FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
FDA/OCBQ 1401 Rockville Pike , Rockville, MD 20852. (301) 827-6191	06/02-10/03 FEI NUMBER 3002806949
NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED	
TO: Andy H. Sneddon, Head of Manufacturing/Site Director Liverpool Facility	
FIRM NAME Evans Vaccines Limited	STREET ADDRESS Gaskill Road
CITY, STATE AND ZIP CODE Speke, Liverpool L24 9GR UK	TYPE OF ESTABLISHMENT INSPECTED Vaccine manufacturer

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DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

1) The following monovalent lots with high levels of bioburden at the [redacted] step were re-processed/re-filtered, processed into trivalent lots, and released into US market for distribution during 2001/2002 Fluvirin campaign without CBE30 and/or CBER notifications:

A) A/Panama lot #760351 with total bioburden volume of 6.48×10^9 cfu was re-filtered into lot #760591 and used in the formulation of trivalent lot #s: 760688, 760641 & 760640 and in at least final Fluvirin released lot #E10821LA.

B) A/New Caledonia lot 759931 with total bioburden volume of 3.29×10^8 cfu was re-filtered into lot #760137 and used in the formulation of trivalent lot #760843 & 760092 and in at least final Fluvirin released lot #E11941LA.

C) A/Panama lot #759864 with total bioburden volume of 4.45×10^{10} cfu was re-filtered into lot 760136 and used in the formulation of two trivalent lots 761025 & 761095 and in at least final Fluvirin release lot #E12821MA.

D.) There is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage. The only stability study that included re-filtered batches, R/0184/07/00 dated August 1, 2000, was not designed as refiltration protocol and assessed only previous monovalent strains, rather than those currently processed. The study also only assessed one syringe and one vial lot in one monovalent strain. The Stability Report does not include volume refiltered or pre-filtration bioburden. There is no protocol for assessment of stability of re-filtered Fluvirin when the monovalent strains change from season to season.

2) Control and failure investigations into bulk Fluvirin monovalent blends/lots at [redacted] step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., 9.66×10^8 cfu, 7.07×10^7 cfu & 1.26×10^7 cfu in year 2000/2001 and 2001/2002 campaigns and no formal investigations has been opened to find the root cause of the high levels of bioburden in these lots.

3) There is no documentation that the decisions to continue with the manufacturing of the Fluvirin monovalent lots with high levels of bioburden levels were based on the pathogenicity of the organisms that were isolated from the sampled lots, e.g., gram negative: *Serratia marcesens, Enterobacter cloacea*, and *Pseudomonas putida*.

4) Sterility failure investigations do not fully include all potential roots of contamination and corrective actions are incomplete. For example,

A.) The NCR investigations of Monovalent Blend Pool Batch #762492 refiltered into Batch #762835 dated July 2002 and batch # 761650 dated May 2002 implicated aseptic connections as potential root causes but failed

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to result in procedural requirements for environmental monitoring during all aseptic connections and evaluation of possible reductions in the number of aseptic connections.

B.) Settling plates were placed on the formulation tank at least 15 minutes after aseptic connections to the tank during the formulation of New Caledonia lot # 764984 observed on June 4, 2003. Viable and non-viable monitoring was initiated at least one hour after all connections were made including those to the [redacted] unit which are made in Class [redacted] conditions [redacted]

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C.) Klebsiella oxytoca was isolated in the Centrifugation [redacted] batch 762450 and the [redacted] Zonal Concentrate batch #762451 that went into batch #762492. K. oxytoca was also isolated in the [redacted] filtration sample as well as the sterile-filtered sample. There was no investigation of water monitoring results or environmental monitoring results prior to this batch.

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D.) From February 28 2002 to July 5, 2002, 14 [redacted] Monovalent Blend Pools failed bioburden testing with a Klebsiella isolate. Closure of the sterility failure investigation of lot# 762635 (refiltered from lot# 762492) on July 9, 2002 did not include reference to nor investigation of the additional failed batches with the same isolate.

E.) There was incomplete review and approval justification for retests in sterility OOS test results reviewed for 2001 and 2002.

5) The following deficiencies were noted in product contact equipment compatibility:

A) There is no filter compatibility and extractable validation studies on filtered Fluvirin monovalent and/or trivalent bulks. In addition, filter compatibility was not considered in the product stability failure investigations. As such, filter compatibility studies has not been eliminated as the reason for loss of potency after the trivalent filtration step that resulted in failures of four out of five Fluvirin lots placed on stability for year 2001/2002 campaign.

B) The [redacted] Tubing used throughout the Fluvirin manufacture process to transfer centrifuged, formulated and finished product for filling was out of specification of [redacted] mg for USP Non-Volatile Residue with result of 1327 mg per [redacted] test result. No investigation, corrective and preventive action has been conducted and no justification/rationale is provided for lack of investigation.

6) The investigation into the reported Fluvirin potency stability test failures in 2001/2002 and 2002/2003 was incomplete. For example,

A.) The conclusion implicating CBER reagents in the test failures was not fully justified. The study did not address that failures primarily occurred only after 6 months on stability. Root cause(s) have not yet been identified, including potential contributing factors specific to the antigen and antiserum and the investigation is ongoing.

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B.) The manufacturing investigation did not include a failed 2000/2001 batch and 2001/2002 batches reviewed were not fully identified in the report (Appendix 14). The root cause investigation was not included in the report.

C.) There was no review and approval of the Summary Report Investigation Into Fluvirin Stability Results by management involved in the investigation. The Summary Report is not dated.

D.) There was no review and approval of the draft Clinical Expert Report dated September 4, 2002 justifying the firm's decision not to execute product recall. The author of the report is not identified and did not sign the report.

7) The Biological Product Deviation (BPDR) reported June 28, 2002 for reported Fluvirin potency and pH stability test failures was incomplete and failed to provide FDA significant information for timely evaluation. Additionally, there is no justification for management's failure to identify the significance of failing and missing test results during review and approval of the results and the ongoing stability program as required by Stability Policy Document SCP041. For example,

A.) The firm simply reported that OOS potency and pH test results had occurred and no failing test results, including failing New Caledonia potency test results and stability test time points (specification minimum [redacted] mcg HA per SRID), were submitted.

B.) Although the firm reported that a failure had occurred for lot# E00931HA, they did not report that the initial failure of the 2001/2002 season (26.8 mcg) occurred at the scheduled 6-mo test point reported February 10 2002, over 5 months prior to BPDR submission. The lot also failed at the 9-mo test point (24.9 mcg) in May 2002 and the 12-mo test point (13.1 mcg). The firm did not have a rounding procedure and reportedly did not consider 26.8 mcg a failure-no report to FDA was made for the 6-mo result.

C.) No information was submitted to FDA on lot #s E12201MA (24.1 mcg) and E11371LA (21.9 mcg) which failed when first tested on stability at the 7-mo test point on May 26, 2002. Required tests at the 1, 2, 3 and 6-month time points were not executed-this was not reported to FDA. No NCR was initiated for missed time points and failure to submit BPDRs and no justifications have been written. Limited data on these lots were submitted without full explanation in the related September 4, 2002 BPDR. Shelf-life Stability Summary Reports for the two lots, reviewed and approved by QA, QC and RA in January 2003, failed to report and evaluate missed time points in the studies.

8) No BPDR was submitted for the Fluvirin pH OOS (7.9) at the 3-month test point on December 18, 2002 for lot # E34652KA 2002/2003 season. A follow-up report to the September 4, 2002 BPDR was not submitted in which the firm reported that additional OOS pH results were likely to occur in other batches.

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9) Corrective action has not been implemented for the previous FDA 483 observation regarding the failed [redacted] System cleaning validation study CVR/0016/00 dated August 16, 2000. For example,

A.) The firm's response to the previous FDA 483 stated the evaluation of the study concluded there was no impact on Fluvirin. From March 2001 through 2002 at least 30 [redacted] Monovalent Blend Pool lots failed bioburden testing.

B.) Validation protocol for the executed study CVP/0011/03 dated April 7, 2003, changing the sanitizing agent to [redacted] did not include bioburden reduction by assessing microbial load prior to use or storage between uses.

C.) Design and operation of the [redacted] filtration unit located in the Formulation area allows operator error to potentially reverse the flow of product under filtration. The [redacted] has a piece of masking tape over the flow direction dial on which is written "Do Not Use". Use of the flow director would reverse the flow of product. The dial is located next to another dial that requires regular use for pressure regulation.

10) It was noted during the observation of formulation of A/New Caledonia Monovalent Blend Pool batch # 764984 on June 4, 2003 that sub-batch [redacted] samples were not taken as required (per SOP ZY033A Release of [redacted] Concentrate to the Formulation Department including the [redacted] day ruling) [redacted] days after the [redacted] centrifugation run on May 22, 2003. There are no procedures to assure samples are taken and there is no information this deviation had ever been previously identified. The NCR investigation to determine additional batches affected by similar deviations was reportedly ongoing.

11) The following was noted during vial filling on June 6, 2003 (under Protocol P/0097/04/03):

A.) There was no documentation in the batch record of missed stoppers or seals and there is no procedural requirement to do so.

B.) A panel, about 8 by 10 inches, was open in the cabinet under the filling machine and there was no information on the length of time this condition had existed or that correction had been scheduled. The open panel area could allow the accumulation of potential contaminates under the filling machine that would be difficult to clean/sanitize.

C.) An operator was noted to be pushing curtains into the area near open empty vials while retrieving tipping vials on 2 occasions disrupting vertical laminar flow.

D.) 2 plastic yellow beakers used for holding forceps were scratched and yellowed.

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12) Regarding sanitizer efficacy validation study protocols,

A.) Study R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi dated July 13, 2001 failed to include the full range of cleaning agents (i.e. [redacted] and manufacturing surfaces (i.e. laminate on doors, Perspex on filling unit curtains). Additional studies, i.e. PQP/0026/01, did not assess cleaning efficacy on manufacturing surfaces.

B.) Acceptance criteria were not met for Study R/0083/05/01 against bacteria including spore-formers and mold and no additional protocols have been written/executed.

13) No protocol deviation was initiated for the failure to execute the portion of Protocol PVR/0005/01 Determination of effects of Holding Times on the potency of Fluvirin Monoblend Pools, requiring that a routine batch be placed on stability. The summary report, reviewed and approved by QA on January 30, 2003, reported that the routine batch was not placed on stability while also stating that no differences between the test batch and routine batch were observed. Another protocol was not executed.

14) Regarding Batch records including review, approval and batch release,

A.) Procedures do not assure full review of deviations prior to release. Worksheets to assure QA batch record review and product release are not included in written procedures, i.e. QA Bulk Trivalent Checklist (not in SOP QASP093 QA Procedure for Review of Finished Product) and Fluvirin Trivalent Vaccine Product Release Checklist (not in SOP PRG020 Release of Finished Products from Quarantine), i.e. Trivalent batch # 762834, filling batch #762925 and Packing batch #E31192HA released September 4, 2002.

B.) An incorrect NCR was referenced in the batch record for the sterility test for batch # 762834.

C.) Labels for working seed cell culture vials are not maintained in the Manufacturing Instruction batch records, i.e. B/Hong Kong/330/01 lot# [redacted] Evans [redacted] passage dated October 25, 2002.

D.) There was no documentation in the filling batch record of a leak in filling tubing causing the filling process to abort for lot# 762838 on June 6, 2002. Although an NCR was initiated, there is no evidence in the batch record the leak occurred.

15) There is no requirement for investigation of consecutive, repeated alert level sample results for water monitoring as allowed by SOP M154 Water Monitoring Excursion Reports.

16) The following deficiencies were noted in the Fluvirin media fill simulations:

A) Media fill simulations are not repreesentative of actual aseptic filling process in that interventions that occurred during aseptic filling processes are not evaluated and considered for incorporation into media fill simulations.

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B) Worst case conditions to be conducted during media fill simulations are not defined in SOP # SCP029 dated 9/9/02: General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulation Utilizing Sterile Media Fills and/or Performance Qualification Protocol # PQP/0067/01.

17) There was no documentation that adverse events (AE) reported for vaccine season 2002/2003 with the same lot numbers reported by different Health personnel/facilities on Fluvirin batches were reviewed, evaluated and/or investigated to determine if the adverse event may be related to the manufacturing process, for example:

A) Ten adverse events reported for batch #E35732HA on injection sites inflammation by eight different healthcare facilities.

B) Five adverse events reported on batch #E33922HA on injection sites inflammation by five different healthcare facilities.

C) Forty-one adverse events reported on batch #E33402HA on injection site reactions reported by two healthcare facilities.

18) Temperature mapping study has not been conducted for the [redacted] degrees centigrade) freezer, Serial [redacted] used in the storage of frozen master and working seeds used in the manufacture of Fluvirin. (Protocol # IOQP/0040/03 dated 5/19/03 for the qualification of the freezer is currently in place).

19) The following deficiencies were noted in the 100% Fluvirin finished vials visual inspections:

A) The 100% visual inspection and re-inspection of finished Fluvirin vials defects are not based on acceptable statistical sampling plans and/or review of historical data but based on [redacted] reject/accept rate that was used to set the initial limits.

B) The 100% visual re-inspections of finished Fluvirin vials are not based on a tighter sampling plan but are conducted at the same accept/reject rate of [redacted] as the initial 100% visual inspections.

C) Critical and non-critical finished vials inspection defects are not defined in SOP #IN017.VI dated 9/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection. In addition, all vial defects are based on the same reject/accept rate of [redacted] for, e.g., appearance, particles, broken glass, empty vials, and seals.

D) There is no Quality Assurance control/verification and/or over site of the 100% finished vials inspection for defects that are performed by manufacturing.

20) SOP #IN018 dated 5/25/03 for the training of Fluvirin 100% finish vials inspection personnel is incomplete, in that it failed to include the length of training of personnel for finished Fluvirin vials defect inspections and the level of supervision of the trained personnel after training.

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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 judgment, 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 unsanitary 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."