DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/OE/DCMO (HFC-210) 5600 Fishers Lane Rockville, MD 20857 (301) 827-0391	4/18-28-2006
	FEI NUMBER 2518760

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Gary K. Chikami, MD, Associate Vice President, Regulatory Affairs, North America

FIRM NAME	STREET ADDRESS
Sanofi Pasteur, Inc.	Discovery Drive
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Swiftwater, PA 18370	Vaccine Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

PRODUCTION SYSTEM

1. The following was observed on 4/19/06 during filtration of A/Wisconsin influenza concentrate lot U08182

A. Operators performing level 1 cleaning in between pre-filtration and sterile filtration operations were observed applying / sloshing disinfectant to the floors of the dirty side of the class C areas (gown room and equipment air lock) and returning to the class B areas without re-gowning. After the required disinfectant dwell time, the solution was vacuumed using a wet/dry vacuum unit in the same manner.

B. A common hallway (Hallway 135) is used in Building 37 without adequate segregation of early production material from material used in sterile processing. This hallway connects Rooms 113A and 113B (sterile gowning suite and equipment airlock to Room 113 where the filtration of Lot U08182 was observed to occur) and Room 140 (where egg candling was observed to occur). Egg carts containing eggs (used in upstream influenza manufacturing) and personnel were observed traveling into Room 140 via this hallway during the filtration operations for Lot U08182. Personnel conducting operations in Room 113 also were observed traveling through this same hallway to access Rooms 113A and 113B. Contaminating organisms found in 11 lots of monovalent influenza concentrate that had been sterile filtered in Room 113 were identified as primarily egg related. ~~No attempt~~ RA 4-26-06

2. There is no assurance that the wet/dry vacuum used for cleaning the floors of classified production areas prevents addition of bioburden in ~~the~~ the production areas in that the HEPA filters on the unit are not routinely integrity tested and the interior drum where dirty solution is collected is not sanitized. DR 4-25-06

3. There is no assurance that the worst-case loads are used for the yearly validation of the Building 46[redacted] Oven as required by SOP A002417, Validation Maintenance Program of Sterilization and Depyrogenation Process as Aventis Pasteur – U.S. Validation. Specifically, not all data used to determine worst-case items from the original 1990 studies are available. The original report identified the 4 worst case items as follows: 1) [redacted], 2) [redacted], 3) [redacted]; and 4) [redacted] However, calculation of average F_h values from the available data from (endotoxin challenge runs) the original validation studies show that the [redacted] are harder to heat than the [redacted] and therefore, more of a worst case.

4. There is no assurance that training / qualification of all operators performing aseptic operations in the flu manufacturing area is complete. Specifically:

A. TMFLU020 – Sterile Filtration training module requires initial Aseptic Technique training and SOP A002254, Aseptic Process Simulation (APS) Validation Requirements for the Sanofi Pasteur-U.S. Aseptic Processing Area requires a [redacted] re-qualification through participation in a process simulation study. Influenza Department Technician SW completed her Aseptic Technique Qualification on 6/3/2003, but has not participated in a media fill since her qualification. This technician has participated in sterile filtration operations of the 2006 influenza campaign.

B. Section 3.2.3.2 of SOP A002254 states that participation of aseptic personnel in a process simulation studies should be tracked and maintained in personnel training files. This is not being done for operators involved in the sterile filtration of flu.

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In addition, the Q4-2005 APS report for simulation of the Influenza Concentrate Sterile Filtration Process documents that there were [redacted] participants in the media fill. Review of the batch record UAPS1990 shows that only [redacted] of those individuals signed the batch record as performing the operation.

5. Cleaning of surfaces within Grade A areas of the influenza manufacturing facility was not consistent with SOP A002328, Requirements for Cleaning/Disinfecting Procedures in Controlled Areas in that surfaces were not wiped with a sterile wipe after disinfectant dwell time. There is no assurance that the disinfectants applied without wiping do not inhibit growth on RODAC surface samples. Qualification studies used to demonstrate the ability of [redacted] to support that the growth of microorganisms is not inhibited by potential exposure to residual antimicrobial agents found on surfaces following cleaning did not specify how surfaces were cleaned for the study (disinfectants allowed to dry on or wiped with sterile wipe after dwell).

6. Vent filters on the [redacted] sterile influenza bulk concentrate tank, and on the [redacted] dispensing siphon unit are not integrity tested.

7. Monovalent influenza concentrate was sterile filtered into [redacted] vessels without performing media simulations to determine the impact of switching from the [redacted] stainless steel tanks to the [redacted] glass vessels.

8. [redacted] working seed lots are not being submitted for approval before use in production. The current working seeds lots are Lot UC1525-43 ([redacted]), Lot UC1507-54 ([redacted]), Lot UC1605-32 ([redacted]), and Lot UC2018-27 ([redacted]). All of these working seed lots have been used to manufacture distributed product.

9. There is no adequate backup storage for the following master seed lots.

A. There is no backup storage for Yellow Fever Master Seed Lot C1600. In addition, there is no SOP which states where Yellow Fever Master Seeds should be stored.

B. The backup storage for [redacted] Master Seed Lots (Lot C1525-23 for [redacted], Lot C1507-1 for [redacted], Lot C1605-6 for [redacted], and Lot C2018-6 for [redacted]) is maintained at a temperature of [redacted]C. This is an unlicensed temperature for [redacted] master seeds.

10. [redacted] Powders ([redacted]) were approved with an 18 month expiration date. The expiration date for these powders is routinely extended by 9 month increments up to 5 years based on a passing potency test. This increase in expiration date has not been approved before use of these powders in the manufacture of distributed lots of Menomune.

11. Regarding aseptic operations:

A. The Suite 7 compounding area located in Room 237 of Building 46 is a Class A area used during the formulation of vaccines for which no sterile filtration occurs after formulation including: Tripedia, Influenza B Strain and A Strain Pools, Preserved Influenza Final Bulks, Diptheria and Tetanus Toxoid Purified Pools and Decavac. Menactra and Influenza No Preserved Final Bulk are also formulated in this area. These are processed with a [redacted] filter. Exposed lights were observed directly underneath the HEPA filters in this area.

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The following observations were made during observation of aseptic filling operations on Filling Line 1 (for Diluent for Haemophilus b Conjugate Vaccine (Tetanus Toxoid Conjugate) 0.4% Sodium Chloride, Lot UE910A) and/or Filling Line 4 (for Menomune Lot UE934A):

A. Empty depyrogenated vials were pushed onto the [redacted] of Filling Line 1 using the outside of the tray that contained the vials. This tray was exposed to a Class C environment and may be held in such an environment for up to 14 days.

B. An operator on Filling Line 4 used the back of forceps to move open (partially stoppered) vials after the back of the forceps had been in the operator's gloved hand.

C. An operator working at the tray off station where partially stoppered vials were loaded onto lyophilization trays was observed with head and upper torso over the partially stoppered vials.

12. Regarding visual inspection practices:

A. No specifications have been established for the light intensity to be used during [redacted] visual inspections of unlabeled filled containers.

B. No specifications have been established for the light intensity to be used during AQL visual inspections of unlabeled filled containers.

13. The firm has a protocol for the qualification of solutions used in Manufacturing. This protocol (Document Number B006830 Version Number 1.0 entitled "Master Stability Program for Buffers and Media Reagents for AvP-US") has been effective since 21 Dec 2004. To date only 2 of the approximately 50 materials used in either the manufacture of products or for cleaning/disinfection (as identified in Appendix 2 of this document) have been qualified.

14. The purity, strength and quality of some critical components in manufacturing are not tested to validate the suppliers test results.

A [redacted] is a critical reagent in the manufacture of meningococcal polysaccharide conjugate vaccine. This reagent has not been tested to verify the [redacted] concentration stated by the supplier.

B .During the review OOS incident report IN04-1758, IN05-0471, and INJ04-1483 it was observed that aberrant standards were the root cause of OOS [redacted] content of several [redacted] intermediates used in the manufacture of meningococcal polysaccharide conjugate vaccine.

15. Sampling of the reaction mixture during [redacted] does not follow an appropriate procedure to prevent introduction of objectionable chemicals and microorganisms. An operator was observed to pour a recently withdrawn sample of the [redacted] mixture into the [redacted] as a routine part of the sampling procedure in a class C room.

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QUALITY SYSTEM

1. On-going investigations into sterility failure investigations of 11 Influenza monvalent concentrate lots manufactured between 2/6/06 and 4/6/06 are deficient for the following reasons:

A. Regarding the increased non-routine surveillance monitoring performed to further evaluate the Building 37 Flu manufacturing facility, there was no plan in place specifying the locations to be tested, method of sampling, and actions to be taken when microbial contamination was noted. Samples containing colony forming units (CFU) were evaluated for morphological characteristics, and only colonies exhibiting Gram-negative characteristics were Gram stained and identified.

B. The [redacted] method used for increased surveillance monitoring of the environment has not been qualified.

C. Investigational media challenge / aseptic process simulations (APS) performed to investigate potential root cause did not simulate the pre-filtration operations and cleaning activities performed immediately prior to sterile filtration.

D. Portions of the failed lots that had not tested positive (i.e. failed sterility) were not re-tested to help determine the extent of the contamination problem.

E. Organisms isolated from routine environmental monitoring in the Building 37 Flu manufacturing facility were not identified to help determine the route of contamination. For example, between 2/22/06 and 4/4/2006, site 31 in Hallway 135 was trending upwards until the alert level was exceeded on 4/4/2006 with a result of [redacted] CFU.

2. Annual Product Reviews (APRs) are not completed in a timely manner. SOP A000177, Annual Product Review, dated 4/22/04, states that APRs covering January 1 to December 31 should be finalized by July 31 of the following year. Eight out of fourteen of the 2004 APRs were finalized after the July 31 due date. For example:

A. The 2004 Menomune APR was finalized on 11/7/05.

B. The 2004 DT APR was finalized on 10/28/05.

C. The 2004 Td APR was finalized on 10/28/05.

3. Quality Assurance review of batch production records does not include an evaluation of the equipment sterilization records for sterile product contact equipment.

4. SWI J003642, Quality Assurance Compliance Procedure for Evaluating and Reporting Biological Product Deviations, dated 12/29/04, states that missed stability timepoints should be reported as BPDRs. DT Adsorbed PF Lot U1047AA was not tested at the [redacted] month timepoint for [redacted] These missed timepoints were not reported.

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5. Complaint investigations are not always completed in timely manner and there is no written justification for the lack of timely completion. Of approximately 45 complaint investigations reviewed 8 were found have been completed outside of the [redacted] day target completion time specified in SOP A000178 entitled "Procedure for Handling Product Complaints".

6. BPDRs were not filed for complaints of glass in product. For example, Complaint CO2005-00209 for Decavac Lot U1212CA and Complaint CO2004-08344 for TD Lot U1188AA.

FACILITES AND EQUIPMENT SYSTEM

1. The [redacted] Smoke Testing conducted as part of the Operational Qualification Testing for the Laminar Air Flow Unit # VLF-0067/68 Room 113, Building 37 was inadequate in that the simulated dynamic operations were described only as "personnel within units". This area is used for the [redacted] operations of Influenza virus concentrate.

2. Investigations to determine product impact are not performed when HEPA filter integrity or airfow failures are detected for any of the classified areas including Class A areas where aseptic filling, filtration, and formulation are performed. For example, 2 leaks (0.58% and 0.31%) were found in the Class A zone of Building 37 Room 181 (Filling Line 1) on 07 June 2005; a leak of 11.3% was found in the Class A zone of Building 37 Room 181 (Filling Line 1) on 05 December 2005; a leak of 0.77% was found in the Class A zone of Building 37 Room 183 (Filling Line 4) on 23 December 2004; 4 leaks (3.69%, 0.91%, 5.11%, and 31.3%) were found in the Class A zone of Building 37 Room 183 (Filling Line 4) on 23 December 2004. No investigations to determine the impact on products filled under these Class A zones was performed. Additionally, 3 leaks (0.38% 0.12%, and 0.42%) were found in the Class B zone of Building 37 Room 113 ([redacted] filtration room) on 13 September 2005. The integrity of the Class B zone filters (since this last certification) in this room was not evaluated as part of the ongoing investigation into the sterility failures of 11 influenza concentrates that were filtered in this in this room.

LABORATORY CONTROLS SYSTEM

1. Regarding the environmental monitoring program of manufacturing areas:

A. Routine surface sampling of the class B and C areas of Building 37 influenza manufacturing facility is not conducted under dynamic conditions. Samples are collected after-cleaning.

B. Failure to follow SOP A001939, Trending and Reporting of Environmental Data and Establishment of Microbial Control Limits, in that quarterly trend reports are not conducted as required.

2. Regarding bioburden testing of in-process influenza vaccine:

A. Qualification studies for no preservative influenza concentrate formulation have not been performed. Samples of both non preserved and preserved formulations are collected in [redacted]

B. The 1 mL bioburden sample is not representative of the lot size in determining pre-sterile filtration bioburden levels.

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3. Corrective Actions have not been fully implemented for an identified root cause of OOS stability results for moisture of the Yellow Fever Vaccine for both 1 dose and 5 dose final containers. This investigation started September 2002. The root cause was identified as transfer of residual moisture in the [redacted]. The following OOSs were observed. The expiration date is 12 months. This is a repeat observation.

A.Lot UB427AA was OOS at 12 months.

B.Lot UE059AA was OOS at 6 and 12 months.

C.Lot UE557AA was OOS at 6 and 9 months.

D.Lot UE498AA was OOS at 6, 9, and 12 months.

E.Lot UE499AA was OOS at 6, 9, and 12 months.

F.Lot UB475AA was OOS at 12 months.

G.Lot UB501AA was OOS at 12 months.

H.Lot UB496AA was OOS at 6 months.

4. Corrective Actions have not been fully implemented for an identified root cause of OOS stability results for physical exam of Bulk Td Adsorbed, Bulk Tripedia, Bulk Td PF Adsorbed, Bulk DT PF, Bulk Flu, and Bulk Menactra. IN05-0974, dated 6/23/05, was initiated to identify a root cause for the increased frequency of OOS physical exam results since 2004. The root cause was identified as the surrogate stability container for bulk for these products not being suitable. This has had an effect on the following bulk stability programs.

A. Six of the eight bulk lots of TD Ads placed on stability since 2002 had resulted in OOS's physical exam.

B. Four of the seven bulk lots of DT PF placed on stability since 2002 had resulted in OOS's for physical exam.

C. Six of the twelve bulk lots of Td Ads PF placed on stability since 2002 had resulted in OOS's for physical exam.

D. Five of the nine bulk lots of Menactra placed on stability since 2004 had resulted in OOS's for physical exam.

E. Fifteen of the twenty bulk lots of Flu placed on stability since 2002 had resulted in OOS's for physical exam.

5. SOP A000730, Stability Program Procedures, dated 2/2/06, states that final stability reports are to be written. There is no due date for writing these reports in this SOP. These final stability reports are not finalized in a timely manner. For example:

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A. Final Container Tripedia Study S2001-25 was completed by November 2003. The final stability report has still not been finalized.

B.Final Container Yellow Fever Study S2001-26 was completed by January 2003. The final stability report has still not been finalized.

C.Bulk Td Adsorbed Study S2002-27 was completed by September 2004. The final stability report has still not been finalized.

D.Bulk Tripedia PF Study S2003-31 was completed by September 2004. The final stability report has still not been finalized.

6. At time of licensure, the stability program for Tripedia included testing at [redacted] and [redacted] months. The current stability program for Tripedia includes testing at [redacted], and expiry. This reduction in stability testing was not approved.

7. The following OOSs occurred during the annual stability testing of bulk products. These bulk products went into manufacture of finished product which has been distributed. These OOS results were not reported as BPDRs.

A.Tripedia Bulk Lot U1369 failed physical exam at 3 and 6 months.

B.Td PF Adsorbed Bulk Lot U1217 failed physical exam at 9 and 12 months.

C.Flu Bulk Lot U1148 failed [redacted] at 6 and 10 months.

D.Flu Bulk Lot U1601 failed [redacted] at 7 months.

E.Menactra Lot U2002 failed [redacted] at 1 and 2 months.

8. The following analytical method validations have not been finalized.

A. SWI J000144, [redacted] (Flu, Protocol B003167).

B. SWI J000160, [redacted] (Flu, Protocol B003320).

C. SWI J000245, [redacted] (Flu, Protocol B006472-1.0).

D. SWI J000649, [redacted] (DT Related, Protocol B003146).

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CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Swiftwater, PA 18370	Vaccine Manufacturer

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED:

E. SWI J000677, A[redacted] (Menomune, Protocol B001991).

F. SWI J000720, [redacted]es (Menomune, Protocol B003305-00).

G. SWI J000844, [redacted] (Multiple Products, Protocol B007638).

H. SWI J000884, [redacted]s (Menomune, Protocol B007727).

I. SWI J000927, [redacted]t (Multiple Products, Protocol B006875).

J. SWI J000996, [redacted] (Diphtheria, Protocol B002788-00).

K. SWI J001146, [redacted] (DT Related, Protocol B003144-00).

9. The SOP SWI J000197 for measuring t[redacted]e was not modified to correct intermittent problems occurring with instrumentation used in the assay. As reported in incident report IN05-1512, it was determined that [redacted] buildup causes the HPLC to yield intermittent retention time changes during the analysis of for [redacted]. The SOP has not been modified to address this problem.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Amy Marie Montemurro Robert S. Sausville	Mihaly S. Ligmond, CSO Ann Marie Montemurro, CSO Robert Sausville, SCSO Tina Roecklein, CSO Willie Vann, Laboratory Chief	4/28/2006