DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

WARNING LETTER

Via FedEx

WL: 320-07-01

FEB 23 2007

Mr. Steve C. Leistner
CEO
Niagara Pharmaceuticals Inc.
60 Innovation Drive
Flamborough, Ontario
L9H7P3
Canada

Dear Mr. Leistner:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Flamborough, Ontario, Canada, by Investigators Carla Lundi and Susan Jackson, during the period of September 11-13, 2006. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21 U.S. Code of Federal Regulations (CFR), Parts 210 and 211) in the manufacture of sterile drug products. These deviations were listed on an Inspectional Observations form (FDA-483) issued to you at the close of the inspection.

These CGMP deviations cause your drug products to be adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (Act) [21 U.S.C. 351(a)(2)(B)]. This section of the Act requires that all drugs be manufactured, processed, packed, and held according to CGMP. Failure to comply with CGMP constitutes a failure to comply with the requirements of the Act. Also, your firm sterilizes its eyewash preparations using [ ] irradiation. Under 21 CFR 310.502(a)(11), drug products that are sterilized by irradiation are new drugs that require an approved application as a condition of marketing. The products are in violation of section 505 of the Act [21 U.S.C. 355] when they are shipped into the U.S.

We have received and reviewed your response letters dated October 6, October 26, November 15, and December 21, 2006. We note that some corrections have been completed, or will soon be implemented. However, your responses continue to be inadequate to address the deficiencies, as explained further below. Based on the review of the establishment inspection report (EIR), specific areas of concern include, but are not limited to:

Unapproved New Drugs

Your firm manufactures an eyewash solution that contains purified water as the declared active ingredient. The product is labeled under various own label distributor trade names. All of the distributors' products bear claims that they are intended to be used to flush loose foreign material from the eyes. In addition, some of these own label distributors' products bear claims that the solution may be used to flush the skin to treat minor acid or alkali burns. Based on the intended use as eyewash and skin flush solutions, these products are drugs as defined in section 201(g) of the Act (Act) [21 U.S.C. § 321(g)]. As eyewash solutions, many of these preparations are also subject to final regulations covering OTC ophthalmic drugs found at 21 CFR Part 349. Others are specifically designed for emergency use and will be subject to the developing regulations for emergency eyewash products within the OTC Drug Review.

You also manufacture an antimicrobial solution that contains, according to the label, chlorhexidine gluconate and propylene glycol as preservative ingredients that are intended to be added to self-contained eyewash stations in order to preserve the emergency eyewash solution in the eyewash station. The preservative solution products are also labeled under various own label distributor trade names. Because these products are intended to be a component of a drug, i.e., eyewash and/or emergency eyewash, they are drugs as defined in section 201(g) of the Act [21 U.S.C. § 321(g)].

Both the eyewash solutions and the antimicrobial preservative solutions cited above are sterilized by[ ]irradiation. The agency has determined by rulemaking procedures that certain drugs are new drugs within the meaning of section 201(p) of the Act [21 U.S.C. § 321(p)]. Drugs that are sterilized by irradiation are included in this rulemaking (see 21 CFR § 310.502(a)(11)). Therefore, the eyewash solutions and the antimicrobial preservative solutions for emergency eyewash stations that your firm manufactures are new drugs that may not be legally marketed in the United States unless they are the subject of an application that has been approved under section 505 of the Act [21 U.S.C. § 355]. Please inform us of your intention with respect to filing applications for these products.

Current Good Manufacturing Practices

1) Testing of each batch of drug product for distribution does not include appropriate laboratory determination of satisfactory conformance to the final specifications prior to release. **21 CFR 211.165(a)**

   We acknowledge your question regarding the appropriate form of[ ]sterilization of your product and the designation of your product as a drug instead of a medical device. [ ]is similar to[ ]but not equivalent. We have determined that your product is a drug, as explained above. Thus, under 21 CFR 211.165(a), appropriate release testing must be performed prior to release of product. This includes[ ]We acknowledge that your firm is now quarantining product while these tests are performed and prior to shipment. Testing should continue to be completed prior to release unless alternate

release methods are provided for in an approved application. When a new drug application is submitted to the agency, the method of[ ]sterilization will be evaluated for acceptability.

2) Procedures designed to prevent microbiological contamination of drug products purporting to be sterile do not include adequate validation of the sterilization process. **21 CFR 211.113(b)**

We acknowledge that your firm has undertaken validation of the sterilization process using [ ]however, your firm's response remains inadequate. We understand that your firm perceived a language barrier between the Investigators and the QA Manager; however, everything that was requested of the QA Manager was also requested of the General Manager. The protocol for[ ]was not submitted for review as part of your response. Please provide us with a copy of the executed validation data for protocol[ ]Also, you reference a correction letter from[ ]Please provide us with a copy of this letter as well.

3) Written production and process control procedures are not followed in the execution of production and process control functions and are not documented at the time of performance. **21 CFR 211.100(b)**

We acknowledge that your firm has updated the batch production records; however, the revised records do not adequately correct the lack of documentation of certain steps. There remains a lack of documentation for several key steps that include, but are not limited to, the documentation of[ ]and[ ]necessary for your product.

4) Records are not maintained so that data therein can be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures. **21 CFR 211.180(e)**

We acknowledge that your firm has created a SOP for annual product reviews and produced a detailed annual product review since the inspection; however, the detailed annual product review submitted to us was only for one of your products, Eyewash 1.9% Boric Acid. Your Water Additive product was not covered and no separate annual product review was submitted. Also, the annual product review that was submitted to the investigator was the first annual product review your firm has ever performed, and did not contain all the necessary requirements for an annual product review as detailed in 21 CFR 211.180(e). Your firm has been shipping both products to the U.S. market for over two years without an annual product review. It is your firm's responsibility to determine the quality standards of both drug products in order to better understand the operating parameters for these products.

5) Batch production and control records do not include in-process results for each batch of drug products produced. **21 CFR 211.188(b)(5)**

We acknowledge that your firm has revised the SOP[ ]however, the documentation of the visual and olfactory characteristics of product by the QA Manager is not included or referenced in the batch production record. The sample logbook would not be adequate to document in-process testing if it is not referenced in the batch record for review during release.

These visual and olfactory results may be overlooked during the review of the batch record since they are not included or referenced in the batch record. In addition, there are no specifications for the visual and olfactory in-process testing.

The issues and violations cited in this letter are not intended to be an all-inclusive statement of violations that may exist at your facility or in connection with your products. You are responsible for investigating and determining the causes of the violations identified above and preventing a recurrence of similar violations. It is your responsibility to assure that your firm complies with the requirements of U.S. law and FDA regulations.

You should take prompt action to correct the violations cited in this letter. Failure to promptly correct these violations may result in legal action without further notice. Failure to correct these issues may result in FDA denying entry of articles manufactured by your firm into the United States, pursuant to Section 801(a)(3) of the Act.

Within 30 working days of receipt of this letter, you should notify this office in writing of the specific steps that you have taken to correct the violations. Include an explanation of each step being taken to prevent the recurrence of similar violations, as well as copies of related documentation.

Please direct your response to Carole Jones, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, written response or concerns regarding these decisions.

U.S. Food & Drug Administration
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Rockville, MD 20852
Tel: (301) 827-9054; FAX (301) 827-8909

Sincerely,

Richard Friedman
Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research