



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Atlanta District Office

60 8th Street, N.E.
Atlanta, Georgia 30309

October 31, 2006

VIA FEDERAL EXPRESS

WARNING LETTER
(07-ATL-01)

Ronald L. Zarrella, Chairman and CEO
Bausch & Lomb
One Bausch & Lomb Place
Rochester, NY 14604

Dear Mr. Zarrella:

During an inspection of your facility located at 8507 Pelham Rd., Greenville, SC 29615, on March 22, 2006 through May 15, 2006, investigators from the United States Food and Drug Administration (FDA) determined that your firm manufactures contact lens solutions. Under section 201(h) of the Federal Food, Drug, and Cosmetic Act (the Act), 21 U.S.C. 321(h), these products are devices because they are intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease, or are intended to affect the structure or function of the body.

This inspection revealed that these devices are adulterated within the meaning of section 501(h) of the Act (21 U.S.C. § 351(h)), in that the methods used in, or the facilities or controls used for, their manufacture, packing, storage, or installation are not in conformity with the Current Good Manufacturing Practice (CGMP) requirements of the Quality System (QS) regulation found at Title 21, Code of Federal Regulations (C.F.R.), Part 820. We reviewed and considered the responses from Mr. Michael Santalucia, VP Regulatory Affairs, dated June 30, 2006, concerning our investigators' observations noted on the FORM FDA 483, Inspectional Observations, that was issued to Mr. Thomas H. Eggleton, VP of Operations. We also acknowledge the recent receipt of your quarterly update dated October 12, 2006, which we will continue to review to help us determine the adequacy of your firm's corrections.

Based on the information we have reviewed, we acknowledge your efforts to address the outstanding inspection deficiencies noted during our March 22 - May 15, 2006 inspection. Also, we acknowledge that Bausch and Lomb has recalled all MoistureLoc contact lens solution worldwide to eliminate the serious risk to health associated with an outbreak of Fusarium keratitis. Although the March - May 2006 inspection focused primarily on the MoistureLoc contact lens solution, the inspection, nonetheless, identified and documented significant QS

regulation violations that were systemic and are relevant to all products manufactured at the Greenville, SC facility. However, during the inspection we did not find problems with the other products currently manufactured at this facility that would warrant product recall or field correction.

Violations noted during the inspection include, but are not limited to, the following:

1. Failure to establish and maintain design plans that describe or reference the design and development activities, and identify and describe the interfaces with other groups or activities, as required by 21 CFR 820.30(b). Specifically, the initial design plan shows Project R0151 began in 2001 and resulted in product [REDACTED]. The formulation contains a different preservative [REDACTED] and was cleared by the Agency in 2003. The product was not commercialized by your firm. Project R0324 is an alternate product project [REDACTED], ReNu with MoistureLoc Multi-Purpose Solution containing Alexidine, which was added to the same original design and development plan in 2004. Initial feasibility and risk assessment show the two products with two preservative agents [REDACTED] (Alexidine) under one design project. The design plan provided to our investigators dated October 25, 2001 - February 4, 2003, does not include any activities relating to the [REDACTED] solution, ReNu with MoistureLoc Multi-Purpose Solution.

A discussion of your response to this observation is combined with the review of item # 3 below.

2. Failure to adequately ensure that when the results of a process cannot be fully verified by subsequent inspection and test, that the process shall be validated with a high degree of assurance and approved according to established procedures, as required by 21 CFR 820.75(a). Specifically,

(a) Raw material specifications were not determined and firmly established prior to process validation. For example, [REDACTED] was used for pre-clinical and clinical studies however; the product formulation was changed to [REDACTED] at initial validation then back to [REDACTED].

(b) Your firm does not have complete validation data for ReNu with MoistureLoc Multi-Purpose Solution [REDACTED]. Initial scale-up activities at the Greenville plant were performed in 2003 on an unnamed similar product [REDACTED] utilizing [REDACTED] in the product formulation. [REDACTED] replaced [REDACTED] (which was used in the original product formulation for pre-clinical and clinical studies) after white particles were noted on soft contact lens while performing a lens compatibility study. The [REDACTED] product was formulated with [REDACTED] and used in the validation study; however, the formulation was not commercialized. In 2004 your firm performed a limited validation study on the currently marketed ReNu with MoistureLoc Multi-Purpose Solution utilizing [REDACTED] in the product formulation. The corrective action to avoid the appearance of white particles on the lenses was to use the [REDACTED] with a European Pharmacopeia clarity test. The validation data available shows that cleaning of the bulk mix tanks

and filling lines, the filling process, the hold time study, and purging processes were not re-validated. Chemistry testing was limited to the compounding batches and no USP sterility testing was performed for the scaled-up batches of ReNu with MoistureLoc Multi-Purpose Solution. [REDACTED] validation data was accepted in lieu of performing a complete re-validation of the manufacturing processes. The validation of the product did not include an evaluation of cleaning, purging, or filling. No hold time studies or purge evaluations were done. Lastly, no tank or filter sterilizations were done for ReNu with MoistureLoc although its ingredients, Alexidine [REDACTED] and Poloxamine, are sterile additions.

Your firm's response to observation 6a is inadequate. Your firm has stated that it will revise SOP 90-008, Validation Program, to perform complete validation for any new product or formulation at the site. Your firm has stated that it will revise SOP 90-044, Preparation of Validation Protocols and Final Reports, to require R&D Process Development and Global Quality to approve the protocols and reports for new or transferred products. Your firm has also begun to perform audits to evaluate the effectiveness of the system. This is inadequate as your firm has not completed any of these actions and submitted documentation of them to FDA for review.

(c) The following deviations are noted in the initial validation study [REDACTED]:

1. The European Pharmacopeia (EP) clarity test was not performed on Lot # 234068 [REDACTED] that was used in the 2003 validation study. Raw material specifications included a requirement for the EP clarity test in 2003.

Your firm's response to observation 6b1 is inadequate. Your firm has proposed to revise SOP 60-052, In-process, Final Product, and Raw Material Chemical Testing, to include an independent QA review and approval of the requirement before it is released for use. You proposed to revise SOP 90-074, New Product Assessment Planning, to include the requirement for effective raw material specifications prior to the start of the validation. This response is inadequate as your firm has not completed these revisions and submitted them to FDA for review.

2. Bacteriostasis/Fungistasis (B/F) testing was not performed for all validation runs as specified in the established protocol (0308-ME-0154). [REDACTED] runs were performed; however B/F testing was performed on only one run.

Your firm's June 30, 2006, response to observation 6b2 is inadequate. Your company has committed to write an addendum to the validation report for the bacteriostasis/fungistasis testing explaining the deviation. In addition to writing an addendum to the validation report for the B/F testing explaining the deviation, the "erroneous protocol" should be revised and updated to remove the requirement in 0308-ME-0154 for the B/F test to be repeated for each validation lot to ensure that protocols and company policy is consistent.

3. The first bottle out of filling on the third batch (PJ3004) was out of specification on the lower end for Osmolality (█████ mOsm/Kg). At the time of fill, the release specification was ██████ mOsm/Kg. The release specification was subsequently lowered to ██████ mOsm/Kg. and this run was accepted.

Your firm's response to observation 6b3 is inadequate. Your firm states that they will develop a procedure to control specifications prior to scale up of product or manufacturing and revise SOP 90-008, Validation Program, to state that when specification changes are identified during a validation, the validation must be started from the beginning. However, this procedure has not been developed and submitted to FDA for review.

3. Failure to establish and maintain procedures for verifying the device design which confirm that the design output meets the design input requirements, as required by 21 CFR 820.30(f). Specifically,

(a) Tasks for determining analytical in-process and finished product specifications were not assigned in the design plan and they were not firmly established prior to the product launch of ReNu with MoistureLoc Multi-Purpose Solution. For example, the Osmolality release specification was lowered after beginning process validation. Your firm did not establish specifications prior to beginning process validation. A specification change was made after validation.

(b) Your firm does not have a test method to evaluate the degradation of Alexidine in the ReNu with MoistureLoc Multi-Purpose Solution.

Your firm's response is partially adequate. The portion of the response that addresses observation 1a-c of the FDA 483 is inadequate. Your firm states that they will develop a separate Design and Development Plan procedure that will expand and clarify Project Plan Requirements and address management and documentation when multiple designs or formulations are moved into development. The new procedures will require the appropriate tracking of multiple formulations and assess them against the new procedure. This response is inadequate as your firm has not made these changes yet and submitted these revised procedures for review.

The portion of your firm's response that addresses observation 1d, appears adequate. Your firm states that you have a method for evaluating Alexidine. Your company provided TP-8230, HPLC Quantitative Determination of Alexidine ██████, which is an assay method that quantifies the level of Alexidine in the presence of interfering degradant peaks for Alexidine and other formulation excipients. Your firm also provided the validation report for this evaluation.

4. Failure to establish and maintain procedures to ensure that the device design is correctly translated into production specifications, as required by 21 CFR 820.30(h). Specifically, the design history file does not contain a statement of readiness from R&D as required in established procedure BL-POL-401, Product Development Management Process.

Your firm's response to observation 1e is inadequate. Your firm has stated that it will revise BL-POL-401, Product Development Management Process for Medical Devices, to remove the duplicative "Statement of Readiness" requirement since your firm has a signature mechanism in place that confirms that each team member is ready to move to the next phase of the process. This response is inadequate as your firm has not completed the revision of the procedure and submitted it to FDA for review.

5. Failure to establish and maintain procedures to ensure that the design requirements relating to a device include a mechanism for addressing incomplete, ambiguous, or conflicting requirements, as required by 21 CFR 820.30(c). Specifically, several design inputs for ReNu with MoistureLoc Multi-Purpose Solution, [REDACTED], are outstanding and were not addressed by the project team before bringing the product to the market. For example, the following value added design inputs remain open: qualification of a [REDACTED] regimen for the [REDACTED]; [REDACTED] of cycled lenses [REDACTED] with [REDACTED] lenses [REDACTED]; ISO/FDA Regimen Test using [REDACTED] and [REDACTED] after [REDACTED] day soak in glass vials; laboratory cleaning study to demonstrate lipid removal with [REDACTED] lenses; and, a biocidal efficacy study that demonstrates efficacy against "clinically significant microorganisms" (non-ISO organisms). The value added design goals and design outputs were not completed prior to finalizing the project.

Your firm's response to observation 2 is inadequate. Your firm states that it will revise documentation and associated design control procedures to allow for only required design inputs on the Design Control matrix and provide training to all Project Managers and team members, however, these revisions have not been completed and submitted to FDA for review.

6. Failure to ensure that formal documented reviews of the design results are planned and conducted at appropriate stages of the device's design development, as required by 21 CFR 820.30(e). Specifically, the post-launch product review for the ReNu with MoistureLoc Multi-Purpose Solution has not been performed as required in the formally established procedures, BL-PRO-408, Project Post Launch Review. The review should occur during the first year after the product is launched. ReNu with MoistureLoc Multi-Purpose Solution was initially distributed from the Greenville site in August 2004. No post-launch has been currently done.

Your firm's response to observation 3 is partially adequate. Your firm has conducted and submitted a copy of the Post Launch Review for ReNu with MoistureLoc on June 23, 2006. Your firm has also stated that it will revise procedures to require that quality related reviews be conducted at specific post-launch time periods after product launch and train all personnel on the new procedures. Your firm also states that they will conduct reviews of quality-related information for all products that have launched within the last 24 months. This portion of your firm's response to observation 3 is inadequate as your firm has not completed these revisions and submitted them to the Agency for review. Additionally, your firm should be conducting reviews for all products lines, not only those launched in the last 24 months.

7. Failure to establish procedures for quality audits and conduct such audits to assure that the

quality system is in compliance with the established quality system requirements of the quality system, as required by 21 CFR 820.22. Specifically,

a) Review of the Internal Audit schedule indicated that your firm has not conducted or established a routine auditing of your complaint handling system.

b) Your firm does not have procedures defining the frequency by which supplier audits will be conducted.

c) Your firm has never audited the supplier of Polyquaternium-10 [REDACTED], a component used to manufacture ReNu with MoistureLoc Multi-Purpose Solution.

d) Contract laboratories/suppliers used in raw material and finished product testing have not been audited at a defined frequency. For example:

-Lab A was last audited on December 11, 1998.

-Supplier A was last audited on September 11, 2001.

-The last biennial audit of Lab B was conducted on December 3, 2003.

Your firm's response to observation 11 is inadequate. Your firm has stated that it has completed audits for the supplier of polyquaternium-10 on June 2, 2006, Lab A on May 31, 2006, Lab B on May 24-25, 2006, and Supplier A on June 8, 2006, however, you did not provide documentation of these audits. Your firm has also stated that it will revise BL-PRO-1701, Global Quality System Audits, assess and modify its supplier management program, and revise metrics for the supplier management program. Your firm has not completed these revisions and submitted them to FDA for review.

8. Failure to establish and maintain procedures to prevent contamination of equipment or product by substances that could reasonably be expected to have an adverse effect on product quality, as required as 21 CFR 820.70(e). Specifically,

a) On April 19, 2006, in the upper mix room, peeling paint and paint chips were observed on agitators located on the tops of tank # [REDACTED] and the solenoid above tank # [REDACTED]. These tanks are currently used for the production of contact lens solutions.

Your firm's response to observation 7a is inadequate. Your firm has installed stainless shields in between motor housings that contain peeling paint on June 9, 2006. You have replaced painted solenoid valve housings with plastic housings on June 10, 2006, and will make other replacements by the end of 2006. Your firm will revise cleaning procedures to require periodic cleaning of stainless steel shields and revise preventative maintenance procedures to require periodic examination of agitator motor housings for condition and repair. The response is inadequate until the changes have been completed and verified by FDA.

b) The cleaning, inspection, and sanitization of fill lines # [REDACTED] used in the production of Opcon A, Sensitive Eyes, Boston Cleaner, and ReNu with Moisture Loc Multi-Purpose Solution were not documented as per SOP #40-102-19, "Weekly and Monthly Cleaning and Inspection of [REDACTED]",

for the monthly cleaning conducted for the month of February 2006.

Your firm's response to observation 7b is inadequate. Your firm has stated that it will retrain all site supervisors in proper change control and procedure management, however, this training has not been completed with documentation submitted to FDA for verification.

9. Failure to establish and maintain procedures to adequately control environmental conditions, as required by 21 CFR 820.70(c). Specifically, temperature conditions within the aseptic processing area are not being documented to ensure such conditions are consistently within established specifications of [REDACTED] degrees Celsius.

Your firm's response to observation 8 is inadequate. Your firm has stated that it has updated the Preventative Maintenance Task List to include space to record specific temperature readings on April 27, 2006. Your company has stated that it will conduct an audit to identify and enhance other temperature documentation practices and will install a continuous temperature and humidity recording system. Your firm has not provided the updated task list to FDA and the temperature audit has not been completed.

10. Failure to ensure that all equipment used in the manufacturing process meets specifications and is appropriately designed, constructed, placed, and installed to facilitate maintenance, adjustment, cleaning, and use, as required by 21 CFR 820.70(g). Specifically, on March 27, 2006, clean, uncapped product transfer hoses that are used in production were observed in direct contact with a shelving unit upon which a visible layer of a white powdery residue was observed. The shelving unit was installed to prevent hoses from coming in contact with the manufacturing room floor.

Your firm's response to observation 13 is inadequate. Your firm states that it revised SOP 40-072, Routine Cleaning of the Pharmacy, Upper Mix and Lower Mix, on May 20, 2006, to require weekly cleaning of the shelving unit in the Upper Mix Area and trained personnel on the new procedures on May 23, 2006. Your firm has not submitted the revised procedures for review.

11. Failure to document maintenance activities, including the date and individuals performing the maintenance activities, as required by 21 CFR 820.70(g)(1). Specifically, integrity testing of the vent filters on the [REDACTED] Hot Purified Water (HPW) tanks was not conducted during the six month interval between June 2005 and March 2006 per SOP # 50-095-08.

Your firm's response to observation 14 is inadequate as your firm states that it has corrected the preventative maintenance task form to require filter testing every [REDACTED] months. Your firm has stated that it will revise SOP 50-001, Preventative Maintenance Program, to require that any changes to the Preventative Maintenance System go through the formal change control process as well as review changes that have been made to the Preventative Maintenance Program to ensure they are not in conflict with existing procedures. Your firm has not provided the task form and has not completed the revisions to these procedures and submitted them for review by FDA.

12. Failure to review, evaluate, and investigate any complaint involving the possible failure of a device labeling, or packaging to meet any of its specifications, as required by 21 CFR 820.198(c). Specifically,

a) The Fusarium Keratitis investigation did not include sterility or biocidal testing for ReNu with MoistureLoc Multi-Purpose Solution product lots implicated in complaints received from Hong Kong.

b) Your firm had not performed sterility testing on the returned/retain samples in conjunction with the Fusarium investigation for complaints received from Malaysia and Singapore.

Your firm's response to observation 9 is inadequate. Your firm states that it has updated the complaint investigation for reports of infectious keratitis to include modified bioburden and biocidal testing for ReNu with MoistureLoc and ReNu MultiPlus on May 8, 2006. Your firm states that it will also evaluate and modify complaint investigation procedures to include modified bioburden and biocidal testing for complaint categories. Your firm has not submitted these documents for review.

13. Failure to establish and maintain procedures to ensure that mix-ups, damage, deterioration, contamination, or other adverse effects to product do not occur during handling, as required by 21 CFR 820.140. Specifically,

a) No documentation, inspection, audit, or checklist were established or conducted to guarantee that the trucking company transporting finished product from the manufacturing plant to the distribution center is protecting materials and finished product from damage and contamination as specified in SOP #15-006-09. Additionally, the trucking company does not have a climate control system in the trailer to monitor temperature conditions.

b) There are no procedures indicating the amount of time finished products are allowed to remain stored in trailers before finding a location in the warehouse for storage.

Your firm's response to observation 12 is inadequate. Your firm has stated that it will revise procedures to require transportation vehicles to be inspected before loading, after reaching the distribution center and will require them to be unloaded within [REDACTED] hours. However, these revisions have not been completed and submitted for review.

14. Failure to establish and maintain procedures for the control of storage areas and stock rooms for product to prevent mix-ups, damage, deterioration, contamination, or other adverse effects, as required by 21 CFR 820.150(a). Specifically,

a) On April 4, 2006, your firm was unable to locate a product lot implicated in a customer complaint, ReNu with MoistureLoc Multi-Purpose Solution, Lot# GG5055, which was identified as being part of the current inventory in your firm's validated inventory control systems [REDACTED] and [REDACTED]).

b) On April 24, 2006, your firm was unable to locate sixteen (16) cases of ReNu with MoistureLoc Multi-Purpose Solution, Lot #AJ5065.

c) On May 9, 2006, your firm was unable to locate [REDACTED] units of ReNu MultiPlus Multi-Purpose Solution, Lot #GC6061.

Your firm's response to observation 10 is inadequate. Your firm has stated that it will revise SOP 70-126, Finished Goods Destruction Notification and Obsolete Inventory/Component Disposition, to require the tracking of lot numbers; SOP 15-057, Customer Returns Processing to clarify the documentation review process and expand the license plate numbering for customer return pallets; SOP 15-117, Cancellation and/or Deallocation of Orders/Order Lines to include steps that will be performed by IT to modify the in-process order line status to indicate that the line item has been cancelled.

Your firm states that it will also conduct a statistical sampling of order accuracy before shipping, and modify the inventory system picking and replenishment processes to provide additional checks to ensure that only released materials are shipped, and will develop an SOP on the use and resulting actions of the Open Order Status Report in Customer Service. These tasks have not been completed and no documentation has been provided to FDA for verification.

Our inspection also revealed that your contact lens solutions are misbranded under section 502(t)(2) of the Act, 21 U.S.C. 352(t)(2), in that your firm failed or refused to furnish material or information respecting the device that is required by or under section 519 of the Act, 21 U.S.C. 360i and 21 C.F.R. Part 803 - Medical Device Reporting (MDR) regulation. Significant deviations include, but are not limited to, the following:

Failure to submit an MDR report within 30 calendar days after receiving or otherwise becoming aware of information that reasonably suggests that a marketed device may have caused or contributed to a death or serious injury, as required by 21 CFR 803.50(a)(1). Specifically,

a) Your firm failed to notify the Agency of 35 serious injury reports of Fusarium keratitis from Singapore's Minister of Health in February 2006 relating to ReNu with MoistureLoc Multi-Purpose Solution. None of the complaints were reported to the Agency as of April 7, 2006.

We have reviewed your response and have concluded that it is inadequate. A review of your complaint #S106000046, which concerns 26 of the cases of Fusarium keratitis reported by the Singapore MoH was conducted. The Office of Surveillance and Biometrics (OSB), CDRH, has determined that these are MDR reportable serious injuries. On April 6, 2006, your firm contacted CDRH/OSB/RSMB about the 35 cases from Singapore. Your firm was told to treat the cases as a literature report and submit a single 3500A that contained all of the information your firm had from the Singapore MoH. Your firm was also told that if it received information on new cases from Singapore MoH this information would need to be submitted as a new literature report.

The rationale provided in the file for not reporting these events at both the regulatory affairs and the corporate level is not supported by the information available to your firm. Your response states that this information did not reasonably suggest that the ReNu with MoistureLoc Multi-Purpose Solution device caused or contributed to the Fusarium infections. FDA disagrees. This information suggested that your ReNu product may have caused or contributed to the event.

Your response also states that there was insufficient information to submit MDRs. FDA disagrees. Bausch & Lomb was required to submit the 26 MDRs within 30 days of becoming aware of the events, regardless of how little information you had.

Bausch and Lomb states that it did not receive adequate input from FDA as to how to submit the MDRs. However, FDA's guidance document "Medical Device Reporting for Manufacturers" has been available since March 1997 and can be accessed easily via FDA's Internet site by choosing Medical Devices, MDR reporting, and then manufacturers. This document explains that each patient event requires submission of a separate 3500A. In addition to the guidance document this site also provides contact information for OSB/RSMB.

b) Complaints #S105000240 - #S105000245 were initially reported to your firm as keratitis complaints in July 2005. These complaints have not been reported to the Agency as of May 9, 2006.

FDA agrees with Bausch & Lomb that the 6 cases of Infiltrative Keratitis included in Complaints #S105000240 - S105000245 are not reportable. It appears that your firm appropriately investigated these events and attempted to obtain additional information.

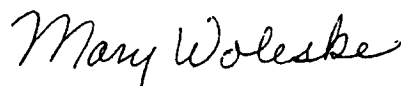
You should take prompt action to correct the violations addressed in this letter. Failure to promptly correct these violations may result in regulatory action being initiated by the Food and Drug Administration without further notice. These actions include, but are not limited to, seizure, injunction, and/or civil money penalties. Also, federal agencies are advised of the issuance of all Warning Letters about devices so that they may take this information into account when considering the award of contracts. Additionally, premarket approval applications for Class III devices to which the Quality System regulation deviations are reasonably related will not be approved until the violations have been corrected. Requests for Certificates to Foreign Governments will not be granted until the violations related to the subject devices have been corrected.

Please notify this office in writing within fifteen (15) working days from the date you receive this letter of the specific steps you have taken to correct the noted violations, including an explanation of how you plan to prevent these violations, or similar violations, from occurring again. Include documentation of the corrective action you have taken. If your planned corrections will occur over time, please include a timetable for implementation of those corrections. If corrective action cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the attention of Serene N. Ackall, Compliance Officer, at the address noted in the letterhead. If you have any questions about this letter, you can contact Ms. Ackall at 404-253-1296.

Finally, you should know that this letter is not intended to be an all-inclusive list of the violations at your facility. It is your responsibility to ensure compliance with applicable laws and regulations administered by FDA. As noted above, the specific violations noted in this letter and in the Inspectional Observations, FORM FDA 483 (FDA 483), issued at the closeout of the inspection may be symptomatic of serious problems in your firm's manufacturing and quality assurance systems. You should investigate and determine the causes of the violations, and take prompt actions to correct the violations and to bring your products into compliance.

Sincerely,



Mary H. Woleske
Director
Atlanta District Office

Enclosure

cc: Mr. Thomas H. Eggleton, VP of Operations
8507 Pelham Rd.
Greenville, SC 29615-9598