

**Warning Letter****Via FedEx**

NOV 21 2002

WL: 320-02-01

Mr. Alexander B. Bell
Vice President Technical Operations
Mayne Pharma Pty., Ltd.
1-23 Lexia Place
Mulgrave North, Melbourne, VIC 3170
Australia

Dear Mr. Bell,

This letter is in response to an inspection of your pharmaceutical manufacturing facility in Melbourne, Australia, by the United States Food and Drug Administration (FDA) on April 8-16, 2002. This inspection revealed significant deviations from U.S. Current Good Manufacturing Practices (CGMP) Regulations (Title 21 CFR, Parts 210 and 211) in the manufacture of sterile drug products. At the completion of this inspection, you were issued a 46-item Inspectional Observations (FDA-483) form. 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.

Our review also included your May 21, 2002, August 22, 2002 and October 11, 2002 written response letters to the FDA-483 observations. We acknowledge the commitments to correct the deficiencies; however, the response lacks sufficient details, explanations, and documentation to address the deviations observed during the April 2002 inspection. In addition, we have the following concerns that include, but are not limited to:

1. In the last two years there were 11 product sterility failures involving the organism [redacted] The investigations into these routine results found no assignable cause for the sterility failures. Some of the failures involved [redacted] sterilized products that included [redacted] There were no corrective actions identified in these investigations and the batches were released on the basis of the survivor test. [21 CFR 211.192]

The production department conducted no investigations, although the production system could not be ruled out as the potential cause of the product contamination.

The response stated that no probable cause was identified in four investigations, i.e., no conclusive evidence that the failure was due to either laboratory or production error

therefore corrective action could not be documented. In three investigations the most probable cause for the sterility positives was deemed to be laboratory error. Further, you acknowledged at a minimum retraining of both production and laboratory staff should have taken place, as a corrective action. The response also indicated that extended review of trends for sterility failures was not undertaken, but will be considered as a corrective action in any future investigations.

In not addressing probable causes and not initiating corrective actions the firm failed to identify the cause of the contamination and neglected to insure that this type of problem would not recur. Furthermore, the drug products that were released failed to meet their established standards or specifications and had no assurance to be free of objectionable microorganisms.

In the three investigations for which the sterility positives were deemed to be laboratory errors, the investigations failed to identify the type of errors or relate them to laboratory errors. In these three cases, the firm identified the sterility positives as laboratory errors only because the product was [] sterilized. The firm failed to implement any corrective actions to insure that the laboratory errors would not occur in the future.

2. The test methods used for sterility testing are inadequate. [21 CFR 211.165] There is a lack of data to demonstrate that the methods are capable of recovering low levels of organisms that would be found in a typical non-sterile drug product. The study summaries and raw data lacked any counts for the inoculated controls and samples, and there is insufficient data to interpret whether the product inhibits growth of organisms. The reproducibility of the method was not demonstrated. For example, only one result following a negative recovery was used to validate the [] Method.

It was also noted that you have not completed [] Validation for 7 of 15 products with []

In the August 22, 2002 response, it states that the methodology complies with the requirements of *USP Sterility Test* [] Validation for [] It clarified that the counts used to initially inoculate the test and control samples are quantified, but you don't explain how the procedure is done. It also states that an update to the validation requirement such that three validation tests will be performed in order to comply with the requirements of Validation of [] from Pharmacopeial Articles []

Further, the response included a commitment to repeating the Validation for [] testing three times for any new formulations/presentations. The validation will be performed twice on existing products the next time the batches are manufactured. As to the products requiring [] inclusion in the validations, this will be scheduled for the next production batches being produced.

Until this validation is completed, the sterility test methods used are inadequate in that there is no documentation, which demonstrates the accuracy and repeatability for [redacted] from Pharmacopeial Articles.

Also there is no assurances that the sterility positive results identified as errors were accurate assessments because of the inadequacy of the test methods.

3. Written procedures designed to prevent microbiological contamination of sterile drug products were inadequate and resulted in: [21 CFR 211.113]

- inadequate monitoring of differential air pressures between clean rooms
- inadequate support of changes for the movement of walls and HVAC modifications made to the [redacted] facility
- inadequate controls and procedures for gowning
- inadequate validation of the sterilization process in no microbiological qualification or determination of the resistance of the biological indicator challenge system was performed for [redacted]

The responses and commitments made by the firm to correct these deficiencies in item #3 appear adequate. However, this raises concerns about the Quality Control Unit. We remind you of their responsibilities in reviewing and approving all procedures related to production, quality control, and quality assurance to assure the procedures are adequate for their intended use.

The CGMP deviations identified above or on the FDA-483 issued to your firm are not to be considered an all-inclusive list of the deficiencies at your facility. FDA inspections are audits, which are not intended to determine all deviations from CGMPs that exist at a firm. If you wish to continue to ship your products to the United States, it is the responsibility of your firm to assure compliance with all U.S. standards for Current Good Manufacturing Practices.

Failure to correct these deficiencies may result in FDA denying entry of articles manufactured by your firm into the United States. The articles could be subject to refusal of admission pursuant to Section 801(a)(3) of the Act in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practices within the meaning of Section 501(a)(2)(b) of the Act.

Please respond to this letter within 30 days and provide documentation regarding corrections of the above deviations. Your response should include data collected in your corrections to the deficiencies cited as well as copies of procedures not already included. Please identify your response with CFN 9610999. Until FDA can confirm compliance with CGMP's and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturer of sterile drug products.

Please contact Anthony A. Charity, 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
CDER HFD-322
7520 Standish Place
Rockville, MD 20855-2737
Tel: (301) 827-0062; FAX (301) 594-1033

To schedule a re-inspection of your facility, after corrections have been completed and your firm is in compliance with CGMP requirements, send your request to: International Operations Branch, HFC-132, 5600 Fisher's Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,



Joseph C. Famulare
Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research