SUMMARY OF SAFETY AND EFFECTIVENESS DATA

I. GENERAL INFORMATION

Device Generic Name:	lotrafilcon A hydrophilic contact lens
Device Trade Name:	Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens
Applicant's Name and Address:	CIBA Vision Corporation 11460 Johns Creek Parkway Duluth, GA 30097
Date(s) of Panel Recommendation:	None
Premarket Approval Application (PMA) Number:	P000030
Date of Good Manufacturing Inspection:	July 12 and September 27, 2001
Date of Notice of Approval to Applicant:	October 12, 2001

II. INDICATIONS FOR USE

Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lenses are indicated for the optical correction of refractive ametropia (myopia and hyperopia) in phakic or aphakic persons with non-diseased eyes with up to approximately 1.5 diopters of astigmatism.

The lenses may be prescribed for extended wear for 1 to 7 days between removals for cleaning and disinfection or disposal of the lens, as recommended by the eye care professional. Lenses should be replaced every month and when removed between replacement times must be cleaned and disinfected with a chemical, not heat, disinfection system before reinsertion.

(The Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens was cleared for Daily Wear under K970746 on May 9, 1997).

III. CONTRAINDICATIONS

Do not use Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lenses when any of the following exists:

- Inflammation or infection of the anterior chamber of the eye
- Active disease, injury or abnormality affecting the cornea, conjunctiva, or eyelids
- Microbial infection of the eye

- Insufficiency of lacrimal secretion (dry eye) that interferes with contact lens wear
- Corneal hypoesthesia (reduced corneal sensitivity)
- Use of any medication that is contraindicated or interferes with contact lens wear, including eye medications
- Any systemic disease which may be exacerbated by or interferes with contact lens wear
- Allergic reactions of ocular surfaces or adnexa that may be caused by or exaggerated by wearing contact lenses
- Allergy to any ingredient in a solution which must be used to care for the contact lenses
- Patient history of recurring eye or eyelid infections, adverse effects associated with contact lens wear, intolerance or abnormal ocular response to contact lens wear
- If eyes become red or irritated

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens labeling (Attached)

V. DEVICE DESCRIPTION

Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lenses are available in a spherical lens design. The lens material is approximately 24% water and 76% lotrafilcon A, a fluorosilicone containing hydrogel which is surface treated. The lens may be prescribed for extended wear in powers ranging from +20.00 D to –20.00 D.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The alternative practices and procedures to correcting vision by wearing the Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens include other daily wear and extended wear contact lenses, rigid gas permeable daily wear and extended wear contact lenses, spectacles, and corrective surgeries such as radial keratotomy, photorefractive keratectomy and LASIK.

VII. MARKETING HISTORY

United States

To date, Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lenses have not been marketed in the United States.

International

Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lenses bear the CE mark and were introduced to the world market in early 1999 for use up to 30 nights extended wear. The lens has over 250,000 users and is marketed in over 40 countries. The Focus^{R} Night and

Day™ (lotrafilcon A) soft contact lens has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Potential adverse effects on health associated with extended wear contact lenses include eye problems such as corneal ulcers, epithelial microcysts, infiltrates and endothelial polymegathism. The risk of corneal ulcer has been shown to be greater among users of extended wear contact lenses than among users of daily wear contact lenses. The risk among extended wear users increases with the number of consecutive days that the lenses are worn between removals, beginning with the first overnight use. In addition, smoking increases the risk of corneal ulcers for contact lens users, especially when lenses are worn overnight or while sleeping. Strict compliance with the proper lens care regimen and wearing schedule is essential in minimizing risk.

IX. SUMMARY OF PRECLINICAL STUDIES

The objective of the preclinical studies was to provide reasonable assurance of the safety of the Focus® Night and Day™ (lotrafilcon A) soft contact lens prior to clinical testing.

Biocompatibility Studies

The following toxicology tests were performed: USP Systemic Injection Test, Primary Ocular Irritation Test, Cytotoxicity Test (USP L929 Agar Overlay, Direct Contact and MEM Elution Assays, and ISO Cell Growth Inhibition Assay), Guinea Pig Maximization Test, 28 Day Ocular Irritation Test, and Leachables Testing. The test results raise no acute toxicological concerns and support the safety of the study lens for its intended use.

Physical and Chemical Characterization Studies:

% Water Content	24 % by weight in normal saline
Oxygen Permeability (Dk):	140 X 10^{-11} (cm^2/sec)(ml O_2/ml x mm Hg) (measured at 35° C Coulometric method)
% Light Transmittance	$\geq$ 99%
Mechanical Properties:	
Young's modulus of elasticity (Mpa)	1.2
Stress at break (mpa)	0.8
% Maximum Elongation	150
Toughness at break (mJ/cm^2)	764
Refractive Index:	1.43

Solution Compatibility Studies:

Cycling studies were performed using the following care products: AOSEPT Regimen, Quick Care Regimen, Focus Lens Drops, Optifree and ReNu Preservative Uptake and release studies were performed for polyquad, sorbic acid and PHMB. All lens care systems were compatible with the Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens.

Shelf-life Stability Studies

An expiration date of 60 months has been established for sterilized lenses packaged in foil sealed blister packs.

Conclusion of Preclinical Studies:

The results of the preclinical studies support the safety of the Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens for its intended use.

X. SUMMARY OF CLINICAL STUDIES

Objective

The objective of this clinical trial was to determine whether the Focus^{R} Night and Day^{TM} Lens, when worn for up to one week extended wear and replaced on a monthly basis, performed as well as or better than the Control lens, when worn for up to one week extended wear and replaced on a weekly basis.

Study Design

This clinical trial was a prospective, randomized, controlled, open label clinical trial lasting one year. A total of 450 subjects (305 test and 145 control) were enrolled at 20 investigational sites throughout the United States. Approximately fifteen test and eight control subjects were to be enrolled at each site. Subjects were randomized to wear either the test or control lens bilaterally for one year.

For the purposes of this study, extended wear meant that lenses were to be applied and worn around the clock, including during sleep. Weekly extended wear meant at the end of any six (6) nights of extended wear, the patient had to remove the lens for one night prior to beginning a new cycle of lens wear. All subjects used the AOSEPT ^{R} system as the primary care regimen when lenses were removed.

Baseline characteristics and demographics were summarized using descriptive statistics such as means, proportions, and standard deviations. The primary safety endpoint analysis was based on the proportion of subjects in each group who developed corneal infiltrates with overlying fluorescein staining and/or grade 3.0 corneal infiltrates if no overlying staining was present. To guard against bias, the dropout rates for each group

were compared. A Cox Model was used to consider all data from all subjects (including dropouts). The Cox Model involves using life table methods to incorporate the exposure time of the discontinued subjects. The primary efficacy endpoint analysis was based on the proportion of subjects in each group able to successfully maintain the extended wearing schedule. This was calculated using the percent of participants that reported at least 6 consecutive nights of lens wear at the 1, 3, 6, 9, and 12 month visits.

Other primary safety data collected during the study included:

- Adverse events
- Discontinuations
- Biomicroscopy
- Subjective symptoms and problems
- Keratometric and refractive changes
- Best-corrected acuity

The primary efficacy data collected during the study included:

- Wearing time and temporary interruptions of lens wear
- Contact lens visual acuities (Snellen)

Subjects were eligible for study participation if they were at least 18 years old, signed informed consent, and complied with inclusion and exclusion criteria specified in the protocol. These criteria permitted inclusion of subjects who needed correction in both eyes that was correctable to a distance visual acuity (VA) of 20/40 or better in each eye with spherical hydrogel contact lenses and excluded subjects with conditions that would interfere with efficacy and safety assessments or expose the subject to an unacceptable risk. Pregnant or lactating women were included in the study as these individuals comprise a significant portion of the contact lens wearing population.

The study population consisted of subjects representative of the general population attending offices for contact lens care. Of the subjects enrolled, 290 test and 145 Control subjects were dispensed lenses. The study population ranged in age from 18 to 61 years (Test mean=34 years, Control mean = 33 years). Lens power ranged from –1.00 D to –6.50 D (Test mean = -3.23 D, Control mean = -3.41 D). Only 26 subjects were neophyte lens wearers. Previous experience was considered to be successful for 404/409 (98.8%) of subjects who reported prior lens wear.

Gender distribution consisted of 66% (191) females in the Focus^{R} Night and Day^{TM} group and 76% (111) females in the Control group. Although each distribution can be considered representative of the contact lens wearing population, the difference is statistically significant. The statistical difference would be lost if just 3 more male subjects and 3 fewer females were enrolled in the Control group. The randomization was done within site and there were no significant differences in the gender distribution by site. However, 15 of the 20 sites had a higher proportion of females in the Control group

compared to the Focus Night and Day group. There was no evidence of any violation in the randomization process that would explain this difference.

Subject Assessments

At each study visit, subjects were given enough lenses to last until the next study visit, allowing for scheduled and unscheduled lens replacements. All other visits for any reason were recorded as Unscheduled Visits. Whenever possible, subjects were evaluated toward the end of the lens replacement cycle. Subjects were allowed to use their Focus Night and Day lenses for up to 35 days before replacement to assure that this was possible. Follow-up visits were scheduled for 24 hours, 1 week, and 1, 3, 6, 9, and 12 months after starting extended wear.

Adverse events were defined as any undesirable clinical occurrence in a subject whether it was considered to be device related or not. Adverse events were classified as adverse device effects, undesirable side effects, or other serious adverse events according to criteria specified in the protocol.

Discontinuations could be due to a variety of reasons such as best interest of the patient, voluntary withdrawal by the subject, protocol deviations, lack of follow-up (lost-to-follow-up = 2 consecutive visits missed), relocation, neophytes who had not initiated extended wear within 45 days of enrollment, and if subjects switched from extended to daily wear indefinitely. Completion was defined as wearing the test or control lenses for 12 months after initiation of extended wear and the subject had the required evaluations performed.

Demographic Data

The dispensed study population ranged in age from 18 to 61 years (mean = 33-34 years. Gender distribution consisted of 66% (191) females in the Focus Night and Day group and 76% (111) females in the Control group.

Data Analysis and Results

Adverse events were defined in the protocol as Adverse Device Effects (ADE) and Undesirable Side Effects (USE). Table 1 shows the number and percentage of adverse reactions, USEs, and any other treatments for each treatment group.

Table 1: Summary of Adverse Reactions, USEs, and Any Treatment

	Completed				Discontinued			
	Focus EW Lens		Control EW Lens		Focus EW Lens		Control EW Lens	
	N	%	N	%	N	%	N	%
Sample Size								
Subjects	235	100%	130	100%	55	100%	15	100%
Eyes	470	100%	260	100%	110	100%	30	100%
One or More Adverse Reactions								
Subjects	0	0.0%	1	0.8%	0	0.0%	1	6.7%
Eyes	0	0.0%	1	0.4%	0	0.0%	1	3.3%
One or More USEs								
Subjects	32	13.6%	19	14.6%	7	12.7%	5	33.3%
Eyes	49	10.4%	27	10.4%	13	11.8%	7	23.3%
Any Treatment								
Subjects	14	6.0%	8	6.2%	4	9.1%	0	0.0%
Eyes	25	5.3%	10	3.8%	6	5.4%	0	0.0%

No Adverse Device Effects were reported for the Focus Night and Day lenses. Two (2) cases of Adverse Device Effect were reported for the Control lens. Subject 15-015 was diagnosed with infiltrative keratitis and secondary iritis in the left eye; subject 17-005 was diagnosed with an infectious ulcer in the left eye. Neither subject had permanent loss of vision. A total of 49 completed eyes in 32 subjects in the Focus Night and Day group experienced one or more USE's (undesirable side effects) as compared to 27 completed eyes in 19 subjects in the Control group.

Although Contact Lens Acute Red Eye (CLARE) was a possible diagnosis in this protocol, many practitioners did not follow the definition of CLARE as outlined in the protocol. Because of the practitioner confusion regarding the definition, CLARE is not used as a diagnosis in the final analysis of the data. CIBA Vision has reclassified subjects diagnosed with CLARE based on the documented signs and symptoms reported on the CRF. If infiltrates were present, the diagnosis of Infiltrative Keratitis was used. If no infiltrates were present, the event was classified based on the most severe biomicroscopy/symptom recorded. Seven out of a total of eleven diagnosed CLARE events did not have the presence of infiltrates as required by the definition. Four of these seven subjects had grade 2 or less limbal and/or bulbar redness with only minimal or moderate symptoms. There were 4 cases of CLARE reported for the Control lens. The test lens, Focus Night and Day, reported 8 cases.

The percentage of completed subjects who received any treatment other than for an ADE or USE (including temporary interruption of lens wear) was similar for Focus Night and Day (6.0%) and Control (6.2%) lens wearers. For discontinued subjects, any treatment was provided to four (9.1%) discontinued Focus Night and Day subjects, but no

discontinued Control subjects. The types of conditions treated were similar for the two treatment groups.

The percent of subjects discontinued is based on the number of subjects dispensed. Overall, 55 (19.0%) of Focus Night and Day subjects and 15 (10.3%) Control subjects discontinued from the trial. Focus Night and Day had a higher discontinuation rate due to discomfort and fit. The Focus Night and Day lens was only available in one design (8.6/13.8) during this trial. Control was available in two base curves (8.4 and 8.8 mm). Forty-two percent (42%) were dispensed with the 8.4mm base curve and the remaining lenses were dispensed with the 8.8 mm base curve. Although approximately 97.9% of the dispensed Focus Night and Day group achieved an acceptable fit rating by the investigators, an inadequate fit may also be judged by subjective reports of lens awareness or by observation of edge lift. Of the 27 subjects discontinued for discomfort, 23 (85%) discontinued within one week of dispensing. This indicates that the discomfort was present very early in the trial and likely due to a less than optimal fit.

Slit Lamp Findings:

Slit lamp findings are presented in Table 2 for completed subjects. Grade 0 slit lamp findings were reported for 89.8% of the Focus Night and Day and 88.3% of the Control lens wearers for all subjects and all visits. Completed subjects with Grade ≥3 had a rate of ≤0.2%; whereas, a rate of ≤0.1% was recorded for discontinued subjects. A mild trend was shown for Focus Night and Day to have a higher percentage of Grade 0 biomicroscopy findings for neovascularization, microcysts, and striae. This was attributed to the oxygen permeability profile of the Focus Night and Day material. Focus Night and Day also showed less limbal and bulbar redness.

Table 2. Slit Lamp Findings (Completed Subjects)

	Focus N&D	Control
limbal Redness		
Grade 0	91.3%	87.0%
Grade 1	7.9%	12.0%
Grade 2	0.4%	0.9%
Grade 3	0.1%	0.2%
Grade 4	0.0%	0.0%
Bulbar Redness		
Grade 0	85.8%	84.5%
Grade 1	12.9%	14.3%
Grade 2	1.0%	1.0%
Grade 3	0.1%	0.1%
Grade 4	0.0%	0.0%
Palpebral Redness		
Grade 0	91.9%	90.2%
Grade 1	7.2%	9.5%
Grade 2	0.6%	0.2%
Grade 3	0.0%	0.1
Grade 4	0.0%	0.0
Epithelial Staining		
Grade 0	82.2%	82.2
Grade 1	16.2%	16.0
Grade 2	1.3%	1.3
Grade 3	0.0%	0.0
Grade 4	0.0%	0.0
Tarsal Abnormalities		
Grade 0	84.8%	84.9%
Grade 1	12.5%	13.5%
Grade 2	2.4%	1.5%
Grade 3	0.1%	0.0%
Grade 4	0.0%	0.0%

	Focus N&D	Control
Conjunctival Staining		
Grade 0	85.8%	82.6%
Grade 1	13.0%	16.0%
Grade 2	0.9%	1.3%
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%
Vascularization		
Grade 0	91.2%	87.9%
Grade 1	8.1%	11.6%
Grade 2	0.4%	0.5%
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%
Microcysts		
Grade 0	94.7%	90.9%
Grade 1	4.4%	8.8%
Grade 2	0.7%	0.3%
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%
Striae/Edema		
Grade 0	98.9%	95.1%
Grade 1	0.8%	4.3%
Grade 2	0.0%	0.5%
Grade 3	0.0%	0.1%
Grade 4	0.0%	0.0%
Infiltrates		
Grade 0	99.1%	98.9%
Grade 1	0.3%	0.5%
Grade 2	0.3%	0.5%
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%
Other		
Grade 0	95.5 %	96.1%
Grade 1	4.0%	2.3%
Grade 2	0.3%	1.6%
Grade 3	0.0%	0.0%
Grade 4	0.0%	0.0%

The primary safety endpoint established for this clinical investigation was corneal infiltrates with any overlying staining and/or infiltrates >Grade 2. A total of 12 (4.1%) Focus Night and Day and 14 (9.6%) Control subjects had infiltrates throughout the clinical trial. Of these, 3.4% (10) and 5.5% (8) Control subjects had corneal infiltrates ≥Grade 2. A life table analysis revealed that Focus Night and Day had a clinical trend towards being slightly better than the Control; however, this observation could not be proven to be statistically significant. For all infiltrates, with or without overlying staining, the life table analysis showed Focus Night and Day to perform both clinically and statistically better than the Control.

Symptoms/Problems/Complaints:

Focus Night and Day and Control performed similarly with respect to subject reported symptoms, problems and complaints. The most frequently reported symptom was dryness with an incidence rate of 21.3% and 14.6% for completed and discontinued subjects respectively in the Focus Night and Day group. The rates for completed and discontinued subjects in the Control group were 25.0% and 23.9% respectively. Discontinued subjects in the Control group had higher rates of complaint regarding dryness (23.9%) as compared to the Focus Night and Day group, 14.6%. Focus Night and Day had higher rates of lens awareness and discomfort that were probably related to the limited range of base curves available as compared to Control.

Keratometric/Refractive Changes:

Keratometric (K) readings were relatively stable as compared to baseline readings. The mean change was +0.01D. The completed Focus Night and Day eyes had a slight mean reduction (flattening) in corneal curvature of –0.21D. There were 15 (2.6%) Focus Night and Day eyes and 4 (1.4%) Control eyes that exhibited increase in K-readings of >1.0 diopters. The maximum change was <2.0D for both test and control groups. The changes of >1.0D in the test lens all resulted in corneal flattening, not steepening. It appears that the majority of these changes are the results of the correction of corneal warpage observed at baseline in patients that had been wearing low Dk lenses. Review of the keratometric change data does not reveal any clinically measured disparities by primary meridian. Additionally, there were very few K-reading changes greater than 1.0D.

Control eyes tended to increase in myopia by an average of –0.14D for completed subjects over the one-year trial. Focus Night and Day subjects showed a hyperopic shift of +0.08. Two Control and three Focus Night and Day eyes had refractive error change greater than 1.0D. These changes were –1.75D and –2.50D in Control and approximately +1.25D in the three Focus Night and Day eyes.

Visual Acuity:

Visual acuity showed that the test and control groups performed similarly. A total of 3 (1.0%) Control and 10 (1.7%) Focus Night and Day eyes had a reduction in acuity of greater than one Snellen line with lenses worn at the final visit. Investigators reported that the reasons for acuity reduction with Focus Night and Day included lens deposits and accommodative problems from beginning presbyopia. None of the subjects had a loss of BSCVA. In contrast, 8 (2.6%) Control and 18 (3.1%) Focus Night and Day eyes had an improvement of more than one Snellen line of acuity with lenses worn at the final visit. Analyses of BSCVA show similar profiles for both test and control lens groups.

Wear Time:

The primary effectiveness endpoint was the percentage of subjects in each group able to successfully maintain the extended wear schedule. For Focus Night and Day subjects, 91.8% were able to wear lenses for 6 consecutive nights. For Control subjects, 92.9% were able to wear lenses for 6 consecutive nights. There are no statistically significant differences for wearing time between the two lenses.

The rates for temporary interruption in extended lens wear were similar between the two groups. When subjects had more than one occurrence of interrupted wear; these were counted for each occurrence. There were a total of 27 Control instances of prescribed temporary interruptions to contact lens wear during the trial affecting 26 subjects (17.9%). For the Focus Night and Day lens, there were 52 Focus Night and Day instances affecting 42 (14.5%) of the subjects. These interruptions were temporary, changed to daily wear, or temporary cessation of lens wear altogether.

Other Issues:

The Control lens was replaced weekly compared to monthly replacement of the Focus Night and Day lens. In the Focus Night and Day group, the fit was described as optimal, acceptably loose or tight for all but 5.2% where the fit was rated as unacceptably loose. Front surface deposits, back surface deposits, and front surface wetting were evaluated using a 9-point scale (0-4 in 0.5 steps) with a score of 3 or 4 representing moderate to severe deposits or deficiency in wetting. The percentage of eyes with a grade of 2.5 or less was 97-99% in both treatment groups for completed eyes and 85-90% in both groups for discontinued eyes.

Subjects' opinions of the lens were rated on a scale of 1 to 10 with 10 being the most favorable outcome. The percentage of subjective ratings of ≥8 was similar for both groups for completed and discontinued subjects, with the smallest percentages for dryness and lens comfort upon awakening. The trend analysis profile also showed similar results between test and control lens groups.

Conclusions Drawn from the Clinical Studies

The data reported in this PMA application indicate that the performance of the Focus Night and Day 7-Day extended wear lens performs as well as the Control 7-Day extended wear lens with respect to the safety and effectiveness endpoints established for this clinical trial. For the primary safety and efficacy endpoints, there were no statistically significant differences between the treatment and control groups.

XI CONCLUSIONS DRAWN FROM STUDY

The results of the preclinical and clinical studies provide reasonable assurance of the safety and effectiveness of the Focus^{R} Night and Day^{TM} (lotrafilcon A) soft contact lens for the subject population, refractive conditions and specified duration of wear. Although

the potential exists for minor differences in physiological response by gender for the target population, minimal number of clinically significant findings does not indicate that gender differences are of clinical importance for this device.

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 October 12, 2001. The applicant's manufacturing facilities were inspected on July 12 and September 27, 2001 and were found to be in compliance with the device Good Manufacturing Practice regulations.

XIV. APPROVAL SPECIFICATIONS

Directions for use: See the labeling.

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

Postapproval Requirements and Restrictions: See approval order.