Inspections, Compliance, Enforcement, and Criminal Investigations

Ranbaxy Laboratories, Ltd., Paonta Sahib, India 16-Sep-08

Department of Health and Human Services

Public Health Service
Food and Drug Administration
White Oak, Bldg. 51
Silver Spring, MD 20993

Warning Letter

September 16, 2008

Via FedEx

WL: 320-08-02

Mr. Malvinder Singh, CEO and Managing Director
Ranbaxy Laboratories Limited
Corporate Office
Plot 90; Sector 32,
Gurgaon - 122001 (Haryana), INDIA

Dear Mr. Singh,

This is regarding an inspection of your pharmaceutical manufacturing facility, Batamandi (Unit II), in Paonta Sahib, India by Investigator Jose R. Hernandez and Chemist Susanna E. Ford, during the period of March 3 -7, 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 Dr. T.G. Chandrashekhar, Vice President Global Quality and Analytical Research, 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)]. Section 501(a)(2)(B) of the Act requires that all drugs be manufactured, processed, packed, and held according to current good manufacturing practices.

The March 2008 inspection also found that the Batamandi (Unit II) site is under the same production and quality management as the existing Paonta Sahib site. In addition, the inspection found that the existing Paonta Sahib site was involved in various aspects of testing and production for the Batamandi site. In a letter dated May 12, 2008, FDA informed you that the duplicative drug registration for the Batamandi (Unit II) facility had been withdrawn by the agency, because we consider the Batamandi (Unit II) facility to be a part of the existing Paonta Sahib facility. As such, the violations observed during the March 2008 inspection are indications of continuing CGMP deficiencies in the quality systems at the Paonta Sahib facility, including the failure of production and quality management to prevent such deficiencies. We issued a Warning Letter to the Paonta Sahib facility on June 15, 2006 citing significant deficiencies related to your stability testing program, including: failure to maintain complete records of data related to stability sample testing, and deficiencies related to storage, inventory management, and testing of stability samples at

defined intervals.

Our review included your May 1, 2008 response to the FDA 483 Inspectional Observations. We acknowledge that some corrections have been implemented, including your withdrawal of the **[redacted]** ANDA due to deficiencies noted in equipment cleaning logs and batch production and control records for the exhibit batches of **[redacted]** manufactured in July - August, 2006. However, we are concerned that these instances of discrepancies observed during the March 2008 inspection, are indications of continuing, systemic CGMP deficiencies at the Paonta Sahib facility. These include:

1 . Written records of major equipment cleaning and use are inaccurate and do not provide assurance that persons double-checked the performance of equipment cleaning, because there is no assurance that those persons responsible for determining that work was performed were present at the time of equipment cleaning [21 CFR 211.182].

During the inspection, our investigative team uncovered fourteen (14) instances **(Observation# Ia, b, c, e, f, g, h, k, l, m p, q, t, and u on the FDA 483)** where cleaning records for equipment used in manufacturing operations (V-blender, **[redacted]**, etc) included initials or signatures of employees who reportedly verified cleaning of equipment but were not shown as present by security log records. According to the security log used to record the entry of all personnel entering and exiting the Batamandi (Unit II) facility, the supervisors who initialed or signed the "Checked by Production Executive" or "Cleared by QA Executive" block were not present in the Batamandi facility on the days this equipment was cleaned. For example, two of these records each involved entries for five separate dates where the employee signing for verification (hereafter "Employee 1") was not present according to the security log records **(Observations #1(a) and (b)).**

With regard to entries made by another employee (hereafter "Employee 2"), your May 1, 2008 response states, "An investigation conducted following the issuance of the 483 revealed that the handwritten logs maintained by the security detail at the gate to the Batamandi (Unit II) facility were not intended to and cannot be assumed to provide an accurate accounting of entry in and out of the facility on any given day." You maintain that the security log was not intended to be accurate, yet you acknowledge its accuracy in the same paragraph of the response when you state, "The security log and other records show that [Employee 2] was present at the facility on every other day on which his signature appears on batch documents."

Your response also acknowledges the accuracy of the security log when referring to entries made by Employee 1 and another employee (hereafter "Employee 3"). With regard to multiple entries made by Employee 3, your response states that this individual was not present to verify cleaning operations . With regard to numerous entries made by Employee 1, your response states:"[Employee 1] apparently was not present during the manufacturing of the exhibit batches and related equipment cleaning. [Employee 1] believed that he did not have to be physically present during an activity in order to sign off as having checked the activity on batch records. Instead, he asked [Employee 4] to bring the batch records to him at the Paonta Sahib facility so he could check and sign them."

This statement in your response regarding Employee 1 demonstrates a lack of knowledge by the employee regarding the fundamental purpose of independent verification under CGMP, and the failure of your firm to ensure that employees conducting and recording these checks understood these essential requirements. The requirement for independent verification applies to functions during drug manufacturing that involve human judgment and consequently are susceptible to human error. Verification of equipment cleaning operations and other critical drug manufacturing operations (e.g., weighing of raw materials, formulation, laboratory calculations) is fundamental to assuring that procedures or work are adequately performed to reduce the risk of human error. This basic function in the manufacture of drug products is an essential part of U.S. CGMP regulations and is one important example of the necessary steps your company needs to implement to ensure product quality.

Incomplete or inadequate cleaning of equipment can lead to cross contamination or inadvertent contamination of drug products with residual cleaning agents or solvents. The purpose of 21 CFR 211.182 is to assure that a second person determine that appropriate cleaning and maintenance

was performed on equipment. Simply reviewing the cleaning log afterwards, without being present at the time of cleaning, does not meet this requirement. We also note that for the multiple examples where you admit that Employee 3 was not present at the time of cleaning, you have failed to provide any explanation for this significant deviation from CGMP requirements.

In your response to this Warning Letter, please explain how the supervisor responsible for verifying the cleanliness of equipment handles verification of cleaning, including whether this individual must inspect the equipment. Please also include documentation regarding your investigation into these incidents, and possible similar incidents not observed by FDA, where employees signed or initialed cleaning records as having verified the steps when, in reality, they were not present at the plant to conduct this verification. Please also describe the steps you have taken to prevent recurrence of these and similar events.

2. Batch production and control records prepared for each batch of drug product produced do not include complete information relating to the production and control of each batch, in that the persons performing, directly supervising or checking each significant step in the operation may not have been present on the dates or times these steps or operations were conducted [21 CFR 211.188(b)(11)].

Our investigative team found four instances **(Observation# 1d, j, o, and s on the FDA-483)** of batch production records containing the initials for Employee 1 in the "Checked by" column for manufacturing steps. According to the security log, though, this employee was not in the Batamandi (Unit II) facility on the dates when he reportedly supervised these manufacturing activities. One record involved six separate dates where the employee signing for verification was not present according to the security log records. These instances include manufacturing steps related to charging of components.

In three instances **(Observation# li, n, and r on the FDA 483)**, the batch production records include the initials of Employee 4 and another employee (hereafter "Employee 5") in the "Carried out by" column after a recorded "Start Time" and "Finish Time." However, according to the security log, these employees were not present at the Batamandi (Unit II) facility at the actual times these operations were conducted.

In these last three instances, your response relies on an interview with the employees to determine that the employee was present on the dates and times specified in the batch record. Your response does not include documentation related to these interviews and the investigation. Moreover, in each instance, the security log documents that Employee 4 and Employee 5 were present on the dates in question, but specifically documents the time of their departure before the time the manufacturing operations were conducted, as recorded on the batch record with their initials.

Your response included a copy of the revised SOP# BPR018-01 "Good Documentation Practices and Correction of Wrong Entries," effective as of April 20, 2008. This SOP indicates, under Section 6.10, that persons performing the checking functions must be "at the place where activity is actually performed." However, your response did not include details on what actions will be taken to ensure that employees supervising or checking significant steps in manufacturing operations are actually present during such operations and that batch production records include complete and accurate information related to the production of each batch.

In addition, our review of SOP#BPR018-01 found that the latter provides instructions, under Section 6.9, whereby "If for some reason the authorized document is not immediately available and immediate recording is [sic] must it can be recorded on blank paper and attach this record with QA approval as raw data with original record. In this case transcribe the entry with reason of transcribing."

This procedure appears to allow manufacturing activities to proceed when an accurate reproduction of the appropriate master production and control record has not been authorized and issued and is not available. This practice violates 21 CFR 211.188(a).

The purpose of this requirement is to ensure that the correct master production and control record has been provided and is available for use in the production of a drug product. Your proposed SOP is inadequate, in that it provides for manufacturing without the use of a batch production and control record. Further, the proposed SOP is inadequate because the practice of transcribing data

from blank paper to a batch production and control record is unacceptable.

Please provide proposed corrective actions related to this specific deficiency in SOP BPR018-01 and what corrective actions you will take to ensure that the batch production and control records are an accurate reproduction of the master production and control records, and that these include complete information relating to the production and control of each batch.

3. The firm's procedures for review and approval of drug product production and control records by the quality unit, including those for packaging and labeling, 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 and other drug products that may have been associated with the specific failure or discrepancy whether or not the batch has already been distributed [21 CFR 211.192].

During the March 2008 inspection, as explained previously, our investigative team documented numerous instances where persons or supervisors reportedly verifying equipment cleaning activities or supervising or checking significant manufacturing steps were not present at the Batamandi (Unit II) facility on the dates or times that these activities occurred. Please explain why your firm's Quality Control Unit (QCU) did not detect and document these deficiencies during their batch production and control record review and what actions will be taken to assure these deficiencies do not extend to other batches of the same or other drug products manufactured at the Paonta Sahib facility and to improve the QCU's handling of such issues.

These deficiencies in equipment cleaning and batch production and control records heighten our concerns regarding the conduct, adequacy, and oversight of the Quality System at the Paonta Sahib site, in particular the integrity and reliability of records for equipment cleaning and batch production and control.

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 CGMP 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.

Until FDA has confirmed correction of the deficiencies and compliance with CGMP, this office will continue to recommend disapproval of any new applications listing the Paonta Sahib facility as the manufacturing location for finished pharmaceutical drug products. In addition, shipments of articles manufactured at the Paonta Sahib site are subject to refusal of admission 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)].

While all shipments of articles manufactured at the Paonta Sahib site are subject to refusal of admission, under the circumstances FDA generally would not refuse shipments of Ganciclovir oral capsules. Because you are the sole source supplier of Ganciclovir oral capsules, FDA considers it important to maintain a sufficient supply of this drug product. Please contact the International Compliance Team immediately to discuss arrangements for your firm to continue importing Ganciclovir oral capsules, which would likely include third-party supervision and verification of each batch prior to release.

Please respond to this letter within 30 days of receipt. Please identify your response with FEI #3002807978. Contact Douglas A. Campbell, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, further information, or further proposals regarding this letter.

U.S. Food & Drug Administration
Center for Drug Evaluation and Research
Division of Manufacturing and Product Quality
International Compliance Team
White Oak Building 51, Room 4224
10903 New Hampshire Avenue

Silver Spring, Maryland 20993
Tel: (301) 796-3201
FAX: (301) 301-847-8742

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

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