

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name: Ultraviolet-absorbing posterior chamber intraocular lens (IOL)

Device Trade Name: C-flex™ intraocular lens (model 570C)

Applicant's Name and Address: Rayner Surgical Inc.
6654 Church Street
Los Angeles, CA 90042
USA

Date(s) of Panel Recommendation: None

Premarket Approval Application (PMA) Number: P060011

Date of Notice of Approval to Applicant: May 3, 2007

II. INDICATIONS FOR USE

The Rayner C-flex™ intraocular lens is indicated for primary implantation for the visual correction of aphakia in adults in whom a cataractous lens has been removed by phacoemulsification. The lens is intended to be placed in the capsular bag.

III. CONTRAINDICATIONS

The C-flex™ IOL is contraindicated in patients:

- Who are less than 21 years
- Who are microphthalmic
- Who have corneal decomposition or corneal endothelial cell insufficiency
- Who have active ocular disease (e.g., chronic severe uveitis, proliferative diabetic retinopathy, chronic glaucoma not responsive to medication)
- Who are pregnant or nursing

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the C-flex™ labeling (Attachment 1).

V. DEVICE DESCRIPTION

The single-piece C-flex™ ultraviolet-absorbing posterior chamber intraocular lens (IOL) is designed to be surgically implanted into the capsular bag of the human eye as a replacement for the crystalline lens following phacoemulsification with an anterior continuous curvilinear capsulorhexis just covering 360° the anterior edge of the IOL optic by 0.5 to 1.0 mm. The overall diameter is 12.0 mm, the optic diameter 5.0 to 5.75 mm, with a refractive index of 1.46. The C-flex™ is made from Rayacryl™ which is a

copolymer of hydrophilic and hydrophobic methacrylates. The hydrophilic nature of the material reduces silicone oil adhesion. C-flex™ IOLs are available from +8.0 to +30.0 Diopters (D) with 0.5 D steps.

VI. ALTERNATIVE PRACTICES OR PROCEDURES

Other approved IOLs may be used in the treatment for visual correction.

VII. MARKETING HISTORY

The C-flex™ IOL has been marketed in over 40 countries worldwide to date. The C-flex™ IOL has not been withdrawn from any market for reasons relating to safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

A multi-center clinical trial with a historical control was conducted to determine the safety and effectiveness of the C-flex™ IOL. Three hundred one (301) patients were enrolled and implanted with the C-flex™ IOL. Data from an additional 182 patients implanted with the Centerflex IOL (identical to the C-flex™ except for minor differences in edge design that were determined not to affect the evaluation of safety and effectiveness) were used as supporting clinical data. Adverse events reported in the study are presented in Table 1. The adverse event rates were not statistically significantly different from the historical control population rate for all of the listed cumulative and persistent adverse events. The major adverse events experienced during the clinical trial were cumulative macular edema (2.3%), persistent macular edema (1.1%), and cumulative surgical reintervention (0.6%).

TABLE 1: Specific Cumulative and Persistent Adverse Events in the Investigational Model and FDA Historical Control at 11-14 Months

	Posterior Chamber Historical Control ^A		Centerflex IOL		C-flex™ IOL		Pooled Centerflex and C-flex™ Data	
	N	%	n/N	%	n/N	%	n/N	%
Cumulative ^B Hyphema	91	2.2	0/182	0.0	0/301	0.0	0/483	0.0
Cumulative Macular Edema	124	3.0	5/182	2.7	6/301	2.0	11/483	2.3
Cumulative Retinal Detachment	11	0.3	0/182	0.0	0/301	0.0	0/483	0.0
Cumulative Pupillary Block	5	0.1	0/182	0.0	1/301	0.3	1/483	0.2
Cumulative Lens Dislocation	5	0.1	0/182	0.0	0/301	0.0	0/483	0.0
Cumulative Endophthalmitis	4	0.1	0/182	0.0	0/301	0.0	0/483	0.0
Cumulative Hypopyon	16	0.3	0/182	0.0	0/301	0.0	0/483	0.0
Cumulative Surgical Reintervention	46	0.8	0/182	0.0	3/301	1.0	3/483	0.6
Persistent ^C Macular Edema	19	0.5	3/166	1.8	2/284	0.7	5/450	1.1
Persistent Corneal Edema	11	0.3	1/166	0.6	1/284	0.4	2/450	0.4
Persistent Iritis	11	0.3	0/166	0.0	0/284	0.0	0/450	0.0
Persistent Raised Intraocular pressure (IOP) Requiring Treatment	17	0.4	0/166	0.0	0/284	0.0	0/450	0.0

Notes:

- A. Annex B – FDA grid of historical controls: Best Corrected Visual Acuity (BCVA) at one year, FDA Intraocular Lens Guidelines, 1999.
- B. Cumulative Adverse Event (AE) for the investigational model intraocular lens (IOL) is computed as any occurrence up to and including the current interval. Historical control cumulative values are up to and including 1 year.
- C. Persistent Adverse Event (AE) for the investigational model is defined as an AE remaining unresolved at the start of the current evaluation interval.

Other potential complications of cataract or implant surgery include, but are not limited to the following: Endophthalmitis, retinal detachment, cyclitic membrane, iris prolapse, hypopyon; corneal edema, corneal endothelial damage, uveitis, hyphema, lens epithelial cell on-growth, secondary glaucoma and precipitates on the lens surface. Secondary surgical interventions may be required for, but is not limited to the following: Vitreous aspiration or iridectomy for papillary block, wound leak repair, retinal detachment repair, lens repositioning, and lens replacement due to refractive error or severe inflammation.

IX. SUMMARY OF PRECLINICAL STUDIES

Rayner performed preclinical studies on the device in accordance with the International Organization for Standardization (ISO) document 10993 Ophthalmic implants – intraocular lens.

Biocompatibility Studies:

The objective of the biocompatibility studies was to establish a complete biocompatibility profile for the IOL material. Summaries of the biocompatibility tests conducted are listed below (Table 2):

TABLE 2: Biocompatibility Tests

Biocompatibility Test	Results and Conclusions
Cytotoxicity: Cell Inhibition	The results showed the lenses were mildly inhibitory
Cytotoxicity: Direct Contact Agarose Overlay	No toxic effects occurred in the treated cells.
Cytotoxicity: Indirect Contact Agarose Overlay	No toxic effects occurred in the treated cells.
Cytotoxicity: Indirect Contact	No toxic effects occurred in the extract treated cells.
Cytotoxicity: Modified Eagle's Media Elution	No cytotoxic reaction was observed on the treated cells
Genotoxicity: Bacterial Reverse Mutation	The lens extract did not induce mutagenic activity
Genotoxicity: Mammalian Chromosomal Aberration	There was no evidence that the extracts induced structural or numerical chromosomal alternation in the Chinese Hamster Ovary cells
Genotoxicity: Mammalian Chromosomal Aberration	There was no evidence that the extracts induced structural or numerical chromosomal alternation the mouse lymphoma cells
Acute Systemic Toxicity	No mortality, no weight loss, and evidence of significant systemic toxicity were observed
Maximization Sensitization	The extractants showed no evidence of causing delayed dermal contact sensitization in the guinea pigs
Ocular Irritation and Sensitization	There was no significant irritation in the test eye of any rabbit

Physiochemical and Engineering

Rayner conducted non-clinical studies on the C-flex™ IOL in accordance with the international standard series ISO 11979 (Ophthalmic implants – Intraocular lenses). Additionally, an on-site facility inspection was used to establish the adequacy of the manufacturing process. Non-clinical testing demonstrated the C-flex™ lens' safety and effectiveness from an engineering and manufacturing perspectives. Summaries of the physiochemical and engineering tests conducted are listed below:

TABLE 3: Physicochemical and Engineering Tests

Physicochemical & Engineering	Test and Conclusions
Extractables and hydrolytic stability (Aged sample)	The aged IOL exhibited no significant residuals, weight change, or UV spectra change. There was no significant change in the formation of bubbles, breaks, dendrites or fissures in the aged IOL.
Extractables	The total level of residual monomer extracted was less than 0.04%.
Hydrolytic Stability	Lenses were extracted in water for real-time equivalent of 9 months. No significant changes to the lenses were detected. These are acceptable hydrolytic stability results.
Photostability	The spectral transmittance through the lenses in the visible regions was slightly decreased after the 20-year equivalent UV exposure (as per ISO 11979-5) but the change was not significant. No significant degradation products were found in solution.
Nd:YAG Laser Damage	The lenses were not cytotoxic after being treated by the Nd:YAG laser.
Lens Discoloration	No evidence of discoloration was observed after 24 hour exposure to in vivo conditions.
Surface Contamination	Residuals from manufacturing processes were not detected above the detection limits of the methods used.
Optical	The MTF (modulation transfer function) values at 100 lp/mm were greater or equal to 70% of that calculated as the maximum attainable for the system of model eye with the IOL.
Visual Inspection	Following simulated injection using injector packaged with lens, lenses were inspected at 10x magnification. Lenses injected with the viscoelastic passed; lenses injected with saline failed because of broken haptics and torn optics.
Power and MTF Measurement	Power and resolution were within tolerance after injection when the viscoelastic was used and failed when only saline was used as the lubricant.
Optic Tilt Measurement	All lenses were less than 0.4 degrees after injection.
Optic Decentration Measurement	All were less than 0.3 mm decentered after injection.
Dynamic Fatigue Durability Measurement	All lenses passed after injection.
Limb Pull Strength Measurement	All were greater than 0.9 N after injection
Compression force measurement	Compression force averaged about 1.6 mN and the lenses were not significantly changed by the injection process.
Axial Displacement Measurement	Axial displacement averaged less than 0.1 mm and the lenses were not significantly changed by the injection process.
Shipping Study	All lenses were undamaged after simulated shipping.

Sterilization, Packaging, Shelf-life and Transport Stability:

The objective of the sterilization, shelf-life and transport stability studies was to establish a complete microbiological profile for the finished IOL. The IOL is packaged in a blister tray with a foil lid. The blister tray is placed in a paper pouch and the package is then terminally sterilized by moist heat. Rayner conducted sterilization revalidation, package integrity, shelf life and transport stability studies on the C-flex™ IOL in accordance with the following standards and pharmacopoeial chapters: ISO 11134 Sterilization of health care products – Requirements for validation and routine control-Industrial moist heat sterilization; ISO 11737-1:1995 Sterilization of medical devices-Microbiological methods – Part 1: Estimation of population of microorganisms on products; BS EN 556 Sterilization of medical-devices-Requirements for medical devices to be designated ‘STERILE’; United States Pharmacopoeia (USP) 29 <71> and 26 <85>; British Pharmacopoeia (BP) 2005 A and A308; the European Pharmacopoeia (EP) Chapter 5.0, Sections 2.6.1 and 2.6.14; ISO 8362-2 Annex C Injection containers for injectables and accessories – Part 2: Closures for injection vials; ASTM F 1929-8

Standard Test Method for Detecting Seal Leaks in Porous Medical Packaging by Dye Penetration; and ASTM F 1140-96 Standard Test Methods for Internal Pressurization Failure Resistance of Unrestrained Packages for Medical Applications and ISO 11979-6 Ophthalmic implants-Intraocular lenses – Part 6: Shelf-life and transport stability. The following tests were conducted to establish the microbiological profile (Table 4):

TABLE 4: Sterilization, Packaging, Shelf-Life & Transport Tests

Sterilization, Packaging, Shelf-Life & Transport	Test Conclusions
Presterilization Bioburden Test	The bioburden percent recovery was within acceptable limits.
Poststerilization Sterility Test	No microbial growth was detected.
Bacterial Endotoxin Testing	Endotoxin levels were below the agency's recommended limit for medical devices.
Bacteriostasis and Fungistasis Test	No antimicrobial inhibition demonstrated.
Seal/Closure Integrity Test	No visible penetration of dye after application of test; thus no leaks were detected in the package or seal.
Dye Penetration Test	No visible penetration of dye into the packaging.
Burst Test	Burst test results were within acceptable limits.
Peel Strength Test	Peel strength test results were within acceptable limits.
Aging Studies	Results were satisfactory to support a 12 month shelf life

The results of these tests were deemed acceptable from a microbiology standpoint. Adequate data was provided to justify a 12 month shelf-life.

Preclinical Results Conclusions:

The overall results of these tests were acceptable from a microbiology, biocompatibility, physiochemical and engineering standpoint.

X. SUMMARY OF CLINICAL STUDIES

Objectives:

The objective of the clinical studies was to assess the safety and effectiveness of the C-flex intraocular lens in the visual correction of aphakia in adults in whom a cataractous lens has been removed.

Study Design:

Primary efficacy analyses are based on Best Case Visual Acuity (BCVA) at one year (11-14 months) post-implantation as determined in the sample of procedures with no pre-existing macular degeneration or with macular degeneration developing at any time during the study, or with a clinically significant violation of the exclusion or inclusion criteria.

Safety was evaluated with regards to specific cumulative adverse event rates and persistent adverse events rates as specified in the FDA Intraocular Lens Guidelines, 1996 and ISO 11979-7 (Ophthalmic implants – Intraocular lenses – Part 7: Clinical investigations). Primary safety analyses are based on data from all enrolled patients with follow-up to at least one-year post implantation. The FDA historical control is derived from weighted averages of the data from 13 large clinical investigations of IOLs (anterior and posterior chamber) between March 1988 and June 1991. The pooled sample size for these clinical investigations was 5162 adverse events.

Study Population:

Three hundred and one (301) C-flex™ patients were enrolled (unilateral implants) in the investigation. Additional data from 182 patients implanted with the Centerflex IOL was included in the analysis. The Centerflex and C-flex™ IOLs are identical except for minor differences in edge design that were determined not to affect the evaluation of safety and effectiveness.

Analysis of the patient demographic reveal an approximately equal number of left (47.4%; 229/483) and right eyes (52.6%; 254/483), a preponderance towards the female gender (63.8%; 308/483), although there was no difference in the safety and effectiveness of the lens based on gender. Corneal status was generally normal and the pre-operative pathology was a low percentage of the total population enrolled. Cataract etiology was 100% senile. The mean age of the patients was 72.8 years. Ethnicity was 99.4% (480/483) Caucasians, 0.4% (2/483) Hispanic and 0.2% (1/483) Asian.

Patient Assessments:

The following table summarizes the study patient's visit schedule and tests performed at each visit window (see Table 5).

TABLE 5: Schedule of Visit Examinations for the C-flex™ Study

Visit Examination	Form 0	Form 1	Form 2	Form 3	Form 4	Form 5	Form 6	Form 7
	Pre-Op/ Op	1-2 days	1-2 weeks	1-2 months	4-6 months	11-14 months	2 years	3 years
Inclusion Criteria	X							
Exclusion Criteria	X							
Informed Consent	X							
Biometry	X							
Corneal Status	X							
Targeted Post Operative Refraction	X							
Cataract etiology	X							
Patient Demographics	X	X	X	X	X	X	X	X
IOP op eye/fellow eye	X	X	X	X	X	X	X	X
Medication used	X	X	X	X	X	X	X	X
UCVA op. eye/fellow eye	X	N/R	X	X	X	X	X	X
BCVA op eye/fellow eye	X	N/R	X	X	X	X	X	X
Keratometry	X	N/R	X	X	X	X	X	X
Refraction op eye/fellow eye		N/R	X	X	X	X	X	X
Complete Ophthalmic Examination (under mydriasis)	X	N/R	X	X	X	X	X	X
Dilated Fundus Exam	X	N/R	X	X	X	X	X	X
Pathology/complication/surgery	X	X	X	X	X	X	X	X
Macular Degeneration	X	N/R	X	X	X	X	X	X
Dilated IOL evaluation		N/R	X	X	X	X	X	X
Fibrosis/Elschnig's Pearls		N/R	X	X	X	X	X	X
Anterior capsular opacification		N/R	X	X	X	X	X	X
Opacities on/within IOL		N/R	X	X	X	X	X	X
IOL discoloration/tilt/decentration		N/R	X	X	X	X	X	X
Glare Questionnaire		N/R	N/R	X	X	X	X	X

N/R – not recorded

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Data Analysis and Results:

Visual Acuity – The C-flex™/Centerflex met or exceeded historical controls for posterior chamber IOLs in all areas for best corrected visual acuity (BCVA) at the 12-month post-operative examination. Best case visual acuity and overall visual acuity greater than 20/40 was 98.2% and 99.5% (see Table 6 and 7). The historical control from the “FDA grid” was 92.5% and 96.7%.

TABLE 6: The Best Case Visual Acuity (% with at least 20/40) of the C-flex™ - Centerflex IOL and the FDA Historical Control at 12-month post-operative

Years of Age	Posterior Chamber Historical Control ^B		Centerflex IOL		C-flex™ IOL		Pooled Centerflex and C-flex™ Data	
	n/N	%	n/N	%	n/N	%	n/N	%
<60	203/206	98.5	6/6	100	24/24	100	30/30	100
60-69	793/822	96.5	41/41	100	61/61	100	102/102	100
70-79	1338/1372	97.5	71/72	98.6	116/117	99.1	187/189	98.9
≥80	601/634	94.8	17/17	100	36/36	100	53/53	100
Overall	2935/3034	96.7	135/136	99.4	237/238	99.6	372/374	99.5

Notes:

^A: Best Case Visual Acuity is summarized for the Primary Efficacy Sample that excludes patients with preoperative ocular pathologies and those with macular degeneration developing at any time during the study.

^B: Annex B – FDA grid of historical controls: BCVA at one year, FDA Intraocular Lens Guidelines, 1999.

TABLE 7: The Overall Visual Acuity (% with at least 20/40) of the C-flex™ - Centerflex IOL and the FDA Historical Control at 11-14 months post-operative

Years of Age	Posterior Chamber Historical Control ^B		Centerflex IOL		C-flex™ IOL		Pooled Centerflex and C-flex™ Data	
	n/N	%	n/N	%	n/N	%	n/N	%
<60	230/235	95.7	6/6	100	24/24	100	30/30	100
60-69	968/1012	93.4	42/42	100	66/66	100	108/108	100
70-79	1793/1920	86.5	83/84	98.8	139/140	99.3	222/224	99.1
≥80	901/1042	92.5	30/34	88.2	51/53	96.2	81/87	93.1
Overall	3893/4210	92.5	161/166	97.0	280/283	98.9	441/449	98.2

Notes:

^A: Overall visual acuity is summarized for All Enrolled Procedures sample that only excludes second implants for any patient implanted bilaterally.

^B: Annex B – FDA grid of historical controls: BCVA at one year, FDA Intraocular Lens Guidelines, 1999.

Patient Satisfaction Survey – A modification of the patient satisfaction questionnaire used by Tester, Pace, Samore and Olson (2000) to assess patient reports of dysphotopsia and patient satisfaction with the C-flex™ IOL was added to the clinical follow-up assessments for patients implanted with the C-flex™. The Centerflex study protocol did not include this assessment. For this questionnaire, patients were asked to rate the severity of symptoms present in their operative and fellow eye. Analyses revealed substantial differences in results between patients in whom their fellow eye had a prior implant. These prior implants were not the C-flex™ lens and were present prior to the patient’s enrollment into this study.

Of the 301 C-flex™ implanted patients, 104 patients (34.6%) were previously implanted in their fellow eye and 197 patients (64.5%) did not have a previous implant in their fellow eye. To determine if a comparison between the C-flex™ operative eye and fellow eye depended on the fellow eye's implant status, three analyses were conducted:

1. All patients regardless of fellow eye implant status
2. Patients with an implant in the fellow eye
3. Patients with no implant in the fellow eye

Satisfaction with corrected vision was larger for the C-flex™ treated eye compared to the fellow eye, a finding driven mostly by the patient subset with no fellow eye implant. Overall patient satisfaction was 89% (268/301).

XI. CONCLUSIONS DRAWN FROM THE STUDIES

RISK BENEFIT ANALYSIS

The Rayner C-flex™ intraocular lens is indicated for primary implantation for the visual correction of aphakia in adults in whom a cataractous lens has been removed by phacoemulsification. The lens is intended to be placed in the capsular bag. The risks associated with eye surgery and this lens included: retinal detachment, endophthalmitis, raised intraocular pressure, uveitis and corneal decompensation. It is reasonable to conclude that the benefits of use of the lens for the target population outweigh the risk of illness or injury when used as indicated in accordance with the directions for use.

SAFETY

The pooled C-flex™ and Centerflex accumulative and persistent adverse event rates at 12-months are lower than the FDA historical control grid in all areas except persistent macular edema, persistent corneal edema and cumulative papillary block. These rates were higher than the grid rate but the differences were not statistically significant.

EFFECTIVENESS

The C-flex™ met or exceeded the effectiveness criteria in all areas for visual acuity at the 12-month post-operative examination.

XII. PANEL RECOMMENDATION

In accordance with the provisions of section 515(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA was not referred to the Ophthalmic Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

XIII. CDRH DECISION

CDRH issued an approval order to Rayner Surgical on May 3, 2007. The applicant's manufacturing facility was inspected and was found to be in compliance with the Quality System Regulation (21 CFR 820).

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XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions and Adverse Events in the labeling.

XV. REFERENCES

Tester R, Pace NL, Samore M, Olson RJ (2000) Dysphotopsia in phakic and pseudophakic patients: Incidence and relation to intraocular lens type. Journal of Cataract Refract Surgery 26:810-816.