DEPARTMENT OF HEALTH & HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PHILADELPHIA DISTRICT

900 U.S. Customhouse
2nd and Chestnut Streets
Philadelphia, PA 19106

Telephone: 215-597-4390

April 7, 2008

Karl Stark
Philadelphia Inquirer
400 North Broad Street
Philadelphia, PA 19101

RE: FOI Request(s) #2008-1756

Dear Mr. Stark:

This is in response to your March 4, 2008 request for record(s) from the Food and Drug Administration pursuant to the Freedom of Information Act regarding Merck and Company, West Point, PA. We are enclosing the requested record(s) consisting of:

FDA-483 dated January 17, 2008.

Please excuse our delay in response.

In order to help processing time and costs, certain material may have been deleted from the record(s) furnished to you because a preliminary review of the record(s) indicates that the deleted information is not required to be publicly disclosed. If, however, you desire to review the deleted material, please make an additional request to the following address: Food and Drug Administration, Freedom of Information Staff (HFI-35), 5600 Fishers Lane, Rockville, MD 20857. Should the Agency then deny this information, you would have the right to appeal such denial. Any letter of denial will explain how to make this appeal.

The following charges may be included in a monthly invoice:

Reproduction $2.10 Search $-0- Review $-0- Total $2.10

The above total may not reflect charges for this request. Please do not send payment unless you receive an invoice for the total monthly fee.

Sincerely,

Robin M. Rivers
Compliance Officer
Philadelphia District Office

Enclosure

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

* 11/26-30/07, 12/3-7, 10-13, 17-21/07, 01/02-04, 1/7-11, 15-17/2008

QUALITY SYSTEM

1. Investigations into unexplained discrepancies did not always extend to other lots / products that may have been associated with the discrepancy. Specifically, the firm failed to quarantine/assess all product or process intermediates affected by atypical events pending completion of investigation as required by Quality SOP 286-125X, Processing Atypical Process Reports (APR) in Vaccine/Sterile Operations. For example,

   A. On-going investigation into [redacted] issued on 8/13/2007 for foaming during filtration of product [redacted] The investigation determined that the foaming was due to [redacted] being extracted from the [redacted] filter membrane into the filtrate. The investigation states that these filters are used for all large scale culture media formulations and "any culture media manufactured with the same lots of filters as the subject lots are potentially impacted by this atypical event." However, the firm has only quarantined the distilled water (WFI) lots associated with the observed foaming even though it was determined that the observation of foam was unique to filling of distilled water as many culture media and buffers have inherent foaming properties, AND the ISSUE MAY BE WITH the FILTERS COULD GO UNNOTICED IN those PRODUCTS. Am 1/17/2008. 1/17/08 AM

      i. The associated filter lots have been identified as used in approximately [redacted] media and buffer formulations, which have been used to manufacture numerous bulk and final product lots including MMR-II, Pedvax HIB, Vaqta, Varivax, Black Widow Spider ANTIVENIN, and Elspar.

      ii. In addition to the [redacted] filters implicated, several other filters used during manufacture bulk and final product consist of the same [redacted] filter membrane. Related [redacted] dated 10/19/2007 and updated 12/7/07, lists numerous final product lots released from April 2007 to date that used a [redacted] sterilizing membrane. These lots were not quarantined pending outcome of the investigation.

      iii. The Director of West Point Product Release made the decision not to quarantine all products affected from the associated filter lots on 9/12/07. Medical assessment and preliminary toxicological data were not dated completed until 9/27/07 and 10/29/07, respectively.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng Jacqueline Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

iv. The toxicological assessment estimated concentrations of [redacted] that were derived from TOC concentrations in the 1st liter WFI collected form the flush of the filter. Additionally, there was no assessment of the potential for higher concentrations extracted with other medias, buffers, and products filtered through these membranes.

v. The BPDR stated that the culture media department implemented a pre-screening of incoming lots of the [redacted] filters prior to use. However, at the time pre-screening was only implemented for the [redacted] filters used in the Culture Media, Department 207. This pre-screen was not implemented for all filters with the [redacted] membrane and in all departments using these filters until December 2007.

B. Atypical Process Report [redacted] was initiated 6/14/2007 for "fibers" being found on the stoppers and in the stopper bowls during the filling of [redacted] lots of MMR [redacted] on line [redacted] lots of Varivax Process Upgrade [redacted] lots of Zoster (PHN) Vaccine [redacted] and [redacted] of Elspar on line [redacted] The root cause of the fibers found in the stopper bowls and on the stoppers was identified to be "a lesser quality" of [redacted] bags received from the vendor. These bags are used for storage of the stoppers through the sterilization process until use. For the stoppers used in lyophilized product, the bags are kneaded after sterilization with the stoppers inside. Kneading of the bags was identified as a contributing factor and the fibers were observed after the kneading. [redacted] lot of the [redacted] bags, vendor lot [redacted] was identified as the source of the fibers. The following deficiencies were noted for the investigation:

i. Not all lots of product that may have been affected by the lot of [redacted] bags in question 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 the [redacted] bag lot in question.

ii. There was no 100% reinspection performed for the entire lots of Elspar lot # [redacted] Zoster (PHN) [redacted] and Varivax lot [redacted] where the fibers were observed during filling. Portions of these lots were segregated, re-inspected and released and portions of these same lots were rejected. For example:

- Elspar lot [redacted] consisting of approximately [redacted] vials was initially inspected manually on

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J. Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

6/25/07. The lot was portioned and grouped due to fibers being found in the stopper bowl [redacted] vials were manually reinspected on 11/12/07. Upon reinspection portion [redacted] was found to have [redacted] vials containing particulates of which [redacted] were found to have fibers. This portion of the lot was released. Portion [redacted] was found to have [redacted] vials of particulates of which all the vials were found to contain fibers and this portion of the lot was rejected. Portions of the lot where the fibers were not observed during filling were released without reinspection. The entire lot was not reinspected for this particulate defect. The released portions of this lot are within expiration date.

- Zoster (PHN) [redacted] consisting of approximately [redacted] vials was initially inspected by the automated [redacted] system on 6/26/07. Fibers were observed on the stoppers during filling. Reinspection of Portion [redacted] which consisted of [redacted] vials was manually reinspected and released. The entire lot was not reinspected for the particulate defect. This lot has been released and is within expiration date.

- Varivax lot [redacted], consisting of approximately [redacted] vials, was initially inspected by the automated [redacted] system on 6/27/07. Fibers were observed in the stopper bowl during filling. The lot was portioned and grouped and approximately [redacted] vials were manually reinspected and released. The entire lot was not reinspected for the particulate defect. This lot has been released and is within expiration date.

2. Merck's packing methods for vaccine products shipped with dry ice permitted ingress of [redacted] eplacing [redacted] in the headspace of vials of lyophilized product. The products included ProQuad, Varivax, Zostavax, M-M-R II, Mumpsvax, Attenuvax, M-M-VAX, and Meruvax. Merck was aware of this ingress as early as 2003 when they confirmed [redacted] in the headspace of Varivax III, lot [redacted] Modified packing methods were implemented incrementally, beginning June 2006, with the last modification made in November 2007.

- In May 2006, Merck submitted a Biological Product Deviation Report [redacted] to FDA concerning a pH failure of Varivax III, lot number [redacted] at the [redacted] time period. Merck did not inform CBER of the other products (which included domestically shipped products) susceptible to [redacted] ingress until the October 2006 update to the BPDR.

- Merck did not inform international regulatory authorities of the [redacted] ingress issue. Merck submitted requests for

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann M. Montemurro Joan A. Loreng Jacqueline Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

approval of changes to packing/shipping methods, but did not acknowledge the [redacted] ingress as the reason for the change.

- For Varivax, lot [redacted], Merck verified the ingress of [redacted] and estimated that at least [redacted] of the lot returned from the international site had [redacted] in the headspace. Potency and sterility testing passed specification at the [redacted] time period; however, although Merck had linked "over-pressurization" with [redacted] ingress, test records do not indicate that the analysts noted over-pressurization in the actual vials tested.

- Merck did not test the other affected products to determine if there were any detrimental effects on those products. Customer complaints have been received citing over-pressurization.

- Studies of real-time shipping and simulated shipping conditions were performed and the conclusion that there would be no effect on container/closure integrity of the vials was based on measurement of headspace pressure and [redacted] concentration, chemical/mechanical specifications of the stopper material, compression force (stopper to vial), microbial mobility at low temperature, etc. The conclusion was based on the size of the gap (between the stopper and vial) possible when the temperature in the shipper reached the glass transition temperature of the stopper material; the studies did not consider the consequences of stopper/seal defects that could go undetected during filling and further enlarge the gap.

3. There is a failure to thoroughly review and/or correct any unexplained discrepancy or the failure of a batch or any of its components to meet any of its specifications. For example,

   A. [redacted] dated 8/24/2006 was issued for the sterility failure of Pedvax bulk lot [redacted]. The contaminant was noted as [redacted]. However, the investigation failed to assess a recent change in the sterilization cycle for [redacted], implemented in July 2006, although a WFI investigation for [redacted] showed a possible route of contamination through processing hoses. The validation of this [redacted] change was subsequently deemed as inadequate during investigation of the failure of a 9/2007 media fill challenge lot, which led to the recall of several PedVax and Comvax lots.

   B. [redacted] dated 3/8/2006 was issued for back pressure rise on the [redacted] filtration manifold during sterile filtration [redacted] causing the stoppage of manufacturing and the addition of a second set of filters in both cases, to complete the filtration processes. The investigation revealed that the

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng Jacqueline Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

filtration fouling was due to insufficient filtration capacity for the [redacted] and the root cause was listed as implementation of improperly sized filters. However, there was no corrective action addressing how the wrong size filters were implemented and inappropriately validated. Additionally, the investigation failed to assess impact on the large scale [redacted] manufacturing of which there have been [redacted] lots subsequently quarantined for to excessive filtration times due to insufficient filtration capacity.

C. Report dated 12/20/2007 for M-M-R®II lot [redacted] Adverse Event Reports of Suspected [redacted] was inadequate for the following reasons:

i. Review of changes was limited to lot-specific change or changes that were newly implemented with these lots. The bulk lots used in lot [redacted] were the first MMR lots formulated with [redacted] These bulk lots were up to [redacted] There was no evaluation of the stability of the bulks relative to [redacted] Existing stability data for the bulks are limited to potency and sterility testing.

ii. Review of APRs was specific to lot [redacted] and the bulk measles, mumps and rubella lots that went into this lot. For example, the investigation did not assess the on-going investigation into reduced Rubella potency with MMR [redacted] as compared to MMR [redacted].

iii. Analysis of adverse events failed to include all adverse events related to [redacted] associated with MMR [redacted] lots.

iv. Review of raw materials, components and culture media inputs documented that those with the highest likelihood of eliciting a patient reaction included stoppers, vials, [redacted] However, only the stoppe[redacted] vendors were contacted by Merck to investigate potential problems in their manufacturing processes.

D. [redacted] dated 5/10/2006 was initiated for the sterility failure of ProQuad l[redacted]. The contaminant was identified as A[redacted] nd the thaw bath was determined as the most likely source of the contamination. The investigation determined the contamination was introduced to the filling operation due to insufficient disinfection of the exterior of the can. The investigation also noted that [redacted] was on-going for cans found during thawing with loose clamps, and stated that container integrity was also a

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng Dian Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

potential mechanism for the sterility failure. However, [redacted] failed to specify how this potential cause was investigated or how it was ruled out.

Additionally, the APR corrective actions related to the thaw baths were closed in June 2006. However, implementation of thaw bath changes was limited to the building 29 thaw baths and did not address global corrective actions related thaw baths used in different buildings. The corrections to the thaw baths in the bulk Rotavirus areas were just completed in January 2008.

E. [redacted] dated 4/14/2006 was initiated for sterility failure of COMVAX® lot [redacted] The investigation failed to include an assessment of the container closures of the sterile bulk inputs: bulk [redacted] Liquid PedvaxHIB, and Recombivax [redacted]. These bulks are stored in [redacted] closures.

F. Atypical Process Report (APR) investigations [redacted] were initiated on **4/21/06** and 4/26/07, respectively, based on [redacted] content results. Neither investigation identified a laboratory root cause. The corresponding manufacturing investigations ([redacted] respectively) were not initiated within 30 days of the identification of atypical and/or OOS results.

G. APR investigation #[redacted] was initiated on 3/15/2007 for an OOS result for [redacted] concentration. According to this APR, two long term corrective actions to improve the method of charging [redacted] to the transfer can during [redacted] preparation were implemented on 5/18/07. On the same day these were implemented, a second OOS result for [redacted] concentration occurred. The corresponding APR investigation (#[redacted] also linked the high [redacted] result to the method of charging [redacted] to the transfer can. This APR also indicates that a notification was performed; however, performance counseling was not completed for the technicians involved in the [redacted] addition.

4. Determinations of product impact as a result of investigations into APRs were not always supported by documented evidence. For example:

A. [redacted] ated 11/11/07 was issued for a leak discovered in conjugate dilution inlet line during [redacted] conjugate bulk re-charge for lo[redacted] due to a small hole in the tubing. The product impact assessment concluded that there would be no microbial ingress from the leak due to the [redacted] unwetted

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joann A. Loreng Jacqueline Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

path, positive pressure and immediate isolation of the leak from the bottle". However, the chronology of events, estimated to the second, attached to the APR was unsigned and undated. Reportedly, this information was derived from a notebook maintained by the production operator. However, the source documentation from the notebook was not maintained.

B. [redacted] dated 3/12/07 was issued for a leak identified at the [redacted] connection on the outlet piping of portable tank [redacted] during filling of Recombivax lot [redacted]. The Quality Manager comments documented that there was no impact on quality "as the product leak began after the product dispense step was initiated (was not observed at the time of initiation) and was stopped immediately upon discovery." However, there is no inspection of the line at product dispense and a leak may have existed but not noticed. There is no assurance that the breach did not exist prior to startup. Additionally, the outlet line is not monitored for positive pressure.

C. [redacted] dated 3/19/07 was issued for a pinhole leak identified on the vertical leg of the portable tank sampling [redacted] during formulation of Gardasil formulation lot [redacted]. The first set of sample bottles were filled without notation of the leak. The product impact states that there was no product impact as the line remained under positive pressure during the entire sampling process and that a [redacted] was immediately placed on the [redacted] tubing to isolate the leak from the [redacted]. However, all samples collected from this line were discarded due to the leak.

D. The rationale for the segregation of trays associated with APRs into glass breakage was not always supported by documented evidence. Specifically:

i. [redacted] 8/26/2007 was issued for broken glass noted on the outbound [redacted] enclosure during the tray [redacted] dose check during filling of Varivax lot [redacted]. The affected portion of the lot was segregated as [redacted] and included trays [redacted] as dose check at tray [redacted] did not note glass. However, there is no assurance that operators were looking for broken glass during the tray [redacted] dose check.

ii. [redacted] ated 9/4/07 was issued for broken glass found under the in-feed [redacted] in the filling enclosure of line [redacted] during filling of MMR® II [redacted]. The investigation documented that the operators "thought they heard glass break while filling tray [redacted] so the line was

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J. DiazAlbertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

stopped and inspected. The glass was found at tray [redacted] so the affected portion of the lot was segregated as [redacted] included trays [redacted] However, there was no documentation in batch record regarding the reported tra[redacted] line stoppage.

5. SOP 1330, Headquarters Review of Lot Numbers for Product Quality Complaints (PQCs), dated 14 May 2007, states that all deaths and life threatening adverse experiences require lot checks with batch record review. This is not always performed.

   A. [redacted] reports a [redacted] was vaccinated with Pneumovax Lot [redacted] on 06 October 2005. The patient was treated on 01 November 2005 with IV antibiotics for an abscess at the injection site that was approximately a half dollar size and redness surrounding it. This was reported to VAERS. No lot check or review of batch record was conducted.

   B. [redacted] reports an intra-uterine death after receipt of Gardasil Lot [redacted] No lot check or review of batch record was conducted.

6. The complaint records and complaint investigations do not mention the possibility of [redacted] ingress as the reason for over-pressurization of Zostavax and ProQuad vials. For example: complaints [redacted] for Zostavax, lot [redacted] concerned over-pressurized vials. This lot was shipped with dry ice, using a new packing method which had been validated to prevent temperature going below the glass transition temperature of vial stoppers. The investigation did not verify the packing method or consider the possibility that the modified packing method might not be functioning as validated.

7. The presence of the "PROVISIONAL" watermark obscuring instructions and data entered into batch records was not identified as a contributing factor to a calculation error in the manufacture of [redacted] lot number [redacted] The only corrective action documented was a performance discussion with the operator.

8. During review of atypical process reports (deviations), QA Release personnel may edit the number of occurrences calculated by the software. This practice is not addressed in the release SOP. 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 [redacted] failures, although related, were recorded as a single occurrence in the deviation tracking system. SOP 223-307X, Laboratory Investigation

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

Procedure, states that if a similar event occurs on multiple days, one investigation may be written for efficiency, but the number of separate occurrences must be maintained.

9. SOP 283-316, Investigating and Writing West Point Product Quality Complaint Reports 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. The SOP does not require trending on fill numbers, although complaints may be associated with processing steps prior to the packaging/labeling operation. Fill number lots may be packaged and labeled in several final finish lots.

10. Complaint records are not complete regarding the date closed. The [redacted] system is not always updated with the complaint closure date. For example: during demonstration of the system on November 27, 2007, complaint record [redacted] concerning Recombivax, lot [redacted] indicated a status of Released. The complaint had been closed/completed September 7, 2007 as indicated on the [redacted] document for the investigation.

11. No BPDR was submitted concerning leaks in Gardasil syringes. [redacted] reports of leaking syringes have been reported as of December 2007 since launch of the product in June 2006.

12. Change Control # [redacted] was for a change in [redacted] in which the [redacted] as optimized to achieve an [redacted] that is closer to the theoretical limit. This change control was closed out on 12 July 2004 and implemented in March 2005. Change Control [redacted] was to modify the dip tube in Tan [redacted] to improve mixing during recirculation for Pedvax Bulk manufacture. This change control was closed on 08 May 2006 and implemented in October 2006. Neither of these changes was reported to the agency for review.

13. Change Request [redacted] was initiated on July 17, 2006 to qualify the use of the [redacted] tunnel after the implementation of a change from the [redacted] filters previously used for the [redacted] filtration to the [redacted] terilizing filter. These filters are used for the filtration of li[redacted] at the source and at each [redacted] tunnel point of use on line [redacted] for flash freezing of lyophilized products in Dept. 285. Between August 2006 and August 2007 there were approximately [redacted] post integrity test failures for these [redacted] ilters at the source as well as at the point of use. The root cause was found to be that the [redacted] Filters were not suitable for use under the conditions of the [redacted] Distribution system for lines [redacted] The corrective action was to change to a more suitable filter.

This Change Request did not include the operational qualification of the [redacted] filters for its intended use at various temperatures ranging from [redacted] The filters were accepted on the COA of the vender and not

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

tested in the [redacted] tunnel prior to use. Additionally, there is no identity testing performed on the [redacted] upon receipt.

14. There is no documentation of the vendor's evaluation, the vendor's description of the root cause, or vendor's recommendations to correct a [redacted] automation issue which occurred during the manufacture of Gardasil, lot [redacted]. The vendor edited the software and configuration. Since Merck employees are not aware of the actual root cause, they could only perform [redacted] testing of the modified software and configuration. Merck employees reportedly evaluated the drop down lists for other products and concluded these did not exhibit the same problem, but could not explain why.

PRODUCTION SYSTEM

15. During VAQTA production the method to determine the amount of hepatitis A virus antigen going into the [redacted] inactivation procedure is inadequate and unreliable. During the 2005 and 2006 campaign [redacted] lots failed lot release due to the antigen result being above the specification limit. Historical data comparing antigen concentrations in purified bulks with antigen concentrations in the subsequent [redacted] bulks indicates that some recent assessments of viral antigen concentrations prior to [redacted] inactivation may have been under estimated. This potentially resulted in antigen concentrations in the [redacted] inactivation process in excess of currently validated levels.

16. Filling line clearance subsequent to glass breakage is inadequate in that it does not require clearance of all potentially affected areas. Specifically, [redacted] dated 7/13/2006 was issued for observation glass fragment in the stopper bowl during filling of MMR w[redacted] The investigation determined that the root cause was due to a broken vial that was misaligned in the [redacted] during initial set-up. Corrective actions to investigate possible methods to prevent or detect broken glass fragments from entering the stopper bowl were determined as not feasible. However SOP 285-230, Operation of Filling Room [redacted], only requires line clearance/cleaning of areas w/in the [redacted] enclosure was not updated to require clearance of the stopper bowl (outside enclosure) in the event of glass breakage.

17. Implementation of the change from one [redacted] filter to [redacted] filters was not validated for worst case conditions. Change Request [redacted] for these filters was closed 1/12/06. The change request included results of a 10/22/2004 developmental [redacted] study. This study only evaluated the filter surface area

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J. Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

requirements for [redacted]. There was no documented rationale as to why the other three [redacted] types were not evaluated. However, a subsequent [redacted] study dated 11/14/2005 for the [redacted] documented that the [redacted] worst case for filter fouling. However, this memo was not used to evaluate the filter surface area requirements for this change.

18. There is no assurance that the PEDVAX processing tanks are held under active positive pressure [redacted] monitoring data is not reviewed, nor are unexplained pressure losses responded to. Specifically,

    A. On 6/25/2007, there was an unexplained pressure loss for approximately [redacted] hours during the [redacted] hold of PEDVAX [redacted]

    B. On 6/6/2007, there was an unexplained pressure loss during hold of [redacted] after the [redacted]

    C. Approximately three weeks after the non-production [redacted], there was an unexplained pressure loss during the tank hold under active pressure.

19. Batch production and control records do not include complete information relating to the production and control of each batch. Specifically, the PEDVAX bulk batch records do not include equipment sterilization records or pre-processing check o[redacted]

20. Regarding process hold times for biological products:

    A. There are no data to support in process hold times for Black Widow Spider Antivenin and [redacted] Horse Serum. For example:

        i. [redacted] Antivenin Serum (product code [redacted] can be held at [redacted]
        ii. [redacted] Antivenin Serum (product code [redacted]) can be held at [redacted]
        iii. [redacted] Horse Serum, undiluted without [redacted] (product code [redacted] can be held at [redacted]
        iv. [redacted] Normal Horse Serum (product code [redacted]) can be held at [redacted]

    B. The hold time validation for the [redacted] storage of filled product for the following vaccines are deficient in that:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J. Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

i. For MMR, the hold time of [redacted]s only performed on one lot.
ii. For Attenuvax, Meruvax, and Mumpsvax, the hold time of [redacted]was not performed.

C. There are no data to support the process hold time for MMR Bulk (product code [redacted]) of [redacted]

21. SOP 209-205X, Determination of the Redispensed Container Volume Measles, Mumps, and Rubella Bulk, allows for a maximum [redacted]redispensing operations [redacted]) prior to filling. To date, there have been no Mumps redispensed bulks that have been placed on stability to validate this operation.

22. Container closure systems do not provide adequate protection against foreseeable external factors in storage and use that can cause deterioration or contamination of bulk vaccines or sterile-filtered solutions. Specifically,

A. Study [redacted] Final Report for the Container Closure Validation of the [redacted] Stopper for Aseptic Assembly [redacted] is inadequate in that affect of storage conditions on the applied torque were not assessed. This container/closure is used for bulk product including Pedvax, Recombivax and [redacted]

B. [redacted] sterile-filtered solutions used in the manufacture of vaccine products are stored in containers that have not been validated for container/closure integrity. These solutions may be stored from [redacted]s in such containers.

23. A set of control samples representing defect types are examined by the automated inspection equipment prior to beginning the inspection process. For lyophilized products, the inspection equipment is deemed acceptable with the following percentage of defects going undetected:

Particulates
Poor Crimp
Product in Stopper
Cracked Vial
Missing Stopper
Missing Seal
[redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

Missing Cap
Empty Vial
Underfill
Dirty Vial [redacted]

Rejects from the first pass through the inspection equipment are sent through the inspection equipment a second time and only those that are rejected a second time are discarded. For example:

- [redacted] defective vials ([redacted] for particulates and [redacted] for poor crimp) were accepted during line set-up for Varivax [redacted] vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and [redacted] rejects were discarded after the [redacted]
- [redacted] defective vials ([redacted] for particulates, [redacted] for poor crimp, and [redacted] for cracked vials) were accepted during line set-up for Varivax [redacted] vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and [redacted] rejects were discarded after the [redacted]
- [redacted] defective vials ([redacted] for particulates, and [redacted] for cracked vial) were accepted on one inspection machine, and [redacted] defective vials ([redacted] for particulates, and [redacted] for cracked vial) were accepted on the second inspection machine during line set-up for Zostavax [redacted] vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and [redacted] rejects were discarded after the [redacted]
- [redacted] defective vials for particulates were accepted on one inspection machine, and [redacted] defective vials for particulates were accepted on the second inspection machine during line set-up for ProQuad, fill lot [redacted] vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and [redacted] rejects were discarded after the [redacted]

24. Process capability limits were not re-established for filling line defects for Zostavax as required by SOP 300-103X, Updating Inspection Attributes in the [redacted] had not been evaluated since February 2006.

25. Validation protocols [redacted] dated 12/6/06 and [redacted] dated 5/7/06 executed for "Detection of Volume-of-Fill Defects for multiple vaccine products filled on lines [redacted] (building 29 Dept.174) and inspected by [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng Jacqueline Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

machines #[redacted] were not representative of the actual automated inspection process in that there was no assessment made for non-defective vials. A known defect set of [redacted] defective vials in each of the [redacted] volume of fill defect categories (underfill and overfill) were assessed, for a total of [redacted] defective vials for each qualification. Routinely there are approximately [redacted] vials inspected at approximately [redacted]

A. [redacted] dated 12/4/07 was initiated to investigate the improper validation of automated inspection machines [redacted] or volume of fill defects, performed in 12/06. The investigation concluded that the results of the validation study may have been biased due to the inadvertent inclusion of particulate defects within the validation defect set. The investigation concluded that all products inspected on [redacted] which include Pneumovax, Recombivax, [redacted] need to be revalidated for Volume of Fill. To date the APR is open and the revalidation studies have not been completed for all the products. (The initial validation performed for Volume of Fill in 12/06, was in response to a previous FDA 483 observation from 2/06)

26. In line Statistical Secondary (ISS) (visual) inspections of products are performed during the filling process for accepted product and the results must conform to the acceptance criteria for a specified Accepted Quality Level (AQL) for all major/minor/critical defects. Lots failing this initial (ISS) inspection for any defect category can be reinspected. Lots failing an (ISS) inspection for a critical defect must be [redacted] reinspected. There are no reject limits established for the individual defect categories of lots reinspected after failing an initial (ISS) inspection.

For example: MMR II 1 Dose [redacted] failed the initial (ISS) inspections in 2/2006 and 7/06, respectively, for the critical defect category of "[redacted] The lots were [redacted] reinspected with no reject limits established for the individual critical defect category of "[redacted] Total reject [redacted] limits were the only criteria evaluated for the release of these lots after the reinspections. Additionally, there were no investigations performed to identify the root cause for the initial (ISS) failures. These lots have been released and are within expiration date.

27. Prior to October 15, 2007, there was no requirement to initiate an investigation into lots of product that failed the initial (ISS) inspection for critical defects other than foreign product, incorrect stopper or container. SOP 290-154X "In-Line Statistical Secondary Inspections of Products Filled in [redacted] Operations"dated April 30, 2007 did not require investigations into (ISS) failures for critical defects such as cracked vials, product in stopper, meltback and "[redacted]

28. There are no data to support the reprocessing/refiltration of the Recombivax [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Anne Marie Montemurro Joan A. Loreng J Diaz Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

For example [redacted] was initiated 2/24/07 for Recombivax S[redacted] having a pressure driven leak in tank [redacted] post sterile filtration from tank ([redacted]). The lot was refiltered on 2/28/07 formulated and filled into multiple final drug product lots Recombivax [redacted], Comvax lot #'s [redacted], Recombivax lot #'s [redacted] and packaged lots Recombivax [redacted] and Comvax [redacted]. These lots have not been released. Additionally, this SFP bulk lot [redacted] has not been placed on stability.

FACILITIES AND EQUIPMENT

29. Procedures for the cleaning and maintenance of equipment are deficient regarding maintenance and cleaning schedules, including, where appropriate sanitizing schedules. For example:

    A. There is no assurance th[redacted] in PedVax bulk processing tanks are changed as required as this change out is not documented. For example, Section VI.A.18 of SOP 204-209P, CIP Procedure for the Conjugate [redacted] requires the replacement of [redacted] is completed directly after completion of a batch.

    B. There is no replacement schedule for the [redacted]x lines used on the Pedvax [redacted] dispensing manifold assembly.

    C. Regarding the WFI transfer hosed used in Pedvax bulk operations and sampling: there is no replacement schedule or routine sterilization for this equipment. [redacted], was issued for WFI sample site [redacted] during week of 4/30/06 above action w/ count of [redacted]. The contaminant was identified a[redacted] The root cause of the contamination was determined to be a result of extrinsic contamination due to the sanitization of hose was not effective to irradicate spore-forming organism. Although the corrective action issued was for the development of a routine sterilization of the hoses, only sterilization was only conducted once.

30. Written procedures are lacking for the use of cleaning and sanitizing agents designed to prevent the contamination. Specifically, SOP 204-608X, Housekeeping Procedures for the [redacted], (building 60, including PedVax bulk operations), does not provide a frequency for performance of the multi-step decontamination with [redacted]

31. Written procedures are not followed for the maintenance of equipment used in the manufacture, processing, packing or

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print orType)	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

holding of a drug product. Specifically,

A. Work order [redacted] dated 8/29/2007 was issued for th[redacted] maintenance on the PedVax [redacted]. The work order required a check of the condition of the vapor seal. This action was documented as "NA". However, there was no documentation as to why this prescribed action was not completed.

B. Work orde[redacted] dated 9/9/2007 was issued for the annual maintenance of the PedVax P[redacted] The first [redacted] inspections listed on the work order were documented as "NA". However, there was no documented reason for the failure to complete these activities.

32. There is no data to support the [redacted]. Specifically, Position Paper for the Post Sterilization / Sanitization Hold time for [redacted] Building 60, Department 200, 201, 202 and 204, dated 8/27/07 is inadequate in that media challenges from tanks in [redacted]s used to support [redacted] hold were not equivalent to the PEDVAX processing tanks. Specifically, the tanks used in barrier operations are bottom mounted with [redacted] and Pedvax tanks are top mounted [redacted] Additionally, the tanks used in Pedvax production include assemblies that are connected to the tank and steam sterilized in place.

33. Single use vent filters (e.g. AERVENT® 50, ACRO®25, ACRO®50, etc.) used as sterileboundaries across manufacturing areas including bulk bacterial vaccine, bulk viral vaccine and formulation/filling operations are not integrity tested.

34. The can database that was instituted to maintain the history and facilitate control over the use, certification testing, and retesting of cans used to store sterile materials contained inaccurate information.. The statuses tracked include "available," "in process," "needs testing," etc. For example: several cans were listed as available when they actually were on hold, decommissioned, or contained product; other cans were listed as in process that had been decommissioned.

LABORATORY SYSTEM

35. CP 9110.735, HPLC Assay for [redacted] in Bacterial Vaccines, dated 18 August 2006, uses a mobile phase solution of [redacted] SOP 160-QP-353X, states that it is the responsibility of all laboratories to have an

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

effective system in place to ensure that all prepared reagents, solutions, and media are prepared and labeled properly. The analyst who performed the HPLC assay on 14 November 2007 prepared the mobile phase solution on that day. The analyst never changed the label on the bottle to reflect this preparation. The solution was still labeled as being prepared on 10 November 2007.

36. CP 9110.718, Molecular Size Analysis of the [redacted] Samples Using [redacted], dated 22Aug05, was re-validated for [redacted] on 05Oct99. The validation report contained a commitment to qualify the remaining [redacted] serotypes. Qualification of [redacted] was completed and summarized in a May 2000 report. Observation V.8 from the previous Level I inspection (2/7-24/2006) noted that the remaining [redacted] were not qualified for use in this assay. Although the firm did provide a report (dated 26May06) summarizing the qualification of [redacted], and [redacted] for use in CP 9110.718, [redacted] have yet to be qualified.

37. Preservative-free RECOMBIVAX HB® Reference Standard Lot [redacted] is stored at [redacted] Each box of [redacted] vials is labeled with an expiration date of 09-November-2004. This material was placed on stability in June 2003. Subsequent expiry extensions were implemented in October 2004, October 2005, November 2006, and November 2007. A certificate of analysis (effective 09-Nov-2007) with the latest extension (09-May-2008) was placed in the basket with the reference standard. As stability results from the corresponding time point (4 years) are under investigation, the current extension was based on historical performance of six markers of critical performance. These data do not support extension of the expiration and should not be used in lieu of acceptable stability data from the 4 year time point.

38. [redacted] polyvalent standard is purchased from [redacted] for use in CP 9110.758, [redacted] Identity and Quantification by [redacted] with Correction for Residual Concentrations, dated 13 July 2007. No expiration date is assigned to this antiserum.

39. [redacted] testing for [redacted] C is performed by MRL. The sample receipt tracking system for MRL is a paper system. On 26 November 2007, [redacted] was logged in as Pedvax [redacted] testing. Pedvax [redacted] not performed by MRL.

40. MRL is responsible for CP 9110.732, Immunization and [redacted] dated 02 May 2007. This procedure takes a total of [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (Print or Type)	DATE ISSUED
	Ann Mary Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

days to perform. Three analysts [redacted] were documented as being trained on 06 February 2007 which was Day 1 of the 21 day procedure. No training SOP exists for training on this procedure. In addition, training does not evaluate data equivalence before being certified as being trained on this procedure.

41. MRL is responsible for CP 9110.732, Immunization and [redacted], dated 02 May 2007 and CP 9110.003, [redacted], dated 26 May 2006. Worksheets for these assays are not controlled in that:

    A. [redacted] was initiated on 18 May 2007 using CP 9110.003 Revision #32. Data are recorded on worksheet [redacted]. The analyst crossed out [redacted] and replaced with [redacted]

    B. Worksheet #[redacted] of CP9110.732 Revision #5 was used for [redacted] initiated 18 July 2007 and [redacted] initiated 11 September 2007.

42. Pedvax Bulk has Out of Long Term Static Process Capability Limits (LTSPCL) for [redacted]. These limits do not reflect the current manufacturing process. A [redacted] was initiated on 26 February 2007 due to Pedvax [redacted] generating results that were out of process capability limits (OOPCL). The root cause of this OOPCL was a change in process for aluminum buffer manufacture implemented March 2005 and a change in equipment for Pedvax manufacture implemented in October 2005. The corrective action from this investigation was for the LTSPCL be updated. This corrective action was incorporated into a much larger corrective action with a target due date of 30 June 2008.

43. Packaged Antivenin Lot [redacted] was not tested for the Identity Test for Presence of Horse Serum Proteins in either the antivenin vial or the Normal Horse Serum Vial. Packaged Antivenin Lot [redacted] was not tested for the Identity Test for Presence of Horse Serum Proteins n the antivenin vial. These tests are required for release of product to market. Lot [redacted] was released on 25 August 2004 and Lot [redacted] was released on 09 October 2006. Investigation [redacted] was initiated for these missed release tests on 21 August 2007. The root cause of this investigation was that the QC analyst and Product Release Coordinator thought these were duplicate tests requested and therefore deleted the requested testing in [redacted] Corrective Action does not address the global concern in that Quality Release was not in a state of control for this to occur and that specifically higher Quality approval is not needed to delete a test in [redacted]

44. Sterility test failure investigation, [redacted] for MMR Re-dispensed Bulk, lot [redacted]

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Ann Marie Montemurro Joan A Loreng J Diaz Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-004	Vaccine / Drug Manufacture

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:

[redacted] into failures that occurred June 2006 were cancelled by a memo dated November 7, 2006, which states that one test canister was visibly leaking and the other exhibited medium beyond the canister closure point. There is no notation on the test record that the test canisters were not intact. The memo, written five months after the actual test date, concerning invalidation of the sterility test failures states tha[redacted] of sample spilled onto the floor during the final examination for microbial growth.

45. CP 9110.001, Sterility Test Methods, 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.

46. The Control Procedure (CP9110.551) for performing plaque assays to measure Varicella potency in the Virology Laboratory and training of the staff to perform this procedure are deficient. Specifically,

    A. There is inadequate monitoring of [redacted] prior to inoculation with virus. Up to [redacted] plates are examined per set of [redacted] plated; this number is not sufficient to provide a thorough overview of the cell density of all plates in the experiments. In preparation of the cell culture plates for inoculation, the CP 9110.551 states as follows, "Observe the cultures microscopically for at lea[redacted] cell confluence and macroscopically for contamination." There is no indication of what proportion of plates should be examined or where in the sequence of plating these should be selected (e.g. beginning, middle and end of the plating procedure).

    B. Extensive cell sheet destruction due to re-feeding or plate manipulation was evident on multiple plates present in the laboratory that had been prepped and was waiting for plaque counting. The procedure to re-feed the infected cell monolayer (after infection) with [redacted] of maintenance medium in CP 9110.551 does not specify methods to reduce cell sheet disruption caused by the force of media addition or other factors.

        i. CP 9110.551 does not provide guidelines for monitoring techniques if re-training of technicians in cell culture re-feeding procedures is required.

    C. After infection and staining the criteria to determine which plates are valid for reading, and the training of staff to assess cell monolayer damage due to viral infection versus poor manipulation of the plates, is inadequate.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print or Type)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

i. The [redacted] estimation for voiding [redacted] Varicella plaque assay plates is not adequate. This does not provide distinction between excessive plaques at that dilution and poorly manipulated plates, the later of which should not be routinely discarded without follow-up.

ii. Laboratory staff were unable to adequately distinguish between "clearings" in the stained monolayers that were due to large numbers of plaques and those that were cell sheet disruptions due to poor re-feeding technique or plate manipulation.

iii. CP 9110.551 does not provide criteria to evaluate whether a stained plate is invalid, nor does it provide stipulation for re-training of the technicians in these evaluation methods if needed.

MATERIALS SYSTEM

47. SOP 204-200BX, Controlled Temperature Storage Units: Organization, Segregation, and Documentation of Materials, dated 09 April 2007, states that material movement and logbook maintenance are the responsibility of the department that manufactured the material and that quarantined and rejected material must be separated from Work in Progress material. Pedvax Bulk Lot [redacted] is a quarantined bulk lot stored in Building 60 Room [redacted] This quarantined lot was not separated from work in progress material.

48. There are no procedures governing first in / first out of materials accepted by the various Sterile Supply groups (verify name of department). For example:

    A. Building 60 Sterile Supply Department 204 is responsible for receipt of various components and product contact equipment including sterilizing filters, vent filters, tubing, etc. These materials are received in directly by the department who verifies the COA. However, there are no procedures describing how these items are to be stored and issued for use.

    B. Merck did not practice First In/First Out (FIFO) for utilization of [redacted] bags prior to the deviations that identified [redacted] particles on vial stoppers, nor was FIFO instituted as a corrective action for this deviation. Since FIFO was not used, Merck could not conclusively identify the timeframe when the unsuitable bags were used.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng Jacqueline Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
USFDA/ORA/DCMO 5600 Fishers Lane, Rockville, MD 20857 (301) 827-0391	*see below
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: John T. McCubbins, Vice President Global Vaccine Manufacturing and West Point Operations

FIRM NAME	STREET ADDRESS
Merck and Co., Inc.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE West Point, PA 19486-004	TYPE OF ESTABLISHMENT INSPECTED Vaccine / Drug Manufacture

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:

PACKAGING AND LABELING SYSTEM

49. Validation of the modified packing configurations using [redacted] focused on preventing the temperature going below the glass transition temperature of the stoppers and did not address the possible link between [redacted] ingress and container/closure integrity due to filling line defects.

GEN. SPEC.
RELEASE
F# 2685-603 DATE 4/3/08
Reviewed by:

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE *(Print orType)*	DATE ISSUED
	Ann Marie Montemurro Joan A. Loreng J Diaz-Albertini	Ann M. Montemurro, Joan A. Loreng, Jacqueline Diaz-Albertini, Investigators / Tina Roecklein, Christian Lynch, Joan Adamo, Marian Major, Product Specialists	1/17/2008