DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
12420 Parklawn Drive, Room 2032 Rockville, MD 20857	10/3/2023-10/10/2023*
	FEI NUMBER 3006210232

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED	
Arvind Kumar Sharma, Managing Director	
FIRM NAME Fresenius Kabi Oncology Limited	STREET ADDRESS Village Kishanpura, Baddi, Tehsil Nalagarh
CITY, STATE, ZIP CODE, COUNTRY Solan, Himachal Pradesh, 174101 India	TYPE ESTABLISHMENT INSPECTED Drug Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established and followed.

1. Procedure SOP/CSP/0015 "Behavior and Aseptic Practices for Persons Working in Aseptic Area" was not followed, because operators did not "Keep the entire body out of the path of unidirectional airflow to minimize disruption" while performing interventions in the (b) (4) RABS during aseptic filling operations. For example:

   a. An operator was observed repeatedly leaning over the sterile product (b) (4) and (b) (4) during an (b) (4) intervention that occurred from (b) (4) on August 29, 2023, until (b) (4) on August 30, 2023, to change the (b) (4) tank during aseptic filling of (b) (4) Injection batch (b) (4)

   b. Operators were observed reaching over open vials and the (b) (4) with the non-sterile RABS (b) (4) in the (b) (4) RAB used to aseptically fill product during (b) (4) Injection batch (b) (4) (distributed to the US market), (b) (4) Injection batch (b) (4) and (b) (4) Injection batch (b) (4)

   c. Operators were observed reaching over open vials with the non-sterile RABS (b) (4) to

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perform interventions at the (b) (4) vial (b) (4) to push jammed vials, pick-up fallen vials, or change environmental monitoring plates during the aseptic filling of (b) (4) Injection batch (b) (4) (distributed to the US market) and (b) (4) Injection batch (b) (4)

2. Procedure SOP-CSP-0202 "Procedure for SKU Change Over in Filling Area" allows (b) (4) (b) (4) batch to be aseptically filled into (b) (4) vial (b) (4) During the SKU changeover, the (b) (4) RABS (b) (4) for extended periods of time to allow manual changing of filling machine (b) (4) by the operators. Exposed sterile contact surfaces like (b) (4) stopper bowls, the stopper track, and sterile stoppers may be left in place during these manual interventions (b) (4) the (b) (4) ABS.

3. Addition of stoppers during (b) (4) Injection batch (b) (4) (distributed to the US market) did not ensure a "smooth flow" of the stoppers as required by procedure SOP/CSP/0129 "Procedure for Performing the Interventions During Normal Production". The operator was observed to shake the stopper container and catch stoppers in the RABS (b) (4) before dropping them in the stopper chute.

   Prior to the stopper addition, the RABS (b) (4) touched the inner surface of the sterile stopper bowl and the operator wiped the bowl for an unknown reason. Wipes are not permitted (b) (4) (b) (4) RABS (b) (4) where the stopper bowl is located.

4. Interventions at the filling machine related to (b) (4) adjustments (b) (4) -03) occurred at approximately 13:06, 13:22, and 13:25 during (b) (4) Injection batch (b) (4) (distributed to the US market). Procedure SOP/CSP/0129 describing this intervention requires all open vials in this area to be rejected during this intervention, but vials were not rejected.

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5. Operators were observed with exposed skin near their cheek during (b) (4) Injection batch (b) (4) (distributed to the US market). Exposed skin was observed during set-up (b) (4) the (b) (4) RABS, during filling operations, and during cleaning after the batch.

OBSERVATION 2

Laboratory records do not include complete data derived from all tests, examinations and assay necessary to assure compliance with established specifications and standards.

During (b) (4) Injection batch (b) (4) (distributed to the US market), (b) (4) Injection batch (b) (4) and (b) (4) Injection batch (b) (4) environmental monitoring records documented collection of surface monitoring samples. The laboratory records reported no growth for all surface monitoring samples. However, review of video recordings made during the operations showed sampling was not performed at the specified sampling points. The (b) (4) different microbiologists responsible for collecting surface monitoring samples for these three batches each confirmed not all samples were not collected and plates were submitted to the laboratory that had never been exposed to the surface.

OBSERVATION 3

Procedures designed to prevent microbiological contamination of drug products purporting to be sterile did not include adequate validation of the aseptic process.

Smoke studies performed for aseptic filling Line (b) (4) and Line (b) (4) do not demonstrate appropriate air flow. For example:

1. There appeared to be turbulent flow or smoke flowing upwards during interventions, for example:

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Line (b) (4) Assembling of Stopper Bowl and Unloading of Stoppers from the (b) (4) Track Adjustment and Removal of Fallen Vial at the (b) (4) and Replacement of (b) (4) (b) (4) and (b) (4)

Line (b) (4) PMS probe adjustment & (b) (4) by Engineer; (b) (4) Track Adjustment and Handling of Spillage in (b) (4) RAB (b) (4)

2. The acceptance criteria during the studies did not include an evaluation of whether interventions disrupt airflow above open vials, sterile stoppers, or sterile contact surfaces.

3. The camera angles, camera zoom, and amount of smoke (too little/too much) are not appropriate to thoroughly evaluate the airflow patterns during interventions.

OBSERVATION 4

Batch production and control records do not include complete information relating to the production and control of each batch.

Batch records do not document all interventions in the aseptic area. Review of videos from the (b) (4) vial (b) (4) and filling machine of (b) (4) Injection batch (b) (4) (distributed to the US market) from 11:36 to (b) (4) identified the following interventions had not been recorded in the batch record:

- 12 interventions to clear a jammed vial at the (b) (4) at approximately 11:56, 12:12, 14:01, 14:04, 14:14, 14:17, 14:45, 14:52, 15:22, 15:51, (b) (4) and (b) (4)

- 2 interventions related to (b) (4) adjustments at approximately 13:22 and 13:25.

- 2 interventions for INH-17-01, air removal from tubing and [(b) (4)] filter at approximately 13:33 and [(b) (4)].
- 1 intervention CI-01 to remove a fallen vial at the [(b) (4)] at approximately 14:10.
- 1 intervention to fasten a cable tie to the [(b) (4)] on the vial [(b) (4)] at approximately 11:36.
- 1 intervention where the operator picks up [(b) (4)] material with forceps in the [(b) (4)] area at approximately 11:45.
- 1 unknown intervention at the [(b) (4)] at approximately 14:08.

OBSERVATION 5

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions.

1. The risk assessments for selection of environmental monitoring samples RAR-BADDI 2-2015-414 and RAR-BADDI 2-2015-566 did not consider the potential environmental monitoring locations and choose sampling locations based on risk. Rather, it provided a justification for the existing sampling points without considering whether other locations were more appropriate. For example, on line [(b) (4)] the settle plates in [(b) (4)] RABS [(b) (4)] are located [(b) (4)] rather than in an area where interventions routinely occur. The surface monitoring in [(b) (4)] RABS [(b) (4)] of line [(b) (4)] did not consider surface monitoring of the stopper bowl or stopper track that contact sterile stoppers.

2. Personnel monitoring of the set-up operator was started approximately 20 seconds after the

operator applied disinfectant to their hands following set-up of the stoppering area during [redacted] Injection batch [redacted] Procedure SOP/QCM/0116 "Viable Environmental Monitoring Program of Production Areas" prohibits sanitization of gloves just prior to sampling. Additionally, this operator did not allow their hands to dry after applying disinfectant during the set-up activities as required by procedure SOP/CSP/0015 "Behavior and Aseptic Practices for Persons Working in Aseptic Area".

3. Procedure SOP/QCM/0116 was not followed for making contact with surface monitoring plates for [redacted] during sampling after batches [redacted] Injection batch [redacted] and [redacted] Injection batch [redacted] Following collection of the samples, the area was not sanitized with disinfectant as required by the procedure "to remove media and avoid microbial growth".

4. Swab samples collected after [redacted] Injection batch [redacted] did not follow procedure SOP/QCM/0116, which required [redacted] of contact during swabbing.

5. Non-viable particle monitoring is only conducted [redacted] in the extended LAF Grade A areas. Non-viable particle count data in these areas is not associated with manual operations including the [redacted] LAF and transfer of machine parts and materials [redacted] RABS, [redacted] RABS interventions, or aseptic connections.

6. The media used to perform air monitoring including settle plates and active air monitoring does not contain any neutralizing agents. Spray disinfectants are used in the aseptic filling rooms where this monitoring media is used.

OBSERVATION 6

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Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the equipment to produce aseptic conditions.

1. Disinfection of RABS (b) (4) in (b) (4) RABS (b) (4) after (b) (4) Injection batch (b) (4) (distributed to the US market) did not ensure the (b) (4) of the (b) (4) was disinfected.

2. Cleaning operators did not follow procedure SOP/CSP/0017 that requires (b) (4) cleaning stroke (b) (4) wipe surface and changing of the wipe after (b) (4) cleaning strokes.

3. Disinfectant efficacy testing has not evaluated (b) (4) used for the RABS (b) (4) that have been used on the aseptic filling line since June 27, 2022.

OBSERVATION 7

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

Your manufacturing equipment cleaning validation/verification studies for Line (b) (4) and Line (b) (4) No. CVD/CPE/0006-009, "Cleaning Validation Protocol (b) (4) Sterile Injectable Facility Line (b) (4), "Periodic Cleaning Verification Report (b) (4) Sterile Injectable Facility (b) (4) Report No. CVR/CPE/0006-011 and "Cleaning Validation Protocol (b) (4) Sterile Injectable Facility Line (b) (4) No. CVD/CPE/0001-012, "Cleaning Verification Report (b) (4) Sterile Injectable Facility Line (b) (4) Report No. CVR/CPE/0001-021, where aseptic filling of (b) (4) finished drug products, including (b) (4) is performed, failed to include cleaning of the (b) (4) used to hold discarded (b) (4) product during manufacturing and used to hold the (b) (4) during interventions which involve manipulation to the (b) (4) and (b) (4) The aforementioned equipment cleaning validation studies also failed to test for residual API the outer shaft

of the (b) (4) The manufacturing equipment used on filling Line (b) (4) and Line (b) (4) is non-dedicated and can be used to fill any (b) (4) drug product.

OBSERVATION 8

The responsibilities and procedures applicable to the quality control unit are not fully followed.

The aseptic processing areas are not designed to permit viewing through windows or the use of cameras to allow the quality unit to provide adequate oversight of the aseptic processing operations. For example,

1. There is no view of interventions at the (b) (4) vial (b) (4) stoppering equipment, or stopper bowl on Line (b) (4)

2. There is no view of aseptic connections made to the (b) (4) tank or views of interventions at the stoppering machine on Line (b) (4)

3. Personnel exiting the aseptic filling areas perform self-monitoring. The self-monitoring is done in a room with no windows or cameras to permit routine oversight.

OBSERVATION 9

Established test procedures are not documented at the time of performance.

SOP/QAD/0007-018, "Good Recording Practices", dictates in section 4.5 that all data should be recorded contemporaneously (at the time the work is performed). Raw data associated with endotoxin test results is input directly into the LIMS system. Analysts were observed, through recordings on CCTV, performing simultaneous tests on (b) (4) different finished drug products, including (b) (4) Review of the LIMS audit trail for these (b) (4) tests showed that in the analysts' data entries for the end of incubation time, end of incubation temperature and final test result, the raw data was not entered

contemporaneously into LIMS and instead was entered more than an hour after the test had been completed.

Additionally, the associated LIMS audit trail for the endotoxin testing is not reviewed.

OBSERVATION 10

Laboratory controls do not include the establishment of scientifically sound and appropriate test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity.

Per Method Validation Protocol Document ID AMVP/2021/0011, "Analytical Method Validation Protocol for Bacterial Endotoxin Test (b) (4) Injection (b) (4) mg (b) (4) mL)", 4/16/2021 and the associated report Document ID AMVR/2021/0011, "Analytical Method Validation Report for Bacterial Endotoxin Test (b) (4) Injection (b) (4) mg (b) (4) mL)", 11/26/2021, your firm established the acceptance criteria for Endotoxin Limit to be (b) (4) EU/mg, using a maximum dose of (b) (4) mg/m². Your firm failed to assess the maximum dose of (b) (4) in mg/m² that is used in standard (b) (4) dosing regiments.

OBSERVATION 11

There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed.

The following investigations were opened when the (b) (4) RABs (b) (4) used to perform interventions during aseptic filling, were found torn or contained holes when visually inspected, following or during filling of a batch:

Investigation PR #s 1605434, 1350279, 1371338, 1401867, 1252285

Your firm determined in each case that the torn (b) (4) resulted from contact with a sharp surface or

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overstretching while performing interventions in the (b)(4) RABs. Your investigations and associated corrective action plans failed to include an assessment of the cleaning/sanitizing agents used inside the (b)(4) ABS in the grade A area and those agents' effect on the integrity of the (b)(4) RABs (b)(4) over time as well as the length of the routine (b)(4) change out interval of (b)(4) Your firm also performs (b)(4) integrity testing (b)(4) this frequency was also not reviewed as part of the investigation and corrective action plan.

***DATES OF INSPECTION**

10/03/2023(Tue), 10/04/2023(Wed), 10/05/2023(Thu), 10/06/2023(Fri), 10/09/2023(Mon), 10/10/2023(Tue)

X Anastasia M Shields
Investigator
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	Justin A Boyd, Investigator Anastasia M Shields, Investigator X Justin A Boyd Investigator Signed By: 2000358686 Date Signed: 10-10-2023 14:43:23	10/10/2023