

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

Memorandum

February 25, 2009

Mr. Malvinder Mohan Singh  
CEO & Managing Director  
Ranbaxy Laboratories Limited  
Corporate Office  
Plot 90; Sector 32  
Gurgaon - 122001 (Haryana)  
India

Dear Mr. Singh:

The Center for Drug Evaluation and Research has determined that Ranbaxy Laboratories Limited (Ranbaxy) submitted untrue statements of material fact in abbreviated and new drug applications filed with the Agency. These findings concern the submission of information, such as from stability test results in support of pending and approved drug applications, from the Ranbaxy Laboratories Limited site located at Paonta Sahib, Sirmour District, Himachal Pradesh, India, (herein referred to as the "Paonta Sahib site"). The following are examples of the observations that support our conclusion that Ranbaxy submitted untrue statements of material fact in drug applications filed with the Agency:

1. Ranbaxy submitted stability information in numerous approved and pending applications that contain untrue statements of material fact, because Ranbaxy failed to include critical information about the storage and testing of the product. During a February 2006 inspection of the Paonta Sahib manufacturing facility, FDA found that hundreds of stability samples, many of which were being used for room temperature or accelerated stability studies, were being stored in refrigerators at approximately <sup>(b)</sup><sub>(4)</sub> between the time they were removed from their stability chamber and the time they were tested. Among other things, FDA investigators found that the sample logbooks did not identify the samples that were being held in the refrigerators, their storage duration in the refrigerators, and the justification for this storage. FDA issued a June 15, 2006 warning letter to Ranbaxy based on its findings during this inspection, including the circumstances of these refrigerated stability samples.
2. Ranbaxy submitted an August 26, 2006 warning letter response that included corrections to the stability data previously submitted to the agency in several abbreviated new drug applications (ANDAs). The corrected stability test reports for Fluconazole Tablets, Ciprofloxacin Tablets, and <sup>(b)</sup><sub>(4)</sub> show instances where stability test dates that previously had been submitted to the applications were false. In some cases stability testing was conducted several months later than the dates reported in the applications. Additionally, the firm reported stability test results for a given batch as occurring at the required accelerated or long term (e.g., 3, 6, 9, 12

month ) time intervals, but actually conducted all of these tests on the same day, or within a period of days.

For Fluconazole Tablets and Ciprofloxacin Tablets, we found that even after Ranbaxy submitted its August 2006 warning letter response with the corrected stability test dates, the firm continued to submit the false stability test dates in annual report submissions to the respective applications.

These submissions of false information about the stability testing of the products were material to FDA's review of the applications.

3. In July 27, 2007 correspondence with the Division of Manufacturing and Product Quality, Ranbaxy's legal counsel, Kate C. Beardsley, provided the results of Ranbaxy's and (b)(4) stability verification project (hereafter referred to as "the verification report"). This report indicates that on February 22, 2006, Ranbaxy found 239 stability samples in the (b)(4) refrigerators which were being used to generate stability data for US drug applications.

The verification report also included an August 22, 2006 listing of 67 stability samples for US filings that were held in the (b)(4) refrigerators. The listing shows that many of the stability samples were from exhibit batches and that, based on Ranbaxy's estimates, the samples were held in the (b)(4) refrigerators between 2 days and 201 days. The report also indicates that the time held in the refrigerator is estimated because documentation was not available which clearly shows the length of time the samples were held in the refrigerators.

This unusual storage condition for stability testing was not defined in the submitted protocol for U.S. drug applications, and prior to the February 2006 inspection, was not reported to FDA. The stability protocols and stability data submitted in Ranbaxy's filings specify the use of controlled room temperature storage of stability samples at (b)(4) and (b)(4) relative humidity (RH) or storage of stability samples for accelerated studies at (b)(4) and (b)(4) RH. Thus, these protocols and stability data submitted by Ranbaxy to the applications, which failed to describe the refrigeration of stability samples, were false. These submissions of false information about the stability of the products were material to FDA's review of the applications.

4. The July 27, 2007 correspondence includes the results of Ranbaxy's verification audit of its stability data associated with the samples held in the (b)(4) refrigerator. The verification report indicates that numerous discrepancies were found in the data, as follows:
  - 129 stability samples (comprising 171 stability test reports) which were on stability were verified from a list of 239 samples for U.S. filings in the (b)(4)

refrigerator. (According to the verification report, the remaining stability samples were for discontinued stability studies.)

- All of the 129 samples were analyzed for all stability stations required by the respective protocol and all results were found to be within specifications.
- Dates of analysis for these 129 samples needed correction in all 171 stability test reports.
- In thirteen instances there was an incorrect estimate of the number of days that the stability samples were held at <sup>(b)</sup><sub>(4)</sub> (Apparently, these instances were found in internal stability reports.)
- There were 122 instances of stability reports having incorrect values for test results (i.e., incorrectly transcribed from raw data).
- The package type was incorrectly reported in one stability report.

The verification report includes copies of updated stability test reports with numerous corrections in the stability data. These submissions of false information about the stability testing of the products were material to FDA's review of the applications.

5. The July 27, 2007 correspondence also includes the results of Ranbaxy's verification audit of the stability data filed with the Agency for approval of <sup>(b)</sup><sub>(4)</sub> pending ANDAs; and audits of the stability data filed in 15 approved ANDAs. The audit results included the following findings:
  - Audit of the stability data in <sup>(b)</sup><sub>(4)</sub> pending ANDAs found 2257 errors in entries for the dates of analysis; and errors in 1385 entries for stability test results, and tests for which corrections were made in specification limits.
  - Audit of the stability data filed in 15 approved ANDAs selected for the audit found a combined total of 1676 errors, which include errors in entries for the dates of analyses, packaging and errors in stability test results.

These submissions of false information about the stability testing of the product were material to FDA's review of these applications.

6. Our review of certain stability reports that were corrected by Ranbaxy based on audits conducted during its verification project, and which were submitted as corrected to the Agency in the July 27, 2007 correspondence from Ms. Beardsley, and in subsequent filings to the affected drug applications, revealed the following:

- The corrected stability test reports show that in numerous instances stability testing actually was conducted several weeks or months later than the dates that originally were reported in the drug applications or annual reports. Additionally, the corrected data shows that in many instances the stability test results reported at different time intervals, (e.g., 3, 6, and 9 months) actually were conducted on the same day or within a few days of each other.
- Simvastatin Tablets are included in Ranbaxy's listing of stability samples for U.S. filings that were held in the (b) (4) refrigerators, and Simvastatin Tablet stability reports that were corrected by Ranbaxy based on its verification audit are included in Ms. Beardsley's July 27, 2007 correspondence with Mr. Campbell.

We observed several differences between the corrected stability reports included in the July 27, 2007 correspondence, and other corrected stability reports for the same batches that were included with Ranbaxy's November 1, 2007 annual report submission to Ohm Laboratories ANDA 76-285, Simvastatin Tablets. Both sets of corrected stability reports show that they were prepared, checked and approved by three individuals of your firm.

For the batches that were identified in the listing of stability samples held in the (b) (4) refrigerators, the corresponding corrected stability reports included with the July 27, 2007 correspondence note that controlled room temperature samples were kept at (b) (4) for varying periods up to 116 days before completion of analysis. In contrast, the corrected stability reports that were submitted to the Office of Generic Drugs with the November 1, 2007 annual report lack any reference to the storage of Simvastatin stability samples at (b) (4). There also are instances where for the same batches, the stability test dates and test results differ between the two submissions of corrected stability reports.

- Corrected stability reports were included in Ranbaxy's June 18, 2007 and September 14, 2007 amendments to pending NDA (b) (4). The June 18, 2007 amendment states that none of the changes made to correct the originally submitted stability data affect previous conclusions about the product's stability; yet the amendment also states that based on the 18 month stability data, Ranbaxy is withdrawing the (b) (4) package configuration. In fact, the corrected data shows that a specified impurity in one batch exceeded the specification limits at the (b) (4) month test interval. This test result would have affected the conclusion about the product's stability at the (b) (4) month test interval had the firm not withdrawn the (b) (4) package configuration.

The September 14, 2007 amendment includes both the uncorrected and corrected stability data, and shows that prior to the verification project the original stability data submitted for approval of the (b) (4) package configuration erroneously

reported a passing result for the same specified impurity at the <sup>(b)</sup><sub>(4)</sub> month stability test interval.

All of the above examples of the submission of false information were material to the review of the applications.

7. During a March 2008 preapproval inspection for pending ANDA <sup>(b)</sup><sub>(4)</sub>, at Batamandi (Unit II) in the Paonta Sahib site, it was found that exhibit batch records previously submitted for FDA approval of the pending ANDA contained the signatures or initials of Ranbaxy employees who were not present in the facility on the dates documented in the batch records. The employees' signatures or initials appeared in blocks documenting the performance and verification of certain manufacturing steps. This observation also is the subject of the FDA Warning Letter issued to your firm on September 16, 2008. The submission of this false information was material to the review of the application. Your firm withdrew its pending ANDAs <sup>(b)</sup><sub>(4)</sub>; and <sup>(b)</sup><sub>(4)</sub>; both of which listed Batamandi as the manufacturing site.

These and other findings indicate a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications (pending and approved) that your firm has filed with the Agency and which contain data developed at the Ranbaxy Laboratories, Paonta Sahib site.

In accordance with FDA policy, the Agency will assess the validity of the data and information in all of Ranbaxy's affected applications which contain data developed at the Paonta Sahib site. This assessment, which is ongoing, is a part of the review of these applications, and thus will take priority over substantive scientific data review until questions of data integrity are resolved. This means that the Agency does not intend ordinarily to conduct or to continue its normal substantive scientific review (including review of data and labeling) of any such pending application or supplement, or of any new application or supplemental applications filed after the date of this letter, that contain data developed at the Paonta Sahib site, during a validity assessment of that application.

In the case of certain applications, however, the Agency may review and act on an application prior to completion of the validity assessment in special circumstances where such an action is clearly in the interest of public health.

The Agency's policies regarding validity assessments and corrective actions that companies may take are described more fully in the Agency's policy entitled "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities, Final Policy" which was published in the Federal Register of Tuesday, September 10, 1991. This Policy states in part:

When FDA finds, based on fraudulent data in an application, that the data in the application are unreliable, the agency intends ordinarily to exercise its authority, under applicable statutes and regulations, to refuse to approve the application (in the case of a pending application) or to proceed to withdraw approval (in the case of an approved application), regardless of whether the applicant attempts to replace the unreliable data with a new submission in the form of an amendment or supplement. Thus, if the applicant wishes to replace the false data with a new submission, the new submission should be in the form of a new application. The new application should identify the parts of the original application that were found to be false. The truthfulness and accuracy of the new application should be certified by the president, chief executive officer, or other official most responsible for the applicant's operations.

Guidance for firms (regarding audits) and the Agency in conducting validity assessments also is contained in a document entitled "Points to Consider for Internal Reviews and Corrective Action Operating Plans" the availability of which was announced in the same issue of the Federal Register.

These documents can be obtained at the following web addresses:

[http://www.fda.gov/ora/compliance\\_ref/frn/fraud\\_ill\\_grat.html](http://www.fda.gov/ora/compliance_ref/frn/fraud_ill_grat.html) and  
[http://www.fda.gov/ora/compliance\\_ref/aip\\_points.html](http://www.fda.gov/ora/compliance_ref/aip_points.html)

If you intend to cooperate with the Agency to attempt to resolve the questions of data integrity and reliability, and/or you wish to discuss the Agency's finding that a validity assessment is warranted, you should arrange a meeting with Mr. Richard L. Friedman, Director, Division of Manufacturing and Product Quality. He can be reached at the following address and telephone number:

Mr. Richard L. Friedman, Director  
Division of Manufacturing and Product Quality  
Office of Compliance  
Center for Drug Evaluation and Research  
U.S. Food and Drug Administration  
10903 New Hampshire Avenue  
Building 51, Room 4224  
Silver Spring, Maryland 20993  
Phone: (301) 796-3267

If you do not intend to address the question of validity with regard to a pending or approved application which contains data developed at the Paonta Sahib site, you may withdraw the application pursuant to 21 CFR 314.150(d). Enclosed is a listing of all Ranbaxy's applications that are currently approved, pending, or for which a not-approvable letter has been issued. Please confirm your agreement with this listing and

inform the Agency of the action you intend to take with regard to each of the applications within ten days of the date of issuance of this letter.

Although the Agency's policy, "Fraud, Untrue Statements of Material Facts, Bribery and Illegal Gratuities, Final Policy" is being applied only to pending and approved applications which contain data developed at the Paonta Sahib site, we note that it is your firm's responsibility to ensure the accuracy and reliability of all submissions to the Agency.

Sincerely,

Janet Woodcock, M.D.,  
Director,  
Center for Drug Evaluation and Research

Enclosure

Cc: Ms. Kate C. Beardsley  
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