Fresenius Kabi Oncology Ltd 12/4/17

10903 New Hampshire Avenue
Silver Spring, MD 20993

Via UPS **Warning Letter 320-18-12**

December 4, 2017

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

Dear Mr. Henrikkson:

The U.S. Food and Drug Administration (FDA) inspected your drug manufacturing facility, Fresenius Kabi Oncology Ltd at D-35, Industrial Area, Kalyani, Nadia, West Bengal, from May 15 to May 24, 2017.

This warning letter summarizes significant deviations from current good manufacturing practice (CGMP) for active pharmaceutical ingredients (API).

Because your methods, facilities, or controls for manufacturing, processing, packing, or holding do not conform to CGMP, your API 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 June 15, 2017 response in detail and acknowledge receipt of your subsequent correspondence.

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

1. Failure to adequately investigate and document out-of-specification results according to a procedure.

Our review of your out-of-specification (OOS) investigations found that you did not use adequate OOS procedures, and lacked scientific justification to invalidate initial OOS results. For example:

a. Investigation report OOS/2015/098 was initiated for an initial OOS result in your related substances test, where **(b)(4)**% and **(b)(4)**% (specification: not more than **(b)(4)**%) was obtained for Impurity **(b)(4)** in **(b)(4)** API batches **(b)(4)** and **(b)(4)**, respectively. Your investigation concluded that over-sonication might have increased the temperature of the water bath and caused degradation of the sample solution.

However, your investigation lacked evidence to support this possible root cause. Instead, your investigation found that the analyst only briefly sonicated the solution (for about **(b)(4)**) at **(b)(4)** temperature. In addition, degradation studies conducted as part of high

performance liquid chromatography (HPLC) validation showed that heat degradation was minimal even after **(b)(4)** at extremely high ((**(b)(4)**^{o} C) temperatures.

Although your investigation was inconclusive, you did not proceed to Phase 2 and investigate potential causes of the OOS result relating to deficient manufacturing and product quality.

b. Investigation report OOS 50989 was initiated following initial OOS results for "related substances–unspecified impurities" for **(b)(4)** API stability batches **(b)(4)** and **(b)(4)**. You concluded that the most probable cause of the OOS result was contamination, although the source of the contamination was not identified or confirmed through your hypothesis study. You invalidated the OOS results (as well as an additional failing retest from a fresh sample preparation by a second analyst for batch **(b)(4)**) and reported the average of six retests. You failed to expand the investigation to review potential causes of the OOS result relating to deficient manufacturing and product quality.

c. Your OOS investigation procedure 036/—/QS/QA permits an analyst to abort a chromatographic run if an apparent OOS is observed prior to completing analysis of all samples scheduled to be injected in the sequence. Your quality control (QC) manager confirmed that analysts abort HPLC analyses if they "expect to invalidate" them later for an assignable cause. For example, you aborted the HPLC sequence of **(b)(4)** API batch **(b)(4)** while observing the chromatographic run on the screen ("online monitoring") in which an individual unknown impurity tested at **(b)(4)**% (specification: NMT **(b)(4)**%). There was no machine malfunction (e.g., unstable system) that would justify aborting the automated analysis.

Our investigators documented approximately 248 instances of aborted sequences.

Your SOP was inadequate. When performing a sample preparation, it may be possible to identify an obvious manual error at the time of the mistake. In such a limited instance, it can be appropriate to discontinue the sample preparation, immediately document the deviation, and justify a new sample preparation. However, it is not appropriate to stop an in-progress automated analysis because of an assumption that an earlier error may be causing an OOS result. Obtaining an unexpected result does not constitute an "assignable cause" and the assumption of such a cause is not a valid basis for interrupting an analysis. The automated analytical sequence should be allowed to proceed to completion, irrespective of the appearance of undesirable analytical results on the computer screen.

We acknowledge your commitment to correct this deficient SOP. Your response was inadequate because your corrections did not ensure that lab investigations will be started immediately after obtaining an OOS result. You acknowledged that in about nine of the examples referenced by the investigator, the original samples were not re-injected due to sample solution stability. Notably, your method validation data show that some of these sample solutions are stable for up to **(b)(4)** at room temperature. Prompt re-testing of the actual stock, working, and HPLC vial solutions is essential to determine if mechanical error or preparation error may have occurred. Timely investigations of potential original laboratory sample preparations are essential to provide clear evidence and credibility for laboratory error hypotheses.

Your response was also inadequate because your OOS procedure failed to ensure that you proceed to Phase 2 whenever you lack conclusive evidence of laboratory error. A possible laboratory error is insufficient to close an investigation at Phase 1. In addition, your procedure indicated that you can close an investigation when a second analyst confirms the initial OOS without moving to a Phase 2 investigation. It remains unclear whether all failing results would be investigated for their manufacturing root causes prior to closing an investigation. Further, even if an OOS result is not confirmed by a second analyst, it should not be assumed that the initial OOS test result was attributable to analytical error. Whenever an investigation lacks conclusive evidence of laboratory error, a thorough investigation of potential manufacturing causes must be performed.

In response to this letter,

- Provide a retrospective review of all invalidated OOS (in-process and finished testing) results obtained for products on the U.S. market. Assess whether the scientific justification and evidence was conclusive. For investigations that conclusively established laboratory root cause, determine adequacy of the corrective action and preventive action (CAPA), and ensure that other laboratory methods vulnerable to the same root cause are identified for remediation. For any OOS with an inconclusive or no root cause identified in the laboratory, include a thorough review of production (e.g., batch manufacturing records, adequacy of manufacturing steps, raw materials, process capability, deviation history, batch failure history). Provide a CAPA plan that identifies the potential manufacturing root causes for each such investigation, and includes process improvements where appropriate.
- Provide an assessment of your overall system for investigating OOS results. Provide a CAPA to improve quality of OOS investigations in all Fresenius Kabi facilities. Elements of your CAPA should include, but not be limited to, enhanced quality assurance participation in individual laboratory investigations, identified adverse laboratory control trends, and proper initiation of the Phase 2 manufacturing quality investigation stage. It should also include improved laboratory supervision of analysts.

- Evaluate all instances in which a chromatographic run was interrupted or aborted. Determine the potential effect on the quality of API released for distribution. Provide your assessment once completed, and a fully remediated SOP.
- Provide your updated laboratory investigation procedure. Describe how your revised procedure ensures that all OOS investigations expand to a review of manufacturing history and potential root causes whenever a cause is not conclusively found in the laboratory. Also describe how investigation of laboratory deviations will be improved.

For more information about handling failing, out-of-specification, out-of-trend, or other unexpected results and documentation of your investigations, see FDA's guidance document, Investigating Out-of-Specification (OOS) Test Results for Pharmaceutical Production, at **https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070287.pdf)**.

2. Failure to ensure that all test procedures are scientifically sound and appropriate to ensure that your raw materials, intermediate and API conform to established standards of quality and purity.

The inspection documented that your test methods were not robust. For example:

a. Investigation report OOS/2015/037, related to an OOS assay result for **(b)(4)** intermediate API, concluded that the standard preparation degraded because the HPLC autosampler temperature was held at **(b)(4)**° C. According to your response, the test method was revised to incorporate the **(b)(4)** of the autosampler at **(b)(4)**° C, because your method previously lacked the needed specificity. Your CAPA did not extend to specificity of your laboratory's other test methods to ensure their parameters were sufficient.

b. Investigation report OOS/2015/124, related to an OOS assay in stability batches of **(b)(4)** API, concluded that the vials of a specific brand were interacting with the sample and the analysis, although these vials had been used in your laboratory for at least six months prior to the OOS results. Your assay method for **(b)(4)** API had not specified the use of a particular brand of vial. Your firm changed the method to exclude use of Waters vials in response to the OOS. We also note that an OOS for another product (RSD for **(b)(4)**) had similarly been attributed to a specific brand of vials.

Your firm's CAPA was insufficient. It did not require that your other analytical methods be assessed to determine if their robustness is also adversely affected by a specific vial (e.g., Waters).

Your response was inadequate because it only addressed the specific examples cited in the inspection but did not include the review of other methods and laboratory equipment that also may have been affected by the same deficiency. In addition, you did not sufficiently address improvements in your quality system to ensure that flaws in written laboratory procedures will be corrected.

In response to this letter, provide an assessment of the historical performance of your firm's test methods. Assess adequacy of instructions for each method, suitability of laboratory equipment, and competency of analysts. Determine errors that have occurred on multiple occasions over the history of the method, and identify further CAPA measures needed to enhance robustness.

Repeat Deviations at Facility
In a previous warning letter (WL 320-13-20), FDA cited similar CGMP deviations. You proposed specific remediation for these deviations in your response.

These repeated failures demonstrate that your facility's oversight and control over the manufacture of drugs is inadequate.

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.

It is essential that you initiate an immediate and comprehensive assessment of your company's global manufacturing operations to ensure that systems and processes, and ultimately, the products manufactured, conform to FDA requirements at all your sites.

In particular, the consultant should comprehensively assess your laboratory and manufacturing systems, retrospectively review all OOS investigations, and assist with remediating overall quality oversight at your firm. 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
Deviations cited in this letter are not intended as an all-inclusive list. You are responsible for investigating these deviations, for determining the causes, for preventing their recurrence, and for preventing other deviations.

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 deviations 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 deviations may also result in FDA refusing admission of articles manufactured at Fresenius Kabi Oncology Ltd at D-35, Industrial Area, Kalyani, Nadia, West Bengal 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 deviations 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 (mailto:CDER-OC-OMQ-Communications@fda.hhs.gov)** or mail your reply to:

Rebecca Parrilla
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 3003519498.

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

cc
Mr. Arvind K. Sharma
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More in 2017 (/ICECI/EnforcementActions/WarningLetters/2017/default.htm)