

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS
5600 FISHERS LANE, ROCKVILLE, MD 20857 USA
TEL: (301) 827-0391/FAX: (301) 827-0342

DATE(S) OF INSPECTION

10/10-15/2004

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME

EVANS VACCINES an affiliate of CHIRON CORPORATION

STREET ADDRESS

GASKILL ROAD

CITY, STATE AND ZIP CODE

LIVERPOOL L24 9GR, UK

TYPE OF ESTABLISHMENT INSPECTED

VACCINE MANUFACTURER

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

1) Regarding Fluvirin Sterility Investigation #R/0198/10/04 dated October 9th 2004:

A) The Fluvirin Sterility Failure Investigation Report states (in part) that [redacted] fumigation took place on May 17, 2004 as a corrective action to increased levels of Gram negative organisms (including *Serratia spp*) during April and May. The area fumigated was the formulation suite. The firm deemed that the fumigation "was successful, as confirmed by ongoing environmental monitoring" and that "it should be noted that there are no confirmed isolates of *Serratia spp.* within the Grade [redacted] LAF unit where aseptic connections are made." The firm further deems this as "a key assessment criteria for further batch processing as part of the Quality Assurance Process". This investigation conclusion is not supported and information reported is inaccurate, in that:

- 1) the firm does not report that Gram negative rods, oxidase negative, were actually isolated in the formulation areas after the fumigation, further Gram negative rods identified as *Serratia spp.* were also isolated, and
- 2) there is no evidence that the firm took further action to correct continued excursions of alert and action levels in formulation rooms [redacted] and [redacted] from May 2004 through September 2004. The firm continued to experience alert and action level excursions for Gram negative organisms, including but not limited to, *Serratia spp.*

B) Regarding retest performed on the sterility test failures for four of nine final vial product lots, there is no investigation into the mixed pass and fail sterility test results for the original two lots and two "sister" lots associated with the failed monovalents.

The original two failed lots [redacted] were retested [redacted] times the normal test sample size (normal test sample size is [redacted] vials). The "sister" lots [redacted] of the two original failed lots were also retested [redacted] times the normal test sample size. Results are as follows:

Lot#	Re-Test Date	Results of each set of 40 vials
[redacted]	22 Jul 04	set of [redacted] vials passed sterility test sets of [redacted] vials failed sterility test
[redacted]	22 Jul 04	sets of [redacted] vials failed sterility test
[redacted]	28 Jul 04	sets of [redacted] vials failed sterility test

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EMPLOYEE(S) SIGNATURE

Paula A. Trost
John D. Finkbohner
David S. Cho
Mark A. Elengold

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Owolunde O. Ogunsanmi, CSO
Paula A. Trost, CSO
John D. Finkbohner, Ph.D. Supv. Chemist
David S. Cho, Ph.D. Microbiologist
Mark A. Elengold, Deputy Director Oper., CBER

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29 Jul 04

sets of vials passed sterility test
sets of vials failed sterility test

- C) SOP M198, Sterility Investigation Report (Version 06), was not followed during the Fluvirin Sterility Failure investigations in that, the SOP required a Non-Conformance Report (NCR) be initiated in accordance with the NCR SOP. This was not done for the nine filled vial lots that were contaminated with *Serratia spp.* Regarding filled vials, the first failure occurred on 8 July 2004. The 9th failure occurred 2 August 2004. There is no documentation to show that root cause, immediate corrective action, or product impact was addressed at the time of each failure (as per the firm's SOP). One NCR (dated 28 September 2004) was generated to cover all nine sterility failures as well as monovalent blend failures and serves only to refer to the final Fluvirin Sterility Failure Investigation dated 9 October 2004.
- D) No documentation of rationale in the Fluvirin Sterility Investigation #R/0198/10/04 dated October 9th 2004 indicating that all three (3) monoblend batches of the Fluvirin trivalent strains with sterility failures are the B/Jiangsu strain.
- E) The investigation of the root cause analyses, corrective/preventive actions, conclusions and recommendations did not include B/Jiangsu bulk batch [REDACTED]. The first of the three (3) monoblend batches implicated in the nine (9) Fluvirin final filled vials sterility failures with bioburden level of 67cfu (specification of [REDACTED]cfu/ml) but failed sterility at the bulk stage (isolate: *Serratia marcesens*). (Was referenced in the Investigation Report)
- F) The investigation did not specifically state that high bioburden levels were noted in the Fluvirin B/Jiangsu strain at the [REDACTED]/Pre filtration step in [REDACTED] (83%) of [REDACTED] monoblend batches manufactured for year 2004 campaign with 170-39,000,000cfu/ml bioburden levels per batch (alert level [REDACTED]cfu/ml). This is higher bioburden than noted for any of the other two Fluvirin monoblend strains.
- G) No documentation in the investigation report of the effect of keeping the monoblend/trivalent formulations at [REDACTED] for up to [REDACTED] during processing was considered. Fluvirin finished vials are labeled for shipment at 2-8°C and Fluvirin monoblend/trivalent bulks are stored at temperature of [REDACTED]°C.
- H) There is a lack of scientific data to support the statistical rationale for the retest sampling and testing plan.

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Paula A. Trost, CSO
John D. Frikbohn, Ph.D. Supv. Chemist
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2) Regarding clean room design and operations for Formulation Room (Filtration) and Formulation Room (Trivalent Blending): The Class (Class area where post filtration aseptic connections take place is equipped with curtains in the form of strips approximately inches wide and are arranged so as to overlap each other and are attached at the ceiling surrounding the HEPA filter. The curtains separate the Class area from the Class (Class area.

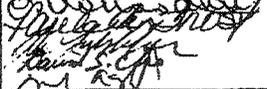
- A) The curtains are approximately from the floor some of the strips are bent leaving gaps between each strip. There is lack of assurance that airflow would not be disrupted. Available smoke videos do not provide assurance that there is no disruption.
- B) The room is arranged so that operators are required to reach into curtains or beneath the curtains and vigorously manipulate equipment only 6 to 12 inches inside the curtains. During a mock demonstration of operations, one operator was observed making aseptic connections approximately from the floor which is below the bottom of the curtains and was required by the design of the equipment to disrupt the curtains that separate the Class and Class areas.
- C) The equipment configuration within the Class environment is such that operators must crouch in the airflow stream sweeping towards the critical area where multiple aseptic connections are made
- D) Available smoke studies do not demonstrate the ability to maintain integrity of laminar airflow within the critical area when operator is present. Furthermore, the operator moves from a Class environment into the Class environment on multiple occasions during aseptic operations

3) Filtration occurs in Formulation Room and trivalent blending occurs in Formulation Room Activities involve operators making aseptic connections at pre and post filtration sites. These operations routinely encompass between in which operators are performing critical operations. Regarding air environmental monitoring in virus formulation areas, there is a lack of assurance that microbial contamination during critical operations would be adequately detected in that:

- A) The firm does not routinely monitor active air while critical operations are taking place. Viable active air sampling is tested using a L sample which takes between for of growth media (a total of air sampling).
- B) Viable active air sampling that is performed in the Class area is not performed in the area where most critical operations are occurring but rather, the air sampler is placed on tables different locations at different times) near the corners of the Class area.

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Paula A. Trost, CSO
John D. Finkbohner, Ph.D. Supv. Chemist
David S. Cho, Ph.D., Microbiologist
Mark A. Elengold, Deputy Director Oper., CBER

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C) Settling plates are not placed in areas where the most activity is occurring and not in areas of critical operations.

D) There is a lack of assurance that the current sampling volume for non viable particulate of [redacted] cu ft/[redacted] is adequate in relation to the time required to perform operations [redacted]. Sampling is not routinely performed in the area of critical process at the time of critical process.

4) Regarding Control of Bioburden in the Manufacturing Facility:

A) [redacted] (60%) out of [redacted] Fluvirin monoblend batches used in the formulations of the trivalent batches manufactured for year 2004 Fluvirin Campaign were out of bioburden alert level of [redacted] cfu/ml with bioburden levels as high as 39,000,000cfu/ml.

B) Out of Specification (OOS) batches of Fluvirin monoblends: A/Wyoming, B/Jiangsu and A/New Caledonia were noted as a result of the high bioburden levels in Observation 2A above and total of 26 out of [redacted] monoblend batches resulted in OOS results for endotoxin levels of up to 5052 Eu/ml (alert level specification for US [redacted] Eu/ml). The monoblends with high endotoxin levels were not used for USA Fluvirin market.

C) Approximately 80% of all microorganisms' growth in the Fluvirin filling room, monoblend aseptic filtration, and trivalent formulation room excursions were not identified to the genus level.

D) Per Non-conformance Report #2004/1071/07 dated July 5th, 2004 Mycoplasma growths were confirmed for Fluvirin A/Wyoming Master Seed batch [redacted] and Working Seed batch [redacted]. Also, per M/2004/1029 dated March 15th 2004, Mycoplasma growth was also confirmed on A/Wyoming Working Seed batch [redacted]. The contaminated seed lots were used in five Fluvirin monoblend batches that were later rejected.

E) Bioburden investigation is incomplete in that there is a lack of documentation that water quality was directly investigated as a potential for contribution to bioburden though purified water does have direct contact with the egg product mixture. For example, purified water is used to clean equipment, including the [redacted] Centrifuge, the [redacted] Centrifuge and [redacted] Machine which come into direct contact with product.

F) Besides the nine (9) batches of Fluvirin that were rejected for sterility failures (Investigation # R/0198/10/04 dated October 9th 2004), additional four (4) batches of finished Fluvirin vials were also rejected due to environmental excursions. For example:

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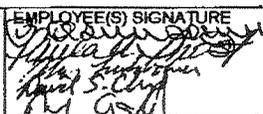
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- 1) Per Non-Conformance Report #2004/1632 dated September 9th, 2004 lot [REDACTED] was rejected due to growth of *Micrococcus spp* on Fluvirin filling needle swab. In addition, two alert levels with microbial growths identified as Gram positive cocci/Gram negative rods were also identified in the [REDACTED] change room" and within the grade [REDACTED] area outside of the filling room sterile corridor respectively.
 - 2) Per Non-Conformance Report #2004/1852 dated October 2nd 2004, batch [REDACTED] *Staphylococcus spp* growth was identified on Fluvirin filling needle swab and on hand plate sample of one aseptic filling room operator. Also alert level growth of *Staphylococcus aureus/Moraxella spp* was detected in the [REDACTED] change room".
 - 3) Per Non-Conformance Report #2004/1863 dated October 4th 2004, batch [REDACTED] microbial growth of gram positive cocci were noted in the grade [REDACTED] aseptic filling room (Class [REDACTED] *Micrococcus spp* were noted on hand plate of one operator. Gram negative rod oxidase negative and gram positive cocci/rods were also isolated from setting plates in the changing room.
 - 4) Per Non-Conformance Report #2004/1625 dated September 8th, 2004 batch [REDACTED] microbial action limits were reached by two (2) Fluvirin filling Operators working in the grade [REDACTED] aseptic filling area (Class [REDACTED] [REDACTED] In addition, growth of *Brevibacillus brevis*, *Bacillus subtilis*, *Micrococcus spp* and Gram negative rods were noted at vial in-feed on the [REDACTED] filling machine.
- G) Although individual investigations were conducted into the following Fluvirin aseptic filling room excursions, no formal overall investigation was conducted to assure adequate corrective and preventive actions.
- 5) Failure to adequately address root causes during failure investigations, noted during the inspection of year 2003 has not been adequately corrected. For example the previous inspection observation noted:
- A) The most recent sterility failure Investigation #R/0198/10/04 for nine (9) filled vials of finished Fluvirin batches concluded that inadequate aseptic technique during aseptic connections was the cause. During the 2003 inspection, the firm was cited for failure to evaluate the reduction in aseptic connection to reduce the possibility of contamination. There is no documentation that adequate corrective action has been conducted.

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B) Control and failure investigations into bulk Fluvirin monoblend/lots at the [redacted] step with high bioburden levels is deficient, in that lots were noted with total high bioburden volumes of 9.66×10^6 cfu, 7.07×10^7 cfu & 1.26×10^7 cfu in year 2000/2001 and 2001/2002 campaigns and no "effect" investigations has been opened to find the root causes of the high levels of bioburden in these lots. (Not corrected from previous inspection of 2003 in that similar occurrences noted during this inspection)

6) Regarding Aseptic Media Fills Simulation:

A) Media fill simulations are not representative of actual aseptic fill processes in that, interventions that occurred during aseptic filling processes are not evaluated and considered for incorporation into the media fill simulations. (Not corrected from previous inspection of 2003) For example;

Media fills conducted as part of the sterility failure investigation Report #R/0198/10/04 into nine (9) filled vials of Fluvirin batches and routine aseptic media fill simulations per protocol #PQR/0142/04 & PQP/0146/02 failed to include the review and evaluation of batch records for syringes and vials for unusual interventions that occurred during routine aseptic filling processes for incorporation into aseptic fill simulations per SOP #SCP029 dated October 26th 2003 titled: General Procedure for Routine Monitoring of Aseptic Manufacturing Processes by Process Simulations Utilizing Sterile Media Fills.

B) Deficiencies were noted in the routine aseptic media fill simulations for Fluvirin monoblend aseptic fill /trivalent aseptic formulation simulations, and trivalent media fill simulation investigation into Fluvirin nine (9) filled vials sterility investigation #R/0198/10/04. Aseptic simulations were not representative of actual aseptic fill conditions: Specifically:

- 1) No Batch record reviews of previously manufactured lots were conducted
- 2) No documentation that interventions were conducted during the media fills
- 3) The routine aseptic media fills for the monoblend and trivalent stages do not encompass all interventions normally performed during production.
- 4) No documentation that worst case challenges were conducted during the aseptic media fills simulations.

7) Regarding quality operations:

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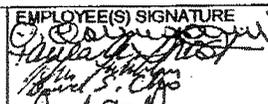
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- A) Monovalent blend pools produced during the 2004 production campaign that have exceeded the alert limit have been forward processed to final product on multiple occasions, even when bioburden results have exceeded alert limit by multiple orders of magnitude. For process stream excursions of the alert limit that have occurred in the downstream processing steps where purification of desirable components may be completed, it is not clear that the investigation assessed potential product quality impact in terms of microbial metabolites, microbial degradation of the desired vaccine components, or introduction of sensitizing agents into the product.
- B) In twenty-four (24) incidences during the 2004 Fluvirin campaign, cultures were used in egg inoculation that exceeded bioburden levels, i.e., [redacted] cfu (alert of [redacted] cfu/ml). This resulted in the inoculation of approximately [redacted] eggs per batch which were used in the manufacturing of Fluvirin Vaccine with high bioburden containing cultures. Although the firm was aware that the live virus inoculum contained high bioburden, the eggs/batches were not rejected but allowed to continue through the Fluvirin manufacturing process.
- C) Technical Report Reference Number R/0123/06/04, revision one, accepted August 12, 2004, states on page 24, "During 2003, no adverse events investigations were performed due to 5 occurrences from one batch." This indicates that no independent review of adverse event reports by batch was performed as a quality control procedure.
- 8) Regarding zonal centrifugation operations:
- A) There is no written procedure or cleaning validation for the manual cleaning of the upper and lower assemblies, which are part of the flow path for the process stream.
- B) The written procedure for cleaning of the main body of the zonal centrifuge rotor describes the flushing of process stream contact parts for a period of [redacted]. There are no directions describing the surfaces to be flushed.
- C) Validation studies for the zonal centrifugation operations characterize material based on [redacted] assays but do not characterize egg proteins, or other specific process or product related impurities.
- 9) Regarding [redacted] processing tanks utilized in the [redacted] production area where purification operations, sterile filtration, and aseptic formulation operations are conducted:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE 	EMPLOYEE(S) NAME AND TITLE (Print or Type) Oranbunde O. Ogunsammi, CSO Paula A. Trost, CSO John D. Finkbohner, Ph.D. Supv. Chemist David S. Cho, Ph.D., Microbiologist Mark A. Elengold, Deputy Director Oper., CBER	DATE ISSUED 15 October 2004
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER
ORA/OE/DIVISION OF COMPLIANCE MANAGEMENT AND OPERATIONS
5600 FISHERS LANE, ROCKVILLE, MD 20857 USA
TEL: (301) 827-0391/FAX: (301) 827-0342

DATE(S) OF INSPECTION

10/10-15/2004

FEI NUMBER

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: ANDY SNEDDON, VICE PRESIDENT OF MANUFACTURING, UK SITE DIRECTOR

FIRM NAME

EVANS VACCINES an affiliate of CHIRON CORPORATION

STREET ADDRESS

GASKILL ROAD

CITY, STATE AND ZIP CODE

LIVERPOOL L24 9GR, UK

TYPE OF ESTABLISHMENT INSPECTED

VACCINE MANUFACTURER

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS, AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT, CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

- A) Prior to August 2004, there was no periodic preventative maintenance program or written assessment of aspects potentially effecting tank integrity such as damage to sealing surfaces, sealing gaskets, valve assemblies, or sterile vent filter assemblies. Difficulties with [REDACTED] valves and integrity of sterile vent filters have been noted in processing.
 - B) Tanks are usually double door passed through the autoclave into the Class [REDACTED] formulation areas; however, on some occasions, the vessels have been single door passed back into the vessel preparation area [REDACTED] and transferred via materials airlock and wiped down into the clean zone.
 - C) Documentation of sprayball coverage for processing tanks is not found in cleaning validation studies or I/OQ studies for these processing tanks. In addition, the written documentation for visual determination of cleanliness is non-specific relative to assessment of soiling on most difficult to clean surfaces.
 - D) Cleaning validation for the CIP process for Vessel [REDACTED] which is utilized in the aseptic formulation of trivalent bulk influenza vaccine, did not include an assessment of sprayball coverage for the vessel. In addition, the study did not include swab sampling of the transfer lines used in the transfer of monovalent blend pools into the mixing vessel [REDACTED] and for transferring the aseptic trivalent formulated bulk back into a sterilized [REDACTED] liter tank in formulation room [REDACTED]
- 10) Manufacturing instructions (batch production record) do not always capture important processing information. For example, processing tanks are not traceable within the batch production record. In addition, it is not possible to consistently trace processing tanks to specific unit operations for a specific lot.
- 11) The specified replacement schedule (annual replacement) for the [REDACTED] filtration [REDACTED] is not supported by production history accumulated since January 2003. For example, [REDACTED] sets of [REDACTED] have been used in the 2003 production campaign, and [REDACTED] in the 2004 campaign. The stated reason for change after initial annual installation is fouling of the [REDACTED] resulting in longer processing times.
- 12) Regarding equipment supporting manufacturing operations in the Egg Virus Unit (EVU):
- A) There is no spray ball coverage cleaning studies for the harvest tank, bulk holding tank, inactivation vessel [REDACTED] and inactivation vessel [REDACTED]
 - B) There are no studies to determine the swab sampling sites for the harvest tank, bulk holding tank, inactivation vessel [REDACTED] and inactivation vessel [REDACTED]

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EMPLOYEE(S) SIGNATURE

[Handwritten Signature]

EMPLOYEE(S) NAME AND TITLE (Print or Type)

Oronizunde O. Ogunsehin, CSO
Paula A. Tross, CSO
John D. Finkbotner, Ph.D. Supv. Chemist
David S. Cho, Ph.D., Microbiologist
Mark A. Elengold, Deputy Director Oper., CBER

DATE ISSUED

15 October 2004

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DURING AN INSPECTION OF YOUR FIRM (WE) OBSERVED:

13) There is no documentation that a manufacturing quality review was conducted in a timely manner on adverse event reports received for twenty-two batches of Fluvirin manufactured in the 2003/2004 campaign where one or more criteria for manufacturing investigation were met per SOP MPD-0022 (Section 7.7), SOP MPD-024 (Section 7.5), and (Section seventeen page 41) of the June 27, 2003 response to the June 10 FD483).

For example:

- A) Seven adverse event reports received for injection site type reactions to batch number 765484
- B) Ten adverse event reports received for injection site type reactions to batch number 765751
- C) Five adverse event reports received for injection site type reactions to batch number 766053

(Incomplete corrective action to the previous inspection of 2003)

14) Regarding product equipment compatibility study:

The [redacted] Tubing used throughout the Fluvirin manufacturing process to transfer centrifuged, formulated and finished product for filling was out specification of [redacted] mg for USP Non-Volatile Residue with result of 1327mg per [redacted] test result. No investigation, corrective and preventive action has been conducted and no justification/rationale is provided for the lack of investigation. (Incomplete corrective action from previous inspection of 2003)

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EMPLOYEE(S) NAME AND TITLE (Print or Type)

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Paula A. Trost, CSO
John D. Finkbohner, Ph.D. Supv. Chemist
David S. Cho, Ph.D., Microbiologist
Mark A. Elengold, Deputy Director Oper., CBER

DATE ISSUED

15 October 2004

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."