DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

GS&2Sd

Warning Letter

Via FedEx

WL: 320-06-02

April 28, 2006

Mr. Drago Frkovic
Director Product Supply
Pliva Croatia Ltd.
Pliva Hrvatska d.o.o.
Prilaz Baruna Filipovica 25
10000 Zagreb Croatia

Dear Mr. Frkovic:

We are writing regarding an inspection of your pharmaceutical manufacturing facility in Zagreb, Croatia, during the period of January 23 – February 8, 2006. The inspection revealed significant deviations from U.S. Current Good Manufacturing Practice (CGMP) Regulations (Title 21 Code of Federal Regulations (CFR), Parts 210 and 211) in the manufacture of drug products. These deviations were presented to you on an Inspectional Observations (FDA 483) form 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 (the Act) [21 U.S.C. 351(a)(2)(B)].

Our review included your March 3, 2006, March 9, 2006, and 21 April 26, 2006, responses to the FDA 483 observations.

We appreciate the global scope of your corrective action plan submitted in your April 26, 2006, correspondence and believe it is not only critical for CGMP compliance, but also for mitigating future repeat deviations. The Agency takes very seriously repeat deviations. It is for this reason that those deviations that were listed on both the August 30, 2002, and the February 8, 2006, FDA 483 Inspectional Observations are included in this letter. We note that many of the repeat deviations resulted from poor peer, supervisory, or quality control unit oversight. Unless otherwise stated we accept your proposed corrective actions.

FACILITIES AND EQUIPMENT SYSTEM

1. Buildings used in the manufacture of injectable drug products are not always maintained in a good state of repair. **21 CFR 211.58**

Water was observed to be dripping from a light fixture in the ceiling of the injectable production area (class C) in front of the [ ] The investigator observed that

there were buckets in the drop ceiling to catch condensate that was dripping from HVAC ducts. At the time of occurrence, the maintenance employees who had placed the buckets in the drop ceiling had not notified the production employees of the problem. And, the production employees had not noticed the leak.

The flexible piping from the exhaust of the [ ]was also ripped and observed to be taped in the same location from a previous tear. We are concerned that maintenance personnel did not notice the ripped exhaust when they had placed buckets in the same area. The investigator states she was informed that production would cease until cleaning was performed, samples were taken, and results were received. She later found out that production continued. Information supplied to the FDA inspection team must be reliable and you should take immediate action to prevent this from recurring.

Your responses state that you have revised procedures, provided training, replaced the flexible piping, and will develop a comprehensive preventative maintenance program. Please explain what you have done to prevent the condensate from dripping through the ceiling to the production area.

2. Equipment and utensils are not always cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination that would alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements. **21 CFR 211.67(a)**

Studies of disinfectants used in the [ ]processing areas have not been conducted to demonstrate that they are appropriate and effective for their intended use. Areas where disinfectants are used include floors, walls, and hands. Your response indicated that you were in the process of methods development for disinfectant studies at the time of the inspection, and that a protocol will be approved in May 2006. Please provide us with a copy of your final report.

[ ]was observed in use even though its alarm light was on. We acknowledge your written commitment to conduct investigations and training, but we are unsure if analysts and other employees understand that they should not use malfunctioning equipment, and if communication between maintenance and laboratory employees has improved.

3. The calibration of instruments was not always conducted at suitable intervals. **21 CFR 211.160(b)(4)**

[ ]used for sterilization of[ ] and a[ ]used for[ ]during the qualification of[ ]were not qualified or calibrated. Please provide an impact assessment for the [ ]processed in these[ ] Your response indicates you will qualify and calibrate these pieces of equipment and identify all critical and non-critical GMP equipment in order to have a more

comprehensive qualification and calibration program. However, failure to calibrate and qualify a[ ]and[ ]was the subject of the first three items on the last FDA 483 issued 8/30/2002. Repeat observations indicate that your corrective action in 2002 was not adequate.

LABORATORY CONTROL SYSTEM

4. Deviations from the written specifications are not justified. **21 CFR 211.160(a)**

During cleaning validation of the[ ]the specification was a maximum of[ ]micrograms per swab and the result was 41.9 micrograms per swab. The cleaning validation was not repeated and the cleaning procedure was not changed until after this inspection. In addition to your proposed corrective actions, provide us assurance that there has been no cross-contamination of other products manufactured on this equipment. The establishment inspection report states that there are more than[ ] other products manufactured on this equipment.

A failing result was identified in the method validation for[ ]analysis of[ ]for [ ]in the[ ]testing for the solvent[ ]The specification is[ ]and the result was 15.8%. In addition, the result was not noted to be out of specification by the chemist, reviewer, or quality personnel and the method validation was approved. There were several record reviewing deviations also noted on the previous FDA 483 issued 8/30/2002.

5. Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity. **21 CFR 211.160(b)**

There were several instances where this occurred. Hold time studies for[ ] Injection and[ ]Injection do not represent actual hold times. All samples were taken at time zero. The[ ]minute time point samples for the[ ]testing of [ ]tablets were not evaluated with a[ ]standard. Potential of [ ]were used for[ ]testing of microbiological culture in the bioanalytical laboratory. These[ ]are not as accurate as is required by your test specification. Although your corrective actions appear adequate, we are concerned because the same kinds of deviations were listed on your previous FDA 483 issued 8/30/2002 as were cited again on the current FDA 483.

6. Test procedures were not always followed. **21 CFR 211.160(a)**

During the qualification of[ ] either were not[ ]on time or were not[ ]at all. The procedure for

checking[ ]of prepared[ ]was also not followed. Not following procedures was cited on the last FDA 483 issued 8/30/2002.

7. Laboratory records did not always include a description and identification of the sample received for testing, the date the sample was taken, the date the sample was received for testing and the data derived from the testing. **21 CFR 211.194(a)**

There was no record that the laboratory received personnel monitoring samples of one person for the[ ]fills of[ ]and[ ]There was no record of analysis, yet the results were reviewed as acceptable. We are concerned about the failure to effectively review records at your facility.

In addition, analysts in the[ ]Microbiology Laboratory do not enter the date on which the results are read into the logbook. Your proposed corrective action appears acceptable, but again there were several logbook recordkeeping deficiencies noted on the previous FDA 483 dated 8/30/2002.

8. There were not always the initials or signature of a second person showing that the original records have been adequately reviewed for accuracy, completeness, and compliance with established standards. **21 CFR 211.194(a)(8)**

There were several instances where there were deviations regarding the review of records. Errors were found in the calculations for in-process content uniformity testing of two batches of[ ] The original reviewer did not catch them, but the person reviewing the data in preparation for the ANDA submission found the errors. An analyst failed to cite the correct SOP and this was not corrected by the reviewer. Laboratory records are not reviewed by a second person in the[ ]Microbiology Laboratory. As mentioned, we are concerned about the many mistakes not caught by reviewers, and that this is a repeat FDA 483 observation.

QUALITY SYSTEM

9. Unexplained discrepancies of a batch or any of its components were not always thoroughly investigated. The investigations did not always extend to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy. **21 CFR 211.192**

Deviation reports were not initiated in a timely manner for the following incidents: a two-hour stoppage between[ ]and[ ] an incorrect program used for the[ ]test, and the failure of a[ ]during[ ] In the first incident, the deviation wasn't initiated until a three-month stability failure for impurities. The second two were identified while reviewing documents for the ANDA submission.

There were three other situations where deviations were not initiated within [ ] hours as specified in your procedure. Two were for [ ] yield and the third for a [ ] failure.

Lastly, there were three deviations for [ ] samples that did not extend to the drug product that could have been affected.

These examples not only demonstrate a pattern of deficiencies, but they identify a failure in quality assurance oversight. The quality control unit has the responsibility to review production records to assure that no errors have occurred or, if errors have occurred, that they have been fully investigated.

General Comments

The same kinds of deviations from the previous FDA 483 issued on 8/30/2002 were also identified as deviations on the current FDA 483. Although your current response promises global corrections and if properly implemented will likely reduce future recidivism, we remain concerned about repeat deviations.

Deficiencies in the oversight and responsibility of the quality control unit were not directly cited on the FDA 483. We recognize the commitments to reorganize and improve the quality organization in your response, but we want to ensure that you understand that the quality control unit is responsible for reviewing failure investigations, control procedures, production records, and other records relating to the approval or rejection of drug products. We also note that many record reviewing deviations were identified while preparing ANDA submissions. You should also explain to us what you are doing to ensure that non-submission data is also checked for accuracy.

Your April 21, 2006, response states that you will conduct retrospective and prospective batch record reviews. Please submit these reports to our office and provide a timeline for all outstanding corrective actions.

Until FDA has confirmed correction of the deficiencies observed during the most recent inspection, and compliance with CGMPs, this office will recommend disapproval of any new applications listing your firm as the manufacturer of finished pharmaceutical drug products. In addition, 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 [21 U.S.C. 381(a)(3)] in that the methods and controls used in their manufacture do not appear to conform to Current Good Manufacturing Practice within the meaning of Section 501(a)(2)(B) of the Act [21 U.S.C. 351(a)(2)(B)].

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 submitted. Ensure that your response to this warning letter addresses the

deviations in a global manner and that documentation supporting corrective actions is submitted to this office in English. Please identify your response with FEI 3002807904. Please contact Karen K. M. Takahashi, Compliance Officer, at the address and telephone numbers shown below, if you would like to schedule a meeting, have any questions, a written response or concerns regarding these decisions.

U.S. Food & Drug Administration
CDER HFD-325
11919 Rockville Pike
Rockville, MD 20852
Tel: (301) 827-9008; 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: Director, Division of Field Investigations, HFC-130, 5600 Fishers Lane, Rockville, MD, 20857. You can also contact that office by telephone at (301) 827-5655 or by fax at (301) 443-6919.

Sincerely,

Nicholas Buhay
Acting Director
Division of Manufacturing and Product Quality
Center for Drug Evaluation and Research