Inspections, Compliance, Enforcement, and Criminal Investigations

Fresenius Kabi Oncology Ltd 7/1/13

Department of Health and Human Services

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

Warning Letter

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

WL: 320-13-20

July 1, 2013

Mr. Mats Henriksson
President and CEO
Fresenius Kabi AG
Else-Kröner-Straß 1
61352 Bad Homburg, Deutschland (Germany)

Dear Mr. Henriksson:

During our January 14, 15, 16, 17 & 18, 2013 inspection of your pharmaceutical manufacturing facility, Fresenius Kabi Oncology Ltd located at D-35 Industrial Area, Kalyani, Nadia, 741 235 West Bengal, India, investigator(s) from the U.S. Food and Drug Administration (FDA) identified significant deviations from current good manufacturing practice (CGMP) for the manufacture of active pharmaceutical ingredients (APIs). These deviations cause your APIs 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), in that the methods used in, or the facilities or controls used for, their manufacture, processing, packing, or holding do not conform to, or are not operated or administered in conformity with, CGMP.

We have conducted a detailed review of your firm's response of February 11, 2013, and note that it lacks sufficient corrective actions.
Our investigator(s) observed specific violations during the inspection, including, but not limited to, the following:

1. We observed and documented practices during the inspection that kept some samples, data and results outside of the local systems for assessing quality. This raises serious concerns regarding the integrity and reliability of the data generated at your Kalyani plant. For example,

> a. Our review of the Chromeleon and Empower II software found that your firm was testing samples unofficially, and not reporting all results obtained. Specifically, "test," "trial" and "demo" injections of intermediate and final API samples were performed, prior to performing

the tests that would be reported as the final QC results.

b. Out-of-specification or undesirable results were ignored and not investigated.

c. Samples were retested without a record of the reason for the retest or an investigation. Only passing results were considered valid, and were used to release batches of APIs intended for US distribution.

d. Unacceptable practices in the management of electronic data were also noted. The management of electronic data permitted unauthorized changes, as digital computer folders and files could be easily altered or deleted.

Your inability to detect and prevent poor data integrity practices raises serious concerns about the lack of quality system effectiveness. It is imperative that the data generated and used to make manufacturing and quality decisions at your firm is trustworthy and reliable. Senior management initially informed FDA investigators that they were unaware of information generated at the Kalyani plant that may have an impact on the quality of API. Your senior management, at the local and corporate levels, is responsible for assuring that strict corporate standards, procedures, resources, and communication processes are in place to detect and prevent breaches in data integrity, and that such significant issues are identified, escalated, and addressed in a timely manner. This responsibility starts with designing computerized systems with appropriate security features and data audit trails, as well as many other elements that assure proper governance of your computerized systems. This indicates that your current quality risk management approach, for identifying and controlling any potential risks to the quality of the drugs you manufacture, was not properly functioning.

2. Your firm combined batches of APIs that failed to meet impurity test specifications with other API batches that passed specifications, in order to meet the final impurity test specifications.

During the inspection, management acknowledged that the some of the chromatograms observed were related to the practice of blending an **(b)(4)** API batch that failed to meet specifications with an API batch that passed specifications. The combined batch was retested and distributed using the new acceptable Quality Control results. Management acknowledged that blending API batches that failed specifications with other batches that passed the established specifications had been occurring at this establishment.

Your response stated that the practice of blending of **(b)(4)** batches occurred in an attempt to resolve an impurity issue that began after process modifications were implemented. **(b)(4)** batches that resulted in high levels of an impurity by your laboratory were then mixed with other API batches. Your response also indicates that interviews by management found no evidence that a request to blend batches of **(b)(4)** came from management.

Your response raises additional concerns, as it shows that your organization operates outside of the framework of a robust quality system. When your employees are able to decide that a failing API can be blended with a passing API batch to obtain a final passing result, this indicates that there is poor quality governance.

Provide a complete investigation report where you have evaluated the extent of the problem, and all potential batches that may be implicated. Determine when this practice may have started. Your assessment should not be solely limited to the **(b)(4)** API, but should be extended to all API batches produced and released for distribution during the last 5 years and/or that may remain within expiration. Your investigation into this practice must also be extended to all batches submitted or referenced in a drug application and DMF. Include the drug name, batch number, date of the initial/original OOS, retest result and date and expiration or retest date assigned. Also include any actions you plan to initiate against batches that were distributed into the market, and that had failed at any point to meet the established specifications. In addition, explain how your

firm will improve manufacturing supervision and quality assurance oversight to ensure that consistently sound decisions on drug quality are made by your firm.

3. Your laboratory control records do not include data derived from all of the tests necessary to establish compliance with standards.

For example, the inspection found multiple raw data chromatograms in digital files labeled "test" and "demo," that were injected prior to the sample injections that were used to conclude that batches were in conformance with the specification. They were:

a. A "demo" chromatogram injected 3/6/12 and the official organic impurities injection on 4/6/12 for **(b)(4)** batch **(b)(4)**.

b. A "demo" chromatogram injected 3/6/12 and the official organic impurities injection on 4/6/12 for **(b)(4)** batch **(b)(4)**.

c. A "test" chromatogram injected 12/9/08 and the official related substances injection on 12/10/08 for **(b)(4)** batch **(b)(4)**.

d. Two "test" chromatograms injected 12/4/08 and the official related substances injections on 12/5/08 for **(b)(4)** batch **(b)(4)**.

e. Five "trial" chromatograms injected 7/5/11 between the official related substances injections which occurred both before and after the "trial" injections for batch **(b)(4)** of **(b)(4)**. The final injections were made on 12/6/11 for this batch.

Your response indicated that for the data identified above, the product impact assessment was unclear. Please provide your assessment of the electronic audit trail information that describes the circumstances surrounding the collection of this data.

Your response also indicates that you have an ongoing investigation with a goal to identify additional data, similar to that above, which is located in your electronic records. As stated in item 1 of this letter, we expect your firm to extend your data integrity investigation to all relevant lots and data. The investigation should identify any data found in your electronic record repositories (or other locations) that is not also described in your product release files and/or batch records. Also, it should include a review of all chronological records that clarify which equipment was used for the testing of the API batches. Finally, it should include a review of the audit trail from the software that describes surrounding events for each piece of extra data identified that represents a finished API batch. In your response to this letter, provide a timeline for completion of this investigation, and a summary of your audit findings.

4. Your laboratory's written procedure failed to establish proper retesting practices for out-of-specification results.

For example,

a. **(b)(4)** USP **(b)(4)** batch **(b)(4)**-month stability interval assay test, was initially performed 03/10/12 and a handwritten note on the system suitability chromatogram printout read, "not considered." Justification for the decision to retest was not available.

b. Your firm invalidated **(b)(4)** batch #**(b)(4)** related substance test results of 02/02/12 that were performed in duplicate. On the same day a retest was run. The FDA investigator was informed that the analyst appeared to have encountered an unknown peak at the **(b)(4)** minutes retention time. Justification for the decision to retest was not available.

Your response indicates that that a combination of your inadequate SOPs, ineffective training and corporate audits failed to identify these deviations. Please provide your assessment of the adequacy of your laboratory operation, and any new standards, controls, and improved oversight that you plan to implement.

You are responsible not only for having controls to prevent omissions in data, but also for recording any changes made to existing data, which should include the date of change, identity of person who made the change, an explanation or reason for the change, and formal documentation as a deviation. Any such changes should also include supervisory evaluation to determine if the change is appropriate, and their concurrence. QA should also have oversight over your deviations and be fully aware of such events when making their batch disposition decision. All changes to existing data should be made only when appropriate, and in accordance with an established procedure. It is your responsibility to ensure that data generated during operations is accurate and that the results reported are a true representation of the quality of your APIs.

In addition, your response should address all laboratory equipment, process-related equipment, and any related software that may be affected by the lack of adequate controls to prevent data manipulation.

During the inspection your firm also repeatedly delayed, denied, limited or refused to provide information to the FDA investigators. Please be reminded that the Food and Drug Administration Safety and Innovation Act (FDASIA) § 707, also deems a product to be adulterated if drugs have been manufactured, processed, packed or held in an establishment by an owner or operator who has delayed, denied, or limited an inspection. Examples of instances where the inspection was either delayed or information denied are as follows:

· Personnel from your firm provided the FDA investigator misleading information related to the practices of "demo" and "trial" testing found during the inspection. Specifically, your employee denied several times that he had performed sample trial injections and performed injections other than those reported in the quality control release testing records. In addition, QC personnel refused to provide requested information regarding observed sample testing practices.

Later your firm admitted that the injections were related to a practice of blending a non-compliant API batch with an API batch that had met the impurities specifications.

· The FDA was informed during the inspection that all electronic raw data files are automatically stored on a central server that is inaccessible by QC staff, and that no data would be found on personal computers (PCs) associated with laboratory equipment. Later in the inspection, FDA found that raw data was being stored in several folders on PCs.

· During the inspection, foreign material was observed inside the **(b)(4)** #**(b)(4)**-103. A request to open the **(b)(4)** was made by the Investigator, which was delayed until a knowledgeable person became available. Upon returning to the area, the **(b)(4)** had been cleaned. The FDA was informed that no material was present and that what appeared to be foreign material was a reflection of the light. However, the next day a deviation report was prepared documenting the presence of the foreign material and the written instruction to clean the equipment.

· An employee was observed attempting to hide manufacturing related records in his pocket from the FDA Investigator.

You have also recently informed us that High Pressure Liquid Chromatography units and PCs were removed from the facility for the duration of the inspection to conceal data manipulations. This action, which apparently also occurred in association with past inspections, is very worrisome to us and should be explained in your response to this letter.

Please provide a list of all manufacturing and laboratory equipment in your facility used to produce and test products intended for the US market.

You failed to establish an effective corporate and local system for managing quality which would include the appropriate organizational structure, procedures, processes and resources, as well as activities to ensure confidence that all APIs produced by your facility will meet the intended specifications for quality and purity.

We highly recommend that you hire an independent third party auditor, with experience in detecting data integrity problems, to assist you with the evaluation of your overall compliance with CGMP and assessing if data submitted to applications was impacted. If a third party is to be hired, please provide the FDA with a copy of their assessment. Also provide a copy of your assessment and investigation into the deficiencies presented in this letter describing the specific findings.

Please provide your corrective action plan that describes your commitment, procedures, actions, and controls to ensure data integrity. This plan should include the corrective actions implemented to ensure that all managers, supervisors, quality unit personnel and other staff are properly trained in detecting data integrity and manipulation. The investigation should provide detailed descriptions of other incidents where your quality unit failed to ensure proper testing of materials and include a retrospective review of all test results generated by your laboratory personnel. If other instances of non-existent, omitted, inaccurate, or unreliable test results are found, your investigation should assess the impact of these discrepancies on the quality of the APIs manufactured at your facility. Provide the documentation of specific training offered to all employees, including management, regarding the importance of following CGMP and ensuring that all required tests are performed, and data recorded completely and accurately.

The violations cited in this letter are not intended to be an all-inclusive list of violations that exist at your facility. You are responsible for investigating and determining the causes of the violations identified above and for preventing their recurrence and the occurrence of other violations.

If, as a result of receiving this warning letter or for other reasons, you are considering a decision that could reduce the number of finished drug products or active pharmaceutical ingredients produced by your manufacturing facility, FDA requests that you contact CDER's Drug Shortages Program immediately, as you begin your internal discussions, at drugshortages@fda.hhs.gov so that we can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Program also allows you to meet any obligations you may have to report discontinuances in the manufacture of your drug under 21 U.S.C. 356C(a)(1), and allows FDA to consider, as soon as possible, what actions, if any, may be needed to avoid shortages and protect the health of patients who depend on your products.

The items listed above, as well as other deficiencies our investigator found, lead us to question the effectiveness of your current quality system to achieve overall compliance with CGMP at your facility. It is apparent that you have not implemented a robust quality system at your firm. Be advised that corporate management is responsible for ensuring the quality, safety, and integrity of drugs manufactured by Fresenius Kabi Oncology Ltd. FDA strongly recommends that your corporate management immediately undertake a comprehensive evaluation of global manufacturing operations to ensure compliance with CGMP regulations.

Until all corrections have been completed and FDA has confirmed corrections of the violations and your firm’s compliance with CGMP, FDA may withhold approval of any new applications or supplements listing Fresenius Kabi, Kalyani as an API manufacturer. In addition, your failure to correct these violations may result in FDA refusing admission of articles manufactured at Fresenius Kabi Oncology Ltd at D-35 Industrial Area, Kalyani, District Nadia 741 235, West Bengal, India into the United States under Section 801(a)(3) of the Act, 21 U.S.C. 381(a)(3). The articles may 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 CGMP within

the meaning of Section 501(a)(2)(B) of the Act, 21 U.S.C. 351(a)(2)(B).

Within fifteen working days of receipt of this letter, please notify this office in writing of the specific steps that you have taken to correct and prevent the recurrence of deviations, and provide copies of supporting documentation. If you cannot complete corrective actions within fifteen working days, state the reason for the delay and the date by which you will have completed the corrections. Additionally, your response indicated that you had suspended manufacture of all APIs manufactured at this facility. Please provide an updated schedule for the timing of the reintroduction of manufacture of your APIs. Please identify your response with FEI # 3003519498.

Please send your reply to: Regina T. Brown, Senior Policy Advisor, Office of Compliance, U.S. Food and Drug Administration, WO Building 51 Room 5212, 10903 New Hampshire Ave, Silver Spring, MD 20993.

Sincerely,
\Michael D. Smedley\
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