

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI:

3000209733

EI Start:

11/26/2007

EI End:

11/29/2007

**TABLE OF CONTENTS**

SUMMARY .....	1
ADMINISTRATIVE DATA .....	2
HISTORY .....	3
INTERSTATE COMMERCE and JURISDICTION.....	4
INDIVIDUAL RESPONSIBILITY and PERSONS INTERVIEWED.....	4
FIRM'S TRAINING PROGRAM .....	5
MANAGEMENT REVIEW & QUALITY AUDITS .....	5
CAPA/ COMPLAINTS/ and MDR PROCEDURES .....	6
LADARVision 4000 COMPLAINT REVIEW and DISCUSSION.....	10
LADAR6000 ROOT CAUSE ANALYSIS REVIEW .....	18
LASER PRODUCT TEST REPORT .....	24
OBJECTIONABLE CONDITIONS AND DISCUSSION WITH MANAGEMENT .....	25
REFUSALS.....	26
SAMPLES COLLECTED .....	26
VOLUNTARY CORRECTIONS.....	26
EXHIBITS COLLECTED .....	26
ATTACHMENTS.....	28

**SUMMARY**

This directed joint follow-up inspection of a Class III medical laser device manufacturer was assigned by DEOBD, DOE A, OC, CDRH (HFZ-331) at the request of CDRH, Field Operations Branch (HFZ-306) under current FACTS assignment # 878029; OC # 070675; to determine current status and effectiveness of Class I Recall (Z-0854-7) for the LADAR6000 Excimer Laser System. Coverage was provided under CP 7382.845C, Medical Device Level III (Compliance) Inspection. ORA Concurrence # 2007092101.

Previous inspection conducted from 3/23/06 – 4/3/07 revealed the firm had made corrections to previously reported observations but reported the firm failed to obtain all possible quality data by not requesting physicians to report device failures and firm failed to include complete information as to results of investigations concerning incidents which were sent to the FDA. The inspection was classified VAI.

Current inspection was directed to the firm's compliance with QSR and MDR regulations to determine the current status and effectiveness of the firm's present Class I recall still in progress and to perform an analysis of the firm's root cause investigation of manufacturing and design procedures of the recalled LADAR6000 Excimer Laser. Review of firm's complaints from 2004 through 2007

**Establishment Inspection Report**

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received for the replacement medical laser, model LADARVision 4000, revealed no serious deviations.

Based on review of firm records, this inspection revealed that the present recall seems effective, but incomplete. At the conclusion of this inspection, seventeen (17) LADAR6000 laser devices were yet to be exchanged for the replacement laser system. This inspection also revealed deviations of the QS and MDR regulations which include, but are not limited to: 1) firm failed to report all injury incidents to FDA; 2) firm failed to report MDR reportable occurrences in a timely manner; 3) firm failed to document all investigations of complaints by field service engineers and "not on site" evaluations of devices; 4) firm failed provide complete rationale for not implementing corrective actions indicated by complaint investigations and 5) firm failed to follow vendor procedures requiring substitution notification of critical components by vendor and firm failed to replace corrected components to field units.

No FDA-483 was issued. All observations were discussed with Mr. Gary A. Woodrell, VP of Manufacturing Operations and most responsible person for this location, who indicated that the observations would be taken under advisement and appropriate corrections made. Appropriate warnings were given to management. No refusals were encountered and no samples were collected.

This inspection was preannounced on November 22, 2007. Two (2) CDRH personnel were assigned to participate in this inspection. Sheryl L. Berman, MD and Bruce A Drum, Ph.D reviewed firm records to assist in making the initial determination concerning the recall effectiveness and root cause analysis of the LADAR6000 system as requested in the assignment. In addition, a random review of complaints for the LADARVision 4000 (L4) received from 2002 to present was conducted to determine if complaints received the model LADARVision 4000 reported similar failures in custom applications.

Except where noted, information contained in this report was provided by the lead investigator for the FLA-DO.

**ADMINISTRATIVE DATA**

Inspected firm: Alcon Refractive Horizons, Inc. (ALCON)  
Location: 2501 & 2800 Discovery Drive  
Orlando, FL 32826-3010  
Phone: (407) 384-1600  
FAX: (407) 513-7854  
Mailing address: 2501 Discovery Drive  
Orlando, FL 32826-3010

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EI End: 11/29/2007

Website: [www.alcon.com](http://www.alcon.com)

Email: [Gary.woodrell@alconlabs.com](mailto:Gary.woodrell@alconlabs.com)

Dates of inspection: 11/26/2007, 11/27/2007, 11/28/2007, 11/29/2007

Days in the facility: 4

Participants: Leo J Lagrotte, Investigator; FLA-DO/TMP-RP - SER/EOS  
Sheryl L. Berman, MD, CDRH/ODE/DOED/Medical Officer  
Bruce A. Drum, Ph.D., CDRH/ODE/DOED/Physicist/Vision Spec.

## HISTORY

All information and/or copies of firm records were provided by or directed through Mr. Gary A. Woodrell, VP of Manufacturing Operations.

This Florida medical device manufacturing facility has been registered with FDA since May 1996. Alcon Refractive Horizon's, Inc. management stated that this facility changed its name in November 2003 to Alcon Refractive Horizons, Inc. and that this is the legal entity registered with the FDA. The firm is a subsidiary of Alcon Laboratories, Inc., 6201 South Freeway, Fort Worth, TX 76134-2099 (FEI: 1610287) registered in the State of Florida as a Foreign Corporation.

The firm had two (2) models of Laser Systems marketed in the United States, LADAR Vision 4000® and LADAR6000™; however as of 2007, all manufacturing operations ceased. The LADAR6000 temporarily ceased manufacturing in February 2007 after spontaneous complaints were received in the latter part of 2006 and early 2007 reporting serious malfunctions that contributed to reports of central islands. The firm initiated a Class I recall on 2/21/07 initially to inactivate software applications for M<sup>3</sup> and A<sup>7</sup> algorithms. Then in August 2007, the recall was expanded to a complete replacement of the LADAR6000, which by this time, had ceased manufacturing operations entirely. According to Mr. Woodrell, the LADARVision 4000 models were no longer being manufactured as of 2004, but are one of the replacement lasers for the LADAR6000. The LADARVision 4000 units will be new or refurbished models from inventory or the Wavelight Laser system manufactured by Wavelight, AG, Erlangen, Germany. According to Mr. Woodrell, [REDACTED]

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Mr. Woodrell stated, on 11/26/07, that twenty (20) lasers systems still needed to be replaced. On 11/28/07, he reported that three (3) units were deactivated and/or contracts negotiated for replacements. He warranted that by December 8, 2007, all remaining seventeen (17) units would be either deactivated by Field Service Engineers (FSE) or removed from their locations. It was confirmed verbally on 12/12/07, from CDRH personnel, that the firm informed the center that this phase of the recall had been accomplished.

**Establishment Inspection Report**

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EI Start: 11/26/2007

EI End: 11/29/2007

**INTERSTATE COMMERCE and JURISDICTION**

This firm is an FDA registered Class III medical device manufacturer. Interstate commerce and jurisdiction have been fully reported in all previous inspections in 2004; 2005 and 2006. However, the firm has ceased all manufacturing operations of the LADAR6000 Excimer laser in 2007.

Although manufacturing of the LADARVision 4000 laser ceased manufacturing in 2004, the firm will be replacing the recalled LADAR6000 units with the LADARVision 4000 or another laser as decided with each customer independently. Mr. Woodrell stated that the firm will be servicing the LADARVision 4000 model until 2011. According to Mr. Woodrell, the firm has estimated that there are sufficient components on inventory and contained within idle devices that can be cannibalized to insure that repairs made to present inventory in the field can be sustained with OEM components until the 2011 timeframe.

The 2800 Discovery Drive location, which served as the manufacturing site is in the process of being fully dismantled. As of 2008, Mr. Woodrell estimated that all Alcon Refractive Horizons, Inc. responsibilities in Florida will end. The facility located at 2501 Discovery Drive will continue to serve as a research and development segment for the company after the 2008 shutdown, according to Mr. Woodrell.

We also discussed the two final PMA supplements for [REDACTED]. According to Mr. Woodrell, the firm received FDA approval of [REDACTED] but never implemented the changes and PMA [REDACTED] was withdraw from FDA review. Documents concerning the approvals and withdrawals of these supplements were provided by Mr. Woodrell and included as Exhibits 24 and 25.

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**INDIVIDUAL RESPONSIBILITY and PERSONS INTERVIEWED**

On 11/26/07, credentials were shown and FDA-482, Notice of Inspection was issued to Mr. Gary A. Woodrell, Vice President Manufacturing Operations and reportedly the most responsible person for the Orlando facility. The Resources for FDA Regulated Businesses was also issued and briefly discussed. Mr. Woodrell accompanied us throughout the inspection and provided us with information concerning the firm's day-to-day operations.

Mr. Woodrell said he is the most responsible individual on site for the operations at this Florida facility. Mr. Woodrell said he reports to Mr. Bill Richardson, Vice President Manufacturing, Surgical Operations, Ft. Worth, TX and General Manager of the Orlando facility who reports to Mr. Andre Bens, Ph.D, Senior Vice President, Global Manufacturing and Technical Support, Ft. Worth, TX who reports to Mr. Cary R. Rayment, President and CEO, Ft. Worth, TX (**Exhibit 3, Organization Charts, pg 2**). He stated that Mr. Rayment is most responsible for the overall operations of Alcon Laboratories, Inc., Fort Worth, TX.

**Establishment Inspection Report**

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FEI: 3000209733

EI Start: 11/26/2007

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On 11/27/07, 11:17 AM another FDA-482, Notice of Inspection was issued and credentials shown to Mr. Woodrell when Dr. Bruce A. Drum, Vision Scientist, arrived at the firm.

During the inspection, we were also introduced to the following individuals who provided information and firm records in their areas of responsibility:

Rebecca G. Walker, Vice President Regulatory Compliance, Ft. Worth, TX  
Keith R. Bell, Vice President Quality Assurance, Surgical, Ft. Worth, TX  
Steven Bott, Ph.D, Vice President Refractive Research & Development, Orlando  
George H. Pettit, MD, Ph.D, Chief Scientist, Orlando  
Brian Green, Senior Quality Engineer, Orlando  
Sherri J. Lakota, Associate Director Regulatory Affairs, Orlando and facilitator for this inspection  
Bill Altonaga, MD, OD, Manager Technical Consumer Affairs, Orlando  
Leslie A. Voll, Quality Analyst II, Orlando and recorder of this inspection  
Sally Thorsen, Manager of Product Assurance, Orlando  
George V. Carroll, Manager, Pre-Production Quality Assurance, Orlando  
Larry Van Horn, Senior Staff System Engineer, Orlando  
Jeanette Richardson, Manager, Technical Support Orlando  
David Gibbs, Program Manager, Research & Development, Orlando

According to Mr. Woodrell, Mr. Rick Kiser replaced Mr. Mark Neal as the Director of Quality Assurance and the firm's Management Representative in September 2007 but Mr. Kiser was unavailable and did not participate in this inspection.

**FIRM'S TRAINING PROGRAM**

The firm's training program was analyzed as it pertained to the firm's assurance that appointed auditors of the firm's quality system were properly trained and not responsible for the areas audited. At the time we reviewed the firm's internal audit procedures and matrix, we reviewed the certificates of training and CV's for two of the firm's appointed internal auditors Mr. Tom Bivens and Ms. Lori Barry (Exhibit 6).

No deviations of FDA Quality System regulations were observed.

**MANAGEMENT REVIEW & QUALITY AUDITS**

At the onset of the inspection on 11/26/07, I was accompanied by Dr. Sheryl L. Berman, Medical Officer. We requested the complete list of all complaints received for the LADARVision 4000

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI:

3000209733

EI Start:

11/26/2007

EI End:

11/29/2007

Excimer Laser, Quality System Manual (Exhibit 1) and an Index of the firm's SOPs (Exhibit 2)

## Establishment Inspection Report

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

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on 11/27/07. The list of complaints encompassed a mixed description of clinical and device function failures. The list of requested complaint files were removed from the 145 pages of the original report and included as **Exhibit 28, 63 pages**.

Dr. Berman discussed the complaint issues concerning the LADAR6000 and the reports of "central islands" with Dr. Altonaga and Mr. Woodrell, which facilitated the firm's spontaneous report of device failures that initiated the recall of the M<sup>3</sup> and A<sup>7</sup> algorithms and subsequent expanded recall of the LADAR6000 from the marketplace, which is still in effect.

According to Dr. Altonaga, when reports were received starting in November 2006, concerning central islands (CI) which in original complaints reviewed mentioned reports of Central Topographical Elevations (CTE), the firm sent each trained user of the LADAR6000 a "Dear Doctor" letter and a questionnaire requesting immediate feedback (**Exhibit 29**). We asked Mr. Woodrell why the trained individuals of the LADARVision 4000 lasers were not also included. He stated the firm's investigations resulted in no evidence that the LADARVision 4000 was having similar problems and that some users of the LADARVision 4000 system were overlapped because of the clinic upgrades to the LADAR6000 system.

Dr. Altonaga stated that the firm conducted a retrospective review of all LADARVision 4000 complaints searching for similarities in the LADAR6000 complaints. He provided a copy of the firm's memos to file, dated 6/7/07 (**Exhibit 26 & 27**) for review. Dr. Altonaga stated that they searched the complaint database for failure codes that would have been reported that would resemble or actually reported as CI. He provided a compiled list of "38 eyes" that were reported as possible issues that could have been CI (**Exhibit 30**). The report includes the LADARVision 4000 serial number, doctor last name, etc. He stated that the final determination of the reports reviewed was that only one (1) possible CI issue was found and that the investigations determined that most were the result of post surgery traumas and/or were corrected after healing.

### COMPLAINT REVIEWS

While waiting for the firm to provide the list of LADARVision 4000 complaints, we requested the firm's CAPA procedures (**Exhibit 9**), CAPA Log and specific procedures used for Complaint handling and MDR reporting (**Exhibits 10 – 18 and 20**) and reviewed all complaint files pertaining to the retrospective analysis of LADARVision 4000 complaints and evaluation of CI issues.

Dr. Berman reviewed all clinical complaint files and I reviewed those that referred to malfunctions and some of the clinical complaints as provided by Dr. Berman on the original thirty eight (38) retrospective complaints on the LADARVision 4000 system. Dr. Berman worked independently and referred questions to Dr. Altonaga while I referred my questions to Mr. Woodrell and other members of the firm responsible for the area in question. The section of this report prepared by Dr. Berman is included in paragraph LADARVision 4000 Complaint Review and Discussion below prefaced with my review of some of the clinical complaints.

I asked Mr. Woodrell what format the complaint database was written and he did not know. I asked if the database could be converted to EXCEL format and if so, requested a copy of the complaint

**Establishment Inspection Report**

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EI End: 11/29/2007

database on CD/R for our review. After several hours of computer downloading, the firm asked Mr. Brian Green if he could determine the problem. Within an hour he was able to provide the information we requested and the CD/R which is included as **Exhibit 21**.

**CAPA REVIEW**

Ms. Leslie Voll provided the requested CAPA log of all CAPAs initiated since the last inspection. I briefly reviewed this report and requested it be provided on CD/R for ease of review; which is included as **Exhibit 19**. On 11/27/07, Dr. Berman and I finished review of the additional eighty-seven (87) complaints selected from the LADARVision 4000 complaint list reported below and on 11/28/07, I turned to the review of CAPAs the firm initiated since the previous inspection.

Mr. Woodrell and I discussed all of the CAPAs listed in **Exhibit 19** and I made several observations:

**CAPA2269**

The firm includes system bug repair as part of a new software change. For example CAPA2269 (**Exhibit 40 & 43**) list of software changes was initiated to correct an issue with the Advanced Assisted Registration of patients and included repair of disk problems reported under CAPA2233 and Centration problems with the limbal ring initiated under CAP 2275.

This CAPA was initiated on 5/3/06 at the time the LADAR6000 was introduced. I discussed this CAPA and the related CAPAs with George V. Carroll, Manager Pre-Production QA. He provided the section of the CAPA development plan I requested (**Exhibit 40**) and the risk analysis of the changes to occur (**Exhibit 41**). I had no objection to the firm's procedures or changes made; however I did object to the firm's failure to implement the corrective actions on the basis that the LADAR6000 was being recalled and removed from the market. According to the CAPA record for 2269, the firm initiated the CAPA in May 2006, determined the corrective action to be taken, but decided on 7/9/07 that the corrective action would not be taken due to the removal of the LADAR6000 from the marketplace. The firm's records indicates: "Update 3/29/07 - Issue reopened so that it could be updated with the final software revision release date."

"Update 7/9/07 - Management determined that this software issue posed no risk to patients and could be held in a status of "verified" until a final decision is made whether to release another software revision."

"Due to the removal of LADAR6000s from the field, a decision was made by Quality Senior Management on September 19, 2007 to close all CA issues with open effectiveness checks. Effectiveness checks are no longer needed for LADAR6000 issues."

I objected that the firm failed to initiate corrective actions indicated by their investigation 18 months after the CAPA was initiated. Based on firm CAPA procedure (**Exhibit 9**) the firm failed to meet



**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

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FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

timeliness requirements. **(Discussion with Management)**. This issue is continued in almost every CAPA reviewed.

**CAPA 2283**

This CAPA reports of a vendor substitution change in a critical component that the firm was not made aware. The firm reports that four complaints were received from four different sites stating that the Tracked image was out of focus on the LADAR6000 (RS060872, RS060775, RS061228, RS061291). Preliminary research indicates that on some systems focus significantly changes when using IR vs. Visible illumination. The firm investigated the cause and determined that the optics vendor made substitutions to lenses incorporated in the Tracker Module Assembly BOM, to include the new Tracked Camera Optics Housing, 6309-0205-01. Mr. Woodrell stated that there were 30 components involved and review of the changes indicated the change was minor and new Tracker Module Assemblies were ordered to replace the units with the incorrect optics.

However, the firm failed to complete the changes and the new Tracked Camera Optics Housings purchased were never changed based on the firm's removal of the LADAR6000 from the marketplace. "Due to the removal of LADAR6000s from the field, a decision was made by Quality Senior Management on September 19, 2007 to close all CA issues with open effectiveness checks. Effectiveness checks are no longer needed for LADAR6000 issues." The corrective actions were not taken.

I also objected to the firm's failure to follow vendor and incoming component inspection procedures by not determining that there was a change made to the tracked camera optics housing before they were installed to devices released to the field **(Discussion with Management)**.

I objected to the firm's failure to make corrective action **(Discussion with Management)**. I told Mr. Woodrell that the CAPA was initiated in October 2006, corrective action analysis was completed, new component tracking assemblies obtained but the corrective action was never implemented. He stated that it was management decision not to make the corrective actions since the LADAR6000 was being removed from the marketplace.

Other CAPAs reviewed with similar outcome are as follows:

**CAPA 2284**

This CAPA was dated 10/5/06 and reports: "A site reported to Alcon that their system was not passing size distortion in Geometry Adjust. The FSE found the calibration ring for video scaling was set to 12mm instead of the target [REDACTED]. Preliminary research by the software department identified this issue to be software related and not a service setup error". The software corrective action was determined but firm management on 8/13/07, failed to execute the corrective action based on the LADAR6000 being removed for the marketplace.

(b)(4)

## Establishment Inspection Report

Alcon Refractive Horizons, Inc.

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FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

### CAPA 2290

This CAPA, dated 11/2/06 reports that: "TS have recently discovered that some calibration and configuration data will not be saved if a POST test is forced from Super User mode before the system is powered down or 'save configuration' in super user dialog box is selected. Calibrations such as Zoom Lens Auto Calibration, DSP DAC Offset values and Geometry Adjust values are affected. Changes to the Configure Laser/Procedure Setup window will also revert to their original values. It is unknown if other calibration and configuration functions are reset by forcing POST; this needs to be investigated. This does not affect calibrations performed in regular operator modes because a POST test can NOT be forced from regular/customer mode." Since the management decided to remove the LADAR6000 from the marketplace, no corrective actions have been planned.

### CAPA 2293

This CAPA dated 11/17/06 reports: "Three complaints have been received for the gas fill error: PMIX >8000 mBar. The cause was determined to be a defective valve. The corrective action was decided to remove and replace defective valves when problems are experienced in fielded systems. No corrective actions were authorized because the product was being removed from market.

Based on the information included in the CAPA log and discussion with management, I objected to the firm's failure to make corrective actions as planned on the basis that the product would be removed from the marketplace. The final determination to remove the LADAR6000 from the marketplace was made in September 2007, but the CAPAs reviewed were in 2006, some as much as 18 months before the decision to remove the LADAR6000 (**Discussion with Management**).

## LADARVision 4000 COMPLAINT REVIEW and DISCUSSION

### This section is provided by Investigator Lagrotte:

As part of the complaint review of the LADARVision 4000 system complaints requested in the assignment, I assisted Dr. Berman in review of some of the clinical complaints that were part of the firm's retrospective review of complaints. I evaluated Complaints RS040992; RS070851; RS070763; RS070695; RS070686; RS070685; RS070691; RS070689 and RS070763. In my (b)(4) evaluation of these complaints, I focused on a series of complaints RS0709685; 686; 689; 691; 695; 693; 762 and 763 (**Exhibits 22 - 22g**) which were reported by one physician [REDACTED]

I discussed these complaints with Mr. Woodrell and he called upon Mr. Larry Van Horn, Senior Staff System Engineer who provided information concerning the use of "not on site" evaluation of the laser databases for investigation to determine if the system functioned according to specifications.

Mr. Van Horn stated that when the firm receives a complaint of a failure of the laser device to perform within specifications, both for either poor outcome complaints or system malfunction, he initially performs a "not on site" evaluation of the laser database which consists of downloading the a Surgery Database Device Report (SDDR) that checks the database and evaluates the system. For

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

example, in analysis of complaint RS070965 and RS070763 both for the same patient, one complaint for each eye on which surgery was performed. The results of the analysis included a check of the Beam Aspect Ratio, Geometry Adjustment Parameters, Center Offset, Size Distortion, Angular Distortion, Rotational Distortion, Minutes Since Calibration, Mean Laser Energy, CD from Mean Laser Energy, Volume per shot and Number of Shots Delivered vs. Planned. (Exhibit 23). I questioned Mr. Van Horn further on Geometry Adjust and requested the actual charts that this evaluation represented (Exhibit 23 pgs 9-14). I had no observations concerning utilization of this investigational tool when the return of the device is not practical. Mr. Van Horn stated that in addition to the "not on site" evaluation, the firm dispatches a Field Service Engineer (FSE) to conduct an "on site" evaluation of the laser system which includes system checks and test firing of the laser to duplicate complaint.

The following complaints include my review of the firm's investigation of complaints other than those included in the retrospective review. I concentrated on the malfunction complaints while Dr. Berman concentrated on clinical complaints. All complaints can be reviewed in CD/R (Exhibit 21) and all CAPAs in CD/R (Exhibit 19). I completed review of 34 of the 87 complaints and some of those reviews are included below:

RS071791- this complaint was received on 10/25/07 and reported failure of the tracker during a procedure in that it took longer for the tracker to perform its function. According to the complaint, the site reported on 10/30/2007 to the Territory Manager (TM) that on 10/25/2007 it took longer than usual to track an eye on their LADARVision 4000 System. This complaint was assigned complaint code 802B-Not able to track complaint class. The TM was unable to duplicate the reported problem, tracked the test targets multiple times, and verified the tracker system to specifications. The TM changed the IR spot balance level from [REDACTED] to [REDACTED] per channel for preventive measures, and successfully completed system verification. No parts were replaced or returned for manufacturing investigation.

(b)(4)

A patient/user impact investigation was performed for complaint RS071791. The Product Applications Specialist (PAS) spoke with the site Technician who stated that for almost all patients treated on 10/25/2007, they had difficulty tracking. However, the Technician stated they were able to complete all patients, and the surgeon stated no patients were harmed or injured.

The LADARVision 4000 System Software [REDACTED] was in use during custom and conventional procedures on 10/25/2007 on unit L4N1619S. The LADARWave System [REDACTED] was in use on unit LWN2847Z.

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A review for 3 months prior to the date of this event showed no previous complaints of the related 802A-Loss of Tracking and no previous complaints of the reported 802B-Not Able to Track complaint classes for this system. No trends observed.

A review of the product family indicates the rate has not exceeded the upper trend threshold of [REDACTED] complaints for the related 802A-Loss of tracking, and [REDACTED] complaints for the reported 802B-Not able

(b)(4)

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

to track complaint classes for the current month, per Job Aid, Upper Trend Thresholds (Exhibit 17d). No trend within this product family is observed.

(b)(4)

Based on the investigation by the TM who was unable to duplicate the reported issue, the root cause of complaint RS071791 is not applicable.

This complaint aligns with a group investigation of 80 Tracker related complaints of the LADARVision 4000 System documented in complaint file RS051207, including those that could not be confirmed. The results and risks of an Unable to Track issue addressed in RS051207 are relevant to complaint RS071791.

Assessment of the frequency in light of this complaint being evaluated does not change the overall frequency as stated in the investigation report. Consequently the analysis, conclusions, safety analysis and recommendations are applicable to this complaint. The safety analysis in RS051207 determined the following levels: Low severity, level III frequency and an overall risk level C.

After the closure of the prior investigation referenced, SOP 7003-1412, Rev. D and later, was released which acknowledges a hazard frequency of Level IV for complaints where the reported event has not resulted in the harm to the patient or operator defined in the hazard severity of the prior investigation. The investigation of this complaint concludes that no patient or operator harm has been observed and therefore the frequency for this complaint is Level IV and the resulting risk code is D.

Based on the above conclusions, the complaint investigation is considered complete.

I then requested the complaint file on complaint RS051207, dated 7/28/05 which also reported tracker issues which initiated CAPA 2230. The corrective action was to make two design changes DCN 5009 and DCN 8470. I reviewed both design changes and had no observations and determined the firm followed their design control procedures.

RS071761, dated 10/18/07, reported a shutter malfunction which was caused surgeries to be canceled but no patient involvement. FSE could not duplicate. No further calls were received from this location and the complaint was closed. The frequency of complaints for this error wer trended and failed to exceed acceptable limits. I had no observations.

RS070383, Technical Consumer Affairs (TCA) was informed of this complaint (RS070803) while following up on a previous complaint (RS070383) for this site. The site informed TCA that their laser stopped firing during a procedure on 4/12/07. The procedure was 96% complete when this occurred. This reported event occurred on their LADARVision 4000 System. The complaint class of 879-Laser Stopped Firing was assigned to this complaint.

# Establishment Inspection Report

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

There was not an on site visit by a Field Service Engineer (FSE) for this complaint. This complaint was confirmed by the surgery database by "not on site" analysis for this system which showed that on 04/12/2007, the procedure was interrupted by a "Excimer Not Firing" event at 139 seconds (96.2%) into the surgery. When the laser stopped firing event occurred the surgeon did not call for service.

A patient/user impact Investigation was performed on 4/26/07. When Consumer Affairs contacted the site to follow up on the previous complaint (RS070383), the site stated that at the time of this event, the surgeon confirmed that there was no patient harm or injury. The site also denied service at the time that TCA became aware of this event.

Based on the analysis of the above information, the root cause for this complaint, RS070803, is undeterminable, since the FSE was not able to visit the site to perform an on site investigation.

The investigation of this complaint concludes that no patient or operator harm has been observed and therefore the frequency for this complaint is Level IV and the resulting risk code is D.

Possible corrective and preventive actions were considered and determined that no further corrective and preventive action was warranted.

Based on the review of this complaint, I had no observations.

**RS061632-** This complaint involved a site that reported laser stopped firing at 21% into a procedure. This event occurred on a LADARVision 4000, on 11/28/06 (**Exhibit 32**). The complaint class code assigned was 879-Laser Stopped Firing. While onsite, the Field Service Engineer (FSE) was unable to duplicate the reported problem, but was able to confirm that it occurred via the surgery database. A system verification was also performed by the FSE to specification.

A Patient/User Impact Investigation was performed on this complaint. The site was contacted and stated that the doctor made several attempts to retrack and hit ablate, but this was not successful. The doctor put the flap down and aborted the procedure. The procedure was completed uneventfully the next day. At the one week post operative exam, the patients UCVA is reported to be 20/20 OU. The site also stated that the patient was not impacted by the event and the doctor was satisfied with the patient's outcome.

A review of the surgery database was conducted by the Senior Technical Consumer Affairs Engineer and showed that there was an "Excimer Not Firing" event during the surgery, TRK.749, after 20 seconds of ablation. The operator attempted to repress the ablate button and the doctor tried to repress the footswitch multiple times. However, this was not successful at restarting the laser. No attempt was made at exiting and reentering the surgery as suggested in the Operation Manual. After several seconds passed, the site untracked the patient and they were unable to reacquire track. This

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

was caused by the patient having a pupil diameter smaller than the minimum specification of [REDACTED]. The surgery was completed the next day after a service call, and the system was verified. (b)(4)

Based on the analysis of the above information and given Alcon's prior experience with Laser Stopped Firing occurrences, the root cause for complaint RS061632 is Code 09-Component Related, specifically related to the normal behavior of [REDACTED] (Alcon Product Technical Summery-Laser Not Firing- PTS 8400-0003). (b)(4)

According to the investigation, this complaint aligns with the investigation performed on 89 Laser not firing complaints, investigated in RS051219, for the LADARVision 4000 System. The prior investigation included complaints with similar issues, including those that could not be duplicated. Therefore, the results and risks would be similar for this complaint, RS061632. Assessment of the probability in light of this complaint being evaluated does not change the overall probability as stated in investigation report RS051219. Consequently the analysis, conclusions, safety analysis and recommendations are applicable to this complaint. The safety analysis in RS051219 determined the following levels: Low severity, Level I probability and overall risk level C.

I objected that the firm failed to file an MDR concerning the malfunction of the laser when the physician was 21% into the procedure. The surgeon had to replace the flap and the procedure was completed the next day. I told Mr. Woodrell that the procedure had been started, had to be stopped due to the device failure and then resumed at a later date. I told him that an MDR should have been filed. He objected and requested Ms. Rebecca Walker be consulted since this same issue was reviewed during the previous inspection. Ms. Walker and Mr. Bell stated that in the previous inspection, the firm was cited that they filed MDRs when no serious injury took place. The original fir procedure listed in SOP-003976, Version 1 (**Exhibit 38**) stated in section 7.3.6.1 that an MDR would be reported: "If the malfunction prevented completion of a procedure within the same surgical session, or ...if the malfunction were to recur, the chance of a death or serious injury would be likely to occur". The new procedure (**Exhibit 39**) approved and implemented on 4/7/06, four days after the conclusion of the previous FDA inspection, removed section 7.3.6.1 indicating a reportable incident if the procedure was not finished during the same surgical session.

I told the firm that I objected since the surgical procedure was not completed due to a possible device malfunction and should have been reported (**Discussion with Management**).

RS061048 (**Exhibit 33**) reports a similar occurrence for which I also objected that the firm failed to report an MDR incident. I told management I would report these objections in my EIR and request District Compliance and CDRH review (**Discussion with Management**).

RS060804, dated 1/20/05 as the date of incident and first aware date of 6/8/06. The complainant reported continual problems with visual acuity 18 months post surgery. The firm failed to file an MDR until 7/19/06. I told the firm that I objected to the late reporting but indicated that this observation would be included as a **Discussion with Management** issue.

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

**RS071435** – The site reported on 08/02/2007 to the Territory Manager (TM) that they would lose tracking intermittently throughout the day on their LADARVision®4000 System. The site was able to re-track and continue. This complaint was assigned the 802A-Loss of tracking complaint class. The TM was able to reproduce the problem one time by tapping on the modules inside the analog box, but then could not reproduce it again. The TM replaced the analog assembly as the most probable cause, and successfully completed system verification. The manufacturing investigation of the returned part was unable to duplicate the reported issue.

A patient/user impact investigation was performed for complaint RS071435. The Product Applications Specialist (PAS) spoke with the site's Refractive Director who said the surgeon stated no patients were harmed or injured, and no patient outcomes were affected.

The LADARVision 4000 System Software [REDACTED] was in use when the site lost track during a conventional procedure on 08/02/2007 on unit L4N1660S. Based on the investigation by the TM who was able to reproduce the reported issue, the root cause of complaint RS071435 is component related, specifically a faulty analog assembly. (b)(4)

This complaint aligns with a group investigation of 80 Tracker related complaints of the LADARVision 4000 System documented in complaint file RS051207, including those that required analog assembly replacement. The results and risks of a Loss of tracking issue addressed in RS051207 are relevant to complaint RS071435.

After the closure of the prior investigation referenced, SOP 7003-1412, Rev. D and later, was released which acknowledges a hazard frequency of Level IV for complaints where the reported event has not resulted in the harm to the patient or operator defined in the hazard severity of the prior investigation. The investigation of this complaint concludes that no patient or operator harm has been observed and therefore the frequency for this complaint is Level IV and the resulting risk code is D.

Possible corrective and preventive actions were considered and no further corrective and preventive action is warranted at this time.

I requested a copy of the service test record to determine exactly what test were performed on site. The service record is included as **Exhibit 31**. No objections were observed.

**This section of the EIR was completed by Dr. Sheryl L. Berman, CDRH/Medical Officer:**

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

*Note: The following summary is related to my involvement in the investigation. Refer to comments by Bruce Drum for additional contributions to E.I.R. written by Leo Lagrotte.*

On 11/26, Leo Lagrotte and Sherri Berman, M.D. arrived at Alcon in Orlando. Mr. Woodrell explained that Alcon's Orlando organization would cease in 2008, that LADARVISION 4000 repairs would continue until responsibility was transferred (repair, complaint handling, etc.), and that manufacture of Excimer laser devices as well as the LADARWave aberrometer would cease. The status of the LADAR6000 recall to date is as follows: there are 20 units still in the field, which will be disabled and/or removed by 12/8/07. The existing LADARVISION 4000 units (including those that replace recalled LADAR6000) will be serviced until 2011 or until available parts are exhausted (7 years from last device manufactured). There are [REDACTED] LADARVision 4000 in the U.S. [REDACTED] units worldwide).

(b)(4)

A complaint database was requested by FDA, as well as SOPs (to include those for complaint handling). Alcon provided a hard copy (**Exhibit #28**) of complaints received from 2002 through present. We later reviewed the entire list and highlighted 87 complaints that represent a wide variety of patient outcome complaints (eg. loss of best corrected visual acuity, undercorrection, overcorrection, etc.) and device malfunction complaints (eg. laser not firing, smoke from unit, etc.). FDA also requested an expanded electronic copy of the complaint database, with additional fields to include Alcon findings and action. This CD was provided the following morning, after technical difficulties transferring their [REDACTED] software database to Excel format is included as **Exhibit 22**. Leo Lagrotte's review of this database and sorting for specific failures and malfunctions revealed a few anomalies which were discussed with management.

(b)(4)

I requested an explanation of Alcon's procedure for complaint trend analysis, with regard to the UCL thresholds (upper confidence limit) noted in the SOP and in complaint file investigation summaries. Mr. Green explained that an UCL is [REDACTED] complaint rates for the device. Reports that exceed the UCL are discussed at weekly trend analysis meetings.

(b)(4)

When asked whether the initial complaints of central islands were reported as "central island," Mr. Altonaga confirmed they were indeed reported as such. Prior to the time frame of 11/06 - 2/07, occasional complaints associated with topographic abnormalities were found to be associated with epithelial healing, and not at rates found with the LADAR6000. Furthermore, Ms. Walker clarified that the Dear Doctor letter from Alcon that informed about the central island reports with the LADAR6000 was addressed only to LADAR6000 trained users, because there were never any spontaneous reports of central islands with the LADARVISION 4000 causing concern about a clinical trend, as there were with the LADAR6000. Alcon's internal investigation (clinical database query for any topographic change complaints since the LADARVISION 4000 has been in use) turned up 37 case reports; it was stated that many cases were subsequently ruled out as central islands by the reporter as well as by Alcon.



**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

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On 11/27, FDA requested the case files for the 37 reports of central islands associated with the LADARVISION 4000 (Mr. Altonaga indicated there were 38 reports to date, the most recent reported on 11/9/07, unconfirmed pending receipt by Alcon of medical records). FDA also requested case files for the 87 highlighted clinical outcome and device malfunction complaints received by Alcon from 2002-2007. These files were provided by Alcon in batches, and were reviewed by myself and Leo Lagrotte. Notes were taken for each file reviewed, regarding factors such as RS# report number, initial complaint, date Alcon aware, date MDR issued, summary of Alcon investigation documented (device history trend analysis, remote device performance verification within specification, assessment of pre-op risk factors, communication with reporting physician regarding Alcon analysis outcome, etc.), presence of clinical records in file, and clinical outcome/injury.

The following general comments summarize my chart review of clinical complaints (*also refer to notes from Leo Lagrotte for summary of charts he reviewed*). No observations reveal deviation from expected procedures for complaint handling. MDRs were issued within 30 days after Alcon aware of complaint, except one case (#RS070243) with MDR found not to be sent due to miscommunication internal to Alcon, subsequently sent 1 month late (when noted), and one case (RS#061102) reported ~40 days from date aware. Files are organized with an investigation plan of action, and a summary report of the Alcon investigation. Alcon SOP for complaint handling appears to have been followed in the sampled files (**please refer to Exhibits 17 – 17i**). The majority of complaints do not have topographic documentation consistent with central island (eg. not present in initial post-op scans, improve over time, asymmetric topographic changes) or have inadequate topography documentation (scales inconsistent over time or very large dioptric scale range). Most files have clinical records—exceptions being #RS041383 (10/04) with documentation of telephone confirmation of “no loss of BCVA,” and #RS041604 (12/04) with verbal confirmation of BCVA. It was clarified by Mr. Altonaga that since that time, the Alcon “Data Gathering Job Aid” was revised to require obtaining medical records in the complaint file. Mr. Woodrell noted that this SOP was revised in 2005. In many cases, despite Alcon documentation of attempts to obtain clinical records, the reporting physician refused to provide records or clinical information after making the complaint, thus limiting Alcon investigation to device performance verification.

FDA requested that Mr. Petit summarize the root cause investigation underway by Alcon. Mr. Bott, who oversaw the analysis, stated that the top cause is believed to be due to the shot pattern (spiral-in) combined with hydration effects, as well as systematic error in spot placement due to device hardware (translator was modified in the LADAR6000 in conjunction with increase in pulse rate)—a vibration/resonance problem that occurred only at certain frequencies (thus sporadic occurrences of central islands), both causes mitigated by individual healing response. In response to FDA question about relation of these root causes to hyperopic treatments, Mr. Bott responded that comparative ablation shows no difference between LADARVISION 4000 and LADAR6000, and that hyperopic algorithm has more erratic shot sequence than myopic treatment. Bruce Drum then evaluated supportive documentation provided by Alcon.

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

On 11/28, in response to FDA request, Mr. Altonaga provided a summary (**Exhibit #30**) of central island reports for the LADARVISION 4000. There was 1 case with documented loss of 2 lines BCVA, 9 cases with loss of 1 line BCVA documented, only 2 cases determined by Alcon to be potential central islands (the other 36 reports were ruled out due to serial resolution of topographic abnormalities, or absence of evidence of topographic abnormality).

Ms. Walker also provided internal Alcon email correspondence dated 5/16/07 (exhibit #37) to justify overcorrection complaints determined by Alcon as non reportable (eg. RS#070615, Alcon aware 3/27/07, overcorrection with 1 line loss of BCVA). The emails indicate that over corrections should be reported as MDR unless there is affirmative documentation from the site that there was no patient injury.

Complaint file review was continued from previous day.

Discussion ensued regarding case RS#061048, a report of the laser stopping halfway through a procedure requiring patient to return next day for remainder of treatment, which Alcon did not report as MDR, though Leo Lagrotte said this should have been reportable. The device failure did not result in any permanent patient injury according to the records. Alcon management was upset by the fact that the prior EIR noted that Alcon had been misinterpreting MDR reporting guidelines because they *had* been reporting all device failures, even without patient injury. Alcon requested that no warning letter be issued, and instead, a way to discuss the situation, since they would have been reporting such device failures had the prior EIR observation not been made. They indicated their willingness to change their MDR reporting procedures per CDRH interpretation, as per their previous procedures. FDA agreed to convey this concern to CDRH (**Please see section of this report completed by Leo Lagrotte concerning other MDRs in question**).

**LADAR6000 ROOT CAUSE ANALYSIS REVIEW**

When Dr. Bruce A. Drum arrived on 11/27/07, we issued another FDA-482, Notice of Inspection and he met with Dr. Steven Bott, VP, R&D, Dr. George H. Pettit, Chief Scientist and Keith R. Bell, VP of QA Surgical to review the root cause investigation and failure analysis the firm had conducted on the LADAR6000 Excimer laser system. According to the explanation of Dr. Bott the firm had conducted the investigation but was still in process of finalizing the report. The remainder of this section will be the report as provided by Dr. Drum concerning his evaluation of the firm's root cause investigation and report. The copies of firm records concerning this investigation remained in the possession of Dr. Drum for review to complete his section of the report and logging of Exhibits.

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

This section of the EIR was completed by Bruce A. Drum, Ph.D., CDRH/Vision Specialist

**CAPA 2300**

My primary assignment was to evaluate Alcon's investigation and analysis of the root cause(s) of the "Central Island" adverse events reported for the LADAR6000 excimer laser system. I first requested a verbal summary of progress to date and asked for all existing documentation of the root cause investigation. Alcon initially provided a 38-page draft report (**Exhibit 45**) that cited 22 appendices. Upon my additional request, the appendices were also provided (**Exhibits 45a-v**) with one exception: Appendix 20 was not complete enough to be useful, but Alcon assured me that they would provide it as soon as it was finished. The main components of the investigation and the findings to date are summarized below.

**Scope of Investigation:**

The report covers the root cause investigation of "central island" (CI) events occurring in eyes treated with the LADAR6000 system, using "CustomCornea" ablation algorithms M3 for spherical myopia or M7 for myopia with astigmatism. The investigation focused specifically on CI complaints submitted between 11/14/06 and 3/20/07. The complaints were filed by 13 of the [REDACTED] LADAR6000 sites in the U.S., and represented 109 eyes of 57 patients. Of these eyes, 90 were confirmed by Alcon to have central corneal topography elevations that resulted in undercorrections of at least 1 diopter. Only one eye was treated for spherical myopia, and the other 89 were treated for myopia with astigmatism. Additional analysis of the topographic results from these eyes and of test ablations on flat plastic showed that in addition to the underablation of the central region the CI corneas, the ablations were "rougher" than comparable ablations with the LADARVision 4000 systems. Alcon suspected that these problems were related to the following design changes between the LADARVision 4000 and LADAR6000 systems:

1. Increase in shot frequency from [REDACTED] to [REDACTED]
2. Replacement of the [REDACTED] with a lighter, stiffer [REDACTED] designed to operate at the higher shot frequency.
3. Change in shot sequence from [REDACTED] to [REDACTED] (b)(4)

In addition, the investigation evaluated the following potential causes of the CI events:

4. Subsystems identical to those in LADARVision 4000 (excimer optics path, excimer profile at eye, treatment algorithms, shot pattern algorithms, and system calibration)
5. Eye tracker problems
6. Excimer laser problems
7. CSPS (Custom Surgery Planning Software) bugs

# Establishment Inspection Report

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

8. LADAR6000 software bugs
9. Plume interference effects.
10. Excimer optics degradation
11. LADARWave (aberrometer) software bugs
12. LADARWave measurement error
13. Microkeratome type used in procedure

## Root Cause Analyses -- Sources Ruled Out

Each of the above potential causes was evaluated and/or tested to determine its possible contribution to the CI and/or ablation roughness outcomes. Items 4-13 were ruled out based on the following arguments or evidence:

4. Subsystems identical to those in LADARVision 4000. Because the rate of CI reports for the LADARVision 4000 was only 4 per 100,000 vs. 403/100,000 for the LADAR6000, Alcon argued that the cause of the high rate in the LADAR6000 systems is likely different from that associated with CIs in the LADARVision 4000. Therefore subsystems that are identical in the two models can be ruled out as root causes.

*Comment: This argument is not logically airtight, since it does not consider the possibility of a root cause that arises from interactions between subsystems. A subsystem that is innocuous in the 4000 could contribute to CI formation when teamed with a modified 6000 subsystem. Indeed, as Alcon demonstrates elsewhere in the report, the fact that the shot pattern is constructed from [REDACTED] contributes to the generation of systematic positional errors only when combined with a faulty [REDACTED] design and the [REDACTED] shot sequence. This is a minor point in this case, since Alcon has described the interaction (even though they did not identify it as such) and its effects on ablation roughness, and I see no apparent interactions involving the other listed subsystems.*

(b)(4)

5. Eyetracker: The eyetracker records were examined for the 12 most severe CI cases. Eyetracker performance was normal in all cases. Details and tracker records are provided in Appendix 2 (Exhibit 45b).
6. Excimer Laser: The excimer laser beam energy for every shot of every procedure is measured and stored in the "instrumentation file". The beam energy records for the 12 most severe CI cases were examined and found to be normal. The results are provided in Appendix 2 (Exhibit 45b).
7. [REDACTED] Software: The [REDACTED] Software generates a file containing patient information and a detailed prescription for the treatment, including Zernike terms for higher

(b)(4)

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

order aberration. A detailed code comparison between the current version [REDACTED] and the baseline version [REDACTED] showed no measurement-related changes that could have caused ablation differences. Details are in Appendix 3 (Exhibit 45c).

(b)(4)

8. LADAR6000 Software: A code comparison between the initial version [REDACTED] of the LADAR6000 software, for which no CIs were reported, and the current version [REDACTED] showed no changes that could have caused a difference in shot patterns, as detailed in Appendix 4 (Exhibit 45d). This was verified by using both versions [REDACTED] (for which no CIs were reported) and [REDACTED] to generate shot patterns from the same [REDACTED] input file. The resulting shot patterns were identical. Details are provided in Appendix 5 (Exhibit 45e).

(b)(4)

9. Plume Removal and Ablation: The [REDACTED] for the LADAR6000 is known to lose efficiency over time. Therefore, a correlation analysis was performed between CI incidence and time since replacement of the plume evacuator filter. No correlation was found. Details are in Appendix 6 (Exhibit 45f). Also, *in vitro* experiments were conducted with bovine eyes to see whether [REDACTED] produced greater "shoot through the plume" interference. Results with a high-speed camera showed that plume removal was complete within [REDACTED] after each shot, well before the onset of the succeeding shot for both shot frequencies. Also, ablation depth per pulse in bovine corneas was compared and found to be equivalent ([REDACTED] vs. [REDACTED]) for [REDACTED] shot rates. Details are provided in Appendix 6 (Exhibit 45f).

(b)(4)

10. Laser System Optics Uniformity: Excimer laser optics degrade over time, resulting in transmittance loss and variation in transmittance profile. This degradation is monitored daily and kept within defined limits by tech support maintenance procedures. These effects were modeled for new optics and at the specified limits of non-uniformity of transmittance, and found to be far below a level that could contribute to CI formation. Details of the modeling and results are in Appendix 7 (Exhibit 45g).

11. Evaluation of a Returned LADAR6000: [REDACTED] returned laser L6N2012S after reporting a number of CIs. Alcon's initial evaluation showed underablation at the ablation center and rough ablated surfaces. A systematic examination of possible causes was conducted, and the roughness and underablation problems were found to be specific to the [REDACTED] shot frequency. Removal and reinstallation of the [REDACTED] changed the characteristics of the ablation errors but did not eliminate them. Results of the investigation are reported in Appendix 9 (Exhibit 45i).

(b)(4)

12. Correlation of CI Incidence to Patient and System Parameters: *(Comment: During my review of the draft report, I noted and mentioned to Alcon that Appendix 8 was not cited. Alcon replied that this was an inadvertent omission, and provided an insert (Section 3.2.8) to the report between pages 11 and 12, summarizing and citing Appendix 8.)* Appendix 8 (Exhibit 45h) reports a statistical analysis of correlations between 98 reported CIs in 4,156 surgeries and a wide variety of patient and system parameters (e.g., time of surgery, humidity, amount of

# Establishment Inspection Report

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

correction, depth of ablation, etc.). None of the measures were linked to CI incidence except for high MRSE and high myopia.

*Comment: Three potential causes listed as ruled out in the report summary (LADARWave software bugs, LADARWave measurement error, and Microkeratome type used in procedure) are not discussed further in the main body of the report. However, it is extremely unlikely that any of these factors differed systematically and selectively in ways that could account for the increased incidence of CIs for the LADAR6000 system, and for the sporadic, unpredictable pattern of CI occurrence observed. For completeness, however, Alcon should discuss these potential causes explicitly in the final version of the report.*

(b)(4)

## Root Cause Analyses -- Sources Supported

The two factors that Alcon initially suspected to be the principal root causes of CIs and surface roughness in the LADAR6000 -- the change in shot sequence from [REDACTED] to [REDACTED] and the increase in shot frequency from [REDACTED] to [REDACTED] -- have been generally confirmed by extensive testing and simulation modeling. However, the results indicate that the causes are much more complex than a simple two-factor model, and that interactions among many interrelated factors conspired to produce the observed defects. A third critical factor that was explained more clearly in discussions than in the draft report was the switch from [REDACTED] to [REDACTED] that turned out to have a flawed design. The following summary explanation draws from the draft report, my notes of discussions with Steve Bott and George Pettit taken during the inspection, and additional supporting documents.

(b)(4)

Increasing the shot rate from [REDACTED] to [REDACTED] required a redesign of the beam-positioning hardware because the old beam [REDACTED] system was too massive and slow to ensure consistently accurate beam placement within the specified limits. Alcon's solution was to switch from [REDACTED] to [REDACTED] units that were lighter, stiffer, and faster than the [REDACTED]. The [REDACTED] were glue-mounted onto rigid bases, whereas the [REDACTED] were clamped into position to allow easier replacement during routine preventative maintenance procedures. In some [REDACTED], it appears that the clamps do not completely secure the [REDACTED] and the [REDACTED] can slide back and forth up to a few microns within their mounts when the [REDACTED] abruptly reverses direction. The result is a positional error on the cornea whose direction depends on the direction of the most recent [REDACTED] jump. The distance between the [REDACTED] and the cornea acts as an optical "lever arm" that converts this slippage into errors of beam position as large as [REDACTED]. Errors of this magnitude are well within the design specifications, and they would be inconsequential if their direction were random. However, the Alcon shot sequence algorithm is not random; it divides the ablation zone into [REDACTED] larger than the beam size, each containing a subarray of programmed shot positions. In order to minimize corneal heating, the shot sequence starts at a position either within the [REDACTED] or within one of the [REDACTED], and jumps to a neighboring [REDACTED] with each successive shot. When a [REDACTED] from the center to the edge (or vice versa) has been traversed, the beam jumps back to

(b)(4)

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

begin the next spiral, and so on, progressing around the ablation zone. For myopic ablations, the shot positions are much more tightly and regularly packed in the [REDACTED] than in [REDACTED]. Because of details in the algorithm rules for selecting the starting point for the next spiral, it turns out that for the [REDACTED], the direction of the last positional jump to the center progresses systematically with successive spirals, but for the [REDACTED] the direction of the first jump from center is more random. For the [REDACTED], the [REDACTED] and its immediate neighbors contain "patches" of shot positions that are all displaced in about the same direction, but the errors in neighboring patches are in different directions. The result is that the edges of neighboring patches overlap too much in some spots and not enough in other, creating significant bumps and dips, or "roughness", even though the average positional error of individual shots is less than [REDACTED]. Alcon has developed a [REDACTED] method, detailed in Appendices 13 and 14 (Exhibits 45m, n), that photographs the exact position of each shot in a sequence, and has documented the hypothesized systematic positional errors. They have also developed a detailed computer simulation model of this process that simulates the observed systematic positional errors and duplicates the observed appearance of myopic treatments with central islands and increased roughness. Details of the model are in Appendix 20 (Exhibit 45t, to be provided upon completion). Graphical results of representative simulations and a map illustrating the shot and [REDACTED] layouts for a myopic ablation are provided in Exhibit 49.

(b)(4)

*Comment: Many of the details in the above account of the explanation for small systematic positional errors were communicated during the inspection in discussions with Steve Bott and George Pettit, but they are not explicitly described in the draft CAPA report. I recommended, and Alcon agreed, that the final version of the report should clearly identify the [REDACTED] design flaws and related instability of performance as a third major root cause of the CI problems.*

(b)(4)

The [REDACTED] effects described above appear to be greatly reduced or extinguished when the shot frequency is reduced from [REDACTED] to [REDACTED] (see analyses in Figs. 11-13, pp. 23-25, of main report (Exhibit 45)) suggesting that the effects may be facilitated by a resonance frequency near [REDACTED]. LADARVision 4000 systems equipped with [REDACTED] but retaining the [REDACTED] at [REDACTED] have been sold into the U.S. Market. The [REDACTED] performance has never been evaluated for these systems. However, of 8,694 treatments with algorithms [REDACTED], only one complaint has been reported, and that complaint was determined not to be due to a central island. At my request, these data were provided in a table (Exhibit 47) detailing the indications for all refractive procedures performed with these systems.

(b)(4)

*Comment: I concluded that these systems are unlikely to present an increased CI risk, and do not need to be recalled or subjected to any special [REDACTED] testing.*

(b)(4)

An initial hypothesis for CI formation was that the [REDACTED] can drive fluid toward the center of the cornea and thus interfere with central ablation efficiency. This hypothesis was tested by comparing [REDACTED] ablations in bovine eyes under otherwise identical conditions and ablation parameters. [REDACTED] ablations averaged [REDACTED] deeper than [REDACTED].

(b)(4)

**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

ablations. These results are consistent with the hypothesis that the [REDACTED] generates excess central fluid that interferes with the central ablation. The study is described in detail in Appendix 21 (Exhibit 45u).

(b)(4)

During the course of the root cause investigation, Alcon has developed a standard operational definition of a central island that includes minimum criteria for the size of the central island [REDACTED] the amount of refractive undercorrection, [REDACTED] and any of the following clinical characteristics: significant negative spherical aberration over [REDACTED], loss of best spectacle corrected visual acuity, complaints of reduced visual quality from the patient, or other subjective complaints, e.g., glare, halos, double vision, ghost images. This definition was formalized in a white paper, provided as Exhibit 46. Because this standard definition was not used uniformly throughout the root cause investigation, Alcon has stated that all analyses included in the draft report that did not use the standard definition will be redone using the standard definition. In most instances, the reanalysis will involve excluding some eyes that do not meet the clinical criteria. All data and analyses in the final version of the report will therefore be comparable with respect to the inclusion criteria used for the presence of central islands.

(b)(4)

The central island problem was not detected prior to commercial distribution because neither Alcon nor FDA appreciated the potential significance of very small but systematic inaccuracies of shot placement on the overall ablation, and because the problem was so specific (affecting only one out of ten approved treatment indications) so sporadic (affecting only about 13% of LADAR6000 systems), and so intermittent (affecting only about 6% of treatments on the affected systems). More extensive testing of more systems over more replications during development of the design changes would have been necessary to detect the CI problem.

As a result of the root cause investigation, Alcon has implemented enhancements to its design verification SOPs in order to prevent the future occurrence of the types of design flaws that led to the central island problems with the LADAR6000. The changes are documented in CAPA Record Report PA24 (Exhibit 48).

**Summary Comment:** Alcon has conducted a thorough root cause investigation that has identified a complex set of interacting factors that plausibly explain the features and the sporadic nature of the CI findings. The results of the investigation have led to recommendations for improved tighter design specifications for positional control of the laser beam, and improved design verification SOPs to ensure that similar design flaws in the future will be detected and corrected prior to FDA approval and commercial distribution. I agree with their expressed intention to complete the final stages of the investigation, redo the analyses based on a consistent operational definition of central islands, and provide a final version of the report of CAPA #2300.

**LASER PRODUCT TEST REPORT**



**Establishment Inspection Report**

Alcon Refractive Horizons, Inc.

Orlando, FL 32826-3010

FEI: 3000209733

EI Start: 11/26/2007

EI End: 11/29/2007

The initial inspection of the laser device for examination of conformity to FDA regulation 21 CFR 1002 and 1040 was conducted on 11/29/07 after the QSIT inspection was completed. This inspection was reported under separate EIR and submitted to CDRH/OCER as required under CP 7386.001, Inspection of Manufacturers of Laser Products. No major deficiencies were observed except that the firm failed to include a reproduction of the laser warning logotypes in their media applications. I requested and reviewed the firm's annual reports required under 21 CFR 1002 and determined that the firm was current and no observations were made concerning their content.

A copy of the LASER PRODUCT TEST REPORT is included as Attachment 3.

**OBJECTIONABLE CONDITIONS AND DISCUSSION WITH MANAGEMENT**

Prior to departure of Dr. Berman on 11/28/07 and Dr. Drum on 11/29/07, we discussed the findings concerning the evaluation of LADARVision 4000 complaints and the Root cause Analysis conducted by the firm. Dr. Berman indicated that she made no major observations in the manner the firm conducted the investigation and determinations of the clinical complaints reviewed for the LADARVision 4000 system. Dr. Berman's report of complaint analysis is included in paragraph LADARVision 4000 COMPLAINT REVIEW and DISCUSSION page 15.

Dr. Drum stated that his initial review of the firm's root cause analysis of the LADAR6000 system seemed adequate, but he would make a complete analysis at the office of the Exhibits he obtained from the firm and report accordingly. His analysis is contained in paragraph LADAR6000 ROOT CAUSE ANALYSIS REVIEW above.

At the conclusion of the inspection I discussed the observations made during the inspection. I warned Dr. Woodrell that the observations listed in the report, although not included in an FDA-483, Inspectional Observations form, could result in warning letter, injunction or other civil penalties if so classified by FDA personnel tasked with the responsibility to make such decisions.

I told Dr. Woodrell and members of management of the Orlando and Fort Worth facilities present that I objected to the firm's determination that corrective actions approved by the firm were not implemented for the LADAR6000 system based on the removal of the system, especially in the earlier dated CAPAs dated in May 2006 just after the LADAR6000 was released.

I also objected to the firm's new procedure for MDR reporting and based on the discussion indicated that I was requesting District Compliance and CDRH review of the procedure. I objected to the firm's failure to report MDR in cases where a surgery was halted due to the device failure requiring rescheduling of the surgery to complete the procedure.

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I objected to the firm's handling of the Tracking Assembly corrective action and the failure to insure changes of components are reported to the firm prior to initiation.

**REFUSALS**

No refusals were encountered

**SAMPLES COLLECTED**

No samples were collected.

**VOLUNTARY CORRECTIONS**

During the review of complaints, it was determined on one occasion that the investigation conducted of the "not on site" LADARVision 4000 device in complaint RS060663 was not documented (Exhibit 35). Mr. Brian Green, Senior Quality Engineer and most responsible person for conducting these investigation evaluations, indicated that the "not on site" report was run but he failed to document it in the complaint database. He performed another "not on site" review of the systems database and included the information in the complaint. A copy complaint RS060663, corrected, (Exhibit 36) was provided for review.

**EXHIBITS COLLECTED**

1. Quality Manual, 41 pages
2. SOP, Table of Contents, 4 pages
3. Organizational Charts, 22 pages
4. Internal Audit Matrix, 3 pages
5. Management Review Agendas, 5 pages
6. Certificates & CV Auditors, 5 pages
7. Management Review Procedure, 4 pages
8. Customer Communication Protocol & Approval Process, 3 pages
9. CAPA Procedures, 19 pages
10. Complaint Handling Process, 7 pages
11. MDR and Vigilance Reporting, 5 pages
12. Adverse Event Reporting in Pre-Market Clinical Investigations, 12 pages
13. Corrections and Removal Process, 5 pages
14. Quality Trend Analysis, 5 pages
15. Accidental Radiation Occurrence Reporting Procedure, 3 pages
16. Technical Consumer Affairs (TCA) Reference Procedures, 9 pages

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17. Complaint Investigation Process, 19 pages
  - 17a. Job Aid: 7032-0025 – Data Gathering for Complaint Investigations, 10 pages
  - 17b. Job-Aid: 7032-0013 – Complaint Investigation Guidelines, 6 pages
  - 17c. Job-Aid: 7032-0019 – Investigation Plan Decision Tree, 4 pages
  - 17d. Job-Aid: 7032-0020 – Upper Trend Thresholds, 9 pages
  - 17e. Job-Aid: 7032-0030 – Explanation – Trend Thresholds and Upper Control Limits, 8
  - 17f. Job-Aid: 7032-0031 – Clinical Hazard Severity Matrix, 18 pages
  - 17g. Job-Aid: 7032-0032 – Complaint Root Cause Analysis Sufficiency, 19 pages
  - 17h. Job-Aid: 7032-0040 – Surgical Configurations, Acronyms/Definitions, 5 pages
  - 17i. Job-Aid: 7032-0049 – Verifying System Performance, 6 pages
  18. Complaint Process & EasyTrak Usage, 23 pages
  19. CD/R- CAPA Log from 5/1/06 – 11/26/07
  20. Sample - Complaint Trend Analysis Meeting, 6 pages
  21. CD/R- LADARVision Complaints Received 2002 – 2007
  22. Complaint RS070685, 7 pages
  - 22a. Complaint RS070686, 8 pages
  - 22b. Complaint RS070689, 8 pages
  - 22c. Complaint RS070691, 8 pages
  - 22d. Complaint RS070695, 8 pages
  - 22e. Complaint RS070693, 8 pages
  - 22f. Complaint RS070762, 8 pages
  - 22g. Complaint RS070763, 8 pages
  23. Sample- Database Recovery of Reports – “Not on Site” Evaluation, 14 pages
  24. P970043/S26 Approval, 6 pages
  25. P970043/S27 Withdrawal, 2 pages
  26. Memo to File – LADARVision 4000 Retrospective Review Of CTE, 7 pages
  27. Memo to File – Addendum LADARVision 4000 Retrospective Review, 5 pages
  28. LADARVision 4000 Complaints Reviewed, 63 pages
  29. LADAR6000 Letter to Doctor and Questionnaires, 5 pages
  30. List – LADARVision 4000 Retrospective Reviews w/ Serial Numbers, 5 pages
  31. Service Verification Record RS071435, 5 pages
  32. MDR Not Reported, RS061632, 13 pages
  33. MDR Not Reported, RS061048, 14 pages
  34. Complaint RS040459, No Documentation of Investigation, 4 pages
  35. Complaint RS060663 as Reviewed, 21 pages
  36. Updated Complaint RS060663, 26 pages

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37. LADAR6000 Overcorrection MDRs, Email Correspondence, 6 pages
  38. SOP-0003976- Spontaneous Refractive Postmarketing Reporting, V1, 8 pages
  39. SOP-0003976- Spontaneous Refractive Postmarketing Reporting, V2, 8 pages
  40. CAPA 2269, Software Changes, 5 pages
  41. CAPA 2269, Risk Analysis, 10 pages
  42. CAPA 2283, 10 pages
  43. CAPA 2269 Report Record, 3 pages
  44. CAPA 2299 Report Record, 2 pages
  45. Root Cause Analysis – Hand deliver to CDRH/OC by Dr. Drum

**ATTACHMENTS**

1. FDA-482, Notice of Inspection 11/26/07
2. FDA-482, Notice of Inspection 11/27/07
3. Laser Product Test Report 11/29/07
4. CDRH Database Search Results – Registration & Listing, 6 pages
5. CDRH Database Search Results – P970043 & Supplements, 4 pages

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Leo J Lagrotte, Investigator, SER/EOS  
FLA-DO/TMP-RP

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Sheryl L. Berman, MD, Medical Officer  
CDRH/ODE/DOED

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Bruce A. Drum, Ph.D., Physicist & Vision Spec.  
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