Inspections, Compliance, Enforcement, and Criminal Investigations

Dabur Oncology PLC

hhsbluebird **Department of Health and Human Services**

Public Health Service
Food and Drug
Administration
Silver Spring, MD 20993

Warning Letter

Via FedEx

WL: 320-09-03

April 22, 2009

Mr. Shyam N. Khante
Head Global (Dosage Form Manufacturing)
Dabur Oncology PLC
Lion Court, Farnham Road
Bordon, Hampshire GU35 0NF
United Kingdom

Dear Mr. Khante,

This letter is regarding an inspection of your pharmaceutical manufacturing facility in Bordon, UK by Investigator Jose A. Cruz and Chemist Miguel A. Martinez, during the period of August 21 - 29, 2008. 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 finished drug products.

These deviations were listed on an Inspectional Observations (FDA-483) form issued to you at the close of the inspection. These deviations cause the drug products to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act. Section 501(a)(2)(B) of the Act requires

that all drugs be manufactured, processed, packed, and held according to current good
manufacturing practices.

We have reviewed the Establishment Inspection Report (EIR) and your response dated October 10, 2008. We note that some corrections have been completed, or will soon be implemented. However, your response continues to be inadequate in addressing several significant deficiencies. Specific areas of concern include, but are not limited to:

1. Appropriate written procedures, designed to prevent microbial contamination of drug products purporting to be sterile, were not adequately established or followed. [211.113(b)]

The Establishment Inspection Report (EIR) provides details relating to three incidents, in April 2006, October 2007, and November 2007, where out-of-limit (OOL) results were reported for environmental monitoring samples collected from the isolators used in the production of
Paclitaxel Injection Lots# (b)(4), respectively. We expect that contamination within isolators be minimal, and most significantly, that any OOL results will be thoroughly investigated before a batch disposition decision.

Furthermore, regarding the above instances, please provide corrective actions related to the following specific deficiencies:

a. Laboratory Investigation Report (LIR)# OOS/M/06019 was generated in response to OOL results from environmental monitoring deviations for samples collected during the manufacture of Paclitaxel Injection, 100 mg Lot# (b)(4) (April 2006). This document indicates that the “Date of Occurrence” was “18 Apr 06.” It also states “form completed retrospectively” and is signed and dated “13 Jun 07.” This lot was shipped to the U.S. on May 31, 2007.

The associated “Failure Investigation and Reporting Form,” identified with Reference # MB04002, indicates that the “Date Deviation Raised” is “20 Apr 06.” It also indicates that the “Date Deviation Report Closed” is “22 June 07.” Please provide details regarding this investigation, including but not limited to: why the OOL evaluation was “… completed retrospectively,” why this failure investigation
was open for more than one year, and why the product was released and shipped to the U.S. before the investigation was closed.

b. LIR# OOS/M/07050 was generated in response to OOL results from environmental monitoring samples collected during the manufacture of

Paclitaxel Injection, 300 mg Lot# (b)(4) (October 2007). The environmental monitoring samples were collected from Glove No.1 in the filling isolator. The associated "Failure Investigation and Reporting Form," identified with Reference # MC10001, states
that the impact on product quality is "low." This document includes a memorandum that states that the contamination includes "a Gram-positive cocci, not yet identified but possibly a *Staphylococcus* spp." This document indicates that the "Date Deviation Report Closed" was "08 Nov 07." This lot was shipped to the U.S. on October 31, 2007.

Please provide details to support the rationale for your firm's assessment of the impact on product quality for this incident. Please explain why the contamination was "not yet identified…" In addition, please provide details regarding why this lot was released and shipped to the U.S. before the investigation was closed.

c. LIR# OOS/M/07053 was generated in response to OOL results from environmental monitoring samples collected during the manufacture of Paclitaxel Injection, 300 mg Lot# (b)(4) (November 2007). This LIR fails to provide information related to the number of colony-forming units (cfu) or the location where the samples were collected.

The associated "Failure Investigation and Reporting Form," identified with Reference# MC11001, indicates that contamination was detected in a "finger dab" sample from Glove 5 in the filling isolator, but fails to include the cfu count. This document also references contamination (1 cfu) which was detected in a settling plate sample taken in the (b)(4) isolator. This document includes a
memorandum that states that the contamination includes "a Gram-positive rod, not yet identified but possibly a *Bacillus* spp."

Please explain why the documentation related to this contamination event fails to include all of the pertinent information. In addition, please explain why your firm did not identify the contamination.

2. Equipment and utensils are not maintained at appropriate intervals to prevent 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)]

Regarding FDA 483 Observation #8(a-f), there were several instances of failure to maintain equipment, including: rust, deterioration, and debris in the mobile and filling isolators in area P14. The presence of rust, deterioration, and debris in isolators used to manufacture sterile

drug products is unacceptable.

Your response does not adequately address our concerns and failed to include documented evidence of corrective actions taken regarding the items specifically listed in this observation. Please provide details related to your corrective actions for these specific deficiencies.

Furthermore, your response provides details for routine preventive maintenance checks, which include looking for “deterioration and chipping of (b)(4) adhered to outfeed chute of the filling isolator.” Please note that the presence of (b)(4) within aseptic processing environments is objectionable. We expect that all surfaces within aseptic processing environments will be constructed and maintained to permit effective cleaning and decontamination/sterilization.

Please provide details related to your corrective actions for this specific deficiency.

3. The acceptance criteria for the sampling and testing conducted by the quality control unit are inadequate to assure that batches of drug products meet each appropriate specification. In addition, the statistical quality control criteria do not include appropriate acceptance and
rejection levels. [21 CFR 211.165(d)]

We have concerns related to your procedures for visual inspection of sterile drug products and the recurring incidents of particulate matter contamination. We expect that the process is designed to minimize the potential for particle contamination, and that any unit with visible
particle or foreign matter be detected and removed during inspection of the final sealed product. Safeguards should be implemented to preclude shipment of product with particulate matter contamination. Our specific concerns include, but are not limited to:

Regarding FDA 483 Observation #5.1, the instructions and acceptance criteria in the previous version of SOP# 02.01.018-02 “Acceptable Quality Level (AQL) Sampling of Filled Vials” were inadequate. Your firm’s acceptance criteria for this type of defect
permitted (b)(4) units of limited AQL sample to have visible matter, without rejection (“Accept with (b)(4) and Reject with (b)(4)”). Paclitaxel Injection 300 mg Lots# (b)(4) were released and shipped to the U.S. using this deficient acceptance criteria for the AQL inspection. Based on your new AQL inspection acceptance criteria, as provided in your firm’s response to the FDA 483 (“Accept with (b)(4) and Reject with (b)(4)”), you would have rejected these lots.

Your response fails to provide information regarding your corrective actions related to the marketed lots, and/or any other lots which may have been released based on the inadequate acceptance criteria. For example, your firm plans to conduct visual inspection in periods no longer than 30 minutes. Please include details on how your firm will document conformance to this standard.

Additionally, based on information provided in your response, it appears that your "Visual Inspectors Qualification Program" was inadequate. Prior to the revisions detailed in your response, the operators who conduct visual inspections were considered qualified if they detected only (b)(4). Therefore, your reliance on the sufficiency of the above described visual inspection process to assure that contaminated vials are excluded from batches is questionable.

4. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are inadequate in that they do not include adequate validation of the aseptic process. [21 CFR 211.113(b)]

Regarding FDA 483 Observation #3.6, the investigator reviewed the (b)(4) qualification for the isolator section that interfaces with the (b)(4). This review disclosed that biological indicators (BIs) placed on the (b)(4) door seal were not completely inactivated by the (b)(4).

Your response fails to provide details of corrective actions or a product impact assessment relating to these positive BIs during the (b)(4) qualification. Please provide details related to your corrective actions. Please also provide the protocol for your (b)(4) re-qualification and a timeline for the completion of this project.

5. Laboratory equipment is not sufficiently calibrated and qualified at suitable intervals in accordance with an established written program containing specific limits for accuracy and precision. [21 CFR 211.160(b)(4)]

Regarding FDA 483 Observation #12 (a) and (b), the operational qualification documentation for the (b)(4) UV-VIS Spectrophotometer, Karl Fisher Titrator (b)(4), and the Karl Fisher (b)(4) did not include complete information to accurately qualify this laboratory equipment.

We acknowledge the corrections that have been proposed in your response. However, your response failed to include documentation for calibration of the following:

- (b)(4) UV-VIS Spectrophotometer, including results from the linearity test;
- Karl Fisher Titrator (b)(4) and the Karl Fisher (b)(4), including results from the reproducibility and electrode accuracy tests.

Please provide this documentation in your response.

6. The firm's procedures for review and approval of drug product production and control records by the quality unit are inadequate to determine compliance with all established, approved written procedures before a batch is released or distributed. Also, investigations into any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications are not extended to other batches of the same drug product, whether or not the batch has already been distributed. The investigations are also not extended to other drug products that may have been associated with the specific failure or discrepancy. [21 CFR 211.192]

a. Regarding FDA 483 Observation #2 (a), your firm failed to conduct an Out-of-Specification (OOS) investigation after OOS results were obtained for in-process assay testing of process validation samples taken for Methotrexate Injection 25 mg/mL Lot# (b)(4).

Your response fails to address the specific OOS referenced in this observation. Please provide information related to your investigation of this OOS, including an assessment of the affect on the Methotrexate Injection 25 mg/mL process validity.

b. With regard to OOS investigations, there were instances where your firm determined the root cause to be analytical error. We expect that any analytical error be fully documented, and that without a definite root cause determination, the original OOS results would be considered to be legitimate and would be included as part of the decision to release the associated batch.

Regarding the OOS investigation referenced in FDA 483 Observation #2 (b)(1), your response states that "the original result was invalidated on establishing enough scientific evidence." There are additional instances, in response to Observations #2 (e)(1) and #2 (e)(2), where your response fails to provide evidence to support analytical error as your root cause determination during OOS investigations. Please provide details related to your corrective actions for these specific deficiencies.

c. Furthermore, please provide information for the following specific deficiencies:

I. Regarding FDA 483 Observation #7 (f), the analyst signed and dated the "Sample Booking In Form" related to in-process samples for Methotrexate Injection, Lot# (b)(4), even though the tests had not been performed.

The documentation practices detailed in this observation are unacceptable. We expect that the documentation practices of all employees be accurate and representative of the actions that had been conducted. Your response fails to address the practice of documentation which misrepresents the actions that were actually conducted. Your response fails to explain why this "error" was not captured during the review process. Further, your response fails to provide an assessment of this missing data on the Methotrexate Injection process validation. Please provide details related to your corrective actions for this deficiency.

II. Regarding FDA 483 Observation #1.3(a), your response references Investigation Report# 16.07.013-01 "Particulate Matter Failure Investigation in Paclitaxel Injection Batches PA07002U & PA07003U," which was initiated in January 2007, and also references a "CAPA originated from the recommendations of the Investigation Report # 06.07.013 were in the process of implementation or not implemented." Further, your practice of including a lot (Paclitaxel Injection, 300mg Lot# (b)(4)) as part of a deviation which has already been closed is inadequate.

Please explain the reason for the delay in implementing these corrective actions. Furthermore, we have concerns that the deficiencies listed above are similar to violations documented during the FDA inspection of your firm in December 2005 and provide evidence of recurring CGMP deficiencies related to investigations for incidents of particulate matter contamination. In addition, please provide information related to the investigation for particulate matter contamination in Lot# (b)(4).

III. Regarding FDA 483 Observation# 1.3(d), four deviation reports (PB04008, PB05002, PB05006, and PB07008) were initiated to document particle contamination incidents during aseptic production operations.

Your response references a probable cause related to the "low impact" designations for particulate matter contamination incidents, but failed to provide documentation to support this justification. Please include this documentation in your response.

7. Laboratory records are inadequate, in that they fail to have initials or signature of a second person showing that original records are reviewed for accuracy, completeness, and compliance with established standards. [21 CFR

211.194(a)(8)]

Regarding FDA 483 Observation #7 (b), multiple instances occurred where the review of analytical test results or an instrument logbook was inadequate, because reviews were performed by the same analyst who performed the tests.

Your response included the revised SOP 02.02.005-06 “Completion of GMP Documentation,” which states, on page 3; item 4.2.6, “The final reviewer may be the operator, checker or an independent supervisor/manager.” This SOP is inadequate, in that it does not clearly define
that a different second person must review original records. We have additional concerns with this SOP, including details of the “final review” and how you state that it is “not a verification of the information.” Please provide details related to your corrective actions for these specific deficiencies.

8. The quality control unit (QCU) is inadequate in that the QCU failed to ensure that the sterile drug products meet their intended specifications for identity, strength, quality and purity. [21 CFR 211.22]

a. The QCU regularly signs off on incomplete or inadequate deviation reports and investigations, as reported under Items #1 and #6 of this letter.
b. The QCU regularly signs off on testing documents or logbooks with inadequate reviews as reported under Item #7 of this letter.
c. The QCU fails to ensure proper equipment maintenance and proper working conditions as reported under Item #4 of this letter.
d. The QCU failed to review documents regarding equipment maintenance performed by contractors as reported in Observation #7 (d) and (e).

Furthermore, we are concerned that the numerous instances of inadequate investigations and inappropriate documentation practices cited during this inspection were similar to those cited during the previous inspection of your firm in December 2005. We recognize the commitments provided in your response. However, your response failed to address global corrections to prevent continued CGMP deficiencies.

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. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence or the occurrence of other violations. You should take prompt action to correct the violations cited in this letter.

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. Until these violations are corrected, any future shipments of drug products manufactured by your firm are subject to refusal of admission to the United States, pursuant to Section 801(a)(3) of the FD&C 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 FD&C Act [21 U.S.C 351(a)(2)(B)]. Until all corrections have been completed and FDA can confirm your firm's compliance with CGMPs, this office may recommend disapproval of any new applications or supplements listing your firm as a manufacturer.

Within 30 days receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct the violations. Include an explanation of each step being taken to prevent the recurrence of violations, as well as copies of related documentation. If you cannot complete corrective action within 30 days, state the reason for the delay and the time within which you will complete the correction.

Please submit your response to Douglas A. Campbell, Compliance Officer, at the address and telephone numbers shown below. Identify your response with FEI #3004749823.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Branch
Building 51
10903 New Hampshire Avenue
Silver Spring, Maryland 20993
Tel: (301) 796-3201
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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 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,

/s/
Richard L. Friedman
Director
Division of Manufacturing and Product Quality
Office of Compliance

Center for Drug Evaluation and Research