Amended MSL 3-30-07

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
CBER/OC/Division of Inspections and Surveillance, HFM-650 USFDA 1401 Rockville Pike, Suite 200-North Rockville, MD 20852 (USA) (301) 827-6220	3/21-23, 26-29/07
	FEI NUMBER 3004066112

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Mike Austin, Senior Director, Site Operations

FIRM NAME	STREET ADDRESS
MedImmune UK, Ltd.	Plot 6 Renaissance Way, Boulevard Industry Park
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
Speke, Liverpool L24 9JW	Vaccine Manufacturer

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

PRODUCTION SYSTEM

1) Regarding control over product bioburden:

A) Per Technical Report #UKTR/0244 dated August 30th 2006, "During the 2006 commercial campaign [redacted] batches of the Filtered Frozen FluMist were manufactured. Out of these [redacted] batches there were 6 in-process bioburden excursions [redacted] involving, 8 sub-lots from a total of [redacted] manufactured". All of these microbial action level monovalent sub-lots/lots were released for further manufacturing into the trivalent FluMist drug products. Microbial organisms such as, *Pseudomononas stuizeri*, *Enterococcus faecalis*, *Escherichia coli*, *Staphylococcus aureus* were isolated. Below are examples of monovalent sub-lots with test results that are above microbial action levels at the [redacted] processing step:

	[redacted] ~~Action Level~~ MSL 3-30-07	[redacted] ~~Action Level~~ MSL 3-30-07
A/Wisconsin		
Lot 600157[redacted]	12,500cfu/ml	9,550cfu/ml
Lot 600157[redacted]	9,400cfu/ml	9,050cfu/ml
A/New Caledonia		
Lot 600150[redacted]	8,150cfu/ml	7,700cfu/ml
~~Specification~~ Action Limit: MSL 3-30-07	[redacted]	[redacted]

B) Regarding bioburden control for year 2007 FluMist campaign, the firm has manufactured [redacted] monovalent lots. Of these one was aborted and the last two manufactured lots contained bioburden levels in excess of the action limit, as follows:

i) FluMist monovalent lot [redacted] possessed a bioburden of 760cfu/ml (Action limit [redacted] at the [redacted] step and a bioburden of 14,000 cfu/ml (alert limit [redacted] at the [redacted] step. (Lot disposition has not been made)

ii) FluMist monovalent Lot [redacted] possessed a bioburden of 570cfu/ml at the [redacted] stage (Alert limits: [redacted] (Lot disposition has not been made).

C) Examples of excursions during the manufacturing of lot 600157 are as follows:

i) Per deviation #3089, with discovery date of April 20th 2006 eleven (11) environmental monitoring plates from the Downstream Processing Room [redacted] were found to be contaminated with molds and adverse trend for the isolation of mold was noted in the processing environment.

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		Mihaly S. Ligmond, CSO Omotunde O. Osunsanmi, CSO Steven A. Rubin, Staff Scientist	3/29/2007

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ii) Per Deviation # 3258, during microbial environmental monitoring of lot 600157, action level excursion of too numerous to count (TNTC) (Action limit [redacted]) were noted in the [redacted] trolley track floor contact on April 21st 2006. plate MSL 3-29-07

iii) Per Deviation #3455, during [redacted] in the [redacted] Room on April 25th 2006, action level excursion of 13cfu/~~ml~~ plate MSL 3-29-07 (Limit [redacted] was raised for an operator left hand plate taken during [redacted] of lot 600157. plate MSL 3-29-07

iv) Per Deviation #3456, in the downstream processing room on April 25th 2006 action level excursion of 16cfu/~~ml~~ plate MSL 3-29-07 (Limit [redacted] was raised for a second operator right hand plate during [redacted] taken during [redacted] and sampling activities of batch 600157. plate MSL 3-29-07

v) Per Deviation #3457, during the [redacted] on April 25th of lot 600157, action level excursion of 252cfu/~~ml~~ plate MSL 3-29-07 was raised for the center of the [redacted] table #12 in [redacted] Room (Limit [redacted] plate MSL 3-29-07

vi) Per Deviation #5043, during QA review, it was noted that pre-cleaning for [redacted] and [redacted] pipette controllers have not been completed on some equipment used in the harvesting process for batch 600157.

2) Regarding investigations conducted into the above microbial action levels of monovalent lots with high bioburden levels:

A) There is no documentation of the review of the validation of the effectiveness of disinfectants used in the cleaning of the facility including product contact and non-product contact equipment.

B) There is no documentation of the review of the Flu Mist manufacturing equipment cleaning validations, i.e. [redacted] Incubators, Biological and Dispensing Safety Cabinets, Silicon Rubber Housing of the Candling Lamps and Pipette Controllers.

C) No documentation that the audit of the egg supplier, [redacted] was conducted to review the farm's sanitation practices and if actions could be taken to minimize microbial contamination of eggs.

D) There is no documentation of the review of the same manufacturing processing operator conducting the pre-cleaning of the manufacturing area followed by manufacturing activities and post clean activities on the same day. For example:

i) An operator could conduct pre-cleaning activities, harvesting of eggs and then post-cleaning activities.

ii) An operator could conduct pre-cleaning activities, inoculation preparation, eggs Inoculation and post clean activities.

E) There is no documentation of literature review in regards to organisms that were isolated at the [redacted] step and the effect that these organisms could have if present in the released FluMist.

3) The following were observed during the set-up, sterile filtration, and/or aseptic dispensing of A/Wisconsin Monovalent Batch 600163 in the Dispensing Room (Room [redacted] on March 28, 2007:

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A) Operators working in the ISO Class (Class area which supports the ISO Class (Class Biological Safety Cabinet (BSC) (which is used to receive the sterile filtered monovalent and to dispense the sterile monovalent into bottles) were observed with exposed skin near the eye area.

B) An operator was observed cleaning his/her personal prescription glasses in the ISO Class area.

C) An operator was observed to sample his/her fingers onto a touch plate and then immediately (without re-gloving or sanitizing gloves) pick up the container within the BSC containing the sterile filtered monovalent in order to mix it.

4) Regarding disinfectant effectiveness studies:

A) The acceptance criteria of reductions for *C. albicans* and *A. niger* of the diluted used as disinfectant in the facility was not met during the disinfectant effectiveness studies dated November 2003. The disinfectant effectiveness study that was suppose to demonstrate sporicidal effectiveness was also found not effective on dried coupon of *A. niger*, However, the firm continued the use of to disinfect its manufacturing facility since the disinfectant validation of April 2003.

B) There are no assurances that the currently used disinfectant is effective against fungi and molds. Per Protocol #VF-41283 dated May 2nd 2002, for the disinfectant effectiveness study for the assay test method validation was for recovery rate. However, the data obtained during the performance qualification demonstrated that the minimum of acceptance criteria established per protocol (VF -41282R) was not consistently obtained during the positive control recovery studies. As such, the post execution acceptance criteria of the studies were changed to recovery of within of the inoculums content.

C) No disinfectant efficacy study has been conducted for the solution used to decontaminate outer egg shells at time of virus harvest.

5) The FluMist Master Production Record (batch record) lacks specificity. For example,

A) The validated hold time for the Ultracentifuge (Equipment #s rotor is not specified as per the Master Production Record for B/Malaysia Batch 600169.

B) No time limit has been established for the step as per the Master Production Record for B/Malaysia Batch 600169.

6) Sterile filtered FluMist monovalent bulks are dispensed into bottles at the following volumes: for storage at Regarding the study justifying the container closure integrity of these containers (Study LT-060174 & 060175):

A) The study did not evaluate the effect of the fill volumes on the integrity of these containers.

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B) The lowest torque documented as applied to the test container caps in the study was [redacted] The allowable range in actual use as per the Master Production record for B/Malaysia Batch 600169 is [redacted]

7) Regarding warehousing activities:

A) There is no written procedure for the control of keys in the warehouse area (Room [redacted] On 3/21/2007 a secure storage area (caged area) in Room [redacted] containing process material was observed secured with a padlock. In order to open this lock an employee was observed obtaining a key to a nearby key lock box (located in Room [redacted]) from another employee. The key to the secure storage area padlock was retrieved from this lock box. There is no written procedure governing this process.

B) There is no written procedure governing the control of access to a MedImmune warehouse area used for the receipt and storage of raw materials located at the [redacted] The [redacted] facility is not owned or operated by MedImmune.

C) On March 21st 2007, rejected products were observed in reject bin commingled with released and unreleased products in the QC liquid media storage area in the warehouse room [redacted]

FACILITIES AND EQUIPMENT SYSTEM

8) Regarding Product Contact Cleaning validations, there is no documentation of cleaning validations for the following product contact equipment in accordance with the associated SOPs. For example:

A) Cleaning validation of the silicone rubber housing per SOP #UKP0154 dated March 27th 2007. Technical Report study of R/0264/10/00 dated December 6th 2000 note that the highest level of contamination was recovered from the silicon rubber housing candling lamps.

B) Cleaning validation for the [redacted] per SOP #UKP0143 dated November 11th 2006. The [redacted] is used to score the specific pathogen free (SPF) eggs prior to harvest.

C) Cleaning validation of the [redacted] Pipette Controllers per SOP #UK0142 dated October 25th 2006. The pipette is used in the dilution of inoculum and to extract the allantoic fluid from the eggs.

D) Cleaning validation of the [redacted] Filter Integrity Tester per SOP #UK0144 dated March 22nd 2007. The integrity tester was noted as the root cause of the source of 11 microbial plate mold excursions during the manufacturing of lot 600157.

E) No validation studies were conducted to the support cleaning of the [redacted]

9) Not all manufacturing ISO Class [redacted] rooms, Biological Safety Cabinets and manufacturing equipment have documentation of cleaning validations. Per Validation Report #VL-400003-PQP-AI-R1 dated March 20th 2007 provided as cleaning validation documentation for the above ISO Class [redacted] Biological Safety Cabinets states: " this validation was to demonstrate that the

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Production Process Rooms Heating Ventilation & Air Conditioning (HVAC) System, Identification Number [redacted] located in the floor utility area of MedImmune's [redacted] Bulk FluMist Production Facility, in Speke UK continues to operate in a safe and effective manner in association with MedImmune procedures for material, personnel and equipment flow following the modifications performed to the [redacted] facility". However, the number of microbial surface samples taken during the above Validation (#VL-400003-PQP-AI-R1) were the same number of samples taken under normal monitoring process of these areas per SOP #UK0192, Environmental Monitoring Program for MedImmune [redacted] Manufacturing Facility. The following areas were covered by Validation Report #VL-400003-PQP-AI-R1:

A) ISO Class [redacted] (Class [redacted] Dispensing Room

B) [redacted] ISO [redacted] (class [redacted] Downstream Microbiological/Dispensing Safety Cabinets and [redacted] Laminar Flow units

C) [redacted] and [redacted] Incubator Units

D) [redacted] Eggs Chiller Rooms

10) Regarding the Purified Water System:

The firm discontinued the microbial sampling of [redacted] sampling points for the Purified Water System on November 2006 even though the microbial levels at these sample points were higher than the prior site incoming water sampling point microbial level. Per Technical Report #UKTR/0203 dated March 6th 2006, "During the performance qualification of the purified water system it was evident that the limits that had been set for points [redacted] were not achievable and therefore no limits were applied". (Set limit of [redacted] Microbial sample results of the discontinued valves compared to the prior incoming city water valve [redacted] with microbial limit of [redacted] are as follows:

	2005 max CFU/ml	2006 Max CFU/ml
[redacted]	18,400cfu/ml	790cfu/ml
	10,000cfu/ml	2,100cfu/ml
	10,000cfu/ml	2,400cfu/ml
	194cfu/ml	160cfu/ml

QUALITY SYSTEM

11. Per SOP #MSP-QA-0056 dated September 6th 2006, titled: Deviation Reporting and Management, manufacturing deviations are to be closed within a defined period of [redacted] calendar days of initiation unless otherwise noted through documentation requests. However, there is no defined period for the closure of corrective and preventive actions that are implemented as the result of

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deviations that are to be closed within [redacted] calendar days. It was noted that from March 2006 to March 2007 that the firm had 261 deviations. The Corrective and Preventive Actions (CAPA) associated with ~~and~~ 66 (25%) of these were closed within [redacted] days. For the remaining 195 (75%), some remained open for up to 8 months. For example: MJL 3-29-07

i) Deviation #4953, discovered June 28th 2006 regarding batch #300639 showing scanning errors on SAP for bottle [redacted] which was identified as [redacted] should have read [redacted] Similarly, bottle [redacted] of the same batch identified as [redacted] should have read [redacted] The deviation was created on June 29th 2006 and the deviation portion of the investigation was closed on July 10th 2006. However, the CAPA portion remained opened for 8 months and was not closed until February 9th 2007.

ii) Deviation #3234 with discovery date of April 27th 2006 regarding three objectionable organism excursions for hand plates from one operator was created on April 27th 2006. The deviation portion was closed on ~~July~~ May 24th 2006. However, the CAPA portion remained open for 6 months and was not closed until October 6th 2006. MJL 3-29-2007

iii) Deviation #5028 with discovery date of July 3rd 2006, regarding three microbial excursions raised for environmental monitoring of the Disinfectant makeup Room was created on July 5th 2006. The deviation portion was closed on August 14th 2006. However, the CAPA portion remained open for 6 months and was not closed until February 6th 2007.

LABORATORY CONTROL SYSTEM

12) Raw data generated in the Quality Control Laboratory is recorded onto uncontrolled data sheets. For example QC release test data for B/Malaysia Monovalent Batch 600169 was recorded onto forms with no tracking or serial number or other apparent means of control other than a date stamp showing the date the forms were generated.

13) SOPs used in the testing of FluMist Monovalents lack specificity. For example:

A) SOP UKC0220 Version 2.0 entitled "Response to Central Chart Recorder Alarms by Quality Control Department" does not specify the amount of time Quality Control Laboratory incubators, refrigerators, and freezers may be out of specification for temperature or humidity before a deviation must be written for expected alarm conditions.

B) Growth promotion testing of microbiological media is not necessarily performed under conditions consistent with the actual use of the media. For example, SOP UKC0043 Version 10.0 entitled "Growth Promotion and Sterility Testing of Microbiological Media" indicates that [redacted] Media (used for water testing) and [redacted] Media (used for environmental monitoring) are incubated for [redacted] depending on organism. SOP UKC0167 Version 6.0 entitled "Microbiological Analysis of Water" indicates that [redacted] agar cassettes are to be incubated [redacted] SOP UKC0004 Version 14.0 entitled "Receipt and Testing of Viable Environmental Monitoring Samples and Reporting of the Monitoring Results" indicates that [redacted]

14) Regarding Aseptic Processing Simulation of Sterile filtration of CAIV-T (Cold Adapted Influenza Virus-Trivalent):

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DURING AN INSPECTION OF YOUR FIRM (I) (WE) OBSERVED: media fill mtc 3-29-07

A) There is no documentation in the batch records or SOP #UKC0278 dated February 2nd 2007 titled: Performance and Evaluation of Aseptic Processing Simulation of Sterile Filtration of CAIV-T, regarding the performance of planned, unplanned and or worst case interventions during any of the aseptic media fills that has been simulated.

B) There is no documentation of batch records review for unusual occurrences during normal aseptic processing for consideration/incorporation into media fill simulations as interventions.

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

1. Pursuant to Section 704(b) of the Federal Food, Drug and Cosmetic Act, or
2. To assist firms inspected in complying with the Acts and regulations enforced by the Food and Drug Administration.

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

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