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September 23, 2002

FOOD & DRUG ADMINISTRATION
466 FERNANDEZ JUNCOS AVENUE
SAN JUAN, P.R. 00901-3223WARNING LETTERSJN-02-12CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Frank Leo
Chief Operating Officer
Automatic Liquid Packaging, Inc.
2200 Lake Shore Drive
Wood Stock, IL 60098-7498

Dear Mr. Leo:

From May 2, 2002 through May 15, 2002, inspectors from the Food and Drug Administration's (FDA) San Juan District office conducted inspections of your finished drug and medical device contract manufacturing facility, Cardinal Health Manufacturing Services B.V., located at Road # 925, Bo. Junquito, Humacao, PR. During that inspection, our investigator documented violations from the Good Manufacturing Practice (GMP) Regulations, found at Title 21, Code of Federal Regulations (CFR), Part 211, in conjunction with your firm's manufacture of inhalation solution. These violations caused these drug products to be adulterated within the meaning of Section 501 (a)(2)(b) of the Federal Food, Drug, and Cosmetic Act (FDCA). Section 501 (a)(2)(b) requires the methods used in, or the facilities and controls used for, the manufacture, processing, packing, or holding of a drug to be in conformity with current good manufacturing practice to assure that such drug meets the requirements of the FDCA as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. Deviations from 21 CFR 211.165 are as follows:

1. Failure to have appropriate laboratory determination of satisfactory conformance to final specifications for the drug product prior to release for each batch of drug product, as required by 21 CFR 211.165 (a) in that:

Your out-of-specification (OOS) investigation report [known as Exception Report #02VALI004/02VALI005] indicated that the microbiological limit tests for the following lots of Afrin Nasal Spray were found positive for the presence of objectionable microorganisms:

- a. Afrin No Drip Original 12 hours pump mist, 15 mL Nasal Spray, lot # [REDACTED] Samples collected from in-process filled units from the beginning of the operation from both filler machine [REDACTED] and [REDACTED] and re-samples of the finished product yielded positive results for the presence of *Serratia liquefaciens*;

- b. Afrin Severe Congestion 15 mL Nasal Spray, lot # [REDACTED] Samples collected from in-process bulk product from tank # [REDACTED] from a re-sample of the finished product yielded positive for the presence of *Serratia liquefaciens* and *Pseudomonas fluorescens/putida*; and,
- c. Afrin Original 12 hours, 30 mL Nasal Spray, lot # [REDACTED] Samples collected from the finished product and re-samples yielded positive results for the presence of *Pseudomonas fluorescens/putida*.

The microbiological specification for these formulas requires absence of members of the *Enterobacteriaceae* family, which includes *Pseudomonas fluorescens/putida* and *Serratia liquefaciens*. These microorganisms were present in these lots, which showed them to be out of conformity with final specifications, as required by 211.165 (a).

Your out-of-specification (OOS) investigation report for Afrin Nasal Spray lot [REDACTED] bottles filled on 1/15-16/2002 and lot [REDACTED] bottles filled on 2/4/2002 (identified as Exception Report # 02VALI004/02VALI005) determined that *S. liquefaciens* was isolated from the inside neck of one out of eight empty bottles sampled from the filling line. For lot [REDACTED] which was positive for the presence of *S. liquefaciens*, your OOS investigation report also indicated the presence of *Pseudomonas fluorescens/putida* in one out of 15 test results. The OOS investigation report contained no additional information assigning a possible cause for the presence of this second microorganism.

Because you did not document an assignable cause for the presence of this second microorganism, your firm failed to establish scientifically sound evidence to assure that the contamination was present in a non-product contact surface area of the container, in violation of 21 CFR 211.165 (a).

Your OOS investigation report (identified as Exception Report #02PROD008) also showed that Afrin Nasal Spray, lot #2B03CR bottles filled on 2/11-12/2002, was positive for *Pseudomonas fluorescens/putida*. This Exception Report #02PROD008 assigns the cause for the presence of this microorganism to be associated with microbiological preparation and testing technique.

2. Failure to reject a lot of drug product which did not meet established specifications in accordance with 21 CFR 211.165 (f) in that:

The microbiological limit test for Afrin Nasal Spray lots [REDACTED] and [REDACTED] were positive for the presence of objectionable microorganism.

These lots were released, distributed and shipped to Schering-Plough Healthcare Products (SPHCP) Distribution Center in Memphis, TN. The release of these lots violated the Quality Agreement between SPHCP and Cardinal Health Manufacturing Services, Puerto Rico approved on November/2001, section 13.0 Finished Product Controls, which reads: "The Contract Manufacturer will not release for shipment any portion of production determined to be out of specification or defective as a result of routine testing/inspection, without a legitimate assignable cause and without conclusive evidence that the exact beginning and end of the non-conforming production has been identified and clearly segregated."

3. Failure to establish and follow appropriate written procedures design to prevent during manufacturing the introduction of objectionable microorganisms in drug products that are not required to be sterile in violation of 21 CFR 211.113 (a). You stated that you based the release of these lots of drug products on the antimicrobial preservative efficacy. However a company's reliance on an antimicrobial preservative to reduce out-of-specification levels of microbes to within specification levels of microbes does not mitigate the requirement to produce products which meet specifications in the first instance.

We acknowledge receipt of your letter, dated June 14, 2002. Your response to Form FDA 483, "Inspectional Observations", was not adequate because we believe you should not have released for shipment (to include distribution centers) any portion of production found to be out of specification or defective as a result of routine testing.

We request that you inform us in writing about the status of the lots that were shipped to SPHCP. Mr. Michael Loney, Vice President and General Manager of Cardinal Health Manufacturing Services B.V., informed the investigator during the inspection that the above mentioned lots were rejected at the distribution center. Your firm's response to the Form FDA 483 echoed this statement. We also request that you inform us in writing what amendments to your records you have made to acknowledge the rejection of these lots.

Neither the above list of deviations nor the Form FDA 483, which was presented to and discussed with Mr. Michael Loney, is intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence to each requirement of the Act and its regulations.

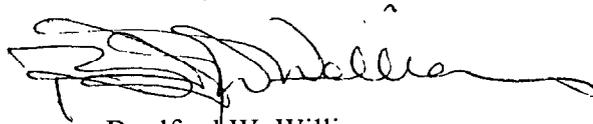
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You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. These actions include, but are not limited to, seizure or injunction. Federal agencies are 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.

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.

You should send your reply to the Food and Drug Administration, San Juan District Office, 466 Fernandez Juncos Ave., San Juan, Puerto Rico 00902-3223, Attention: Jorge L. Gonzalez, Compliance Officer.

Sincerely,

A handwritten signature in black ink, appearing to read "Bradford W. Williams", written over a horizontal line.

Bradford W. Williams
Acting District Director

Enclosures:

FDA Form 483

cc: Mr. Michael A. Loney, VP/Gen. Mgr.
CHMS, Humacao, PR