DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
U.S. FDA CBER Office of Compliance and Biologics Quality 10903 New Hampshire Ave W071-5128 Silver Spring, MD 20993-0002 TEL: 240-402-9159 Industry Information: www.fda.gov/oc/industry	09/01/2022 - 09/09/2022
	FEI NUMBER 3005315117

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mr. Greig S. Rooney, Managing Director

FIRM NAME	STREET ADDRESS
Valneva Scotland Limited	Oakbank Park Road
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Livingston, Scotland EH53 OTG	Vaccine Sterile Bulk 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 (I) (WE) OBSERVED:

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

A. Deviations are not always closed in a timely manner. LIV-SOP-0209 [14], entitled "Deviations and Investigations", section 6.5.4 stipulates deviations should be closed within 30 days. Section 6.5.5 from this SOP stipulates that form LIV-FRM-0214 [06], entitled "Interim Report/Extension Request/Withdrawal Request" has to be filled out for deviations not closed within 30 days. 17% of the deviations initiated from 09/01/2019 to 09/05/2022 were not closed within 30 days. These deviations were overdue for 1 day to 184 days without extension approval.

B. There is a lack of timely review and tracking of change management requests by the quality unit.

i. CHANGE-REQ-00582 was raised on 06/12/2020 for (b) (4) assay verification testing for a total of (b) (4) raw materials used in the manufacturing of IXIARO. This change request remains open to date.

ii. CHANGE-REQ-00488 was raised on 03/06/2020 for additional validation for specificity of the (b) (4) (b) (4) Assay (b) (4) This change plan remains open to date.

iii. DR/285/20 was initiated on 12/22/2020 for an open pack of (b) (4) containing one IXIARO syringe found in the QC lab areas. A cross check confirmed this syringe was in relation to product technical complaint PTC/026/19 already closed on 12/27/2019. However, no sample was logged for this complaint. CHANGE-PLN-00878 was raised on 04/23/2021 to update PTC procedure. This change plan remains open to date.

C. There is a lack of timely review and tracking of test recall by the quality unit. Specifically, test recall RC/020/001 for IXIARO batches was initiated on 12/15/2020. Per LIV-SOP-0618 [04], entitled "Product Recall", section 6.14.2, the final report should be issued within 60 days after the final reconciliation. However, the RC/020/001 final report was not completed until 09/05/2022 during the current FDA inspection.

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SEE REVERSE OF THIS PAGE	/S/	Eileen A. Liu, Lead CSO Priscilla M. Pastrana, CSO	09/09/2022

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D. There is a lack of timely review and tracking of internal audit reports by the quality unit. Specifically, LIV-SOP-0210 [7], entitled "Internal Quality Audits", section 16 requires audit reports be issued in one month from the date of audit. Three internal audits had been performed in Q1-Q2 2022; however, reports were not issued per SOP requirement. The concerned internal audits are IA/001/21, audit date 04/13/2022 for JEV (b) (4) IA/006/21, audit date 05/23/2022 for JEV (b) (4), and IA/007/21, audit date 06/14-15/2022 for (b) (4) Reports were later issued on 09/07-08/2022 during the current FDA inspection.

2. There is a failure to thoroughly review any unexplained discrepancy to meet any of its specifications whether or not the batch has been already distributed. Specifically,

These is a lack of adequate investigations conducted and corrective actions implemented regarding to the particles found in the U.S. licensed JEV final vaccine batches from April 2019 to August 2022.

A. A total of 51 particle-related investigations were conducted from April 2019 to August 2022 for 34 JEV final vaccine batches. 21 out of the total 34 batches are for the U.S. market and 17 BPDRs were submitted to the agency from April 2019 to February 2022 for products already distributed.

B. The observed particles were identified as (b) (4) However, the firm did not perform risk assessment to evaluate the impact of the particles to the safety and effectiveness of the final vaccine.

C. No corrective action has been implemented to resolve the particles found in the JEV final vaccine.

3. Written procedures are not established or followed for evaluations done at least (b) (4) and including provisions for a review of investigations conducted for each drug product. Specifically,

There are deficiencies in the reporting of (b) (4) product quality review and are shown below:

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A. An increase in the % invalid tests for the (b) (4) and (b) (4) from (b) (4) and (b) (4), respectively were observed from year (b) (4) to (b) (4) However, no follow up investigations nor corrective actions (if necessary) of these increasing trends of % invalid tests was performed. Also, no discussion/conclusion regarding to these increasing trends was included in the (b) (4) product quality review.

B. There is a lack of written procedures to govern the calculation of % invalid tests for the analytical assays for release and stability. Specifically, inconsistent results on the % invalid tests for (b) (4) and (b) (4) (b) (4) were reported in (b) (4) and documents provided by Subject Matter Expert (SME) during the current inspection.

C. (b) (4) product quality reviews are not adequately reviewed by your firm's QA and QC regarding data accuracy. For example, in the quality product review (b) (4) it was listed that (b) (4) batches were tested in (b) (4) (b) (4) assays with 1 invalid test and (b) (4) batches tested in (b) (4) assay with 1 invalid test for (b) (4) while the documents provided by the SME during the onsite interview indicated that (b) (4) batches were tested in (b) (4) assays with 5 invalid tests and (b) (4) batches were tested in (b) (4) assays with 1 invalid test.

4. Biological Product Deviation Reporting (BPDR) were not reported within the 45-calendar day timeframe. Specifically,

Seven out of a total of 23 BPDRs were reported outside the 45-calendar day timeframe. These BPDRs had discovery to report days from 73 days to 567 days. The firm claimed that the BPDR submissions cannot be confirmed as the Center of Biologics Evaluation and Research (CBER) website only retains records of the previous six-month submissions.

5. Appropriate controls are not exercised over computers or related systems to assure that changes in master production and control records or other record instituted only by authorized personnel. Specifically,

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Local procedures for fully reviewing audit trails have not been established. Currently, no audit trail reviews have been conducted at the Valneva Scotland site for the manufacturing of IXIARO. Specifically, there are no audit trail reviews for computer systems used in the facilities management, laboratory operations, and manufacturing operations to assure system security and data integrity.

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

There is a lack of Building Manufacturing System (BMS) validation for the new (b) (4) system installed in the JEV manufacturing area in 2019. According to Installation Operational Qualification Protocol (IOQP)/50004-01, JEV (b) (4) Upgrade, approved on 06/21/2019 and Equipment Qualification Report (EQR)/50004-JEV (b) (4) -13May2019-01, approved on 06/21/2019, a new BMS system was installed in 2019 to control the operation of the new (b) (4) (Asset Number (b) (4) that serves the JEV manufacturing area. The BMS interfaces with the existing Facility Monitoring System (FMS) for the retrieval of (b) (4) data from the Grades (b) (4) rooms in the JEV manufacturing area. However, there is no documented validation of the BMS.

7. Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not followed. Specifically,

On 09/06/2022, we observed (b) (4) dated 10/13/2020 for the setup, cleaning, and (b) (4) formulation of final bulk vaccine batch JEV20H42 conducted in Room (b) (4) Final vaccine lot JEV20H42 was released to the (b) (4) on 07/16/2021. We observed the following deficient aseptic practices.

A. LIV-SOP-0188 [13], entitled "Cleanroom Behaviour", section 6.3.1 states operators must regularly (b) (4) (b) (4) with (b) (4) We observed the key (Grade (b) (4)) operator (b) (6), (b) (7) set up (b) (4) (located in the (b) (4)) for (b) (4) (b) (4) . However, operator (b) (6), (b) (7) did not follow written procedure to (b) (4) before resuming aseptic processing of batch JEV20H42 to protect product from contamination.

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B. LIV-SOP-0551 [06], entitled "Aseptic Behaviour in Cleanrooms", section 6.2.6 Note describes, "It is important (b) (4) are (b) (4) before (b) (4) . We observed Grade (b) (4) operator (b) (6), (b) (7)(C) (b) (4) with (b) (4) but did not allow (b) (4) before conducting aseptic processing. Operator (b) (6), (b) (7) did not follow written procedure. (b) (4) can introduce contamination to the aseptic preparation and should be (b) (4)

8. Aseptic processing areas are deficient regarding the system for cleaning and disinfecting the room to produce aseptic conditions. Specifically,

A. (b) (4) Validation Report for Disinfectant Efficacy Testing (b) (4) (b) (4) and (b) (4) Effective Date 02/19/2021 is deficient.

i. Not all manufacturing surfaces were included in the study. Only (b) (4) and (b) (4) surfaces were used in the study, which are not representative of all surfaces in the manufacturing area.

ii. USP standard microorganisms were not challenged in the study. Only environmental isolates from Valneva Scotland and Sweden sites were challenged in this study.

B. Cleaning procedure was not followed. Specifically, LIV-SOP-0174 [19], entitled "Cleaning of Controlled Environments at Valneva Scotland", Cleaning/Technique section 8.2 requires using (b) (4) in a (b) (4) (b) (4) and to (b) (4) so a (b) (4) is used for (b) (4) to reduce the risk of potential cross contamination. On 09/06/2022, we observed (b) (4) dated 10/13/2020 for the setup, cleaning, and aseptic formulation of final bulk vaccine batch JEV20H42 conducted in Room (b) (4) . We observed (b) (4) operator (b) (6), (b) (7)(C) did not always apply (b) (4) in a (b) (4) or use a (b) (4) for the cleaning of Grade (b) (4) . The final vaccine lot JEV20H42 was released to the (b) (4) on 07/16/2021.

9. Laboratory controls do not include the establishment of scientifically sound and appropriate reference standard

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designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,

Neither expiry date nor stability data was established for the (b) (4) reference standard. This reference standard is used in the JEV (b) (4) assay for (b) (4) for the (b) (4) The (b) (4) is one of the release tests for Drug Substance and the (b) (4) (b) (4) is crucial for (b) (4) to formulate final drug product.

10. Employees are not given training in current good manufacturing practices. Specifically,

Your firm currently employs a total of (b) (4) working in various areas, including but are not limited to QA, JEV manufacturing, (b) (4) manufacturing, Chikungunya (CHIK) vaccine regulatory submission, and internal & external audits. However, neither initial induction CGMP training nor (b) (4) CGMP training are given to these employees.

/S/
9/9/2022

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The observations of objectionable conditions and practices listed on the front of this form are reported:

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or

2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

Section 704(b) of the Federal Food, Drug, and Cosmetic Act (21 USC 374(b)) provides:

"Upon completion of any such inspection of a factory, warehouse, consulting laboratory, or other establishment, and prior to leaving the premises, the officer or employee making the inspection shall give to the owner, operator, or agent in charge a report in writing setting forth any conditions or practices observed by him which, in his judgement, indicate that any food, drug, device, or cosmetic in such establishment (1) consists in whole or in part of any filthy, putrid, or decomposed substance, or (2) has been prepared, packed, or held under insanitary conditions whereby it may have become contaminated with filth, or whereby it may have been rendered injurious to health. A copy of such report shall be sent promptly to the Secretary."