patient Survey	2 or 3, 4	300	2 or 3, 4	150
Visual Fields	4	20	4	20
Defocus Curves	4		4	
small pupils		10 ²		10 ²
medium pupils		10 ²		10 ²
large pupils		10 ²		10 ²
Fundus Photography	4	15	4	15
Contrast Sensitivity/ Low Contrast Acuity	4+5 (if capsulotomy)		4+5 (if capsulotomy)	
Distance				
photopic test		75 ³		75 ³
photopic test + glare		75 ³		75 ³
mesopic test		75 ³		75 ³
mesopic test + glare		75 ³		75 ³
Near				
photopic test		75 ³		75 ³
photopic test + glare		75 ³		75 ³
Low Visibility Driving Performance	4 or later	open	4 or later	open

¹ Numbers of cohort subjects recommended for the tests that are listed in the first column. Each subject's multifocal test eye should be paired with a monofocal control eye, either the subject's fellow eye or a monofocal eye in an age- and gender-matched control subject. Each driving substudy test subject with bilateral multifocal IOLs should be paired with an age- and gender-matched bilateral monofocal control subject. Fewer control subjects may be acceptable in some instances if a satisfactory statistical justification is provided.

² If 10 subjects are not available in any pupil size category, then the maximum number available should be used.

³For each of the test conditions, 25 subjects from each of the three pupil size categories should be tested for a total of 75 subjects. If 25 subjects are not available in any pupil size category, then the maximum available should be tested.

APPENDIX D

VISUAL ACUITY AND REFRACTION DATA AT FORM 4

	MULTIFOCAL IOL EYE							FELLOW EYE						
PT. #	UD	UN	CD	CN	SPHERE D	CYLIN D	AXIS	NEAR ADD D	SPHERE D	CYLIN D	AXIS	NEAR ADD D	CD	CN

- 1.
- 2.
- 3.
- 4.
- 5.
- etc.

UD = Uncorrected Distance Visual Acuity (VA)
UN = Uncorrected Near VA
CD = Corrected Distance VA
CN = Corrected Near VA
D = Diopter