Fresenius Kabi Oncology Limited (Baddi) 12/18/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS
Return Receipt Requested

Warning Letter 320-18-19

December 18, 2017

Mats Henriksson
Chief Executive Officer
Fresenius Kabi AG
Else-Kröner-Straß 1
61352 Bad Homburg
Germany

Dear Mr. Henriksson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Fresenius Kabi Oncology Limited Baddi at Kishanpura Village, Baddi, Gurumajra, Himachal Pradesh, India, from April 6 to 14, 2017.

This warning letter summarizes significant violations of current good manufacturing practice (CGMP) regulations for finished pharmaceuticals. See 21 CFR, parts 210 and 211.

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your drug products are adulterated within the meaning of section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 351(a)(2)(B).

We reviewed your May 10, 2017, response in detail and acknowledge receipt of your subsequent correspondence.

During our inspection, our investigators observed specific violations including, but not limited to, the following.

Your firm failed to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed (21 CFR 211.192).

You failed to adequately investigate the sterility failure of **(b)(4)** injection (lot **(b)(4)**). This test, performed in January 2017 as part of routine stability testing, reported *Bacillus subtilis*, *Pseudomonas putida*, and *Pseudomonas entomophila* growth. Microbiological growth was observed in both the **(b)(4)** and **(b)(4)** media canisters.

According to your investigation, the most probable root cause was laboratory error. Specifically, your May 10, 2017, response states that an analyst failed to immerse sterility test sample vials and other materials in sporicidal solution before transferring them from the Grade C to the Grade B sterility testing room. Instead, the analyst performed a spray disinfection. You indicated that spraying with a sporicide will disinfect the top and sides of samples, but that the bottom of units might not be fully decontaminated.

However, during the transfer step, the exterior of the units were spray-disinfected with the validated sporicidal disinfectant solution and held for a specified contact time. The units were also placed on a **(b)(4)**, which is intended to facilitate exposure of the bottom of units to the sporicide. Further, following this transfer to the sterility testing room, the vials were exposed to an aggressive sporicidal agent two more times. These additional sporicidal disinfections were performed as part of the **(b)(4)** staging and transfer steps, and occured before the vials were used in the sterility test. The disinfections included exposure to a **(b)(4)** cycle in the sterility testing room for **(b)(4)**, followed by a another spray disinfection with **(b)(4)**. One or more extensive sporicidal disinfections, such as these, normally ensure suitability of samples for use in the sterility test.

In addition:

- The sterility test was performed using a **(b)(4)** filtration system. This **(b)(4)** testing system was used inside an ISO-5 closed restricted access barrier system (cRABS). Both provisions significantly minimize the potential for introduction of adventious contamination during a sterility test.
- No microbiological contamination was observed in the negative controls.
- No aseptic breaches were observed during the sterility test.
- Environmental monitoring data did not indicate that the sterility testing cRABS had a loss of control.
- Other materials used in performing the sterility test were also subjected to additional sporicidal disinfections.

Your investigation was deficient in that it did not sufficiently address these factors and thoroughly investigate potential manufacturing root causes. Your manufacturing investigation substantively assessed environmental data for only the week before and the week after the product's December 2015 manufacture date. It did not sufficiently address whether adverse trends or related incidents had occurred in the manufacturing area over a longer period and did not address the atypical findings of

gram negative bacteria (e.g., *Pseudomonas,* spp.) earlier in the year in the production cRABS. Your review of environmental data was insufficient as it only addressed near term data trends and relied too heavily on cumulative contamination rates in assessing the potential routes of contamination in your manufacturing operation.

In response to this letter, provide:

- Your plans and procedures to ensure that future sterility failure investigations include
  - a more thorough review of long term trends,
  - sufficient investigation of potential vulnerabilities in the manufacturing operation
  - potential correlations with past incidents (e.g., your extensive history of attributing sterility positives to poor material disinfection; gram negatives detected in the ISO 5 or other clean areas)
- An assessment of your overall system for investigations of deviations, atypical events, complaints, out-of-specification results, and failures. Your corrective action and preventive action (CAPA) plan should include, but not be limited to, improved rigor in reviewing the sources of variation in your operation that may cause deviations, failures, or defects.
- A detailed explanation of how **(b)(4)** sterility samples and other sterility testing materials are immersed in a sporicidal disinfectant, whether these materials are completely immersed, and a CAPA if the latter is done.
- A review of your aseptic processing operation. Provide a formal assessment of microbiological contamination risks in your current process, equipment, and facility, and a CAPA plan to address identified hazards.

Repeat Observations

In an inspection from May 14 to 22, 2015, FDA cited a similar CGMP observation in which you invalidated sterility test failures without adequately investigating the root causes, and failed to take timely and appropriate corrective actions. Although you proposed remediations in your responses following the 2015 inspection, and discussed these plans during a 2016 regulatory meeting with the Agency, our current inspection found that your facility's oversight and control over the manufacture of drugs remains deficient.

Inadequate investigations into out-of-specification results is a recurring issue in your company's network. Warning Letter 320-18-12 was issued to you on December 4, 2017.

Your executive management remains responsible for fully resolving all deficiencies, and ensuring ongoing CGMP compliance. You should immediately and comprehensively assess your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements.

CGMP Consultant Recommended

Based upon the nature of the violations we identified at your firm, we strongly recommend engaging a consultant qualified as set forth in 21 CFR 211.34 to assist your firm in meeting CGMP requirements.

In particular, the consultant should comprehensively assess risks in your manufacturing operation, retrospectively review all sterility failure investigations since 2014, retrosepctively evaluate chemistry out-of-specification investigations to determine their adequacy, and assist with improvements to your investigation systems. Your use of a consultant does not relieve your firm's obligation to comply with CGMP. Your firm's executive management remains responsible for fully resolving all deficiencies and ensuring ongoing CGMP compliance.

Conclusion

Violations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these violations, for determining the causes, for preventing their recurrence, and for preventing other violations in all your facilities.

If you are considering an action that is likely to lead to a disruption in the supply of drugs produced at your facility, FDA requests that you contact CDER's Drug Shortages Staff immediately, at drugshortages@fda.hhs.gov, so that FDA can work with you on the most effective way to bring your operations into compliance with the law. Contacting the Drug Shortages Staff also allows you to meet any obligations you may have to report discontinuances or interruptions in your drug manufacture under 21 U.S.C. 356C(b) 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.

Until you correct all violations completely and we confirm your compliance with CGMP, FDA may withhold approval of any new applications or supplements listing your firm as a drug manufacturer.

Failure to correct these violations may also result in FDA refusing admission of articles manufactured at Fresenius Kabi Oncology Limited Baddi, Kishanpura Village, Baddi, Gurumajra, Himachal Pradesh, India, into the United States under section 801(a)(3) of the FD&C Act, 21 U.S.C. 381(a)(3). Under the same authority, articles may be subject to refusal of admission, 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 FD&C Act, 21 U.S.C. 351(a)(2)(B).

After you receive this letter, respond to this office in writing within 15 working days. Specify what you have done since our inspection to correct your violations and to prevent their recurrence. If you cannot complete corrective actions within 15 working days, state your reasons for delay and your schedule for completion.

Send your electronic reply to CDER-OC-OMQ-Communications@fda.hhs.gov or mail your reply to:

Brooke K. Higgins
Compliance Officer
U.S. Food and Drug Administration
White Oak Building 51, Room 4359
10903 New Hampshire Avenue
Silver Spring, MD 20993

USA

Please identify your response with FEI 3006210232.

Sincerely,
/S/
Francis Godwin
Acting Director
Office of Manufacturing Quality
Office of Compliance
Center for Drug Evaluation and Research