Inspections, Compliance, Enforcement, and Criminal Investigations

Ranbaxy Laboratories Limited 15-Jun-06

Department of Health and Human Services

Public Health Service
Food and Drug Administration

Rockville, MD 20857

Warning Letter
WL: 320-06-03

Via FedEx

June 15, 2006

Mr. Ramesh Parekh
Vice President, Manufacturing
Ranbaxy Laboratories Limited
Paonta Sahib, Simour
Himachal Pradesh 173 025 India

Dear Mr. Parekh:

We are writing regarding an inspection of your. pharmaceutical manufacturing facility in Paonta Sahib, India, during the period of February 20-25, 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.

Those deviations observed by the investigators 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)].

Your failure to retain **[redacted]** analytical raw data, undocumented stability sample test intervals, the unclear purpose of "standby samples," our FDA lab results for your Isotretinoin capsules, and the inadequate staffing and resources in the stability laboratory heightens our concerns regarding the conduct, adequacy and oversight of your drug product stability testing and monitoring program.

Our review included your March 20, April 20, and May 25, 2006 responses to the FDA 483 Inspectional Observations issued at Paonta Sahib. We acknowledge your actions to restructure the stability group and institute a Management Review Committee to oversee the stability program. While some of the inspectional observations have been adequately addressed in your responses, we still have concerns regarding the observations shown below.

1. Laboratory records do not include a complete record of all data secured in the course of each test, including all graphs, charts, and spectra from laboratory instrumentation, properly identified to show the specific drug product and lot tested [21 CFR 211.194(a)(4)].

Review of stability data by our investigative team disclosed that prior to November 2004, your firm did not maintain documentation of **[redacted]** operating conditions and settings used for **[redacted]** analysis nor the complete raw data. After November 2004, the operating parameters

were maintained with the relevant **[redacted]**. However, the **[redacted]** electronic raw data was not saved. According to the Director of Quality Assurance, Ranbaxy began saving **[redacted]** electronic raw data just recently at the beginning of February 2006. However, that was not observed during the inspection.

Furthermore, our investigators noted that the SOP entitled, **[redacted]** Analysis and Documentation **[redacted]** effective date "20/11/2004" provides for "discarding" of **[redacted]** data or for the data to be "disregarded." The SOP allows ,"discarding " data due to "variation in the **[redacted]** area, faulty **[redacted]** abnormal **[redacted]** or any other reason." The SOP has not been revised to clearly provide for maintaining complete data derived from all tests.

All of your laboratory practices should be reviewed to ensure these practices are eliminated.

2. Your firm failed to establish and follow an adequate written stability testing program designed to assess the stability characteristics of drug products and to determine appropriate storage conditions and expiration dates in that:

A. There is no assurance that stability sample test intervals for each attribute examined have been met to assure valid estimates of stability [21 CFR 211.166(a)(1)].

FDA investigators observed hundreds of samples in storage chambers **[redacted]** maintained at **[redacted]**. When asked to see the
sample logbooks for these chambers, the investigators were informed that no logbooks were maintained identifying the contents of the stability chambers.

As a result of the observation, a manual inventory of the contents of both **[redacted]** chambers was conducted and this inventory list was provided to the investigative team. The inventory list shows that 172 samples were stored in chamber **[redacted]** and 1,147 samples in chamber **[redacted]**. However the list does not indicate when the samples were initially placed in the **[redacted]** chambers, when these have been removed for interval testing and returned to the chambers, and how long these samples have been stored in the two chambers. Furthermore, no documentation was provided at the time of the inspection or in your responses showing the reasons for collecting and storing these samples.

In your May 25, 2006 response you state that "Ranbaxy maintains at all times a hard copy handwritten master list, the Date-in Register that identifies all the samples placed in each of the stability chambers **[redacted]** as well as both **[redacted]**. This Date-in Register was not observed by the investigators during their inspection of the **[redacted]** storage chambers on February 23, 2006, nor was it mentioned or provided to the investigative team when they initially requested the sample logbook or throughout the inspection. Furthermore, copies of the Date-in Register, submitted as Attachment 9, only show data for stability samples received during the period of January through May 2006. No documentation was provided during the inspection or in your responses for stability samples received prior to January 2006. The register shows the "Received Date", "Date in" and storage"Condition" for these stability samples, but does not document the dates when samples were removed for stability testing at specified intervals and returned to the respective storage chambers.

Your May 25, 2006 response also states, "Quality Assurance maintains a 'working log' of samples, the Sample Location List, in a **[redacted]** program for each stability chamber **[redacted]** as well as for each of the **[redacted]** separately." This list, submitted as Attachment 10, provides information on what samples are present in each of the chambers and includes "PRODUCT NAME", "B. No." "DATE IN" and "TRAY". You maintain that this list is kept in the stability rooms but again, this "Sample Location List" was not observed nor provided to the investigative team when they asked to see a logbook for samples stored in the **[redacted]** chambers **[redacted]**Attachment 10 is a representative copy of the **[redacted]** list of samples stored at **[redacted]** (Stability Chambers **[redacted]**) which were not the subject of the FDA 483 observation. Please submit a complete printout from the **[redacted]** program for the **[redacted]** storage chambers.

In your April 20, 2006 response, you report that only 495 samples of the 1319 samples noted in both **[redacted]** chambers were for "routine" stability testing purposes, and the remaining 824 samples are kept as "stand by" samples For those samples you note as designated for stability testing, you have failed to provide any documentation concerning the storage and testing of these

samples. You also clarify that "stand by" samples are kept at the **[redacted]** conditions for "investigational" purposes only and that these samples are used for detailed investigations of "'*Impurity Profile*' trending/deviations during complete stability program." We disagree with your assertion. The samples cannot be for both "investigational purposes" only and "impurity profile trending/deviations " because impurity testing is part of the drug product stability program.

The 2006 stability register, a handwritten logbook provided to the investigators that indicates which stability samples need to be tested, listed approximately 33 untested samples at the time of the inspection. This list does not account for all the other samples in the **[redacted]** stability chambers.

Since these samples in the **[redacted]** stability chambers could not be accounted for in either the stability register or in a logbook, we are unable to ascertain if you intended to test these samples as part of your stability program and, if so, whether they have in fact been tested at appropriate intervals (i.e., 3, 6, 9, 12, 24, 36 months or more) to support assigned expiration dates for your drug products. Please provide complete documentation showing that these samples were tested at appropriate intervals in accordance with your established stability schedule.

B. Storage conditions for samples retained for stability testing are not adequately documented [21 CFR 211.166(a)(2)].

An extensive backlog of untested samples has resulted because of your practice of removing stability samples from the appropriate accelerated and long term storage conditions and holding them at **[redacted]** until they can be tested. Your procedure entitled, "Post Production Stability Study" **[redacted]** effective date "15/09J2005" states that when accelerated stability samples have passed a scheduled test date by **[redacted]**days, samples shall be stored at **[redacted]** before testing. In addition, when long term stability samples are within minus **[redacted]** weeks to plus **[redacted]** weeks of a scheduled test date, samples shall be stored at **[redacted]** before testing. The procedure further states that the holding time should not exceed **[redacted]** days for accelerated stability samples and **[redacted]** days for long term stability samples. Neither the *Sample Location List nor the Date in Register* submitted with your May 25, 2006 response or any other documentation we have seen thus far provide the dates when stability samples were moved into or removed from **[redacted]** stability chambers for testing and if these samples were moved in accordance with this written procedure.

Please provide additional information on the inventory of the **[redacted]** chamber samples including the drug name, dosage, expiration date, batch number, date the samples were removed from the conditions specified in the protocol, the stability testing intervals, the type of stability sample (long term, accelerated or "investigational"), and copies of reports of analysis.

Also, please clarify how samples intended for impurity profile trending and deviations as part of your "complete stability program" are for "investigational" use only and provide scientific rationale for storage of these samples at this **[redacted]** temperature: An impurity profile is a description of the identified and unidentified impurities in a drug product. Manufacturers are expected to summarize degradation products observed during stability studies of the drug product. This summary should be based on sound scientific appraisal of potential degradation pathways in the drug product and impurities arising from the interaction with excipients and/or the immediate container/closure system after prolonged room temperature storage. This testing is a crucial component of a drug product stability monitoring program. As described by you, the storage of these samples for "investigational use only" fails to include this testing component and summary.

Your May 25, 2006 reports that the "stand by" samples, previously reported as samples intended for impurity profile trending and deviations, are for "regulatory filings globally" and may be stored at **[redacted]** for up to **[redacted]** months. Thus, the purpose of these "stand-by" samples remains unclear. Please clarify if these samples are for "investigational" purposes, "impurity profile" trending, or for "regulatory global filings" and explain the rationale for storage of these samples at **[redacted]**' for up to **[redacted]** months.

Your May 25, 2006 response also reports that Ranbaxy performed an analysis of the stability testing results for all samples, approximately 100 products that had been stored at **[redacted]**. You maintain that the data shows that there is no adverse effect of **[redacted]** storage on the

stability samples or analysis and provided data on 15 representative examples for our review. Please provide data on the remaining 85 reviews comparing drug products stored at **[redacted]** with non-refrigerated samples of the same batches.

Your most recent response also reports that Ranbaxy has ceased storing stability samples at **[redacted]** and has completed stability testing of 239 samples in the **[redacted]** which were primarily exhibit batches to support US ANDA filings. All samples were found to be within the approved/proposed specifications. Please submit complete stability data (accelerated, room temperature, **[redacted]** etc.) for these 239 samples.

3. The Quality Control Unit lacks adequate laboratory resources (personnel and equipment) for conducting stability testing of drug products [21 CFR 211.22(b)].

During the inspection, our investigative team observed that the stability laboratory consists of two rooms with **[redacted]** in one room and the other room used as a wet chemistry lab. The stability laboratory employed 16 people. During 2004, the stability laboratory received over 3000 samples for testing and during 2005 the laboratory received over 6000 samples. An inspection of the two **[redacted]** stability chambers uncovered hundreds of samples waiting to be tested.

Your May 25, 2006 response states that the stability sample testing backlog has now been eliminated following the employment of **[redacted]** additional analysts, the use of analysts from other sites, and the purchase of **[redacted]** new **[redacted]**. Please provide documentation that all stability testing requirements have been met for all drug products covered by U.S. approved, tentatively approved, and pending approval applications.

In addition to the above, FDA analysis of three batches of Isotretinoin 10, 20 and 40 mg. capsules in April 2006 showed assay results of 92.6% (batch **[redacted]**) 92.3% (batch **[redacted]** and 92.7% (batch **[redacted]**)Batch **[redacted]** is labeled with an expiration date of August 2007, whereas batches **[redacted]** and **[redacted]** are labeled with an expiry date of December 2007. According to certificates of analysis, the assay at the time of product release for lot **[redacted]** was 108.0% and for lot **[redacted]** was 100.8%. Therefore, the FDA analyses show much lower potencies in these batches within approximately three and six months of release, and well before their expiration dates. Please provide an explanation regarding this quick degradation.

FDA analysis of samples of the antiretroviral drugs Lamivudine and Zidovudine, manufactured at the Paonta Sahib and Dewas facilities and collected from distribution warehouses in Uganda and Nigeria, has uncovered several abnormalities. Several batches of Lamivudine tablets were marked **[redacted]** and others marked "RX919°. Ranbaxy's application for Lamivudine 150 mg. tablets, ANDA 77-357, tentatively approved by FDA on May 27, 2005 describes the drug product as a "white to off white, capsule shaped biconvex, film coated tablet with 'RX919' debossed on one side and plain on the other side."

Some batches of Zidovudine were marked **[redacted]** and others marked "RX920". Ranbaxy's application for Zidovudine 300 mg. tablets, ANDA 77-327, tentatively approved by FDA on July 13, 2005 and receiving full approval on September 19, 2005, describes the drug product as "white to off-white, round, film-coated tablets with 'RX920' debossed on one side and plain on the other side." The tablet description is confirmed by the long term stability data you submitted with your May 25, 2006 response for Zidovudine 300 mg. tablets, Batch **[redacted]**manufactured in October 2004.

Please provide us with a detailed explanation and documentation regarding the differences found in the markings by our laboratory in these batches of Lamivudine and Zidovudine. Until these matters are resolved as they pertain to the Dewas facility we can not make a final determination on the compliance status of the Dewas facility.

Until FDA has confirmed correction of the deficiencies observed during-the most recent inspection and compliance with CGMPs, this office will recommend withholding approval of any new applications listing your Paonta Sahib facility 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 systematic manner and that documentation supporting corrective actions is submitted to this office.

Please contact Karen K. M. Takahashi, Compliance Officer, at the address and telephone numbers shown below, if you have any questions, further information, or further proposals regarding this letter.

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Sincerely,

/S/

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

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