This guidance was written prior to the February 27, 1997 implementation of FDA's Good Guidance Practices, GGP's. It does not create or confer rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statute, regulations, or both. This guidance will be updated in the next revision to include the standard elements of GGP's.

Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers

This document is intended to provide guidance in the preparation of a regulatory submission. It does not bind the FDA or the regulated industry in any manner.

Diagnostic and Surgical Devices Branch
Division of Ophthalmic Devices
Office of Device Evaluation

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While this guidance document represents a final document, comments and suggestions may be submitted at any time for Agency consideration by writing to Morris Waxler, Ph.D. (HFZ-460). For questions regarding the use or interpretation of this guidance, contact Morris Waxler, Ph.D. at (301) 594-2018. [This guidance document replaces “Draft Clinical Guidance for the Preparation and Contents of an Investigational Device Exemption (IDE) Application for Excimer Laser Devices Used in Ophthalmic Surgery for Myopic Photorefractive Keratectomy (PRK) which was issued on June 8, 1990.]

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

Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers

(See Appendix A and CFR 21 812.20(b) for list of required elements.)

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Checklist of Information Usually Submitted in an Investigational Device Exemptions (IDE) Application for Refractive Surgery Lasers

(See CFR 21 812.20(b) for list of required elements.)

1.0 Name and address of sponsor or sponsor-investigator.

2.0 Report of Prior Investigations.

2.1 Prior Laboratory Studies

The report of prior laboratory studies should include descriptions of testing procedures and results for all device performance tests. If information is not available for one of the following items at the time of the original submission of the IDE, the sponsor should discuss plans for obtaining the information and submitting it prior to a major expansion of the clinical trial.

A. fluence calibrations;

B. beam homogeneity (profile) measurements;

C. pulse stability through the longest procedure and gas life;

D. tests of fluence control and fail-safe systems;

E. tests of beam and eye alignment systems and procedures;

F. software validation and verification, including ablation profile tests in plastic (PMMA) blocks compared with programmed ablation profile;

G. in vitro ablation tests of corneal tissue from human cadaver eyes.

2.2 Prior Animal Studies

The report of prior animal studies cover include descriptions of all study designs, testing procedures, results, data analyses (e.g., comparisons to laboratory data) and interpretations.

2.3 Prior Clinical Studies

The report of prior clinical studies should include both U.S. and foreign studies, and should include:

A. subject inclusion and exclusion criteria;

B. numbers and characteristics of subjects;

C. kinds and ranges of refractive errors treated;

D. details of treatment protocols;

E. subject accountability and follow-up;

F. refractive and visual outcomes;

G. preoperative and postoperative assessments of vision, with a description of the procedures and protocols for obtaining and analyzing the data;

H. retreatments;

I. fellow eye treatments;

J. adverse events;

K. informed consent documents and institutional review board (IRB) approval information.

3.0 Investigational Plan

3.1 Purpose and Objectives

The purpose of the clinical investigation should be to collect safety and effectiveness data for *(name of the device)* in sighted eyes for the correction of (*kind of refractive correction*) to support the submission of a Premarket Approval Application (PMA).

The sponsor or sponsor/investigator should evaluate the ability of this laser to perform *(name of treatment, such as PRK or LASIK)* to correct *(kind of refractive correction)* from *(give range of dioptric powers to be included*) by studying the safety, effectiveness and *(specify any other parameters to be studied, for example the difference between bilateral simultaneous and sequential surgery).*

3.2 Proposed Protocol: description of the methodology to be used and analysis

See Appendix A and CFR 21 812.20(b) for list of required elements.

demonstrating its soundness.

3.2.1 Definitions of Major Safety Endpoints and Target Values:

These endpoints and target values are based primarily on recommendations of the Ophthalmic Devices Panel. However, these endpoints and values are only guidance.

A. Less than 5.0% of subjects lose more than 2 lines of best spectacle corrected visual acuity (BSCVA)

B. Less than 1.0% of subjects have BSCVA worse than 20/40

C. Haze beyond 6 months with loss of greater than 2 lines of BSCVA should occur in less than 1.0% of subjects

D. Induced manifest refractive astigmatism of greater than 2.0 D should occur in less than 5% of subjects

E. Adverse events to occur in less than 1.0 % of population.

Note 1. The specific post-treatment times should be clearly defined in order to estimate the time-specific proportions.

Note 2. Measurement of endothelial cell loss is not necessary as long as laser refractive surgery is 250 microns from the corneal endothelium and the laser parameters (e.g., wavelength and fluence) used are unlikely to damage the endothelium from this distance.

Note 3. Measurement of contrast sensitivity and glare are not necessary as long as patients are provided with appropriate precautionary language in the informed consent during the IDE study and the device is labeled with such precautionary language after PMA approval. See Appendix B.

3.2.2 Definitions of Effectiveness Endpoints and Target Values:

These endpoints and target values are based primarily on recommendations of the Ophthalmic Devices Panel. However, these endpoints and values are only guidance.

A. Report the proportion of eyes that achieve uncorrected visual acuity (UCVA) of 20/40 or better following treatment (For myopes under 7D, minimum of 85% of

subjects). Also, report the proportion of eyes that achieve UCVA of 20/40 or better following treatment as a function of the pretreatment UCVA.

B. Report the proportion of eyes that achieve predictability (attempted versus achieved) of the manifest refraction spherical equivalent of ±1.00D and ±0.50D at the point at which stability is first reached. (For myopes under 7D, minimum of 75% of subjects should have an achieved refraction within ± 1.00 D of the attempted refraction and at least 50% of the subjects should be within 0.50D of the attempted refraction)

C. Report the proportion of eyes that achieve stability of the manifest refraction. (For myopes under 7D, minimum of 95% of subjects should be stable) .

D. For astigmatic correction protocols, report the proportion of eyes that achieve minimal residual astigmatism.

:

Note. The specific post-treatment times should be clearly defined in order to estimate the time-specific proportions.

3.2.3 Study Design

This clinical investigation should be designed as a controlled cohort study *(name the kind of study, e.g., prospective, randomized/ non-randomized, one center /multicenter*). This investigation should include a *specific number of eyes and subjects* and should be conducted at a *specific a number* of clinical investigational centers within the United States. Multi-center trials are not necessary in order to determine a reasonable assurance of safety and effectiveness of a sponsor's refractive surgery laser; single site studies may suffice if adequate data are provided to demonstrate that the device can be used safely and effectively by other practitioners. Sponsors who choose to conduct single site IDE studies of a singular laser device to support a PMA submission should follow the guidance provided in this document. This document applies equally to single and multi-center studies. Sponsors of single site IDE studies should identify and control biases and should obtain data from multiple investigators.

The duration of the investigation should be specified. If data collected during that time require further follow-up, the investigation should be extended as needed.

3.2.3.1 Fellow eye treatments

The fellow eye may be treated as early as (*specify minimum time*) after the first eye is treated. Stability of the treatment with the sponsor's laser should be established first in order to determine the appropriate time frame for performing fellow eye treatments. Fellow eye treatments should not be performed in the presence of any complications or

adverse events in the initially-treated eye.

If the outcomes of the first eye will be used to modify surgery in the second eye, then describe how this information will be used.

3.2.3.2 Retreatment procedures

Retreatment should not be carried out until a minimum of (*specify minimum time*) after the initial surgery and the following conditions are met:(*specify minimum UCVA and refractive criteria*). The retreatment procedure should be described. Refractive stability should be used to determine timing of the repeated surgery.

Retreatments done to improve refractive outcome are not necessarily considered treatment failures; however, the number of retreatments planned for refractive purposes should be stated in the protocol and in the informed consent. Retreatments done to achieve resolution of an adverse event are considered treatment failures. A separate and complete analysis of the data for retreatment populations should be submitted.

3.2.4 Patient Population (Inclusion/Exclusion Criteria)

The sponsor may submit whatever inclusion /exclusion criteria he/she chooses. However, the inclusion of subjects with systemic or ocular conditions which may be especially risky for laser refractive surgery should be accompanied by appropriate written informed consent, stratification of the data, and substudies if the laser later is to be marketed for these conditions. The following criteria usually have been used in IDE studies of refractive surgery lasers:

3.2.4.1 Inclusion Criteria:

A. Subjects should be (state minimal age) years of age or older

B. State refractive criteria (include spherical and cylindrical components)

C. BCVA should be 20/40 or better in both eyes

D. Contact lens wearers should:

1. remove soft or gas permeable contact lenses two weeks prior to baseline measurements

2. remove hard contact lenses three weeks prior to baseline measurements, and have two central keratometry readings and two manifest refractions

taken at least one week apart that do not differ by more than 0.50 diopter in either meridian; mires should be regular.

E. Spherical or cylindrical portion of manifest refraction should progress 0.50 diopter or less during the year prior to the baseline exam.

F. Subjects should be willing and capable of returning for follow-up examinations for the duration of the study.

G. Videokeratography should be normal.

3.2.4.2 Exclusion Criteria

A. Any residual, recurrent, or active ocular disease or corneal abnormality

B. Signs of keratoconus

C. Taking systemic medications likely to affect wound healing, such as corticosteroids or antimetabolites

D. Immunocompromise (e.g., AIDS, autoimmune disease)

E. Previous intraocular or corneal surgery of any kind in the eye to be treated

F. Carrying diagnosis of autoimmune disease, connective tissue disease, clinically significant atopic disease or diabetes

G. Unstable central keratometry readings with irregular mires

H. Known sensitivity to study medications.

I. History of glaucoma or an intraocular pressure > 21 mm of Hg.

J. Participation in other ophthalmic clinical trials during this clinical investigation.

K. History of herpes simple or herpes zoster keratitis

L. Women who are pregnant or nursing or who plan to become pregnant over the course of this clinical investigation.

3.2.5 Study Procedures, Examination Conditions and Techniques

A detailed description of each test and instrumentation to be used in the study should be provided. Standard references may be used for generally accepted tests and instruments. However, distances, luminances, and other settings on tests and instruments should be provided.

3.2.5.1 Preoperative Evaluation and Surgical Plan

The pre-operative examination and evaluation should include a complete medical history and an examination of both eyes. (See the examination schedule for the specific tests to be usually conducted.)

The preoperative surgical plan should indicate the intended correction and the intended refractive outcome for each eye. This information should be entered on the preoperative planning protocol forms. At the time of surgery, the surgeon should record whether there is any deviation from this original decision and why. The preoperative variables should be identified, e.g., for LASIK the following variables are usually identified: diameter of the corneal flap, width of the hinge, diameter of ablation zone, surgical nomogram and depth of ablation.

3.2.5.2 Surgical Procedure

Describe in detail each step of the procedure.

3.2.5.3 Operative Report

An operative report on all treated subjects, and on those subjects on whom a procedure was attempted but not completed, should include the information on attempted spherical correction, attempted cylindrical correction, number of laser pulses, time for entire procedure, whether procedure was interrupted and drug treatment before, during and after the procedure (for PRK the time from epithelium removal to ablation should be included.) These operative reports should be maintained at each investigational site; they should not be submitted to FDA.

3.2.5.4 Schedule of visits

All subjects should be followed for *(specify duration)* or until the discontinuation of the clinical investigation. The current recommended follow-up period is one (1) year for PRK and six (6) months for LASIK. During this time subjects should be evaluated according to a schedule similar to the following one:

Pre/Preoperative Evaluation	(-60 to -1 days)
OP/ Operative Evaluation	(Day 0)
D1 / Day 1	(24 to 36 hours postop)
RE-EP/ Observation	(specify frequency) until re-epithelialization is complete (for PRK)
W1/ Day 7	(5 to 9 days) (for LASIK)
M1/ Month 1	(3 to 6 weeks postop)
M3/ Month 3	(10 to 14 weeks postop)
M6/ Month 6	(20 to 26 weeks postop)
M9/ Month 9	(35 to 43 weeks postop)
M12/ Month 12	(11 to 14 months postop)
M18/ Month 18	(16 to 20 months postop)
M24/ Month 24	(22 to 26 months postop)

3.2.5.5 Post-operative Evaluation

All examinations should be performed under standardized room lighting conditions. Specify the medication by which cycloplegia will be achieved. At each postoperative visit, information concerning the preoperative examination and previous postoperative examinations should not be made available to the individual conducting the examination until the postoperative examination is completed. The test should be carried out according to the examination schedule.

3.2.5.6 Postoperative Medication Regimen

The postoperative medical regimen to be followed should be described in detail. Specify whether bandage contact lenses are to be used and if anti-inflammatory drugs are used to modulate the healing response of the cornea to the laser surgery. Indicate how medications will be altered if at any time in the postoperative course IOP level exceeds 25 mm Hg or the change in IOP exceeds 10 mm Hg from the preoperative baseline.

EXAMINATION SCHEDULE

	PRE (Both eyes to be examined.)	OP	D1	RE-EP	W1	M1	M3	M6	M9	M12	M18	M24
Patient's name, exam date and time, investigator's name, subject's ID #, operative eye, current medications	X	X	X	X	X	X	X	X		X	X	X
Patient's birth date, sex, race, PMHx, POHx, contact lens hx, refraction stability	X											
Distance UCVA	X		X	X	X	X	X	X	X	X	X	X
Distance BSCVA [1]	X				X	X	X	X	X	X	X	X
Manifest Refraction	X				X	X	X	X	X	X	X	X
Cycloplegic Refraction	X							X		X		X
Near UCVA	X				X	X	X	X		X	X	X
Near BSCVA	X							X		X		X
IOP	X				X	X	X	X	X	X	X	X
Slit Lamp Exam [2]	X		X	X	X	X	X	X	X	X	X	X
Pupil Size [3]	X		X	X	X	X	X	X	X	X	X	X
Dilated Fundus Exam	X							X		X		X
Pachymetry, keratometry, axial length [4]	X											
Topography	X					X	X	X		X		X
Patient Questionnaire [5]	X				X	X	X	X	X	X	X	X
Adverse Events / Complications		X	X	X	X	X	X	X	X	X	X	X

See Appendix A and CFR 21 812.20(b) for list of required elements.

Notes for the Examination Schedule

1 - If the visual acuity with spectacle correction is $\geq$2 lines below that obtained preoperatively, a hard contact lens over refraction should be performed to determine the effect of irregular astigmatism and to estimate the best possible corrected visual acuity.

2 - The slit lamp exam should include a complete survey of the anterior segment. The cornea should be examined in detail with specific recordings and gratings (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).

3 - Pupil size should be assessed whenever VA measurement is done

4 - Pachymetry, keratometry and axial length should be assessed on all eyes preoperatively and if needed to assess anomalous results in the postoperative course

5 - The questionnaire 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.

3.2.6 Adverse Events and Complications

Adverse events defined as serious and unanticipated must be reported to FDA within 10 days of the investigator's learning of them and, if applicable, within another 10 days of the sponsor's learning of them (21 CFR 812.150(a)(1)). (Note: See 21 CFR 814 for premarket approval reporting requirements and 21 CFR 803 for medical device reporting of legally marketed devices.) Complications should be documented as well, but individual reports need not be submitted to FDA as part of the IDE process. Adverse events and complications could include, but are not limited to, the following lists:

3.2.6.1 Adverse Events

A. Corneal infiltrate or ulcer
B. Persistent central corneal epithelial defect at one month or later (PRK only)
C. Any corneal epithelial defect involving the keratectomy at one month or later (LASIK only)
D. Corneal edema at I month or later (for LASIK specify flap or bed)
E. Epithelium in the interface (LASIK only)
F. Lost, misplaced or misaligned flap (LASIK only)
G. Melting of the flap (LASIK only)
H. Uncontrolled IOP with increase of >5 mm HG above baseline, and any reading above 25 mm Hg
I. Late onset of haze beyond 6 months with loss of 2 lines (10 letters) or more BSCVA
J. Decrease in BSCVA of >10 letters not due to irregular astigmatism as shown by hard contact lens refraction, at 6 months or later
K. Retinal detachment
L. Retinal vascular accidents

3.2.6.2 Complications

A. Corneal edema between one week and one month after the procedure
B. 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)
C. Epithelium in the interface (LASIK only)
D. Recurrent corneal erosion at one month or later (PRK only)
E. Foreign body sensation at 1 month or later
F. Pain at one month or later
G. Ghost/double images in the operative eye
H. Flap is not of the size and shape as initially intended or microtome stopped in mid-cut (LASIK only)

3.2.7 Data Collection and Management/ Statistical Methods

3.2.7.1 Sample Size

A **sample** size of subjects should be chosen to obtain statistically valid estimates of the outcome rates. The expected rates of adverse events and complications should determine the calculation of sample size. A sample size of 300-400 subjects for each refractive indication is usually sufficient to assess the safety and effectiveness targets listed in section 3.2.2 above. The sample size for studies with refractive surgery lasers which ablate tissue within 200μ of the endothelium or for lasers with fluences greater than 230mJcm^{-2} or for lasers which raise other safety issues should be calculated based on the expected rates of adverse events and complications for these lasers.

The statistical calculations used to arrive at the appropriate sample size should be described by the applicant. Appendix C provides a sample size for complications and adverse events only. For continuous or quantitative measurement data, the sample-size formula for one treatment group, based on the desired precision (d) and Gaussian assumption, is:

$$\text{sample size (n)} = (Z_\alpha)^2 \times \sigma^2 / d^2,$$

where: $Z_\alpha = 1.96$, the standardized normal deviate corresponding to the 95% confidence level;
σ^2 is the variance of the original data, which may need to be estimated; and,
d is the desired precision of the deviation between the estimated value from the true value.

A larger sample size is needed for larger variance or better precision (d).

3.2.7.2 Estimates of Safety Targets

Since subjects'clinical outcomes recorded and the number of subjects evaluated will change frequently over time, it is important that the numerator and denominator used in estimating the safety target proportions at various follow-up times be clearly defined.

3.2.7.3 Estimates of Effectiveness Targets

In order to estimate the proportion of eyes that achieve uncorrected visual acuity (UCVA) of 20/40 or better following treatment the specific follow-up times should be clearly defined.

The 95% confidence interval for the true proportion of eyes that achieve predictability

(attempted versus achieved) of the manifest refraction spherical equivalent (SE) of ±1.00D and ±0.50D should be estimated. However, the transformation of originally continuous measurement of SE to binary (achieved versus not achieved) would lose valuable information concerning SE effectiveness. An alternative analysis is to use Student's paired t- statistic, assuming normal or Gaussian distributed SE data, or the nonparametric Wilcoxon signed rank statistic, to compute the mean paired difference between attempted and achieved results and the corresponding 95% confidence interval of the true mean difference. Such information may be useful for clinical interpretation. Follow-up times should be specific.

The 95% confidence interval should be estimated for the true proportion of eyes that achieve stability of the manifest refraction, and, for astigmatic correction protocols, for the true proportion of eyes that achieve minimal residual astigmatism. Again, follow-up times should be specific.

:

3.2.7.4 Control Group Considerations

From a statistical viewpoint, the prospective, randomized, concurrent control trial should provide more objective results than a trial without any control group. The use of the other eye from the same patient as the control group may be better than no control group at all. In either one of the two control groups employed, randomization and masking procedures should be considered to control for observer's bias in evaluating clinical outcomes.

If the other eye from the same patient were used as the control, then a matched-pair analysis could be performed. For example, for visual acuity, the following k by k matched-pair table could be constructed at each specific follow-up time for all study subjects :

Laser treated eye	Other eye (Control eye)		
	20/20 or better	20/25-20/40 . . .	20/200 or worse
20/20 or better			
20/25-20/40	Entered the numbers of PAIRED subjects here.		
.			
.			
.			
20/200 or worse			

The null hypothesis (no difference) and alternative hypothesis (laser treated eyes

have improved visual acuity) could be tested by applying appropriate statistical analysis to these ordinal scale data.

3.2.7.5 Accountability

There should be detailed **accountability** of the subjects treated with device so that bias is not a significant factor in the study. The loss to follow-up typically should not exceed 10.0% at one year. It is not easy to perform effective statistical analysis if large numbers of subjects fail to show up at the intermediate follow-up times, but reappear at the last follow-up. For a 10% loss to follow-up in ONE YEAR, the sample size (n) is usually adjusted to n':

n' = n/ (1-0.1) = n/ 0.9, where n is the initial estimated sample size based on statistical/clinical considerations.

Every effort should be made to follow every patient originally enrolled throughout the whole follow-up. Any missing patient information during any follow-up time would,not only reduce the study sample size, but would bias the estimates of clinical targets at that time. All study clinical effectiveness and safety targets, clinically important patient characteristics and covariates and other variables which may affect the final clinical outcome, should be clearly recorded at EACH follow-up time to facilitate further statistical analyses (to be discussed later). It is not easy to perform valid statistical analyses if a significant proportions of subjects miss their scheduled follow-up. It is also not easy to ascertain the type of missing data, such as data missing due to patient medical condition or other clinically important variables related to the study clinical targets. Statistical analyses based on available patient data alone may considerably underestimate the true safety or overestimate the true effectiveness of the device. Particularly, if no control groups were used, trend analysis based on a small number of evaluable subjects in one treatment group at various follow-up times would not provide useful information about true device performance over time.

3.2.7.6 Outcome Considerations

Success rates (percentage of eyes) for uncorrected distance visual acuity with and without cycloplegia should be reported by each line of visual acuity and summarized for: 20/20 or better, 20/25 - 20/40, 20/50-20/100, and 20/200 or worse. Rates of each major outcome will be computed and stratified by age and attempted correction. Multivariate models will then be used to identify preoperative and intraoperative factors independently associated with predictability and uncorrected visual acuity.

Refractive stability should be defined as a change of less than or equal to 1 D of manifest spherical equivalent refraction between two refractions performed at least 3

months apart. Feasibility studies or continued follow-up of early population of first eyes treated should be used to establish the point at which stability is first reached

The analysis of **astigmatic data**, whether for correction of pre-existing cylinder or for cylinder which is induced by treatment, should include two approaches. Cylinder should be reported independently from measurements of sphere as a distribution of intended vs achieved (as for other refractive outcomes), accompanied by a distribution of axis shifts. Vector analysis should also be performed and reported. The stability of the cylindrical as well as spherical component of the correction should be assessed over time. Absolute and proportional changes in net astigmatism should be presented stratified by age and attempted.

Data analyses should be performed separately for those subjects undergoing **more than one procedure** in the same eye. Potential associations (e.g. preoperative refraction) with eyes undergoing more than one procedure should be explored. The principal effectiveness outcomes of those eyes undergoing more than one procedure should be computed and compared to those undergoing one procedure.

3.2.7.7 Statistical Analysis (See other sections of 3.2.7 also.)

Appropriate statistical analysis is longitudinal data analysis to estimate the clinical outcomes adjusted for clinically important patient characteristics or covariates. The generalized estimating equation (GEE) is very useful for such analyses. (For details see Diggle, PJ., Liang, KY., and Zeger, SL. Analysis of Longitudinal Data, Oxford Science Publications, 1994.) The patient clinical data layout may be constructed as follows:

		Postoperative		
Patient	Preoperative	Time 1	Time 2.....	Last Time
1	$X_1,...X_p, Y_1,...Y_m$	Same as Preoperative		
2				
3				
.				
.				
.				
n				

In the above table layout, for each patient and for each preoperative and postoperative follow-up times, all clinically important patient characteristics or covariates ($X_1,...X_p$), can be time-invariant (not change over time) or time-dependent (change over time) , and clinical response variables ($Y_1,...Y_m$), should be objectively recorded. A statistical multivariate model, such as GEE or the generalized linear model (GLM), can be used to

estimate clinical outcomes at various times while simultaneously adjusted for clinically important patient covariates. This model is applicable to data of various types, such as ordinal (visual acuity), binary (presence or absence of complications or adverse events), count (endothelial cell count), or quantitative/continuous (spherical equivalent). However, if the single or joint effect of clinically important covariates on the clinical outcomes were not of interest, then the effectiveness of the above multivariate model would be much reduced. The model could account for correlation among repeated measures from the same patient and multiple events, if any, from the same patient during the follow-up period.

3.2.7.8 Study Expansion Plans

3.2.7.8.1 Initial Study

IDE studies on refractive surgery lasers should obtain sufficient data (i.e., enroll subjects) for submission of a PMA within one year. A plan should be submitted showing how the applicant will phase their study to accomplish this goal. Ideally an IDE study should be expanded to the applicant's proposed sample size from an initial cohort of subjects without interruptions between phases. Study expansion can be achieved if no untoward problems have been identified, a satisfactory progress report has been submitted to FDA, and a request for expansion of the study submitted more than 30 days before enrollment limits are reached (see 3.2.7.4.4).

The results from initial subjects may be used to estimate the sample size for the full IDE study. The size of the initial phase of subject entry which is approved by FDA for an IDE study is based on the completeness of the original IDE application, the apparent safety of the applicant's laser, and the scientific quality of the investigational plan.

3.2.7.8.2 Explicit Study Phases Not Necessary

Standardized phases defined by FDA were the previous approach. These are no longer necessary. Additionally, there is no need to have a series of stopping points as the trial expands. The sponsor should time requests for study expansion such that phase limits are not reached before approval for expansion to the next phase. <u>However, every expansion of an IDE study still requires FDA approval prior to study expansion.</u> Also, the sponsor may request (and receive) approval for a change in the device at any point during the clinical trial without necessarily interrupting the trial. Sponsors whose IDE studies are currently proceeding by explicit phases should consider submitting expansion requests before phase enrollment limits are reached. The following information should be submitted to the Agency in such requests.

3.2.7.8.3 Information Needed Prior to Expansion

See Appendix A and CFR 21 812.20(b) for list of required elements.

Requests from applicants to expand their IDE studies should be approved by the Agency if preceded by:

A. a progress report demonstrating reasonable assurance of safety and effectiveness (see sections 3.2.1 and 3.2.2);

B. timely submission of adequate descriptions of important aspects of the device (see section 3.4); and,

C. prior Agency approval of all changes in the investigational plan and in the device submitted in the original IDE application.

3.2.7.8.4 PMA Application Expected

Sponsors and sponsor/investigators of IDE studies not intended for submission of a PMA should explain the reasons why a PMA will not be submitted and the reasons why the study is being conducted. These sponsors should complete their studies within two (2) years. Sponsors who do not submit a PMA application within one (1) year of approval of the IDE study should assume completion of their study within two (2) years.

3.3 Risk/Benefit Analysis

The risks of performing (PRK / LASIK) on sighted eyes include improper correction, decrease in best corrected visual acuity, glare, halo, foreign body sensations, corneal scarring, corneal ulceration or perforation, intraocular infection, corneal decompensation, persistent corneal edema, hyphema, hypopyon, endophthalmitis, microbial keratitis or cataract. Also the long term risks of the procedure are unknown. The LASIK procedure has additional risks related to the characteristics of the microkeratome. There should be a discussion of steps taken to mitigate the risks of PRK or LASIK.

The principal benefit of PRK/LASOK in justification of the above risks is the potential freedom from or reduced dependence on spectacles and/or contact lenses for the correction of refractive error.

3.4 Device Description

Provide a description of each important component, property and principle of operation of the device and any anticipated changes in the device during the investigation. The description should be detailed enough to permit a thorough understanding of the function of the device. It should also identify all significant risks to subjects attributable to the device, and should provide evidence that these risks have

been acceptably minimized. The device description provides the basis for evaluating device problems or changes during the course of the clinical studies. For refractive laser systems, the description should include, but not be limited to, the following items:

3.4.1 Device Information Needed Before IDE Approval

Prior to approval of an IDE application, even for a feasibility study, the sponsor or sponsor-investigator should provide the following information:

3.4.1.1 Electrical Safety

Certification that the device conforms to a recognized national or international electrical safety standard for medical devices (e.g., Underwriters Laboratories, UL544 76; Canadian Standards Association, C22.2 No.125-M1984; British Standards Institute, BS 5724; International Electrotechnical Commission, IEC 601-1-2; Japanese Industrial Standard, JIS T1001);

3.4.1.2 Feature Disabling

A detailed description of all hardware, firmware, and software features enabled and disabled for the IDE study;

3.4.1.3 Critical Engineering Aspects

A detailed scientific and technical analysis of the following critical engineering aspects of the device should be submitted.

A. It is very important to provide detailed descriptions and analyses of the ablation patterns for the treatment of refractive error (i.e., myopia, astigmatism and hyperopia). These descriptions and analyses should include both a narrative and a graphic portrait of the evolution of the new corneal surface. The descriptions should include, but not be limited to, detailed diagrams and explanations of all masks, annulae, crescents, diaphragms, multizones, multipasses, and scanning patterns used to change the shape of the cornea. Any differences between surface and intrastromal ablation patterns should be clearly described and explained.

B. The laser characteristics should be described in detail. The description of the laser should include, but not be limited to, the type (e.g., excimer), frequency

conversion method (if applicable), cooling method, laser cavity output, wavelength (include the fundamental and secondary wavelengths of solid state lasers), pulse repetition rate, pulse width (duration, full width half maximum), pulse energy, spatial dimensions and beam divergence.

C. A narrative description should be provided of the beam calibration methodology, the calibration schedule and how the schedule was derived based on estimates of the likely frequency of use of the device after PMA approval.

D. A detailed system hazard analysis should be provided which includes, but is not limited to, the following information. This information should be revised and resubmitted to FDA whenever changes are made in the device.

1. a top-down (fault tree) hazard analysis of those critical subsystems whose malfunction or failure could result in sight-threatening problems or in functionally significant errors in refractive correction, e.g., fail-safe mechanisms to prevent excessive ablation depth and maintain laser parameters, safeguards against foot-pedal failures, data entry safeguards to minimize errors in calculating ablation depth, microkeratome features and SOPs, centration features, fixation, eye tracking, and variable apertures.

2. failure modes of all safety critical and safety-related functions and how they are mitigated, eliminated or controlled through either hardware, firmware, software or user training. All procedures for validating failure mode controls should be described, and any performance specifications that are controlled by software should be identified.

3. all safety critical software functions. A safety critical software function is any software function whose failure would produce a hazard.

4. all safety-related software requirements. A safety-related software requirement is a software requirement that was included in the design to mitigate a specific hazard that was identified in the hazard analysis.

5. all safety-related software requirements or safety critical software functions that will be implemented or controlled by Off-The-Shelf (OTS) software.

3.4.2 Device Information Needed Prior to Approval (or Expansion) of an IDE Study of More Than 20 Subjects

See Appendix A and CFR 21 812.20(b) for list of required elements.

3.4.2.1 Description of Device Problems and Changes Before Expansion

Evidence of the absence of major device failures or of their satisfactory resolution should be submitted. The number of subjects and sites approved in an expansion from a feasibility study will depend on the adequacy of the description and resolution of any problems, and on their documentation. Feasibility studies should be submitted as needed and evaluated on a case-by-case basis. Engineering changes in critical functions or in laser output should be described by the sponsor and evaluated and approved by FDA before any expansion to a larger clinical trial.

3.4.2.2 Adequate Engineering Descriptions Before Expansion

The following engineering descriptions of the device should be provided in order to facilitate resolution of device problems and the evaluation of changes in hardware, firmware, and software.

A. Provide a narrative description (with diagrams) of the following subsystems and components:

1. optical system, including the beam paths and characteristics of the treatment laser, the aiming system and the cornea alignment system;

2. operating microscope subsystem, including geometry and eye illumination levels; and,

3. subsystem for on-line monitoring and adjustment of laser beam fluence;

4. narrative optical component description, to include:

   a. component type (e.g., mirror, lens, beam dump, crystal)

   b. material (e.g., quartz)

   c. coatings (if applicable)

   d. threshold for radiation damage

   e. optical performance (as appropriate), such as focal length, clear aperture, reflectivity, transmission, crystal conversion efficiency and absorption.

5. mechanics of beam modulation (e.g., scanning, masking, etc.).

6. beam characteristics at the treatment plane, e.g., total energy, beam profile (fluence across the beam) and positional accuracy (for scanning systems), with variability specified where applicable.

7. feedback control of laser output and beam characteristics.

8. corneal alignment accuracy (eye centering and eye stability techniques).

9. mechanical systems, including:

    a. subject alignment and centration provisions;

    b. gas handling, containment and monitoring systems;

    c. manual control systems;

    d. shutters for controlling laser beam configuration.

10. software systems, including:

    a. description and flowchart of the software lifecycle of the device. The standard operating procedures for and records of the software lifecycle should not be submitted; however, they should be available upon request.

    b. a flow diagram and narrative about the function of the software and about how the software interacts with the hardware. Outline the test procedures and passing criteria used for validation and verification of the safety critical software.

    c. Certification: If the software design, development and maintenance system have been certified to an international or national standard, specify to which standard and provide the name of the organization that performed the certification.

3.4.2.3 System Validation Before Expansion

A. Identify problems during the system validation which will be corrected during a later system revision or update.

B. Indicate how these problems are handled currently (by labeling, training, interim fix, etc.) and how they will be corrected during a later system revision

or update.

3.4.3 Device Information Needed Before PMA Approval

An IDE submission ideally should contain all the engineering information required for a PMA submission; however, given the investigational status of the device, the following information may be submitted as the study expands.

A. A detailed description of all hardware, firmware, and software features locked-in or locked-out because of conditions of PMA approval. If hardware, firmware, and software features available on units sold domestically are different from those sold internationally, then inventory control should be described and records maintained.

B. A recommended separation distance (see note below) between the laser and other electrical medical devices, OR specify that the laser should be housed in a separate facility away from other electrical medical devices and provide a warning in all labeling that the effects of the laser on implantable medical devices are not known.

> Note: The separation distance is determined by the furthest point (of those in various directions) from the laser where the electromagnetic energy is not greater than 3 V/m, as measured: (a) using the technique and equipment described in IEC CISPR 11 and 16, (b) for frequencies from 26 MHZ to 1 GHz, and © while the laser is firing.

C. Information on conformance of the device to Good Manufacturing Practices;

D. Detailed engineering information to assure that adequate maintenance procedures exist;

E. Model comparability should be established through comparison of specifications of the replacement model with the earlier model(s) in terms of the treatment approach and beam characteristics at the treatment plane, supplemented, as needed, with measurements of the beam characteristics at the treatment plane. Confirmatory clinical data may be requested if there are major safety and effectiveness concerns.

Note: Data from IDE studies do not, in and of themselves, show the manufacturer can reliably manufacture a device in accordance with good manufacturing practices (GMPs).

Appendix A
Summary of Regulatory Requirements for an IDE Application

As summarized from CFR 21 812.20(b), an IDE application must include, in the following order:

1. Name and address of sponsor or sponsor-investigator.

2. Report of Prior Investigations.

The report of prior investigations must include complete reports of all prior laboratory, animal and clinical testing of the device (CFR 21 812.27). In addition, the report must include:

a. *Publications:* A bibliography of all publications, whether adverse or supportive, that are relevant to an evaluation of the safety and effectiveness of the device;

b. *Unpublished Information:* A summary of all unpublished information, whether adverse or supportive, that is relevant to an evaluation of the safety and effectiveness of the device;

c. *Adverse Information:* Copies of all published and unpublished adverse information concerning the device; and

d. *GLP Compliance Statement:* If nonclinical laboratory data are provided, a statement that such studies have been conducted in compliance with the good laboratory practice (GLP) regulation (CFR 21 58; also see Appendix H of the IDE manual). If the study was not conducted in compliance with the GLP regulation, include a brief statement of the reason for noncompliance.

3. Investigational Plan.

The investigational plan shall include the following items in the order listed:

a. *Purpose.* The name and intended use of the device and the objectives and duration of the investigation.

b. *Protocol.* A description of the methodology to be used and an analysis demonstrating its soundness.

c. *Risk Analysis.* A description and analysis of all increased risks to the subjects

and how these risks will be minimized; a justification for the investigation; and a description of the subject population, including the number, age, gender and condition.

d. *Device Description.* A description of each important component, ingredient, property and principle of operation of the device and any anticipated changes in the device during the investigation.

e. *Monitoring Procedures.* The sponsor's written procedures for monitoring the investigation and the name and address of each monitor (see Chapter 5 of the IDE manual).

4. Manufacturing Description.

A description of the methods, facilities and controls used for the manufacture of the device in enough detail to allow a judgement about the quality control used in its manufacture.

5. Investigator Agreements:

a. Example of investigator agreement to be signed by investigators
b. List of the names and addresses of all investigators
c. Certification that:
   I. all investigators have signed the agreement;
   ii. the list of investigators includes all investigators in the study;
   iii. new investigators will sign the agreement before joining the study.

6. Institutional Review Board (IRB) Agreements:

a. List of the name, address and chairperson of each IRB reviewing the study;
b. Certification of the action taken by each IRB.

7. Other Participating Institutions:

The name and address of any institution at which a part of the investigation may be conducted that has not been identified in **6** above.

8. Sale Price.

If the device is to be sold, the amount to be charged and an explanation of why the sale will not constitute commercialization.

9. Environmental Assessment.

Environmental Assessment Document (CFR 21 25.31) or a claim for categorical exclusion from this requirement (CFR 21 25.24e(7)).

10. Labeling.

Copies of all labeling for the device.

11. Informed Consent.

Copies of all forms and informational materials to be provided to subjects to obtain informed consent.

Appendix B
Contrast Sensitivity and Glare Testing for Refractive Surgery Lasers

Sponsors of IDE studies for refractive lasers may choose not to conduct contrast sensitivity and glare tests if they agree to include in their labeling a precautionary statement to the effect that PRK (LASIK) may impair or disable visual performance under adverse visibility conditions such as those encountered while driving at night or in inclement weather. For indications of low to moderate myopia (<-7 diopters) and a 6 mm diameter central optical ablation zone, the following is an example of the usual precautionary language:

Precaution: Although the effects of PRK (LASIK) on visual performance under poor lighting conditions have not been determined, it is <u>possible</u> that you will find it more difficult than usual to see in conditions such as very dim light, rain, snow, fog, or glare from bright lights at night.

The justification for allowing precautionary labeling to substitute for contrast sensitivity and glare studies is that contrast sensitivity data under standard photopic conditions are available from several sources, and these data consistently show that PRK for low to moderate myopia is associated with a statistically significant but small loss of contrast sensitivity. This loss is not functionally significant under high visibility conditions, but can be predicted to impair visual performance under low visibility conditions. This justification may not apply to other indications that raise new safety concerns and for which no contrast sensitivity and glare data are available, or to lasers with other output characteristics. When the optical characteristics of the treatment predict a worse retinal image than that produced by PRK for -1 to -7 D myopia, stronger precautionary labeling commensurate with the predicted worst case performance loss will be required. The following are examples of treatment characteristics for which a substudy should be considered. Note that examples a-c apply equally to surface PRK and intrastromal PRK (LASIK).

1. Optical ablation zone smaller than 6 mm.
2. Multi-zone ablation with transition zone(s) within 6 mm
3. Astigmatic correction resulting in aspheric corneal shape

An example of likely precautionary language is as follows:

Precaution: Although the effects of PRK (LASIK) on visual performance under poor lighting conditions have not been determined, it is <u>likely</u> that you will find it more difficult than usual to see in conditions such as very dim light, rain, snow, fog, or glare from bright lights at night.

Sponsors may attempt to justify exclusion of the precautionary labeling by conducting a substudy of contrast sensitivity under mesopic lighting conditions, both with and without glare. The background luminance of the contrast sensitivity test should be reduced to less

than 3 cd/m² (about 0.2 cd/m² preferred) and the ambient illumination should be even lower. The test targets may be either grating contrast sensitivity charts or low contrast letter acuity charts. In order to limit pupil constriction and maintain uniform glare conditions across the test chart, the glare source should be an array of two or more small spots symmetrically positioned around the chart. The glare source should be bright enough to significantly reduce the contrast sensitivity of young adult subjects with normal corneas and normal vision. If the above conditions cannot be implemented, the BAT may be used as an alternative glare source if the subject's pupil is dilated and the above brightness criterion is met. Control data may be obtained either from the preop PRK subjects or (preferably) from a sample of normal subjects with the same age, gender and refractive error distributions as the postoperative test subjects. The subject population should be large enough to detect 0.1 log contrast sensitivity differences with 80% power (E.g., if the standard deviation is 0.3 log unit, about 80 subjects would be needed to meet this target.) Postoperative testing should be conducted after visual function has stabilized.

Important: Prior to PMA approval (or post-approval) FDA may request contrast sensitivity and glare studies for any refractive surgery laser device and indication if data from the IDE study, or other scientific studies, demonstrate that visual function is likely to be impaired sufficiently to jeopardize the safety of subjects.

Appendix C: Table of Confidence Limits

Two-sided and one-sided upper 95% confidence limits (worst case) for percentages of complications*, for given sample size (number of subjects) and observed number of complication cases. (* computed by binomial probability distribution)

Sample Size(n)	Number of cases (x)	Observed complication percentage(%)	Two-sided 95% confidence limits (%)	One-sided upper 95% confidence limit (%)
100	0	0	0, 3.62	2.95
	1	1	0.03, 5.45	4.66
	2	2	0.24, 7.04	6.16
	3	3	0.62, 8.52	7.57
	4	4	1.10, 9.93	8.92
	5	5	1.64, 11.28	10.23
200	0	0	0, 1.83	1.49
	2	1	0.12, 3.57	3.11
	4	2	0.55, 5.04	4.52
	6	3	1.11, 6.42	5.83
	8	4	1.74, 7.73	7.10
	10	5	2.42, 9.00	8.33
300	0	0	0, 1.22	0.99
	3	1	0.21, 2.89	2.56
	6	2	0.74, 4.30	3.91
	9	3	1.38, 5.62	5.18
	12	4	2.08, 6.88	6.40
	15	5	2.83, 8.11	7.59
400	0	0	0, 0.92	0.75
	4	1	0.27, 2.54	2.27
	8	2	0.87, 3.90	3.58
	12	3	1.56, 5.18	4.82
	16	4	2.30, 6.41	6.01
	20	5	3.08, 7.62	7.18
500	0	0	0, 0.74	0.60
	5	1	0.33, 2.32	2.09
	10	2	0.96, 3.65	3.37
	15	3	1.69, 4.90	4.58
	20	4	2.46, 6.11	5.76
	25	5	3.26, 7.29	6.91

Appendix D
Agency Decisions on IDE Submissions.

Disapprovals (812.30(b)).

"*Grounds for disapproval or withdrawal.* FDA may disapprove or withdraw approval of an application if FDA finds that:

(1) There has been a failure to comply with any requirement of this part or the act, any other applicable regulation or statue, or any condition of approval imposed by an IRB or FDA.

(2) The application or a report contains an untrue statement of a material fact, or omits material information required by this part.

(3) The sponsor fails to respond to a request for additional information with the time prescribed by FDA.

(4) There is reason to believe that the risks to the subjects are not out-weighed by the anticipated benefits to the subjects and the importance of the knowledge to be gained, or informed consent is inadequate, or the investigation is scientifically unsound, or there is reason to believe that the device as used is ineffective.

(5) It is otherwise unreasonable to begin or to continue the investigation owing to the way in which the device is used or the inadequacy of:

(I) The report of prior investigations or the investigational plan.

(ii) The methods, facilities, and controls used for the manufacturing, processing, packaging, storage, and, where appropriate, installation of the device, or

(iii) Monitoring and review of the investigation."

Conditional Approvals.

IDE applications should be conditionally approved by the Agency only if the description of the investigational plan (see section 3.1, 3.2, and 3.3) and the device (see sections 3.4) are determined inadequate by the Agency but do not compromise the safety and rights of human subjects treated during the conditional approval period of 45 days;

Approvals

Agency approvals (including conditional approvals) of original IDE submissions should identify problem areas in the submission which might compromise a later determination by FDA that the data do not constitute "valid scientific evidence". The Agency should identify these problems by reference to broad topics, and, where possible to specific details. The scientific validity of the data generated during an IDE study is the responsibility of the sponsor.