



DEPARTMENT OF HEALTH & HUMAN SERVICES

May 23, 2000

Food and Drug Administration

WARNING LETTER  
SJN-00-11

466 Fernandez Juncos Avenue  
Puerta De Tierra  
San Juan, Puerto Rico 00901-3223

CERTIFIED MAIL  
Return Receipt Requested

Mr. C. Glen Bradley  
Chief Executive Officer  
CIBA Vision Corporation  
Ophthalmic Business Unit  
11460 Johns Creek Parkway  
Duluth, Georgia 30097-1556

Dear Mr. Bradley

Investigator Jose A. Cruz from the Food and Drug Administration Mayaguez, PR Post conducted an inspection of your drug manufacturing operations which are conducted under contract by [REDACTED] located at [REDACTED], [REDACTED] P.R, on April 4 to 18, 2000. At the conclusion of that inspection our investigator presented and discussed an FDA-483, Inspectional Observations form.

The inspection and FDA-483 document several significant deviations from Title 21, Code of Federal Regulations, Part 211, Good Manufacturing Practice Regulations for Finished Pharmaceutical. These deficiencies are in connection to your firm's manufacturing of ophthalmic drug products causing these to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food and Drug & Cosmetic Act (the Act), as follows:

1. Failure to establish specifications, standard, testing procedures, or other laboratory controls for impurities identified in your ophthalmic drugs in accordance with 21 CFR 211.160(a) and (b). You have not implemented a testing program to characterize and monitor impurities, including their quantification, toxicity and clinical effects, in a timely manner. For instance:
  - a) In April 1997, 4-(butylamino) benzoic acid, a hydrolysis by-product of the active ingredient in Tetracaine HCl, ophthalmic solution 1/2% Dropperettes<sup>®</sup>, was identified when the assay test method was changed from [REDACTED] to [REDACTED] analysis. Yet, since then, no testing program had been implemented to characterize, quantify and monitor this impurity, even after it continued to show-up in stability testing.
  - b) Since March 1982, when qualification and validation of the HPLC analytical method for Vasocidin<sup>®</sup>, Sulf-10<sup>®</sup> and Vasoulf<sup>®</sup> ophthalmic solutions were done, sulfanilamide, a degradant of the active ingredient sodium sulfacetamide, was identified in each of these products. But, it was not until 12/30/99 when test

procedures were changed that included specific testing for impurities, even though historical stability data has continually shown the presence of this impurity.

- c) In December 1988, during qualification and validation of the HPLC assay stability indicating method for Vasocon® A Eye Drops, degradant peaks of the two active ingredients were discovered and identified. But it was not until 4/7/99, that procedures were changed to include specific testing for these impurities, even though Stability Alert Reports for unknown peaks dating back to 6/10/98 had been issued.
2. Failure of the quality control unit to appropriately justify changes to finish product release and/or stability specifications of ophthalmic drug products based on sound scientific judgement and appropriate documentation of test procedure design in accordance with 21 CFR 211.160, 211.166, 211.194(b) and 211.22(c), as follows:
    - a) Stability assay specification for the active ingredient in Atropisol® 1% (atropine sulfate) ophthalmic solution was changed without proper justification. On June 15, 1999 a decision was made to change the assay upper limit specification from [REDACTED] to [REDACTED] due to stability data, (including OOS incidents as far back as 1995), that showed a tendency of the product to increase in concentration with time.
    - b) The PET (preservative effectiveness test) for Tetracaine HCl ophthalmic solution was discontinued as a release criterion without appropriate studies to assess the concentration specification of the preservative (chlorobutanol) in a new HPLC assay method. The initial assigned concentration of NLT [REDACTED] was changed to [REDACTED] and then to "for information only", within the past year. These changes appear to be prompted by OOS reports in stability testing which indicate a decrease in concentration, and not based on studies to show appropriate concentrations over time.
  3. Failure to have controls to track and ensure Incident Reports (IRS) and Stability Alerts Reports are handled, investigated, and completed in a timely manner in accordance with 21 CFR 211.192. For instance, OMJ Pharmaceuticals issued IRS #98-772 on 6/10/98 for unknown peaks discovered while conducting assay tests on three stability lots of Vasocon® A, however, this IRS was not closed until 4/15/00, 10 months later. Other examples are; Stability Alert #99-002 issued 8/2/99 and IRS #99-332 issued on 4/12/99, both of which were closed in April 2000.

We acknowledge receipt of your letter dated May 15, 2000 responding to the FDA-483. Our review of the responses finds that you have adequately address significant aspects of the concerns brought to your attention by our investigator. We particularly point to your diligence in voluntarily initiating recalls of two products (Atropine® and Vasoulf® ophthalmic solutions) that were deemed to not meet quality standards, and promptly performing health hazard evaluations for these. Also, we endorse your commitments to conduct additional studies to assess and ensure the identity, strength, purity and, quality of your products

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that you outlined. However, we believe that the above cited items have not been satisfied in that, these items transcend the specific observations and reflect activities and decision making that were out-of-control, and not conducive to Good Manufacturing Practices.

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure adherence with each requirement of the Good Manufacturing Practice Regulations. Federal agencies are advised of the issuance of all warning letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include seizure and/or injunction.

Please notify the San Juan District office in writing, within 15 working days of receipt of this letter, of the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of these or similar violations.

Your reply should be sent to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00901-3223, Attention: Andres Toro, Compliance Officer.

Sincerely,



Mildred R. Barber  
District Director

cc:

Mr. Thomas Rowe  
Executive Director Quality and Technical Affairs  
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