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Inspections, Compliance, Enforcement, and Criminal Investigations

Ranbaxy Laboratories, Ltd., Dewas, India 16-Sep-08

Department of Health and Human Services

Public Health Service
Food and Drug AdministrationWhite Oak, Bldg. 51
Silver Spring, MD 20993**Warning Letter****Via FedEx**September 16, 2008
WL: 320-08-03

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 in Dewas, India by Investigators Thomas J. Arista and Robert D. Tollefsen during the period of January 28 - February 12, 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 sterile and non-sterile finished products. In addition, violations of statutory requirements, Section 501(a)(2)(B) of the Act, were documented with respect to the manufacturing and control of active pharmaceutical ingredients (APIs).

These CGMP 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 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 in compliance with current good manufacturing practice.

We have reviewed the Established Inspection Report (EIR) and your April 3, 2008 response to the FDA-483 observations. We acknowledge that some corrections appear to have been completed, or will soon be implemented. However, your response fails to adequately address multiple, serious deficiencies. Specific areas of concern include the following: beta-lactam containment program and inadequacies in batch production and control records, failure investigations, quality control program and aseptic operations.

Beta-Lactam Containment Control Program

Interim controls for the containment of beta-lactam antibiotics such as penicillins, cephalosporins, and penems are inadequate. Specifically:

1. Failure to adequately establish separate or defined areas for the manufacture and processing of non-penicillin beta-lactam products to prevent contamination or mix-ups [21 CFR 211.42(c)(5)].

Operations related to the manufacturing, processing, and packaging of penicillins are not adequately separated from non-penicillin products [21 CFR 211.42(d)].

A. During the inspection, our investigators observed inadequate containment practices regarding the handling and movement of personnel, equipment, and materials as follows:

1. QC personnel move about freely collecting samples and engaging in other activities (i.e., documentation) between the manufacturing blocks for betalactam (penicillin, cephalosporin, and penem) and non-beta-lactam products.
2. Batch production and control records for beta-lactam (penicillin and cephalosporin) products were moved from their respective manufacturing blocks through the campus to the administration building for storage.
3. Personnel that dispatch and work in the beta-lactam API warehouses (penicillin and cephalosporin) move about freely on the manufacturing campus.
4. Personnel working in the cephalosporin API **[redacted]** dispensing area were observed with powder on their gowns and coming in direct contact with the outer surface of a bulk material bag that was then placed on transport equipment that can enter non-beta-lactam areas.
5. Operators and transport equipment (i.e., forklift) used to convey beta-lactam and non-beta-lactam materials to their respective manufacturing blocks on the manufacturing campus were observed interacting with and in very close proximity to other personnel that move about freely on the campus.

In your response, you reported that personnel in beta-lactam dispensing areas are required to decontaminate their gowns by wiping with **[redacted]** when powder is observed on their gowns before leaving the dispensing booth with bagged material. However, your response lacked data to ensure that all gown parts can be adequately decontaminated, and the procedures (SOPs) provided in your response (attachment #s 16[i] and [ii]) have no instructions on how the operators ensure adequate decontamination of their gowns. Furthermore, these SOPs do not provide the wiping steps intended to render operator gowns, plastic bags, corrugated cardboard boxes, and other surfaces mentioned in the SOPs, free of beta-lactam contamination. In your response to this Warning Letter, please provide an explanation of this approach, its capacity for robustness, methods and qualification of the wiping techniques on the aforementioned materials to ensure decontamination of beta-lactam residues with the **[redacted]**. Your response also failed to address the decontamination **[redacted]** effectiveness in neutralizing beta-lactams on the items that procedures require to be wiped with **[redacted]**. The effectiveness of this neutralizing **[redacted]** on different materials should be demonstrated through lab studies.

B. Your containment control and monitoring programs are inadequate to prevent cross contamination of non-penicillin pharmaceutical products (APIs and finished dosage forms) with possible residues of penicillin, cephalosporin, or penem compounds, as follows:

1. The containment monitoring program failed to include monitoring (surface sampling/testing) for residual traces of penem (i.e., imipenem) type betalactams in non-penem manufacturing blocks **[redacted]** and **[redacted]**.
2. Surface monitoring (sampling/testing) for residual traces of penicillin type beta-lactams is not performed in the Penem Block where penem sterile parenterals are manufactured or in Block **[redacted]** where multiple cephalosporin finished products are manufactured.
3. Surface monitoring for residual traces of cephalosporin type beta-lactams is not performed in the General Block **[redacted]** where multiple non-beta-lactam finished products are manufactured or in the Penem Block where sterile parenterals are manufactured.
4. There was no written documentation reflecting the decontamination of materials, documents, and sample containers prior to removal from the penicillin or cephalosporin manufacturing blocks through the **[redacted]**
5. There were no written procedures established to address decontamination methods with the **[redacted]**

6. The containment control program does not include contingency (corrective action) procedures when beta-lactam contamination is found exceeding established action levels in the manufacturing blocks.

Your April 3, 2008 response, although lengthy, raised many concerns. For example, your response indicates that you are aware, as reported in your Environmental Control Program (Attachment 16.d [ii]), that beta-lactam compounds such as penicillins (i.e., amoxicillin), cephalosporins (i.e., cefaclor, cefadroxil), and penems (i.e., imipenem) have human sensitizing and cross-reactivity properties that require manufacturing controls to prevent cross contamination of non-penicillin (non-beta-lactams and among beta-lactams) products in your multi-product manufacturing campus. However, your procedures lack any sampling of production areas for traces of penem compounds, and various production locations were not sampled for the penicillins and cephalosporins you process.

Furthermore, your response did not include procedures addressing how to respond to a situation in which beta-lactams are found in the plant. Containment control program procedures should include provisions for detecting and correcting containment deficiencies. Beta-lactam contamination on surfaces alerts a firm that contamination is present in the manufacturing environment due to poor containment practices. This can lead to cross contamination of pharmaceutical products that were exposed in that environment. Your procedures should require adequate investigations to determine the cause of a positive residue finding and the extent of any contamination. In addition, the procedures should define the steps to be taken to determine the extent of the contamination and for identifying products potentially affected if such a breach occurs.

Aside from the above, additional information is needed regarding the validity of the reported negative test result findings from the site assessments for residues of penicillins and cephalosporins performed during July 2006 through March 2008, as follows:

i. Your response lacked data showing that surface testing is capable of reflecting true levels of contamination. The swab surface sampling recovery studies should establish that a valid swab sampling technique is in place for penicillins and cephalosporins on all types of surface substrate material mentioned in your firm's reports. Also, the surface recovery studies should demonstrate recovery of the **[redacted]** different types of cephalosporin compounds processed in Block **[redacted]**. Your response only provided data on 2 of the **[redacted]** products. The sampling procedures should address sampling from qualified surfaces. Validation data should show that surface sampling is capable of reflecting true levels of contamination and include the percentage of recovery for each type of surface sampled. Recovery study results should be provided in your response.

We are concerned that it could be difficult to detect beta-lactam contamination on porous surface materials such as operator gowns, corrugated cardboard boxes, and other types of materials mentioned in these reports. Furthermore, the sites identified by your firm for sampling should be sufficient, representative, and include worst case areas. Justification for the selected sampling sites should be provided in your response.

ii. We are concerned about the units reported in your response letter for sample test results of air, product and surfaces. For example, the air samples were reported in surface area units **[redacted]** and not in the volume of air sampled (see response page 51). Product testing was also reported in surface area units **[redacted]** and not in weight, volume amounts, or dosage type sampled (see response page 50). The surface sampling was reported in **[redacted]** and not **[redacted]** (see response page 52). The larger swab sampling area provides more reliable detection of contamination. It is important to note that the purpose of the swabbing program is to detect low levels of a sensitizing drug in the environment and sampling smaller areas may not ensure detection.

iii. We are concerned with your justification for decontaminating an area a month after the prior site assessment reported no traces of beta-lactam contamination (see response page 52). For example, this assessment reports that the archival room that stored beta-lactam batch production records (located in the Administration block) had no traces of beta-lactam contamination [Attachments 16a (iii) through 16a (vi)] in February 2008. However, your March 2008 reports

states that the archival room was decontaminated and re-assessed for beta-lactam contamination [see Attachments 16a (viii) and (ix)].

iv. Your response (page 50) indicates that testing of non-penicillin products for traces of penicillin or cephalosporin contamination indicated results below the limit of detection (e.g., [redacted] for penicillin). We are concerned with your response since testing for residues of beta-lactams in other beta-lactams usually requires much more sophisticated test methodology than the [redacted] method you are currently employing. (We note that you are using a method similar to FDA's codified method under 21 CFR 211.176). However, as reported in your Environmental Control Program (Attachment 16d (ii)), the codified method is limited to detection of a few penicillins in a limited number of products. Therefore unless you can demonstrate to the contrary, this method is not appropriate. In your response to this Warning Letter, please indicate which products were tested, and specify whether testing included traces of penicillin residues in cephalosporin products or cephalosporin residues in penem products or any other drug products.

v. The Contamination Control and Risk Analysis provided in your response [Attachment 16d (i)] failed to address potential contamination between betalactams to include all the deficiencies mentioned above under item 1 of this letter.

Production Records

2. Batch production and control records do not include complete information relating to the production and control of each batch produced [21 CFR 211.188(b)] in that:

A. Production records failed to document weight or measure of excipients dispensed and used in production of non-sterile finished drug products that are manufactured in the following plants: Semi-synthetic Penicillin Block ([redacted]-Block), General Block ([redacted]-Block), and Cephalosporin Block ([redacted]-Block).

B. Production records also lack second person verification to ensure that the weight or measure of excipients was correct.

C. Media fill batch production records for sterile finished products lacked complete information. For example, records did not document the name or initials of the individual operators who executed the manufacturing instructions, nor the individuals who performed the visual inspection of the media filled vials. These media fill batches were submitted in support of the ANDA.

D. Media fill batch production records for sterile APIs also were incomplete in that they failed to document whether the required [redacted] integrity test was executed. These media fill batches were provided as supportive information to the ANDA.

Your response only addresses procedural improvements and discusses some related training. It failed to include an assessment of all batches shipped to the U.S. market with production records that lacked documentation of weight or measure of excipients dispensed in production of non-sterile finished drug products manufactured in the following plants: Semisynthetic Penicillin Block [redacted] Block), General Block [redacted] Block and Cephalosporin Block [redacted] Block). Our records indicate that batches produced in Blocks are being shipped to the U.S. market for distribution. Please provide an assessment or a affected US batches.

Failure Investigations

3. Your procedures do not provide for a thorough review of unexplained discrepancies or failure of a batch or any of its components to meet its specifications whether or not the batch has been already distributed [21CFR 211.192].

A. Sterility failures of four sterile API batches were inadequately investigated, as follows:

1. The investigation failed to confirm the root cause conclusion that microbes found in [redacted] water samples were the cause of the contamination, in that these isolates were not shown (characterized to their genus and species level) to be related to the batch sterility failure isolate [redacted].

2. The investigation failed to accurately report results. The investigation report dated September 4, 2007 inaccurately states that isolates from each of the 4 batches were further identified to their genus and species level. However the contaminant of one of the API batches that failed sterility

[Batch **[redacted]**] was never characterized to genus and species level.

3. Environmental and personnel monitoring microbial sample results were not addressed by the sterility failure investigation reports. We note that your firm collects numerous samples with results from personnel, equipment, and air, from within the sterile API production area, and identifies these microbes. However, these data were not assessed or reported and the failure investigation reports are missing this testing.

Your response to the FDA 483 observation concerning the root cause conclusion in the investigation commits to implementing procedural changes that will address future sterility failures to ensure full characterization of investigational isolates. However, your response does not address how you intend to complete the failure investigation for the four API batches that failed sterility testing, to ensure the root cause for the failures is identified and appropriate corrective and preventive measures are implemented. Your response to the inaccuracy of your records for sterile API batch **[redacted]** does not address which controls will be implemented to ensure completeness and accuracy in reports. Your response to unreported data in failure investigation reports also does not address FDA's concern on the existence of unreported data associated with the manufacture of other drug products that may be in the U.S. market. Please provide this information in your response.

B. Your rejection of two (2) non-sterile finished product batches for failing to meet release specifications for **[redacted]** was inadequately investigated in that:

1. There were no records identifying assignable cause, nor implementation of corrective measures. For example, the investigation report did not identify any assignable cause or follow-up measures to determine the cause.

2. Review of the batch production records for the rejected batches found that the actual weights or measures of the **[redacted]** excipient was not documented in the batch production records of the two (2) failed batches. This information was not noted by the failure investigation.

Your response failed to address the reason the actual weight or measure of the **[redacted]** excipient was not documented in batch production records and was not addressed by the failure investigation reports. The lack of weight or measurement information in records prevents verification that the correct amounts of excipients were dispensed for the two failed lots. Additionally, your April 3, 2008, response indicates that the Quality Assurance Unit will complete a review of other investigation reports lacking root cause and response action, and supplement these reports if necessary by April 30, 2008. Please provide this information in your response to this letter.

Quality Control Unit

4. The Quality Control Unit (QCU) failed to ensure that its organizational structure, procedures, processes, resources, and activities are adequate to ensure that APIs and drug products, sterile and non-sterile, meet their intended specifications for quality and purity [21 CFR 211.22]. This same issue also applies to APIs produced at this site.

A. The QCU regularly signs off and approves production records although the records are incomplete for weight or measure of excipients used in non-sterile finished drug products as reported under item 2.A. of this letter.

B. The QCU failed to evaluate cleaning and sanitizing of the **[redacted]**. Additionally, the CU did not evaluate microbial and non-viable particle ingress from the **[redacted]** into the aseptic filling areas where finished sterile drugs are processed as reported under item 5.D.2. of this letter.

C. The QCU regularly signs off and approves inadequate failure investigation reports related to sterility failures of sterile APIs and rejections of non-sterile drug products as reported under items 3.A. and 3.B. of this letter.

Furthermore, we are concerned that deviations regarding inadequate recordkeeping and failure investigations cited on the current FDA-483 are similar to the deviations from the previous FDA-483 issued to your site on March 2, 2006. For example, the previous inspection conducted 2/27 - 3/2/06 resulted in the issuance of a 6-item FDA-483, which included inadequate failure

investigations and lack of controls for analytical test records and batch production records. It is evident that your firm has not corrected the documentation and investigative practices at this site.

The FDA-483 observations and your previous responses indicate that the Quality Control Unit (QCU) was not independent and did not properly discharge its quality assurance and quality control responsibilities. We recognize the commitments to improve the quality organization in your response. However, your response failed to address global corrections to prevent reoccurrence.

Aseptic Operations

5. Procedures designed to prevent microbiological contamination of drug products and APIs purported to be sterile are not adequately written and followed to include adequate validation of the aseptic process. [21 CFR 211.113(b)]

A. Process simulations (media fills) for sterile API processes do not simulate actual commercial production procedures in that the 2005 2006 and 2007 media fills failed to include a media fill with the operator held [redacted] product loading lines from the API sterile [redacted] train to the [redacted].

Your response indicates that the revised media fill protocols now include the loading lines. Your response indicates that the new media fills would be completed by May 15, 2008 in the API facility, although we have not received further updates on the conduct and findings of these media fills.

B. Media fills for parenteral (sterile drug products) filling operations were inadequately performed to qualify aseptic processes in that documentation failed to include the specific reasons (assignable cause) filled vials were removed and not [redacted] during the media fill operation. The removal and destruction of filled vials [integral units] can present a bias to the final media fill results.

Your response indicates that the corrected media fill protocols and procedures will account (reconciliation) for all filled units during media fill runs. Your response indicates that the new media fills would be completed by April 30, 2008 in the finished dosage facility. However, you have not provided updates on the latest media fills.

C. Various instances of poor aseptic practices were observed throughout the manual unloading and transferring processes of the [redacted] sterile API during aseptic processing. These include:

1. Production personnel were observed handling a [redacted] hose without sanitizing its outer surfaces. The exterior surface of this [redacted] hose comes in direct contact with the [redacted] sterile API.

2. Operators were observed handling or touching various work surfaces, equipment, small stools, and tables, which were not wiped with sanitizing [redacted].

3. There were no records to document that the [redacted] door or external surfaces of the [redacted] are sanitized as required by procedures.

D. Various instances of poor aseptic practices during aseptic parenteral filling were also observed during the manual installation of the [redacted] transfer tubes, and the [redacted] flowing device as part of the aseptic transfer of the sterile API (in the [redacted]) to the finished dosage aseptic filling line. These include:

1. During the aseptic connection of the [redacted] and electrical connection an operator was observed coming in direct contact with the unsanitized [redacted] surfaces of the [redacted].

2. The aseptic equipment and areas where aseptic connections were performed were positioned below the [redacted] and within close proximity of its [redacted], which were not cleaned and sanitized, exposing this area to possible contamination.

3. There is also a contamination risk during aseptic filling due to the unsanitized equipment (e.g., possible contamination due to ingress from access panel and [redacted])

Your response to 5.D.2 above a ears to provide adequate corrective actions for the cleaning and sanitization of the [redacted]. However, the lifting of the [redacted] above, and in close proximity to the filing line, is unacceptable. This practice promotes ingress of microbial and non-viable contamination. Your response does not address the effect of the [redacted] position on the

unidirectional airflow and maintenance of ISO [redacted] conditions during aseptic manual connections, transfer and filling of sterile product.

E. Utensils and equipment that directly contact sterile API during transfer and [redacted] of the [redacted] are inadequate to ensure that these APIs are maintained sterile and pyrogen-free. For example:

1. Several pits/holes were observed in the weld at the end of the large [redacted]. Additionally, there was a crack observed between the handle and the end of the large [redacted]. These holes and crack create a challenge for sterilization of this [redacted].
2. There were no written standard operating procedures or records documenting that the small [redacted] a.k.a., "Product Uniformity Tool"), that contacts sterile API during the [redacted] process, was depyrogenated prior to use.

Your response failed to include the actual depyrogenation qualification of the Product Uniformity Tool. Provide an assessment for all utensils and equipment to determine possible effects of inadequate design for use with sterile products and a corrective action plan to ensure repair or replacement with proper design and function.

6. The controls to prevent contamination or mix-ups in defined (critical and supporting clean) areas are deficient regarding operations related to aseptic processing of drug products [21 CFR 211.42(c)(10)].

A. For parenteral operations, smoke studies were not conducted to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions during numerous aseptic operations in classified areas of the vial filling facility. For example:

1. Various manual operations performed with the [redacted] such as dispensing sterile API and connecting equipment to this [redacted] were not included in smoke studies.
2. Other significant manual aseptic activities that can affect airflow, including opening and closing the fill equipment access panels during routine aseptic filling operations, were not evaluated in smoke studies.
3. There was no evaluation performed to demonstrate that personnel activities (e.g., manual transfer of material into or out of the ISO [redacted] and ISO [redacted] areas) do not compromise the unidirectional airflow pattern.
4. There was no evaluation performed to demonstrate that the horizontal airflow from the [redacted] does not negatively impact upon the vertical airflow within the aseptic Willing areas.

Your response indicates that you have prepared a comprehensive protocol for performing airflow pattern testing to include all aseptic operations in both the dispensing and filling areas and hope to video record these tests. Your response also indicates that the Quality Review of these smoke studies will be completed and approved prior to initiation of media fill studies, which were targeted to be completed by April 30, 2008. However, your firm has not provided an update on all airflow pattern findings and your evaluation of these study results.

B. For sterile API operations, smoke studies were not representative of actual operations to demonstrate unidirectional airflow and sweeping action over and away from the product under dynamic conditions during numerous aseptic operations in classified areas processing sterile APIs. For example:

1. There are no smoke study evaluations to demonstrate that the personnel activities during the [redacted] of sterile API from the [redacted] do not disturb the unidirectional airflow in front of the to prevent compromising the sterile API.
2. The smoke study performed for the set up of the [redacted] equipment did not actually reflect the manner with which the equipment and manual aseptic connections are made.
3. There are no controls (e.g. physical barrier, curtains) in place to ensure that the [redacted] room's ISO [redacted] unidirectional airflow conditions were not compromised during routine operations performed within the ISO [redacted] area.