DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Center for Biologics Evaluation
and Research
1401 Rockville Pike
Rockville MD 20852-1448

May 24, 2007

CBER-07-010

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. David M. Mott
President and Chief Executive Officer
MedImmune, Inc.
One MedImmune Way
Gaithersburg, MD 20878

Dear Mr. Mott:

The Food and Drug Administration (FDA) conducted an inspection of MedImmune U.K. Ltd, a subsidiary of MedImmune, Inc. (hereinafter "MedImmune" or "your firm"), Plot 6 Renaissance Way, Boulevard Industry Park, Speke, Liverpool L24 9JW, United Kingdom, between March 21 and March 29, 2007. During the inspection, FDA investigators documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of FluMist bulk monovalent lots used to manufacture Influenza Virus Vaccine Live, Intranasal. These deviations from CGMP include deviations from the applicable requirements of Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), as well as requirements of your biologics license application approved under Section 351(a) of the Public Health Service Act (PHS Act) and Title 21, Code of Federal Regulations (21 CFR), Part 601.

At the close of the inspection, FDA issued a Form FDA 483, Inspectional Observations, which described a number of significant deviations in the manufacture of your bulk monovalent lots that are used to formulate Influenza Virus Vaccine Live, Intranasal, FluMist. Specific areas of concern include, but are not limited to:

INVESTIGATION OF BIOBURDEN EXCURSIONS

1. As a condition of the December 22, 2005, approval of a supplement (pursuant to 21 CFR 601.12(b)) to your Biologics License Application (BLA) for Influenza Virus Vaccine Live, Intranasal (STN 125020/12), you committed to FDA to agreed-upon

interim bioburden alert and action limits, to investigate any excursions from those limits under defined conditions, and to re-evaluate the interim limits based on data from the 2006/2007 campaign. During the 2006/2007 campaign, five out of [redacted] FluMist bulk monovalent lots manufactured between February 2006 and April 2006 exceeded the [redacted] virus harvest interim bioburden action limit of [redacted] cfu/ml and/or the [redacted] virus harvest interim bioburden action limit of [redacted] cfu/ml. Three of the five FluMist bulk monovalent lots that exceeded the interim bioburden action limits were used in the formulation of final product (lots 600147, 600153, and 600157). We acknowledge that the subsequently filtered monovalent lots and the final vaccine product resulting from those lots met all specifications. However, based on FDA's experience, there is a high probability that the observed CGMP deviations, if not corrected, would substantially increase the risk of product failures. Of particular concern are your inadequate investigations into such excursions, and your lack of implementation of appropriate corrective and preventive actions, coupled with deficiencies in: aseptic practices by personnel, cleaning validation of equipment and effectiveness of the cleaning and disinfection processes used in your manufacturing facility and by your personnel. Adequate investigations and correcting deficiencies in the process before they result in product failures are underlying principles of CGMP.

The investigations that your firm performed for the interim bioburden action limit excursions did not adequately satisfy your December 2005 commitment to the agency which was incorporated into you BLA through the approval of your supplemental application (STN 125020/12). In addition, your investigations were not performed in accordance with CGMP because they were inadequate, and because corrective and/or preventive actions were neither identified nor implemented to prevent recurrence. Specifically:

a) Your firm generally concluded that all isolates from the interim bioburden action limit excursions were associated with eggs. However, some microorganisms identified included those commonly associated with the environment and/or water (e.g., *Brevibacterium ssp, Pseudomonas stutzeri, Staphylococcus aureus*), in addition to those commonly associated with eggs (e.g., *Enterococcus faecalis, Escherichia coli*). We also note that the microorganisms you have identified as being associated with eggs have also been identified during environmental monitoring of your manufacturing facility and your personnel (see item c below). No corrective actions have been proposed or implemented to control microbial contamination of the eggs or to minimize the introduction of microbial contamination from the manufacturing facility or personnel, all of which are important in ensuring the quality of your product.

b) For any of the action limit excursions you identified as being associated with eggs, your firm did not perform a review of the flock from which the eggs were obtained and/or make a determination as to whether the flock should be used for future production of vaccine. You committed to perform such a review for each action limit excursion in your December 8, 2005 correspondence to the agency, which was incorporated into your BLA through the approved supplemental application. Such a

review should also include an evaluation of your egg suppliers' sanitation and handling practices to determine whether any corrective actions could be implemented to minimize microbial contamination of eggs.

c) Your firm's conclusions after investigations conducted into the interim bioburden action limit excursions, which your firm repeated in its response to the agency, are contradicted in many cases by documentation collected during our inspection. For example:

During the manufacture of A/Wisconsin lot 600157, two of the [redacted] sub-lots exceeded the [redacted] virus harvest interim bioburden action limit of [redacted] cfu/ml: 1.25 x 10^4 and 9.4 x 10^3 cfu/ml, respectively. Deviation Report 3463, initiated for those interim bioburden action limit excursions for A/Wisconsin lot 600157, concluded that that "the root cause investigation conducted has not determined any anomlies [anomalies] or deviations associated with either the QC testing or manufacture of batch 600157 that could have resulted or contributed to the bioburden excursion observed...." The report also stated: "Environmental control was maintained throughout. It is likely that the contamination originated from the eggs and were [was] present before use within manufacturing." The product impact assessment concluded that there are not "product implications" and includes the following reasons: "Environmental control was maintained throughout the critical and non-critical manufacturing stages," and "No deviations or anomalies were identified from the manufacturing review which could have resulted in the bioburden excursion."

We also note that the deviation reports associated with the interim bioburden action limit excursions generally contain the very same conclusions.

Contrary to those conclusions – that nothing in the environment or personnel could have contributed to the high bioburden in the monovalent sub-lots – your firm's records reveal environmental and personnel monitoring excursions directly associated with the manufacture of this lot during harvest and downstream processing operations. The isolates identified from the environment and personnel included the same microorganisms identified in the interim bioburden action limit excursions (e.g. *Staphylococcus aureus, Escherichia coli, Brevibacterium spp., and Enterococcus faecalis*.) Consequently, your firm should have investigated the possibility that the bioburden in the lots came, at least in part, from your facility's environment and/or personnel. In addition, according to your own firm's Quality Assurance review, you used some [redacted] and the [redacted] pipette controllers to manufacture this lot before your firm finished pre-cleaning that equipment. Clearly, several potential sources could have contributed to the lot's high bioburden, and your firm should have investigated those potential sources thoroughly.

d) Your firm's investigations also did not include review of the cleaning validation status for the [redacted] the [redacted] incubators, the dispensing and Biological Safety Cabinets, or the silicon rubber housing of the

candling lamps (see Item 6) or the effectiveness of your cleaning and disinfection processes used in your manufacturing facility and by your personnel (see Item 4).

We acknowledge that you did re-evaluate the interim limits based on data from the 2006/2007 campaign and that you set bioburden limits for the 2007/2008 campaign, in accordance to your commitment. Based on the data, the virus harvest alert and action limits were increased to cfu/ml and cfu/ml, respectively, and the virus harvest alert and action limits were decreased to cfu/ml and cfu/ml, respectively.

At the time of the inspection, two of the bulk monovalent lots that had been produced for the 2007/2008 campaign exceeded the adjusted bioburden action and/or alert limits that you established based on your own data from last season. You must investigate those excursions thoroughly, as you committed to the agency to do, and as your BLA now requires. Your investigations into these excursions were ongoing at the time of the inspection.

PRODUCTION AND PROCESS CONTROLS

2. You failed to ensure that operators performing setup, sterile filtration and /or aseptic dispensing use proper aseptic techniques to prevent microbial contamination of monovalent lots. Specifically:

a) Operators were observed wearing safety glasses allowing for skin to be exposed and, therefore, increasing the opportunity for contamination.

b) On March 28, 2007, an operator was observed removing his/her safety glasses, then removing and cleaning his/her prescription type glasses, thus allowing for skin to be exposed.

c) Also, an operator was observed sampling his/her fingers onto an agar touch plate and without sanitizing or changing his/her gloves, mixing the sterile filtered monovalent.

3. Master and batch production records lack specificity. This issue was discussed with senior management at your firm during the March 6 to March 9, 2006, inspection and correction was promised, but has not been achieved. For example:

a) Master Production Record for B/Malaysia/2506/04 Batch Number: 600169 entitled "The Decontamination and Disassembly of the Ultracentrifuge within the Downstream Processing Room" does not document the maximum soiled hold time limit you established for the Ultracentrifuge rotor. Such documentation is important to ensure that subsequent cleanings are performed within validated timeframes. It is important to clean within the validated timeframes to ensure complete removal of product related material and microorganisms.

b) Master Production Record for B/Malaysia/2506/04 Batch Number: 600169 entitled "Filter Preparation, Sterile Filtration and Dispensing of Monovalent Bulk" does not include an established time limit for the aseptic dispensing step.

BUILDINGS AND FACILITIES

4. You have failed to establish the effectiveness of the cleaning and disinfection processes used in your manufacturing facility and by your personnel. For example:

a) From April 14- May 3, 2006, there were numerous environmental monitoring excursions for mold in Downstream Processing Room [redacted] Deviation report 3089 discusses the isolation of mold from the curtains around the laminar flow units after cleaning; from an operator's hand during filter connection activities in the Biological Safety Cabinet; from the ceiling Heating, Ventilation and Air Conditioning (HVAC) vent; and from the filter integrity tester, in addition to other locations. During this time, monovalent lots 600156 and 600157 were processed in room [redacted] One of the conclusions of your firm's root cause analysis was as follows, "A number of environmental monitoring excursions investigations have come to the conclusion that the cleaning performed in UK-1 [Medimmune's manufacturing site] may not always be effective." However, there is no indication that you reviewed the effectiveness of the cleaning or disinfecting agents used.

b) In addition, other microorganisms were found in the egg incubator, on a harvesting room operator's hand, on the harvest room table, and on a downstream processing room operator's hands. These microorganisms, including *Staphyloccoccus aureus, Escherichia coli,* and *Enterococcus faecalis* are the same isolates found in sub-lots of monovalent 600157. There is no indication that you reviewed the effectiveness of the cleaning or disinfecting agent used.

c) The November 2003 disinfectant effectiveness validation study of [redacted] used to disinfect your facility, did not meet your established [redacted] log reduction acceptance criterion for [redacted] set forth in your validation study protocol. [redacted] is the study microorganism used to evaluate the effectiveness of cleaning agents on fungi and mold.

d) There is no assurance that the disinfectant [redacted] is effective against mold, since it did not meet your established recovery rate acceptance criterion in the December 2001 "Disinfectant Validation and Efficacy Study of [redacted] by the Surface Test Method" study.

e) There has been no evaluation of whether the [redacted] solution, used to decontaminate outer egg shells during the virus harvest step, is effective in the manner used by your firm.

5. Your firm failed to establish separate or defined areas or other control systems for your operations to prevent contamination or mix-ups. For example:

a) There is no procedure in place regarding controlled access to the MedImmune offsite warehouse used for receipt and storage of raw materials known as [redacted]

b) Rejected materials were observed stored with released and un-released raw materials.

CLEANING AND MAINTENANCE OF EQUIPMENT

6. Cleaning validation for the [redacted] the [redacted] incubators, the dispensing and Biological Safety cabinets, and the silicon rubber housing of the candling lamps has not been performed.

The deficiencies described in this letter are indicative of your quality control unit not fulfilling its responsibility to assure the identity, strength, quality, and purity of your components/in-process materials. Please describe in detail how MedImmune will attain CGMP compliance with regard to monovalent bulk failure/deviation investigations. Please include in that description how MedImmune will use all of the relevant information to conduct a root cause analysis, to ensure that adequate steps are taken to evaluate whether deviations impact product, and to implement effective corrective and preventive actions.

We acknowledge receipt of your written response dated April 27, 2007, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection. Corrective actions addressed in your letter may be referenced in your response to this letter; however, we believe that your response did not provide sufficient detail to fully assess the adequacy of the corrective actions. Our comments and requests for further information regarding corrective action are detailed below. The items correspond to the observations listed on the Form FDA 483:

Production system, items 1-2

We agree with your response that excursions above alert or action limits do not necessarily mean that product should be rejected and we also agree with your statement that comprehensive investigations should be performed when alert and/or action limits are exceeded. We also acknowledge your previous discussions with CBER regarding the establishment of interim bioburden action/alert limits.

However, as described in this letter, MedImmune has not performed adequate and complete investigations into the deviations, as required by section 501(a)(2)(B) of the FD&C Act and by your biologics license application that FDA approved under section 351 of the PHS Act, as supplemented pursuant to 21 C.F.R. §601.12(b). Although your firm did perform investigations for the interim bioburden action limit excursions, the investigations were not performed in accordance with CGMP in that they were inadequate, and that corrective and/or preventive actions were not identified or implemented to prevent recurrence. In addition, the investigations did not satisfy your

December 2005 commitment to the agency, which was incorporated into your BLA, to investigate the root cause and determine appropriate corrective actions when interim bioburden action/alert limits were exceeded.

Please provide all investigation reports for the bulk monovalent lots produced for the 2007/2008 campaign which exceeded the bioburden action and/or alert limits

Production system, item 4a-b

Your response states that relevant [redacted] Standards were used in the study protocols to set the criteria for disinfectant ([redacted]) effectiveness and that although the results did not meet the stated [redacted] Standard acceptance criterion, the study demonstrated that the disinfectant was reasonably effective in fungal inactivation. Your response also states that a disinfectant ([redacted]) effectiveness study was performed and that pre-established recovery rate acceptance criterion was not consistently met during the execution of the protocol. Based on the environmental monitoring results mentioned above, we recommend that you perform disinfectants effectiveness studies in which all your acceptance criteria are met.

We also note that beginning in 2007 the European Union banned the use of [redacted] and [redacted] disinfectants. Please provide us your plans for the replacement of these disinfectants and their validation.

Facility and Equipment systems, items 8b and 9b-c

Your response indicates that microbiological control of non-product contact surfaces, including equipment and ISO classified rooms is validated for cleaning effectiveness utilizing the standard IQ, OQ, and environmental monitoring PQ approach. However, based on the documentation collected during our inspection, there is no assurance that your cleaning is effective, since microorganisms associated with eggs have also been identified during environmental monitoring of your manufacturing facility and your personnel.

Neither this letter nor the list of inspectional observations (Form FDA 483) is meant to be an all-inclusive list of deficiencies that may exist at your facility. It is your responsibility as management to assure that your establishment is in compliance with the provisions of the FD&C Act, PHS Act, and applicable federal regulations. Federal agencies are advised of the issuance of all Warning Letters about drugs so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in FDA initiating regulatory action without further notice. Such action may include license suspension and/or revocation.

To facilitate your remediation effort we request a meeting with you and other senior management at MedImmune to further discuss the issues cited in this letter and your proposed responses to address them. Given the potential contributions of safe, pure and potent influenza virus vaccine to the public health, we encourage regularly scheduled and

frequent interactions between your technical staff and FDA in an effort to help MedImmune move forward with corrective actions as rapidly as possible.

Please notify us in writing, within 15 working days of receipt of this letter, of any additional steps you have taken or will take to correct the noted violations and to prevent their recurrence. Include any documentation necessary to show that correction has been achieved. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your reply should be sent to me at the U.S. Food and Drug Administration, Center for Biologics Evaluation and Research, HFM-600, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448. If you have any questions regarding this letter, please contact Mr. Robert A. Sausville, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

Mary A. Malarkey
Director
Office of Compliance and Biologics Quality
Center for Biologics Evaluation and Research

Cc: Mike Austin
Senior Director, Site Operations
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