DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CDER/OPQ/OPMA/Division of Biotechnology Manufacturing 10903 New Hampshire Avenue; White Oak Building 51, Room 2269 Silver Spring, MD 20993 E-mail: OPFBLAInspection483Responses@fda.hhs.gov	03/10/2022-03/17/2022 FEI NUMBER 3013702557

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED
Reem Malki, Chief Quality Officer

FIRM NAME	STREET ADDRESS
Alvotech Hf	Sæmundargata 15-19
CITY, STATE, ZIP CODE, COUNTRY Reykjavík, Iceland, 101	TYPE ESTABLISHMENT INSPECTED Drug Substance and Drug Product 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

Your firm lacks procedural control to ensure that incoming materials are adequately qualified. An investigation has not been initiated in the firm's deviation management system (Veeva) for the progressively increasing trend of critical quality defects identified for incoming (b) (4) mL (b) (4) (b) (4) stopper lots. (b) (4) stopper lots have been received since August 2020, of which 14 lots were rejected or have failed AQL inspection ((b) (4) % failure rate). Outside of the Veeva system, Quality Assurance has not been involved in the release or reject decisions for raw materials failing acceptance criteria. Release decisions have not been made for 8 of the 14 lots identified as failing AQL inspection.

1. Critical defects have been found since August 2020, but only one type of defect has been placed on a tighten level of inspection. Three stopper lots received in August 2020 were rejected in October 2020 due to splits/cuts in the stoppers, most likely caused by lack of concentricity of the plug, causing weak bonds (b) (4) The supplier, (b) (4) reported they do not have a process to measure eccentricity and their visual inspection equipment, Envision system, may not be able to detect the splits. The inspection criteria for splits and cuts were not changed.
2. Since October 2020, six other stopper lots were inspected with three lots ((b) (4) (b) (4) released in October and November 2020 without undergoing a l defects.
3. Document Change Control # DCC-003609 approved June 2021 implementing a tightened inspection criteria for Defect # DEF350-14 "Critical defect leading to unsterility" after two incoming stopper lots received in September 2020 were found with deformed (b) (4) The tightened inspection increased the sample size from (b) (4) stoppers and had inspection criteria of accept on (b) (4) . Other critical defects maintained their sample size of either (b) (4) No other defects (including critical defects) were counted if found above these sample sizes.

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SEE REVERSE OF THIS PAGE		Madushini Dharmasena, Ph.D., Senior Pharmaceutical Quality Assessor Yetao Jin, Ph.D., Chemist Cynthia Jim, Consumer Safety Officer	03/22/2022

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OBSERVATION 2

The manufacturing areas are not under control for bacteria and mold.

1. There is an unacceptably high number of mold recoveries in the classified rooms used for manufacture of (b) (4) drug substance and drug product. Specifically, mold recoveries were 46 and 176 in 2020 and 2021, respectively. The mold action limits (Grade C/D > (b) (4) CFU) are inadequate to initiate environmental monitoring investigation or deviation. In addition, the mold contaminants recovered via the EM Program have not been trended in a meaningful manner to identify trending patterns.
2. There have been 91 and 89 microbial excursions in 2020 and 2021, respectively. The corrective and preventive actions (CAPA) implemented due to reoccurring microbial excursions were inadequate to avoid future occurrences of similar excursions.

OBSERVATION 3

The microbial ingress risk during recurring drug substance and drug product in-process (b) (4) is not adequately mitigated. The (b) (4) observed for deviations DEV-0847, Dev-0548, Dev-001764, Dev-001777, DEV-001797 did not include additional bioburden sampling from the (b) (4) bag or any risk assessment before forward processing the in-process (b) (4).

OBSERVATION 4

The stopper defects were not appropriately classified.

1. Subsequent findings of stopper split/cut defects were not classified as DEF350-14, instead have been classified as either Defect # DEF350-15 “Critical defect potentially leading to unsterility”, with sample size of (b) (4) and acceptance criteria of accept on (b) (4) or DEF350-12 “minor cosmetic defect not impairing function/sterility”, with sample size of (b) (4) and acceptance criteria of accept on (b) (4) No studies have been conducted to assure that stoppers with

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open tears/cuts/splits through the [(b) (4)] can be properly sterilized, can maintain sterility if used in a filling operation, or can maintain container closure.

a. Stopper lot # [(b) (4)] received in September 2021 passed AQL inspection acceptance cri plit defects were found in one stopper and a second stopper also found with a split defect. The split of one stopper covered more than half the circumference of the stopper [(b) (4)] mm) and the second stopper defect described as [(b) (4)] measured at [(b) (4)] µm. The first split was categorized as DEF350-15 and second split stopper categorized as DEF350-12 "minor cosmetic defect not impairing function/sterility".

b. Stopper lot # [(b) (4)] received in September 2021 passed AQL inspection acceptance criteria. The split/cut defect found in one stopper was categorized as DEF350-15, described as [(b) (4)] size of [(b) (4)] mm. The tearing also appeared to impact on the shape of [(b) (4)] but the defect was not classified as Defect DEF350-14.

2. Split defects have also been classified as defect # DEF350-12, a minor cosmetic defect. Stopper lot # [(b) (4)] was pre-released on 07 January 2022. Inspection on 01 December 2021 found split defect in one stopper, [(b) (4)] size [(b) (4)] mm and was classified as a critical defect # DEF350-15. On 08 December 2021, this defect was reclassified as a minor cosmetic defect # DEF350-12.

3. Stopper inspections have also found stoppers with missing [(b) (4)] a defect classified as "Defect leading to non-sterility" by [(b) (4)] [(b) (4)] on system was not programed to detect for missing [(b) (4)]. Stop ots inspected in 2020 and 2021 have not received a tighten inspection for critical defect [(b) (4)] which has an acceptance criterion of accept on [(b) (4)]

4. Stoppers found with biological contamination (i.e. human hair) was classified as "Defect leading to non-sterility" by [(b) (4)] Stopper lots inspected in 2020 and 2021 have not received a tighten inspection for critical defect, "Contamination of biological origin such as hair or insect (visible with naked eye)", which has an acceptance criterion of accept on [(b) (4)].

5. Defects identified as [(b) (4)] created due to inadequate trimming during molding where [(b) (4)] remains on stoppers in thread like appearance. These thread like appearing defects on stoppers are not included in the defect counts. Inspection of Stopper lot # [(b) (4)] a lot that passed acceptance criteria, found [(b) (4)] [(b) (4)] measured to approximately 10.9mm in length was identified as [(b) (4)] [(b) (4)] 34 other stoppers with [(b) (4)] defects were found, but not included into the defect

counts for Cosmetic defects. Minor Cosmetic defects not impairing function/sterility has acceptance criteria of accept on (b) (4) The lot would have failed acceptance criteria if the (b) (4) defects were added to the 8 stoppers already found with cosmetic defects.

OBSERVATION 5

The specifications for the incoming stoppers from (b) (4) are inadequate. (b) (4) has responded to complaints of stopper defects by saying some identified defects are "not considered a defect by (b) (4)". The internal classification for the defects were then changed to "not a defect", but these same defects are identified during 100% manual visual inspection as defects and (b) (4) rejected. For example,

1. 100% inspection found "embedded particle in (b) (4) (b) (4). (b) (4) Complaint # 190, Investigation Report dated 15 December 2021, defect 20 & 21 (b) (4) and (b) (4) (b) (4) were not considered a defect by (b) (4). "Dots" are classified by (b) (4) as (b) (4) (b) (4)
2. The finding of "asymmetrical stopper" during incoming inspection was classified by (b) (4) as "cosmetic defect not affecting function/sterility". For incoming inspection of (b) (4) 10 (b) (4) were found but only 1 stopper was classified as minor cosmetic defect # DEF350-12.
3. The finding of (b) (4) on incoming visual inspection were not provided a classification and were not counted as defects. 100% visual inspection of filled lots has rejected (b) (4) with (b) (4) or (b) (4) like particle located on (b) (4)
4. The finding of "shiny spot in third cavity" or "3x loose embedded foreign matter" have been reevaluated as not being a defect. 100% visual inspection of filled lot has identified embedded matter as particles subject to rejection.

OBSERVATION 6

The incoming material are released for manufacturing operations prior to completing the final testing. At least (b) (4) stopper lots have been pre-released for use in filling operations prior to final testing were

completed. For example, stopper lots (b) (4) were both pre-released for filling operations and subsequently obtained full release. The use of these (b) (4) stopper lots has been linked to increased findings of major and minor defects during 100% visual inspection of the filled lots. No acceptance criteria for 100% inspection were in place for Critical, Major, or Minor defects, but deviations were initiated for the high reject rates seen.

1. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 35.4%. The highest defect was 17.3% for "particle/fibre/droplet in (b) (4) stopper".
2. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 40.3%. The highest defect was 19.7% for "particle/fibre/droplet in (b) (4) stopper".
3. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 41.6%. The highest defect was 14.8% for "particle/fibre/droplet in (b) (4) stopper". The inspection also found product with (b) (4) – damaged".
4. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 42.5%. The highest defect was 15.9% for "particle/fibre/droplet in (b) (4) stopper". The inspection also found product with (b) (4) topper – damaged".
5. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 24.1%. The highest defect was 10.7% for "particle/fibre/droplet in (b) (4) stopper". The inspection also found product with (b) (4) stopper – damaged".
6. (b) (4) – (b) (4) mg fill # (b) (4) was found with a total reject rate of 14.9%. The highest defect was 5.5% for "particle/fibre/droplet in (b) (4) stopper". The inspection also found product with (b) (4) stopper – damaged".
7. (b) (4) – (b) (4) mg fill # (b) (4) was found with total reject rate of 25.8%. The highest defect was 16.5% for "particle/fibre/droplet in (b) (4) stopper". The inspection also found product with (b) (4) stopper – damaged".

OBSERVATION 7

Inventory and analysis of raw materials are inadequate. The incoming visual inspection of (b) (4) lots by QC Raw Material were also found to vary from the 100% visual inspection of filled pro d changes were made to adjust the100% visual inspection criteria. The majority of (b) (4) defects found from the above lots were for glass deformity, scratched (b) (4) and (b) (4) discoloration/embedded material.

1. The reinspection by QC Raw Material technicians of the defects identified by 100% visual inspection operators of filled lot # (b) (4) dentified differences in inspection criteria. For example, during 100% visual inspection 99 "airline" defects were identified which QC Raw Material technicians agreed that only 62 defects were "airline" defects. QC Raw Materials technician only identified "airlines" as a defect if the airline measures > (b) (4) mm. QC Raw Materials technicians also only identified scratches as defects if the length of the scratch is > (b) (4) mm. In Deviation 001718, the firm summarized that not all airlines and scratches were defects since they may have been smaller than (b) (4) mm.
2. SOP # 0558, Manual Inspection of Product (b) (4) implemented inspection criteria for "Airline", a major defect. The inspection requirement indicates that (b) (4) airlines (b) (4) (b) (4) stopper, not in contact with the product are not considered defects.
3. SOP # 0558 also changed the inspection criteria for scratches, a minor defect. As of 10 March 2022, a scratch is "a gross scratch on the (b) (4) … minor scratches can be accepted".
4. Whereas during media fills, all defects identified as "airline" are rejected and not incubated.

OBSERVATION 8

The PTS endosafe endotoxin detection method used to detect endotoxin in (b) (4) in-process, and drug substance and drug product release samples was not adequately qualified and the sample preparation is inadequate. Specifically,

1. The accuracy of the archived calibration curves generated by an external laboratory, which are used to calculate the endotoxin content of (b) (4) in-process and release drug substance and drug product samples, was not adequately verif house at Alvotech.
2. Factory control record setting of the Endosafe PTS Reader was updated due to high rate of invalid assays. However, operation qualification was not performed after the update of the factory control record setting.
3. The preparation of samples does not include instruction to (b) (4) (b) (4)

OBSERVATION 9

Written procedures are inadequate or do not provide adequate details to ensure product quality. Specifically:

1. There are no written procedures for the handling of (b) (4) transfer of the in-processing (b) (4)
2. Media and buffer preparation instructions in SOP - 0592 "Use of Media and (b) (4) (b) (4) (Version: 5.0, Effective Date: 05 Oct 2021), SOP – 0730 "Buffer Preparation, (b) (4) (Version: 2.0, Effective Date: 14 May 2021) or MBR - 0012 (Version: 11.0) do not specify the (b) (4) media hold time.
3. There are not instructions on the path to follow for the manual visual reinspection of product filled lots that failed either 100% manual visual inspection or AQL inspection.
4. Gowning qualification procedures do not provide a clear path for actions to take when gowning qualification monitoring fails acceptance criteria. There is no requirement to initiate a deviation failure investigation when an employee fails gowning qualification/requalification. There is no criterion for the number of times an employee can fail gowning qualifications prior to disqualification. One engineer technician who has had 24 Grade B entries since April 2018, failed personnel monitoring 11 times (46% failure rate), prior to disqualification.

OBSERVATION 10

The SOPs for Deviation handling, Handling of Product Quality Complaints, Handling of OOS, OOT and OOE results lack clarity on the period of each extension and the times of extensions for the cases that cannot be closed during the original targeted period. For example:

1. SOP - 0922 Deviation handling in Veeva (Version: 6.0, Effective Date: 21 Feb 2022) includes Section 6.20 Extension Requests but does not describe how long one extension period could be and how many extensions can be requested before closing a deviation in Veeva.
2. SOP - 0785 Handling of Product Quality Complaints (Version: 5.0, Effective Date: 11 Mar 2022) describes potential extensions in Section 6.1.4.1. However, the SOP does not describe the period of each extension and the times of extensions.
3. Section 6.11 Extension requests in SOP - 0259 Handling of OOS, OOT and OOE results (Version: 6.0, Effective Date: 05 Jan 2022 and Version: 7.0) includes the procedure of extension request but does not specify the period of each extension and the times of extensions.

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OBSERVATION 11

Procedures to control environmental conditions have not been adequately established. Specifically,

1. Materials to be used during filling operations are transferred into the Grade B filling suite through the same path that persoonel gown into the Grade (b) (4) filling suite. For example:
   a. (b) (4) bagged (b) (4) are transferred from warehouse and sequentially into Grade B area; (b) (4) (b) (4) L (b) (4) (b) (4) (b) (4) (b) (4)
   b. Unwrapped items such as particle monitor; (b) (4) integrity tester and related parts; cleanroom tablets; cables; (b) (4) parts; maintenance tools, etc.

   One location uses a settle plate to monitor the Grade B side of the personnel air lock (PAL) and (b) (4) (b) (4) iter (b) (4) sample is obtained to represent material transfer, gowning of personnel for set up, gowning for personnel performing filling, and gowning for personnel for end of fill activities.

2. The personnel monitoring limits established for operators performing operations in the (b) (4) RABS are inadequate to meet acceptance criteria for Grade A (ISO 5). During the filling operation set up on March 16, 2022 the operator did not wear sterile sleeve covers and operator's lower forearm and the upper arms moved (b) (4) RABS. However, as per SOP – 0358 (b) (4) Personnel monitoring (Version: 10.0, Effective Date: 07 Feb 2022) only operator's right and left hand finger monitoring limits meet Grade A acceptance criteria. The right lower forearm monitoring limits meet the requirements for Grade B (ISO 7). The left lower forearm, the left upper arms and the right upper arms are not monitored.
3. (b) (4) Grade A contact plate sampling of the (b) (4) is required to be taken within the (b) (4) but a sample from (b) (4) ken during end of fill monitoring on 10 March 2022. In addition, the (b) (4) was sample instead of (b) (4) (b) (4)

OBSERVATION 12

The accuracy of test methods has not been established and documented. Specifically,

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1. Verification of the suitability of the testing methods is deficient in that they are not performed under actual conditions of use. Specifically,
   a. (b) (4) Cleanroom Swabs are used for collecting environmental monitoring samples in the Grade A RABs (b) (4) (b) (4) A microbial recovery study was not conducted to ensure that the swabs are capable of recovering microorganisms that are potentially present on the filling line.
   b. (b) (4) Cleanroom Swabs are used to collect environmental monitoring samples on the Grade A RABs Filling Line. The swab samples are incubated at 30-35°C from (b) (4) (b) (4) whereas growth promotion testing of the swabs requires incubation of swabs at 30-35°C for maximum of 3 days and incubation at 20-25°C for a maximum of (b) (4) for microbial recovery.
2. The Swab Neutralization Study conducted in September 2017 was not performed according to protocol requirements.
   a. The protocol required (b) (4) swabs will be assessed", but only one swab lot was included in the
   b. The objective of the protocol was to verify the performance of the swabs used for environmental monitoring but not all surfaces monitored by swabs were included in the study. For example, (b) (4) monitored with swabs are made of plastic. Plastic was not included in t
   c. The protocol required, "incubate the swabs at 30-35°C for the bacteria and at 20-25°C for fungi growth is observed". The incubation temperatures were not documented.
   d. The protocol required, "all microbial swabs must show microbial growth within the specified incubation periods". The dates of incubation were not documented.
3. Personnel that perform manual visual inspections are required to be tested for visual acuity and color blindness. The results obtained only report whether the person has passed or failed. There is no information as to whether the person has passed for far or near visual acuity, if the person requires corrective lenses to obtain passing test results, and if personnel need to be tested further when the score for color blindness is not optimal (mild color blindness).

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OBSERVATION 13

Investigations of an unexplained discrepancy did not extend to other drug products that may have been associated with the specific failure or discrepancy. Specifically,

The firm failed to perform product impact assessment after failure of the annual requalification of the (b) (4) used to decontaminate (b) (4) containers and other miscellaneous wrapped material (b) (4) the Grade B filling suite. The system was successfully requalified in 2019 and ualification of the system in July 2021 under VALQ-5580 failed. DEV-001535 was raised when 2021 VALQ-5580 failed to meet acceptance criteria, in that multiple (b) (4) turned up positive. The requalification was repeated two more times with (to validate a (b) (4) product cycle) and both runs turned up additional positiv (b) (4) A new cycle was developed with increased (b) (4) time of (b) (4) and validated Production cycle (b) (4) All acceptance criteria were met. Since the previous successful requalification, lots were filled between October 2020 to June 2021.

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