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DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration

June 15, 2004

Dallas District
4040 North Central Expressway
Dallas, Texas 75204-3145

**Ref: 2004-DAL-WL-19**

**WARNING LETTER**

**CERTIFIED MAIL**
**RETURNED RECEIPT REQUESTED**

Ms. Darlene M. Ryan, President
Pharma Fab
2940 N. Hwy. 360
Suite 100
Grand Prairie, Texas 75050

Dear Ms. Ryan:

During a January 5 through January 14, 2004, inspection of your pharmaceutical manufacturing facility located at 2940 N. Hwy. 360, Grand Prairie, Texas, Investigators Daniel J. Lahar and David M. Beltran, from this office documented serious deviations from current Good Manufacturing Practice (cGMP) regulations as delineated in Title 21, Code of Federal Regulations, Part 211.

This inspection revealed your firm's Quality, Production, Facilities and Equipment, and Materials systems employed during the manufacturing, processing packing and holding of your firm's cough and cold prescription drug products, do not conform to cGMPs. Therefore, these drug products are adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act).

At the close of the inspection, you were issued a Form FDA-483, Inspectional Observations, which contained a number of significant cGMP deviations. The following are examples of the significant deficiencies regarding your firm's operating systems.

1. **Failure of your Quality Control Unit to review and approve drug product production and control records to determine compliance with all established approved written procedures before a batch is released or distributed; and failure to investigate the failure of a batch or any of its components to meet any of its specifications [21 CFR 211.192].**

   For example, the purified water USP produced on December 19, 2003, failed to meet microbiological specification with too numerous to count values (TNTC) reported. Purified water from that day was used to manufacture [redacted] Lot # 4001. The Quality Control Unit (QCU) failed to review and

investigate the records for Lot # 4001, and no microbiological testing was performed on the finished drug product before it was released into commercial distribution. The purified water microbiological contamination could alter the safety, identity, strength, quality and purity of the drug product from established requirements. In addition, the Investigators found that the QCU was not routinely notified of the out-of-specification results obtained from the purified water system.

Your written response, dated February 5, 2004, indicates that the [redacted] Lot # 4001, manufactured on December 19, 2003, was sent to an outside laboratory testing facility for microbiological testing on January 13, 2004 (after our Investigators noted the incident). The microbial analysis by the outside laboratory showed no microbial growth in the product. Your corrective action plan also states that all liquid products manufactured at your firm will be held under quarantine until verification of microbiological determinations is received by your QCU (i.e., QA Department) for product release purposes. Your corrective action plan appears adequate.

2. **Failure to establish and follow written procedures designed to prevent objectionable microorganisms in drug products not required to be sterile [21 CFR 211.113(a)].**

Despite sanitization of the purified water system in December 2003, multiple TNTC results were obtained for sample port [redacted] in January 2004. The water monitoring results obtained from [redacted] are indicative of conditions inside the main storage vessel and are used as an indicator of a potential sanitization requirement prior to the purification water [redacted] The QCU also failed to identify the TNTC colonies, which might help determine the source of the water contamination, therefore leading to adequate corrective action plans and prevention of future deviations. Purified water is used in your formulation of liquid pharmaceutical products, the production of wet granulated materials and in the final rinse cycle for equipment cleaning.

Our Investigators also observed that tubing, used to transport water into the transport tank, was placed into a poly bag with residual moisture inside. This condition creates a static moist environment conducive to microbial growth. This practice violated your requirement to store tubing in a manner to facilitate complete drainage and drying, as required by SOP # Equip-3536-01, Title: *Operation, Maintenance, and Calibration of the Purified Water System USP.*

Your response states that identification of microorganisms recovered from the purified water system will be performed to establish a database to document the normal flora of the purified water system. Also, an environmental monitoring study will be performed on the manufacturing environment. Time frames and the planned corrective measures appear adequate. We also acknowledge your commitment to monitor the tubing used for the collection of purified water

samples and to perform personnel training to minimize the potential for microbial contamination during water collection.

3. **Failure to follow written production and process control procedures in the execution and documentation of production and process control functions at the time of performance [21 CFR 211.100(b)].**

   For example, as previously stated, the purified water system testing reported TNTC microbial counts on several occasions. The Laboratory Manager or designee was not notified of the OOS occurrences and the water system was not properly shutdown, investigated and/or sanitized and retested before use as required by your SOP #QC1245-01 Title: *Microbiological Testing of Purified Water USP.*

   Your February 5, 2004, response provides a revised SOP #QC1245. The SOP now indicates the notification, investigation, and corrective measures to be implemented when an alert or action level is exceeded at a point of use valve. The QC microbiologist will initiate a lockout system and the purified water system will then be sanitized. The action plan appears to be adequate.

4. **Failure to establish and follow written procedures prescribing a system for reprocessing batches that do not conform to standards or specifications, and the steps to be taken to insure that the reprocessed batches will conform with all established standards, specifications, and characteristics. [21 CFR 211.115(a)].**

   For example, there are no procedures for reprocessing batches due to cosmetic defects or employee calculation errors, as seen in the reprocessing of Lot No. 2794 [redacted] This lot was reprocessed due to a visual imperfection, yet an investigation was not conducted to determine the cause of the visual imperfection. There is also no data to determine reproducibility of the same reprocessing steps on subsequent batches of this product.

   Your response indicates that the reprocessed lots were placed on long-term room temperature stability studies using [redacted] testing intervals. Please provide a stability commitment indicating the action plan for any reprocessing of batches.

5. **Failure to establish a written testing program designed to assess the stability characteristics of drug products [21 CFR 211.166(a)].**

   For example, you do not have a uniform rationale to determine which liquid pharmaceutical products will be tested for microbiological determinations and preservative effectiveness. Any liquid formulation that contains a preservative system to control against bacteria or fungi growth must be evaluated for its intended preservative effectiveness.

Your February 5, 2004, response indicates that SOP QC1215-00, Title: *Microbial Monitoring of Liquid Products*, will require microbiological and Preservative Effectiveness Test determinations on liquid pharmaceutical products, with guidelines for routine product monitoring. The stability protocol should specify the use of a microbiological test method in the drug products' stability testing program (e.g., chemical analysis of preservative content). Please submit a revised stability testing program for our evaluation.

Your written response dated March 3, 2004, states that SOP QC-1215-00 requires only [redacted] of the [redacted] compendial indicator organisms (i.e., [redacted] and [redacted] referenced in USP <61> Microbial Limit test, must be absent from your finished drug product. If USP <61> is to be followed, your SOP should state that the test results must indicate an absence of all [redacted] of the compendial indicator organisms (i.e., to include Staphylococcus Aureous and Pseudomonas) from the finished drug products tested. If this is not your intent, please provide a detailed scientific rationale to justify the omission of [redacted] of the [redacted] indicator organisms.

6. **Failure to place an adequate number of batches of each finished drug product on stability studies to determine an appropriate expiration dating period [21 CFR 211.166 (b)].**

The liquid pharmaceutical products manufactured at your facility were not placed on accelerated and long-term room temperature stability studies to justify the assignment of a tentative expiration dating period of [redacted] The only accelerated stability data obtained was for development batches (approx. [redacted] liters) that were not representative of routine production batches (approx. [redacted] liters). Our Investigators found no documentation or data to support or demonstrate equivalence between development and commercial batches with regards to equipment, components, and manufacturing processes.

Your February 5, 2004, response states that development batches will no longer be made and used for accelerated stability studies to support a [redacted] expiration date. The proposal to manufacture pilot batches of [redacted] of the final batch size for all new products, and place them on accelerated studies is adequate. However, your response did not address whether the pilot batches will be using equivalent equipment, components, and manufacturing processes. Please provide a time frame for completion of the corrective action plans, and a more detailed stability commitment particularly as it relates to assignment of the expiration date.

7. **Failure to review complaints as part of your annual product review in order to evaluate the quality standards of each drug product to determine the need for changes in drug product specifications or manufacturing or control procedures [21 CFR 211.180(e)(2)].**

For example, your firm lacks documentation to demonstrate a comprehensive annual evaluation of the Adverse Event Log to determine significant trends as directed by SOP #QA-1091-00, Title: *Adverse Event Reports.*

Your February 5, 2004, response includes a revised SOP #QA1091, Title: *Adverse Events Reports,* effective February 4, 2004. This SOP identifies serious adverse events and requires that the information be filed using FDA MedWatch Form 3500A. This action plan appears adequate.

8. **Failure to clean, maintain and sanitize equipment and utensils at appropriate intervals to prevent malfunctions and contamination that would alter the safety, identity, strength, quality or purity of the drug product [21 CFR 211.67(a)].**

As stated above, our Investigators observed that the purified water system is not adequately controlled or monitored. Your firm failed to investigate the TNTC results collected from the purified water system, and the tubing used to collect the water sample from sampling port [redacted] was not properly stored and/or sanitized.

A properly validated water distillation system will provide purified water that meets USP compendial requirements. The purified water storage condition must be such that microbes are not inadvertently introduced into the system, which could result in microbial growth and proliferation. Please provide a validation protocol for the purified water system. The protocol should address time frames for the sanitization of the system and the specific cleaning procedures for removing contamination to predetermined levels of acceptability after sanitization is completed. Appropriate tests should be conducted before and after sanitizing and cleaning the purified water system in order to identify the effectiveness of the intended sanitization procedure.

In addition, the production and commercial distribution of liquid pharmaceutical products was initiated in December 2002, without equipment cleaning validation studies being conducted.

Your February 5, 2004, response states that the "The Cleaning Validation Master Plan, Section 5.3.1.1 states that initial cleaning Performance Qualifications (PQs) may be completed under first available challenge conditions." Your response also included a cleaning validation schedule for liquid production equipment. The action plan and estimated completion time frame appear adequate. Be aware that the cleaning procedures should be proven to be effective and appropriate cleaning agents should be identified in the cleaning validation protocol. The cleaning procedure should remove residues to predetermined levels of acceptability after a manufacturing process is complete.

All of the above deficiencies are indicative of your Quality Control Unit's inability to meet requirements impacting the identity, strength, quality, and purity of your drug products [21 CFR 211.22]. The above statements are not intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to assure that your firm's operations and controls adhere to all current regulations applicable to your operations.

We are in receipt of your written responses dated February 5 and 13, 2004, and March 3, 2004. We acknowledge that the corrective actions you listed address some of the above stated specific concerns. Corrective actions will be verified during the next establishment inspection. It will not be necessary for you to re-submit the revised documents already provided, unless another revision is necessary.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions include, but are not limited to, seizure and/or a court injunction against further marketing of your prescription drug products. In addition, Federal Agencies are advised of the issuance of all Warning Letters so that they may consider this information when awarding government contacts.

Please notify this office in writing within fifteen (15) working days from the date you received this letter. Your response should include all requested information, identify the actions you are taking to correct the violations, and provide specific timeframes for achieving compliance. Your reply should be sent to Edwin Ramos, Compliance Officer, at the above stated address. If you have any questions concerning the stated matters, you may contact Mr. Ramos at 214-253-5218.

Sincerely,

Michael A. Chappell
Dallas District Director

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