SUMMARY OF SAFETY AND EFFECTIVENESS

I. General Information

A. Device Generic Name: Intraocular Fluid (Hydroxypropyl methylcellulose)

B. Device Trade Name: CELLUGEL®
Ophthalmic Viscosurgical Device

C. Applicant's Name/Address: ALCON LABORATORIES, INC.
6201 South Freeway
Fort Worth, Texas 76134

D. Premarket Approval (PMA) Application Number: P990023

E. Date of Panel Recommendation: N/A

F. Dates of Good Manufacturing Practice (GMP) Inspection:

07/02/1999

Manufacturing Site: Alcon-Couvreur SA
Rijksweg 14
B-2870 Puurs, Belgium

G. Date of Notice of Approval to the Applicant: FEB 2 4 2000

II. Indications for Use

CELLUGEL® is indicated for use during surgery in the anterior segment of the eye. CELLUGEL® is designed to create and maintain space, to protect the corneal endothelium and other intraocular tissues and to manipulate tissues during surgery. CELLUGEL® may also be used to coat intraocular lenses and instruments during cataract extraction and intraocular lens insertion.

III. Contraindications

At present, there are no known contraindications to the use of CELLUGEL® ophthalmic viscosurgical device (OVD) when used as recommended.

IV. Precautions

Precautions are limited to those normally associated with the surgical procedure being performed. As with all ophthalmic viscosurgical devices, a transient rise in intraocular pressure (IOP) in the early postoperative period has been reported in some cases. It is therefore recommended that CELLUGEL® be removed by the anterior chamber by thorough irrigation and/or aspiration at the end of surgery to minimize post-operative IOP increases. IOP should be monitored postsurgically and appropriate therapy instituted if significant increases occur. In addition to the above, the following precautions should be observed:

- Do not reuse cannulas.
- Use only if material is clear.
- Avoid trapping air bubbles within CELLUGEL® before injection.
- **This product contains dry natural rubber.**

V. Device Description

CELLUGEL® Ophthalmic Viscosurgical Device is a sterile, nonpyrogenic, noninflammatory viscoelastic solution of highly purified non-proteinaceous 2% hydroxypropyl methylcellulose (HPMC) with an average molecular weight of 300,000 daltons dissolved in an isotonic, physiological buffer.

Each milliliter of CELLUGEL® contains 2% HPMC, 0.525% sodium chloride, 0.075% potassium chloride, 0.048% calcium chloride, 0.03% magnesium chloride, 0.39% sodium acetate, 0.17% sodium citrate, and water for injection q.s.

The osmolarity of CELLUGEL® is 315 ± 35 mOsM/kg, the pH 7.2 ± 0.4, and the viscosity 30,000 ± 10,000 cps (at 0.2 sec^{-1}, 25°C).

VI. Alternate Practices and Procedures

Prior to ophthalmic viscosurgical devices, air, gases, or irrigating solutions were utilized as anterior chamber maintainers and surgical aids. Numerous other ophthalmic viscosurgical devices exist today and have been on the market since 1983.

VII. Marketing History

CELLUGEL® has been marketed and sold internationally between the years 1991-1996 by Vision Biology, Inc., (VBI) in countries whose Ministries of Health have approved the sale. Alcon Laboratories, Inc. purchased the device from VBI in 1996. CELLUGEL® has been CE Marked by Alcon Laboratories, Inc., under the Medical Device Directive in February 1999. Product has been marketed in the EU bearing the CE Mark beginning in May 1999. More than 130,000 syringes have been marketed since

1991. CELLUGEL® has not been removed from the market in any countries for reasons related to safety or effectiveness.

Table 1

VBI Approvals to Market CELLUGEL

COUNTRY	APPROVAL DATE
Sweden	8/26/88
Hong Kong	8/26/88
The Netherlands	8/26/88
Chile	8/26/88
Switzerland	8/26/88
Portugal	8/26/88
Peru	9/22/88
Denmark	1989
Andorra	1989

VIII. Potential Adverse Effects of the Device on Health

In Clinical Studies C-96-48 and C-98-22, adverse events were reported in patients receiving CELLUGEL® and in patients receiving the control substance (a commercially available sodium hyaluronate viscoelastic that has been on the market for at least five years). In the two clinical studies, a total of 348 patients received CELLUGEL® and a total of 344 patients received the control OVD. Adverse events occurring at a frequency $\geq 1\%$ are presented in Table 2. Adverse events occurring at a rate of $< 1\%$ are listed in the text following Table 2.

No patients were discontinued from C-98-22 and no patients were discontinued from C-96-48 due to a device-related adverse event.

Table 2

Ophthalmological Adverse Events Occurring at a Rate ≥ 1%

Observation	OVD	C-96-48[a]		C-98-22[b]	
		N	%	N	%
External Slit-lamp Observations[c]	Cellugel	110	55.3	3	2.0
	Control	87	44.2	1	0.7
Posterior Capsule Haze	Cellugel	94	47.2	13	8.7
	Control	87	44.2	13	8.8
Intraocular Slit-lamp Observations[d]	Cellugel	70	35.2		
	Control	80	40.8		
Macular Degeneration	Cellugel	34	17.1	17	11.4
	Control	34	17.3	20	13.6
Lid Observations[e]	Cellugel	34	17.1	2	1.3
	Control	35	17.9	1	0.7
Posterior Segment Observations[f]	Cellugel	26	13.1	2	1.3
	Control	24	12.2	4	2.7
Nd: YAG Posterior Capsulotomy	Cellugel	20	10.1		
	Control	11	5.6		
Dry Eye[g]	Cellugel	11	5.5	5	3.4
	Control	8	4.1	2	1.4
Iris Atrophy	Cellugel	10	5.0		
	Control	6	3.1		
Macular Edema	Cellugel	9	4.5	1	0.7
	Control	8	4.1	3	2.0
Secondary Glaucoma	Cellugel	6	3.0		
	Control	5	2.6		
Hyphema	Cellugel	5	2.5		
	Control	2	1.0		
IOL Repositioning or Exchange	Cellugel	4	2.0		
	Control	2	1.0		
IOP >40 mmHg	Cellugel	3	1.5	6	4.0
	Control	2	1.0	8	5.4
Vitreous in the Anterior Chamber	Cellugel	2	1.0	1	0.7
	Control	4	2.0		
Endothelial Damage	Cellugel	2	1.0	3	2.0
	Control			3	2.0
Cells (AC Cells ≥ grade 3)	Cellugel			2	1.3
	Control				

Corneal Edema (≥ grade 3)	Cellugel			1	0.7
	Control			2	1.4
Nd: YAG Anterior Synechiolysis	Cellugel	2	1.0		
	Control	1	0.5		
Retina Procedure	Cellugel	2	1.0		
	Control	4	2.0		
Lid Procedure	Cellugel	2	1.0		
	Control	3	1.5		
Conjunctival Cyst/Filament Removal	Cellugel	2	1.0		
	Control				
Subjective Complaints[h]	Cellugel			6	4.0
	Control			7	4.8

[a] Clinical Study C-96-48 - Cellugel (N=199); Control (N=196 with one patient not returning for follow-up).
[b] Clinical Study C-98-22 – Cellugel (N=149); Control (N=147).
[c] Includes conjunctival injection, conjunctival hemorrhage, superficial punctate, keratitis, ecchymosis, arcus senilus, conjunctival chemosis, pinguecula, subconjunctival hemorrhage, hyperemia, conjunctival gape and corneal abrasion.
[d] Includes corneal folds, Descemets folds, endothelial folds, striae, guttata, trace endothelial changes, cortical remnants, endothelial pigment, endothelial debris and microcystic corneal edema.
[e] Includes blepharitis, dermatochalasis, lid edema, ptosis, collarettes, and chalazion.
[f] Includes posterior capsular folds/wrinkling, retinal pigment epithelial changes and posterior vitreous detachment.
[g] Includes poor tear film.
[h] Includes foreign body sensation, ocular pain and diplopia.

Other ophthalmic adverse events considered unrelated to the use of the OVD and occurring among patients at a rate of <1% included: eye discomfort, IOL membrane, puritus, retinal hemorrhage, blurred vision, IOL repositioning with vitrectomy, removal of residual lens cortex and foreign body removal.

IX. Summary of Preclinical Studies

An extensive battery of toxicity studies have been performed with CELLUGEL Ophthalmic Viscosurgical Device to evaluate the safety of this material as an adjunctive device for use during intraocular surgery.

Toxicology testing was conducted in accordance with ISO 10993 and the draft ISO Viscoelastic standard (ISO/WD 15798.2). All tests were conducted in compliance with Good Laboratory Practices (21 CFR 58) regulations.

No evidence of cytotoxicity, hemolysis, sensitization, mutagenic potential, or ocular irritation was found in any test performed on CELLUGEL. The results of these studies are summarized:

Table 3

Toxicological Studies

Study Type	Study Title	Species	Dose	# Animals Per Dose	Outcome
Cytotoxicity	*In vitro* Cytotoxicity Study (Agar Overlay Method) in the L929 Mouse Fibroblast Cell Line	L929 Mouse Fibroblast Cell	0.1 mL	N/A	Noncytotoxic
	In vitro Cytotoxicity Study (MEM Elution) in the L929 Mouse Fibroblast Cell Line	L929 Mouse Fibroblast Cell	25% Test solution	N/A	Noncytotoxic
Mutagenicity	Ames Mutagenicity	*Salmonella typhimurium*	0.1 mL	N/A	No mutagenic effects
	E. coli Plate Incorporation Mutagenicity Assay	*E. coli*	100 mg/mL	N/A	No mutagenic effects
Single Dose Toxicity	Acute Intraperito-neal Toxicity in Mice	Mouse (non-Swiss Albino CFI derived)	6 mL/kg	10	6 ml/kg, not a toxic dose
	Acute Oral Toxicity in the Rat	Rat (Sprague Dawley)	5 g/kg	10	5 g/kg, not a toxic dose
Immuno-genicity	Dermal Sensitization Study (Maximi-zation Method) in Guinea Pig	Guinea pig	Induction 0.1 ml intra-dermal Induction	10	No immuno-genic effects

Study Type	Study Title	Species	Dose	# Animals Per Dose	Outcome
			and challenge 0.3 mL topical		
	Systemic Antigenicity in the Guinea Pig	Guinea pig	10 mL/kg of a 25% test solution	6	No immuno-genic effects
Hemolysis	*In vitro* Hemolysis Study (direct contact)	N/A	0.2 mL blood added to a 20% test solution	N/A	Nonhemo-lytic

Study Type	Study Title	Species	Dose	# Animals Per Dose	Outcome
Local Tolerance	Primary Skin Irritation Test in the rabbit	Rabbits (NZW)	0.5 mL	6	Nonirritating
	Intraocular Irritation Study In the Rabbit (with Tonometry and Specular Photography)	Rabbits (NZW)	0.15 mL anterior chamber	6	Nonirritating
	Intraocular Irritation Evaluation of CELLUGEL in rabbits	Rabbits (NZW)	0.1 mL anterior chamber injection	8	Nonirritating
	Intraocular Irritation Evaluation of CELLUGEL in Primates	Cynomo-logous monkey	0.1 mL anterior chamber injection	4	Nonirritating
	Intraocular Irritation Evaluation of CELLUGEL in Rabbits	Rabbits (NZW)	0.1 mL posterior chamber injection	8	Nonirritating
	IOP and Ocular Irritation Evaluation	Rabbits (NZW)	0.1 mL anterior chamber injection	16 eyes	Nonirritating; No IOP raising potential

X. Summary of Clinical Studies

A. Overview of Clinical Investigations

A total of five clinical studies were conducted using CELLUGEL® during the period of 1989 to 1999. Of these, two studies are presented in key support of safety and efficacy (C-98-22 and C-96-48). The remaining three studies were conducted outside the United States by Vision Biology (VBI) and are supportive of a safe and effective product (C-99-23, C-99-24, C-99-25).

The two key studies presented in support of safety and efficacy are Protocol C-96-48, conducted by Vision Biology, Inc., and Protocol C-98-22, conducted by

Alcon Laboratories, Inc. Clinical Protocol C-96-48 was a controlled, randomized, multicenter study among 396 patients which was designed to demonstrate that CELLUGEL® was: 1) equally effective to the control in its ability to protect corneal endothelial cells and maintain the anterior chamber during surgery and 2) equivalent to the control in its effects on postoperative IOP. Based on the results from this study, Clinical Protocol C-98-22 was designed to specifically address IOP elevation during the expected peak period, 6 hours postsurgery, since this data had not been collected during the previous C-96-48 clinical trial.

In order to obtain a more accurate representation of CELLUGEL®'s effect on IOP during the early postoperative period, no prophylactic medications were administered to patients in the C-98-22 study prior to the 6-hour IOP measurement.

The following table gives an overview of the two clinical studies that were considered key to support safety and effectiveness. These two studies compared CELLUGEL® to a marketed sodium hyaluronate viscosurgical device.

Table 4

CELLUGEL Clinical Studies

Protocol Number	Countries	No. of Sites	Study Duration	Patient Follow-up	CELLUGEL Subjects	Control Subjects
C-96-48	United States	9	1/93-6/95	6 Months	199	197
C-98-22	United States, Canada	9	7/98-2/99	21 Days	149	147
TOTAL Key Studies[a]	-	**18**	**1/93-2/99**	-	**348**	**344**

B. Patient Population and Accountability

1. Demographics

a. Clinical Study C-98-22

No statistically significant differences between CELLUGEL® and the control were found for gender, race, age category and iris color. The treatment groups were similar for mean age for all patients enrolled.

b. Clinical Study C-96-48

No statistically significant differences between CELLUGEL® and the control were found for gender, age category and mean age among all patients enrolled. Information on patient race was not collected in this study. However, all patients who were eligible for the study were included.

Table 5

Key Studies C-98-22/C-96-48 Patient Demographics

Key Studies	Treatment	Enrolled	Male	Female	Mean Age
C-98-22	CELLUGEL	149	53	96	71.7
	Control	147	51	96	73.5
	Total	296	104	192	72.6
C-96-48	CELLUGEL	199	87	112	70.8
	Control	197	80	117	72.1
	Total	396	167	229	71.4
TOTAL		692	271	421	71.9

2. Inclusion Criteria

Clinical Studies C-98-22 and C-96-48

The total study population included 692 patients (male or female), of any race, who were scheduled for the removal of a cataract with the implantation of an intraocular lens. In addition, Clinical Study C-96-48 allowed the inclusion of aphakic patients requiring secondary IOL implantation (1 patient).

3. Exclusion Criteria

a. Clinical Study C-98-22

Patients were excluded from this study if they had other planned surgical procedures or the planned use of an investigational intraocular lens. They were also excluded if they had glaucoma in either eye or ocular hypertension (IOP > 21 mmHg) in the operative eye. Patients with proliferative diabetic retinopathy or uncontrolled diabetes mellitus were excluded from this study, as well as patients with any abnormality

that prevented reliable Goldmann applanation tonometry. In addition, patients with lens pseudoexfoliation syndrome, previous ocular trauma to the operative eye, a history of chronic or recurrent inflammatory eye disease or a congenital ocular abnormality were excluded. Patients were also excluded if they had iris atrophy, significant endothelial guttata or corneal dystrophy.

b. Clinical Study C-96-48

Patients were excluded from participation if they had acute ocular infection or inflammation, chronic uveitis, iritis, iridocyclitis or rubeosis iritis, uncontrolled glaucoma, aniridia, proliferative diabetic retinopathy, iris atrophy, or systemic disease with ocular manifestations.

4. Patient Accountability

All patients who received the randomly assigned study device were evaluable for safety (Intent to Treat data set). A subset of the entire population was also used for some key analyses; this is the Per Protocol data set. The Per Protocol data set included those patients who met inclusion/exclusion criteria and complied with the protocol. In keeping with current standards for the analysis of clinical data, where a patient's fellow eye was enrolled into the study, the patient's second eye was removed from the Per Protocol data set (but remained in the Intent to Treat data set). In addition, a few patients experiencing significant vitreous loss during surgery were excluded from the Per Protocol data set (prior to revealing the treatment codes) as vitreous in the anterior chamber can elevate intraocular pressure and may confound the data. After breaking treatment code, it was observed that an equal number of patients in the CELLUGEL® and the control groups had been excluded.

In general for equivalence hypotheses, the Per Protocol analysis is a more conservative approach. Therefore, primarily Per Protocol analyses have been presented, where equivalence arguments have been made. However, in both studies, the Intent to Treat and Per Protocol data sets support the same conclusions.

Table 6

Key Studies C-98-22/C-96-48 Patient Accountability

Key Studies	Treatment	All Patients (Intent to Treat)	Per Protocol Patients	Patients who did not complete the study
C-98-22	CELLUGEL	149	140	0
	Control	147	140	0
	Subtotal	**296**	**280**	**0**
C-96-48	CELLUGEL	199	169	20
	Control	197	164	25
	Subtotal	**396**	**333**	**45**
TOTAL		**692**	**613**	**45**

a. Patients who did not complete the Study

1) Clinical Study C-98-22

All patients completed this 3-week study.

2) Clinical Study C-96-48

Forty-five patients did not complete the course of this 6-month study for the following reasons (Table 7). This attrition rate is not unusual for a study of this size and duration. The numbers of patients who did not complete the study were similar for both CELLUGEL® and the control groups. Although intercurrent illnesses, including those leading to death, occurred in this study, adverse events were not collected for these patients.

Table 7

Reasons for Not Completing the Study (C-96-48)

Reason	CELLUGEL		Control	
	No. of Patients	Percent	No. of Patients	Percent
Lost to follow-up	11	5.5%	4	2.0%
Noncompliant with protocol	7	3.5%	10	5.0%
Patient requested withdrawal	0	0%	6	3.0%
Illness	1	0.5%	0	0%
Died	1	0.5%	5	2.5%
Total Patients in Study (N)	**199**	**10.0%**	**197**	**12.5%**

C. Efficacy Results

1. Endothelial Cell Density

a. Clinical Study C-98-22

No endothelial cell density data were captured in this 21-day IOP study.

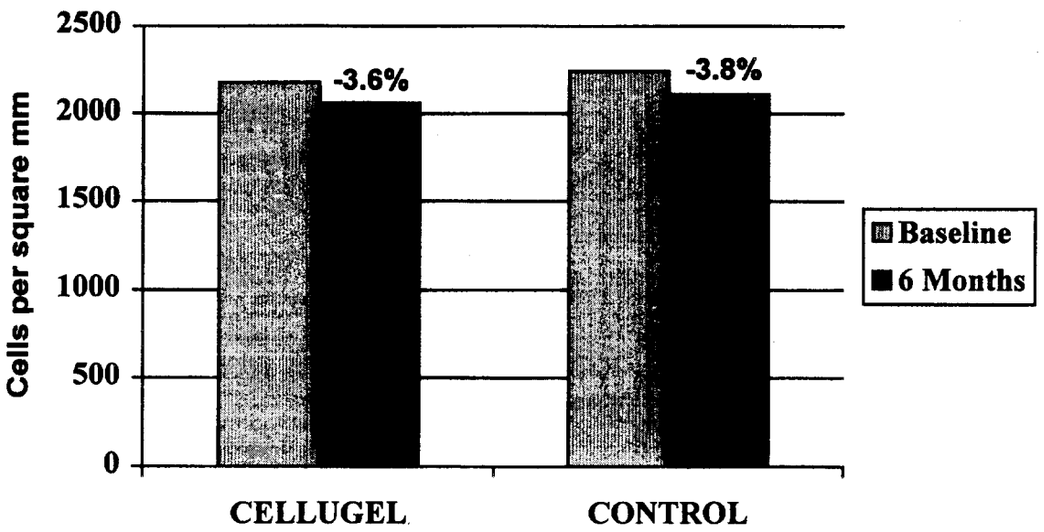
b. Clinical Study C-96-48

CELLUGEL® was similar to the control in its ability to protect corneal endothelial cells during cataract/IOL surgery.

Endothelial cell densities were measured by specular microscopy prior to and, again, 6 months following surgery in the C-96-48 study. Endothelial cell density losses were similar for both CELLUGEL® and the control in both the Per Protocol and Intent to Treat analyses. The mean percent change in cell density from baseline to 6 months was not statistically different between groups.

Figure 1

Change in Endothelial Cell Density (cells/mm^2) at 6 Months (Per Protocol)



In the Per Protocol analyses, mean endothelial cell losses, measured at 6 months, were 3.6% and 3.8%, respectively when CELLUGEL (n=138) and control (n=130) were used to maintain anterior and posterior chamber spaces during surgery. At 6 months, CELLUGEL patients lost an average of 119 cells/mm^2, while control patients had lost an average of 135 cells/mm^2.

In the Intent to Treat analyses, endothelial cell loss was slightly higher in both groups although, again, the difference between groups was not statistically significantly different (CELLUGEL, 4.1%, n=152; control, 4.4%, n=146). At 6 months, CELLUGEL patients, on average, had lost an average of 127 cells/mm^2, while control patients had lost an average of 151 cells/mm^2.

The calculation of mean cell density change from baseline was based upon patient eyes that had a density measurement at both the preoperative baseline visit and the six-month postoperative visit. Patients who discontinued from the study and patients who were missing either a baseline or a 6-month endothelial cell density measurement were therefore excluded from analysis of the mean change from baseline.

2. Anterior Chamber Maintenance

Efficacy was also evaluated by the viscoelastic's ability to maintain a deep anterior chamber depth during surgery. CELLUGEL® was equal to or better than the control in maintaining the anterior chamber depth during surgery as reported by the investigators.

a. Clinical Study C-98-22

The viscoelastic's ability to maintain anterior chamber depth was a subjective evaluation, which was reported by the surgeon. In the Per Protocol data set, CELLUGEL® maintained the anterior chamber depth in a statistically significantly larger proportion of patients than did the control ($p < 0.001$). During anterior capsulotomy, CELLUGEL® maintained the anterior chamber depth in 97.9% of patients compared to 78.6% of the control patients. Thirty (21.4%) shallow anterior chamber depths were reported in the control patients compared to 3 (2.1%) CELLUGEL® patients.

During phacoemulsification, CELLUGEL® maintained the anterior chamber depth in a statistically significantly larger proportion of patients than did the control ($p=0.005$). The anterior chamber was maintained in 99% of the CELLUGEL® patients compared to 92% of the control patients.

During IOL insertion, CELLUGEL®and the control performed similarly (97.1 % Cellugel vs. 92.1 % Control) at maintaining the anterior chamber depth ($p=0.109$).

b. Clinical Study C-96-48

In the Per Protocol data set, the viscoelastic maintained a normal anterior chamber depth in 99.4% of patient eyes in both CELLUGEL® and the control. Only one patient in each group was reported to develop a shallow anterior chamber depth during surgery.

D. Safety Results

1. Intraocular Pressure

a. Mean Intraocular Pressure

1. Clinical Study C-98-22

Clinical Study C-98-22 was designed to evaluate the postoperative IOP profile of CELLUGEL® compared to the control. Patients received either CELLUGEL® or the control during cataract surgery (phacoemulsification) with posterior chamber intraocular lens implantation. No prophylactic IOP-reducing medications were administered at surgery. Immediately following the 6-hour IOP measurement, physicians were allowed to administer IOP-reducing therapy if the IOP was ≥ 30 mmHg. At all subsequent visits, investigators were allowed to prescribe IOP-reducing therapy as needed. IOP-reducing therapies were administered to a similar number of patients in the CELLUGEL® (n = 24) and the control (n = 22) groups. With the exception of one control patient, all IOP-reducing therapies were discontinued the day following surgery.

CELLUGEL® and the control were statistically equivalent in their effects on postoperative intraocular pressure. This conclusion was based on a statistical test of noninferiority. At each visit, the upper 95% confidence limit for the mean difference in IOP between CELLUGEL® and the control was less than 3.5 mmHg for both the Per Protocol and Intent-to-Treat data sets. Table 8 presents the mean IOPs at each visit for the Per Protocol data set.

Table 8

Mean IOP (mmHg) and Mean IOP Change From Baseline (mmHg) by Visit for Per Protocol (C-98-22)

Treatment		Visit				
		Baseline	6 Hour	24 Hour	Day 7	Day 21
CELLUGEL	Mean	15.80	22.99	19.29	15.54	15.52
	Std	2.57	8.35	4.91	3.34	3.09
	N	140	139	140	140	140
	Min	9	6	10	6	8
	Max	21	54	36	24	24
	Mean Chg.	-	7.22	3.49	-0.26	-0.28
Control	Mean	15.94	21.63	19.58	15.38	14.96
	Std	2.65	7.91	5.93	3.11	3.14
	N	140	139	140	138	140
	Min	10	2	5	7	8
	Max	21	50	40	24	28
	Mean Chg.	-	5.71	3.64	-0.60	-0.98
Difference (CELLUGEL-Control)[b]		-0.14	1.36	-0.29	0.16	0.56
Upper 95% Confidence Limit[ab]		0.47	2.43	0.77	1.23	1.62

[a] A one-sided 95% confidence interval was constructed. CELLUGEL® is noninferior to the control if the upper 95% confidence limit is less than 3.5 mmHg.

[b] Based upon the difference in Least Squares (LS) Means. The LSMeans may differ slightly from the Arithmetic Means.

2) Clinical Study C-96-48

The postoperative mean IOP results from Study C-98-22 are supported by the mean IOP data from a subpopulation in the C-96-48 study that was similar to the population of C-98-22 (non-glaucoma patients without prophylactic IOP therapy at surgery). There were no statistical differences between the mean IOPs at all visits for these patients (Table 9). [T-test of the largest difference (0.6 mmHg at Day 90) yields $p > 0.05$.]

Table 9

Mean IOP (mmHg) in Nonglaucoma Patients Without Prophylactic IOP Therapy for Per Protocol (C-96-48)

Treatment		Visit					
		Baseline	24 Hour	Day 7	Day 30	Day 90	Day 180
CELLUGEL	Mean	15.8	19.0	14.7	14.7	13.9	14.4
	Std	2.4	6.5	2.7	2.8	2.5	2.9
	N	63	62	61	62	49	59
	Min	10	7	9	7	8	9
	Max	21	38	19	23	18	24
Control	Mean	16.0	18.7	14.6	15.0	14.5	14.2
	Std	2.9	6.6	2.7	2.7	2.7	2.3
	N	70	70	69	65	56	60
	Min	10	8	9	8	10	9
	Max	28	40	21	22	21	19

b. Frequency of IOPs ≥ 30 mmHg

1) Clinical Study C-98-22

With this study design, where prophylactic medications are prohibited, it can be useful to evaluate the frequency of patients presenting in the early postoperative period with IOPs ≥ 30 mmHg.

Table 10

Frequency of Patients With IOP ≥ 30 mm Hg for Per Protocol (C-98-22)

	Treatment		Visit				
			Baseline	6 Hour	24 Hour	Day 7	Day 21
IOP ≥ 30 mmHg	CELLUGEL	%	0.0	15.8%	4.3%	0.0	0.0
		N	0	22	6	0	0
		Total	140	139	140	140	140
	Control	%	0.0	12.2%	8.6%	0.0	0.0
		N	0	17	12	0	0
		Total	140	139	140	138	140

The incidence of IOPs greater than or equal to 30 mmHg were evaluated in the C-98-22 IOP study. At 6 hours following surgery, 15.8% of the CELLUGEL® patients (n = 22) and 12.2% of the control patients

(n = 17) had an IOP ≥ 30 mmHg. By 24 hours, a smaller percentage of CELLUGEL® patients had IOP ≥ 30 mmHg than the control; 4.3% of the CELLUGEL® (n = 6) and 8.6% of the control (n = 12) patients had an IOP ≥ 30 mmHg. These differences are not statistically significant (Fisher's Exact Test yields: p=0.49 at 6 hours and p=0.22 at 24 hours). By the Day 7 examination, there were no IOP elevations ≥ 30 mmHg.

2) Clinical Study C-96-48

In the C-96-48 Per Protocol group, the incidences of early IOP elevations ≥ 30 mmHg were similar to C-98-22. At 24 hours, 11 CELLUGEL® patients (6.5%) and 11 control patients (6.7%) had an IOP ≥ 30 mmHg. In the subgroup of Per Protocol patients without glaucoma who did not receive prophylactic IOP-reducing medication at surgery, the incidences of IOPs ≥ 30 mmHg were 9.7% in CELLUGEL® patients (n = 6) and 8.6% in the control patients (n = 6) at 24 hours.

2. Device Failures

There were no device failures or replacements reported during these clinical trials using CELLUGEL®.

XI. Conclusions Drawn from Studies

Results from these clinical studies support the following conclusions:

- CELLUGEL® is clinically equivalent to a marketed control OVD in protecting corneal endothelium cells and maintaining the anterior chamber depth during cataract surgery and IOL insertion.
- CELLUGEL® is clinically equivalent to a marketed control OVD in its effects on postoperative intraocular pressure.
- CELLUGEL® is reasonably safe and effective among patients undergoing cataract surgery and IOL implantation.

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 Devices 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

FDA issued an approval order on FEB 24 2000. The applicant's manufacturing facility was inspected on July 2, 1999 and was found to be in compliance with the device Good Manufacturing Practice regulations.