

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**21-257**

**CORRESPONDENCE**

UNCLASSIFIED  
BL



February 28, 2001

Dr. Wiley Chambers  
Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

Scott Krueger  
Sr. Director, Regulatory Affairs  
Telephone: 817/568-6116  
Telefax: 817/551-4630

Re: NDA 21-257  
TRAVATAN™ (travoprost ophthalmic solution) 0.004%  
Final draft insert text

Dear Dr. Chambers:

Please find attached our final draft insert text and a red-lined version reflecting changes from our February 15<sup>th</sup> version as agreed to during our teleconference of this date.

Please note that one additional change has been requested by our Trademarks department concerning the need to reference the TIMOPTIC trademark in the *Clinical Studies* sub-section of the Clinical Pharmacology section. Also, Trademarks has advised me that the ™ symbol need not be used with every occurrence of TRAVATAN. This will be adjusted during final insert layout. We trust that there should be no issues with this changes.

If you have any questions or comments please don't hesitate to contact me at 817/568-6116 or by fax at 817/551-4630.

Sincerely,

Scott Krueger  
Senior Director Regulatory Affairs

SK/bb  
Airborne Express

DUPLICATE



Food and Drug Administration  
Rockville MD 20857

FEB 20 2001

Gerald Cagle  
Senior Vice President  
Research and Development  
Alcon Research, LTD.  
6201 South Freeway  
Fort Worth, Texas 76134

Dear Mr. Cagle:

Between January 3 and 8, 2001, Mr. Phillip D. Waldron, representing the Food and Drug Administration (FDA), conducted an inspection of the monitoring practices of Alcon Research for a clinical study of the investigational drug Travatan (travoprost ophthalmic solution). This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections to determine the validity of clinical studies that may provide the basis for drug marketing approval and to assure that the rights and welfare of human subjects have been protected by appropriate monitoring procedures.

This inspection focused on protocol #C97-73, "A Six-Month, Multicenter, Triple-Masked, Placebo-Controlled Adjunctive Therapy Study of the Safety and Efficacy of AL-6221 0.0015% and AL-6221 0.004% Ophthalmic Solution in Patients with Open-Angle Glaucoma or Ocular Hypertension Maintained on TIMOPTIC 0.5%." Monitoring of this study was contracted to ClinSites/Pharmaceutical Development Associates, Inc.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and good clinical investigational practices governing the monitoring of clinical studies of investigational new drugs and the protection of human subjects.

We appreciate the cooperation shown Investigator Waldron during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, we invite you to contact me by letter at the address given below.

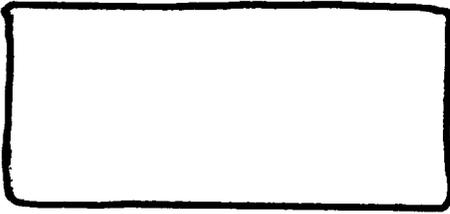
Sincerely yours,

/s/

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place, Room 125  
Rockville, MD 20855

Food and Drug Administration  
Rockville MD 20857

FEB 1 2001

Dear Dr. 

Between September 26 and 27, 2000, Mr. Paul L. Figarole, representing the Food and Drug Administration (FDA) met with Dr. Mark S. Gorovoy and Becky B. Barr to review your conduct of a clinical study (protocol #C-97-71) of the investigational drug Travatan (travoprost ophthalmic solution), performed for Alcon Laboratories Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects.

We appreciate the cooperation shown Investigator Figarole during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,

/S/

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855

A1

# Alcon

RESEARCH, Ltd.

December 27, 2000

Mike Puglisi, Project Manager  
Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

Scott Krueger  
Sr. Director, Regulatory Affairs  
Telephone: 817/568-6116  
Telefax: 817/551-4630



Re: NDA 21-257  
TRAVATAN™ (travoprost ophthalmic solution) 0.0015% and 0.004%  
Media fill data requested by Dr. Peter Cooney

Dear Mr. Puglisi:

We are amending NDA 21-257 per the request of Peter Cooney as follows:

(1) Explanation and reconciliation of numbers presented in Exhibit 7.B.5-1:

[Redacted]

(2) Documentation used to assure interventions are conducted in the same manner during media fills as during regular production runs; and

(3) Results of three new successful, successive media fills run [Redacted] incorporating commitments made to the agency following the October 12-27, 2000 [Redacted]

[Redacted]

Sincerely,

Scott Krueger  
Sr. Director, Regulatory Affairs

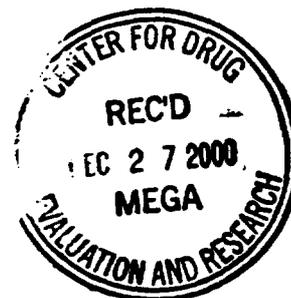
ORIGINAL

December 27, 2000

**Alcon**  
RESEARCH, LLC

Dr. Wiley Chambers  
Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Blvd.  
Rockville, Maryland 20850

Scott Krueger  
Sr. Director, Regulatory Affairs  
Telephone: 817/568-6116  
Telefax: 817/551-4630



Re: **NDA 21-257**  
**TRAVATAN™ (travoprost ophthalmic solution) 0.004%**  
**Proposed revised package insert**

Dear Dr. Chambers:

In follow-up to our telephone discussion of 26 December 2000 concerning the draft package insert for Travatan™ 0.004%, please find enclosed our proposed revised package insert text. I have also provided a red-line version for your convenience.

In support of this text, I have provided summary information from our 120-day safety update which addresses the performance of TRAVATAN™ 0.004% in black patients. Additionally, based upon our discussion concerning the Adverse Events identified in the FDA proposed insert text, I have prepared a tabular presentation for C-97-71 and C-97-72, the two large U.S. pivotal trials. Alcon believes that it would be appropriate to utilize the mean incidence from these two studies for listing of adverse events in the package insert.

I look forward to discussing our proposal with you at your earliest convenience.

If you have any questions please don't hesitate to contact me at 817/568-6116 or by fax at 817/551-4630.

Sincerely,



Scott Krueger  
Sr. Director, Regulatory Affairs

SK/bb Airborne 9528736232

**DUPLICATE**



**Alcon**  
RESEARCH, LTD.

December 26, 2000

Terry Dagnon  
Manager, Regulatory Affairs  
Tele: 817/551-4325

Wiley A. Chambers, M.D.  
Deputy Director  
Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, Maryland 20850

NDA 21-257 APPROVABLE LETTER  
AZ

Re: **NDA 21-257**  
**TRAVATAN™ (travoprost ophthalmic solution), 0.0015% and**  
**TRAVATAN™ (travoprost ophthalmic solution), 0.004%**  
**Response to 12/22/2000 Approvable Letter (Action Letter)**

Dear Dr. Chambers,

In accordance with 21 CFR 314.110 (1), please find enclosed two copies of our responses to issues one (1) through fourteen (14), as detailed in the Approvable letter dated 12/22/2000.

In accordance with 21 CFR 314.5 (d)(5)(vi)(b), please be advised, there is not any new safety information since the submission of our 120-Day Safety Update on 11/6/00. We are however providing final study reports for two carcinogenicity studies, a renal PK study, and an open-label study conducted in Mexico which were completed following the safety update.

Please see the table of contents located on the following page for a detailed breakdown of the responses by volume.

Two additional desk copies of the submission are being sent directly to Michael Puglisi, the Project Manager. In addition to the paper copies, we are providing a CD-ROM to the Project Manager, which contains the electronic versions of the four (4) completed studies as well as the responses to the issues presented in the Approvable letter.

If you require additional information, I may be reached at (817) 551-4325 or fax at (817) 551-4630.

Sincerely,

Terry Dagnon  
Manager, Regulatory Affairs



*Huglisi*

Food and Drug Administration  
Rockville MD 20857



NOV 1 1999

Dear 

Between October 3 and 5, 2000, Mr. Carl J. Montgomery, representing the Food and Drug Administration (FDA) met with you to review your conduct of the clinical study (protocol #C-97-72) of the investigational drug Travatan (travoprost ophthalmic solution), performed for Alcon Laboratories Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects

We appreciate the cooperation shown Investigator King during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,

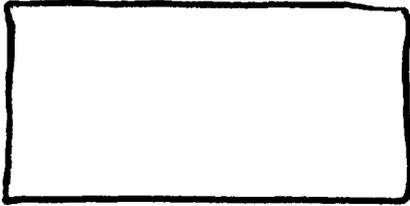
**/S/**

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855

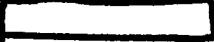


*Duglisi*

Food and Drug Administration  
Rockville MD 20857



NOV 20

Dear Dr. 

Between September 26 and 29, 2000, Ms. Martina E. LaGrange, representing the Food and Drug Administration (FDA) met with you to review your conduct of the clinical study (protocol #C-97-72) of the investigational drug Travatan (travoprost ophthalmic solution), performed for Alcon Laboratories Inc. This inspection is a part of FDA's Bioresearch Monitoring Program, which includes inspections designed to validate clinical studies on which drug approval may be based and to assure that the rights and welfare of the human subjects of those studies have been protected.

From our evaluation of the inspection report and the documents submitted with that report, we conclude that you did not adhere to all pertinent federal regulations and/or good clinical investigational practices governing your conduct of clinical investigations and the protection of human subjects. We note that at the conclusion of the inspection, Ms. LaGrange presented and discussed with you her inspectional observations. The discussion included, but was not limited to, your failure to conduct the study in accordance with the approved protocol in that you enrolled subjects #2301, #2302, #2303, #2316 and # 2329 despite not meeting the inclusion criteria. We acknowledge your response and your promise to make corrections/changes in your procedures to ensure that the finding noted above is not repeated in any ongoing or future studies.

We appreciate the cooperation shown Investigator LaGrange during the inspection. Should you have any questions or concerns about any aspect of the clinical testing of investigational drugs, please contact me by letter at the address given below.

Sincerely yours,

**/S/**

Antoine El-Hage, Ph.D.  
Branch Chief  
Good Clinical Practice II, HFD-47  
Division of Scientific Investigations  
Office of Medical Policy  
Center for Drug Evaluation and Research  
7520 Standish Place  
Rockville, MD 20855

ORIGINAL

November 6, 2000

Mike Puglisi  
Project Manager  
Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, Maryland 20850



**Alcon**  
RESEARCH, LTD.

Terry Dagnon  
Manager, Regulatory Affairs  
Tele: 817/551-4325

Re: **NDA 21-257**  
**TRAVATAN™ (travoprost ophthalmic solution), 0.0015% and**  
**TRAVATAN™ (travoprost ophthalmic solution), 0.004%**  
**120 Day Safety Update**

Dear Mr. Puglisi,

Please find enclosed the Four-Month Safety Update for TRAVATAN™ (travoprost ophthalmic solution).

Included in this submission is a safety update from 5 additional studies that have been completed or are ongoing. Two studies have been completed with reports pending (C-99-97, C-98-09), and three studies that are ongoing at this time [redacted]

Additionally, you will find included two (2) recently completed ADME reports, summaries of the mouse and rat carcinogenicity study results, summaries of two (2) toxicokinetic studies, and a flash electroretinogram study report. We have included a revised package insert that reflects the information contained in the safety update.

I am sending two copies to the document control room, two desk paper copies directly to you, and a CD-ROM which contains the electronic form of the Four-Month Safety Update. The CD has been scanned utilizing Norton Anti-virus NT V5.0. A signed copy of the biostatistics report that has been included is available upon request.

If you require additional information, I may be reached at (817) 551-4325 or fax at (817) 551-4630.

Sincerely,

Terry J. Dagnon  
Manager, Regulatory Affairs

Airborne #  
305 3283 284

# Alcon

September 15, 2000

AMENDMENT

BC

ALCON RESEARCH LTD.  
6201 South Freeway  
Fort Worth, Texas 76134-2099  
(817) 293-0450

Dr. Wiley Chambers  
Division of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, Maryland 20850



Re: NDA 21-257  
Travatan™ (travoprost ophthalmic solution) 0.0015% & 0.004%  
Amendment to Pending Application: Responses to August 29, 2000 Letter

Dear Dr. Chambers:

Attached are responses to the issues communicated in the letter dated August 29, 2000. At this point, we have no other pending issues.

Archival and review copies for this amendment are included in this communication. Two desk copies have been sent to Mike Puglisi under separate cover to facilitate the review process.

If you require additional information, please contact me at 817-551-4517.

Sincerely,

Handwritten signature of Sarah J. Cantrell in cursive.

Sarah J. Cantrell  
Manager, Regulatory Affairs

Enclosure  
cc: Mike Puglisi – 2 Desk Copies

ORIGINAL

Airborne #  
305 3283 181

September 14, 2000

NDA 21-257 AMENDMENT

ALCON RESEARCH LTD.  
6201 South Freeway  
Fort Worth, Texas 76134-2099  
(817) 293-0450

Dr. Wiley Chambers  
Division of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
9201 Corporate Boulevard  
Rockville, Maryland 20850

BC



Re: **NDA 21-257**  
**Travatan™ (travoprost ophthalmic solution) 0.0015% & 0.004%**  
**Amendment to Pending Application:**  
**Responses to August 11, 2000 Letter & August 22, 2000 Letter**

Dear Dr. Chambers:

Attached are responses to the issues communicated in the letters dated August 11, 2000 and August 22, 2000. Each packet of information is clearly identified by the date of the letter. We wish to express our appreciation for communicating these issues to us in a timely manner so that we can respond expeditiously.

Archival and review copies for this amendment are included in this communication. Two desk copies have been sent to Mike Puglisi under separate cover to facilitate the review process.

If you require additional information, please contact me at 817-551-4517.

Sincerely,

Sarah J. Cantrell  
Manager, Regulatory Affairs

ORIGINAL

Enclosure  
cc: Mike Puglisi - 2 Desk Copies

**Travoprost Ophthalmic Solution  
0.0015% & 0.004%**



**NDA 21-257**



July 6, 2000

**Alcon**  
RESEARCH, LTD.

Division, of Analgesic, Anti-inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
12229 Wilkins Avenue  
Rockville, Maryland 20850

Scott Krueger  
Senior Director, Regulatory Affairs  
Tel: 817/568-6116 Fax: 551-4630

Re: **NDA 21-257**  
**TRAVATAN™ (travoprost ophthalmic solution) 0.0015% and 0.004%**  
**Original New Drug Application – User Fee ID # 3922**

Dear Sir or Madam,

As an authorized U.S. representative of Alcon Universal Ltd. (AUL), I hereby submit a New Drug Application (NDA) for TRAVATAN™ (travoprost ophthalmic solution) 0.0015% and 0.004%. This NDA is being submitted pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.54.

Alcon is requesting priority review for this submission. Travoprost, the active ingredient in TRAVATAN™ Ophthalmic Solution 0.0015% and 0.004% is a new chemical entity. The data presented in this NDA support TRAVATAN to be safe and effective in reducing intraocular pressure in patients with ocular hypertensive and open angle glaucoma. TRAVATAN™ Ophthalmic Solution 0.0015% and 0.004% demonstrate a better duration and extent of IOP lowering effect than other ocular hypertensives currently on the market. Additionally, TRAVATAN™ Ophthalmic Solution 0.004% offers additional IOP lowering benefit for Black patients over existing drug therapies.

Consistent with discussions with the Division, the Chemistry, Manufacturing and Controls (Item 4) and Microbiology (Item 7) sections were presubmitted on May 10<sup>th</sup>.

The application consists of a paper archive copy, an electronic archive copy and a reviewer copy. These copies have been generated utilizing the CDER compiler of CoreDossier version 4.0.2 and in accordance with the following FDA guidance documents:

1. Regulatory Submissions in Electronic Format; General Considerations (Issued 1/1999, Posted 1/27/1999)
2. Regulatory Submissions in Electronic Format; New Drug Applications (Issued 1/1999, Posted 1/27/1999)
3. NDA Conformance Check List (2/22/2000)

**Travoprost Ophthalmic Solution  
0.0015% & 0.004%**

**NDA 21-257**

DAAODP, HFD-550, CDER  
Food and Drug Administration  
July 6, 2000

Page 2

Please note that since the hard copies were generated from the electronic file, signatures on some documents were not reproduced. Signed copies of documents are on file and are available upon request.

The submission is organized as follows:

		<u>Volume Number</u>
Item 1	Form 356H and Index	1
Item 2	Labeling	1
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Item 19	Other (Financial & Pediatric)	165

\* Presubmission volumes 2-13

\*\* Presubmission volume 14

I certify that a true copy of the CMC and Microbiology sections have been provided to the District Office in Dallas, Texas.

Establishment Information: A list of all facilities listed in this application is included as an attachment to the Form FDA 356h. All the facilities listed are ready for inspection.

Pagination: Consistent with FDA guidance, each page identifies the item number, page number, and the paper volume number. Pagination information is located in the footer of each page, with paper volume numbering located in the lower left. The consecutive page number is located in the lower right of each page, and employs the format of "item number" - "consecutive page number" (e.g., 4 - 0051).

**APPEARS THIS WAY  
ON ORIGINAL**

**Travoprost Ophthalmic Solution  
0.0015% & 0.004%**

**NDA 21-257**

DAAODP, HFD-550, CDER  
Food and Drug Administration  
July 6, 2000

Page 3

Virus Protection: The CD-ROM and all files contained on the submitted CD have been scanned with Norton Anti-Virus for Windows NT Ver. 5.02.00 for workstations. There were no detected viruses.

Electronic (WORD) versions of key documents and SAS data sets are being sent under separate cover directly to the Project Manager as desk copy review aids.

If you have any questions or comment concerning this submission please contact me by phone at 817-568-8116 or fax at 817-551-4630.

Sincerely,



Scott Krueger  
Senior Director, Regulatory Affairs

**APPEARS THIS WAY  
ON ORIGINAL**

May 5, 2000

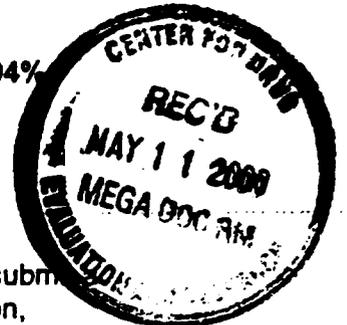


Alcon

Division, of Analgesic, Anti-Inflammatory and  
Ophthalmic Drug Products, HFD-550  
Center for Drug Evaluation and Research  
Food and Drug Administration  
Document Control Room  
12229 Wilkins Avenue  
Rockville, Maryland 20850

Scott Krueger  
Senior Director, Regulatory Affairs  
Tele: 817/568-6116 Fax: 551-4630

Re: **NDA 21-257**  
**TRAVATAN™ (Travoprost Ophthalmic Solution) 0.0015% and 0.004%**  
**Original New Drug Application – User Fee ID # 3922**



Dear Sir or Madam,

As an authorized U.S. representative of Alcon Universal Ltd. (AUL), I hereby submit this New Drug Application (NDA) for TRAVATAN™ Travoprost Ophthalmic Solution, 0.0015% and 0.004%. This NDA is being submitted pursuant to the provisions of Section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.54. The drug product is indicated for the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Consistent with discussions with the Division, this is a pre-submission of the Chemistry, Manufacturing and Controls (Item 4) and Microbiology (Item 7) sections. Within 120 days of this date, the full NDA which will include the remaining sections, (Summary, Proposed Labeling, Preclinical, Clinical/Statistical) will be submitted.

The application consists of a paper archive copy, an electronic archive copy and a reviewer copy. These copies have been generated utilizing the CDER compiler of CoreDossier version 4.0.2 and in accordance with the following FDA guidance documents:

1. Regulatory Submissions in Electronic Format; General Considerations (Issued 1/1999, Posted 1/27/1999)
2. Regulatory Submissions in Electronic Format; New Drug Applications (Issued 1/1999, Posted 1/27/1999)
3. NDA Conformance Check List (2/22/2000)

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**Establishment Information:** A list of all facilities listed in this application is included as an attachment to the Form FDA 356h. All the facilities listed are ready for inspection.

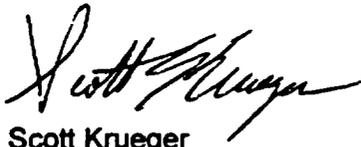
**Letters of Authorization:** Letters of authorization to cross-reference all NDAs and DMFs listed in this application follow the establishment information.

**Pagination:** Consistent with FDA guidance, each page identifies the item number, page number, and the paper volume number. Pagination information is located in the footer of each page, with paper volume numbering located in the lower left. The consecutive page number is located in the lower right of each page, and employs the format of "Item number" - "consecutive page number" (e.g., 4 - 0051).

**Virus Protection:** The CD-ROM and all files contained on the submitted CD have been scanned with Norton Anti-Virus for Windows NT Ver. 5.02.00 for workstations. There were no detected viruses.

If you have any questions or comment concerning this submission please contact me by phone at 817-568-6116 or fax at 817-551-4630.

Sincerely,



Scott Krueger  
Senior Director, Regulatory Affairs

Attachment