

SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name: 3% Sodium Hyaluronate Ophthalmic Viscosurgical Device

Device Trade Name: Healon® EndoCoat Ophthalmic Viscosurgical Device

Applicant's Name and Address: Abbott Medical Optics Inc.
1700 E. St. Andrew Place
Santa Ana, CA 92705

Premarket Approval Application (PMA): P110007

Date of Panel Recommendation: None

Date of FDA Notice of Approval: July 2, 2012

Expedited: Not applicable

II. INDICATIONS FOR USE

Healon® EndoCoat Ophthalmic Viscosurgical Device (OVD) is an ophthalmic viscoelastic containing 3% sodium hyaluronate indicated for use as a surgical aid in patients undergoing ophthalmic anterior segment surgical procedures including:

- Cataract surgery with an intraocular lens
- Cataract surgery without an intraocular lens
- Secondary intraocular lens implantation

Healon® EndoCoat OVD maintains a deep chamber during anterior segment surgery, enhances visualization during the surgical procedure and protects the corneal endothelium and other ocular tissue. The viscoelasticity of the solution maintains the normal position of the vitreous face and prevents formation of a flat chamber during surgery. It may also be used to coat intraocular lenses and insertion instruments prior to intraocular lens implantation.

III. CONTRAINDICATIONS

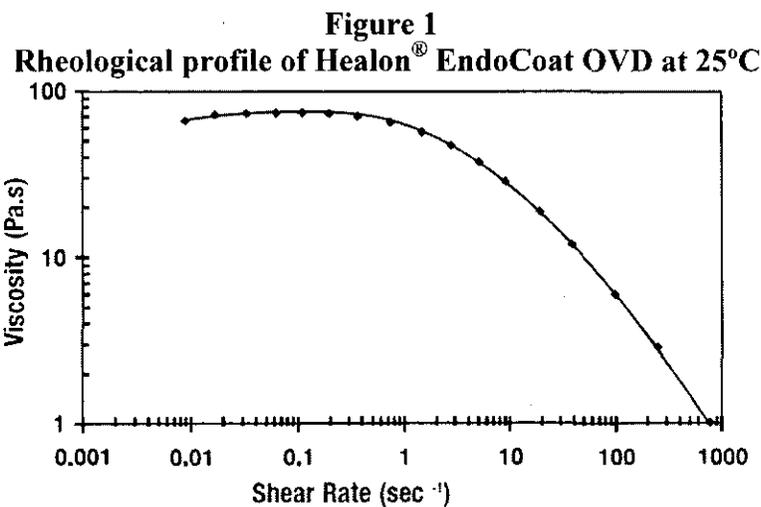
At present, there are no contraindications to the use of Healon® EndoCoat OVD when used as recommended.

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Healon® EndoCoat OVD labeling.

V. DEVICE DESCRIPTION

Healon® EndoCoat OVD is a sterile, single-use non-pyrogenic solution of purified sodium hyaluronate (NaHA) with rheologically dispersive properties. NaHA is a linear polysaccharide composed of repeating disaccharides of sodium glucuronate and N-acetylglucosamine. Healon® EndoCoat OVD contains 3 wt% (30mg/ml) NaHA that is obtained from a bacterial fermentation source and has an average molecular weight (MW) of approximately 800,000 Daltons (Da), an osmolality of approximately 320 milliosmoles/kg, a viscosity of approximately 50,000 centipoise, and a pH of 7.2 when dissolved in physiological buffered salt solution. Figure 1 shows the rheological profile for the OVD.



Each milliliter of Healon® EndoCoat OVD contains NaHA (30.00 mg), sodium chloride (5.00 mg), potassium chloride (0.56 mg), calcium chloride (0.36 mg), magnesium chloride (0.22 mg), sodium acetate (2.92 mg), sodium citrate (1.28 mg), sodium phosphate monobasic monohydrate (0.06 mg), sodium phosphate dibasic heptahydrate (0.42 mg), and water for injection q.s. It is available in two fill-volume configurations:

Model Number	Syringe Delivery System	Target fill sizes	Cannula Size
VT585U	1.0mL syringe	0.85mL	25 gauge
VT465	2.25mL syringe	0.65mL	23 gauge

The Healon® EndoCoat OVD is provided single-use and is packaged in a borosilicate glass syringe. It is supplied with a cannula for delivery of the solution to the anterior chamber of the eye. The delivery systems consist of six components:

- Syringe barrel
- Tip cap

- Backstop
- Plunger stopper
- Plunger rod
- Cannula with sheath
- Cannula guard (1.0 mL configuration only)

The secondary packaging consists of a thermoformed tray with a lid and a protective cardboard unit box. The OVD is aseptically filled prior to terminal sterilization by ethylene oxide (EO).

VI. ALTERNATIVE PRACTICES AND PROCEDURES

Other OVDs of varying formulations and properties are available. Each alternative has its own advantages and disadvantages. A surgeon should fully consider these alternatives before selecting the OVD with the properties that best meet the individual patient's and surgeon's needs for a particular surgical case.

VII. MARKETING HISTORY

Healon[®] EndoCoat OVD is available outside of the United States (OUS) and has been distributed OUS in more than 40 countries, in some since 2004. Leading markets include the European Union, Brazil, and Canada, as well as some non-regulated countries. As of March 2012, over 850,000 Healon[®] EndoCoat units (marketed as Vitrax II or Healon[®] EndoCoat) have been sold OUS. There was a voluntary recall of all lots of Vitrax II in October 2009 due to the pH of the product in some syringes being out of specification. The causative agent was determined to be EO penetration during secondary sterilization. This issue was corrected.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device that have been identified in the product labeling. The most serious and most common potential adverse effects include the following: increased intraocular pressure, secondary glaucoma, postoperative inflammatory reactions (iritis, hypopyon, endophthalmitis), corneal edema, and corneal decompensation. For the specific adverse events (AEs) that occurred in the clinical study of Healon[®] EndoCoat OVD, and the incidence rates of these events, please see Section X.D of this document.

IX. SUMMARY OF PRECLINICAL STUDIES

A. Laboratory Studies

1. Biocompatibility

Biocompatibility studies were performed on finished Healon[®] EndoCoat OVD, or a similar 3% Sodium Hyaluronate product, and the delivery system for the Healon[®] EndoCoat OVD. The biocompatibility is performed in accordance with International Organization for Standardization (ISO) 10993-1:2003, Biological

Evaluation of Medical Devices - Part 1 Evaluation and Testing. These studies were conducted in conformance with the Good Laboratory Practices (GLP) Regulation (21 CFR Part 58). **Table 1** shows the *in vitro* biocompatibility studies performed for the delivery system components.

Table 1
***In Vitro* Biocompatibility Tests for Delivery System**

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity (Agar diffusion)	Evaluate biocompatibility	Is not cytotoxic	No cell lyses or toxicity to cells

Table 2 shows the *in vitro* biocompatibility studies performed for the Healon[®] EndoCoat OVD.

Table 2
***In Vitro* Biocompatibility Tests for Healon[®] EndoCoat OVD**

Test	Purpose	Acceptance Criteria	Results
Cytotoxicity (Agar diffusion)	Evaluate biocompatibility	Is not cytotoxic	No cell lyses or toxicity to cells

2. Physicochemical Properties

Finished Healon[®] EndoCoat OVD, or a similar 3% NaHA product, was subjected to physicochemical tests according to ISO 15798:2010E "Ophthalmic Implants-Ophthalmic Viscosurgical Devices." The tests and results are summarized in **Table 3** below.

Table 3
Physicochemical Tests for Healon[®] EndoCoat OVD

Test	Purpose	Results/Acceptance Criteria
Absolute Complex Viscosity	Characterize physicochemical property	The rheological profile was characterized at a constant stress of 8 Pa over a frequency range of 0.001 to 100 Hz at a temperature of 25°C ± 2°C using a rheometer.
Chemical/Biological Contaminants	Evaluate potential impurities (e.g., protein, nucleic acids, and solvents from processing)	Observed contaminants and their respective levels included: protein (≤ 0.003%), nucleic acids (≤ 0.012 Absorbance units (AU)/mg of NaHA), acetate (< 0.03%), ethanol (≤ 0.015%), isopropyl alcohol (< 0.015%), methanol (<0.0075%), heavy metals (As ≤ 2ppm, Cd ≤ 5ppm, Cr ≤ 5ppm, Co ≤ 10ppm, Cu ≤ 10ppm, Fe ≤ 51ppm, Pb ≤ 10ppm, Hg ≤ 10ppm, and Ni ≤ 5ppm), and silicone oil (≤ 210 µg/syringe). Levels were

		justified by risk analyses.
Concentration	Evaluate physicochemical property	Determined using high performance liquid chromatography (HPLC). Concentration found to be approximately 3% (acceptance criterion of 2.7 – 3.3%).
Elasticity	Characterize physicochemical property	Profile was characterized in the same manner as the absolute complex viscosity over a frequency range of 0.001 to 100 Hz.
Molecular Weight (MW) and MW Distribution	Characterize physicochemical property	Characterized by gel permeation chromatography (GPC) equipped with light scattering and refractive index detectors. Average MW (800 kDa) and MW distribution were reported. Average polydispersity was found to be 1.32. MW was consistent across lots which was further verified by the polydispersity.
Osmolality	Evaluate physicochemical property	Determined using an osmometer per USP <785>. Osmolality determined to be approximately 320 mOsm/kg (acceptance criterion of 300 – 340 mOsm/kg).
Particulates	Evaluate potential impurities	Particulate quantification was performed per USP <788>. Particulate characterization employed optical and fourier transform infrared (FT-IR) spectroscopy. Acceptance criteria were $\leq 37/g$ for particles $\geq 10\mu m$ in diameter, and $\leq 8/g$ for particles $\geq 25\mu m$ in diameter. These limits were justified by risk analyses.
pH	Evaluate physicochemical property	Performed per USP <791> at $25^{\circ}C \pm 2^{\circ}C$. pH range determined to be approximately 7.2 (acceptance criterion of 6.8 – 7.6).
Refractive Index	Characterize physicochemical property	Characterized per USP <831> with a refractometer at $25^{\circ}C \pm 2^{\circ}C$. The refractive index was 1.339 and consistent across lots.
Apparent Viscosity	Evaluate physicochemical property	Determined using a viscometer at a shear rate of $2 s^{-1}$ at $25^{\circ}C \pm 2^{\circ}C$. Viscosity determined to be approximately 50,000 cps (acceptance criterion of 49,000 – 56,000 cps).
Spectral	Characterize	Determined using an ultraviolet-visible

Transmittance	physicochemical property	(UV-vis) spectrophotometer over a range of 300 to 1100 nm. Found to be >95% transmittance over evaluated range.
Expulsion Force	Characterize physical property	Determined the force required to expel OVD from syringe at a delivery rate of 3 ml/min. The average expulsion force for the 1.0 ml configuration was 20.7 N and 23.9 N for the 2.25 ml configuration. In addition, the rheological properties of the OVD were evaluated following expulsion with either a 23G or 25G cannula. There were no statistical differences between cannulas.

B. Animal Studies

In vivo biocompatibility studies were performed on finished Healon[®] EndoCoat OVD, or a similar 3% Sodium Hyaluronate product, and the delivery system for the Healon[®] EndoCoat OVD. The biocompatibility is performed in accordance with ISO 10993-1:2003, Biological Evaluation of Medical Devices - Part 1 Evaluation and Testing. These studies were conducted in conformance with the GLP Regulation. **Table 4** shows the *in vivo* biocompatibility studies performed for the delivery system components.

Table 4
***In Vivo* Biocompatibility Tests for Delivery System**

Test	Purpose	Acceptance Criteria	Results
Sensitization (Guinea pig maximization)	Evaluate biocompatibility	Does not demonstrate sensitization	No evidence of delayed dermal contact sensitization
Systemic Toxicity (mouse model)	Evaluate biocompatibility	Does not demonstrate systemic toxicity	No evidence of systemic toxicity

Table 5 shows the *in vivo* biocompatibility studies performed for the Healon[®] EndoCoat OVD.

Table 5
***In Vivo* Biocompatibility Tests for Healon[®] EndoCoat OVD**

Test	Purpose	Acceptance Criteria	Results
Sensitization (Guinea pig maximization)	Evaluate biocompatibility	Does not demonstrate sensitization	No evidence of delayed dermal contact sensitization

Systemic Toxicity (mouse model)	Evaluate biocompatibility	Does not demonstrate systemic toxicity	No evidence of systemic toxicity
Ocular Irritation (Rabbit model)	Evaluate biocompatibility	Not an ocular irritant	No evidence of irritation throughout the 72 hour observation period
4 Week Intraocular Irritation Study (Rabbit model)	Evaluate biocompatibility	Not an ocular irritant	No irritation to the intraocular tissue and no evidence of inflammation or prolonged intraocular pressure (IOP) increase

C. Additional Studies

The objectives of the sterilization, shelf life and transport stability studies were to establish a complete microbiological profile for the finished Healon® EndoCoat OVD as well as ensure the physicochemical properties are conserved over the proposed shelf life.

The tests conducted in support of the sterilization validation, package integrity, shelf life, and transport stability are summarized in **Table 6** below. Healon® EndoCoat OVD in its packaging is validated for a shelf life of 12 months when stored at a temperature between 2 – 25°C.

**Table 6
Sterilization, Package Integrity, Shelf Life, and Transport Stability Tests for Healon® EndoCoat OVD**

Test	Purpose	Results/Acceptance Criteria
Aseptic Fill Validation	Evaluate sterility	Performed per ISO 13408-1: 2008. Acceptable results achieved in a fill event equal to or exceeding 3000 units. No growth was detected in any syringes, for a 0% contamination level.
Sterilization Validation	Evaluate sterility	Performed per ISO 11135, "Sterilization of health care products – Ethylene Oxide."
Sterilant Residuals	Evaluate sterility	Ethylene Oxide (10 ppm) and Ethylene Chlorohydrin (ECH) (21 ppm) limits are acceptable. Acceptable limits were based on risk analyses.

Bioburden	Evaluate sterility	Pre-sterilization bioburden levels were within acceptable limits (≤ 50 cfu/g)
Bacterial Endotoxin	Evaluate sterility	Testing for endotoxins was performed per ISO 15798, section 6.2.3. and a test is performed on each lot of product using the USP <85> kinetic turbidimetric method. Tests completed on six lots of similar product were found to be within specification. All lots were found to be within acceptable limits (≤ 0.25 EU/ml).
Sterility Test	Evaluate sterility	Tested per USP <71>. No microbial growth was detected
Bacteriostasis/ fungistasis test	Evaluate sterility	No bacteriostatic/fungistatic effect was observed
Package Evaluation – Dye penetration	Evaluate package integrity	No dye penetration was observed in the packaging.
Package Evaluation – Burst strength	Evaluate package integrity	The packaging met the requirements for strength. The lowest result was 4.57 psi (acceptance criterion of 1.0 psi).
Package Evaluation – Microbial barrier	Evaluate package integrity	The test samples and negative controls showed no growth, while the positive controls exhibited growth.
Transport Stability	Evaluate package integrity	The results showed that there was no damage to the units after transportation and distribution simulation tests.
Physicochemical Properties Tests	Evaluate stability of OVD	pH, osmolality, viscosity, NaHA concentration and particulates were tested according to criteria in Table 3 (except for viscosity which has an acceptance criterion of 42,000 – 58,000 cps).

X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study in the U.S. to establish reasonable assurance of safety and effectiveness of Healon[®] EndoCoat OVD for use as a surgical aid in patients undergoing ophthalmic anterior segment surgical procedures. Healon[®] EndoCoat OVD was evaluated under the USA Clinical Evaluation of the Vitrax II Viscoelastic investigational device exemption (IDE) study G090104 (the name Vitrax II was changed to Healon[®] EndoCoat in P110007 and is referred to as Healon[®] EndoCoat in this summary). Data from this study were the primary basis for the PMA approval decision. A summary of this clinical study is presented below.

A. Study Design

Patients in the primary clinical study were treated between September 10, 2009 and November 1, 2010. The database from this study for this PMA reflected data collected through November 30, 2010 and included 400 patients. There were 11 US investigational sites.

This study was a prospective, multi-center, partially masked (technician and subject), randomized, controlled trial to evaluate the safety and effectiveness of Healon[®] EndoCoat OVD during cataract surgery with phacoemulsification and intraocular lens implantation as compared to a legally marketed OVD with similar indications for use. Although the investigators were not masked at the time of surgery as to which viscoelastic was used, the technicians taking the IOP measurements and the subjects were masked throughout the study. Four hundred subjects undergoing cataract extraction with intraocular lens (IOL) implantation at 11 investigative sites were enrolled and randomized in a 1:1 fashion to receive the investigational device (Healon[®] EndoCoat OVD) or the control OVD.

Subjects were followed from the initial preoperative examination until three months postoperatively to determine cumulative IOP spike rates (defined as IOP \geq 30 mm Hg), endothelial cell loss, and complications, particularly inflammation. Prophylactic administration of IOP-lowering medications was not allowed during the study. A medical monitor and a clinical trial monitor were appointed. A reading center was used for analysis of specular microscopy photos captured at study sites to determine endothelial cell counts (ECC).

For the cumulative IOP spike rate, a non-inferiority hypothesis testing was formulated in the study protocol to compare Healon[®] EndoCoat OVD to the control OVD with a non-inferiority margin of 13%. The null and alternative hypotheses are:

$$H_0 : \pi_t - \pi_c \geq \delta \quad \text{vs.} \quad H_a : \pi_t - \pi_c < \delta$$

where π_t = rate of IOP spikes of 30 mm Hg or greater in the Healon[®] EndoCoat OVD group, π_c = rate of IOP spikes of 30 mm Hg or greater in the control OVD group, and δ = non-inferiority margin of 0.13. The hypothesis test was planned to be conducted with one-sided two-sample t-test at a one-sided $\alpha=0.05$ level of significance.

For ECC, a non-inferiority hypothesis testing was formulated in the study protocol to compare the Healon[®] EndoCoat OVD to the control OVD with a non-inferiority margin of 5%. The null and alternative hypotheses are

$$H_0 : \mu_t - \mu_c \geq \delta \quad \text{vs.} \quad H_a : \mu_t - \mu_c < \delta$$

where μ_t = Mean within-eye percent ECC loss for the Healon[®] EndoCoat group, μ_c = Mean within-eye percent ECC loss for the control OVD group, and δ = non-inferiority margin of 5%. The hypothesis test was planned to be conducted with one-sided two-sample t-test at a one-sided $\alpha=0.05$ level of significance.

The study was to be considered a success if the non-inferiority of Healon[®] EndoCoat OVD compared to the control OVD was demonstrated for both of the two primary endpoints.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the USA Clinical Evaluation of the Vitrax II Viscoelastic study was limited to subjects who met the following inclusion criteria:

- Age 18 or greater
- Cataract for which phacoemulsification extraction and posterior IOL implantation was planned in at least one eye
- Visual potential of 20/40 or better in the study eye after cataract removal and IOL implantation
- Clear intraocular media other than cataract
- Signed informed consent
- Availability, willingness, and sufficient cognitive awareness to comply with examination procedures

Subjects were not permitted to enroll in the USA Clinical Evaluation of the Vitrax II Viscoelastic study if they met any of the following exclusion criteria:

- Concurrent participation or participation in the last 30 days in any other clinical trial
- Known steroid IOP responder
- Taking medications that may affect vision, IOP, or ease of cataract surgery (e.g., Flomax, glaucoma medications, etc.)
- Acute or chronic disease or illness that would increase risk or confound study results (e.g., diabetes mellitus, immunocompromised, etc.)
- Uncontrolled systemic or ocular disease
- History of ocular trauma or prior ocular surgery
- Corneal abnormalities (e.g., stromal, epithelial or endothelial dystrophies)
- Known pathology that may affect visual acuity; particularly retinal changes that affect vision (e.g., macular degeneration, cystoid macular edema, diabetic retinopathy, etc.)

- Any visual disorder predicted to cause future acuity loss to a level of 20/40 or worse
- Pseudoexfoliation
- Ocular hypertension (≥ 20 mm Hg) or glaucomatous changes in the optic nerve
- Endothelial cell counts lower than 1800 cells/mm² preoperatively (based on the lowest value of three cell counts performed by technician at investigative site)
- Patient was pregnant, planned to become pregnant, was lactating or had another condition associated with the fluctuation of hormones that could lead to refractive changes

2. Follow-up Schedule

All patients were scheduled to return for follow-up examinations at 6 hours, one day, one week, one month, and 3 months postoperatively. The clinical study visit schedule is presented in **Table 7**, and the clinical parameters evaluated at each visit are presented in **Table 8**.

Table 7
Study Visit Schedule

Visit	Exam	Visit Window
1	Preoperative Exam (Pre-op)	Within 30 days prior to 1st surgery
2	Operative (Op)	0-30 days following preoperative exam
3	Postop 1 (PO1) (6 hours postoperative)	4-8 hours
4	Postop 2 (PO2) (1 day postoperative)	20-28 hours
5	Postop 3 (PO3) (1 week postoperative)	5-9 days
6	Postop 4 (PO4) (1 month postoperative)	23-37 days
7	Postop 5 (PO5) (3 months postoperative)	75-105 days

**Table 8
Parameters Evaluated at Each Study Visit**

Examination	Pre-op	Op	PO1	PO2	PO3	PO4	PO5
Ocular History, Inclusion/Exclusion Criteria	X						
Demographics	X						
Informed Consent	X						
Cataract Status	X						
Potential Visual Acuity (VA)	X						
Uncorrected and Best Corrected Distance VA by Snellen	X						
Uncorrected and Best Corrected Distance VA by 100% ETDRS*					X	X	X
Refraction	X				X	X	X
Lens Power/Serial Number		X					
Viscoelastic Characteristics		X					
Surgical Procedures		X					
Intraocular Pressure (IOP)	X		X	X	X	X	X
Biomicroscopic Slit-Lamp Exam**	X		X	X	X	X	X
Endothelial Cell Count (ECC)	X						X
Medications	X	X	X	X	X	X	X
Complications/Adverse Events (AEs)		X	X	X	X	X	X

* Early Treatment Diabetic Retinopathy Study (ETDRS)

** Biomicroscopic slit-lamp exam includes determination of medical complications including cells/flare, corneal edema, etc.

The key timepoint for safety was cumulative through three months and for effectiveness it was at three months postoperatively, and AEs and complications were recorded at all visits.

3. Clinical Endpoints

With regard to safety, the primary endpoint was cumulative rate of IOP spikes 30 mm Hg or greater measured postoperatively through 3 months. IOP spikes of 30 mm Hg or greater at 6 hours, one day, one week, one month and 3 months postoperatively were also evaluated. Secondary endpoints included cumulative rates of AEs and distribution of grade of inflammation.

With regard to effectiveness, the primary endpoint was the mean percent change in ECC measurements from preoperative to 3 months postoperatively.

As indicated above, the study was to be considered a success if non-inferiority of Healon[®] EndoCoat OVD compared to the control OVD was demonstrated for both of the primary endpoints.

Analysis Populations

- Intent-to-treat (ITT) Population – Includes all subjects randomized into the study. For this population, missing values were imputed and subjects are analyzed according to the treatment they were randomized to.
- Per-Protocol (PP) Population – Includes all subjects who were randomized correctly and have no protocol deviations as determined prior to database lock. No imputation was performed for missing data.
- Safety Population – This population consists of all subjects with available data who were exposed to either viscoelastic product. Missing values were not imputed and subjects are analyzed according to the treatment they actually received.

B. Accountability of PMA Cohort

A total of 400 subjects from 11 investigational sites were enrolled and randomized in a 1:1 fashion to the investigational device group (n=199) or the control group (n=201). However, one subject randomized to the control group incorrectly received the Healon[®] EndoCoat OVD, which is why the ITT cohort (all subjects randomized into the study with their outcomes analyzed according to the treatment to which they were randomized) includes 199 subjects in the investigational device arm and 201 in the control arm. For this analysis population, missing values were imputed. For the safety analysis population (all subjects with available data at any timepoint during the study who were exposed to either viscoelastic product with their outcomes analyzed according to the treatment they actually received), there were 200 subjects in each treatment group. Missing values were not imputed for this analysis population.

Among the 400 enrolled subjects, 399 completed the final three-month visit, with one subject in the control OVD group discontinued prior to the one-week postoperative visit. In addition, four subjects missed a postoperative study visit, one in the investigational device group missed the one-week visit, two in the control group missed the 6-hour evaluation, and one in the control OVD group missed the one-month visit.

C. Study Population Demographics and Baseline Parameters

Demographics for all study subjects (ITT populations) in each group are presented in **Table 9**. Among the 400 enrolled subjects, 247 (61.8%) were females and 371 (92.8%) were Caucasians. No clinically significant differences in the baseline demographics or pre-operative parameters were detected between the two study groups.

**Table 9
Demographics
(ITT Population)**

		Healon [®] EndoCoat N = 199		Control OVD N = 201	
		n	%	n	%
Age (years)	Mean	68.0		70.1	
	Std	8.90		8.84	
	Median	69.0		71.0	
	Min	45		49	
	Max	90		90	
Sex	Male	73	36.7	80	39.8
	Female	126	63.3	121	60.2
Race	Caucasian	184	92.5	187	93.0
	African American	14	7.0	13	6.5
	Asian	1	0.5	1	0.5
Iris Color	Blue/Gray	77	38.7	76	37.8
	Brown/Black	79	39.7	71	35.3
	Green/Hazel	43	21.6	54	26.9

D. Safety and Effectiveness Results

1. Safety Results

Intraocular Pressure (IOP)

Based on the ITT population and Markov Chain Monte Carlo (MCMC) multiple imputation method which was used to impute a total of seven missing IOP values from five subjects, the IOP spike rate at each visit and the cumulative IOP spike rate are presented in **Table 10**. The estimated cumulative IOP spike rate was 10.6% for the investigational device group and 7.6% for the control OVD group; the difference between the investigational device group and the control OVD group was 3.0% with a 90% confidence interval (CI) of (-1.74%, 7.72%). The null hypothesis that the cumulative IOP spike rate for the investigational device group is at least greater by 13% than that for the control OVD group was rejected in favor of the investigational device group with a p-value of 0.0003. The primary safety endpoint, cumulative IOP spike rate, was met. The same conclusion also held for both the safety and per-protocol (all subjects who were randomized correctly and had no protocol deviations as determined prior to database lock, outcomes analyzed with no imputation for missing data) populations.

TABLE 10
Percent IOP \geq 30 mm Hg by OVD Group, Visit and Cumulative
(ITT Population[†])

Visit	OVD group	N	Rate of spikes (%) (90%CI)	p-value*
6 Hours	Healon [®] EndoCoat	199	7.5	-
	Control	201	6.1	-
	Difference	-	1.4	-
1 Day	Healon [®] EndoCoat	199	2.5	-
	Control	201	2.0	-
	Difference	-	0.5	-
1 Week	Healon [®] EndoCoat	199	1.0	-
	Control	201	1.0	-
	Difference	-	0	-
1 Month	Healon [®] EndoCoat	199	0	-
	Control	201	0	-
	Difference	-	0	-
3 Month	Healon [®] EndoCoat	199	0	-
	Control	201	0	-
	Difference	-	0	-
Cumulative	Healon [®] EndoCoat	199	10.6(6.97, 14.14)	-
	Control	201	7.6(4.49, 10.63)	-
	Difference	-	3.0(-1.74, 7.72)	0.0003

* p-values are calculated using a 1-sided non-inferiority t-test with $\delta = 13\%$.

[†] Missing values are imputed by MCMC multiple imputation. Therefore, percent IOP \geq 30 mm Hg rather than number of IOP \geq 30 mm Hg is reported.

Grades of Inflammation

In the early postoperative period, anterior chamber cells were the most reported form of inflammation reported in both groups (**Tables 11 and 12**). At the six-hour postoperative visit, 80.5% (161/200) of subjects in the Healon[®] EndoCoat group were reported with cells, and at the one-day visit, 69.0% (138/200) were reported with cells; however, the majority of these reports at all intervals were trace (1+). In the control OVD group, 75.3% (149/198) of subjects were reported with cells at the six-hour postoperative visit, and at the one-day visit, 72.0% (144/200) were reported with cells; again, the majority of these reports were trace. Reports of cells diminished over time to minimal levels by the one-month visit in both OVD groups.

Corneal Edema

The majority of subjects in each group were reported with “none” for corneal edema at each postoperative interval. Early postoperative incidence rates of epithelial and stromal edema were low with similar rates in both groups, with rates diminishing over time.

Table 11
Anterior Segment Inflammation
Healon® EndoCoat vs. Control OVD Comparison Over Time (6 hours – 1 week postop)
(Safety Population)

Grade of Inflammation		Healon® EndoCoat 6 Hours N = 200		Control OVD 6 Hours N = 198		Healon® EndoCoat 1 Day N = 200		Control OVD 1 Day N = 200		Healon® EndoCoat 1 Week N = 199		Control OVD 1 Week N = 199	
		n	%	n	%	n	%	n	%	n	%	n	%
		Cells	NONE	39	19.5	49	24.7	62	31.0	56	28.0	141	70.9
	Present	161	80.5	149	75.3	138	69.0	144	72.0	58	29.1	58	29.1
	Trace	111	55.5	83	41.9	93	46.5	99	49.5	48	24.1	47	23.6
	Mild	27	13.5	44	22.2	33	16.5	34	17.0	8	4.0	9	4.5
	Moderate	22	11.0	20	10.1	10	5.0	11	5.5	2	1.0	1	0.5
	Severe	1	0.5	2	1.0	2	1.0	0	0.0	0	0.0	1	0.5
Flare	NONE	147	73.5	143	72.2	156	78.0	157	78.5	191	96.0	192	96.5
	Present	53	26.5	55	27.8	44	22.0	43	21.5	8	4.0	7	3.5
	Trace	33	16.5	35	17.7	35	17.5	35	17.5	6	3.0	4	2.0
	Mild	14	7.0	15	7.6	6	3.0	4	2.0	1	0.5	3	1.5
	Moderate	5	2.5	5	2.5	3	1.5	4	2.0	1	0.5	0	0.0
	Severe	1	0.5	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0
Fibrin presence	NONE	200	100.0	198	100.0	199	99.5	200	100.0	199	100.0	199	100.0
	Present	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0
	Trace	0	0.0	0	0.0	1	0.5	0	0.0	0	0.0	0	0.0

Table 12
Anterior Segment Inflammation
Healon® EndoCoat vs. Control OVD Comparison Over Time (1 month – 3 months postop & cumulative rate)
(Safety Population)

Grade of Inflammation		Healon® EndoCoat		Control OVD		Healon® EndoCoat		Control OVD		Healon® EndoCoat		Control OVD	
		1 Month		1 Month		3 Months		3 Months		Cumulative*		Cumulative*	
		N = 200		N = 198		N = 200		N = 199		N = 200		N = 200	
		n	%	n	%	n	%	n	%	n	%	n	%
Cells	NONE	196	98.0	194	98.0	199	99.5	198	99.5	32	16.0	37	18.5
	Present	4	2.0	4	2.0	1	0.5	1	0.5	167	83.5	163	81.5
	Trace	4	2.0	2	1.0	1	0.5	1	0.5	139	69.5	134 [†]	67.0
	Mild	0	0.0	2	1.0	0	0.0	0	0.0	55	27.5	68	34.0
	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	29	14.5	27	13.5
	Severe	0	0.0	0	0.0	0	0.0	0	0.0	3	1.5	3	1.5
Flare	NONE	200	100.0	198	100.0	200	100.0	199	100.0	136	68.0	135	67.5
	Present	0	0.0	0	0.0	0	0.0	0	0.0	61	30.5	64	32.0
	Trace	0	0.0	0	0.0	0	0.0	0	0.0	57	28.5	56	28.0
	Mild	0	0.0	0	0.0	0	0.0	0	0.0	19	9.5	19	9.5
	Moderate	0	0.0	0	0.0	0	0.0	0	0.0	8	4.0	6	3.0
	Severe	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
Fibrin presence	NONE	200	100.0	198	100.0	200	100.0	199	100.0	196	98.0	199	99.5
	Present	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0
	Trace	0	0.0	0	0.0	0	0.0	0	0.0	1	0.5	0	0.0

* Cumulative includes data from interim visits.

[†] Two subjects reported with cells at these visits were diagnosed with iritis: 805 (one month) and 472 (interim visit, approximately two months postoperative).

Adverse events that occurred in the PMA clinical study:

Thirty nine (39) subjects (22 in the Healon[®] EndoCoat OVD group and 17 in the control OVD group) experienced adverse events (AEs) in the study (Table 13). None of the AEs were considered unanticipated. The majority of the AEs were IOP \geq 30mm Hg, occurring at an incidence rate of 10.5% (21/201) in the Healon[®] EndoCoat OVD group, and 7.5% (15/199) in the control OVD group.

**Table 13
Adverse Events
(Safety Population)**

ADVERSE EVENT	Healon [®] EndoCoat N = 200		Control OVD N = 200	
	n	%	n	%
Elevated IOP \geq 30 mm Hg	21*	10.5	15*	7.5
IOL Exchange	0	0.0	1	0.5
Injection for treatment of CME	1	0.5	0	0.0
Removal of Foreign Body**	0	0.0	1	0.5
TOTAL Subjects Experiencing Adverse Events	22		17	

* One subject in each group experienced two separate incidences of IOP \geq 30 mm Hg.

** Intraocular foreign body was noted at the one month postoperative visit.

Most of the IOP \geq 30 mm Hg readings occurred at the six-hour postoperative visit (Tables 14 and 15).

Overall incidence rates of IOP \geq 30 mm Hg AEs were similar between the Healon[®] EndoCoat and control OVD groups.

TABLE 14
IOP \geq 30 mm Hg Rate Over Time - Healon[®] EndoCoat
(Safety Population)

IOP	6 Hours		1 Day		1 Week		1 Month		3 Months	
	N = 200		N = 200		N = 199		N = 200		N = 200	
	n	%	n	%	n	%	n	%	n	%
< 30 mm Hg	185	92.5	195	97.5	197	98.9	200	100.0	200	100.0
\geq 30-39 mm Hg	11	5.5	4*	2.0	2*	1.0	0	0.0	0	0.0
\geq 40-49 mm Hg	2	1.0	1	0.5	0	0.0	0	0.0	0	0.0
\geq 50 mm Hg	2	1.0	0	0.0	0	0.0	0	0.0	0	0.0

* One subject experienced an IOP spike one day postoperatively of 38 mm Hg and an IOP of 31 mm Hg at one week postoperatively off of IOP lowering medications

TABLE 15
IOP \geq 30 mm Hg Rate Over Time - Control OVD
(Safety Population)

IOP	6 Hours		1 Day		1 Week		1 Month		3 Months	
	N = 198		N = 200		N = 199		N = 198		N = 199	
	n	%	n	%	n	%	n	%	n	%
< 30 mm Hg	186 [‡]	93.9	196 [‡]	98.0	197	99.0	198	100.0	199	100.0
\geq 30-39 mm Hg	10* [†]	5.1	2 [†]	1.0	1 [‡]	0.5	0	0.0	0	0.0
\geq 40-49 mm Hg	2	1.0	2*	1.0	1*	0.5	0	0.0	0	0.0
\geq 50 mm Hg	0	0.0	0	0.0	0	0.0	0	0.0	0	0.0

* One subject experienced an IOP of 39 mm Hg at six hours postoperatively. Although IOP lowering medications and/or treatments were administered, the IOP rose to 41 mm Hg at one day postoperatively. The IOP measured 46 mm Hg at one week postoperatively off of IOP lowering medications

[†] One subject had an IOP of 35 mm Hg six hours postoperatively. After IOP lowering medications and/or treatments were administered the IOP measured 32 mm Hg at one day postoperatively.

[‡] One subject had an IOP of 38 mm Hg at 1 week postoperatively, which had been preceded by unmedicated IOPs of 28 mm Hg at 6 hours postoperatively and 26 mm Hg at 1 day postoperatively

2. Effectiveness Results

Endothelial Cell Count - ECC (Specular Microscopy)

Based on the ITT population and MCMC multiple imputation method, which was used to impute the missing endpoint data, the mean percent loss in ECC ((ECC at 3 month post-operative visit - ECC at pre-operative visit)/ECC at pre-operative

visit) in the investigational device group was -4.7% (standard deviation (std) = 0.71%) and the mean percent loss in ECC in the control OVD group was -7.0% (std = 0.92%). The difference in the mean percent loss of ECC from preoperative to three months postoperative between two study groups was 2.3% with 90% CI (0.23%, 4.33%) in favor of the Healon[®] EndoCoat. The null hypothesis that the mean percent loss in ECC for the investigational device group was at least greater by 5% than that for the control OVD group was rejected in favor of the investigational device group with a p-value less than 0.0001(1-sided t-test). The primary effectiveness endpoint, mean percent change in ECC measurements, was met. The same conclusion also held for both the safety and per-protocol populations.

Although not included in the primary outcome parameters, the surgical time spent on OVD removal was recorded during the study. A subjective response was requested from surgeons at the end of the case regarding the ease of removal of the viscoelastic (choices were: easy, average, difficult, or hard). See **Table 16**.

Table 16
Operative Parameters - Removal of OVD
(Safety Population)

OVD Removal		Healon [®] EndoCoat N = 200		Control OVD N = 200	
Viscoelastic removal time (seconds)	Mean	149.1		133.7	
	SD	37.92		35.21	
	Median	135.0		121.0	
	Min	60		60	
	Max	300		454	
Ease of viscoelastic removal (no. of cases)	Easy	7	3.5%	9	4.5%
	Average	126	63%	142	71%
	Difficult	66	33%	49	24.5%
	Very Difficult	1	0.5%	0	0%

3. Subgroup Analyses

Not applicable

XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Not applicable

XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

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. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Effectiveness Conclusions

For preventing endothelial cell loss, statistical analysis demonstrated that Healon[®] EndoCoat OVD was non-inferior to the control OVD. Healon[®] EndoCoat OVD took slightly more time on average to remove and was considered somewhat more difficult to remove. The clinically significant results from the study support the effectiveness of the device.

B. Safety Conclusions

The risks of the device are based on nonclinical laboratory and animal studies as well as data collected in clinical study conducted to support PMA approval as described above.

The risks associated with the use of the device include inflammation, corneal edema, increased IOP, secondary glaucoma and corneal decompensation. These risks may all result from the surgery itself, and it can be very difficult to assign a specific causation as a result. The most common risk encountered is increased IOP postoperatively, which can be mitigated by careful and thorough removal of the OVD at the conclusion of the surgery. In addition, careful postoperative monitoring of IOP can capture this event and effective IOP lowering medications or treatments can be immediately administered.

For the cumulative incidence of IOP spikes, statistical analysis demonstrated that Healon[®] EndoCoat OVD was non-inferior to the control OVD. Thirty nine subjects experienced adverse events in the study. None of the AEs were considered unanticipated. Ninety-two percent of the adverse events were IOP \geq 30 mm Hg; IOP \geq 30 mm Hg occurred at a rate of 10.5% in the Healon[®] EndoCoat OVD group, and 7.5% in the control OVD group. The one AE that occurred in the Healon[®] EndoCoat OVD group that was unrelated to IOP could not be attributed to the OVD.

C. Benefit-Risk Conclusions

The probable benefits of the device are based on data collected in a clinical study to support PMA approval as described above and prior experience with this type of device (OVD). The benefits of the device include the ability to protect the corneal endothelium, and potentially other intraocular structures, during anterior segment surgery, including routine cataract surgery. This benefit is likely to be experienced to some degree by all patients in whom this OVD is administered. Additional factors considered in determining probable risks and benefits for the Healon[®] EndoCoat OVD included the uncertainty surrounding the potential adverse effects of the OVD from the effects of surgery and the other devices and medications used during surgery. In conclusion, given the available information above, the data support that the probable benefits of Healon[®] EndoCoat OVD for use as a surgical aid in patients undergoing ophthalmic anterior segment surgical procedures and outweigh the probable risks.

D. Overall Conclusions

The data in this application support the reasonable assurance of safety and effectiveness of this device for the indications for use when used in accordance with the instructions for use. The benefit of corneal endothelial protection outweighs the risk of transient IOP spikes and other less common risks. A significant portion of the patient population is expected to achieve clinically significant benefits with the use of the device.

XIV. CDRH DECISION

CDRH issued an approval order on July 2, 2012.

The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

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

Post-approval Requirements and Restrictions: not applicable