



APR 28 2008

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

OEWL-08-02

EXPRESS MAIL

Richard T. Clark
President and Chief Executive Officer
Merck and Company, Inc.
770 Sumneytown Pike
West Point, Pennsylvania 19486-004

Dear Mr. Clark:

The Food and Drug Administration (FDA) conducted an inspection of Merck and Company, Inc., West Point, Pennsylvania, between November 26, 2007, and January 17, 2008. During the inspection, the FDA investigators documented significant deviations from current good manufacturing practice (CGMP) in the manufacture of licensed biological vaccine products, bulk drug substances, and drug components. These products include Liquid PedvaxHIB®, RECOMBIVAX HB®, ProQuad®, Gardasil®, VAQTA®, and COMVAX®. These deviations from CGMP include non-compliance with Section 501(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the requirements of your biologics license application approved under Section 351 of the Public Health Service Act (PHS Act), and Title 21, Code of Federal Regulations (21 CFR) Parts 210 and 211.

At the close of the inspection, the FDA investigators issued a Form FDA 483, Inspectional Observations, which described a number of significant objectionable conditions relating to your firm's compliance with CGMP. Significant deviations observed during the inspection include, but are not limited to, the following:

CGMP DEFICIENCIES CONCERNING DRUG PRODUCTS

1. You failed to thoroughly investigate any unexplained discrepancy of a batch or any of its components to meet any of its specifications whether or not the batch has already been distributed and to extend the investigation to other batches of the same drug product and other drug products that may have been associated with the specific failure or discrepancy [21 CFR 211.192]. For example:
 - a. You submitted a Biological Product Deviation Report to FDA in October 2006, due to the [redacted] of Varivax III being out-of-specification at the two month stability time point. This product had been shipped to the [redacted] and then returned to the United States before being placed on stability. The product was not licensed in the United States at the time of the deviation. Your investigation concluded that the

failure was due to the ingress of [REDACTED] into the vial headspace during shipment [REDACTED]. Your investigation did not include testing of other potentially affected products shipped [REDACTED], for example, ProQuad®, to determine if there were any detrimental effects on these products.

- b. Numerous customer complaints have been received citing over-pressurization of vials. For example, Complaints 48891 and 53106 for Zostavax®, lot [REDACTED] concerned over-pressurization of vials. The investigations did not address the possibility of [REDACTED] ingress as the reason for over-pressurization of vials. The investigation also did not consider the possibility that the packing method might not be functioning as validated.
 - c. Not all lots of product that may have been affected by fibers being shed from [REDACTED] lot [REDACTED] were assessed. Only [REDACTED] lots of product, where the fibers were observed during filling, were quarantined and assessed. Approximately [REDACTED] lots of lyophilized product and [REDACTED] lots of liquid products were filled during the time of receipt and use of [REDACTED] lot [REDACTED].
 - d. Product lots that failed the initial [REDACTED] visual inspection for critical defects such as [REDACTED] and [REDACTED] were not thoroughly investigated. For example, MMR II® lots [REDACTED] and [REDACTED] failed the critical defect category for [REDACTED] and no investigations were performed. These lots were subsequently distributed.
2. You failed to establish adequate written procedures describing the handling of all written and oral complaints regarding a drug product [21 CFR 211.198]. For example, Standard Operating Procedure (SOP) 283-316, [REDACTED] directs that a lot history be performed. This lot history is performed for the final finish lot number, which is the packaging/labeling lot number. However, complaints such as leaking vials/syringes and various container/closure defects would be associated with a fill lot number, and a fill lot number may be associated with several final finish lot numbers.
3. Your firm failed to assure that there are written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess [21 CFR 211.100(a)]. For example:
- a. The validation performed in December 2006 for [REDACTED] machines 2, 3, and 4 is not representative of the actual automated inspection process for detection of [REDACTED] defects, in that there was no assessment of acceptably filled vials. This equipment is used to inspect multiple vaccine products from filling lines 131 and 138.
 - b. Process control limits were not evaluated and re-established for filling line defects for Zostavax® as required by SOP 300-103X. The SOP states that the Process Control Limits (PCL) should be evaluated after the first [REDACTED] lots and again after [REDACTED] lots or sooner if changes were made to the process. [REDACTED] lots

were inspected by the [REDACTED] from February 2006 to September 2007, yet the limits have not been evaluated.

4. You failed to assure that equipment used in the manufacture, processing, packing and holding of a drug product is calibrated, inspected, or checked according to a written program designed to assure proper performance [21CFR 211.68(a)]. Specifically, a set of control samples representing defect types are examined by the automated inspection equipment prior to beginning each inspection process. The reject set testing allows high rates of known rejects to be accepted by the equipment. In addition, the first time non-accepts are sent back through the equipment and only those rejected a second time are discarded.
5. You failed to exercise appropriate controls over computer or related systems to assure that changes in master production are instituted and input and output from the computer or related system of formulas are checked for accuracy and maintained [21 CFR 211.68(b)], in that there is no documentation to support software manufacturing change performed to the [REDACTED] code used in the manufacture of Gardasil®, lots [REDACTED] and [REDACTED].
6. You failed to establish test procedures or other laboratory control mechanisms designed to assure that drug products conform to appropriate standards of identity, strength, quality, and purity and to assure that any deviation from the written test procedures or laboratory control mechanisms shall be recorded and justified [21 CFR 211.160(a) and (b)]. For example:
 - a. During review of atypical process reports (APR's), QA release personnel may edit the number of occurrences calculated by the software. This practice is not addressed in the product release SOP. In addition, the practice has been used inconsistently. The number of occurrences is reportedly decreased if the root causes of the multiple deviations are not related; however, the opposite logic was applied to nine test failures for VAQTA®. These nine test failures, although related, were recorded as a single occurrence in the deviation tracking system.
 - b. CP 9110.001, [REDACTED] does not direct that any anomaly concerning the product or sample preparation such as leaking vials or test canisters, over-pressurized vials, or particles be documented on the testing worksheet. The procedure only addresses foreign material in test media and the inability to reconstitute lyophilized product. In these cases, the instructions are to notify the supervisor.
 - c. There are no data to support extension of expiration for preservative-free RECOMBIVAX HB® Reference Standard Lot [REDACTED] to [REDACTED] years, as [REDACTED] year stability data are not yet available.

CGMP DEFICIENCIES CONCERNING BULK DRUG SUBSTANCES AND DRUG COMPONENTS

Additionally, significant deviations in manufacture of your bulk drug substances and drug components were observed during the inspection. These deviations cause your bulk drug substances and drug components to be adulterated within the meaning of Section 501(a)(2) (B) of the FD&C Act. Specific areas of concern include, but are not limited to:

Production and Process Controls

1. You failed to assure that there are written production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess. For example:

- a. SOP 209-205X, [REDACTED] allows for a maximum of three re-dispensing operations prior to filling. To date, there have been no stability studies initiated for [REDACTED] re-dispensed bulk.
- b. There are no data to support the [REDACTED] post [REDACTED] hold time for tanks used in the [REDACTED] Manufacturing Complex ([REDACTED]). Specifically, the tanks used for media challenges to support the [REDACTED] post [REDACTED] hold were not equivalent to the PedvaxHIB® processing tanks. The tanks used are [REDACTED] with [REDACTED] while the PedvaxHIB® tanks have [REDACTED] with [REDACTED]. Additionally, the tanks used in PedvaxHIB® production include assemblies that are connected to the tank and [REDACTED] in place.

Failure Investigations

2. Failures are not fully investigated and documented, nor extended to other batches as appropriate. For example:

- a. You failed to quarantine numerous process intermediates associated with the use of [REDACTED] filter membranes that were identified to cause foaming during filtration. This foaming was found to be associated with leaching of [REDACTED] into process intermediates. These process intermediates were used to further manufacture MMR®II, PedvaxHIB®, VAQTA®, VARIVAX® product lots.
- b. Your investigation into leaks discovered in the [REDACTED] during [REDACTED] recharge for lot [REDACTED] concluded that the leaks resulted from a small hole in the [REDACTED]. The investigation also concluded there was no impact "due to the isolation of the leak and immediate remediation of the leak." Attached to the investigation was an unsigned and undated

chronology of events, estimated to the second. This information was derived from a notebook maintained by the production operator. However, these pages from the notebook are no longer available.

- c. APR 2006-204C-0034 dated 8/24/2006 was issued for the sterility failure of Pedvax bulk lot [REDACTED]. The contaminant was noted as [REDACTED]. The investigation failed to assess a recent change in the SIP cycle for [REDACTED] tank [REDACTED], implemented in [REDACTED]. The validation of this SIP change was subsequently implicated during investigation of the failure of a [REDACTED] media challenge, which led to the recall of several PedVaxHIB® and COMVAX® lots.

Laboratory Controls

3. Laboratory controls do not include scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure components and products conform to appropriate standards of identity, strength, quality and purity. For example, there has been no evaluation of the stability of [REDACTED] measles, mumps and rubella drug components over the multiple year storage and use periods. Existing stability data for the drug components are limited to potency of the vaccine components and sterility testing.

Building and Facilities

4. Written procedures for the use of cleaning and sanitizing agents designed to prevent contamination of your facility are incomplete. Specifically, SOP 204-608X, [REDACTED] does not provide a frequency for performance of the multi-step decontamination with [REDACTED].

Maintenance of Equipment

5. Written procedures are not followed for the maintenance of equipment used in manufacture, processing, packing or holding. Specifically:
 - a. Work order 1400076, dated August 29, 2007, issued for the 6-month maintenance on the PedvaxHIB® [REDACTED] tank [REDACTED], required a check of the condition of the [REDACTED]. This action was documented as "NA". However, there was no documentation as to why this prescribed action was not completed.
 - b. Work order 1415800, dated September 9, 2007, issued for the annual maintenance of the PedvaxHIB® [REDACTED] on [REDACTED], documented the first ten (10) inspections on the work order as "NA". However, there was no documented reason for the failure to complete these activities.

Containers and Closures

6. You failed to assure that container closure systems provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of bulk drug substances and sterile solutions used in production. For example:

- a. Study FR #99-053, [REDACTED] did not include an assessment of the effect of storage conditions. This container/closure is used for bulk drug substances including Pedvax®HIB, RECOMBIVAX®, and [REDACTED].
- b. [REDACTED] sterile filtered solutions used in the manufacture of vaccines are stored in containers for [REDACTED]. Validation studies have not been conducted to assure container/closure integrity.

The deficiencies described in this letter are indicative of your quality control unit's inability to fulfill its responsibility to assure the identity, strength, quality, and purity of your drug product and drug substance.

We acknowledge receipt of your written response dated February 15, 2008, which addresses the inspectional observations on the Form FDA 483 issued at the close of the inspection, and we have reviewed its contents. Corrective actions addressed in your letter may be referenced in your response to this Warning Letter; however, we believe that your response(s) 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:

Observation 2

Your response indicates that although direct testing of other products susceptible to ingress was limited in scope, there was no detrimental affect on product potency and/or sterility. However, your investigation states that impact to vaccine potency for MMR can not be extrapolated from the results obtained for the Varivax III product. In addition, your investigation states that due to the limited capacity of the ProQuad® single dose product (04984-00), impacts the vial headspace and the resulting lower upon reconstitution. Please provide an explanation to clarify these statements.

Observation 3

Please note that the investigation report dated December 20, 2007, for MMR Lot [REDACTED] is referred to as the final investigation report in the letter preceding the report. This report was also presented to the investigator as the Final Manufacturing Investigation. Alternatively, you refer to this report in your response as "a summary of your comprehensive investigation...in response to the request from [REDACTED]" Please explain if this is a final report or a summary of the final report.

Observation 14

Your response did not provide any documentation of the inputs and outputs generated during your investigation of the incident that caused the omission of the coding observed during the manufacture of Gardasil® lots. Additionally, your response did not include an explanation of the code, which controls the updates and downloads in the [REDACTED]

Observation 15

In your response you state "Independent of the high antigen content, an analysis of the Enzyme ImmunoAssay (EIA) method indicates that it is performing within historical parameters..." you also state that the findings from your investigation to date conclude that: "The EIA was underestimating the antigen content at the [REDACTED] step. This measurement is used to determine the antigen concentration taken into the [REDACTED]" As these statements seem to contradict each other, please provide a detailed explanation to clarify these statements.

Observation 16

In your response you acknowledge the importance of effective glass management in vial filling areas and the need to ensure that the line clearance procedures address the removal of broken glass from critical processing areas and equipment. We acknowledge the formation of a Glass Breakage Management Team and the issuance of a guidance document entitled, "Management of Glass Breakage," on October 15, 2007. Please provide an update relating to your divisional glass breakage initiative. Please include the status of the three action items mentioned at the end of your response to this observation.

Observation 18

Your response seems to be adequate and will be followed up at the next inspection. However, we noted that during the inspection, information was given that does not correlate with the information in your response. During the inspection, your production supervisor indicated that the [REDACTED] system recorded the data but that there was no review of the monitoring data collected by the system. Also, at two different times during the inspection your production supervisor was unable to provide any information to explain the cited pressure losses.

Observation 20 C

Your response indicates that no marketed product has been manufactured with measles drug components held for more than [REDACTED] years and that all measles drug components in inventory at or greater than [REDACTED] years have been quarantined. However, your response does not address how the potency out-of-specification stability result will affect the expiration dating of measles drug components and vaccine drug products made from these drug components. Please comment.

Observation 25

Your response stated that independent of the validation of [REDACTED] #2 and #3 for volume of fill, there was no impact to product quality for all lots produced since there is an additional 100% manual inspection for [REDACTED]. Please provide the procedure(s) in

place prior to and after the current inspection covering the 100% manual inspection for volume of fill.

Observation 34

Your response states that you have verified that none of the data entry errors impacted the [REDACTED] leak test results or resulted in the incorrect use of the [REDACTED] within your manufacturing areas. Furthermore, you state that you conducted and completed a thorough investigation into the root cause for these errors and you list several corrective actions that will be implemented to address the causes. Please provide information on how you verified the [REDACTED] leak test results or that no [REDACTED] were used in manufacturing. Additionally, the investigation and relevant documents as well as the updated SOPs you mention in your response should be available for review at the next inspection.

Observation 37

Your response included the same historical data for two of the markers [REDACTED] in CP9110.780 and the Historical Reference Curve ED₅₀ Values in CP9110.780) that were reviewed during the inspection. Furthermore, updated data submitted in support of the historical [REDACTED] parameter in CP9110.780 continue to show a downward trend with respect to the upper and lower control limits. These data are also inadequate to support the expiry extension. Commitments to evaluate the expiry date for the November 2006 and November 2007 extensions (based on historical performance evaluation markers) and update the extension parameters in SOP 129.022 [REDACTED] are noted; however, these do not address the problems with IVRP assay. Please provide the results from the investigation of the 48 month stability time point investigation and additional information regarding storage of the gold standard reference material (Lot [REDACTED]).

Observation 38

Your response indicates that you will establish a [REDACTED] year re-evaluation date on [REDACTED] based on the supplier's [REDACTED] years stability data at [REDACTED]. If this critical reagent has a re-evaluation date, please explain your criteria for extending the date. Also, please clarify whether or not the [REDACTED] is stored at -20°C and whether there is data to support the [REDACTED] year storage at [REDACTED].

Observation 43

Your response indicates that by March 31, 2008, you will have established the following: 1) a procedure clearly defining those individuals that had authority to delete tests in [REDACTED] (would coincide with modification of [REDACTED] users accounts) and what documented approvals would be required prior to deletion of a test; and 2) a report which will summarize all deleted tests, which will be reviewed and approved by laboratory management and then forwarded for approval to the Director/Associate Director of Product Release on a monthly basis. Copies of the relevant SOPs as they relate to your enhancements regarding test deletions and reports summarizing all deleted tests should be available for review at the next inspection. Finally, it was stated during the inspection that your firm was also going to conduct an evaluation of the need to assess all

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Merck and Company, Inc.

pharmaceutical products to confirm that all release tests were performed. What is the status of that evaluation?

Neither this letter nor the observations noted on the Form FDA 483, which were discussed with you at the conclusion of the inspection, are intended 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 Federal Food, Drug, and Cosmetic Act, Public Health Service Act, all applicable federal laws and regulations, and the standards in your license. Federal agencies are advised of the issuance of all Warning Letters about biological products so that they may take this information into account when considering the award of contracts.

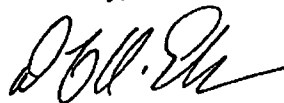
To facilitate your remediation efforts we request a meeting with you and other senior management at Merck to further discuss the issues cited in this letter and your proposed responses to address them. Given the potential contributions of safe, pure, and potent vaccines to the public health, we encourage frequent interactions between your technical staff and FDA in an effort to help Merck move forward with corrective actions as rapidly as possible.

Please notify this office in writing, within 15 working days of receipt of this letter, of any 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. Failure to promptly correct these deviations may result in regulatory action without further notice. Such actions may include license suspension and/or revocation, seizure or injunction.

Your response should be sent to Food and Drug Administration, Office of Regulatory Affairs/Office of Enforcement/Division of Compliance Management and Operations, HFC-210, 15800 Crabbs Branch Way, Rockville, Maryland 20855.

If you have any questions regarding this letter, please contact Jacqueline Little, Ph.D., Team Biologics Compliance, Division of Compliance Management and Operations, at (240) 632-6863. To schedule a meeting at your earliest convenience, please telephone Julie D. Bringger, Compliance Officer, Team Biologics Compliance, at (904) 281-1924, ext. 104, to discuss an appropriate date and time for the meeting.

Sincerely,



David K. Elder
Director
Office of Enforcement
Office of Regulatory Affairs