



DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration
New Orleans District
Nashville Branch Office
297 Plus Park Blvd.
Nashville, TN 37217

Telephone: 615-781-5380
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August 18, 2004

Warning Letter No. 2004-NOL-33

FEDERAL EXPRESS
OVERNIGHT DELIVERY

Victor J. Santos
President
Natureplex, LLC
122 Cumberland Street
Memphis, Tennessee 38112

Dear Mr. Santos:

During an inspection of your facility located at 122 Cumberland Street, Memphis, Tennessee, on February 23-26, 2004, our investigators documented violations of the Current Good Manufacturing Practice Regulations (CGMPs), Title 21, *Code of Federal Regulations*, Part 211. These violations caused your drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (the Act). In addition, your ophthalmic drug products, Eye Drops Allergy Relief, Eye Drops Artificial Tears, and Eye Drops Extra Relief, are misbranded within the meaning of Section 502(a) of the Act. The violations include, but are not limited to, the following:

Adulteration

1. Failure to establish and follow written procedures designed to prevent microbiological contamination of drug products purporting to be sterile [21 CFR 211.113(b)]. Ophthalmic drug products currently manufactured at your firm are not aseptically processed nor terminally sterilized to prevent microbial contamination.
2. Failure to clean and sterilize drug product containers and closures to assure they are suitable for their intended use [21 CFR 211.94(c)]. Containers and closures used in the manufacture of ophthalmic drug products are not sterile upon receipt, and are not sterilized prior to their use. In

addition, you have not established written standards or specifications, methods of testing, and methods of cleaning and sterilizing drug product containers and closures [21 CFR 211.94(d)].

3. Failure to conduct appropriate laboratory test on each batch purporting to be sterile [21 CFR 211.167(a)]. Your firm does not test each batch of ophthalmic drug product purporting to be sterile to determine conformance to such requirement.
4. Failure to test in-process materials for identity, strength, quality, and purity as appropriate and to approve or reject in-process materials by the quality control unit (QCU) [21 CFR 211.110(c)]. In addition, you have not established written procedures describing in-process controls and tests or examinations to be conducted on appropriate samples of in-process materials for each batch to assure batch uniformity and integrity of drug products [21 CFR 211.110(a)]. For example, you failed to have a sampling program to assure drug product quality.
5. Failure to have control systems necessary to prevent contamination during the course of aseptic processing operations, including an air supply filtered through high-efficiency particulate air [REDACTED] filters under positive pressure [21 CFR 211.42(c)(10)(iii)]. The manufacture of your ophthalmic drug products is not conducted in a controlled room environment or under appropriate [REDACTED] filtered air supply necessary to prevent contamination.
6. Failure to establish an adequate QCU that has the responsibility and authority to approve or reject all components, drug product containers, closures, in-process materials, packaging material, labeling, and drug products. The responsibilities and procedures applicable to the QCU shall be in writing and followed [21 CFR 211.22(a) and (d)]. Your QCU does not currently perform any production record reviews, final label reviews, approve or reject incoming components, drug packaging and does not perform periodic evaluation of quality standard of each drug product. In addition, the firm does not have any written policies and procedures applicable to the QCU.
7. Failure to have adequate batch production and control records [21 CFR 211.188]. Your firm failed to have written records for the production of ophthalmic drug products manufactured at your facility. Batch production records currently used during the manufacture of topical OTC drug products do not include complete information relating to the production and control of each batch. In addition, you failed to have master production and control records that include complete manufacturing and control instructions, sampling and testing procedures, specifications, special notations, and precautions to be followed [21 CFR 211.186(a) and (b)(9)].
8. Failure to have adequate written procedures for production and process controls designed to assure drug products have the identity, strength, quality, and purity they purport to possess [21 CFR 211.100(a)]. For example, your firm does not have any written procedure, including production and process controls and microbiological contamination control.
9. Failure to establish adequate written procedures for cleaning and maintenance of equipment, including utensils, used in manufacture, processing, packing, or holding of a drug product [21 CFR 211.100(b)]. For example, your firm does not have written procedures for equipment cleaning and maintenance. In addition, cleaning procedures have not been validated [21 CFR 211.67(a)] and documentation of equipment cleaning, maintenance, and use is not maintained [21 CFR 211.182].

10. Failure to assure each person engaged in the manufacture, processing, packing, or holding of a drug product has the education, training, and experience, or any combination thereof, to enable that person to perform the assigned function. Training shall be in the particular operation that employee performs and in Current Good Manufacturing Practice (CGMP) regulations as they relate to the employee's function [21 CFR 211.25(a)]. Your firm fails to conduct any CGMP training for employees or supervisors involved in the manufacture of over-the-counter drug products, including ophthalmic drug products.
11. Failure to test or examine, as appropriate, and withhold from use each lot of components, drug product containers, and closures [21 CFR 211.84(a)]. Components, drug product containers, and closures are only checked against the invoice and/or packing list for accuracy and placed on the shelf for immediate use. In addition, you have not established written procedures that describe in sufficient detail the receipt, identification, storage, handling, sampling, testing, and approval or rejection of components and drug product containers and closures [21 CFR 211.80(a)]. You also failed to identify each container or grouping of containers for components or drug product containers, or closures with a distinctive code for each lot in each shipment received [21 CFR 211.80(d)].
12. Failure to identify drug product components removed from original containers to another with the component name or item code, receiving or control number, weight or measure, and batch for which component was dispensed, including product name, strength and lot number [21 CFR 211.101(b)]. At least [REDACTED] unlabeled plastic containers or baggies with unknown material were observed on the components rack in the cream/ointment production room and amongst ophthalmic drug product components.
13. Failure to establish and follow written procedures describing in sufficient details the receipt, identification, storage, handling, sampling, examination, and/or testing of labeling and packaging materials [21 CFR 211.122(a)]. Your firm currently does not sample or examine incoming labels upon receipt or before use.
14. Failure to establish a procedure designed to reconcile the quantities of labeling issued, used, and returned, to evaluate any discrepancies found, and to exercise strict controls over labeling issued for use in drug product operations [21 CFR 211.125].
15. Failure to establish and follow adequate written procedures designed to assure correct labels, labeling, and packaging materials are used for drug products [21 CFR 211.130]. You failed to assign unique lot codes to each batch of drug products you manufacture. Instead, you currently use pre-printed labels of different drugs, which bear the same lot number and expiration date.
16. Failure to collect, maintain, and identify reserve samples of each lot of active ingredient and each lot of finished drug product manufactured for one year after the expiration date of the drug product [21 CFR 211.170(a) & (b)].

Misbranding

The Eye Drops Allergy Relief, Eye Drops Artificial Tears, and Eye Drops Extra Relief ophthalmic drug products are misbranded under section 502(a) of the Act because they each fail to bear a tamper-evident packaging labeling statement [21 CFR 211.132(c)].

The above identification of violations is not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Current Good Manufacturing Practice Regulations and to correct the violations noted in this letter and the Form FDA 483 issued at the conclusion of the inspection.

Federal agencies are advised of the issuance of all warning letters about drugs so they may take this information into account when considering the award of contracts. Additionally, pending NDA, ANDA, or Certificates to Foreign Governments requests will not be approved until the above violations are corrected. You should take prompt action to correct these violations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include seizure and/or injunction.

The Eye Drops Allergy Relief and Eye Drops Artificial Tears ophthalmic drug products each bear the warning statement "Ask a doctor before use if you have narrow angle glaucoma." The final regulations on OTC ophthalmic drug products found in 21 CFR 349 set forth the conditions whereby OTC ophthalmic drug products are considered generally recognized as safe and effective and not misbranded. These conditions include appropriate warnings based on the presence of specific ingredients. The ingredients present in Eye Drops Allergy Relief and Eye Drops Artificial Tears do not require a warning regarding narrow angle glaucoma. Therefore, use of that warning on the product labels is misleading, and misbrands the products under section 502(a) of the Act.

On March 26, 2004, we received written correspondence from your attorney, [REDACTED], indicating your commitment to cease all manufacturing and shipping operations of all products produced at your facility until you have evaluated your ability to continue operations as a viable business. You also indicated your intention to fully cooperate in the ongoing recall of your ophthalmic drug products.

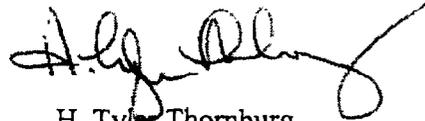
On May 3, 2004, we received your written response to the Form FDA 483 indicating Natureplex "...decided to cease manufacture of all drug products including the eye drops..." You also indicated your firm has...plans to move to a new facility and is actively in the process of evaluating such facility...to adequately manufacture the quantity of OTC drug products Natureplex intends to manufacture." Your response stated "Natureplex has conducted an extensive evaluation and has no future plans for manufacturing a sterile product." However, you continue to say "...Natureplex made the decision to seek new facilities for future usage. Until this facility is located, Natureplex will cease manufacture of the sterile drug products and limit manufacture of the other products." You concluded your response by saying "Natureplex will only be engaged in the manufacture of Dietary Supplements and Cosmetics at this time. Prior to resuming drug product manufacturing, Natureplex will once again notify your offices." Based upon your response, it is uncertain whether you intend to resume manufacture of OTC drug products. Therefore, it is vital to convey to you the significance of the deficiencies found during the February 2004 establishment inspection.

If you do intend to resume manufacturing of OTC sterile ophthalmic drug products and/or OTC topical drug products in the future, please notify this office in writing, within fifteen (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 similar violations.

If corrective action cannot be completed within fifteen (15) working days, state the reason for the delay and the time within which the corrections will be completed. Your reply should be directed to the attention of Kari L. Batey, Compliance Officer, Food and Drug Administration, 297 Plus Park Boulevard, Nashville, Tennessee, 37217.

Sincerely,

A handwritten signature in black ink, appearing to read "H. Tyler Thornburg", written over a horizontal line.

H. Tyler Thornburg
Director, New Orleans District

Enclosures:

-Form FDA 483

-Memo from attorney dated March 12, 2004