DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

AUG 3 2004

# Warning Letter

**Via FedEx**

**WL: 320-04-04**

John Tramontana
Director
Bigmar-Bioren SA
Via Cadepiano 24/26
CH-6917 Barbengo,
Switzerland

Dear Mr. Tramontana:

We have completed our review of the inspection of your pharmaceutical manufacturing facility in Barbengo, Switzerland by Investigators Susan Bruederle and Christine Twohy, during the period of May 6-13, 2004. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21, Code of Federal Regulations, Parts 210 and 211) in the manufacture of sterile drug products. These deviations were listed on an Inspectional Observations (FDA-483) form issued to Mr.[ ]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.

Our review also included your May 27, 2004 response to the FDA-483 observations. We note that many corrections have been completed, or will soon be implemented. There are also issues which we believe need more comprehensive corrections. Specific areas of concern include, but are not limited to:

QUALITY SYSTEM

1. Written control procedures were not always followed when changes were made to test methods and validated systems, for example:

   a. No positive control has been used while conducting the USP[ ]test since December 2002. This inappropriate change to the test method was made without Quality Control Unit (QCU) review. As a result, [ ]batches of product were released for export to the US based on invalid USP test results. [21 CFR 211.160]

b. The [ ] process recipe changes to the [ ] points, listed as critical parameters, in the manufacture of [ ] batches were made without any documentation of Quality Control Unit (QCU) approval. [21 CFR 211.100]

2. Written procedures for investigating deviations were not followed on at least six occasions in 2004, when recording charts showed malfunctions in either the [ ] or the [ ] in the equipment used to distribute [ ] a critical ingredient in all of your products. [21 CFR 211.192]

3. Your firm does not have an adequate number of trained people to carry out the responsibilities of your quality assurance department. Approximately [ ] batches of product were shipped to the US during the period of 2002 to 2004, and our investigators observed that only one person conducted the dual functions of quality control and quality assurance. [21 CFR 211.22]

Your response indicates that you will address the lack of QC personnel by having one other management official sign off on the QA and QC reviews. The response does not provide any qualifications for this official, any procedures that will be used, or show how this will correct the problem of inadequate oversight. It also indicates that you have corrected the practice of making changes without QCU approval, by revising written procedures and training of employees. Many of the other deficiencies on the FDA-483, and on previous FDA-483s appear to be a result of an inadequate quality system. We do not believe these corrective actions are comprehensive enough to adequately address this deficiency.

LABORATORY SYSTEM

4. Laboratory controls were inadequate, for example:

a. Since December 2002, no positive controls were run with samples analyzed for [ ] [21 CFR 211.167]
b. One analyst did not follow the sterility testing protocol for [ ]. [21 CFR 211.167]
c. [ ] used in the annual re-qualification of [ ] cycles in August 2003 were not [ ] immediately after the tests were conducted. [21 CFR 211.160]
d. On several occasions the exposure time for [ ] was exceeded. [21 CFR 211.160]
e. The [ ] test at the 12-month time point was never conducted as required by your stability protocol for [ ] [21 CFR 211.167]

Your written response addresses each of these deficiencies individually but fails to address the overall problem of the failure to follow written procedures indicated by these observations. Your corrective action is to retrain employees, retest samples, and revise the written procedures. Similar deficiencies observed during previous inspections were reportedly addressed in the same way. We recommend a thorough audit of all actual procedures as compared to written procedures, and a thorough corrective action plan that will require adequate supervision and provide adequate quality assurance.

5. Laboratory records and documentation were inadequate, for example:

   a. Results for test of finished product conducted on August 29, 2003 were missing for two column entries. [21 CFR 211.194]
   b. There were no recorded results for identification of an isolate recovered from the filling area. [21 CFR 211.194]
   c. Changes were made to the raw data on a test record of a[ ]test performed on October 29, 2003, with no supporting data to indicate that a retest was done. [21 CFR 211.194]

The written response addresses these deficiencies with only revised written procedures for documentation. We recommend a thorough review of all documentation procedures and more thorough supervision and more frequent auditing of laboratory records.

PRODUCTION SYSTEM

6. Production and control procedures designed to prevent microbiological contamination were inadequate or were not always followed, for example:

   a. Intact vials were removed during the visual inspection of[ ]filled vials and were not[ ][21 CFR 211.113]

   b. No SOPs were instituted for employees to respond to audible[ ]alarms in the[ ]area during operations. [21 CFR 211.113]

Your written response states that you will revise[ ]fill procedures and perform new [ ]fill studies before production is resumed, and that the procedure for responding to alarms has been revised. Revising written procedures may not be adequate. Similar deficiencies were observed during previous inspections and revision of the written procedures has not prevented the current deficiencies. You should develop a more comprehensive corrective action plan that will prevent these kinds of deficiencies.

FACILITIES AND EQUIPMENT SYSTEM

7. Equipment was not always adequately maintained.

   a. Six lots of [ ] were rejected in 2003 because of problems with the [ ] and four of these occurred immediately after the annual maintenance. [21 CFR 211.67]

   b. The [ ] system was not adequately maintained. The [ ] system was not in operating condition during the entire period of the FDA inspection. [21 CFR 211.67]

   c. Records for maintenance and sanitization performed were not always maintained, For example:

      i. There were no records of maintenance of the critical equipment used in the distribution of [ ] when multiple malfunctions of equipment occurred in March and April 2004. [21 CFR 211.67(c)]

      ii. Maintenance performed on the [ ] in September and October 2003 was not correctly recorded. [21 CFR 211.67(c)]

      iii. There was no documentation of the verification of the [ ] as required by the SOP. [21 CFR 211.68]

Your response states that you have only written new procedures and implemented new logbooks for recording maintenance performed. The response fails to address the larger issue of inadequate record keeping throughout the facility or provide any plan or quality system that might prevent continued deficiencies.

We acknowledge your response of May 27, 2004, and are aware that new SOPs have been put in place. However, our investigators have reported that even though SOPs have existed in the past, they were not always followed; therefore, the changes may not be effective and will need to be monitored and verified. We also acknowledge the voluntary shut down of production until a review of the status of the [ ] system and the [ ] system is completed and the cause of problems are identified and corrected. However, we caution you that your corrections should not be limited to the observations made by the FDA, but rather the approach taken should be towards global improvements in your supervision and quality system.

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 of receipt. Your response should include data collected in your correction to the deficiencies cited as well as copies of procedures not already included. Please identify your response with CFN 9614432. Until FDA can confirm compliance with CGMPs and correction to the most recent inspection deficiencies, this office will recommend disapproval of any new applications listing your firm as the manufacturer of drug products. Please contact Albinus D'Sa, 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
Montrose Metro II
11919 Rockville Pike
Rockville, MD 20852

Tel: (301) 827 9044; FAX (301) 827-8909

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: Division of Field Investigations, International Branch, HFC-134, 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