EVANS VACCINE, Ltd.
GASKILL ROAD.
SPEKE, LIVERPOOL L24 9GR UK.
DATES OF EI: 6/02-10/03.

SUMMARY OF FINDINGS:

This inspection of a foreign manufacturer of licensed Flu Vaccine Product (Fluvirin) was conducted pursuant to Core Team Biologics FY'03 Workplan. This inspection was conducted in accordance with CP 7345.002 Inspection of Licensed Vaccine Product. In addition, assignment from the Office of Compliance and Biologics Quality, Division of Inspections and Surveillance dated 5/16/03 was also covered during this inspection.

The previous PAI inspection dated 5/11/01 was for a new ---------- Syringe filling line and deficiencies were noted in the firm's manufacturing process, such as: lack of documented failure investigations, failure to close non-conformances within time frames, deficient equipment cleaning and autoclave validations, and lack of documentation of the inspection of media filled units. FDA-483 was issued and the firm promised corrective actions.

The cGMP inspection of 3/09/01 disclosed deficiencies in Fluvirin process validation, the cleaning validation of the ---------- ---------- - System and lack of validation of the ---------- Vial Filler speed and vial/stopper washing process. In addition, failure of non-conformance reports to include adequate information, e.g., bioburden levels and correct dates of microbiology laboratory notifications were noted. Deficiencies were also noted in sterility test failure investigations, inaccuracies in Master Production Records, WFI sample collection for routine monitoring, and failure of the Quality Control Unit to conduct monitoring of various production operations. FDA-483 was issued and the firm's officials promised corrective actions.

This inspection disclosed the firm has corrected most of the observations that were cited during the PAI and cGMP of 5/11/01 & 3/09/01. However, this inspection noted inadequate corrective actions to Observations #1C, 7, 11, 20 & 28 for the cGMP inspection dated 3/9/01. Deficiencies were also noted during the review of FDA-483 issued during the PAI inspection 5/11/01. For discussion on deficiencies noted during the review of corrective actions to FDA-483 issued during the cGMP and PAI inspections, please see discussions in this EIR under corrective actions to previous observations.

The current inspection revealed the following deficiencies in the firm's manufacturing operations for Biologic products:
At least there monovalent lots with high levels of bioburden at the ---------- step were re-processed/re-filtered and processed into trivalent lots, and released into US market for distribution during 2001/2002 Fluvirin campaign without CBE30 and/or CBER notifications. In addition, there is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage. Control and failure investigations into bulk Fluvirin monovalent

blends/lots at---------- step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., $9.66x10^6$ cfu, $7.07x10^7$ cfu & 1.26×10^7 cfu during year 2000/2001 and 2001/2002 Fluvirin campaigns and no formal investigations has been opened to find the root cause of the high levels of bioburden in these lots. Also, there is no documentation that the decisions to continue with the manufacturing of the Fluvirin monovalent lots with high levels of bioburden were based on the pathogenicity of the organisms that were isolated from the sampled lots, e.g., gram negative organisms such as: *Serratia marcesens, Enterobacter cloacea*, and *Pseudomonas putida.*

The inspection noted the lack of filter compatibility and extractable validation studies on filtered Fluvirin monovalent and/or trivalent bulks and the---------- --------- Tubing used throughout the Fluvirin manufacturing process to transfer centrifuged, formulated and finished products for filling was out of specification of --- mg for USP Non-Volatile Residue with result of 1327 mg per ---------- test result. Also, the inspection noted incomplete investigations into the reported Fluvirin potency stability test failures for year 2001/2002 and 2002/2003. Additionally, the Biological Product Deviation (BPDR) reported on June 28, 2002 and the reported Fluvirin potency and pH stability test failures in the BPDR were incomplete and failed to provide FDA with significant information for timely evaluation.

Furthermore, the inspection noted that corrective action has not been implemented for the previous FDA 483 observation regarding the failed---------- System cleaning validation study CVR/0016/00 dated August 16, 2000. It was also noted during the observation of the formulation of A/New Caledonia Monovalent Blend Pool batch # 764984 on June 4, 2003 that ---- -batch endotoxin samples were not taken as required (per SOP ZY033A Release of ------ ---------- Concentrate to the Formulation Department including the - -day ruling) f---- days after the ---------- --- centrifugation run on May 22, 2003.

In addition, during the June 6th 2003 walk through of the firm's facility it was noted that there was no documentation in the batch record regarding missed stoppers or seals and there is no procedural requirement to do so. Also, 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 that this condition had existed or that repairs had been scheduled. Furthermore, 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 and 2 plastic yellow beakers used for holding forceps were observed scratched and yellowed.

Furthermore, deficiencies were noted in the sanitizer efficacy validation study protocols, batch records review, approval and batch release documentation. In addition, failure to have requirement for investigation of consecutive, repeated alert level sample results for water monitoring as allowed by SOP M154 Water Monitoring Excursion Reports was

noted. Also, deficient Fluvirin media fill simulations, adverse events (AE) investigation to determine if the adverse event may be related to the manufacturing process and failure to conduct temperature mapping study for the ---------- degrees centigrade) freezer were documented during this inspection.

At the close of the inspection, FDA-483, Inspectional Observations was presented to, Mr. Andy H. Sneddon, Site Director for Liverpool who identified himself as the most responsible official located at the firm even though Mr. Staph Bakali, Director of Operations for PowderJect Pharmaceuticals was present at the firm during the issuance and discussion of the FDA-483. Mr. Sneddon acknowledged the receipt of the observations and promised corrective actions. For a list of the firm's personnel present during the FDA-483 issuance, see **Exhibit #OOOA.**

HISTORY OF BUSINESS:

The firm continues to be a manufacturer of one licensed flu vaccine referred to as Fluvirin and other bio-pharmaceutical products that are not imported into the United States. It should be noted that Evans Vaccine is a Wholly Owned Subsidiary of PowderJect Pharmaceuticals with headquarters located at PowderJect Pharmaceuticals plc, Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA, United Kingdom. The firm's history of business including manufactured products remains the same as stated in the previous EIR of 3/01. According to Mr. John O'Brien, Head of Operations, the firm currently has ----- employees. He also stated that the firm's business hours are 8:00am to 4:45pm and manufacturing hours are usually 24 hours/day 7 days/week.

Per Mr. O'Brien, the firm made several significant changes in its officials since the last inspection of 3/01. Mr. O'Brien stated Mr. Jim Williams was added to CBER Official Correspondent for United States, and that Mr. Andy Sneddon currently holds a newly created position of Head of Manufacturing and Site Director replacing Mr. Joseph Caldwell who was previously the Managing Director of Evans Vaccine. Also that Mr. Simon Bryson Head of Quality replaced Peter Earps, who was promoted to the position of VP of Quality.

For documentation of the firm's interstate commerce provided by Dr. Tony Pawson, Quality Assurance Manager, see **Exhibit #OOOB**.

For a list of consultants provided by Mr. Tony Pawson, Quality Assurance Manager, see **Exhibit #OOOC.**

For a list of the firm's personnel that assisted the Investigators during the inspection and Firm's Annual Report, see **Exhibit #OOOD & E.**

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INDIVIDUAL RESPONSIBILITIES/PERSONS INTERVIEWED:

On June 2nd 2003, credentials of Omotunde O. Osunsanmi, CSO (Lead), Robert W. Jennings, CSO, and Jonathan McInnis, Biologist were presented to Mr. Andy Sneddon, Head of Manufacturing/Site Manager who identified himself as the most responsible official for Evans Vaccine manufacturing. Present during the credentials presentation were: Mr. Jim C. Williams, VP of US Regulatory Affairs; Mr. Simon P. Bryson, Head of Quality; John O'Brien, Head of Operations for Liverpool. Also, on June 3rd 2003 credentials of Ms. Robin Levis, Ph.D., Regulatory Coordinator were presented to Mr. Sneddon in the presence of the above named firm's officials. The investigation team was later introduced to Mr. Staph Bakali, Chief Operating Officer of PowderJect and member of the Board who was on one of his regularly scheduled visit to the firm.

According to Mr. Staph Bakali, Chief Operating Officer, he has been with the firm since year 2001. Per Mr. Bakali, he is responsible for the firm's overall operations, which includes quality assurance/assuring regulatory product compliance, environmental health, sales and marketing. According to Mr. Bakali, he visits this Evan's facility twice per month for two to three days. Mr. Bakali stated he reports directly to Mr. Paul R. Drayson, CEO and also a member of the Board. Mr. Bakali was not present during the inspection. **If necessary all Correspondences regarding this inspection should be sent to Mr. Bakali at his official business address of PowderJect Pharmaceuticals plc, Robert Robinson Avenue, The Oxford Science Park, Oxford OX4 4GA, United Kingdom and/or Mr. Andy Sneddon at the above firm's EIR official business address.**

Andy Sneddon, Head of Manufacturing/Site Manager: According to Mr. Sneddon, he has been with the firm since December 2001. Per Mr. Sneddon, he has Degrees in Pharmacy and Pharmacology. Mr. Sneddon stated he is responsible for this facility manufacturing, engineering operations, and business improvement. Also that he reports directly to Mr. Staph Bakali, COO. According to Mr. Sneddon, he is part of product recall committee and responsible for informing his superiors on product recall. Per Mr. Sneddon, he could spend up to - ---------- without prior approval for corrections to FDA-483 observations and to make improvements in the manufacturing facility.

Simon Bryson, Head of Quality: per Mr. Bryson, he has been with the firm since June of 2003 and has a degree in Biochemistry with Post-graduate Degree in Pharmaceutical Sciences. According to Mr. Bryson, he is responsible for all product quality activities at this facility, validation, quality systems/compliance, quality control, quality assurance operations and third party vendor quality assurance.

For the firm's current organizational chart as well as Quality Assurance/Regulatory Affairs organization charts, see **Exhibit #OOOF.**

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For maps of Evans Vaccine manufacturing sites provided by Mr. Tony Pawson, see **Exhibit #OOOG.**

CBER Special Assignment Requests:

(RL)

1) Review of Annual Report: Review of annual report for year 2001-2002 revealed no objectionable conditions.

(RL/RWJ)

2) Review of Biological Deviations:

Please see discussion under **Observation #s 7 & 8** of this EIR

(OOO)

3) Review of Complaints/Adverse Experience Files: No objectionable conditions were noted during the review of complaints for all Fluvirin vaccine products manufactured and distributed. For deficiencies noted during the review of the adverse event files please see discussion under **Observation #17** of this EIR.

(RL)

4) Review of Bovine Spongiform (BSE):

The firm does not use any bovine containing materials in their manufacturing process.

5) Product Shipping Validation:

(RL)

Please see discussion under (RL) titled “Discussion Items” of this report.

Corrections to Previous FDA-483 cGMP Inspection dated 3/09/01:

(OOO)

The inspection revealed the firm has adequately corrected Observation #1A, 1B, 2, 3, 4, 5, 6, 8, 9, 10, 12, 13, 14, 16, 17, 18, 19, 21, 22, 23, 24, 25, 26, 27, 29, 30 & 31.

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The following observations have not been adequately corrected: 1C, 7, 11, 20 & 28.

Observation #1C: T*he cleaning validation study for the ---------- --------- System (CVR/0016/00) failed to meet the acceptance criteria in at least one of the three runs for conductivity, formaldehyde or bioburden*. Please see discussion under **Observation #9** of this report.

Observation #7: *Inaccuracies were noted in the Master Production Records (Manufacturing Instructions MI) for Fluvirin…….*

Although the inspection noted that corrections were made to the observation, but the deficiencies noted during the previous EI continued as noted and discussed under **Observation #14** of this EIR.

Observation #11: *The-- ------ -- --- Vial Filler did not have a validated filling speed….*

Deficiencies were noted in the firm documentation of validation of the vial filling speed. It was noted that only the speed of the vial filling machine was validated, time, and pressure of the vial over seal were not part of the validation. In addition, there was no documentation that the operation parameters of the vial sealing machine per the SOP were reviewed and considered during the validation. Mr. O'Brien agreed with the observation and promised corrective action.

Observation #20: *During July through December 2000, 15 of 250 WFI samples collected revealed the presence of microorganisms. These samples were collected between 7:00-8:30AM daily when ambient loop - C began to cool down to ---C……..There is no provision for periodic steam or chemical sanitization of loop - C distribution.*

The inspection noted that the above observation was corrected. However, the review of SOP #GEP408 Version #1 dated 11/7/02 disclosed that the WFI loops are sanitized once every ----------. I informed Dr. Pawson that the whole WFI system should be sanitized at least once/year. Dr. Pawson agreed to consider my suggestion.

Observation #28: *There is no testing performed to determine the compatibility of the vaccine formulations with the manufacturing equipment.*

Please see additional discussion under **Observation #5** of this EIR on the inadequacy of the corrective action to the observation.

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Corrections to Previous FDA-483 Pre-Approval Inspection dated 5/11/01:

(RWJ)
Corrective actions to the FDA 483 issued for the PAI of May 2001 were covered and found to be generally adequate. No reporting of those determined to be fully adequate will be made. The corrective actions to an observation noted to be not fully adequate which required focused coverage during the current inspection included:

1. The corrective action included simply a brief post-event investigation report stating that no root cause was found for the three environmental excursions that resulted in batch rejection. There was no detail provided as to how the firm attempted to determine contributory factors to the excursions. Although the firm combined several types of deviations into the NCR system, the NCR SOP was noted to lack procedures for root cause investigation, including instructions for investigations which do not result in a clearly assignable route cause. Investigation procedures were reported on the current FDA 483.

PRODUCT COVERED DURING THIS INSPECTION:

(OOO)
Influenza Virus Vaccine (Fluvirin): The license holder for Fluvirin is Evans Vaccine, a sterile parenteral for intramuscular use. Fluvirin is a purified split virus preparation from the extra-embryonic fluids of embryonated chicken eggs which contain the virus that is harvested and clarified by centrifugation and filtration prior to inactivation with betapropiolactone. The inactivation is concentrated and purified by zonal centrifugation. Dr. Pawson provided me with lists of monovalent, trivalent and finished lots of Fluvirin manufactured since the last inspection, (**Exhibit #OOO1J & 1K)**. For Fluvirin manufacturing flow chart, see **Exhibit #OOOH.** For Fluvirin product insert, see **Exhibit #OOOJ.** For a list of Fluvirin distributors in the United States provided by Mr. O'Brien, see **Exhibit #OOOK.**

INSPECTIONAL COVERAGE:

This inspection was conducted in accordance with CP 7345.002 Inspection of Licensed Vaccine Product.

The following systems/areas were covered during the cGMP inspection:

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(OOO)
Adverse events/complaints/recalls, water system maintenance/trends, microbiology laboratory OOS, In-process/finished product failure investigations, validations of critical manufacturing parameters, e.g., bulks/buffers hold times, media fills/aseptic filling operation, cleaning validations and environmental monitoring/trending/excursions specific to manufacturing locations of Fluvirin product.

No significant observations were noted in the review of the trend data for water system maintenance and environmental monitoring.

(RWJ)
Coverage included, but was not limited to the following areas in addition to routine Compliance Program coverage: environmental/water monitoring & excursions, cleaning validation/cleaning procedures/sanitizer efficacy studies, smoke studies (observed for syringe filling line), batch records and quality batch review/release, sterility failures, re-filtration, non-conformance investigations, centrifugation, ultra-filtration, aseptic processing, working seed passages, re-fortification, quality management controls, stability program, Biological Product Deviation Reporting, process validation, and sterilization of vials/stoppers. In addition, set-up and formulation of monovalent/trivalent lots and set-up and vial filling operations were observed during this inspection.

(RL)
Inspection coverage included the following areas of the firm and product manufacture: Review of BLAs, process flow charts, Product Quality Specifications for bulks and final product, process validation studies, QA/QC GLP laboratories, BLA annual reports, annual product reviews, stability program and data for product, biologic product deviation reports, out of specification log and reports, process deviation log/ nonconformance reporting, rejected lots and batches released, review of BSE, and product shipping procedure and validations.

Unless specifically stated as an observation or a discussion item the review of the above items are satisfactory.

OBJECTIONABLE CONDITIONS/DISCUSSIONS WITH MANAGEMENT:

Prior to the discussion of each FDA-483 item, the firm's management was advised that the findings were observations made during the inspection. It was further stated that the conditions observed might be determined by the FDA after review of all the facts to be violations.

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1) The following monovalent lots with high levels of bioburden at the ---------- 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 $6.48x10^9$ 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 $3.29x10^9$ 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 $4.45 x10^{10}$ 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.

(OOO)
The review of failure investigations into flu vaccine batches for the year 2001/2002 flu campaign disclosed the above noted observations. The inspection noted that monovalent batches of flu vaccine with initially high bioburden levels after the ---------- step were re-filtered due to high bioburden levels before they were combined with the remaining two monovalent batches to make the final trivalent flu vaccine lots. The high levels of bioburden resulting in re-filtration/rework of the monovalent lots were brought to the attention of Mr. Tony Pawson, Quality Assurance Manager and he informed me that since the firm was informed during the last cGMP inspection that re-filtered flu batches are considered reworked and not to be distributed without CBER knowledge that none of the re-filtered monovalent lots were distributed in the United States. It was noted that the cGMP Inspection Report dated March 9th 2001 page #21, paragraph titled: Regarding Fluvirin reprocessing SOP states:

"The reprocessing SOP has been changes to reflect current procedures, and acceptance criteria. Medeva has decided not to include the re-filtration re-process step for Fluvirin distribution in the United States. If this step is required for the US lot they will submit the necessary information for approval prior to distribution. I asked that the SOP reflect that reprocessing step for re-filtration states that this is not yet approved for US Fluvirin lots".

Although the discussion took place during the inspection dated March 9th 2001, the above reference SOP #BLE024 dated December 20th 2002 titled: Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage was not revised until 12/20/02, **(Exhibit #OOO1L).** Also, re-filtration of Fluvirin lots continued after it was discussed with the firm

during the inspection. Per the review of the three re-filtered lots in the above Observation #s 1A, 1B & 1C non-conformance initiation dates for the lots high bioburden levels/re-filtration were: August 30th 2001, July 27th 2001 and July 19th 2001 respectively.

My review of the monovalent lots with the high bioburden levels and the final/released trivalent flu lots disclosed that some of these monovalent lots were indeed used in trivalent lots that were released into the US market as stated in the above observations. My concerns regarding the observations of high bioburden/re-filtered/reworked monovalent lots was discussed again with Dr. Pawson and I was informed that the firm has approval from CBER to re-filter Fluvirin monovalent lots and that the firm's regulatory affairs department was searching for the approval correspondence and will present me with the approval letter. I was also asked to give the firm's management time to review the rework/re-filtered approval documents in order to present me with chronological correspondences with CBER regarding re-work/re-filtration of monovalent flu batches. As such, time was set for the presentation of the documentation for later on during this inspection.

The presentation of the presumed approval letter for re-filtration was presented by Simon Bryson, Head of Quality and Dr. Pawson in the presence of Mr. John O'Brien, Head of Operations. Per Mr. Bryson, the firm does not have documentation of an approval letter from CBER to re-filter monovalent flu batches. He further stated that after the inspection of 3/01 when the discussion on re-filtered batches were raised the firm was informed by the Investigations that CBER notification regarding re-filtered monovalent batches was needed before the final vials of the trivalent lots could be distributed. Per Mr. Bryson, the firm responded to CBER with reworked/reprocessed SOP and the firm's assumption was that it was okay to re-process monovalent lots with high bioburden levels. He stated that after further consideration in year 2002 the firm decided not to re-filter any monovalent flu lots designated for US distribution. He also stated that the noted re-filtered lots that went into trivalent lots and final vials for US distribution as noted by me during this inspection were released into US market by mistake. Mr. Bryson promised immediate corrective actions.

The inspection noted that at least 6 re-filtered monovalent lots that were further processed into trivalent lots were filled into final vials with some of these lots packaged for US market distribution. For example:

The inspection noted that monovalent A/Panama batch #760351 with total bioburden volume of 6.48×10^9 cfu was re-filtered into lot #760591 and was used in the formulation of trivalent lot #s: 760688, 760641 & 760640 and in at least final Fluvirin released lot #E10821LA. For initial monovalent batch record #760351 and evidence that the lot was re-filtered into lot #760591 and documentation of bioburden levels test results for before and after re-filtration, see **Exhibit #OOO1A1, page #1 & page #8, 12-15**.For, trivalent

lots 760688, 760641 & 760640 that were made from re-filtered lot # 760591, see **Exhibit #OOO1A2, 1A3, 1A4, 1F & 1G**.

Furthermore, monovalent A/New Caledonia batch 759931 with total bioburden volume of $3.29x10^9$ 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. For initial monovalent batch record # 759931 and documentation of bioburden levels test results before and after the re-filtration process, see **Exhibit #OOO1B1 page # 8-10,** For trivalent batch records for 760843 & 762920, see **Exhibit #OOO1B2, 1B3, 1F & 1G)**. Please note the indications on **page #1 of Exhibit #OOO1B1** that batch #759931 was re-filtered into lots 760137 for further processing.

Also, monovalent A/Panama batch #759864 with total bioburden volume of $4.45 x10^{10}$ 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, For initial batch record 759931 with indications on page #1 of re-filtration into batch # 760136 and documentation of bioburden levels test results before and after lot was re-filtered, see **(Exhibit #OOOC1, page #7-9.** For the use of this lot in the trivalent formulation lots761025 & 761095 that were eventually released into US market, see **Exhibit #OOO1C2 & 1C3, 1F, & 1G).**

For a list of OOS monovalent flu lots that were re-filtered and further manufactured into trivalent lots and distributed into USA and Rest of the world, see **Exhibit #OOO1D**. It should be noted that monovalent lots that were further manufactured into trivalent lots and distributed in the USA/Rest of World were designed as such by Dr. Pawson in red pen.

For a list of monovalent lots that were re-worked/re-filtered provided by Dr. Pawson, see **Exhibit #OOO1E**. It should be noted that not all of the listed re-worked monovalent lots that were manufactured into trivalent batches were distributed in the USA.

For listing of monovalent/monoblend lots and the newly re-assigned lot number after re-filtration for year 2001/2002 including the final/finished Fluvirin vial lots that the monvalent lots with high bioburden levels were used and referred to on the list as “Pack Lot”, see **Exhibit #OOO1F & 1G.**

For a list of manufactured rejected trivalent lots, see **Exhibit #OOO1H**.
For listing of all trivalent bulk/vials flu vaccine distributed in the USA for the year 2001/2002 with indications of re-filtered lots by Dr. Pawson, see **Exhibit #OOO1J &1K.**

For SOP #SP155 dated April 19th 2003, titled: General Procedure for Performing Rework Operations in all Areas, see **Exhibit #OOO1M.**

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Pre Mr. O'Brien and Dr. Pawson, the firm's rationale for releasing monovalent lots with high levels of bioburden after it meets the bioburden specification of <---- cfu after re-filtration was based on---------- validation of microbial retention of the ----------µ---------- filter, **(Exhibit #OOO1N).** Per Mr. O'Brien/Dr. Pawson and as stated in the investigation report conclusions of the monovalent lots with high bioburden levels: the monovalent lots were successfully filtered because of the bacteria retention capacity of ------ and ---------- total surface volume of the sterilizing filter used. According to Mr. O'Brien and Dr. Pawson, the filtered lots bioburden levels were within the validated limits of the filter's retention capability of ---------- for bioburden, **(Exhibit #OOO1A1, page #8 & 12-15, 1B1-3 page #8-10 & 1C1-3 page #7-9).**

D.) There is no procedure that requires stability assessment of re-filtered batches, including SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage (Ex R-1). The only stability study that included re-filtered batches, R/0184/07/00 (Ex R-2) 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.

R-1 SOP BLE024 Fluvirin Reprocessing at Monovalent and Trivalent Blend Stage
R-2 Protocol R/0184/07/00

(RWJ)
Concerns expressed by Investigator Osunsanmi, reported as observations 1a-c, resulted in a reply by Simon Bryson that the firm had stability data to support re-filtered Fluvirin. The data supplied by the firm was the study R/0184/07/00 which John O'Brien stated was the only stability data the firm had generated for re-filtration.

Discussion with O'Brien revealed that the study was a routine stability program performed in 1999 that happened to include 2 lots that were re-filtered-the protocol was not designed as a validation protocol for re-filtration.

Current stability data for re-filtration does not fully support the process and there are no considerations for product changes from season to season.

We discussed the possibility of designing a protocol to place the next series of re-filtered lots on stability and obtaining concurrence from CBER. Firm reps stated that no re-filtered lots would be distributed prior to submission of a CBE-30 to CBER with stability data.

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2) Control and failure investigations into bulk Fluvirin monovalent blends/lots at ---------- step with high levels of bioburden is deficient, in that lots were noted with total volume of high bioburden levels of e.g., 9.66x10 ^{6} cfu, 7.07x10^{7} cfu & 1.26 x 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.

(OOO)
The inspection noted that the firm has been experiencing high levels of bioburden since year 2000 per previous inspection reports and this inspection. The review of the bioburden levels non-conformances noted that in most instances failure investigations were conducted into individual occurrences. The noted preventive action-to prevent reoccurrence of non-compliance indicated on the Non-conformance Investigation Report Form included in SOP #SCP009 dated September 9th 2002 revealed the following notations on at least three collected non-conformance reports: "Not Applicable", "None" & 'None", **(Exhibit #OOO1A1 page #3, 1B1 page #3 & 1C1 page #3).**

The inspection noted that on the individual non-conformance reports that were review no attempts were made by the firm to investigate the root cause of the higher than expected bioburden levels. In addition, there was no documentation that the firm opened a formal investigation into the high levels of bioburden levels to find the root cause and eliminate the potential source/sources of the contaminations. For SOP #SCP009 dated 9/9/02 titled: Non-conformance Investigations, see **Exhibit #OOO2A.**

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.*

The review of high bioburden Fluvirin lots and justifications for the release of these lots revealed that decisions to release lots with high bioburden levels for further manufacturing into trivalent lots were not based on the review of the pathogenicity of the organisms identified. Although the organisms in the sampled lots were isolated and identified, and the results of the sampled re-filtered lots were within bioburden specification of ------ cfu however, the decision to release the monvalent lots for further manufacturing failed to include the review of the identified organisms ability to cause serious illnesses and/or types and levels of toxicity production that could be harmful to humans, **Exhibit #OOO1A1-4, 1B1-3 &1C1-3.**

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 (Ex R-3) and batch # 761650 dated May 2002 (Ex R-4) implicated aseptic connections as potential root causes but failed to result in procedural requirements for environmental monitoring during all aseptic connections and evaluation of possible reductions in the number of aseptic connections.

R-3 NCR 2002/618/07 lot # 762492
R-4 NCR 2002/163/07 lot # 761650
R-5 NCR SOP SCP009

Note: Monovalent batch # 762492 was re-filtered into batch # 762635 (not batch #762835).

(RWJ)
The QA investigation for NCR 2002/618/07 for batch # 762492, page 4/5 for Manufacturing Areas states "there is a possibility that the monovalent blend pools could have become contaminated during aseptic connections." The NCR Conclusion, page 5, states "the most likely source of the contamination is from aseptic connections within then Formulation area." Corrective actions were reported as only maintenance of aseptic operator's gowning and aseptic procedure qualifications. There was no discussion of aseptic connection procedures or monitoring.

The QA investigation for NCR 2002/163/07 for batch #761650 reports two possible routes of contamination, rotors during centrifugation and operators during formulation. The Actions section states to "review the applicability of reducing the number of aseptic connections during the filtration process." There is no evidence in the NCR of corrective actions taken or studied.

There was little evidence that corrective actions were investigated for sterility failure investigations in NCRs reviewed.

The NCR SOP SCP009 states that is the responsibility of the appropriate Manager and QA Manager to follow-up any corrective and preventive actions raised. The SOP, sections 7.16-7.20, includes CAPA instructions. However, there are no specific instructions that detail how proposed corrective actions will be discussed, implemented (or not) and closed in NCR reports.

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. Active viable and non-viable monitoring was initiated at least one hour after all connections were made including those to the---------- unit which are made in Class ----------conditions ---------- .

R-6 Manufacturing Instruction lot# 764984

(RWJ)
I observed the set-up for Monovalent formulation of New Cal lot# 763984. There was no monitoring during the aseptic connection process. Previous investigations implicating aseptic connections in bioburden and sterility failures did not result in monitoring of connections.

C.) Klebsiella oxytoca was isolated in the Centrifugation -------batch 762450 and the ---------- Zonal Concentrate batch #762451 that went into batch #762492. K. oxytoca was also isolated in the----------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.

(RWJ)
NCR 2002/618/07 (Ex R-3) reported the information cited. In addition to the lack of investigations of previous EM results and water monitoring, sterile filtration validation, cleaning validation and additional potential routes of contamination by equipment, cleaning agents and personnel were not investigated.

Concerns were expressed that the organism was repeatedly isolated throughout the process, even after the sterile filtration process.

Firm reps had no explanation for these occurrences but pointed out that this had not occurred regularly.

D.) From February 28 2002 to July 5, 2002, 14 ---------- 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.

R-7 ---------- Isolates 2002 and 2001

(RWJ)

Again, NCR 2002/618/07 (Ex R-3) is the investigation cited. The number of contaminated ---------- lots is less than 10% of lots processed. However, ongoing issues with the ---------- system have been reported in both previous and current inspections. The firm reviewed the possibility of changing to a different ---- system but was still using the ---------- during the current inspection with the historical cleaning procedure. Review of the contaminated batch microbial isolate data also demonstrated 14 batches contaminated with Serratia spp. from March 2001 to July 2002. Several additional batches were contaminated with Enterobacter spp.

Although firm quality reps stated that the contamination issues were repeatedly discussed at meetings, there was no summary investigation report of the issues.

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

R-8 Log of sterility OOS results 2001-2002
R-9 M198 Sterility Investigation Reports
R-10 M001 Sterility Testing
R-11 SIR 02/002 batch #761650 2/02

(RWJ)
There were no sterility failures for filled vials. Failures occurred at the monovalent blend pool stage, including after sterile filtration, however:

Procedures for investigation of sterility failures including M198, Ex R-9, and M001 Sterility Testing, do not provide clear instructions for the initiation of retest after an initial test reported contamination.

For example, the Sterility Investigation Report SIR 02/002 for Batch # 761650 in February 2002 simply reported that an initial test failed and a retest was performed. There was no justification for the retest and results were reported as valid.

Simon Bryson stated that improved sterility investigations were a priority upon his arrival at the firm in 2002. It appeared that investigations had improved in completeness in 2003.

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

(OOO)
The review of the cGMP FDA-483 dated March 2001 revealed that the following Observation #28 was cited:

"There was no testing performed to determine the compatibility of the final vaccine formulations with the manufacturing equipment".

Also, the Pre-approval Inspection of May 11th 2001 cited Observation #11 as follows:

"There were no extractable studies performed on-------- tubing used in the filling of the product".

The inspection revealed the firm's failure to conduct comprehensive review of its operations in relation to previously cited observations to assure adequate corrective actions. For example, the firm failed to include the filter compatibility/extractable studies in its corrective action to the above observations noted during the Pre-approval/cGMP inspections. The review of the filter compatibility and extractable studies disclosed that the firm has not conducted compatibility and extractable studies for the ---------- ----- μ------ ---------- filter. The filter is used in the filtration of the monovalent lots and the final aseptic filling of the trivalent lots. Dr. Pawson and Mr. O'Brien agreed with the observation and promised corrective actions.

The inspection noted that the firm conducted corrective action to the May 2001 PAI observation. However, deficiencies in the corrective action were noted as discussed in Observation #5B above. The inspection also noted that the ---------- ---------- Tubing used throughout the Fluvirin manufacture process to transfer centrifuged, formulated, and finished products for filling was out of specification of --- mg for USP Non-Volatile Residue with result of 1327 mg per---------- test result, **(Exhibit #OOO5B page #3)**. However, no investigation, corrective and preventive action has been conducted and no justification/rationale is provided for the lack of investigation. I

informed Mr. O'Brien that after the tubing test result was OOS for USP specification of --- mg for Non-Volatile Residue with results of 1327mg that the firm should have provided documented justification for the continued use of the ---------- tubing as well as future planned corrective action. Furthermore, I suggested to Mr. O'Brien that the firm could show through documented studies that the level of the ---------- tubing non-volatile residue is within acceptable level in the monovalent/final product.

Per Mr. O'Brien, the firm is currently testing other tubing with Fluvirin to determine compatibility. Mr. O'Brien also promised corrective action to the observation.

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

R-12 Summary Report Investigation into Fluvirin Stability Results

(RL/JM/RWJ)

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.

This observation was made by Jonathan McInnis and written by Robert W. Jennings

(JM)
Evans presented for review a summary of experiments performed to investigate the problem of loss of potency in the New Caledonia (H1) component of their trivalent vaccine in both the 01-02 and 02-03 flu seasons.

The summary also included test results and information regarding ---------- levels found in some the lots failing stability. The summary appears to fully address the --- issue, presenting an outline of their experimental approach and providing supporting data. Evans has theorized that ---------- from the ---------- in the Ready-ject Syringe (RS) presentation of the vaccine in the form of ----- ---------- is reacting with components of the vaccine to produce -- ---------- ---------- ---------- causing a ---------- . Based on the results from these studies, Evans is ---------- ---------- ---------- for the upcoming flu campaign.

The summary, however, does an inadequate job of addressing the loss of potency issue. Evans theorizes that a problem with reagents from CBER, namely the reference antigen, is causing the potency of the H1 component of their trivalent to appear subpotent. A

matrix type study was conducted wherein reagents from CBER are compared with reagents from National Institute for Biological Standards and Control (NIBSC) using several different reagent combinations, **(Exhibit R-12, page# 11)**. The study does demonstrate that differences do exist between the reagents but the implication that the CBER reference antigen is the causative agent is not supported as the study can not identify which of the reagents is responsible for the differences.

These issues were discussed with Evans and during a presentation to the inspectors, Evans has acknowledged that they are unable to identify the root cause and that they will formulate their trivalent bulks with a higher H1 concentration to assure that they remain at or above the potency specification throughout the dating period.

(RWJ)
The investigation Summary Report states that "there is currently no explanation for the differences in potency results obtained using reagents from CBER, NIBSC and TGA-consideration is being given to further investigative work on this issue at the molecular level. "

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.

R-13 Appendix 14 of the Fluvirin stability investigation
R-14 BPDR summary table

(RWJ)
There is no identification of the full scope of 2001/2002 batches reviewed in the report. A 2000/2001 pH failure for lot# E59230GA, reported in a BPDR summary table (Ex R-14) was not included.

According to the firm representatives, an extensive root cause investigation was performed. There was no evidence of the investigation in the investigation 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.

Ex R-12 is the summary report. It is not signed nor 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.

R-15 Clinical Expert Report draft dated September 4 2002

Ex R-15 is the draft Clinical Expert Report. It is not signed nor dated and the author is not identified in the report. Additionally, there is no evidence a final report was generated, signed, reviewed and approved by QA.

The conclusion of the Clinical Expert Report, after repeated stability failures for ph and potency for Fluvirin, states that "the available data does not suggest any significant drop-off in immunogenic for HA content in the range of ----------ug/ml. In particular, the A/New Caledonia strain used in the Fluvirin 2002/2003 formulation has been tested at concentrations as low as 1----ug/ml with a good retention of immunogenicity."

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,

R-16 BPDR submitted June 28, 2002
R-16A Stability Policy Document SCP041

(RWJ/JM/RL)
This observation was made and written by Robin Levis, Jonathan McInnis and Robert Jennings.

(RWJ)
The concerns expressed in this observation and related discussions included the failure to submit information necessary for timely FDA review. In particular, the limitations of the BPDR reporting requirements (45 days), combined with the limited shelf-life of Influenza vaccine and the further limited use period, usually less than 6 months, was discussed. It was pointed out to the firm the importance of early and timely reporting of potential issues. In the case cited, the first and really only potency failure information that was likely to impact current supplies and the current flu season, was not reported to FDA. Additional information was not reported. Management was encouraged to discuss these issues verbally with CBER product specialists as soon as they arose and management agreed.

(JM)
As a subpoint to the stability failures, review of the Evans 2001 Annual Report revealed that during the 2000-2001 flu season several stability test time points were missed for multiple batches (E12201MA-no data for months 1,2,3 or 6; 759881-no 1 month data;

759819 and 759872-no 2 month data). Considering the problems with failed stability lots and the sparse number of lots in the program, it is notable that some testing was not conducted as required. When asked why the tests were not conducted the Evans' response was that they were simply overlooked. It was recommended that Evans be more diligent in this area in the future and also to add more lots to their stability program.

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 --- mcg HA per SRID), were submitted.

R-17 Table 1 Fluvirin Stability pH and SRD data (2001/2, 2002/3)

(JM/RL/RWJ)
The BPDR did not include specific test results and none were submitted via follow-up reports. Ex R-14 is a summary of data pertinent to the BPDR that was not submitted. similar presentation is Table 1 Fluvirin pH and SRD A/New Caledonia stability data Ex R-17. At least 5 lots failed SRD in 2002/3 on stability.

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.

R-18 Stability Report for lot# E00931HA

(RWJ)
Ex R-17 shows the failure of lot# E00931HA at the 6-month time-point. This was not included in the BPDR summary document prepared for this inspection. Per John O'Brien and Lisa Bissett, Stability Manager, 26.8ug was not considered a failure. However, the firm had no rounding procedure and there is no documentation that the test result was reviewed and dispositioned a pass. Per the firm reps, the result would now be considered a failure.

However, the stability report for lot#E00931HA states in the Discussion section, page 7, the SRD assay at the 6, 9, 12 and 13-month time points for A/New Caledonia did not comply with the specification at these time points. The stability report references the reported BPDRs in June and September 2002 but fails to explain the exclusion of the failure at the 6-month time point.

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SCP041 Stability Policy requires reporting and evaluation of all results and missed time points.

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.

(RWJ)
Ex R-17 shows the missed time points as (-) dashes. The additional data is also presented for lot #s E11371LA and E12201MA which both failed at 7-months in May 2002. The information is included in the specific stability reports for these lots, Exs. R-19 and R-20.This information was not included in the June report but was included in a follow-up BPDR report in September (Ex R-21), only on a limited basis.

R-19 Stability Report Lot# E11371LA
R-20 Stability Report Lot#E12201MA
R-21 BPDR September 4, 2002

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.

(RWJ)
Ex R16 shows the failure of Fluvirin pH on stability for lot#E34652KA at the 3-month time point in December 2002. Firm reps stated that they did not consider it necessary to report additional failures once a BPDR had been submitted indicating that additional failures were likely.

I stated the firm was expected to submit a detailed follow-up report appending data to the original report.

9) Corrective action has not been implemented for the previous FDA 483 observation regarding the failed ---------- 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 ---------- Monovalent Blend Pool lots failed bioburden testing.

R-22 Response to Inspectional Observations issued on March 9, 2001

(RWJ)
The observation reported that the cleaning validation did not meet acceptance criteria and the response stated that their evaluation "concluded that there is no impact upon the quality, potency and safety of the Fluvirin processed by the ---------- ." The response also stated that a draft protocol for Cleaning of the---------- System was attached. The ---------- system was never implemented.

As discussed above in observations 2 and 4, bioburden issues have repeatedly arisen ---------- - . The firm has failed to fully correct these issues.

B.) Validation protocol for the executed study CVP/0011/03 dated April 7, 2003 (Ex R-23), changing the sanitizing agent to ---------- ---------- , did not include bioburden reduction by assessing microbial load prior to use or storage between use.

(RWJ)
The firm decided to execute an additional cleaning validation study on the----------, CVP/0011/03, Ex R-23 and attempt to validate cleaning with ---------- --------- The firm simply executed a study under routine use but there is no information on pre-load bioburden or storage conditions between uses.

C.) Design and operation of the---------- filtration unit located in the Formulation area allows operator error to potentially reverse the flow of product under filtration. The---------- 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.

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R-24 BLE022 Operation of---------- System

(RWJ)
This condition was noted during observation of formulation operations. The tape is not included in the SOP for operation of the ---------- . This condition was reportedly corrected during the inspection and training was pending.

10) It was noted during the observation of formulation of A/New Caledonia Monovalent Blend Pool batch # 764983 on June 4, 2003 that sub-batch ---------- samples were not taken as required (per SOP ZY033A Release of ---------- Concentrate to the Formulation Department including the - -day ruling) ----- days after the ---------- ------ 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.
Note: The batch # observed was 764983 not 764984.

R-25 Partial batch record for New Caledonia lot# 764983 blending
R-26 Release of ---------- Concentrate to the Formulation Department including---day ruling.

(RWJ)
During the observation of formulation of New Caledonia lot# 764983 blending on June 4, 2003 I asked the procedure for monitoring endotoxin during ---------- ---------- - batches. The firm has an SOP for Release of the ----------Concentrate to the Formulation Department including - -day ruling, Ex R-26, which requires - ---------- sampling and testing every - days (section 7.8 of the SOP). These samples were not executed for lot# 764983 prior to blending. There was no procedure to assure the samples were taken prior to formulation.

The firm had initiated an investigation to determine if additional batches were implicated in this oversight as well as SOP revisions after this observation and before the closeout of the inspection.

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

R-27 P/0097/04/03 Filling Instructions for Filling of Fluvirin containing different preservatives

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

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(RWJ)
This observation applies to both routine filling, and media fills. I noted missed stoppers and seals on the turntable. They are not documented.

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.

(RWJ)
Filling on June 6, 2003 was the first filling on the Fluvirin line for the 2003/2004 campaign. The open panel remained from the maintenance period. However, there was no information as to whether it may have been open last year or would have been corrected without the observation.

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.

(RWJ)
In order to retrieve tipped vials it is necessary for an operator to enter an arm into the LFU. With the current design of the LFU unit, an improved practice would be to breach the laminar flow through the curtains without pushing the curtains into the LFU, if possible. If this proved difficult, another possibility would be to redesign the barriers and place plexi-glass “Perspex” in the U.K., on the unit. This was discussed with the firm reps.

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

(RWJ)
This observation was reportedly corrected during the inspection although preventive training had not been executed.

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.----------) 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.

R-28 R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi
R-29 SCP017 Approved Cleaning and Disinfectant Agents

(RWJ)
The combined sanitizer efficacy studies failed to address all the cleaners used in current SOPS, i.e. SCP017 Approved Cleaning and Disinfectant Agents, Preparation of Working Strength Solution and Rotation Policy, Ex R-29 and materials noted during tour of the filling and preparation-for-filling areas.

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.

(RWJ)
The conclusion of the study is that "although --- ---------- and----------did not achieve minimum requirements….the activity achieved would be sufficient to effectively "kill" the resident microbial population, with the exception of *Bacillus licheniformis and Aspergillus versicolor. "*

The firm reportedly planned additional studies.

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.

This observation was made by Robin Levis (RL) and written by Robert W. Jennings. (RWJ).

R-30 Protocol PVP/0005/01 Determination of the effects of Maximum Holding times on the potency of Fluvirin April 2001
R-31 Report PVR/0005/01 dated January 2003
R-32 SOP VAL002 Executing Validation Protocols

(RWJ)
The firm's procedure for validation studies VAL002 states that in the event an error is found in a protocol a Validation Comment Form must be completed (Section 7.9.3.) Firm reps stated this procedure was not followed but is intended to include protocol deviations during execution in addition to significant issues identified in protocols themselves. The written procedure does not explicitly state that Comment Forms also apply to protocol deviations

(RL)
In addition to not including a protocol deviation report, the process validation report, R-31 PVR/0005/01 dated January 2003, is misleading in that the discussion of results obtained did not take into consideration that data is missing from the final analysis. The firm stated that the scope of report discussions will be expanded to include deviations and all events which influence the outcome of the study.

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 Ex R-33 (not in SOP QASP093 QA Procedure for Review of Finished Product, Ex R-34) and Fluvirin Trivalent Vaccine Product Release Checklist Ex R-35(not in SOP PRG020 Release of Finished Products from Quarantine Ex R-36), i.e. Trivalent batch # 762834, filling batch #762925 and Packing batch #E31192HA released September 4, 2002.

R-37 Product Release Checklist for Packing lot E31192HA dated September 4, 2002.

(RWJ)
Review of the firm's release procedures revealed a lack of assurance that all deviations were reviewed prior to batch release. Worksheets for bulk and finished product release were not included in written release procedures. Only three batches were briefly reviewed for identification and review of deviations prior to release.

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

R-38 Corrected sterility test NCR in the batch record for lot# 762834

(RWJ)
QA reps corrected the sterility test document on June 9, 2003 by crossing out the incorrect NCR referenced (2002/969/03) and documenting the correct NCR 2002/1052/02.

The incorrect NCR was reported by QC and not identified by QA during batch review.

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# --------- Evans - ¨ passage dated October 25, 2002.

R-39 Batch Record -------- dated 10/25/02
R-40 MI0350 Passage of Influenza Seed Material

(RWJ)
The firm labeled the passaged working seed vials but the labels were not put into the batch records. The Manufacturing Instruction MI0350 does not require it.

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.

This observation was made by Robin Levis and written by Robert W. Jennings (RWJ).

R-41 NCR/827/02 dated September 5, 2002
R-42 Filling batch record, selected pages, lot# 762838 June 7, 2002.

(RWJ)
The firm initiated an NCR, Ex R-41, for a leak during filling that required aborting of the fill. The batch record for lot# 762838 did not report the incident. The NCR was closed 3 months after the incident.

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.

R-43 M154 Water Monitoring Excursion Reports

(RWJ)
The firm proposed to correct this deficiency by establishing a sampling rationale for alerts. The SOP M154 has no requirements for investigation of repeated alerts.

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

A) Media fill simulations are not representative 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.

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.

(OOO)
The review of the Fluvirin media fill simulations disclosed that from year 2001 to 2002 the firm had no media fill failures, **(Exhibit #OOO16A1).** However, the review of the media fills/aseptic fills batch records disclosed no assurances that media fill simulations are representative of routine aseptic filling processes. In addition, there are no documentation in the media fill batch records that interventions, which occurred during routine aseptic filling processes were incorporated into the media fill simulations, **(Exhibit #OOO16A2 & 16A3)**. In addition, it was noted that SOP #SCP029 dated September 9th 2002 tilted: General Procedure for Routine Monitoring of Aseptic Manufacturing Process Simulation Utilizing Sterile Media fills, failed to include the requirement to simulate interventions that occurred during aseptic filling processes. Furthermore, it was noted that SOP # SCP029 dated 9/9/02 failed to require or specifically state/define the simulation of worst case conditions that are to be conducted during media fill simulations, **(Exhibit #OOO16B).**

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.

(OOO)
The review the adverse event files with Ms. Vivian Pearce-Higgins, Manager Pharma-co-vigilance in the presence of Mr. Jim C. Williams, Vice President of US Regulatory Affairs, disclosed that all adverse events were reported to FDA within the allowable time frames. Further review of the adverse event files revealed the above noted observations and the firm's failure to review the implicated lots manufacturing deviation reports/failure investigations to assure that they were not related to the Fluvirin reported adverse events, **(Exhibit #OOO17A, 17B & 17C).** For a listing of adverse events for year 2001/2002 showing the number of reported adverse events/lot, see **Exhibit #OOO17D.**

The review of the firm's Adverse Events SOP #MA 4901 dated June 18th 2001 titled: Processing, reviewing and expedited reporting of adverse events for marketed products, revealed the SOP has no requirements for when manufacturing process investigations are to be conducted when several adverse events with similar lot numbers/different indications of adverse events are received from the same healthcare facility/doctor or when adverse events with the same lot number/similar reported adverse events are received from several healthcare facilities/doctors, (**Exhibit #OOO17E**). During the inspection, draft corrections to the SOP to incorporate the above concerns regarding requirements for the review of manufacturing deviations/failure investigations was presented to me by Ms. Pearce-Higgins, **(Exhibit #OOO17F)**. Although no evidence of personnel training was presented the corrections to the Adverse Events SOP was found to be adequate.

18) Temperature mapping study has not been conducted for the --- ---------- degrees centigrade) freezer, Serial ---------- 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).

(OOO)
For Protocol # IOQP/0040/03 dated 5/19/03 for the qualification of the freezer, please see **Exhibit #OOO18A.**

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 ------ 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 ------ 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 ------ 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.

(OOO)
The review of Fluvirin finished vials inspection closed that the 100% visual inspection and re-inspection of finished Fluvirin vials defects are not based on acceptable statistical sampling plans. It was noted that all of the defects, e.g., particles, glass, seals, broken glass, and vial product volume are all based on - ----- reject/accept rate. Also, the inspection revealed that the reject/accept rate is not based on review of historical data but based on ------ reject/accept rate that was used to set the initial limits, **(Exhibit #OOO19A, page #3).** In addition, the inspection revealed that 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 ------ as the initial 100% visual inspections per SOP #IN017.VI dated 9/13/01; General Procedure for Performing Re-examination in Manual and Semi Automatic Inspection, **(Exhibit #OOO19A page 3-4).**

Furthermore, the inspection noted that 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, **(Exhibit #OOO19A page #3).**

The review of the firm's quality assurance control over the inspections of finished vials disclosed that there is no Quality Assurance control/verification and/or over site of the 100% finished vials inspection for defects that are performed by manufacturing. Mr. O'Brien promised corrective action to all of the finished Fluvirin vials inspectional observations cited above.

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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.

(OOO)
The review of SOP #IN018 dated 5/25/03, titled: Inspection Assessment disclosed the above noted Observation #20, **(Exhibit #OOO20A).** The review of the SOP and deficiencies were reviewed with Dr. Pawson and he promised corrective action to the observation.

DISCUSSION WITH MANAGEMENT:

The following verbal observations were reported by RWJ to management:

- Smoke study video observed for syringe filling line lacked, in some instances, a demonstration of vertical laminar from the filter face to the work surface. (It was recognized that this was difficult to demonstrate in this study due to the small areas in the filling cabinet.)
- Vial-filling area-torn ------ - curtain outside tank transfer room; one -------- curtain outside cabinet edge stopper bowl cabinet/filling cabinet interface-where non-viable monitoring line entered cabinet; station for check weights is located in Class ------- - room outside the filling room requiring numerous (10+) trips into and out of the filling room during set-up and start-up operations.
- Supporting records were not attached to EM excursion reports, i.e. EMER/03/FORM 004
- Current Calibration/qualification status was not reported on critical equipment, i.e. LF Hoods

Observations made by Investigator Robert W. Jennings were discussed primarily with John O'Brien, Head of Technical Services and Simon Bryson, Head of Quality. Stability issues were also discussed with Lisa Bissett. There was general agreement regarding the reported facts of the observations and requirements for corrective actions. Firm representatives made a point of both expressing the firm's intent to correct cited deficiencies and also, where possible, to discuss proposals for correction and demonstrate early corrective actions, if applicable.

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The following verbal observations were reported by JM to Management:

Mislabeled samples sent to CBER

Each monovalent batch is tested for potency at CBER. Samples from Evans are sent to DPQC and subsequently forwarded to the CBER flu lab for potency assignment. This season and last, CBER flu lab received mislabeled samples (i.e. vials labeled as B/Hong Kong actually contained A/New Caledonia) from the firm. Review of the samples mislabeling documentation during this inspection revealed that no NCR was issued on the previous/last season mislabeled occurrence, but NCR was issued for this season occurrence. The review of the issued NCR disclosed it did not contain any information for corrective actions. Additionally, no formal procedure or SOP exists to describe how the sample is collected and checked for accuracy in labeling prior to shipment to CBER. It was recommended that a system be implemented to eliminate this type of error.

Refortification of lots

The inspection team recommends that lots that have been refortified by Evans have an indication on the protocols sent to CBER that a reworking has occurred on that particular batch. This information would be useful to have at CBER to investigate any lots that appear subpotent.

The following verbal observations were reported to management by RL:

- Review of OOS report # V/OOS/2001/033 showed that two copied data sheets contained in the OOS report had been altered after initial use. No explanations for these alterations were included in the OOS report. (The firm was able to explain the alterations and will update the way in which data sheets can be altered.)
- A general review of the OOS reporting system shows that since the CBER inspection held in 2001, the reporting of OOS results and follow-up investigations has gotten better. The nonconformance reporting (NCR) documents are much more thorough and inclusive of information than the OOS reports. (The firm has drafted a new SOP for generating OOS reports which will update the way these results and subsequent investigations are handled.)
- During inspection of the warehouse and cold storage ------- ° C) facilities many large, unmarked containers were present in the cold storage. These containers held retain samples from -------- left over from a previous arrangement. It was suggested to the firm that the containers be labeled as to the contents and to the expiration or end of hold time. (The firm stated that the samples would be either correctly labeled or disposed of.)

- Review of the process validation report for study POP073 to evaluate the maximum time allowed for holding product at intermediate stages showed that an error in study execution occurred. (See 483 observation #13.) Samples from the normally processed lot were not retained for stability testing. In addition to the observation sited, the error in sample retention led to the acceptance criteria for the study not being met and the validation failed. It was suggested that the firm requalify this assay or consider repeating this validation assay.
- Review of the stability program showed several areas that needed to be changed.
    - Lots selected for inclusion in the stability program are not selected on a random basis. It was suggested that a system be developed for selecting lots for stability testing that was unbiased. (The firm developed a lot selection method that was satisfactory.)
    - The stability data collected to date on the flu strain New Caledonia A suggest that this strain is less stable than other strains included in the vaccine. To ensure the potency of New Caledonia A in the product for this season, it was suggested that the firm increase the amount of this strain included in the product. (The firm agreed to add at least --- micrograms/dose [an increase of -----] of this strain.) In addition, it was suggested that stability surveillance on this strain be increased to include an additional lot put on stability early in the manufacturing campaign and additional testing of the product early in the shelf life. (The firm agreed to implement this additional testing.)

ATTACHMENTS:

1) FDA-483 dated 6/02/03 issued to, Mr. Andy Sneddon, Head of Manufacturing /Site Director Liverpool.

2) CBER Assignment dated 5/16/03

EXHIBIT #OOO:

A) List of firm's personnel present during the FDA-483 close out discussion
B) Interstate Records
C) Consultants used for Fluvirin
D) List of firm's personnel that assisted Investigator during the inspection
E) Firm's Annual Report for year 2002
F) Firm's Organizational Chart
G) Manufacturing building diagrams
H) Fluvirin Manufacturing Flow Charts

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I) No Exhibit
J) Fluvirin Product Insert
K) USA Fluvirin Distributors
1A1) Non-conformance Investigation Report for lot 760351
1A2) Quality Control/Protocol Checklist for batch #760688
1A3) Quality Control/Protocol Checklist for batch #760641
1A4) Quality Control/Protocol Checklist for batch #760640
1B1) Non-conformance Investigation Report for batch #759931
1B2) Quality Control/Protocol Checklist for batch #760843
1B3) Non-conformance Report for batch #762920
1C1) Non-conformance Investigation Report for batch #759864
1C2) Quality Control/Protocol Checklist for batch #761025
1C3) Quality Control/Protocol Checklist for batch #761095
1D) OOS log for Microbiology QC Laboratory for 2001/2002
1E) List of Manufactured Lots-Reworked
1F/1G) List of Monoblend/Re-filtered, Trivalent and Pack lot for year 2001/2002
1H) List of Manufactured Lots Rejects
1J) List of Trivalent Bulk Lots
1K) List of Released US Vials/Syringes
1L) SOP #BLE024
1M) SOP #SP155
1N) ---------- Validation Report of filter microbial retention
2A) SOP #SCP009
3) No Exhibit for observation #3
4) No Exhibit for observation 4
5B) Testing Results for ---------- ---------- Tubing
16A1) Broth Fill Summary for Year 2001/2002
16A2) Performance Qualification Protocol dated 6/4/01
16A3) Media Simulation Worksheet dated 2/6/03
16B) SOP #SCP029
17A-17C) Adverse Events report per batch
17D) List of Fluvirin Reported Adverse Events per batch
17E) SOP #MA 4901
17F) Draft Proposal for Revision to Adverse Event SOP
18A) Installation Operational Qualification Protocol
19A) SOP #IN017
20) SOP #IN018

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EXHIBITS (RWJ)

R-12 Summary Report Investigation into Fluvirin Stability Results
R-13 Appendix 14 of the Fluvirin stability investigation
R-14 BPDR summary table
R-15 Clinical Expert Report draft dated September 4 2002
R-16 BPDR submitted June 28, 2002
R-16A Stability Policy Document SCP041
R-17 Table 1 Fluvirin Stability pH and SRD data (2001/2, 2002/3)
R-18 Stability Report for lot# E00931HA
R-19 Stability Report Lot# E11371LA
R-20 Stability Report Lot#E12201MA
R-21 BPDR September 4, 2002
R-22 Response to Inspectional Observations issued on March 9, 2001
R-23 CVP/0011/03 dated April 7, 2003
R-24 BLE022 Operation of ---------- ---------- System
R-25 Partial batch record for New Caledonia lot# 764983 blending
R-26 Release of ---------- Concentrate to the Formulation Department including -- day ruling.
R-27 P/0097/04/03 Filling Instructions for Filling of Fluvirin containing different preservatives
R-28 R/0083/05/01 Evaluation of Disinfectant Products using Qualitative European Surface Tests for both Bacteria and Fungi
R-29 SCP017 Approved Cleaning and Disinfectant Agents
R-30 Protocol PVP/0005/01 Determination of the effects of Maximum Holding times on the potency of Fluvirin April 2001
R-31 Report PVR/0005/01 dated January 2003
R-32 SOP VAL002 Executing Validation Protocols
R-33 QA Bulk Trivalent Checklist
R-34 SOP QASP093 QA Procedure for Review of Finished Product
R-35 Fluvirin Trivalent Vaccine Product Release Checklist
R-36 SOP PRG020 Release of Finished Products from Quarantine
R-37 Product Release Checklist for Packing lot E31192HA dated September 4, 2002.
R-38 Corrected sterility test NCR in the batch record for lot# 762834
R-39 Batch Record--------- dated 10/25/02
R-40 MI0350 Passage of Influenza Seed Material
R-41 NCR/827/02 dated September 5, 2002
R-42 Filling batch record, selected pages, lot# 762838 June 7, 2002.
R-43 M154 Water Monitoring Excursion Reports