1/24/2020

Allison Lucas, Esq.
Informed Consent Action Network
200 Park Avenue, 17th Floor
New York, NY 10166
Via Email: foia@sirillp.com

Dear Requester,

The attached record(s) are being provided by the Office of Regulatory Affairs (ORA) Division of Information Disclosure Policy – In response to your request [2020-451] dated 1/13/2020 for record(s) from the Food and Drug Administration pursuant to the Freedom of Information Act regarding:

A copy of any letter from the FDA to Merck regarding any inspection at any time between March 2008 and the present by the FDA of Merck's facility in West Point, Pennsylvania, concerning the Gardasil vaccine; etc

After a thorough review of the responsive records, we have determined that portions of the documents are exempt from disclosure under FOIA exemption (b)(4) and (b)(6) of the FOIA 5 U.S.C. § 552, as amended and delineated below:

- Exemption (b)(4) permits the withholding of "trade secrets" (TS) and "commercial confidential information" (CCI). Disclosure of this information would impair the government's ability to obtain necessary information in the future and cause substantial harm to the competitive position of the person from whom the information was obtained. Under the balancing test of this exemption, we are withholding all proprietary information identified as TS and CCI.

- Exemption (b)(6) permits the withholding of information which, if released, would constitute a clearly unwarranted invasion of personal privacy. In this case, it was determined that there is no countervailing public interest qualifying under the standard set forth, under exemption (b)(6), to release the personal identifying information of certain third parties

Our office considers your request closed. If you have any questions about this response, you may contact me at 803-252-4866, ext. 1104

You have the right to appeal this determination. By filing an appeal, you preserve your rights under FOIA and give the agency a chance to review and reconsider your request and the agency's decision. Your appeal must be mailed within 90 days from the date of this response, to:

Agency Chief FOIA Officer
U.S. Department of Health and Human Services
Office of the Assistant Secretary for Public Affairs
Room 729H
200 Independence Avenue, S.W.
Washington, DC 20201
E-mail: FOIARequest@PSC.hhs.gov.

Please clearly mark both the envelope and your letter or e-mail "**FDA** Freedom of Information Act Appeal."

If you would like to discuss our response before filing an appeal to attempt to resolve your dispute without going through the appeals process, please contact **person that worked on request**. You may also contact the FDA Public Liaison for assistance at

Office of the Executive Secretariat
U.S. Food & Drug Administration
5630 Fishers Lane, Room 1050
Rockville, MD 20857
E-mail: FDAFOIA@fda.hhs.gov.

If you are unable to resolve your FOIA dispute through our FOIA Public Liaison, the Office of Government Information Services (OGIS), the Federal FOIA Ombudsman's office, offers mediation services to help resolve disputes between FOIA requesters and Federal agencies. The contact information for OGIS is as follows:

Office of Government Information Services
National Archives and Records Administration
8601 Adelphi Road–OGIS
College Park, MD 20740-6001
Telephone: 202-741-5770
Toll-Free: 1-877-684-6448
E-mail: ogis@nara.gov

Please do not submit payment until you receive an invoice. The following charges for this request to date may be included in a monthly invoice:

Reproduction=$0.00 Search=$46.00 Review $368.00 Other $5.75 **Total=$419.75**

Sincerely,

Mayra E. Rivera -S

Digitally signed by Mayra E. Rivera -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300088400, cn=Mayra E. Rivera -S
Date: 2020.01.24 09:59:08 -05'00'

Mayra Rivera
Government Information Specialist

Attachments:
Merck West Point PA 483Resp 2-15-2008_Redacted
Merck West Point PA 483Resp 03-13-2009_Redacted
Merck West Point PA WLResp 5-15-2008_Redacted

U.S. Food and Drug Administration
5630 Fishers Lane, Room 1035
Rockville, MD 20857
www.fda.gov

William J. Mullin
Vice President
West Point Quality Operations

Merck & Co., Inc.
WP36M-5
770 Sumneytown Pike
PO Box 4
West Point PA 19486-0004
Tel 215 652 6620
Fax 215 993 3400
william_mullin@merck.com

MERCK
Manufacturing Division

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CBER/DCC

15 February 2008

Via UPS Overnight

Jacqueline Little, Ph.D.
Team Leader, Team Biologics Compliance
U.S. Food and Drug Administration
Office of Enforcement
15800 Crabbs Branch Way, HFC-210/Suite 110
Rockville, MD 20855

RE: Team Biologics Inspection
Merck & Co., Inc. / West Point, Pennsylvania
26-Nov-2007 to 17-Jan-2008

Attached you will find a letter that responds to the FDA Form 483 observations presented at the conclusion of the Team Biologics Inspection at our West Point, Pennsylvania, facility on 17-Jan-2008. After a communication with Ms. Malarkey, she indicated that our response should be directed to your attention.

We are fully committed to assuring that our response completely addresses all of the inspectional observations in a thorough and effective manner. We will follow up with you in approximately 10 business days to request a meeting with FDA staff in order to clarify any of our proposed responses or provide additional background, as needed.

Sincerely,

William J. Mullin

Attachment

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Merck & Co., Inc.
P.O. Box 4
West Point, PA 19486-0004

MERCK
Manufacturing Division

15 February 2008

Ms. Mary Anne Malarkey
Director, Office of Compliance and Biologics Quality HFM-600
Center for Biologics Evaluation and Research
1401 Rockville Pike, Suite 200N
Rockville, Maryland 20852-1448

RE: 2007 Team Biologics Inspection
Merck & Co., Inc. – West Point, PA
26-Nov-2007 to 17-Jan-2008
Form 483 Responses

Enclosed with this letter are our responses to the FDA Form 483 observations from the Team Biologics Inspection of our West Point, Pennsylvania facility that was conducted from 26-Nov-2007 to 17-Jan-2008.

In these responses, we address the specific issues presented in each of the observations and also describe the steps that we are taking to enhance our overall Quality Systems. We will ensure the uninterrupted supply of safe and efficacious vaccines, especially for those products where we are the sole and/or key supplier.

In 2006, following our response to the Team Biologics (2006) Inspection, and our subsequent meeting with FDA personnel on 10-May-2006, the West Point Senior Leadership Team made several commitments regarding the actions we were taking to significantly enhance our Quality Systems framework and methodology. Toward this end, we retained an external GMP consulting firm, (b) (4), to assist the Senior Leadership Team in performing a comprehensive assessment of 12 Quality Systems. Our assessment and subsequent actions were communicated to FDA on a routine basis in a series of written updates, the first of which was submitted in August 2006.

This broad based Quality Systems assessment reviewed the following 12 systems:

- Annual Product Review
- Change Control
- Complaint Management
- Deviation Management
- Facilities and Equipment Qualification
- Process Validation
- Product Release
- Regulatory Reporting
- Stability
- Sterility Assurance
- Sterility Control
- Training

While no system-wide failure was noted in any of the 12 systems that were assessed, we did identify 11 areas for enhancement and initiated actions to strengthen those areas. In addition to the many self-identified actions, we have undertaken significant enhancements

(as described in prior communications to the Agency). These enhancements include: 1) improvements to our deviation management system, such as implementation of deviation alerts, 2) an environmental monitoring self assessment ensuring our practices and procedures are reflective of current regulatory expectations, 3) a Failure Mode Effects Analysis (FMEA) initiative focused on a detailed process review of our vaccine and sterile pharmaceutical operations, with an emphasis on strengthening sterility assurance, and 4) the development of an aseptic training facility to provide an opportunity for our personnel to train and/or retrain on aseptic technique and processing.

As part of our commitment to continuous improvement, we communicated to FDA in our September 2007 periodic update that we had engaged a second external consulting firm, (b) (4), to perform an independent assessment of all of the key inspection themes from all Team Biologics Inspections. As a result of this assessment, we initiated a series of additional actions to further strengthen our systems.

The West Point Senior Leadership Team fully recognizes that a key attribute for an effective Quality System is that all system components are robust and mature. As such, the Senior Leadership Team is committed to building on the already-established framework in order to drive our systems to a full state of maturity.

In addition to having the full support of Merck Senior Management, several of whom were in attendance at the FDA Close-Out Meeting, we are working closely with (b) (4), the Vice President of (b) (4) from (b) (4), who was also in attendance at the FDA Close-Out Meeting. (b) (4) participation enabled us to build upon the work we have already undertaken and to immediately initiate systems-based actions in response to the FDA Form 483 observations.

It is important to note that while deviations were identified in the observations, many were previously self identified as a result of our comprehensive Quality Systems enhancement efforts described above. Our responses present additional context where we have already implemented or had plans to implement corrective actions prior to the start of the inspection.

Our responses detail certain additional areas that will be subjected to external expert review as a result of the 2007 Team Biologics Inspection. These include, but are not limited to the following:

- Use of an additional GMP expert and external consultant, (b) (4) (b) (4), to specifically assist our operations in (i) making focused improvements in the atypical and complaint investigation process and (ii) enhancing our corrective action/preventative action system. This project will be initiated in March 2008.

- Use of an external technical consultant, (b) (4), to develop a standardized and consistent methodology regarding (b) (4) systems as a result of our investigation into the PedvaxHIB® media challenge non-conformance. These actions have already been initiated.

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- Starting in March 2008, we will periodically meet with our external GMP Consultants to ensure that all of our proposed actions fully align with Agency expectations, thereby enhancing our Quality Systems.

During the inspection, the Investigators reviewed several discussion items not noted in the FDA Form 483. We will ensure that all discussion items are evaluated and where appropriate, addressed and tracked to completion. We will also thoroughly review the Establishment Inspection Report, once available, and will determine if any additional actions are required.

Finally, we believe all of these actions demonstrate our organization's on-going commitment to make fundamental enhancements to our Quality Systems. In doing so, we will further ensure our ability to provide an uninterrupted supply of safe and efficacious vaccines.

We will follow up with you in approximately two weeks after your receipt of these responses to request a meeting to review our actions with you and your staff.

Sincerely,

John T. McCubbins, Ph.D.
Sr. Vice President
Global Vaccine Manufacturing &
West Point Operations
215-652-6342

William J. Mullin
Vice President
West Point Quality Operations
215-652-6620

Enclosure

Copies:
U. S. Food and Drug Administration:
J. Adamo, Staff Fellow
J. Diaz-Albertini, Investigator
T. Gardine, District Director, Philadelphia Office
J. Loreng, Investigator
C. Lynch, Biologist
M. Major, Research Microbiologist
A. Montemurro, Lead Consumer Safety Officer
T. Roecklein, Consumer Safety Officer
Merck & Co., Inc.,
M. J. Angelo, Ph.D., Sr. Vice President, Quality
R.T. Clark, Chairman, President & CEO .
W.A. Deese, Executive Vice President and President, Merck Manufacturing Division

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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, (b) (4) (b) (4). For example,

   A. On-going investigation into APR 2007-207-0016 issued on 8/13/2007 for foaming during filtration of product 40661 (b) (4) lots 2120187, 2121515, 2122548 and 2123313. The investigation determined that the foaming was due to poly-Hydroxypropyl acrylate ester (poly-HPA) being extracted from the (b) (4) 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 (b) (4) lots associated with the observed foaming even though it was determined that the observation of foam was unique to filling of (b) (4) as many culture media and buffers have inherent foaming properties, and the issue with the filters could go unnoticed in those products.

      i. The associated filter lots have been identified as used in approximately (b) (4) 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 (b) (4) filters implicated, several other filters used during manufacture bulk and final product consist of the same (b) (4) filter membrane. Related BPDR 07-009, dated 10/19/2007 and updated 12/7/07, lists numerous final product lots released from April 2007 to date that used a (b) (4) filter 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.

      iv. The toxicological assessment estimated concentrations of polyHPA that were derived from TOC concentrations in the (b) (4) 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 (b) (4) filters prior to use. However, at the time pre-screening was only implemented for the (b) (4) filters used in the Culture Media, Department (b) (4). This pre-screen was not implemented for all filters with the (b) (4) membrane and in all departments using these filters until December 2007.

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B. Atypical Process Report (APR) 2007-285-0101 was initiated 6/14/2007 for "fibers" being found on the stoppers and in the stopper bowls during the filling of (b) (4) lots of MMR w/rHA on line (b) (4) (b) (4) lots of Varivax Process Upgrade 1 dose and (b) (4) lots of Zoster (PHN) Vaccine 1 dose on line (b) (4), and (b) (4) lot of Elspar on line (b) (4). The root cause of the fibers found in the stopper bowls and on the stoppers was identified to be "a lesser quality" of (b) (4) 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 (b) (4) product, the bags are (b) (4) with the stoppers inside. (b) (4) of the bags was identified as a contributing factor and the fibers were observed after the (b) (4). One lot of the (b) (4) bags, vendor lot # (b) (4), 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 (b) (4) bags in question were assessed. Only (b) (4) lots of product, where the fibers were observed during filling, were quarantined and assessed. Approximately (b) (4) lots of lyophilized product and (b) (4) lots of liquid products were filled during the time of receipt and use of the (b) (4) bag lot in question.

ii. There was no 100% reinspection performed for the entire lots of Elspar lot # 0658678, Zoster (PHN)-1 dose lot # 0658860 and Varivax lot #0659068 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 #0658678 consisting of approximately (b) (4) vials was initially inspected (b) (4) on 6/25/07. The lot was portioned and grouped due to fibers being found in the stopper bowl. (b) (4) vials were (b) (4) reinspected on 11/12/07. Upon reinspection portion O group II was found to have (b) (4) vials containing particulates of which (b) (4) were found to have fibers. This portion of the lot was released. Portion A group II was found to have (b) (4) 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)-1 dose lot #0658860 consisting of approximately (b) (4) vials was initially inspected by the (b) (4) system on 6/26/07. Fibers were observed on the stoppers during filling. Reinspection of Portion O group II which consisted of (b) (4) vials was (b) (4) 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 #0659068, consisting of approximately (b) (4) vials, was initially inspected by the (b) (4) system on 6/27/07. Fibers were observed in the stopper bowl during filling. The lot was portioned and grouped and approximately (b) (4) vials were (b) (4) reinspected and released. The entire lot was not reinspected for the particulate defect. This lot has been released and is within expiration date.

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Response 1: *We understand the importance of fully and timely investigating all atypical reports including ensuring that all affected material is assessed, quarantined, and evaluated. In addition, we agree that all product release decisions should be made based on thorough investigations, pre-defined quality acceptance criteria, and appropriate segregation and disposition of implicated lots. Furthermore, we understand that both the investigations and the release decisions must be fully documented. In order to further enhance our systems, we will do the following:*

- *Vice President of West Point Quality Operations will issue a directive to all applicable site staff in Operations, Science and Technology, and Quality emphasizing the importance of timely, detailed, and well-documented investigations. The directive will also highlight the importance of effectively documenting the rationale and depth of the investigation and ensuring that the investigation is fully considered in all product disposition decisions and that the investigation is fully consistent with the learnings as a result of this observation.*

- *SOP 286-125X* (b) (4) (b) (4) *will be enhanced to provide more detailed guidance for timely and detailed documentation of material assessment and quarantine decisions. This procedure will also be updated to require all potentially affected material to be quarantined until a medical opinion is obtained, when requested. The SOP and training of site personnel will be completed by 14-Mar-2008.*

- *We will review all segregation and reinspection procedures with one of our outside cGMP consultants by 07-May-2008 to ensure that these procedures are fully aligned with cGMP expectations.*

Below are our responses to the specific observations contained in Observation 1.

Response 1Ai-Av: *As stated in the observation, APR 2007-207-0016 relates to foaming observed during sterile filtration of* (b) (4) *, a product that does not normally have foaming properties. The foaming occurred while using* (b) (4) *filters with* (b) (4) *membranes. The issue was self identified by Merck on 05-Sep-2007 and was reported to CBER in a BPDR on 19-Oct-2007. Merck and* (b) (4) *are partnering together to study the incidences of filter foaming to assess if any modifications to the manufacturing, use, and/or handling of the filters should be implemented.*

Executive Summary of Investigation and Product Disposition
We maintain that our investigation was conducted appropriately at each stage of the investigation based on the facts that were known at that time. Because this filter membrane is used across the site and industry, our initial investigation focused on the specific conditions of this culture media and our procedures for filtering (b) (4) *. It also needs to be emphasized that the observed foaming was very limited in occurrence and not representative of our experience with these* (b) (4) *filters in general.*

The first noted observation of foaming occurred on 18-Apr-2007 with a second occurrence on 10-Aug-2007. Corrective actions related to cleaning and storage of equipment were identified as an outcome to the initial investigation, but were not fully implemented at the time of the second occurrence. Between these two events, there were (b) (4) *lots of* (b) (4) *processed with no foaming observed. Based upon the*

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facts known at the time of the second occurrence, it was appropriate to conclude that the filter foaming was related to the operations within the culture media department where the event occurred.

Following our initial investigation of the above two events and deployment of corrective actions, a third event of filter foaming occurred during the filtration of (b) (4) *on 05-Sep-2007, indicating that another potential causative attribute must be involved. Therefore, as a result of the third event, which occurred subsequent to our corrective actions, we initiated a new investigation to identify other contributing factors to the filter foaming phenomena, including review of components received from external vendors.*

As part of this investigation, (b) (4) *communicated to Merck on 12-Sep-2007 that: (i) the foaming, that was detected by Merck and is described in further detail below, was not a contaminant extrinsic to the manufacturing process, (ii)* (b) (4) *had conclusively identified the foaming agent as a poly-acrylate ester, specifically poly-Hydroxypropyl acrylate ester (poly-HPA), and that it is common and present in all* (b) (4) (b) (4) *membranes, (iii) poly-HPA is not toxic based upon results from United States Pharmacopeia (USP) Class VI Biological Tests for Plastics and USP Mouse Safety Test that met all pre-determined acceptance criteria, and (iv) poly-HPA is a known extractable of the filter. On 12-Sep-2007, based upon the information from* (b) (4) *, the Director, West Point Product Release, concluded that a quarantine of other potentially affected lots was not required as there was no impact on product quality. On 13-Sep-2007, the Director, West Point Product Release, immediately convened a cross-functional team, including Medical Services, to better understand why filter foaming is now occurring (use of these filters is widespread within the industry as well as within Merck.) The Director of West Point Product Release, with input from the cross-functional team, including Medical Services, reconfirmed his conclusion that a quarantine of other potentially affected lots was not required as there was no impact on product quality. A formal documented medical opinion was requested at that time and obtained on 27-Sep-2007.*

Our investigation procedure SOP 286-125X (b) (4) (b) (4) *" requires an evaluation of adjacent lots or other lots that may be associated with an atypical event due to a common root cause, raw material, bulk inputs, components, or process equipment. All lots determined to be impacted by an atypical event are quarantined. For the APR that is the subject of this observation, the facts of the investigation detailed below indicate that the appropriate quarantine decisions were made throughout the investigation. Our assessment included the impact of using the* (b) (4) *membrane filters in the manufacturing of bulk and final product lots, including M-M-R®II, PedvaxHIB®, VAQTA®, VARIVAX®, Black Widow Spider ANTIVENIN, and ELSPAR®. The* (b) (4) *lots, where foaming was observed, remain quarantined until the completion of the investigation per our procedures. The decision not to quarantine additional lots was based upon the determination that the root cause for foaming was identified as a known extractable from the* (b) (4) (b) (4) *filter membranes and that the extractable has an established safe toxicological profile.*

The (b) (4) *filter membranes are commercially available filters used throughout the biotechnology and pharmaceutical industry. These filters have an extensive history of use at Merck with no previous observations of foaming, and no changes to the handling and use of these filters at Merck have been identified.*

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We fully understand the cGMP expectations surrounding product release decisions as related to atypical event investigation and documentation. The actions taken during our investigation are aligned with these cGMP expectations, and we are confident in the material assessments and quarantine decisions made in these cases. We do acknowledge that the rationale and timing of events for these assessments could have been documented in greater detail. Therefore, SOP 286-125X (b) (4) (b) (4) " will be enhanced to provide more detailed guidance for timely and detailed documentation of material assessment and quarantine conclusions. The SOP and training of site personnel will be completed by 14-Mar-2008. The subject APR will be updated in accordance with the revised SOP by 31-Mar-2008.

Additional Background

The following paragraphs provide further detail regarding root cause identification, quarantine decisions, timing of activities, and our medical assessments.

Observation of Third Foaming Event, including Quarantine Decisions

Upon a third observation of filter foaming on 05-Sep-2007, the team isolated the (b) (4) filter as the source of the foaming. On 10-Sep-2007, within three business days of the third observation of foaming, Merck and (b) (4) identified the root cause of the foaming as a poly acrylate ester, specifically, poly-Hydroxypropyl acrylate ester (poly-HPA). The fluid from the foaming event was analyzed using (b) (4) (b) (4) analysis and the presence of poly-HPA was confirmed. Poly-HPA is a known non-toxic extractable from the (b) (4) (b) (4) membrane in the (b) (4) filter. Through our investigation, we confirmed that poly-HPA can cause foam in water. On 12-Sep-2007, (b) (4) confirmed, through existing toxicological data, that poly-HPA is non-toxic and present in all (b) (4) membranes. Furthermore, it is our understanding that the (b) (4) membrane is contained in filters widely used throughout the pharmaceutical industry. (b) (4) had previously conducted extensive testing and concluded that all components of the (b) (4) filter, and all (b) (4) membranes, are non-toxic. This determination was based upon results from United States Pharmacopeia (USP) Class VI Biological Test for Plastics and USP Mouse Safety Test that met all pre-determined acceptance criteria.

Based upon the determination that poly-HPA is a known extractable of the filters, in conjunction with the safe toxicological profile from (b) (4) for that extractable, the decision was made on 12-Sep-2007 to continue to release all other products that used (b) (4) filters and/or other (b) (4) membranes.

On 13-Sep-2007, the Director, West Point Product Release, immediately convened a cross-functional team, including Medical Services, to better understand why filter foaming is now occurring (use of these filters is widespread within the industry as well as within Merck.) The Director of West Point Product Release, with input from the cross-functional team, including Medical Services, reconfirmed his conclusion that a quarantine of other potentially affected lots was not required as there was no impact on product quality. A formal documented medical opinion was requested at that time and obtained on 27-Sep-2007.

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Subsequent Merck Medical Assessment

Although the (b) (4) filters have broad application throughout the industry and within Merck, the investigation team required that a Merck medical assessment be conducted (independent of the investigation) to ensure the toxicological data were reviewed in a product specific context. To support this assessment, Merck identified the worst-case final product for potential poly-HPA concentration and calculated a worst-case concentration of poly-HPA for this product. As part of the investigation, samples from filter lots at West Point were evaluated to assess frequency of foaming. In the filter with the worst foaming presence, the extractable level measured in the first liter of filtrate from any filter was 50 ppm Total Organic Carbon (TOC) in Distilled Water. Industry practice is to utilize model solvents during extractable studies because it is difficult to quantify extractables in the presence of media, buffers, or other products. Given that the Merck products are aqueous in nature, water is the appropriate model solvent. This TOC level is compared to the target level of <1 ppm TOC after completing a flush of the filter. Based on the information provided by (b) (4), the predominant extractable from (b) (4) is poly-HPA. These technical data were confirmed by our FTIR testing on the filtrate from the third foaming event.

Using the 50 ppm TOC level and the molecular weight of poly-HPA, a worst-case concentration of poly-HPA was derived. Worst-case contributions of poly-HPA (based on 50 ppm) were assigned to each unit operation where (b) (4) are used in the process from raw materials through final container. As a result, this analysis captured all potential cumulative effects of poly-HPA levels. Given the sporadic nature of the foaming both in level and frequency, this is a highly conservative assessment. This worst-case concentration, together with the toxicological data from (b) (4) was supplied to a Merck physician and toxicologist and formed the basis for an independent medical assessment that was documented on 27-Sep-2007. In a report documented on 29-Oct-2007, poly-HPA concentrations were subsequently calculated for all other vaccine products, confirming our original assumptions for the medical assessment were worst-case.

The medical assessment memo, dated 27-Sep-2007, included no additional toxicological information beyond that which was known on 12-Sep-2007 and also aligned with the assessment received from (b) (4) on 12-Sep-2007. Based upon the information available at the time of this medical assessment, using the worst case assumption of poly-acrylate ester levels and no impact on sterility or potency, the risk of associated medical harm is extremely remote. At the request of the Investigator, the complete rationale for product release was provided during the inspection in a memorandum from the Director of West Point Product Release, dated 04-Jan-2008.

Investigation Timeline of Third Filter Foaming Event

The details of the ongoing investigation were shared during the inspection, and updates regarding this issue were previously provided to CBER via BPDR 07-009 on 19-Oct-2007 and 07-Dec-2007.

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A table listing the timeline of events associated with this investigation is summarized below:

Table 1: Timeline of Events Associated with OPTICAP® Filter Investigation

Date	Event
05-Sep-2007	*Merck observed third foaming event during filtration of Distilled Water*
	Merck isolated the (b) (4) filter as the source of the foaming and notified (b) (4)
10-Sep-2007	*(b) (4) identified poly-HPA as the root cause of the foam and communicated to Merck*
12-Sep-2007	*(b) (4) issued formal report to Merck, confirming the safe toxicological profile for poly-HPA*
	Based on the toxicological profile for poly-HPA provided by (b) (4) Merck determined that additional quarantines were not required for other products manufactured with (b) (4)
13-Sep-2007	*The Director of West Point Product Release immediately convened a cross-funcitonal team, including Medical Services, to better understand why filter foaming is now occurring (use of these filters is widespread within the industry as well as within Merck).*
	The conclusion of the Director, West Point Product Release, with input from the cross-functional team, including Medical Services, was that a quarantine of other potentially affected lots was not required as there was no impact on product quality.
27-Sep-2007	*Merck completed calculations of poly-HPA concentration for the product with the highest potential poly-HPA concentration*
	Merck completed a medical assessment based upon the worst-case poly-acrylate ester concentrations in products and the existing toxicological data. The assessment concluded that the risk of associated medical harm is extremely remote
29-Oct-2007	*Merck completed calculations of poly-HPA concentration for all other (non-worst-case) products*

Toxicological Assessment

A toxicological assessment was performed that estimated concentrations of poly HPA that were derived from TOC concentration in the first liter of WFI collected from the flush of the filter. This assessment was appropriate given that validation data from Merck and (b) (4) demonstrate that the highest level of extractables from (b) (4) (b) (4) are observed during the first liter of the flush. Based upon this information, a worst-case assessment of poly-HPA in the final product was performed based upon a 50 ppm concentration observed in the first liter of Distilled Water flushed through a (b) (4). Despite the fact that the incidence of foaming was limited to a small number of filters across a given lot, the worst case extractable level was assumed to enter the product with each filter used across bulk manufacturing and filling. This cumulative worst case extractable assumption was used for the medical assessment.

Industry practice is to utilize model solvents during extractable studies because it is difficult to quantify extractables in the presence of media, buffers, or other products. Given that the Merck products are aqueous in nature, water is the appropriate model solvent. Therefore, Merck conducted extractable studies on the (b) (4)

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(b) (4) *using water as the model solvent. In addition, toxicological testing was performed by* (b) (4) *utilizing a range of solvents (i.e., water, alcohol, and polyethylene glycol 400). Since alcohol and polyethylene glycol would extract higher levels of extractable from the* (b) (4) *than would water, these three selected model solvents ensure that the extractable levels in the toxicological studies appropriately bracket the theoretical extractable levels in our products. All toxicological test results met pre-determined acceptance criteria.*

Timing and Implementation of Filter Pre-Screen in December 2007

Although the pre-screen was implemented only in Department 207 - Culture Media, with the 10" OPTICAP® filter, this pre-screen was the pilot for a comprehensive pre-screen program. Specifically, this filter pre-screen project plan, which was reviewed during the inspection, was designed as a method to aid in the development of any corrective and preventative actions and to test the efficacy of a pre-screening procedure in controlling filter inventory. Based upon the results of this initial pilot, the scope will be expanded as appropriate to other filters used by other departments.

It is important to note that the 10" OPTICAP® filter was selected for the pre-screen program due to its large surface area coupled with the frequency of use. These factors together provide the best opportunity for the detection of foam. Department 207 – Culture Media was selected for the pilot since it is in this area that foaming is most readily observed since this department filters Distilled Water. In other 10" OPTICAP® filter applications, visual observation of foaming may not be as readily observed.

Under the pre-screening conditions, a sampling of each 10" OPTICAP® filter lot will be flushed to detect the presence of foam and to measure Total Organic Carbon (TOC). If TOC levels are unacceptable, the filter lot will not be used within manufacturing. If non-dissipating foam is observed, surface tension will be measured to assess the disposition of the filter lot.

Future corrective actions and the need to control incoming filter lots via pre-screen will be communicated in updates to BPDR 07-009. The next update to the BPDR will be on 22-Feb-2008 and will include an update on investigational work completed by both Merck and (b) (4) .

Conclusions

The root cause of the observed foaming was identified as poly-Hydroxypropyl acrylate ester (poly-HPA), which is a known, nontoxic, and chemically inert extractable of the (b) (4) *membrane. The* (b) (4) *membrane is a standard item from* (b) (4) *and is used widely at Merck and throughout the pharmaceutical industry. Merck and* (b) (4) *continue to partner together to study the incidences of filter foaming to assess if any modifications to the manufacturing, use, and/or handling of the filters should be implemented. While the investigation remains ongoing, the Distilled Water lots associated with the foaming events remain quarantined. The decision to not quarantine additional bulk and final product lots that used* (b) (4) *membrane was appropriate, given the identification and nature of poly-HPA. Poly-HPA is a known filter extractable with an established safe toxicological profile.*

In parallel to the ongoing collaboration between Merck and (b) (4) *, pre-screening efforts for* (b) (4) *membranes have commenced, starting initially with the* (b) (4) *filters. Progress updates and any additional corrective actions will*

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continue to be communicated in updates to BPDR 07-009. The next update to the BPDR will be on 22-Feb-2008.

Response 1Bi-ii: *We understand this observation relates to the importance of fully investigating atypical events, including ensuring all potentially implicated lots are included in the investigation and controlled. We believe our overall systems operated as intended enabling both the identification of the fibers and facilitating the appropriate management of the impacted lots. Our investigation included appropriate quarantine, reinspection, and release decisions based on the significant number of in-process checks and procedural controls that enabled the self identification of fibers.*

Specifically, the root cause for the fibers was determined to be a combination of an isolated lot of (b) (4) *bags from* (b) (4) *and the* (b) (4) *or* (b) (4) *of the bags containing the* (b) (4) *stoppers. The two week timeframe of use of this isolated bag lot was defined, and all lots filled in that timeframe were assessed as part of the investigation. The material potentially impacted in this timeframe was identified and quarantined based on how the fibers were generated, observations made during numerous in-process verifications, and segregation of product in response to the identification of fibers during processing. Reinspection was completed on all segregated lot portions/groups and was conducted in accordance with our site SOP 286-122X* (b) (4) *Release decisions for the material were based on segregation of material that was not impacted and expanded inspection of impacted portions/groups. Although the information and data presented below support the release decisions taken, we will be enhancing our procedures as follows:*

- *APR 2007-285-0101 will be updated by 18-Mar-2008 to more clearly delineate the rationale and timing of events for these assessments and decisions.*
- *The Sterile Supply area, which manages the* (b) (4) *bag inventory, will update procedures by 30-Apr-2008 to utilize a First In / First Out (FIFO) system with appropriate documentation for all stopper bags.*
- *We will review all segregation and reinspection procedures with one of our outside cGMP consultants by 07-May-2008.*

The following paragraphs provide further detail regarding root cause identification, quarantine decisions, and timing of activities.

Breadth of Investigation to Include All Implicated Lots and Quarantine of Implicated Lots

Atypical Process Report (APR) 2007-285-0101 was initiated for "fibers" being found on the stoppers and in the stopper bowls during the filling of several lyophilized product lots including M-M-R®II, VARIVAX® Process Upgrade, ZOSTAVAX®, and ELSPAR®. The root cause for the fibers was determined to be a combination of an isolated lot of (b) (4) *bags received from the vendor and the* (b) (4) *or* (b) (4) *of the bags containing the* (b) (4) *stoppers. Kneading of the bags containing* (b) (4) *stoppers is necessary due to extensive drying during sterilization that creates stopper clumping.*

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The investigation determined that one lot of bags (Lot (b) (4) received from the vendor (b) (4) was inferior due to the fact that the (b) (4) material used for that one lot of bags allowed shedding of fibers to occur. It is important to note that upon testing as part of the investigation, this bag lot was confirmed by Merck and (b) (4) to shed fibers where other lots of bags received from (b) (4) subjected to this same testing did not shed. In response to this event, (b) (4) test was added by (b) (4) in order to ensure that released (b) (4) bags, supplied to Merck do not shed. In addition, for stoppers used in lyophilization operations, we have switched as of 27-Jun-2007 to a bag from (b) (4), that is better suited to handle the (b) (4) required for lyo stoppers. The implementation of the new bag was tracked for the lyophilized products through our internal change control system.

The timeframe of use of this isolated bag lot was determined based upon our receipt date and stopper processing activities. (b) (4) cases, (b) (4) bags per case, from Lot (b) (4) were available for use from 09-Jun-2007 until 25-Jun-2007, at which point the new type of (b) (4) bags were implemented for use in Lyo Filling. Although all lots processed in this timeframe were not quarantined as part of the investigation, the lots were assessed and quarantine decisions were based upon the following:

- *A determination of how the fibers were generated;*
- *The observations made during numerous in-process verifications; and*
- *The segregation of product in response to the identification of fibers during processing.*

There were (b) (4) product lots, comprised of (b) (4) lyophilized (lyo) product lots and (b) (4) liquid product lots, filled in the two week timeframe of this event when stoppers in the affected Tyvek® bag lot were available for use.

No liquid product lots were quarantined as part of this investigation based upon the following:

- *There were no observations of fibers during the filling of any of the (b) (4) liquid product lots.*
- *Stoppers for Liquid Filling do not require (b) (4) due to (i) different stopper design and configuration and (ii) the fact they are not subjected to extensive drying during sterilization that creates stopper clumping.*
- *Stoppers used for Liquid Filling do not have abrasive surfaces which could cause the generation of fibers.*

With respect to the (b) (4) lyo product lots, fibers were identified during filling in (b) (4) of the (b) (4) product lots (b) (4) additional product lots were also considered affected as a result of association due to shared stopper bowls. Fibers were not found in the remaining (b) (4) product lots during filling. It is important to note that (b) (4) other lots of (b) (4) bags were available for use in filling in Building (b) (4) during this two week timeframe. As a result, only a portion of the lyo product lots produced used the (b) (4) bag Lot (b) (4) in question. Therefore, this reinforces the low frequency of fibers observed during filling in this timeframe.

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Consistent with our procedure (SOP 286-122X), when foreign material is identified during filling operations, the product lot is segregated (grouped/portioned) into affected and unaffected material. The entire product lot is quarantined and each group/portion is evaluated separately for product quality impact. With respect to APR 2007-285-0101, each group/portion was deemed unaffected if the following two criteria were met: 1) a change out of the stopper bowls and use of new stoppers occurred and 2) no fibers were observed following the change out. Any group/portion where fibers were identified was subjected to additional inspection. Due to the limited opportunity for use of the affected (b) (4) bag Lot (b) (4) as well as the low frequency of fibers observed during filling, we maintain that our release decisions were appropriate.

In addition to the quarantine and segregation procedures described above, we also took the following steps prior to release of any product to the market to ensure that a fiber, if present, would not affect product quality:

1) *We assured that the presence of a fiber in a vial that was lodged between the stopper and the vial would not affect container closure integrity. This was detailed in Protocols (b) (4) and (b) (4)*

2) *We assured that the presence of a fiber in a vial would not affect sterility of the product within the vial. The (b) (4) bags are sterilized as part of the stopper sterilization.*

3) *The presence of fibers in a vial was also assessed from a medical perspective. The medical assessment concluded that the safety, sterility, and efficacy of the products would not be compromised. In addition, the risk of medical harm was assessed. This medical assessment deemed the risk of medical harm remote for ELSPAR®, since it is intravenously injected, and extremely remote for M-M-R®II, VARIVAX®, and ZOSTAVAX®, since each of these vaccines is subcutaneously injected. This was detailed in the memo entitled (b) (4) (b) (4) dated 23-Jul-2007.*

Summary of Existing Procedural Controls and Opportunities to Detect Fibers

During the course of filling activities, there are several routine checks where operators and other operational personnel have the opportunity to identify fibers either in the stopper bowl or on stoppers as the vials are being filled or handled. The fibers are white in contrast to the gray stoppers and stainless steel bowls. There are numerous points during production where operators are required to look closely at the stoppers and vials to perform procedural checks. This includes routine checks for proper volume of fill, residual product at the vial/stopper interface, and proper stopper insertion depth. Also in Lyo Filling, operators remove vials from the line every (b) (4) trays filled to perform dose checks and in Liquid Filling, they perform checks every (b) (4) minutes as described in the batch records for each fill. The stoppers of these vials are removed to perform the dose check; and therefore, it would be very evident if fibers were present on the stoppers.

In addition to procedures during filling, other personnel also perform activities in which fibers on stoppers would be detected. The end of fill environmental testing requires an Environmental Monitoring Technician to take a (b) (4) sample from (b) (4) f the stopper bowl. Additionally, operators placing the vials for inspection on the in-feed belt are required to look at vials from all (b) (4) sides of the tray with

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stoppers at eye level to identify raised stoppers. Our routine procedures were working as intended in that they were able to detect and correct the presence of fibers. Therefore, had fibers been present in other lots, there were numerous opportunities to find these fibers.

Rationale for Lot Portioning/Grouping and Re-inspection of Lot Segments

In response to the event of identifying fibers during filling operations, procedures for lot segregation were followed according to SOP 286-122X (b) (4) *." This procedure provides instruction for responding to identification of foreign material or components found in the stopper bowl during the filling operation. When such an event occurs, the filling supervisor must* (b) (4) *and attempt to identify the source of the foreign material within the bowl. The suspect bowl/stoppers are* (b) (4) *clean and sterilized bowl/stoppers. Filling operations* (b) (4) *and* (b) (4) *A lot is grouped due to the presence of foreign material and is portioned for the change in sterilized equipment.* (b) (4) *is the material filled after the replacement of the bowl and components (non-affected material) and* (b) (4) *represents affected materials. All lots controlled under this investigation were segregated in accordance with this procedure.*

With respect to sampling and reinspection, (b) (4) *sampling of the affected material was conducted that included inspecting a* (b) (4) *of vials based on* (b) (4) *specifically looking for fibers followed by decrimping and reconstituting those vials and again examining under* (b) (4) *for fibers. This was completed for the affected groups/portions* (b) (4) *of the* (b) (4) *lots;* (b) (4) *lots were to be discarded in response to an unrelated atypical event. Based on the results of the* (b) (4) *sampling, additional material from* (b) (4) *lots was discarded based upon the high number of defects found during the* (b) (4) *sampling. The remainder of the material was* (b) (4) *100% re-inspected and met all of its predefined criteria as defined in further detail below.*

Release Rationale for ELSPAR®, ZOSTAVAX®, and VARIVAX®

For ELSPAR® Lot 0658678, ZOSTAVAX® Lot 0658860, and VARIVAX® Process Upgrade Lot 0659068, the affected group/portion was 100% (b) (4) *re-inspected. The remainder of these lots was not re-inspected due to the change in stopper bowls and components and the fact that no fibers were identified following that change. Product disposition required satisfactory* (b) (4) *Sampling* (b) (4) *checks following the 100%* (b) (4) *re-inspection in order to release the material.*

Specifically, with respect to ZOSTAVAX® Lot 0658860, and VARIVAX® Process Upgrade Lot 0659068, there were zero (0) defects found during the (b) (4) *Sampling following the re-inspection. In addition, they met the two other pre-defined quality criteria of satisfactory reinspection and confirmation of a low-level of fiber defects (alert level of* (b) (4) *fiber rejects for the reinspection).*

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With respect to ELSPAR®, this lot was portioned and grouped as follows:

Table 2: Groups/Portions for ELSPAR® Lot 0658678

Trays	Action	Group	Portion	Disposition
(b) (4)	*Fibers found at Tray* (b) (4) (b) (4)	(b) (4)		*Reinspected Released*
	Fibers found at Tray (b) (4) (b) (4)			*Reinspected Rejected*
	No Fibers Found			*No additional Inspection Released*

- *With respect to Portion* (b) (4) *Group* (b) (4) *out of* (b) (4) *vials inspected were rejected during inspection since fibers were observed.*
- *With respect to Portion* (b) *, Group* (b) (4) *out of* (b) (4) *vials inspected were rejected during inspection since fibers were observed.*
- *With respect to Portion* (b) (4) *Group* (b) (4) *no reinspection was required because stopper bowls and components were changed and no fibers were observed.*

The release decision for Portion (b) (4) *Group* (b) *was based on satisfactory reinspection, passing* (b) (4) *Sampling following reinspection and confirmation of a low-level of defects present in the Portion (alert level of* (b) (4) *fiber rejects for the reinspection).*

The reject decision for Portion (b) (4) *Group* (b) (4) *was based on not meeting the alert level of* (b) (4) *fiber rejects for the reinspection, although it was reinspected and passed the* (b) (4) (b) (4) *Sampling.*

2. Merck's packing methods for vaccine products shipped with (b) (4) permitted ingress of CO_2 replacing argon 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 CO_2 in the headspace of Varivax III, lot 1076M. 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 (BPD 06-003) to FDA concerning a pH failure of Varivax III, lot number 0265P, at the two month time period. Merck did not inform CBER of the other products (which included domestically shipped products) susceptible to CO_2 ingress until the October 2006 update to the BPDR.
    - Merck did not inform international regulatory authorities of the CO_2 ingress issue. Merck submitted requests for approval of changes to packing/shipping methods, but did not acknowledge the CO_2 ingress as the reason for the change.

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- For Varivax, lot 0265P, Merck verified the ingress of CO_2 and estimated that at least (b) (4) of the lot returned from the international site had CO_2 in the headspace. Potency and sterility testing passed specification at the 2 month and 12 month time period; however, although Merck had linked "over-pressurization" with CO_2 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 CO_2 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.

Response 2: *We understand this observation relates to our investigation associated with over pressurization complaints and the potential for CO_2 to enter the head space of some vials of vaccine products that are shipped using (b) (4) under certain shipment configurations. Prior to providing our written response to the points discussed in the observation, we would like to provide a complete summary of all aspects of our investigation since 2005. This will include the following:*

A) Over Pressurization Complaints Investigation.

B) Testing on Importation Investigation- pH Out-of Specification (OOS) Result.

C) Root Cause Investigation Regarding Potential For CO_2 Ingress Into Vial Head Space.

D) Assessment of Product Quality Assurance- Sterility and Potency.

E) Identification of Corrective Actions.

Over Pressurization Complaints Investigation

Prior to 2005, Merck received periodic complaints for over pressurization in vaccines. Typically, these complaints were described by the user as (i) the syringe plunger pushing back, (ii) liquid spraying out of the vial stopper, or (iii) difficulty during product reconstitution or withdrawal. Due to the high incidence of complaints occurring during health care provider manipulation, complaint investigations originally focused on health care provider technique during administration as the likely root cause. For example, failure to adequately purge air from the syringe prior to reconstituting the lyophilized product could result in an apparent pressurization of the sealed vial.

In 1st Quarter 2005, West Point Quality Operations made a recommendation to perform a detailed assessment of over pressurization complaints. In July 2005, during a meeting of

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the West Point Site Senior Leadership Team, an update was provided that included current investigation status and additional areas to pursue including a planned shipping study and vial head space analysis. This investigation team included members of Quality Operations, Science and Technology, Manufacturing Operations, and Packaging Technology. The investigation team executed a systematic review of historical complaint data, evaluated all investigative efforts to date, and visited a medical office that had experienced a high frequency of over pressurization complaints. As a result of this site visit, there was a recognition that while health care provider technique may be a contributing factor to over pressurization complaints, our investigation should be expanded to aggressively consider other potential root causes for this complaint type.

Testing on Importation Investigation

In April 2005, Merck's Haarlem, Netherlands site reported a pH OOS result for Lot 1052P identified during testing on importation. This OOS result was systematically investigated. As part of the report of the OOS pH result from Haarlem, it was noted that elevated pressure in the vials was observed during reconstitution of the vials for the pH test. This was explored further through a confirmatory study in Haarlem during which pH testing was repeated with specific instructions to note the vial headspace condition during reconstitution. This confirmatory study indicated a link between vial headspace pressure and low pH. Additionally, as part of our systematic review, we identified an earlier (2003) OOS pH result that was seen by Haarlem; however, as part of the investigative efforts, we had also identified that there were (b) (4) *lots between these* (b) (4) *occurrences (2003-2005) that met the pH specification upon testing on importation in Haarlem.*

As part of the thorough investigation conducted in 2005, we implemented the following actions:

- *Measuring the vial headspace pressure destructively and nondestructively,*
- *Measuring CO_2 content in the vial headspace, and*
- *Measuring pH of vials with over pressure.*

The results of the tests performed on vials from the 2003 Lot 1076M associated with the OOS pH result that were returned from Haarlem were reviewed as part of the 2005 investigation. The 2003 OOS pH event investigation, together with the 2005 investigation, were instrumental in understanding the root cause and in identifying actions to be taken. This in-depth investigation was shared with the Investigator during the 2007 Team Biologics inspection.

While the 2003 investigation identified the correlation between CO_2 ingress, over pressurization and low pH, the 2003 investigation was not able to recreate over pressurization in vial headspace or to identify a root cause for CO_2 ingress. As a result, this 2003 investigation focused on circumstances that could lead to over pressurization, with primary emphasis on trying to re-create over pressurization in vials during shipment. This 2003 investigation looked at such factors as: pressure changes and aluminum seal conditions as contributing factors. These contributing factors were challenged through studies which were not able to re-create over pressurization in vials. It was not until the expanded systematic 2005 investigation where special emphasis was placed on trying to understand the link between CO_2 ingress, over pressurization, and low pH that the root cause mechanism was identified revealing how these factors were interrelated.

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Root Cause Investigation

As stated earlier in the previous two sections, we took all of the information gained from the 2005 investigation and focused our efforts on determining a root cause mechanism that would explain how CO_2 ingress, over pressurization, low pH could be linked.

We subsequently determined in January 2006, based on direct measurements of the thermo mechanical properties of the vial, stopper, and (b) (4) *seal that the root cause for potential CO_2 ingress into the vial head space of certain vials during shipment with* (b) (4) (b) (4) *was attributed to exposure of certain vials to extremely low temperatures during shipments. The shipping configuration consisted of* (b) (4) *product boxes* (b) (4) *with* (b) (4) *of* (b) (4). *The* (b) (4) *created a CO_2 atmosphere in the shipper container.*

When certain vials are exposed to extreme cold temperatures (b) (4), *the elastic properties of the stopper are significantly reduced (i.e., become* (b) (4). *The stopper glass transition temperature was measured as* (b) (4). *Therefore, at temperatures below the glass transition temperature, the sealing properties of the stopper are affected. The result of this is the potential for CO_2 ingress into vial headspace. Our studies for assessing the potential impact of CO_2 ingress will be discussed in greater detail in the product quality assurance section below.*

Product Quality Assurance

Upon achieving an understanding of the mechanism for CO_2 ingress, we focused our investigation specifically on the effect of CO_2 / low pH on the potency and sterility of VARIVAX®III in cases where the low pH OOS results were observed.

Sterility Assurance *– An in-depth investigation regarding the sterility of VARIVAX®III in cases where the potential existed for ingress of CO_2 in the headspace was conducted. Merck concluded that sterility of VARIVAX®III for vials that were susceptible to the potential for CO_2 ingress in the headspace were unaffected since the* (b) (4) *seal provides sufficient compression on the stopper, independent of the stopper glass transition temperature, ensuring a consistent barrier and therefore providing assurance of sterility. The sterility assurance assessment included the review of two distinct interfaces between the vial and stopper shown in the figure below.*

(b) (4)

(b) (4)

(b) (4)

(b) (4)

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As described in response to Observation 2, Bullet 3, actual sterility testing of VARIVAX®III Lot 0265P was performed. Given that (b) (4) *vials from VARIVAX®III Lot 0265P were used in sterility testing, there is well over* (b) (4) *probability that at least one over pressurized vial was tested for sterility. Further, there is* (b) (4) *confidence that between* (b) (4) *and* (b) (4) *over pressurized vials were sterility tested. All sterility test results conformed to specification at two sterility testing intervals, including testing conducted through expiry. These probabilities and the passing sterility and potency results from the VARIVAX®III Lot 0265P testing support that sterility and potency are not impacted by over pressurization. This is further supported by the discussion below.*

Detailed analysis demonstrated that the compression of the stopper flange onto the top horizontal surface of the vial by the (b) (4) *seal creates a level of compression that ensures container closure equivalent to* (b) (4) *studies. This was determined by direct measurement of the thermo mechanical properties of the vial, stopper, and* (b) (4) *seal that showed that a minimum compression on the stopper of at least* (b) (4) *at the time of sealing was required to maintain compression at Interface 1 at all temperatures, including temperatures* (b) (4) *Direct measurements of stopper compression confirmed that actual compression was an order of magnitude greater than* (b) (4) *microns.*

The fact that CO_2 was in the headspace indicates that, on a portion of vials exposed to extremely low temperatures, a transient condition is created where the seal may become permeable allowing the molecular ingress of CO_2. The pressure differential between the interior of the vial and the surrounding CO_2 environment creates a driving force allowing the molecular ingress of CO_2. In this situation, although there was gas exchange, sterility was not compromised. The basis for this conclusion is as follows:

- *The* (b) (4) *seal maintains compression on the stopper flange and the horizontal surface of the vials at all temperatures.*

- *While compression was assured at the stopper flange, an analysis was conducted of the interface of the vial neck and the stopper* (b) (4) *Our analysis showed that at the gap of* (b) (4) *, there was no longer a driving force for bioburden movement because there was equilibrium between vial headspace and the shipper environment.*

- *We acknowledge that bioburden may be present in shippers; however, bioburden is not motile at these conditions and our analysis showed that there is no driving force after the vials reach equilibrium. These conditions combined with compression of the stopper flange on the horizontal surface of the vials allow for molecular ingress of CO_2 while not permitting bioburden ingress. This is further supported by sterility testing of over pressurized vials as described below.*

In summary, the combination of the direct sterility testing of vials subject to over pressurization coupled with the technical information described above support our conclusion that the vials maintain sterility under the conditions described above.

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Product Potency *– It was determined through testing that VARIVAX®III potency was not impacted by the presence of CO_2 in the vial head space. This was done by identifying over pressure vials and vials with typical headspace pressure. These vials were reconstituted and tested for pH and potency* (b) (4) *reconstitution and* (b) (4) *reconstitution* (b) (4) *It was experimentally confirmed that the CO_2 in the vial head space did not affect the pH of the non reconstituted product. Upon reconstitution of the over pressurized vials, the pH was out of specification, while vials not exposed to over pressurization remained within specification. Furthermore, there were no statistically significant decreases in potency between the over pressurized vials and those vials not exposed to over pressurization over the thirty minute hold time.*

Patient Impact *– A medical assessment was performed for VARIVAX®III to determine if there was any patient impact due to the potential for over pressurization in the vial headspace caused by CO_2 ingress. Because the investigation determined that potency and sterility were not impacted by CO_2 in the head space, the medical assessment focused on the impact of decreased pH in the reconstituted product. The medical assessment concluded that the risk of an increase in adverse experiences due to a decrease in pH is remote as other vaccines are used at lower pH ranges and the risk of associated medical harm is remote.*

Product Quality Assurance Summary *– The 2005 investigation conducted a product quality assessment for VARIVAX®III that included an evaluation of the potential impact to sterility, the potential impact to product potency, and the potential impact to patients during administration. This assessment was done through analysis of all components of the vial, direct measurement of various conditions, and a medical assessment. The investigation determined that sterility was unaffected, that product potency was unaffected, and that there was a remote chance for an increase of adverse experiences due to the potential local injection site irritation.*

Identification of Corrective Actions

Upon confirmation of the root cause for CO_2 ingress into vial headspace, a team was immediately chartered to identify and implement corrective actions, including the primary corrective action that was identified to ensure that product vials were not exposed to temperatures (b) (4) *temperature of the stopper. This was accomplished by specifying that shippers could not expose product to temperatures below* (b) (4) *well* (b) (4) *temperature* (b) (4)*. The temperature exposure of vials during shipping was controlled to the newly specified minimum temperature by either modifying the existing shipper configurations or by developing and implementing new shippers (the* (b) (4) (b) (4) *"). The* (b) (4) *utilize* (b) (4) *or* (b) (4) *in a modified shipping configuration to maintain the shipping temperatures required for each product. All shipment methods for products that utilize* (b) (4) *were evaluated and corrective actions were pursued to fully remediate the potential for product exposure to low temperatures during shipment. This approach addressed all potentially impacted Merck products. A phased implementation of the* (b) (4) (b) (4) *was begun in June 2006, with full implementation for shipments within the United States by July 2006; and for the international markets, by November 2007. Notifications of the changes for the* (b) (4) *in the United States were communicated in the individual product Annual Reports. It*

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is important to note that the (b) (4) for the international markets were implemented over a longer timeframe due to the need to file and receive regulatory approval from various international regulatory agencies.

Since implementation of the (b) (4), we have seen a (b) (4) reduction in associated complaints (b) (4) complaints per million to (b) (4) complaints per million) for over pressurization across all potentially affected products.

Our corrective action assessment also included an evaluation of all other products that are shipped using (b) (4). The assessment included:

- *Sterility and Potency: While other products utilize a different stopper than VARIVAX®III, the rubber formulations for the stoppers are the same, and therefore, the (b) (4) temperature is the same. We also confirmed that various stopper types have equivalent dimensional characteristics. These properties ensure, as shown in our investigation into VARIVAX®III vials, that sterility would not be impacted. As further support, our testing on importation, as summarized later in the Response 2, Bullets 3 and 4, provides added assurance that sterility and potency are not affected. Therefore, we concluded that the sterility and potency are not affected.*

- *Analysis was conducted to determine the impact of CO_2 if present in the head space of measles, mumps, rubella containing products. Experimental studies conducted by (b) (4) in (b) (4) exposed M-M-R®II to CO_2 and demonstrated that the product pH remained within specification. Evaluation of the buffering capacity of the measles, mumps, rubella family of products, including ProQuad® Refrigerated, MUMPSVAX®, ATTENUVAX®, MERUVAX®, and M-M-VAX® concluded that the pH of these products would also remain within specification.*

- *This potential for ingress does not exist for ProQuad® Refrigerated and ZOSTAVAX® Refrigerated because (b) (4) is not used for shipments of these two products.*

Below is a detailed discussion of the response to the specific observations, including additional actions and enhancements that relate to the specific observations.

Response 2, Bullet 1: *BPDR 06-003 was submitted to FDA on 26-May-2006 with updates provided on 31-Oct-2006 and 19-Jul-2007. The BPDR was submitted due to a stability failure of VARIVAX®III, Lot 0265P. The failure was for out of specification pH measurement that occurred at the two month stability time point. In the initial BPDR, the root cause (CO_2 in the headspace of the vials) of the out of specification pH result, was communicated. Also, the detailed product impact assessment of VARIVAX®III was summarized.*

The defined corrective action for this specific issue was replacement of (b) (4) with (b) (4) for shipments of VARIVAX®III. The 26-May-2006 communication also stated that "all shipments of Merck & Co., Inc. products that utilized (b) (4) have been evaluated and corrective actions are being pursued in an expedited manner to fully remediate the potential for product exposure to low temperatures during these shipments".

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In the 31-Oct-2006 update to BPDR 06-003, the corrective actions for other products were explicitly stated in order to communicate the actions taken (or to be taken) with respect to implementing the (b) (4) *for each product and the associated timing for implementation based upon regulatory approval. The BPDR update on 19-Jul-2007 communicated that all corrective actions related to the initial BPDR were completed.*

Although we believe that our communications with CBER were at all times appropriate and communicated the actions we were taking for all potentially impacted products, as well as the corrective actions taken and the associated timing, we acknowledge that the BPDR and the updates could have been written with more specificity to highlight each of the products potentially impacted as opposed to a general statement regarding "all other affected products". Nevertheless, independent of the clarity of our language chosen, our actions did, in fact, apply to all of the potentially impacted products, including VARIVAX®III, VARIVAX®, ZOSTAVAX®, M-M-R®II, ProQuad®, MUMPSVAX®, ATTENUVAX®, M-M-VAX®, and MERUVAX®. As a result of the learnings from this observation, SOP 283-303X "Biological Product Deviation Reports" will be updated to include specific instruction to clearly indicate which products are potentially impacted and to ensure clarity in all communications. This update will be completed and applicable personnel will be trained by 29-Apr-2008.

Response 2, Bullet 2: *As a result of this observation, we fully recognize that while the international supplements identified the changes we were making to the pack out procedures for distribution, the supplements did not clearly specify the basis for making these changes. Therefore, Guideline 108.008 "Guideline* (b) (4) (b) (4) *Approved Biologics Products" will be revised to indicate that variations must clearly indicate when a change is made in response to a quality investigation. The Guideline will be updated and personnel will be trained by 14-Apr-2008.*

Response 2, Bullet 3: *Although we acknowledge that during sterility and potency testing of VARIVAX®III Lot 0265P, analysts did not note over pressurization in the actual vials tested, we have a high level of assurance that over pressurized vials were sterility tested, given the frequency of over pressurized vials being present in VARIVAX®III Lot 0265P. Through direct measurement of the headspace pressure of* (b) (4) *vials in* (b) (4) *packaging boxes from Lot 0265P, it was determined that* (b) (4) *of the vials in this lot exhibited over pressurization. These vials were randomly distributed within and between the boxes returned for stability testing. Given that* (b) (4) *vials from VARIVAX®III Lot 0265P were used in sterility testing, there is well over* (b) (4) *probability that at least* (b) (4) *over pressurized vial was tested for sterility. Further, there is 99% confidence that between 13 and* (b) (4) *over pressurized vials were sterility tested. All sterility test results conformed to specification at* (b) (4) *sterility testing intervals, including testing conducted through expiry. These probabilities and the passing sterility and potency results from the VARIVAX®III Lot 0265P stability study support that sterility and potency is not impacted by over pressurization.*

Additionally, sterility and potency testing are performed in (b) (4) *upon agency batch release of M-M-R®II and VARIVAX®. These countries received shipments that were susceptible to the potential for CO_2 ingress. From 1998 to 2006,* (b) (4) *packaged lots were tested for sterility and potency by the Agencies in these*

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countries. None of these lots have failed sterility or potency tests. This provides further assurance that there is no impact to sterility or potency as a result of over pressurization.

Response 2, Bullet 4: *The potential of CO_2 ingress in the head space of other products was also evaluated to determine whether there is an impact on pH and on sterility as described earlier in our response.*

We acknowledge that direct testing of other products susceptible to CO_2 ingress was limited in scope as our initial conclusion determined that no other products would be impacted. As a result of this observation and detailed discussions with the Investigator, we understand the importance of (b) (4) *testing of our products susceptible to the potential of CO_2 ingress in order to confirm product quality. A plan will be developed to simulate CO_2 ingress, measure pH, and test the potency of the simulated product. ZOSTAVAX® Frozen, ProQuad® Frozen, VARIVAX®, and M-M-R®II will be evaluated as part of the plan. This plan will be approved by 28-Feb-2008.*

It is important to note that although direct testing of other products susceptible to CO_2 ingress was limited, there are test data which support the fact that there was no detrimental affect on product potency and/or sterility.

- *Testing on importation was coordinated in Europe by Merck's Haarlem, Netherlands facility for VARIVAX®III and M-M-R®II. These products were shipped under* (b) (4) *conditions and were susceptible to the potential for CO_2 ingress. All such tests were within specification other than the two results (2003, 2005) discussed previously and one subsequent (2006) result for a lot rejected during testing on importation and documented in APR 2005-285-0076.*

- *In Europe, formal batch release is required to be performed by the* (b) (4) (b) (4) *). Satisfactory potency testing by the* (b) (4) *is a requirement for VARIVAX®III and M-M-R®II batch release. As of 11-Jan-2008, no batches shipped under* (b) (4) *conditions have been reported by the* (b) (4) *as having out of specification results.*

- *Additionally, sterility and potency testing is performed in* (b) (4) *upon Agency batch release of M-M-R®II and VARIVAX®III. No test failures have been noted.*

Response 2, Bullet 5: *We would like to clarify that during the multi-year investigation, we did consider the consequences of stopper / seal defects on the potential for over pressurization.*

Specifically, one study focused on vials from VARIVAX®III Lot 1052P, which were returned from Haarlem. VARIVAX®III Lot 1052P failed testing on importation in Haarlem for out of specification pH. (b) (4) *vials, which had out of specification pH due to CO_2 in the head space, were examined. Vial and stopper examination was comprised of an assessment of seating and tightness of the seal, inspection of the vial and stopper under* (b) (4) *, and vial flange thickness and inner diameter measurements. The inspection did not reveal any component defects that could explain the increased pressure reported for the vials.*

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A second study was conducted using (b) (4) shippers and vials with varying seal forces of the (b) (4) seal compressing the stopper. These vials were subjected to an international shipping trial utilizing the (b) (4) shipper that had resulted in over pressurized VARIVAX®III vials. The shippers, (b) (4) were packed out with (b) (4) of test vials with (b) (4) The (b) (4) were shipped to Haarlem, the Netherlands, and shipped back to West Point, Pennsylvania. Pressure and CO_2 measurements on the returned vials did not indicate CO_2 ingress or over pressurization, even in the vials without caps and with a low seal force.

As demonstrated by these two studies, Merck did consider stopper / seal defects going undetected during filling. The potential for components to be a contributing factor will be evaluated for each future over pressurization returned sample.

Nonetheless, we recognize the importance of ensuring vials are properly sealed. As a result, to provide greater assurance that seals are consistently applied to vials, effective as of 19-Dec-2007, SOP 290-299 (b) (4) " was updated to include the requirement that residual seal force measurements are taken for each lyophilized lot. To further enhance our investigation into over pressurization complaints, a formal protocol for evaluation of over pressure complaints will be developed and implemented by 19-Mar-2008.

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. APR 2006-204C-0034 dated 8/24/2006 was issued for the sterility failure of Pedvax bulk lot 2116084-1. The contaminant was noted as *Bacillus cereus*. However, the investigation failed to assess a recent change in the sterilization cycle for (b) (4) (b) (4), implemented in July 2006, although a WFI investigation for *B. cereus* showed a possible route of contamination through processing hoses. The validation of this SIP 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. APR 2006-232-0011 dated 3/8/2006 was issued for back pressure rise on the (b) (4) (b) (4) during sterile filtration HPV type (b) (4) lots 2113179 and 2113180 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 filtration fouling was due to insufficient filtration capacity for the Type (b) (4) 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 HPV manufacturing of which there have been (b) (4) HPV type (b) (4) 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 1529U, Adverse Event Reports of Suspected Anaphylaxis was inadequate for the following reasons:

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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 1529U were the first MMR lots formulated with rHA. These bulk lots were up to 6 years old. There was no evaluation of the stability of the bulks relative to rHA. Existing stability data for the bulks are limited to potency and sterility testing.

ii. Review of APRs was specific to lot 1529U 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 with rHA as compared to MMR with HSA.

iii. Analysis of adverse events failed to include all adverse events related to anaphylaxis associated with MMR rHA 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 (b) (4) (b) (4). However, only the stopper and rHA vendors were contacted by Merck to investigate potential problems in their manufacturing processes.

D. APR 2006-285-0131 dated 5/10/2006 was initiated for the sterility failure of ProQuad lot 0654599. The contaminant was identified as *Ralstonia* species and the (b) (4) 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 APR 2006-285-0117 was on-going for cans found during (b) (4); and stated that container integrity was also a potential mechanism for the sterility failure. However, APR 2006-285-0131 failed to specify how this potential cause was investigated or how it was ruled out.

Additionally, the APR corrective actions related to the (b) (4) were closed in June 2006. However, implementation of (b) (4) changes was limited to the building (b) (4) and did not address global corrective actions related (b) (4) used in different buildings. The corrections to the (b) (4) in the bulk Rotavirus areas were just completed in January 2008.

E. APR 2006-115-0058 dated 4/14/2006 was initiated for sterility failure of COMVAX® lot 0654907. The investigation failed to include an assessment of the container closures of the sterile bulk inputs: bulk Alum Diluent, Preservative-Free Bulk Liquid PedvaxHIB, and Recombivax Preservative-Free Bulk. These bulks are stored in 45 L bottles with True Union closures.

F. Atypical Process Report (APR) investigations #2006-160S-0034 and #2007-160NS-0032 were initiated on **4/21/06** and 4/26/07, respectively, based on phenol content results. Neither investigation identified a laboratory root cause. The corresponding manufacturing investigations (APRs #2006-305-0024 and #2007-305-0007, respectively) were not initiated within 30 days of the identification of atypical and/or OOS results.

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G. APR investigation #2007-305-0004 was initiated on 3/15/2007 for an OOS result for phenol concentration. According to this APR, two long term corrective actions to improve the method of charging phenol to the transfer can during phenol preparation were implemented on 5/18/07. On the same day these were implemented, a second OOS result for phenol concentration occurred. The corresponding APR investigation (#2007-305-0007) also linked the high phenol result to the method of charging phenol 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 phenol addition.

Response 3: *We recognize the importance of ensuring that we have robust procedures and systems to investigate deviations. We recognize that these systems must support the determination of root cause based on comprehensive evaluations of available data. In 3Q2006, as part of our efforts to enhance our Quality Systems and prior to the start of this inspection, West Point Quality Operations chartered an initiative throughout Vaccine and Sterile Operations to strengthen our deviation management system. This initiative was piloted in 1Q2007 and formally implemented site-wide on 03-Sep-2007. The key enhancements include:*

- *Improved training for all personnel conducting investigations, including clear expectations on the quality expectations for investigations and associated documentation.*
- *Implementation of the Deviation Alert form to document facts surrounding a deviation at the time of the event within either the laboratories or manufacturing operations.*
- *Standardization of root cause investigation tools such as the* (b) (4) (b) (4) *and the* (b) (4) .
- *Categorizing atypical events based upon the nature of the reported deviation and the associated timeline for targeted completion of any investigation.*
- *Consolidated manufacturing and laboratory investigations upon notification of Out-of-Specification (OOS) Results.*

These enhancements collectively ensure that a thorough investigation is conducted and documented in a timely manner. In January 2008, Quality Operations initiated an oversight program to assess the effectiveness of the implementation of the new deviation management system.

We believe that, with the implementation of the above actions, we have enhanced the thoroughness of our investigations and have ensured that sound conclusions are drawn based on the technical data available at the time of the investigation. This observation, coupled with several of the other observations, emphasizes the criticality of thoroughly investigating all atypicals and deviations and documenting them accordingly. Therefore, we will build on the actions highlighted above that were taken in 2007 to strengthen our investigation process by using an external cGMP consultant, (b) (4) (b) (4) *to help us identify additional areas where the investigation methodology and corrective action/preventative action (CAPA) process can be enhanced further. This activity will be initiated in March 2008 and will first focus on an assessment*

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followed by a project plan, implementation and associated training. The outcomes of this effort will be summarized and provided to the FDA in subsequent updates.

Our responses to the specific observations are presented below.

Response 3A: *We understand that this observation relates to the thoroughness of our investigation of Atypical Process Report (APR) 2006-204C-0034 as it relates to considering and evaluating all potential root causes for any atypical or other deviation.*

PedvaxHIB® Bulk Lot 2116084-1 Investigation Including Change in (b) (4) (b) (4)

We respectfully submit that the investigation into the sterility failure associated with PedvaxHIB® was comprehensive and thorough and drew sound conclusions based on the collection and review of technical data at the time of the investigation. A summary is presented below.

APR 2006-204C-0034 was initiated on 24-Aug-2006 as a result of a sterility failure for PedvaxHIB® bulk Lot 2116084-1 for Bacillus cereus. The following were considered as part of the investigation.

- *The most probable root cause was identified as an isolated event related to pressure testing of valve assemblies. It is important to note that there were no sterility failures in over five years of bulk PedvaxHIB® manufacturing and* (b) (4) *consecutive passing media challenges between 2001 and 2006.*

- *The* (b) (4) *cycle was in fact investigated and documented in APR 2006-204C-0034. The* (b) (4) *change was assessed, and the investigation concluded that this change was not the root cause for the sterility failure. This conclusion was based upon the data available at the time, which included the validation of the modified* (b) (4) *cycle with* (b) (4) *validation studies and the successful 2006 annual media challenge that was performed using the modified* (b) (4) *procedure.*

- *As part of the sterility investigation, a passing media challenge in November 2006 was performed and was observed to be free of any microbial contamination.*

- *Additionally, expanded sterility testing was initiated in December 2006 on five bulk and intermediate lots of PedvaxHIB® made after the sterility failure (expanded testing of* (b) (4) *tested of product as opposed to routine release testing of* (b) (4) *tested of product). This expanded sterility testing plan provided a* (b) (4) *assurance that if the level of contamination observed in Lot 2116084 were present in the adjacent lots, such contamination would be detected. All expanded testing passed for all lots tested.*

Therefore, we respectfully submit that our investigation was thorough and comprehensive, utilizing the best information available at that time and that the most conservative actions were taken at each step of the investigation process using sound scientific principles. We would like to emphasize that the very unique nature of this non-conformance, with a very low level and low frequency of microbial presence, made detection quite difficult by standard assessment methods. Lastly, it was in fact our own Quality systems and investigative efforts that ultimately identified the root cause of this

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occurrence and our decision to recall the potentially affected products from the market place.

Water for Injection (WFI) Investigation in the PedvaxHIB® Chemistry Suite
We wish to clarify that the sterility failure investigation mentioned above also evaluated the presence of Bacillus cereus in the processing hoses at the WFI site as a potential root cause. This WFI site is used to flush filters that are subsequently autoclaved and as a water source for a (b) (4) skid. Because the process equipment is subsequently sterilized by (b) (4) the WFI excursion, while accurate as a potential source of this organism, was concluded not to be a root cause for the sterility failure since the presence of any microbial bioburden would be eliminated by the (b) (4) cycle. Therefore, to conclude this was not a root cause for the failure was valid at the time of the investigation. As mentioned earlier, the nature of the microbial contamination detected as part of our comprehensive investigation was at extremely low levels and at a very low frequency.

Finally, we communicated this investigation routinely to the FDA through a series of verbal and written communications in October and November 2007 and frequently updated the Investigators during the Team Biologics Inspection. Merck submitted a BPDR 08-001 on 08-Jan-2008 that also summarized all of our investigation activities and actions taken as part of the PedvaxHIB® investigation starting in October 2007.

Conclusion
In conclusion, as described in detail above, we respectfully submit that the PedvaxHIB® investigation was thorough and comprehensive and made sound scientific conclusions based upon the information available at that time.

Response 3B: *We fully understand that the observation relating to HPV (b) (4) filtration highlights the importance of comprehensive investigations and documentation of the results.*

Implementation of Redundant Filtration in the New Product Suite (NPS)
The sterile filtration of Human Papillomavirus (HPV) Type (b) (4) results in progressive blockage of the membrane pores during the filtration process. At a threshold amount of pore blockage, a sharp increase in back-pressure occurs and is typically known as the point of filter (b) (4). In August 2005, West Point Vaccine and Sterile Operations implemented a change to require (b) (4) filtration in the (b) (4) facility [i.e., the (b) (4) in response to European regulatory guidance. This change entailed using (b) (4) filters instead of a (b) (4) filter. There were no issues observed with the (b) (4) filtration of HPV Types (b) (4) and (b) (4) However, the first (b) (4) Type (b) (4) lots made in the (b) (4) in March 2006 experienced a large increase in pressure resulting in the need for a (b) (4) filters to complete the process. While the filters were not sized correctly in terms of filtration capacity, there was no adverse impact to product quality (i.e., sterility, potency) as noted in our investigation 2006-232-0011, which was reviewed with the Investigator. A corrective action of using (b) (4) (b) (4) filters in the (b) (4) was implemented on 07-May-2006 (Reference CBE-30 approved 31-Jul-2007, STN BL 125126/362). We acknowledge that the initial selection process was not complete for the filtration change in (b) (4) in that the reduction in filter surface area and its impact on filtration capacity should have been more fully evaluated. We intend to evaluate this particular process change to determine what enhancements

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are needed to strengthen our change management and validation systems to prevent a future occurrence; this evaluation will be completed by 29-Apr-2008.

Filter Selection of the Building (b) (4) Facility

The (b) (4) facility (i.e., Building (b) (4)) has a (b) (4) batch size but a (b) (4) filtration area compared to the initial (b) (4) filtration process in the (b) (4). Because the filtration process is specific to the batch size and the filtration area, the events in the (b) (4) are not directly relevant to the process in Building (b) (4), although this was not documented in the (b) (4) investigation. We performed additional filtration experiments in November 2005 to support the Building (b) (4) filtration process, and we proactively initiated efforts to increase the filtration capacity in March 2007, which is currently underway. (Note that there was no HPV Type (b) (4) manufacturing in Building (b) (4) between November 2005 and August 2007.) While (b) (4) HPV Type (b) (4) lots made in August 2007 (using the originally validated filters) exceeded the defined maximum filtration time, it is unlike the March 2006 (b) (4) experience in that additional filters were not required to complete filtration. It is important to note that the Building (b) (4) lots remain in quarantine pending submission and approval of a license supplement to increase the maximum filtration time.

Conclusion and Corrective Actions

We acknowledge that: 1) the selection process was not complete for the filtration change in (b) (4) in that the reduction in filter surface area and its impact on filtration capacity for all HPV types should have been more fully evaluated; and 2) there was inadequate communication within the HPV technical group regarding learnings from the NPS and Building 60A facility. We intend to evaluate this particular process change to determine what enhancements are needed to strengthen our change management and validation systems to prevent a future occurrence; this evaluation will be completed by 29-Apr-2008.

Response 3C: *On 10-Dec-2007, (b) (4) notified Merck's subsidiary in Canada, Merck-Frosst, of (b) (4) reported cases of suspected anaphylaxis localized in (b) (4) (b) (4) and requested an investigation into the associated M-M-R®II Lot 1529U. Due to the seriousness of these reported adverse events and the potential impact on public health, we immediately conducted a thorough and timely investigation including the following: the manufacturing conditions specific to Lot 1529U, the manufacturing performance in the timeframes of interest, adverse event reporting for the M-M-R®II product containing recombinant Human Albumin (rHA), and lots that contained bulk inputs (i.e., individual components, measles, mumps, and rubella) and raw materials common with Lot 1529U. We believe the facts associated with the investigation, as detailed below, reinforce the completeness of our investigation, communications, and conclusions.*

The report referenced in Observation 3C, dated 20-Dec-2007, was a summary of our comprehensive investigation, which was tailored to provide specific manufacturing details related to M-M-R®II Lot 1529U in response to the request from (b) (4). Our investigation encompassed the (b) (4) bulk inputs and the raw materials associated with the (b) (4) M-M-R®II lots containing rHA that were distributed to Canada. We also analyzed, process performance trends for M-M-R®II manufacturing from October 2005 through January 2007 (approximately (b) (4) lots in total). Coupled with the epidemiology analysis, the manufacturing assessment did not reveal any concerns related either to the specific manufacturing of M-M-R®II Lot 1529U or M-M-R®II manufacturing in the timeframes of

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interest. On 31-Dec-2007, Merck received notification from (b) (4), indicating its satisfaction with the fact that the chemistry and manufacturing of Lot 1529U complies with all approved specifications.

Throughout the investigation, Merck participated in frequent communication with CBER, (b) (4) and other regulatory authorities and has provided requested information in a complete and prompt fashion. Information exchange continues with (b) (4) until their local epidemiology investigation concludes.

Below is a summary of the key aspects of our investigation:

Epidemiology Review
The epidemiology investigation evaluated adverse events for all distributed M-M-R®II lots containing rHA and all M-M-R®II lots containing common bulk inputs to Lot 1529U. The adverse events reported for these populations were consistent with our historical base-line performance with the M-M-R®II product containing human serum albumin.

Furthermore, the incidence of (b) (4) reported cases of suspected anaphylaxis associated with a single vaccine lot in a small geographical region is uncommon. These two factors led to a focus on the specific manufacturing conditions of Lot 1529U and a review of the adjacent timeframes in manufacturing. An update to Merck's epidemiology investigation is included below in Response 3Ciii.

Manufacturing Investigation
The manufacturing investigation report, dated 20-Dec-2007, included consideration for both the specific manufacturing conditions for Lot 1529U as well as the process performance for both bulk and filling manufacturing in the relevant timeframes. Specifically:

- ***Change Control** – To evaluate change control, a trend of changes implemented within the M-M-R®II product family from 1999-2007 was reviewed, focusing on the 2001-2002 timeframe for bulk manufacturing and the 2006 timeframe for filling manufacturing. No process changes were noted that could be related to the reports of suspected anaphylaxis.*

  - ***rHA Containing Bulks** – The conditions for bulk manufacturing, including the age and performance of the rHA-containing bulks, were reviewed including evaluation of bulk stability data, process performance trends for filling of M-M-R®II containing rHA, and the adverse event reporting for all M-M-R®II containing common bulk inputs with Lot 1529U. This review revealed no atypical events or trends that could be associated with the adverse event reports.*

  - ***Laboratory, Environmental Monitoring, and Manufacturing Deviations** – Laboratory, environmental monitoring, and manufacturing deviations were reviewed as part of the investigation. While the investigation into rubella potency performance in the rHA-containing M-M-R®II product was not referenced in the report, it was considered during the investigation and deemed unrelated to the adverse event reports.*

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- ***Raw Materials*** *– The key raw materials used in M-M-R®II manufacturing were reviewed through change requests and quality control testing at both the vendor and at Merck. Vendor investigations were requested for cases where either the material was newly introduced into the M-M-R®II product (applies to rHA and stoppers) or where there was limited use of the specific material lot in manufacturing (applies to stoppers only). All other raw materials were successfully used in the manufacturing of numerous M-M-R®II lots as well as other products and were, therefore, determined to be unlikely as potential contributing factors.*

On-24-Jan-2008, BPDR 08-002 was submitted to the FDA to formally document the adverse event reports, including the manufacturing investigation dated 20-Dec-2007, the updated epidemiology report, and the requested release testing data on retain samples from Lot 1529U.

Below are our specific responses to Observation 3Ci–3Civ. We respectfully submit that this information highlights the comprehensiveness of our systems in place requiring the execution and documentation of a thorough investigation.

Response 3Ci: *Upon notification,* (b) (4) *initiated a lot check investigation into M-M-R®II Lot 1529U. In accordance with SOP 283-322 "Processing of Adverse Event Reports", a lot check evaluation was conducted to include the following: an investigation summary, check for association with a market action and/or market action investigation, check of quarantine status, a review of release testing data results and laboratory testing results (as applicable), and a batch record review for serious adverse events. This lot check as required by SOP 283-322 was completed for Lot 1529U on 11-Dec-2007.*

Because of the number of adverse event cases involving the single M-M-R®II Lot 1529U and the serious nature of the adverse event reports, an extensive manufacturing investigation, exceeding the core requirements for lot checks, was conducted to include two perspectives: a review of manufacturing trends in the relevant time frames as well as a thorough review of lot-specific manufacturing details associated with M-M-R®II Lot 1529U and Diluent Lot 0814U.

Observation 3Ci indicates that the evaluation into associated manufacturing changes was too narrow and that the age of the bulk inputs was not evaluated. While the final investigation report, dated 20-Dec-2007, documented the conclusions of our investigation, the approach to reach these conclusions was comprehensive and broad in nature. Specific details on the 1) change control evaluation and the 2) data available on bulk age are noted below:

Change Control Evaluation
M-M-R®II Lot 1529U was manufactured on 10-Aug-2006. The bulk inputs for Lot 1529U were manufactured in the 2001-2002 timeframe.

The change control section within the manufacturing investigation (dated 20-Dec-2007) summarized conclusions specific to Lot 1529U for (b) (4) *, given that the reported cases of anaphylaxis were associated with this single lot. To bracket both the bulk and filling timeframes, a trend of the change requests implemented between 1999 to 2007*

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was obtained for the M-M-R®II product family. A summary of the analysis is provided below:

- *For filling, the change control trend was reviewed, with a focus on changes that were implemented in the 2006 timeframe. This timeframe was selected because routine use of rHA containing bulk lots was initiated in early 2006 within filling. M-M-R®II Lot 1529U was filled in August 2006.*

- *For bulk manufacturing, the change control trend was reviewed, with a focus on changes implemented into bulk manufacturing in 2001-2002. This timeframe corresponds to when bulk manufacturing with rHA was initiated, including manufacturing oft the bulks inputs for Lot 1529U.*

- *For raw materials and culture media, a review of both internal change requests and vendor change notifications was conducted for all inputs into M-M-R®II bulk and filling operations.*

The conclusion of this review did not identify any internal or vendor change requests that could have been associated with the reported cases of suspected anaphylaxis.

Evaluation of Bulk Stability and Age

It was acknowledged that a recent change was adopted into the M-M-R®II product, replacing Human Serum Albumin (HSA) with rHA. Albumin is utilized within the bulk manufacturing process as a protein source during virus propagation. The bulk inputs for M-M-R®II Lot 1529U were manufactured in 2001-2002 as part of the process validation lots used to support rHA introduction. The bulk lots remained in inventory, stored frozen at (b) (4), until approval was obtained for rHA in the U.S. on 31-Aug-2005. Routine filling of M-M-R®II product containing rHA was initiated in early 2006, primarily using bulk lots manufactured in 2001-2002. The first lot release to the U.S. market occurred in September 2006.

Observation 3Ci states that stability of the bulks was not thoroughly evaluated in terms of the rHA content. It is acknowledged that routine stability studies conducted on drug substance (bulk) utilizes potency and sterility testing to assess stability. To holistically evaluate the bulk inputs of Lot 1529U, the stability data, coupled with the process performance of the resulting drug product and the adverse event reporting, were assessed within the manufacturing investigation, revealing no link to the reported events of anaphylaxis. A summary of the evaluation is included below:

- ***Bulk Stability** – As part of bulk process validation in 2001-2002, (b) (4) rHA containing lots of each bulk antigen (measles, mumps, and rubella) and corresponding M-M-R®II fill lots were placed on stability in the 2001-2002 timeframe. The mumps and rubella bulk inputs for M-M-R®II Lot 1529U were included as part of the bulk stability series and were used in M-M-R®II Fill Lot 0644173 that was included in the drug product stability series. Representative measles bulk lots containing rHA were placed on stability and were used in the initial filled lots placed on stability. The bulk stability studies remain on-going, with all potency and sterility data to date being satisfactory. The fill study was completed with satisfactory results.*

- ***Process Performance** – Process performance trending for the M-M-R®II product from October 2005 to January 2007 (approximately (b) (4) lots) was conducted as part*

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of the investigation. In the 2006 timeframe in filling, bulk inputs that were manufactured in 2001-2002 were predominantly used. The release specifications for lots manufactured in this time frame were consistently met, including measles, mumps, and rubella potency, moisture content, pH, and restoration timing.

- ***Adverse Event Reporting*** *– The epidemiology investigation evaluated adverse event trends for all distributed M-M-R®II lots containing rHA and the (b) (4) M-M-R®II lots containing common bulk inputs to Lot 1529U. (b) (4) lots have been released to the U.S. market between September 2006 and July 2007. The adverse events reported for these populations were consistent with our historical base line performance with the M-M-R®II product containing human serum albumin.*

  A search of the (b) (4) database and (b) (4) database was conducted for reports of anaphylactic reaction involving the referenced (b) (4) lots. This search identified (b) (4) reports of anaphylactic reactions and (b) (4) report of dyspnea. Approximately (b) (4) doses of these lots had been distributed for an overall reporting rate of approximately 1 per (b) (4) doses distributed. This is comparable to the spontaneous reporting rate of 1 per (b) (4) doses reported by the Advisory Committee on Immunization Practices (ACIP) of the Centers for Disease Control and Prevention.[1]

The process performance data trends, the adverse event reports, and drug substance and drug product stability data do not indicate any issues with product quality associated with the age of either the bulk inputs or the rHA contained within the bulk product. In our clinical experience to date, the adverse event reporting for M-M-R®II with rHA is consistent with M-M-R®II containing HSA.

Regarding the specific reference to rHA stability, our supplier, (b) (4) conducted a (b) (4) stability study on the rHA raw material, when stored at (b) (4) with satisfactory results. Stability of rHA as a component of our bulk product has not been evaluated directly, given that the protein structure of rHA is identical to human serum albumin. The bulk product is stored frozen at (b) (4) in order to preserve stability of the live virus. Given our history with human serum albumin, it is expected that the rHA protein would remain stable over the course of the bulk hold time at ≤ (b) (4). This assertion is supported by our review of the satisfactory stability, drug product performance and adverse event reporting trends, referenced above.

Response 3Cii: *As discussed with the Investigator, a thorough review of deviations was completed as part of the overall investigational plan, including manufacturing, laboratory, and environmental monitoring investigations. Some deviations were specific to given lots associated with the manufacture of M-M-R®II Lot 1529U. Other deviations, such as APR 2006-242-0024 (vendor issue related to tubing) affected multiple lots and multiple products (i.e., beyond Lot 1529U). Because the reported adverse events from Alberta, Canada were all associated with a single M-M-R®II lot, a summary of investigations was organized within the report in this context.*

As referenced in the observation, there is an on-going investigation to improve understanding of the rubella performance within M-M-R®II containing rHA. Higher

[1] (b) (4)

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rubella process losses have been noted across the formulation of M-M-R®II containing rHA. The rHA content and rubella potency trends were reviewed for the relevant manufacturing timeframe and the results for Lot 1529U were comparable to adjacent M-M-R®II lots. In addition, the adverse event reporting for M-M-R®II with rHA is consistent with our historical reporting rates. Based on these data, it was concluded that the rubella investigation, although not formally documented in this investigation, was unrelated to the reported cases of suspected anaphylaxis.

Response 3Ciii: *Observation 3Ciii states that not all adverse events related to anaphylaxis were considered in the evaluation for Lot 1529U. We would like to assure the Agency that a careful and comprehensive review of adverse events was completed as part of the investigation. This information was provided as part of BPDR 08-002.*

In December 2007, a Merck physician reviewed all adverse event reports associated with distributed lots of M-M-R®II containing rHA and identified (b) (4) reported cases of anaphylactic reactions and (b) (4) report of (b) (6) who developed "breathing difficulty" (dyspnea) (b) (6) and was treated with (b) (6) (b) (6) These (b) (4) cases were classified as suspected anaphylaxis and are the basis of the analysis calculations reported in the investigation dated 20-Dec-2007.

In January 2008, the Investigator discussed another report (b) (4) which describes a (b) (6), with a history of reactive airway disease on albuterol as needed, who developed, (b) (6) hives on his face, wheezing, dyspnea, chest tightness, swollen eyelids, and erythema on face, hands, and back. The (b) (6) was treated with (b) (6) with recovery. This case was not reported as an anaphylactic reaction. Because of the medical history of reactive airway disease and the fact that this report was not originally classified by the reporter as anaphylactic reaction, it was not initially counted as a report of anaphylactic reaction in our assessment.

Two Merck clinicians have re-reviewed all reported adverse events associated with M-M-R®II lots containing rHA. Based on this review, they have decided to include this case (b) (4) in our analysis and have upgraded it as a suspected case of anaphylaxis. We have also updated our distribution numbers based on confirmation from the Order Management Center.

The inclusion of the additional report of anaphylaxis does not alter the conclusions of our original assessment. With the additional case (using (b) (4) cases within approximately (b) (4) (b) (4) doses of M-M-R®II with rHA distributed), the reporting rate is (b) (4) doses distributed. This assessment is consistent with the reporting rate for a passive surveillance system per the ACIP of approximately 1 per (b) (4) doses distributed.

Response 3Civ: *Observation 3Civ indicates that our investigation into raw materials associated with M-M-R®II manufacturing was inadequate given the lack of vendor investigations for all raw materials and components considered. Release testing data (on vendor certificate of analysis and at Merck), performance in manufacturing, and any associated changes (internally and at vendors) were reviewed for each key raw material and component. Investigational requests to our vendors were made in cases where either:*

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1) *The raw material and/or component was new to the M-M-R®II family (applies to rHA and stoppers) or*

2) *There were insufficient data internal to Merck to ensure a comprehensive technical assessment (applies to stoppers).*

The other raw materials mentioned in the response (e.g., (b) (4), (b) (4) etc) remained unchanged and were widely used in M-M-R®II and/or other vaccine products within the manufacturing timeframes. These other raw materials were, therefore, determined to be unlikely as potential contributing factors. A summary of the investigational assessment is described below:

- *Of the raw materials utilized in bulk manufacturing, (b) (4), (b) (4) are used for a wide range of lots and also for other products. As an example, the bulk inputs associated with M-M-R®II Lot 1529U were utilized in (b) (4) other M-M-R®II lots that were distributed to the market. Thus, raw materials utilized in bulk manufacturing, specifically (b) (4) (b) (4), would also be common to these (b) (4) lots. A review of these lots from a process performance, stability, and adverse event reporting perspective did not reveal any atypical observations that were associated with anaphylaxis. In addition, Lots 0182U, 0183U, and 0184U were formulated with the (b) (4) bulk inputs used in Lot 1529U, were distributed to the U.S., and have no associated reports of anaphylaxis.*

- *Overall, (b) (4) Lots were utilized in the manufacturing history of Lot 1529U. (b) (4) additional lots (b) (4) released doses) have utilized at least (b) (4) (b) (4) of these (b) (4) lots with (b) (4) reports of suspected anaphylaxis. (b) (4) Lot (b) (4) associated with the Filling Process for Lot 1529U was utilized in (b) (4) additional lots (b) (4) doses) with (b) (4) reports of suspected anaphylaxis. (b) (4) Lots (b) (4) and (b) (4) associated with the Bulk Manufacturing for Lot 1529U were utilized in (b) (4) additional lots (b) (4) released doses) with no reports of suspected anaphylaxis.*

- *rHA Merck Lot C141464 ((b) (4) Lot (b) (4)) was utilized for all bulk inputs associated with Lot 1529U. Overall, rHA Lot 0209-10 has been utilized in (b) (4) additional M-M-R®II lots (approximately (b) (4) released doses). Given that rHA was recently introduced into the M-M-R®II family and is not utilized in other vaccine products, a review of the rHA manufacturing conditions was requested from (b) (4) (vendor) to further bolster the information available for the incoming raw material and its use in manufacturing. No concerns related to the reports of suspected anaphylaxis were noted from the vendor investigation.*

- *Review of the internal release documentation for the stoppers utilized for Lot 1529U revealed passing results and no atypical events. The same lot of stoppers that was used in Lot 1529U was utilized in two additional lots of M-M-R®II, Lot 0184U and Lot 1680U, with no reports of suspected anaphylaxis. Given that a new stopper configuration was implemented with the M-M-R®II product containing rHA and the limited use of the specific stopper lot within distributed M-M-R®II lots, a review of the stopper manufacturing conditions was requested from the vendor, (b) (4), to further supplement our investigations. No concerns were noted from the vendor investigation.*

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Response 3D: *We understand Observation 3D relates to the following: 1) Investigation of potential root cause of loose clamps and 2) implementation of corrective actions to* (b) (4) *. Each of these points will be addressed separately.*

1) Investigation of Potential Root Cause of Loose Clamps

The first observation appears to be linking an investigation into loose (b) (4) *with another investigation for final container sterility out of specification results. The concerns were that the sterility investigation did not specifically note how loose* (b) (4) *identified in a potentially related atypical event were investigated and ruled out.*

We are confident in the root causes identified in sterility investigation 2006-285-0131. The sterility investigation considered the investigation into loose (b) (4) *(2006-285-0117) as a potentially related event and this was shared with the Investigator during the inspection. Since there were no observations of loose clamps noted for the ProQuad® Refrigerated lots during our investigation of the sterility failure, we did not consider this to be a contributing factor. As part of our comprehensive investigation, we identified a number of opportunities for enhancements, including mitigating the potential for loose clamps. This is the reason why the potential for loose clamps is documented in investigation 2006-285-0131.*

We acknowledge that investigation 2006-285-0131 contained limited documentation related to the loose (b) (4) *evaluation for 2006-285-0117. Therefore, an addendum to the sterility investigation to enhance the conclusions already in the investigation was included on 08-Feb-2008 to improve clarity of the investigation. It is important to emphasize that the conclusions of the investigation and identified root causes remain valid and that the actions taken as a result of the investigation would not be altered by these additional details.*

Finally, we will update validation procedures 240-356X (b) (4) *" and 240-150X "Standard Procedure for* (b) (4) *" to specify that validation data are required to support integrity of the closure system over all anticipated conditions of storage and use. In particular, the SOP will specify that* (b) (4) *studies should be performed when validating closures on containers intended for extended storage where* (b) (4) *is an element of the closure system. The changes will be implemented by 23-Apr-2008. In addition, an assessment will be completed to identify any additional bulk closure systems for which additional data are required to support the conditions of storage and use. The assessment and approval of any resulting action plans will be completed by 30-Sep-2008.*

2) Implementation of Corrective Actions to (b) (4)

Observation 3D states that implementation of (b) (4) *changes arising from corrective actions in APR 2006-285-0131 were limited to the* (b) (4) *and building used for the out of specification (OOS) lot and did not document site-wide corrective actions related to* (b) (4) *used in different buildings. While this is true, prior to the close-out of this investigation on 09-Nov-2006, efforts were underway to identify and implement corrective actions for similar* (b) (4) *used across the West Point site.*

As discussed with the Investigator, a team was chartered in October 2006 in order to establish the requirements for all West Point Manufacturing (b) (4) *for product* (b) (4) *Subsequently, an evaluation of each affected* (b) (4) *was performed and mechanical*

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modifications were identified and executed. These modifications focused on ensuring that all (b) (4), and in some cases, these modifications were scheduled and executed during the first available production shutdown. Where the (b) (4) could not immediately be modified to (b) (4) a (b) (4) procedure was instituted, which provided an added level of assurance for environmental control. As discussed with the Investigator, all corrective actions were in place in the bulk manufacturing areas for measles, mumps, and rubella by 06-Aug-2007, for varicella by 19-Nov-2007 and for rotavirus by 16-Jan-2008.

To strengthen our communication of such events on a system wide basis, a site-wide notification procedure will be established by the Quality organization. This system will ensure similar events are not only communicated but tracked appropriately to ensure that all affected areas are aware of important findings and can react in a timely manner. This procedure will be implemented and training will be completed by 30-Jun-2008.

Response 3E: *As part of the investigation, a container closure assessment was conducted for the sterile bulk inputs as required by our site procedure. APR 2006-115-0058 included a confirmation by our site validation department that an approved container validation had been performed for the (b) (4) bottles with (b) (4) closures used for storage of the sterile bulk inputs. While this assessment confirmed that an approved container closure validation study was performed, it did not challenge whether data existed to support the effect of storage on the bulk containers. However, as containers are verified to be secure upon receipt in the formulation area, the root cause conclusion that the contamination occurred downstream of the (b) (4) bottles remains valid.*

This conclusion is based on the following:

- *The container closures were confirmed to be secure upon receipt in the formulation area. Upon receipt, as per SOP 173-407X "Receipt And Delivery Of Bulk Product", the bulk input bottles are inspected for defects that would compromise sterility including that the "closure is secure".*

- *The sterility results for the Final Formulated Bulk (FFB), 2113937, associated with Fill 0654907 were satisfactory. The FFB is sampled at the completion of formulation after all bulk inputs have been combined.*

The above facts, coupled with all evidence presented in the investigation, support the conclusion that the contamination occurred in process steps which are downstream of where the (b) (4) bottles are utilized.

As a result of this Observation, SOP 286-335X (b) (4) (b) (4)" will be enhanced with specific guidance to require a review and assessment of the container closure as part of sterility investigations. These enhancements and associated training will be completed by 18-Apr-2008.

Response 3F: *As part of our site wide initiative to enhance and strengthen our Quality systems, we implemented an enhanced atypical investigation process which now requires a consolidated laboratory and manufacturing investigation upon generation of any OOS or Out of Process (OOP) capability result. This consolidated investigation model requires concurrent investigations to occur within the laboratory and manufacturing*

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areas and targets completion of the consolidated investigation within 30 days from the date of the OOS / OOP result. This enhanced investigation process was piloted during 1Q2007 and was formally implemented site wide as of 03-Sep-2007. Specifically, SOPs 286-125X (b) (4) " and 223-307X "Laboratory Investigation Procedure" were revised on 03-Sep-2007 and 27-Aug-2007, respectively, and all laboratory and manufacturing areas were trained on the new procedure prior to implementation.

We acknowledge that the initiation of the manufacturing investigations noted in the observation was delayed by 14 days. It should be noted that both of these investigations were initiated prior to Sep-2007 under our former investigation process which required sequential investigations (initial investigation in the laboratory and then if no laboratory root cause was determined then a manufacturing investigation would be initiated). We are confident that after implementation of our current investigation procedure, this delay in the initiation of the manufacturing investigation would not have occurred since our procedures require otherwise. As a result, we believe that no further corrective actions are required.

***Response 3G:** We would like to clarify that while the second OOS result for phenol concentration was reported on 18-May-2007, it was actually associated with a lot manufactured on 19-Apr-2007, prior to the implementation of the identified corrective actions on 18-May-2007. The effectiveness of the corrective actions is demonstrated by the fact that since its implementation more than (b) (4) lots have been manufactured with no OOS results for phenol concentration.*

The investigations concluded that the root cause of both events was not personnel related, but rather due to a lack of specificity in the (b) (4) ', which has been corrected. Accordingly, neither APR included a corrective action for performance counseling, but rather focused upon improvements to our systems to prevent recurrence. However, upon identification of the second event, the OOS was communicated to the operators in the area as part of daily department communication for awareness.

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

   A. APR 2007-2004C-0001 dated 11/11/07 was issued for a leak discovered in (b) (4) (b) (4) line during (b) (4) for lot 2115617 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 (b) (4) 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.

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B. APR 2007-135-0043 dated 3/12/07 was issued for a leak identified at the (b) (4) connection on the outlet piping of portable tank (b) (4) during filling of Recombivax lot 0400U. 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. APR 2007-135-0046 dated 3/19/07 was issued for a pinhole leak identified on the (b) (4) (b) (4) of the portable tank sampling (b) (4) during formulation of Gardasil formulation lot 2119864. 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 (b) (4) was immediately placed on the (b) (4) tubing to isolate the leak from the (b) (4). 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. APR 2007-285-0063 dated 3/26/2007 was issued for broken glass noted on the outbound (b) (4) enclosure during the tray (b) (4) dose check during filling of Varivax lot 0658178. The affected portion of the lot was segregated as Group II and included trays (b) (4) as dose check at tray (b) (4) did not note glass. However, there is no assurance that operators were looking for broken glass during the tray (b) (4) dose check.

ii. APR 2007-285-0168 dated 9/4/07 was issued for broken glass found under the in-feed (b) (4) in the filling enclosure of line (b) (4) during filling of MMR® II w/rHA lot 0659878. The investigation documented that the operators "thought they heard glass break while filling tray (b) (4) so the line was stopped and inspected. The glass was found at tray (b) (4), so the affected portion of the lot was segregated as Group II included trays (b) (4). However, there was no documentation in batch record regarding the reported tray (b) (4) line stoppage.

Response 4: *We understand the importance of a detailed and thorough investigation of all APRs that is supported by documented evidence and that includes the thorough review of product impact and determination of product disposition based on scientific evidence.*

Response 4A: *For clarification, the Atypical Process Report (APR) number referenced in Observation 4A is 2007-204C-0001 was identified on 1/11/2007 (as opposed to 11/11/2007). We acknowledge that an unsigned and undated attachment was included in APR 2007-204C-0001 as noted in the observation. This is not consistent with our existing procedures for recording information related to atypical events as this information should not be documented in personal notes. At a minimum, the memo attached to the APR file should have included an author signature, subject (referencing the APR), and date. As a result of this observation, we will retrain personnel in the core requirements for effective cGMP documentation practices by 16-Apr-2008. This re-training will include*

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all West Point Sterile and Vaccine Operations personnel involved in witnessing, writing, reviewing, and approving GMP documentation.

For your background, this event preceded an internal enhancement to our deviation management system that was implemented in (b) (4) (b) (4) *in April 2007. Our current procedure prevents this type of documentation error from happening by employing the use of a* (b) (4) *. The* (b) (4) *is the* (b) (4) (b) (4) *. The* (b) (4) *serve as the initial source documentation for information which may not always be recorded directly in the batch record. It is important to note, however, that the existence of a* (b) (4) *is required to be documented in the batch record by procedure. We will update SOP 286-125AX* (b) (4) (b) (4) *to further emphasize the requirement that all personnel must document, in the relevant cGMP record (e.g., Batch records, notebooks, worksheets) events that occur that are outside normal operations. This SOP will be updated with associated training completed by 29-Feb-2008.*

Response 4B: *We understand that this observation relates to the necessity for personnel to identify and document any potential issues at the time that the issue occurs. Personnel working in our GMP facilities are trained that any deviation from routine and expected operation must be: 1) brought to the attention of the supervisor and 2) documented in a timely fashion as required by SOP 286-125AX* (b) (4) (b) (4)

With respect to the specific event noted in Observation 4B (APR 2007-135-0043), the supervisor appropriately documented an observed leak, at the time of occurrence, utilizing a (b) (4) *The observation of this leak was also recorded in the batch record. With respect to the observation questioning whether the leak occurred prior to the start of manufacturing, our investigation concluded that the leak did not exist prior to startup for the following reasons:*

- *First, prior to the start of manufacturing, it is a supervisory practice to inspect the tank outlet, as well as the entire product path. Had any leaks or other anomalies existed at the start of the fill, they would be noted and documented accordingly. In accordance with practice when a leak was observed, the supervisor specifically noted the following in the* (b) (4) *was dispensed at 9:47 P.M. No leaks were observed at this time. Supervisor observed the leak at 11:10 P.M." All observations and documentation were made by the same supervisor. It should also be noted that documentation of the leak occurred in the batch record at the time of the event.*

- *Although it is true that the outlet line is not monitored for positive pressure, the fluid pressure within the filling system, including the outlet piping line, is controlled and monitored to* (b) (4) *at the start of and throughout filling operations. At this fluid pressure, product would be driven through a leak point and subsequently observed, if present at the start of the fill. The principles by which this investigation was managed are consistent with those published in the* (b) (4) (b) (4) *, which notes that this type of pressure driven leak in* (b) (4) *can*

[2] (b) (4)

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provide an effective barrier against microbial ingress and that the integrity of the sterile boundary can be maintained during such leaks, if they are addressed promptly, as was the case for this event.

As stated in APR 2007-135-0043, the root cause of the leak was identified. It was recognized that we do not monitor pressure at this point; therefore, the investigational report included a corrective action to replace the (b) (4) connection on the outlet piping (b) (4) to eliminate the potential for a leak at this connection.

Additionally, we will enhance our leak management procedures as follows:

- *We will review our existing procedures to ensure that they contain sufficient detail to effectively capture our current leak management practices. We will also enhance these procedures to include periodic, documented leak checks of the (b) (4). To ensure that this is done consistently across all vial and syringe filling areas, existing procedures in these sterile filling departments will be updated by 30-Apr-2008.*

- *An assessment will be conducted throughout Vaccine Operations to identify the other processing areas where these leak management procedures should be applied. This assessment will be completed by 31-Jul-2008. Corrective actions will be implemented following this assessment, as appropriate.*

Lastly, we will reinforce the cGMP expectations that all investigations properly consider and document potential root causes and explain the rationale for exclusion with the West Point Product Release group.

Response 4C: *We understand the importance of fully investigating all atypical events including those associated with samples. Specifically, APR 2007-135-0046 was issued for a breach in the tubing used in sampling the Final Formulated Bulk (FFB) for HPV Lot 2119864. The leak occurred and was observed on the sample line immediately upon use, did not present a risk to the FFB, and only had the potential to compromise the samples because the leak was isolated to the sample line. This line is dedicated for sampling only and not part of the processing of product downstream. Furthermore, the sampling line is under positive pressure based on the volume of product in the (b) (4) tank. Immediately upon detection of the leak, the sample line was closed off from the (b) (4) tank. Based on the fact that the sample line can only implicate the samples taken and not the (b) (4) tank, it was appropriate to discard the samples since there was no assurance that they were representative of the lot.*

The principles by which this investigation was managed are consistent with those published in the (b) (4) l.[2] We believe that our reasoning associated with this investigation was scientifically sound. To further ensure that leaks are assessed in a consistent fashion, all atypical events regarding tank leaks are now elevated for review and approval by the Director, West Point Sterile Product Release. This elevation process was made effective on 11-Feb-2008.

Response 4D: *Merck recognizes the importance of documented evidence relating to the segregation of product associated with glass breakage, in order to ensure product quality. Whenever broken glass is discovered on the filling line due to an observed or unobserved event, the following events occur:*

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- *The filling line is cleared of potentially impacted filled and unfilled vials and, where appropriate, stoppers.*
- *The filling line is cleared of broken glass.*
- *Prior to resuming filling, appropriate stationary filling equipment and surfaces are disinfected, and sterilized equipment is replaced with new sterilized equipment, where appropriate.*

If any lot of product is impacted by glass breakage, the potentially impacted portion is segregated as per procedure SOP 286-122X (b) (4) (b) (4) ;". Because each glass breakage event is unique based on the location and severity, the rationale for the segregated product is case specific and is documented in the Atypical investigation based on the facts gathered at the time of the event. The segregation mechanism allows for the isolation and evaluation of the affected part of the fill as part of the investigation.

***Response 4Di**: Our Operations area personnel are trained on APR and Deviation management standard operating procedures which require them to use deviation alerts as the initial source documentation for the steps leading up to an event, the event itself, and the actions taken at the time of the event in response to the event. As documented in the (b) (4) for this APR, broken glass was observed at the outfeed (b) (4) at Tray (b) (4). The location of the outfeed (b) (4) is (b) (4) (b) (4) are pulled off of the filling line and is clearly visible to the operator who is pulling the dose check vials. The operator, who performed the Tray (b) (4) dose check, also performed the previous dose check at Tray (b) (4) and did not observe broken glass at Tray (b) (4). Our filling operators are trained to be observant during routine operations in order to detect unexpected events which could occur during processing. As a result of this operator's observations, the lot was portioned, with material between Trays (b) (4) and (b) (4) identified as potentially affected material. When the operator observed the broken glass at Tray (b) (4) processing, the filling line was stopped, and appropriate line clearance procedures were followed in accordance with SOP 285-230 "Operation of Filling Rooms (b) (4) ". As described earlier in our response and consistent with our procedures, Trays (b) (4) were implicated in this investigation and were subsequently rejected.*

We will review our existing procedures to ensure that they contain sufficient detail to effectively capture our current glass breakage management principles and practices. To ensure that this is done consistently across all vial and syringe filling areas, existing procedures in the sterile filling departments will be reviewed and updated, as appropriate. This will be done to ensure that (i) existing glass breakage monitoring is effectively documented, (ii) periodic monitoring is conducted and documented for known areas where potential glass breakage could occur, (iii) line clearance instructions are clear, and (iv) documentation of glass breakage events is clear and consistent across all vial and syringe filling areas. Applicable procedures will be updated by 31-Mar-2008.

***Response 4Dii:** As documented in APR 2007-285-0168, while filling Tray (b) (4) of Fill (b) (4) the Operators on the line believed they heard glass break. The filling line was stopped and inspected for broken glass throughout the filling enclosure. During this inspection, no broken glass was found. As stated in previous responses, if broken glass*

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was observed at Tray (b) (4), the filling operation would have been stopped and the line cleared of potentially impacted vials, in accordance with current procedure. Since no glass was observed, this line clearance was not required nor performed and the fill continued. Subsequently, the line was stopped at Tray (b) (4) upon observation of broken glass. At that time, the line was cleared and cleaned in accordance with SOP 285-230 "Operation of Filling Rooms (b) (4) ". These details were documented in the deviation alert form. The event was determined to be isolated to Trays (b) (4) based upon the fact that at Tray (b) (4), the operators specifically stopped the line and looked for glass breakage. Trays (b) (4) were subsequently rejected. It should be noted that this glass breakage event was identified in accordance with our normal operating procedures.

As noted in Response 4A, SOP 286-125AX will be updated to further emphasize the requirement that all personnel must document in the relevant cGMP record (e.g., Batch records, notebooks, worksheets) events that occur that are outside normal operations. This SOP will be updated with associated training by 29-Feb-2008. Additionally, in response to Observation 4D, SOP 286-122X (b) (4) (b) (4) " will be enhanced to include specific guidance on segregation rationale. The SOP enhancement and associated training will be completed by 18-Apr-2008.

Divisional Glass Breakage Initiative

Furthermore, glass breakage management has been identified as a manufacturing divisional priority. As a result, the manufacturing divisional Quality Assurance department formed a glass breakage management team in July 2007, resulting in the issuance of a document "Management of Glass Breakage" on 15-Oct-2007. The document outlines divisional expectations, principles, and actions to be taken with regard to glass breakage management. These actions are underway throughout the Merck Manufacturing Division (MMD) to ensure consistent and comprehensive glass breakage management. Actions specific to West Point Sterile and Packaging Operations (SPO) include:

- *Awareness training, which was completed on 09-Jan-2008, for all SPO production employees to reinforce the importance of identifying and documenting glass breakage.*

- *A Failure Modes and Effects Analysis (FMEA) will be performed for each West Point sterile filling area to identify and address potential areas for glass breakage. Additionally, we will assure that historical glass breakage investigations are revised as part of the FMEA analysis. These evaluations will be completed by 30-Apr-2008.*

- *A feasibility evaluation to employ automated inspection utilizing vision systems or other technology will be completed for the filling lines used in SPO sterile filling areas. The evaluation will be completed by 30-May-2008.*

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5. SOP 1330, (b) (4) 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. (b) (4) reports a (b) (6) was vaccinated with Pneumovax Lot 649989/0579P on (b) (6). The patient was treated on (b) (6) 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. (b) (4) reports an intra-uterine death after receipt of Gardasil Lot 654741/0013U. No lot check or review of batch record was conducted.

Response 5: (b) (4) (b) (4), *dated 14-May-2007, has required, since its inception on 17-Apr-2006, a lot check with a batch record review for all reports of deaths associated with a specific lot number, all reports of life threatening adverse experiences associated with a specific lot number, and all lots that are associated with a serious adverse experience and deemed of interest or concern by the reporting health care provider or as a result of internal review. Prior to 17-Apr-2006, this procedure required a lot check only in the event of a death or a life threatening adverse experience.*

As discussed with the Investigators, (b) (4) *was initially reported to Merck on 05-Feb-2006 and was assessed consistent with the procedures in place at that time. The reporter indicated that the patient had recovered from the event and that they did not feel the event was life threatening. The reporting healthcare professional and the Merck physician reviewing the case did not conclude that the reported event was considered life-threatening and hence, as per our procedures, a lot check was not done.*

Following our discussion with the Investigator, we have further enhanced our lot check procedure, (b) (4) *effective 14-Jan-2008, to include additional physician review for the consideration of a lot check for adverse experience reports received for a vaccine or a biologic product in which a lot number is provided and the patient has a positive culture.*

Regarding Observation 5B, we recognize that the (b) (4) (b) (4) *as written and followed, focuses on the primary recipient of a Merck product and did not delineate "offspring" of recipients of a Merck product. We will update our procedure to specifically include intra uterine death in a potentially exposed fetus as criteria for doing a lot check and batch record review, thereby addressing concerns expressed during discussions with the Investigators regarding* (b) (4). *The update for the* (b) (4) *with associated training was completed by 15-Feb-2008.*

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6. The complaint records and complaint investigations do not mention the possibility of CO_2 ingress as the reason for over-pressurization of Zostavax and ProQuad vials. For example: complaints (b) (4) and (b) (4) for Zostavax, lot 0290U, concerned over-pressurized vials. This lot was shipped with (b) (4) 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.

Response 6: *We understand this observation relates to the comprehensiveness of our complaint investigation, including documentation in the complaint report, and the need to reconsider all potential causative factors in light of new over pressurization complaints.*

Comprehensiveness of Complaint Investigation/Complaint Record
We acknowledge that the complaint investigation did not consider nor document the possibility of CO_2 ingress as the reason for over pressurization of ZOSTAVAX® and ProQuad® vials. In hindsight, this should have been part of the assessment and documented in the complaint record.

As of 10-Jan-2008, all over pressurization complaints relating to frozen lyophilized products, including ZOSTAVAX® and ProQuad®, are assessed for the potential of CO_2 ingress as part of all over pressurization complaint investigations. Additionally, this will include verification that the proper pack-out components and procedures were followed. As committed in our response to Observation 2, Bullet 5, to further enhance our investigation into over pressurization complaints, a formal protocol for evaluation of over pressurization complaints will be developed and implemented by 19-Mar-2008. This protocol will be utilized for all new over pressurization complaints. In addition, we will re-train all West Point Complaint Unit personnel on SOP 283-316 (b) (4) (b) (4) " by 06-Mar-2008 in order to reinforce the expectation of timely and complete documentation of all aspects of the complaint investigation.

It is important to note that in June 2006, we implemented an enhancement to our Complaint Management system to include in each complaint investigation the documentation linking the potential of CO_2 ingress associated with over pressurization for M-M-R®II and VARIVAX®. These two products were the original basis of the investigation into over pressurization as the vast majority (b) (4) of over pressurization complaints affected these two products. Effective 08-Nov-2007, each complaint investigation into over pressurization relating to M-M-R®II and VARIVAX® examines whether the shipping method is a contributing factor. To date, all complaints of over pressurization for M-M-R®II and VARIVAX® have involved products that were shipped prior to the implementation of the new shipping method.

As stated above on 10-Jan-2008, we expanded the scope of the over pressurization complaint investigations for ZOSTAVAX® and ProQuad® to include the possibility that the shipping method may be a contributing factor. This lag in time of not including shipping methods as part of our complaint investigation into over pressurization complaints of ZOSTAVAX® and ProQuad® was due to human error as well as a miscommunication between departments where it was not clearly highlighted to the West Point Complaint Unit that the shipping method for these two products (ZOSTAVAX® and ProQuad®) had changed. Upon the realization that the shipping method had changed for

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these products, the Complaint Unit immediately expanded the scope of the complaint investigations to include this potential root cause.

In order to aid in our complaint investigations relating to over pressurization complaints, as of 22-Jan-2008, the Complaint Unit implemented a product specific table broken down by markets for all lyophilized live virus vaccine products that indicates the following: the previous shipping method, the current shipping method, the type of shipping container and the implementation date for such changed shipping method. Currently, the West Point Complaint Unit's practice is to review this information as part of all complaint investigations into over pressurization. This expectation will be formalized into West Point Complaint Unit SOP 283-316 (b) (4) (b) (4) *and training will be completed by 01-Apr-2008.*

It should also be noted that effective 10-Jan-2008, each over pressurization complaint is also being reviewed in conjunction with Sterile Process Technology and Engineering personnel to monitor and track performance of the enhanced shipping methods that were implemented to reduce the potential for CO_2 ingress during shipment. As part of this, a (b) (4) *meeting will be held between the West Point Complaint Unit, Sterile Process Technology and Engineering, Distribution and Logistics, and West Point GMP Compliance to discuss any data and monitor whether any trends are emerging. The first such meeting will be held by 21-Mar-2008.*

Verification of Packing Method/Validation

Although it is true that the two noted complaints (b) (4) *did not include a specific documented review of the validation for the packing method or consider whether the shipping method utilized was a contributing factor, since September 2007, we monitored the enhanced shipping methods in order to ensure that there was a reduction in over pressurization complaints. As of 31-Jan-2008, we have not received any over pressurization complaints for either MMR®II or VARIVAX®III shipped using these new shipping methods. Additionally, we have seen a dramatic decrease* (b) (4) *complaints per million reduced to* (b) (4) *complaints per million) in the number of over pressurization related complaints received for all live virus lyophilized products since deployment of the enhanced shipping containers and pack out procedures. Any future over pressurization complaint will be fully assessed as previously described in this response.*

In order to further ensure that our packing methods are functioning as intended, West Point Sterile Process Technology and Engineering will initiate a reevaluation of the shipper validation studies by 01-May-2008. Furthermore, West Point Quality Operations will audit the practices and procedures being used by the distribution department personnel to assure they are in alignment with the validation study. This audit will be completed by 14-May-2008.

7. The presence of the (b) (4) watermark obscuring instructions and data entered into batch records was not identified as a contributing factor to a calculation error in the manufacture of HPV Type 18 MBAP, lot number 2115021 The only corrective action documented was a performance discussion with the operator.

Response 7: *The calculation error on Lot 2115021 was the result of an operator error which was identified during the required batch record review by production operations. The calculation error was documented in the batch record. Regarding the cause for the*

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error, the operator subtracted a quantity that should have been added. While the watermark appears in the vicinity of the error, we believe that the watermark in this case did not obscure the instructions and therefore, did not contribute to this deviation. As a result of discussion with the Investigator, we committed to evaluate the feasibility of removing or relocating the watermark on batch records. We will complete this evaluation by 19-May-2008 and implement any enhancements as appropriate.

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 (b) (4) test failures for Vaqta. These (b) (4) failures, although related, were recorded as a single occurrence in the deviation tracking system. SOP 223-307X, Laboratory Investigation 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.

Response 8: *Our atypical process report system provides the QA Release personnel limited flexibility when trending similar root cause investigations in our (b) (4) (b) (4). The practice described in the observation is used to enhance our automated trending capabilities by allowing previous investigations to be either included or excluded based on the root cause. We do not believe this practice affected the outcome of any of our investigations; however, we acknowledge that we can improve the consistency of the practices for adjusting the number of occurrences. As a result, we will implement the following corrective actions:*

- *SOP 286-125X (b) (4) (b) (4) will be updated to include instructions for adjusting the occurrence number.*
- *The following SOPs will include consistent language for performing both an automated and manual trend and standardized instructions requiring that multiple occurrences may be combined into one atypical investigation, but the number of individual occurrences of the same root cause will be trended as separate occurrences.*
  - *SOP 262-221X (b) (4)*
  - *SOP 262-137X (b) (4) for Environmental Monitoring Investigations"*
  - *SOP 262-137AX " (b) (4) Environmental Monitoring Investigations"*
  - *SOP 236-378X "Atypical Process Report"*
  - *SOP 223-126X "Investigation Procedure Using (b) (4) (b) (4)*

All SOP revisions will be completed with associated training by 14-Mar-2008.

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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.

Response 9: *SOP 283-316 "Investigating and Writing West Point Product Quality Complaint Reports" will be updated to include guidance for complaint categorization. Additionally, once categorized, the SOP will specify the following:*

- *For complaint reports that are associated with the* (b) (4) *the lot history must include a* (b) (4) (b) (4).
- *For complaint reports that are associated with a* (b) (4) *the lot history must include a* (b) (4) (b) (4).
- *For complaint reports that are associated with the* (b) (4) *the lot history must include a* (b) (4) (b) (4)

The SOP will be updated and training will be completed by 01-Apr-2008.

10. Complaint records are not complete regarding the date closed. The (b) (4) system is not always updated with the complaint closure date. For example: during demonstration of the system on November 27, 2007, complaint record (b) (4) concerning Recombivax, lot 1022F, indicated a status of Released. The complaint had been closed/completed September 7, 2007 as indicated on the WORD document for the investigation.

Response 10: *The West Point Complaint Unit documents final complaint closure, including acknowledgement to the complainant, in the* (b) (4) *system in the* (b) (4) *field. The date on which the investigation is finalized precedes the final complaint closure date. However, as noted in the observation, the date the complaint investigation is finalized is not currently captured in the* (b) (4) *system.*

This difference in dates does not impact the schedule we follow for complaint investigations or our ability to track investigation closures. However, to provide visibility of the investigation finalization date, SOP 283-316 "Investigating and Writing West Point Product Quality Complaint Reports" will be updated to ensure that the date the Complaint Investigation is finalized is also reflected in the (b) (4) *system. The* (b) (4) *System will be updated to include this requirement, and the requirement will be incorporated into the SOP with training complete by 01-Apr-2008.*

11. No BPDR was submitted concerning leaks in Gardasil syringes. (b) (4) reports of leaking syringes have been reported as of December 2007 since launch of the product in June 2006.

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Response 11: *The West Point Complaint Unit SOP 283-316 "Investigating and Writing West Point Product Quality Complaint Reports" requires that the West Point Complaint Unit evaluate all product quality complaints associated with marketed product. If such complaint investigation indicates that a regulatory notification may be necessary, the SOP requires that West Point Quality Management be notified immediately. The West Point GMP Compliance SOP 283-303X, which is fully aligned with 21 CFR 600.14 and the "Guidance for Industry, Biological Product Deviation Reporting for Licensed Manufacturers of Biological Products Other than Blood and Blood Components" dated October 2006, requires that, upon notification from the West Point Complaint Unit, West Point Quality Operations together with Divisional Quality Assurance, the functional areas involved in the complaint investigation, and other relevant groups determine whether a Biologics Product Deviation Report (BPDR) is required. If a BPDR is required, then West Point GMP Compliance ensures that one is drafted and filed in a timely manner. If a BPDR is not required then West Point GMP Compliance ensures that the rationale for such decision is documented, reviewed and approved by Senior Quality Management.*

In the case noted in this observation, the procedures described above were followed. Senior Quality Operations Management, Senior Divisional Quality Management, the person responsible for the complaint investigation, and other relevant personnel reviewed product quality complaints related to leaking GARDASIL® syringes in February 2007 and concluded that no BPDR was required. This decision was based on the following:

- *The complaints do not represent a deviation from current good manufacturing practices, applicable regulations, applicable standards, or established specifications that may affect the safety, purity, or potency of that product. This conclusion was supported by an investigation into manufacturing and packaging which did not reveal any atypical or other deviation during manufacturing or packaging which could have caused the syringe leaks. Furthermore, the overwhelming majority of leak complaints reported (b) (4) are associated with use and handling by the healthcare practitioner of this novel device, and therefore, these complaints occurred post distribution of the product. It is important to note that we have distributed (b) (4) doses worldwide of this novel syringe image. Based upon the investigation and the facts reported by the complainant, we concluded that there was no deviation from current good manufacturing practices, applicable regulations, applicable standards, or established specifications and therefore, this criterion for filing a BPDR as set forth in 21 CFR 600.14 was not met.*

- *The complaints do not represent an unexpected or unforeseeable event that may affect the safety, purity or potency of that product. The safety device was a novel device and health care practitioners lacked familiarity with this new device. Therefore, it was foreseeable that the non-familiarity of health care practitioners with this novel device might create certain challenges with the use. This was further supported by the fact that the overwhelming majority of leak complaints reported (b) (4) were associated with use. Therefore, we concluded there was no systematic malfunction or quality related issue identified nor was this an unexpected or unforeseeable event. Thus, this criterion for filing a BPDR as set forth in 21 CFR 600.14 was likewise not met.*

Therefore, we concluded and documented in February 2007 that no BPDR was required.

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It is important to note that as part of our continuous improvement efforts, we chartered a team to perform a Failure Mode and Effects Analysis (FMEA) of the syringe life cycle to identify if potential West Point manufacturing or packaging process steps could predispose a syringe to leak or a health care practitioner to report a leaking syringe. In October 2007, this analysis noted the following in a risk assessment report:

- *The design of the safety device itself can increase the chance of complaints of this nature from customers;*
- *The misuse of the device by healthcare practitioners may also result in additional complaints; and*
- *The potential exists for defects to be introduced and/or created during the manufacturing process involving the safety device.*

This risk assessment report identified areas of potential risk to be considered by a cross-functional West Point Site Senior Leadership team in order to evaluate whether there is any product quality impact as well as whether there is a need to modify current manufacturing/packaging operations.

After discussion with the Investigator during the inspection, we agree that in light of this FMEA analysis, we should have re-evaluated whether a BPDR was required, focusing on whether the potential risks identified in the FMEA analysis have ever been observed during actual manufacturing operations. As a result, we will review the FMEA analysis with a multi-functional team including Quality Operations, West Point Operations, West Point Complaint Unit, Sterile Process Technology and Engineering Science, and Packaging Technology by 21-Mar-2008. If this review determines that there was a systemic manufacturing or packaging event or events that caused the leaking complaints, then a BPDR will be submitted in accordance with SOP 283-303X "Biological Product Deviation Reports". All conclusions of such evaluation will be discussed and reviewed with our outside cGMP consultant to ensure that our conclusions are in alignment with GMP expectations.

Furthermore, West Point GMP Compliance will update and review SOP 283-303X with the West Point Site Senior Leadership Team to require a periodic review by the West Point Site Senior Leadership Team of all decisions that no regulatory communication is required. This periodic review will ensure that we formally review regulatory communication decisions in order to ensure that the original assumptions are still valid. SOP 283-303X will be updated and re-training complete by 29-Apr-2008 in order to emphasize regulatory notification expectations and requirements.

Lastly, we would like to highlight the following actions that we have taken during the course of our comprehensive investigation into GARDASIL® syringe complaints:

1) *We launched an improved instructional video to end users detailing the proper use of the safety syringe to prevent mishandling of the device (completed May 2007);*
2) *In conjunction with the manufacturer of the safety device (SSI), we are currently identifying design opportunities to reduce the possibility of defects or mishandling by the user (ongoing).*

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3) *Based on customer feedback, we are actively pursuing the introduction of a syringe image without the safety device in the U.S. market by 19-Dec-2008 to provide user choice for a syringe with or without the safety device.*

12. Change Control #WP2-04-003 was for a change in DF control in which the DF process was optimized to achieve an aluminum level in Alum Buffer that is closer to the theoretical limit. This change control was closed out on 12 July 2004 and implemented in March 2005. Change Control #WP2-05-0463 was to modify the (b) (4) in Tank (b) (4) 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.

Response 12: *These changes were reviewed by our Regulatory and Analytical Sciences-Biologics (RAS-B) group at Merck, a Quality group independent of manufacturing operations. RAS-B determines the reporting category based on the potential to adversely affect the identity, strength, quality, purity, or potency of the product, in accordance with Guidance for Industry Changes to an Approved Application: Biological Products. For both WP2-04-0003 and WP2-05-0463, the changes were evaluated and deemed not reportable since they had no potential to adversely affect the product. No critical process parameters or allowable ranges for critical quality attributes were changed. In the case of WP2-04-0003, the change resulted in a better centering of the aluminum level within the specified limits. In the case of WP2-05-0463, the change was made to improve the consistency of mixing, to maintain the aluminum level within the specified limits.*

After discussion with the Investigators and upon further consideration, we will amend the Annual Report filings for each of the affected products (i.e., GARDASIL®, PedvaxHIB®, VAQTA®, RecombivaxHB®, and COMVAX®) and the Drug Master File for the Alum Diluent by 02-May-2008. As of 14-Feb-2008, we reviewed these cases with the RAS-B group so that similarly situated changes are handled consistently in the future.

13. Changes Request WP2-060212 was initiated on July 17, 2006 to qualify the use of the (b) (4) tunnel after the implementation of a change from the (b) (4) filters previously used for the (b) (4) Filtration to the (b) (4) filter. These filters are used for the filtration of liquid nitrogen at the source and at each (b) (4) tunnel point of use on line (b) (4) for (b) (4) of lyophilized products in Dept. (b) (4) Between August 2006 and August 2007 there were approximately (b) (4) post integrity test failures for these (b) (4) filters at the source as well as at the point of use. The root cause was found to be that the (b) (4) Filters were not suitable for use under the conditions of the (b) (4) Distribution system for lines (b) (4). The corrective action was to change to a more suitable filter.

This Change Request did not include the operational qualification of the (b) (4) filters for its intended use at various temperatures ranging from (b) (4). The filters were accepted on the COA of the vendor and not tested in the (b) (4) tunnel prior to use. Additionally, there is no identity testing performed on the liquid Nitrogen upon receipt.

Response 13: *We understand this observation relates to validation robustness, the use of these filters for the sterile filtration of liquid nitrogen supplied by a vendor, and the potential to impact product quality.*

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Our progress and results with liquid nitrogen filters have been communicated on an ongoing basis to the FDA in the following updates: "FDA Team Biologics Inspection Update, Merck & Co., Inc., West Point, Pennsylvania, 07-24-Feb-2006" dated 12-May-2006, 15-Aug-2006, 20-Dec-2006, 29-Mar-2007, and 28-Sep-2007. Specifically, the issues associated with the (b) (4) filters were communicated in these quarterly updates:

- ***12-May-2006 Update (Not Liquid Nitrogen Specific)***
  Provided a summary of all corrective actions associated with the Team Biologics Inspection. The original commitment regarding liquid nitrogen filters was defined in Merck's 23-Mar-2006 response to the inspection observations.

- ***15-Aug-2006 Update (Liquid Nitrogen Specific Update Provided)***
  Liquid nitrogen filter implementation: Completed review of filter technology for (b) (4) (b) (4) filtration; a candidate filter was identified and development of a project implementation plan was completed.

  Environmental monitoring of (b) (4) tunnels: Implemented microbial surface testing at the end of each filling operation (31-May-2006), updated procedure to document key operational parameters prior to placing exposure plate in the (b) (4) tunnel, and demonstrated that growth promotion was acceptable for (b) (4) tunnel exposure plates.

- ***20-Dec-2006 Update (Liquid Nitrogen Specific Update Provided)***
  Completed as built drawings of the (b) (4) tunnels.

  Environmental monitoring of (b) (4) tunnels: Technical feasibility of taking a microbial air sample from the (b) (4) tunnel during process operations was completed; microbial air sampling of the (b) (4) tunnel during process operations will be implemented in January 2007, routine monitoring of liquid nitrogen source filtration site was implemented on 01-Sep-2006.

- ***29-Mar-2007 Update***
  Liquid nitrogen filter implementation: (b) (4) filter selected for liquid filtration implemented (b) (4) filter at source and on (b) (4) filling lines in August 2006, the (b) (4) filter was unsuccessful at obtaining consistent satisfactory post-use filter integrity, collaborative root cause investigation with the vendor was on-going.

  (b) (4) tunnels meeting Grade A microbial limits during processing as supported by microbial and particulate testing subsequent to the main source filter, microbial surface testing at the tunnel inlet and exit, and microbial air sampling within the (b) (4) tunnels.

- ***28-Sep-2007 Update***
  Communicated the root cause, no product quality impact, and corrective actions due to the (b) (4) filter being unsuccessful at obtaining consistent satisfactory post-use filter integrity.

Performance History with the (b) (4) Filter

With respect to the issue regarding a lack of operational qualification, the (b) (4) filter was initially selected based on filter validation data (SLS No. (b) (4) supplied by the vendor

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indicating that it would be compatible for use in a liquid nitrogen environment. The report indicated that filters, which were sterilized and then exposed to liquid nitrogen (at (b) (4) , demonstrated satisfactory filter integrity and microbial clearance of (b) (4) . The validation data provided by the vendor supported the filter's intended use over the range of operating temperatures. These data are referenced in the Merck filter validation assessment VRA06-028. Therefore, the filter was implemented based on our evaluation of a package of technical data that was provided by the vendor. The filters are accepted for production use based on vendor Certificate of Analysis (COA) in conjunction with the validation assessment that was performed prior to implementation.

However, since implementation and after significant work with the vendor, we were not able to re-create the performance outcomes as specified in the vendor validation data. This followed an exhaustive effort with the vendor in attempting to re-create such data, focusing not only on the filter but on the specific conditions the filter is exposed to during processing at Merck. In addition, the limited number of available filters on the market rated for use with liquid nitrogen, coupled with the vendor's continued assertion that the filter should be compatible in our use setting, focused our efforts on doing everything possible, in conjunction with the vendor, to try and achieve successful performance with this filter. It is because of these factors that we were reluctant to discontinue use of the (b) (4) filters. Rather, we studied the filter in actual operations to understand why the filters were failing, despite the vendor's claims that the filters are compatible with nitrogen tunnel conditions. It was our hypothesis that these data would reveal something in our processing that was causing the filter to fail. During this time, we did consider impact to product quality and concluded that this risk was minimal. (See Product Quality Assessment Section below for more detail on this evaluation.)

As a result of this observation and after discussion with the Investigator, we will enhance our procedures to clarify expectations and requirements for Operational Qualification of filters. Enhanced procedures will be implemented by 30-May-2008.

We also wish to clarify that the (b) (4) filter, which is referenced in the observation, is no longer in use and was discontinued prior to the inspection. A new filter, the (b) (4) (b) (4) filter, has been in use since November 2007. There have been a total of (b) (4) integrity tests performed on the (b) (4) filters, and all results have passed. The (b) (4) filter was qualified and validated prior to implementation. The validation consisted of a prospective microbial challenge study. For the study, the filters were placed into the actual production configuration and exposed to liquid nitrogen at normal process conditions of temperature, pressure, and flow rate. The activities to identify and implement the (b) (4) included the use of internal and external filtration experts, a pre-defined project plan, test results, and a conclusion that the assessment of this new filter met sterile filtration expectations as defined in Pharmaceutical Drug Association (PDA) Technical Report 26 "Sterilizing Filtration of Liquids".

Product Quality Assessment

The observation correctly indicates that integrity test failures had been obtained with the (b) (4) filters. The integrity test failures were investigated, and the potential risk to product quality was evaluated at that time. We concluded that the risk to product sterility was minimal based on the following:

1) *The pre-liquid nitrogen filtration bioburden is low, and the extremely cold liquid nitrogen conditions can suppress microorganism survival and proliferation.*

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2) *The path to potential bioburden deposition into a vial is arduous given that at least (b) (4) filters and (b) (4) must be bypassed.*

3) *The enhanced environmental monitoring program for the liquid nitrogen and the tunnels and the resulting satisfactory data continue to provide assurance that the liquid nitrogen and (b) (4) tunnels are meeting Grade A microbial conditions during processing.*

Liquid Nitrogen Identity Testing
We wish to clarify that for each liquid nitrogen delivery, a Certificate of Analysis (COA) is obtained from the vendor identifying the product as Nitrogen. Additionally, (b) (4) identity testing is performed, consistent with current site procedures, on the nitrogen gas sourced directly from the liquid nitrogen tank.

We will investigate with the vendor and outside cGMP experts if there is a suitable method for performing identity testing on liquid nitrogen in a manner that does not represent a safety concern for those employees responsible for sampling and testing. We will complete this assessment by 02-Jun-2008.

Independent of the outcome of the evaluation described above, we will initiate a (b) (4) identity test of the liquid nitrogen (tested in its gaseous state) at the source filter site in the Building (b) (4). The (b) (4) test frequency will provide a representative sampling of the (b) (4) liquid nitrogen deliveries per (b) (4). The sampling will be performed on a (b) (4) basis until sufficient data exist to support a reduced test frequency. Standard Operating Procedure 262-113X "Environmental Monitoring of Classified Areas and Systems" will be updated and personnel will be trained to require (b) (4) identity sampling of the Building (b) (4) liquid nitrogen system at the source filter site in the Building (b) (4) by 01-April-2008.

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 (b) (4) automation issue which occurred during the manufacture of Gardasil, lot 2121579 and lot 2121693. The vendor edited the software and configuration. Since Merck employees are not aware of the actual root cause, they could only perform (b) (4) 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.

Response 14: *After review of the observation, we realize we failed to communicate all relevant information during the inspection. We wish to clarify that the investigation and any resulting change to the code were, in fact, fully documented by the vendor and Merck engineers in Merck's Automation Change Control (ACC#2007071001) documentation.*

During the investigation of the incident, Merck automation engineers were seeking to identify the root cause in the Merck owned custom (b) (4) code which would cause the automation error observed during the manufacture of the GARDASIL® lots. Due to the vendor's familiarity with the Merck (b) (4) code, the vendor was requested to assist in the investigation. For clarity, it is important to note that the vendor did not perform any independent evaluation of the error or independent modification to the software. Rather, the vendor worked on-site along with the Merck automation engineers. The Merck /

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vendor team identified the root cause as the omission of coding to control the sequence of updates/downloads in the (b) (4) screen, and subsequently revised the code.

Our procedure SOP 227-154X "Automation Change Control" was followed which requires that all automation changes be documented and tested. We wish to clarify that while the observation refers to (b) (4) testing, the Merck / vendor team did not conduct (b) (4) (b) (4) testing, but rather utilized targeted testing since all of the software code was available and used to identify the root cause of the error. In addition, Merck automation engineers performed a peer review of the code (i) to confirm that all the red-lined changes were implemented properly and (ii) to ensure that the changes had met the design intent.

The purpose of the evaluation of all drop down lists within the system was to verify that they did not have the same coding issue. The conclusion of the evaluation and testing was that all drop down lists were coded properly (no omissions of code were present), and all drop down lists functioned as intended.

PRODUCTION SYSTEM

15. During VAQTA production the method to determine the amount of hepatitis A virus antigen going into the formaldehyde inactivation procedure is inadequate and unreliable. During the 2005 and 2006 campaigns (b) (4) out of 36 (b) (4) Alum Adsorbed Bulk 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 alum adsorbed bulks indicates that some recent assessments of viral antigen concentrations prior to formaldehyde inactivation may have been under estimated. This potentially resulted in antigen concentrations in the formaldehyde inactivation process in excess of currently validated levels.

Response 15: *An increase in antigen content within our bulk VAQTA® process occurred in 2005. Lots manufactured since that time have had high antigen content, with several being outside of the upper limit of the current antigen specification. Independent of the high antigen content, an analysis of the (b) (4) method indicates that it is performing within historical parameters, because we have seen no corresponding shifts in antigen content values for final container lots or for the assay's positive control, which is also a final container. Furthermore, a corresponding yield shift for Hepatitis A bulk product is reflected in other methods, such as the (b) (4) assay, which further supports that this is not an assay related event.*

This antigen-related issue was self identified and subsequently resulted in a shut down of the production facility on 21-Dec-2006 (i.e., last lot manufactured). A root cause investigation was initiated under APR 2006-221-0029 and is ongoing. All lots released to the market have met the pre-defined critical process parameter of maximum antigen concentration into the inactivation process as well as the antigen specification for the Alum Adsorbed Bulk.

The findings from our investigation to date conclude:

a) The increase in yield is related to bioreactor conditions and resin properties. Elevated antigen values, as measured by (b) (4) were observed through all steps of the

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process, both upstream and downstream of the (b) (4) (b) (4) process step.

b) *The (b) (4) was underestimating the antigen content at the (b) (4) step. This measurement is used to determine the antigen concentration taken into the (b) (4) step.*

c) *The antigen concentration input to the (b) (4) is a critical process parameter; inactivation for an antigen concentration up to (b) (4) units/mL has been validated.*[3]

d) *Merck had previously used the Alum Adsorbed Bulk (AAB) antigen values to assess (i.e., (b) (4) the antigen values for the product for certain lots.*[4,5]

All of the lots from the 2005-2006 campaigns considered for release met the antigen concentration critical process parameter of (b) (4) units/mL, as measured on the (b) (4) samples. Given the potential underestimation, the same methodology was employed to (b) (4) the antigen from the AAB antigen values[6] *for all lots to reconfirm that the process had been run within its validated range. Data are presented in Table 1. All lots that were released met the following criteria: the (b) (4) Release specification; the (b) (4) specification (as measured on the (b) (4) sample); and did not exceed the validated range, as described in d) above. All other lots were quarantined, as highlighted in the Table below.*

(b) (4)

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Table 1: Upper Prediction Limit for (b) (4). Lots in which the upper (b) (4) prediction limit for (b) (4) exceeded (b) (4) are highlighted in bold italics and are quarantined.[7]

(b) (4)

[7] (b) (4)

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In addition, as part of lot release, each lot must pass the extensive (b) (4) (b) (4) *assay, ensuring inactivation of the antigen.* (b) (4) *is tested using a* (b) (4) *culture method. Passing results must display no viral replication, and all test articles must contain in excess of* (b) (4) *units of antigen (equivalent to* (b) (4) *adult doses). All lots that have been released have demonstrated passing* (b) (4) *results. These results support the conclusion that no active virus is present in these lots.*

We remain strongly committed to fully understand the root cause for the increase in antigen bulk content. To that end, the investigation team has been augmented with Merck Research Laboratory Scientists and other experts, as appropriate, in order to ensure that the root cause is conclusively identified. These results and any other enhancements will be detailed in a Post Approval Supplement (PAS) targeted in 2008. As we make progress and learn new information as it becomes available during the ongoing investigation, we will continue to inform CBER. We will modify the (b) (4) *assay to ensure the antigen level is not underestimated and that a robust method is implemented by 17-Apr-2008.*

16. Filling line clearance subsequent to glass breakage is inadequate in that it does not require clearance of all potentially affected areas. Specifically, APR 2006-285-0193, dated 7/13/2006 was issued for observation glass fragment in the stopper bowl during filling of MMR w/ rHA lot 0655420. The investigation determined that the root cause was due to a broken vial that was misaligned in the (b) (4) wheel 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 Rooms (b) (4) and (b) (4) only requires line clearance/cleaning of areas w/in the (b) (4) enclosure was not updated to require clearance of the stopper bowl (outside enclosure) in the event of glass breakage.

Response 16: *We understand that this observation relates to filling line clearance procedures associated with vial breakage, including the deployment of appropriate corrective actions.*

As noted in the observation, APR 2006-285-0193 was issued when a glass fragment was detected in the stopper bowl during the filling of Tray (b) (4) *of M-M-R®II with rHA Lot 0655420. The root cause was determined to be vial breakage which occurred during*

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line set-up. As a result of the investigation, Trays (b) (4) of this lot were rejected and subsequently discarded. These trays represent all of the vials filled from set-up until the time that the glass was observed.

As also noted in the observation and as part of the investigation and assessment of possible corrective actions, the feasibility of installing engineering changes to the filling line to prevent recurrence were evaluated. In this evaluation, West Point Sterile Process Technology & Engineering assessed the feasibility of implementing a non-intrusive (b) (4) sensor at the stopper bowl opening that would trigger an alarm if the optical plane is broken by a piece of glass entering the stopper bowl. This was deemed not feasible due to the constant addition of stoppers to the bowl during filling. Similarly, the installation of a barrier to "shroud" or cover the bowl was also assessed. Due to the design of the equipment, this was also deemed not feasible since a shroud or cover would not respect the GMP "first-air" principle.

At the time this investigation was closed, we based our conclusions that the current procedural controls were appropriate on the following: (i) the stopper bowl was outside of the (b) (4) filling enclosure and (ii) the existing procedure (SOP 285-230 "Operation of Filling Rooms (b) (4) provided sufficient detail regarding the required instructions to remove all glass within the (b) (4) filling enclosure.

As part of our efforts to continuously improve our operations and upon re-review of the atypical investigation referenced in this observation, we recognize the need to modify our procedures to include all potentially affected areas during both routine and non-routine set-up and operations. SOP 285-230 "Operation of Filling Rooms 127 and 122" will be enhanced to ensure that all such potentially affected areas, including the stopper bowl outside of the filling enclosure, is addressed in the line clearance procedures. This SOP will be revised and training will be completed by 31-Mar-2008.

We acknowledge the importance of effective glass management in vial filling areas and the need to ensure that line clearance procedures address the removal of broken glass from all critical processing areas and equipment. Glass breakage management has been identified as a manufacturing priority. As a result, the manufacturing divisional Quality Assurance department formed a glass breakage management team in July 2007, resulting in the issuance of a guidance document entitled, "Management of Glass Breakage" on 15-Oct-2007. The document outlines divisional expectations, principles, and actions to be taken with regard to glass breakage management, throughout all vial and syringe filling operations where glass breakage is possible. These actions are underway throughout the Merck Manufacturing Division (MMD) to ensure consistent and comprehensive glass breakage management. Actions specific to West Point Sterile and Packaging Operations (SPO) include:

- *Awareness training, which was completed on 09-Jan-2008, for all (b) (4) production employees to reinforce the importance of identifying and documenting glass breakage.*

- *A Failure Modes and Effects Analysis (FMEA) will be performed for each West Point sterile filling area to identify and address potential areas for glass breakage. The FMEA will be completed by 30-Apr-2008.*

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- *A feasibility evaluation to employ automated inspection utilizing vision systems or other technology will be completed for the filling lines used in (b) (4) sterile filling areas. The evaluation will be completed by 30-May-2008.*

17. Implementation of the change from (b) (4) filter to (b) (4) (b) (4) filters was not validated for worst case conditions. Change Request WP2-04-0137 for these filters was closed 1/12/06. The change request included results of a 10/22/2004 developmental Vmax study. This study only evaluated the filter surface area requirements for HPV type 11. There was no documented rationale as to why the other three HPV types were not evaluated. However, a subsequent Vmax study dated 11/14/2005 for the V_{max} documented that the HPV type (b) (4) worst case for filter fouling. However, this memo was not used to evaluate the filter surface area requirements for this change.

Response 17: *For reference, this observation pertains to the same events described in Observation 3B related to HPV sterile filtration. The sequence of events that led to the selection of the 4 inch filters is outlined below.*

- *The initial HPV manufacturing process used a (b) (4) filter. The selection of this filter size was based upon process development data for all four HPV Types and concluded that a (b) (4) filter provided a greater than three-fold safety factor in filter surface area for sterile filtration of all four HPV types.*

- *Redundant filtration consistent with European regulatory guidance was implemented in August 2005.[8] The selection of (b) (4) filters in series was based upon the fact that the (b) (4) filter was oversized for sterile filtration of all four HPV Types, as well as an evaluation of HPV Type (b) (4) which was believed to be representative of all four HPV types. We acknowledge that our rationale for not evaluating the other three HPV types should have been documented. HPV Type (b) (4) lots were successfully manufactured with the (b) (4) filters, while the first two Type (b) (4) lots had a significant decrease in flow rate such that another set of filters was needed to complete the filtration process. Hence, Type (b) (4) now requires (b) (4) filters.*

After implementation of the change in August 2005, additional filtration data were obtained in November 2005 that showed that HPV Type (b) (4) presented a worst-case for filter surface area. These data were not available at the time the change was initiated and therefore, could not have been used to evaluate the filter surface area requirements.

This oversight regarding the filter selection process and the communication and documentation of technical data and rationale will be part of our evaluation of the events surrounding the management of the HPV sterile filtration process, as committed to in Observation 3B.

18. There is no assurance that the PEDVAX processing tanks are held under active positive pressure post-SIP in that the PI monitoring data is not reviewed, nor are unexplained pressure losses responded to. Specifically,

[8] (b) (4)

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A. On 6/25/2007, there was an unexplained pressure loss for approximately 9 hours during the post SIP hold of (b) (4) tank (b) (4)

B. On 6/6/2007, there was an unexplained pressure loss during hold of (b) (4) (b) (4) tank (b) (4) after the non-production SIP.

C. Approximately three weeks after the non-production SIP on tank (b) (4), there was an unexplained pressure loss during the tank hold under active pressure.

Response 18A, 18B, and 18C: *We understand these observations are focused on the verification of positive pressure on tanks post sterilization and the response to pressure losses that could potentially impact the sterility of the tank. As discussed with the Investigator, our current pressure monitoring for these tanks does include documented checks of positive pressure at specific steps within the process. Additionally, pressurization data for the full duration of the post-SIP period are recorded by the Process Information (PI) monitoring system in each of the PedvaxHIB® processing tanks, except for Tank (b) (4) We agree our systems should be enhanced (as detailed later in our response) to further ensure that changes to the positive pressure conditions of the tanks that may occur between these checks are identified and investigated.*

It should be noted that the examples detailed in this observation do not represent unexplained pressure losses, but rather planned events governed by procedure. In both Observation 18A and 18C, the pressure change in the tank was executed in preparation for media challenges. In Observation 18B, the pressure change was executed to verify the installation of the vent filter, where venting is required as a safety precaution.

For the three instances cited in Observation 18A, 18B and 18C, the change in pressure was the consequence of routine processing which is documented in our procedures and in the batch record. The change in pressure associated with Observation 18A (Tank (b) (4), 6/25/07) and Observation 18C (Tank (b) (4) also 6/25/07), occurred as expected as part of the set up for the media challenge. This set up requires replacing the nitrogen that is used initially for creating positive pressure in the tank with compressed air. The compressed air is used during media challenges to provide an aerobic environment appropriate for the challenge study. This is performed according to SOP 204-257 (b) (4) and was documented in Work Order number 1402278. The work order was closed out on 27-Jun-2007.

The change of pressure associated with Observation 18B occurred in accordance with the SOP for SIP of Tank (b) (4), SOP 204-209Y (b) (4) (b) (4) SOP 204-209Y specifies that the tank should be vented at the end of the SIP operation to enable a visual inspection of the tank vent filter. Upon completion of the visual inspection, the tank is re-pressurized. Safety procedures require venting and depressurizing the tank prior to the vent filter inspection. We wish to clarify that Observation 18B refers to Tank (b) (4); however, our records show that the pressure loss that occurred on this date, 06-Jun-2007 occurred on Tank (b) (4).

In order to address the monitoring of our tanks for positive pressure conditions, we will enhance our procedures as follows:

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1) *For the PedvaxHIB® processing tanks, pressure monitoring capability will be added to TK(b) (4), and the data will be recorded in the (b) (4) system.*

2) *Prior to the use of each tank for a production batch, the PI data will be reviewed and the confirmation of appropriate tank pressurization will be documented in the (b) (4) (b) (4) Also, the PI data will be printed and attached to the batch record for review during batch release.*

3) *The Production and West Point Product Release group procedures will be revised, and training completed, to include instructions for the review of the PI data.*

All such enhancements will be completed by 31-Mar-2008, prior to the manufacture of the next commercial batch of bulk PedvaxHIB®.

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 of SIP/CIP.

Response 19: *Prior to July 2007 in the PedvaxHIB® bulk area, the system for assuring the proper completion of sterilization and pre-processing checks of CIP/SIP was documented in the batch record which is reviewed as part of batch release. While the batch record did not include a copy of the equipment sterilization records or CIP/SIP record, our procedures required that critical cleaning and sterilization parameters were met, verified, and subsequently documented by the Departmental Supervisor / Facilitator, before the cycle was considered complete and acceptable for subsequent processing.*

Since July 2007, PedvaxHIB® manufacturing operations have been suspended due to our ongoing sterility investigation. It is important to note that the items detailed in this observation were self-identified as part of this investigation. Enhancements to our procedures are in progress, as detailed below, and will be in place prior to the restart of operations. Additionally, the management of sterilization records across our manufacturing operations was identified prior to the inspection as an area for enhancement, and a project plan to enhance this system was approved on 27-Sep-2007 which includes full implementation by 14-Apr-2008.

CIP/SIP Records

For each piece of equipment utilized to manufacture PedvaxHIB®, CIP/SIP is documented in the cleaning and use log. Prior to using equipment for a production batch, the cleaning and use log is checked by operations personnel to confirm that the CIP/SIP occurred and was documented as complete and satisfactory. Operations staff then document this verification in the batch record before the equipment is deemed available for use in processing, thereby assuring that the CIP/SIP was complete and is within pre-established hold times.

In order to enhance our current practice, all CIP/SIP cycle reports for PedvaxHIB® will be attached to a pre-processing checklist and included in the bulk manufacturing batch record. The pre-processing checklist and the cycle reports will be reviewed by both Operations and Quality as part of the batch release. Modifications to our procedures to effectuate these changes will be completed and personnel will be trained prior to the re-start of our production.

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With respect to the handling of CIP/SIP records within Sterile and Vaccine Operations, a project plan will be established for all similar CIP/SIP processes. This plan will be completed by 30-May-2008 and will detail a phased approach for implementation to all Sterile and Vaccine Operation areas. The final implementation is targeted for completion by 12-Dec-2008.

Sterilization Records
Prior to the inspection, we identified sterilization record approval as an area for enhancement. A project plan was developed, presented to, and accepted by, our site senior management on 26-Sep-2007, with full implementation completed by 14-Apr-2008. Our documented project plan requires a review of sterilization records by Quality staff. Since one sterilization load may include equipment used in several batches, actual sterilization runs will not be included as part of each batch record; however, as part of our Quality review of sterilization records, we are ensuring that only equipment that has been processed through a successful sterilization run is utilized.

In addition, a site-wide systems evaluation will be performed to ensure that other batch production and control records, in addition to those cited above, are included and reviewed by Quality as part of the batch release process. The documented evaluation and corresponding action plan will be completed by 30-Jun-2008.

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 Normal Horse Serum. For example:

i. Bulk Antivenin Serum (product code 38404) can be held at (b) (4)
ii. Pooled Antivenin Serum (product code 04084) can be held at (b) (4).
iii. Normal Horse Serum, (b) (4) (product code 38252) can be held at (b) (4).
iv. (b) (4) Normal Horse Serum (product code 38264) can be held at (b) (4)

B. The hold time validation for the (b) (4) storage of filled product for the following vaccines are deficient in that:

i. For MMR, the hold time of (b) (4) is only performed on one lot.
ii. For Attenuvax, Meruvax, and Mumpsvax, the hold time of (b) (4) was not performed.

C. There are no data to support the process hold time for MMR Bulk (product code 38451) of (b) (4).

Response 20: *In response to the February 2006 Team Biologics Inspection, we committed to fundamentally enhance the bulk stability program. Consistent with our commitments in 2006, all actions were taken to enhance our bulk stability program and were reviewed in detail with the Investigator during the 2007 inspection. These included enhancements to the duration of the hold times, containers used, and testing performed across the different products. We believe our stability system enhancements were*

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implemented in accordance with our 2006 commitment previously communicated to the Agency. Based upon discussions with the Investigator, the specific issues detailed in this observation relate to the following:

1) *Failure to modify the hold times for the ANTIVENIN intermediates to be in alignment with available retrospective stability data. (Observation 20Ai-20Aiv)*

2) *Our understanding that Response 1.3.H provided to the 2006 Team Biologics Inspection was acceptable to the Agency. (Observation 20Bi – 20Bii)*

3) *Our understanding that concurrent stability data generation has been generally accepted through the license approval process. (Observation 20C)*

Responses to the individual observation issues follow:

Response 20Ai-iv: *In response to the February 2006 Team Biologics observation regarding Black Widow Spider ANTIVENIN (BWSA) and Normal Horse Serum (NHS) intermediate hold times, we committed to perform a retrospective hold time analysis. A retrospective data analysis approach was used due to the limited manufacture and availability of these intermediates. No intermediates existed that were held to the maximum hold time. Therefore, our analysis was limited to data from the longest hold times used in manufacturing to date. The results of the retrospective study were documented in Retrospective Study Hold Time Evaluation for BWSA, issued 31-May-2007.*

We acknowledge that we did not reduce the allowable hold times for the intermediates until the inspection and acknowledge that this should have been reduced as of 31-May-2007. (It should be noted that no lots have been released that exceeded the hold times supported by the retrospective evaluation). As communicated during the inspection, we implemented the reduced hold times listed in Table 1 and will file these times with CBER. Any extension to these times will be formally submitted to the Agency. In principle, we believe it is appropriate to seek Agency approval for hold times that are longer than currently available stability data on the basis of prospective, concurrent stability studies conducted according to a filed protocol. However, the limited availability of ANTIVENIN does not allow for this approach. Therefore, we will submit the reduced hold times described below.

Table 1: Hold Times for Black Widow Spider ANTIVENIN and Normal Horse Serum Intermediate Products

Product	*Storage Temperature*	*Hold Time*
Bulk Antivenin Serum	(b) (4)	(b) (4)
Pooled Antivenin Serum		
Normal Horse Serum		
Diluted Normal Horse Serum		

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Response 20Bi: *We will supplement the existing (b) (4) data for M-M-R®II. Specifically, for M-M-R®II with rHA, two additional transfer studies will be performed (lots will be held for (b) (4) followed by long term storage at (b) (4)). These studies will be initiated by 02-Apr-2008.*

It is important to note that in our response to the February 2006 Team Biologics observation regarding the hold time for M-M-R®II, we communicated the data that were used to support the practice of (b) (4) storage of filled product as follows:

- *One lot of M-M-R®II with rHA (recombinant human albumin) held for (b) (4) at (b) (4) followed by long term storage at (b) (4) These supporting data were also included in the regulatory application for M-M-R®II with rHA, approved by CBER on 31-Aug-2005 (STN 101069/5068).*

- *Historical data for (b) (4) lots of M-M-R®II with HSA stored at (b) (4) through a (b) (4) (b) (4) shared during the inspection.*

Since M-M-R®II with rHA and M-M-R®II with HSA have been shown to demonstrate similar stability profiles through product expiry, we concluded that these data supported the long term storage conditions of M-M-R®II manufactured with either HSA or rHA.

The data generated from the two additional transfer studies will provide additional assurance for the long term storage conditions of M-M-R®II.

Response 20Bii: *We respectfully submit that the hold times for the (b) (4) storage of the monovalent vaccines are appropriate and supported by data. In response to the February 2006 Team Biologics observation, we communicated our position that the existing M-M-R®II data were supportive of the monovalent products ATTENUVAX®, MERUVAX®, and MUMPSVAX®, due to similarity of the sample matrix and concluded that no additional studies were necessary. For these monovalent products, the approved (b) (4) storage time is (b) (4)*

Based upon discussion with the Investigator, we will supplement the existing (b) (4) data for these products. Due to the formulation similarities between the monovalent and trivalent products, one study of each monovalent product will be performed in support of the (b) (4) hold time. (Lots will be held for (b) (4) at (b) (4) followed by long term storage at (b) (4) .) These studies will be initiated by 30-Apr-2008, depending upon the production schedule of the monovalent products, ATTENUVAX®, MERUVAX®, and MUMPSVAX®.

Response 20C: *We understand this observation is related to the (b) (4) stability bulk hold time for measles. The current (b) (4) hold time for measles, mumps, and rubella pooled clarified bulks was previously approved for both the ProQuad® (approved 06-Sep-2005, STN 125108/0) and M-M-R®II with rHA submissions (approved 31-Aug-2005; STN 101069/5068). Approvals for the bulk hold times were granted based on stability data which were less than (b) (4) at the time of approval. In addition, data supporting (b) (4) hold times for measles, mumps, and rubella pooled clarified bulks were presented during the 2006 Team Biologics Inspection, and no concerns regarding the dating periods were raised at that time. Since concurrent data generation has been generally accepted through the license approval process and was understood to be*

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acceptable during the previous inspection, no further action was taken to reduce the hold times to shorter than (b) (4) .

As reviewed during the inspection, the available data for measles pooled clarified bulk manufactured with human serum albumin [(HSA) (product code 38451)] are summarized in Table 2.

Table 2: Measles HSA Pooled Clarified Bulk Stability Studies

Lot	*Satisfactory Stability Data*
2056964	(b) (4)
2063031	
2063828	

However, an open investigation is associated with the (b) (4) *for measles pooled clarified bulk, Lot 2063828. Beginning in June 2007, any measles bulk in inventory at or* (b) (4) *was quarantined. Additionally, an internal hold time control of* (b) (4) *will be instituted in our materials control system in alignment with the acceptable data currently available by 20-Feb-2008. We also confirmed that there is no marketed product within expiry manufactured from a measles bulk held* (b) (4) *Supplemental stability data for this product will be submitted to CBER as they become available in support of the hold time.*

21. SOP 209-205X, (b) (4) (b) (4) , allows for a maximum (b) (4) redispensing operations (b) (4) To date, there have been no Mumps redispensed bulks that have been placed on stability to validate this operation.

Response 21: *Our bulk stability program includes studies incorporating all of our monovalent bulk vaccines inputs for M-M-R®II. In regard to monovalent bulk vaccines that have been processed through re-dispensing steps, we have completed the stability studies for the redispensed bulk measles and rubella monovalent vaccines. We are committed to completing the bulk stability study for the mumps bulk vaccine to validate the maximum number of re-dispense operations. This study will include one lot that has been subjected to* (b) (4) *re-dispensing operations* (b) (4) *followed by storage at* (b) (4) *The initiation of the stability study is dependent upon scheduling the re-dispense operation in the manufacturing area. The re-dispensing operation is planned to occur by 12-May-2008.*

It is important to note that (b) (4) *of measles and rubella bulk have been placed on stability as of 14-Nov-2006 and will be studied through the maximum expiries of these bulks. Samples from these lots represent bulks which have been redispensed* (b) (4) (b) (4) *for the maximum* (b) (4) *times* (b) (4) *These studies were reviewed with the Investigator and deemed appropriate to validate the redispensing operation for measles and rubella. Measles, mumps, and rubella demonstrate similar stability profiles* (b) (4) *as demonstrated by the stability studies, of the monovalent bulk vaccines.*

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In order to ensure that all bulks which undergo multiple re-dispense operations are supported by stability data, a review was conducted to determine if any additional studies are required to evaluate redispensed bulks. In addition to M-M-R®II, which is discussed above, only RotaTeq® is redispensed (b) (4) *. RotaTeq® bulk may be redispensed only* (b) (4) *and the stability program includes adequate studies to support this operation.*

We will update our Merck Divisional Guidance GDL6.43 "Drug Substance Retest and Expiry Periods and Manufacturing Dates" to ensure that the guidance is specific to include a requirement to evaluate biologic bulks subjected to the maximum allowable number of redispensing operations (b) (4) *. This Guideline will be updated and personnel will be trained by 30-May-2008.*

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 (b) (4) (b) (4), 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 Alum diluent.

B. (b) (4) 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 (b) (4) in such containers.

Response 22A: *(b) (4) and (b) (4) testing were used to validate the closure as a sterile boundary and are documented in MV97-767 "* (b) (4) (b) (4) *. In addition, the* (b) (4) *closure was challenged as part of a media challenge including air transportation, documented in FR07-064* (b) (4) (b) (4) *. Also, stability studies on bulk products stored in bottles using the* (b) (4) *closures include sterility testing at the end of the expiration date. These studies have demonstrated that the containers are integral and have proven that the closures prevent microbial ingress during storage.*

In accordance with our current procedures, we tighten all of our (b) (4) *closures to a specified torque; however, we agree that the validation of the* (b) (4) *closure should be enhanced with data that assess the effects of storage conditions on applied torque. Studies will be designed and initiated by 30-Jun-2008 to assess the affect of storage conditions on the applied torque. In addition, we will update validation procedures 240-356X* (b) (4) *and 240-150X "Standard Procedure for* (b) (4) *" to specify that validation data are required to support integrity of the closure system over all anticipated conditions of storage and use. In particular, the SOP will specify that torque relaxation studies should be performed when validating closures on containers intended for extended storage where torque is an element of the closure system. The changes will be implemented by*

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23-Apr-2008. In addition, an assessment will be completed to identify any additional bulk closure systems for which additional data are required to support the conditions of storage and use. The assessment and approval of any resulting action plans will be completed by 30-Sep-2008.

Response 22B: *(b) (4) sterile filtered solutions referred to in the observation are all raw material intermediates that are subsequently sterile filtered (b) (4) in the manufacturing process. Container closure integrity requirements are applied at the point of product sterile filtration or where products are aseptically produced. Consequently, a requirement was not established for these raw material intermediates for container closure validation.*

As a result of this observation, we will revise SOP 240-356X (b) (4) (b) (4) " and conduct any associated training by 23-Apr-2008 to specify that a documented risk assessment should be performed for the (b) (4) sterile filtered solutions. The risk assessment will determine whether there is a need for validation of the closure system associated with any of the referenced (b) (4) solutions and will consider the nature of the solution (i.e., propensity for growth proliferation and endotoxin accumulation), the storage conditions (e.g., classified space or not), the nature of the closure, the hold time (i.e., the (b) (4) months cited above), and the use of the solution. This risk assessment will be completed by 29-Aug-2008.

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 (b) (4)
Poor Crimp (b) (4)
Product in Stopper (b) (4)
Cracked Vial (b) (4)
Missing Stopper (b) (4)
Missing Seal (b) (4)
Missing Cap (b) (4)
Empty Vial (b) (4)
Underfill (b) (4)
Dirty Vial (b) (4)

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:

- (b) defective vials ((b) (4) were accepted during line set-up for Varivax PU, fill lot 0659606; (b) (4) vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and (b) (4) rejects were discarded after the 2nd pass.
- (b) defective vials (b) (4) were accepted during line set-up for Varivax PU, fill lot 0659604; (b) (4) vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and (b) (4) rejects were discarded after the 2nd pass.

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- (b) defective vials (b) (4) were accepted on one inspection machine, and (b) defective vials (b) (4) (b) (4) were accepted on the second inspection machine during line set-up for Zostavax Refrigerated, fill lot 0655791; (b) (4) vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and (b) (4) rejects were discarded after the 2nd pass.

- (b) defective vials for particulates were accepted on one inspection machine, and (b) defective vials for particulates were accepted on the second inspection machine during line set-up for ProQuad, fill lot 0657748; (b) (4) vials from the lot failed first pass inspection, the failing vials were sent through the equipment again, and (b) (4) rejects were discarded after the 2nd pass.

Response 23: *We understand this observation is related to the appropriateness of the acceptance criteria in place for the control standards used during equipment set-up prior to the inspection of each batch and the appropriateness of the two-pass inspection process.*

We acknowledge that the control standards acceptance criteria should be updated to reflect our inspection equipment's demonstrated capabilities. We would like to clarify, however, that the current control standards criteria do not reflect the actual performance of the inspection equipment. The inspection equipment is operating as intended and has demonstrated through validation to statistically meet or exceed manual inspection performance, for all defect types, for all products inspected.

Acceptance Criteria for Control Standards
Control standards (i.e., a set of vials containing representative product defects) are used as part of the inspection machine set-up procedure prior to each run. The standards confirm proper set up and operation of the equipment and provide evidence that the inspection system is maintaining a consistent level of performance. Defects contained within the control standards are selected and created to represent typical defects which may occur in production. The preparation and maintenance of these control standards are controlled by procedure.

The acceptance criteria for the control standards inspection on the current lyophilization inspection equipment (b) (4) were initially based on the criteria established for an older technology that was inspecting the same products. These criteria do not reflect the true detection capabilities of the (b) (4) and should have been updated earlier. As a result, we will update the acceptance criteria established for the control standards used during equipment set-up, to reflect the actual performance of our lyophilized product inspection machines by 31-Mar-2008.

As discussed with the Investigator, a sampling of standard control run results (greater than (b) (4) across the validated life of the (b) (4), as well as across all products, was compiled. As outlined in Table 1 below, this sampling demonstrates that the inspection equipment actually has a high level of defect detection, for all defect types; the rate of control standard defects being detected during our set up runs is (b) (4) for the majority of defect types and (b) (4) or greater for all defect types.

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Table 1: Detection of Defected Vials

Defect Category	(b) (4) *Control Standards (% of defects detected)*
Particulates	(b) (4)
Poor Crimp	
Product in Stopper	
Cracked Vial	
Missing Stopper	
Missing Seal	
Missing Cap	
Empty Vial	
Underfill	
Dirty Vial	

For those standard control detection rates that are less than (b) (4) *the undetected defects are usually associated with control standard defect sets that have degraded over time and use, not with the detection capability of the inspection equipment. The* (b) (4) *defect categories that demonstrated the lowest detection rates* (b) (4) *are known to present challenges as the associated defect sets can degrade over time and use:*

- *Particulate vial standard set defects can degrade with use as the lyo cake begins to erode, potentially obscuring defects on the cake surface;*
- *Cracked vial standard set defects may break within the inspection equipment with repeated manipulation and use;*
- *Dirty vial standard set defects are created by marking the outside of the vial with a marker to mimic residue on the vial. The marking on the outside of the vial can wear off after repeated use.*

We recognize the importance of continuously improving our systems and enhancing the robustness of our control standard defect sets. To that end, we will take the following actions:

1) *To ensure consistent creation and maintenance of the control standard defect set, the procedure for creating the control standards for the* (b) (4) *will be updated. This update and the associated training will be completed by 31-Mar-2008.*

2) *To ensure consistency across all manufacturing areas, an assessment of control standards inspection acceptance criteria, for all automated inspection systems used to inspect vaccine product in the formulation-fill-inspect areas at West Point, will be completed by 30-Apr-2008 and appropriate actions will be implemented, as required.*

(b) (4) ***Inspection Process***

The automated inspection of our lyophilized product is a two-pass process. Vials are (b) (4) *inspected using the* (b) (4) *inspection machine and* (b) (4) (b) (4) *are inspected* (b) (4) *by the* (b) (4) *inspection machine and are separated into* (b) (4) *. The rejected vials from the second pass are discarded.*

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By using the (b) (4) approach, the inspection system detection capability can be set to a high sensitivity facilitating the detection of true defects, while controlling the false rejection of good product. With the equipment tuned to a high sensitivity, the (b) (4) will generally yield a relatively high number of false rejects. This (b) (4) inspection methodology is common in industry and is validated against a manual inspection baseline for each product inspected. These validation studies have demonstrated that the (b) (4) (b) (4) inspection process statistically meets or exceeds the detection capability of manual inspection, for all defect categories, for all products.

In addition to the automated inspection system, each lot of product produced is subsequently assessed by performing an (b) (4) inspections and (b) (4) Sampling (b) (4). The results of each of the (b) (4) must conform to the acceptance criteria for a specified Acceptable Quality Level (AQL) for all critical/major/minor defects. Current procedures require that lots failing the (b) (4) for any defect category automatically require an investigation.

The effectiveness of our (b) (4) inspection process is further evidenced by an analysis of the complaint data from our lyophilized products on the market. Table 2 below shows the external complaints registered for our lyophilized products and the associated frequency (b) (4) in the West Point Complaint Database (b) (4) from 01-Feb-2006 to 31-Dec-2007. The complaint data for this period of time indicate that we have seen (b) (4) complaints per (b) (4) vials distributed, for our Lyophilized products for any of the defect types.

Table 2: External Complaints for Lyophilized Products

Defect Type	Complaint Category				
	Primary Component Irregularities	Particles	Volume of Fill	Dosage Form Irregularity	Doses Distributed
Total Count	(b) (4)				
CPM	(b) (4)				

This low level of complaints is reflective of a process operating within (b) (4) levels and provides further assurance of the effectiveness of the current inspection process.

Specific Lots Referenced in Observation 23

Observation 23 listed four Lots [0659606 and 0659604 (VARIVAX® PU), 0655791 (ZOSTAVAX® Refrigerated) and 0657748 (ProQuad®)] that met the acceptance criteria for defect detection during the control standards inspection, but had less than (b) (4) detection of the standard rejects and which were subsequently inspected via the (b) (4) (b) (4) process. The two lots of VARIVAX® PU identified above were both inspect using our older inspection equipment. This equipment has since be decommissioned and has been replaced by new inspection equipment (b) (4). As noted earlier, all four lots were inspected using a validated process that was demonstrated to statistically meet or exceed the manual inspection baseline. The control standards set up results noted were likely related to known issues with creating and maintaining the challenge vials, and not related to inspection system capability. For all four lots, the (b) (4) (b) (4) results were passing, and there were no inspection-related batch sheet observations.

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In summary, we are confident in the quality of these lots inspected by the automated inspection equipment, based on the validated detection capability of the inspection equipment which meets or exceeds manual detection capability, and the passing (b) (4) sampling results post inspection. The corrective actions identified earlier will ensure that our control standard samples are more effectively created and maintained and will also ensure that the acceptance criteria for the inspection of the control standards during equipment set-up are properly adjusted to reflect the capability of the inspection equipment.

24. Process capability limits were not re-established for filling line defects for Zostavax as required by SOP 300-103X, (b) (4) (b) (4) The PCLs had not been evaluated since February 2006.

Response 24: *As discussed with the Investigator, the inspection Process Control Limits (PCLs) were not re-calculated for ZOSTAVAX® Frozen, as required by procedure for products associated with inspection related process changes.*

In accordance with SOP 300-103X (effective 15-Oct-2007) (b) (4) (b) (4) the inspection reject rate PCLs are static limits. These static PCLs are re-calculated only in the case of a process change impacting inspection or in the case of a shift in performance.

We will further strengthen our inspection process in the detection of shifts in our production processes by enhancing our procedures by 30-Apr-2008 to ensure that the PCLs are evaluated at least (b) (4), in accordance with the conditions set forth in the SOP 300-103X.

In the case of ZOSTAVAX® Frozen, the inspection of this product was first performed on the (b) (4) Inspection Machine (b) (4) on 01-Jul-2005. The last batch inspected on the (b) (4) prior to transition of inspection to the (b) (4) Inspection Machine (b) (4) occurred on 08-Sep-2007. Because the (b) (4) inspection represents a significant process change, new inspection PCLs specific to this process must be calculated. The ZOSTAVAX® Frozen PCLs for (b) (4) inspection will be calculated once sufficient data are available according to SOP 300-103X.

25. Validation protocols PVP06-065 dated 12/6/06 and PVP06-011 dated 5/7/06 executed for "Detection of Volume-of-Fill Defects for multiple vaccine products filled on lines (b) (4) and (b) (4) (building (b) (4) and inspected by (b) (4) machines (b) (4) 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 (b) (4) defective vials in each of the 2 volume of fill defect categories (underfill and overfill) were assessed, for a total of (b) (4) defective vials for each qualification. Routinely there are approximately (b) (4) vials inspected at approximately (b) (4) vials/minute.

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A. APR 2007-174-0079 dated 12/4/07 was initiated to investigate the improper validation of automated inspection machines (b) (4) and (b) (4) for 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 (b) (4) and (b) (4) which include Pneumovax, Recombivax, Sterile Diluent, Cogentin, and Vasotec 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)

Response 25: *In accordance with our commitment to the 2006 Team Biologics Observation, the (b) (4) validation studies for the detection of volume-of-fill defects were executed according to their respective protocols and were closed successfully with passing results in May 2006 (b) (4) and December 2006 (b) (4).*

With respect to the observation relating to the design of the validation studies in that non-defect vials were not included in the sample set, the validation studies were designed without non-defective vials because automated inspection machines view each vial independently. Each vial is individually captured by the equipment inspection turret and analyzed. Therefore, our validation challenge was designed to only include defect vials.

Additionally, for these studies, the vials were inspected using the same line speed set points as in production. (Refer to Table 1.)

Table 1: EISAI Line Speeds

Inspection System	Routine Production Set Points	Line Speed Set Points During Validation
(b) (4) – all products	(b) (4) vials/hour	(b) (4) vials/hour
(b) (4) – all products	(b) (4) vials/hour	(b) (4) vials/hour
(b) (4) – all products except multi-dose RECOMBIVAX HB®	(b) (4) vials/minute	(b) (4) vials/minute
(b) (4) - multi-dose RECOMBIVAX HB®	(b) (4) vials/minute	(b) (4) vials/minute

In order to better simulate the process, we will modify our procedures to include non-defective vials during validation of automated inspection machines by 30-May-2008.

Response 25A: *In accordance with our 2006 Team Biologics Commitment, the (b) (4) validation studies for the detection of volume-of-fill defects for (b) (4) and (b) (4) were executed according to their respective validation protocols and were closed successfully with passing results in December 2006 (b) (4). For (b) (4) the validation for detection of volume-of-fill defects was closed successfully with passing results in May 2006. These studies were performed using defect sets prepared manually consisting of low and high volume-of-fill defects.*

On 30-Nov-2007, during an investigation involving (b) (4) we identified that a manually prepared vial defect for volume of fill could be rejected as a particulate defect because of how it was originally prepared. For (b) (4) it was determined that the batch records

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are such that the defect type is recorded for each rejected vial. This allowed a retrospective review of the 2006 validation data. This review found that after accounting for the vials that were rejected due to the presence of particulates, the results still met the validation study acceptance criteria. As a result of the findings on (b) (4) an investigation was initiated (04-Dec-2007) for the 2006 validation studies for (b) (4) and (b) (4). For (b) (4) and (b) (4) the batch records do not contain the necessary information to do a similar retrospective review of the data. Thus, it was decided to execute new validation studies in which the rejected vials will be identified according to the defect type identified by the (b) (4). The validation studies will be completed prior to inspection of any future batches of product on these machines, which is targeted for completion by 31-Mar-2008. Independent of the validation of (b) (4) and (b) (4) for volume of fill, there was no impact to product quality for all lots produced since there is an additional 100% manual inspection for volume of fill.

26. (b) (4) (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 (b) (4) inspection for any defect category can be reinspected. Lots failing an (b) (4) inspection for a critical defect must be (b) (4) reinspected. There are no reject limits established for the individual defect categories of lots reinspected after failing an initia (b) (4) inspection.

For example: MMR II 1 Dose w/rHA lot #'s 0654444 and 0655487 failed the initial (b) (4) inspections in 2/2006 and 7/06, respectively, for the critical defect category of (b) (4) The lots were (b) (4) reinspected with no reject limits established for the individual critical defect category of (b) (4) Total reject % PCL 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 (b) (4) failures. These lots have been released and are within expiration date.

Response 26: *We understand this observation includes two concerns related to the re-inspection process.*

Limits for Re-Inspected Lots

The observation states that there are no reject limits established for individual defect categories for reinspected material. Our current procedure, SOP 290-154X (b) (4) (b) (4) requires that accepted material from reinspected lots be assessed by performing (b) (4) (b) (4) inspections as well as (b) (4) Sampling (b) (4). The results of each of the (b) (4) must conform to the acceptance criteria for a specified Acceptable Quality Level (AQL) for all critical/major/minor defects. As such, the quality of all reinspected lots is assured based on the passing statistical sampling associated with each re-inspection, the passing packaging statistical sample inspection results, and the passing release tests.

We acknowledge that our re-inspection procedures do not require pre-defined limits for individual defect categories. To strengthen our re-inspection process, the appropriate procedures will be updated to require pre-defined limits for individual defect categories for re-inspected product. Any value exceeding the pre-defined acceptance criteria will require an investigation. The updated procedures will be in place with training completed by 08-Apr-2008.

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Investigation for Lots Failing (b) (4) Inspections

The observation regarding investigations relating to the two M-M-R®II Lots 0654444 and 0655487 requires clarification. We acknowledge that at the time Lots 0654444 and 0655487 were manufactured, our procedures did not require an investigation for ISS failures. This issue was self identified prior to the start of the 2007 Team Biologics Inspection and was addressed with a procedural update to SOP 290-154X (b) (4) (b) (4) " on 15-Oct-2007.

The observation states that there were no investigations performed to identify the root cause for the initial (b) (4) failures. We would like to clarify that after the completion of the 2007 Team Biologics Inspection, we did confirm that both (b) (4) failures were investigated as part of separate investigations triggered by out of process control limits. Investigations 2006-290-0060 and 2006-290-0017 were completed for both of these lots as they each exceeded the predefined process control limits for product appearance. The investigations were issued in accordance with SOP 174-103X (b) (4) (b) (4) " and identified that in addition to exceeding the inspection process control limits, the lots failed the in-line statistical secondary inspections. The investigations evaluated the (b) (4) results, identified the root cause, and appropriately evaluated the potential product impact.

The (b) (4) inspection investigations were incorporated within the same investigation as they were directly related. Therefore, we believe these events were properly investigated and all procedures were followed. Additionally, procedures are in place to require an investigation should an out of specification (b) (4) (b) (4) inspection event occur.

In both investigations, the root cause was determined to be the over-insertion of stoppers into vials, which resulted in the generation of atypical amounts of product appearance defects. Corrective actions included improving the detection of the lyophilized product inspection equipment for product appearance (implemented on 31-Mar-2006) and defining, documenting, and training personnel on the appropriate stopper insertion depth (completed on 18-Oct-2006). The corrective actions have prevented recurrence of product appearance (b) (4) failures for this issue since 02-Oct-2006.

The quality of the two M-M-R®II Lots 0654444 and 0655487 is assured based on the (b) (4) re-inspection of each lot, the passing statistical sampling associated with each re-inspection, the passing packaging statistical sample inspection results, and the passing release tests.

27. Prior to October 15, 2007, there was no requirement to initiate an investigation into lots of product that failed the initial (b) (4) inspection for critical defects other than foreign product, incorrect stopper or container. SOP 290-154X (b) (4) (b) (4) "dated April 30, 2007 did not require investigations into (b) (4) failures for critical defects such as cracked vials, product in stopper, meltback and (b) (4)

Response 27: *In 2007 and prior to the inspection, we identified inconsistencies across the formulation and filling areas with respect to the management of statistical sampling results of product evaluated after visual inspection. This inconsistency included that we only required an investigation for four of the critical defect categories and not all*

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categories, as noted in the observation. Effective 15-Oct-2007, SOPs 290-154X (b) (4) (b) (4) ", 174-321X (b) (4) (b) (4) ', and 135-318X (b) (4) (b) (4) which govern this statistical sampling across the formulation and filling areas, were updated to require a deviation alert be written if the statistical sampling failed to meet acceptable quality levels (AQL) for all critical, major, or minor defect categories. The sampling plans are based on (b) (4) (b) (4)

Prior to 15-Oct-2007, the statistical sampling procedure for the inspection of lyophilized products, SOP 290-154X, required the following if there was a failure of (b) (4) (b) (4) inspection:

1) *Notification to Quality to quarantine the lot.*

2) *Re-inspection of the lot if a critical defect is found. A statistical sampling (b) (4) of the re-inspected lot is evaluated against acceptable quality levels (AQL) for critical, major, and minor defect categories.*

3) *Initiating an investigation for critical defects of foreign product, incorrect stopper, or incorrect container.*

Prior to the 15-Oct-2007 procedural update, the quality of released material that initially failed (b) (4) for any critical defect is assured based on the following. Each lot required (b) (4) re-inspection and a passing statistical sampling associated with this re-inspection. In addition, all packaged product is statistically sampled and is evaluated for critical, major, and minor defect categories as per SOP 315-219 (b) (4) (b) (4) ". This additional evaluation in Packaging and the release testing provide further assurance of product quality.

As mentioned in the observation, since 15-Oct-2007, the statistical sampling procedures for the inspection of lyophilized products (SOP 290-154X) now require an investigation to be initiated in the event of (b) (4) failure, for any defect category.

28. There are no data to support the reprocessing/refiltration of the Recombivax HB Sterile Filtered Product (SFP) (b) (4). For example APR 2007-202-001 was initiated 2/24/07 for Recombivax SFP bulk lot #2118647 having a pressure driven leak in tank (b) (4) post sterile filtration from tank (b) (4). The lot was refiltered on 2/28/07 formulated and filled into multiple final drug product lots Recombivax Dialysis lot #0660885, Comvax lot #'s 0659285 and 0660293, Recombivax lot #'s 0660507 and 0060951 and packaged lots Recombivax 1737U and Comvax 1550U. These lots have not been released. Additionally, this SFP bulk lot #2118647 has not been placed on stability.

Response 28: *The process for RECOMBIVAX HB® allows for re-filtration (STN 101066/5001) of the Sterile Filtered Product (SFP) made in the (b) (4) (b) (4) We understand from the observation that reprocessing pertains only to a re-filtration event, as there is no additional reprocessing allowed for SFP.*

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Investigation APR 2007-202-0001 for the re-filtration of Lot 2118647 determined that the re-filtration did not affect the final protein concentration showing that there was no protein aggregation. This bulk lot was, therefore, released for downstream processing. In order to further support the re-filtration process, we have initiated a concurrent stability study using a final container lot that was made from SFP Lot 2118647. Specifically:

- *A stability study was initiated on 23-Jan-2008 using a (b) (4) mcg/mL RECOMBIVAX HB® Dialysis image lot (Lot 0660885, reference site stability protocol # (b) (4)*

The Dialysis image is made from the bulk lot without any added solutions (i.e., (b) (4) (b) (4) and is, therefore, directly representative of the bulk lot.

In addition, we will perform an assessment to assure that we have stability data to support any re-processing steps that are approved in the product license for all vaccine and sterile pharmaceutical drug substance or drug product. This assessment will be completed by 20-May-2008, including an implementation plan if any additional stability studies are required.

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 that (b) (4) ports 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 (b) (4) (b) (4) requires the replacement of (b) (4) on each of the (b) (4) Ports on tank (b) (4) if the CIP is completed directly after completion of a batch.

B. There is no replacement schedule for the (b) (4) lines used on the Pedvax Alum adsorption tank (b) (4) 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. APR 2006-204C-0027, was issued for WFI sample site (b) (4) during week of 4/30/06 above action w/ count of (b) (4) CFU. The contaminant was identified as *B. Cereus* (a spore former). 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.

Response 29: *It is our understanding that this observation pertains to cleaning, maintenance, and sanitization procedures specific to the (b) (4) components of our manufacturing systems as noted in Observation 29A and 29B and that the procedures should be enhanced. It is important to note that the specific examples cited were previously identified in October 2007 during our internal PedvaxHIB® media challenge failure investigation and were subsequently shared with*

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the Investigators during the inspection. We agree that there is an opportunity to enhance our procedures and we will evaluate and implement as appropriate the enhancements described below across West Point Vaccine and Sterile Operations. Specifically, we will perform a system based review of our equipment maintenance, cleaning, and sanitization procedures related to (b) (4) *components (e.g.,* (b) (4) *and hoses,* (b) (4) *) such as those referenced in the examples given below. This evaluation will be completed by 30-Sep-2008, including an implementation plan for any identified actions. Furthermore, we will also update the related procedures identified below to ensure that the change-out activities are documented.*

Response 29A: (b) (4) *ports are present on Tank* (b) (4) *and* (b) (4) *in the PedvaxHIB® Chemistry suite. The Clean in Place (CIP) SOPs for TK-4160 [i.e., SOP 204-210L "CIP Procedure for the* (b) (4) *"] and* (b) (4) *[i.e., SOP 204-209P "CIP Procedure for the* (b) (4) (b) (4) *include the instructions to remove the* (b) (4) *port plugs, replace the* (b) (4) *and re-install the* (b) (4) *port plugs on the tank after each batch. We will enhance our procedures to document that these steps were performed after each batch. SOPs 204-210L and 204-209P will be updated with training completed by 29-Feb-2008 to include a checklist documenting the performance of these steps.*

Response 29B: *As part of the system improvements identified in the 2007 media challenge failure investigation, the* (b) (4) *skid has been redesigned to reduce the complexity of the dispensing manifold. This redesign was completed in January 2008 and eliminated the need for the dispensing manifold assembly.*

There will continue to be some permanent (b) (4) *flex lines on the PedvaxHIB® skids* (b) (4) *that are integral to the tank systems and are required for appropriate system performance. These permanent flex lines are cleaned- and sterilized in place (CIP and SIP) with the rest of the* (b) (4) *tank system. The flexible hoses on the* (b) (4) *tanks were replaced between 17-Apr-2007 and 26-Apr-2007 under Work Orders* (b) (4) *. Additionally, preventative maintenance procedures were established in January 2008 to replace these flex lines on a time-based frequency (reference Preventative Maintenance Plans* (b) (4) *).*

Response 29C: *We acknowledge that the corrective action issued for APR 2006-204C-0027 was to develop a routine sterilization procedure for the hoses used for processing and WFI sample collection. Due to an error, it was incorrectly assumed that a* (b) (4) *sterilization would be sufficient and that the corrective action was closed out accordingly without appropriate justification.*

During the PedvaxHIB® media challenge failure investigation in October 2007, it was internally recognized that there was no routine sanitization or maintenance of the flex hoses in the suite used for filter flushing, WFI flushing, and CIP. As part of this investigation, new hoses were purchased, arrived on site on 08-Jan-2008, and will be placed into service prior to start-up of manufacturing operations. Preventative maintenance procedures have been established to replace all hoses used in the PedvaxHIB® Chemistry suite on a time-based frequency (reference Preventative Maintenance 54215). In addition to routine replacement of all existing hoses, SOP 204-210Q ' (b) (4)

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(b) (4) *will be updated and associated training will be completed by 29-Feb-2008 to include* (b) (4) (b) (4) *of flex hoses.*

As mentioned above, we will also perform a system based evaluation of our equipment maintenance, cleaning, and sanitization procedures related to (b) (4) *components. This evaluation and an associated project plan for corrective actions will be completed by 30-Sep-2008. Furthermore, we will update SOP 286-314X "Corrective Action/Follow-Up (CAFU) Management Procedures" and SOP 262-137X* (b) (4) (b) (4) *" to include a review and approval by the next level Quality management of any corrective action that has changed. The procedural updates and associated training will be completed by 31-Mar-2008.*

30. Written procedures are lacking for the use of cleaning and sanitizing agents designed to prevent the contamination. Specifically, SOP 204-608X, (b) (4), (building (b) (4), including PedVax bulk operations), does not provide a frequency for performance of the multi-step decontamination with (b) (4).

Response 30: *The observation is correct in that SOP 204-608X* (b) (4) (b) (4) *" does not specify a frequency for the routine application of a sporicidal agent (e.g.,* (b) (4) *However, the SOP 204-608X does specify the circumstances following which a decontamination procedure with a sporicidal agent should be conducted (e.g.,* (b) (4) *etc.). Nevertheless, we agree that our cleaning and disinfection program should be enhanced by including an application of a sporicidal agent routinely in addition to the current event driven requirements. As a result, we will update SOP 204-608X to include this requirement by 20-Feb-2008.*

Additionally, we will conduct a systems review of our other processing areas throughout manufacturing operations to ensure disinfection procedures include a pre-determined frequency of routine decontamination with a sporicidal agent. This systems review will be completed by 31-Jul-2008.

31. Written procedures are not followed for the maintenance of equipment used in the manufacture, processing, packing or holding of a drug product. Specifically,

A. Work order 1400076 dated 8/29/2007 was issued for the 6 month maintenance on the PedVax (b) (4) tank (b) (4). The work order required a check of the condition of the (b) (4). 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 9/9/2007 was issued for the annual maintenance of the PedVax (b) (4) pump on skid (b) (4). The first (b) (4) inspections listed on the work order were documented as "NA". However, there was no documented reason for the failure to complete these activities.

Response 31: *Preventive Maintenance activities are documented in the site's work order system. The instructions on these documents, include steps which are conditional*

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based on the "as found" condition of the equipment. In the two specific examples cited in this observation, the mechanics' actions were appropriate, were reviewed by the supervisors, and were documented at the time of the event. Additionally, both the supervisors and the mechanics appropriately placed an "N/A" next to the conditional steps in the work orders.

However, we agree that the rationale for placing an "N/A" next to the conditional steps that are not executed was not adequately explained on the work orders. This is supported by our review of these events with our mechanics subsequent to the inspection, where we determined the root cause was the lack of specific instruction in the work orders.

In order to enhance our preventative maintenance system, we will take the following actions:

- *Communicate this observation, these findings and actions to all Maintenance personnel. This communication will reinforce the principles of cGMP documentation as well as the need for a documented rationale for decisions surrounding the execution of maintenance work. This was completed on 01-Feb-2008.*
- *Document the rationale for all steps on Work Orders 1400076 and 1415800 where an N/A was placed. This was completed on 01-Feb-2008.*
- *Train all maintenance personnel on proper cGMP techniques for documenting the rationale for job steps which are conditional. This will be completed by 03-Mar-2008.*
- *Enhance the instructions in all cGMP Preventative Maintenance work orders to include a specific decision tree to assist the mechanic in documenting the rationale for not performing conditional work. Updates to the work order instructions will begin immediately and be completed site wide by 01-Jul-2009.*

Below is our response to each of the individual observations.

Response 31A: *In Work Order 1400076, dated 29-Aug-2007, the mechanic recorded "N/A" for the step to "check condition of (b) (4) ". The mechanic checked the (b) (4) (b) (4) pressure, found it to be acceptable, and recorded the (b) (4) pressure in the notes section of the work order. This information was not referenced as the justification for the step which was noted as "N/A". The verification of the (b) (4) pressure satisfied the requirement to "check condition of (b) (4) and as such, the step was actually completed. We agree, however, that the rationale should have been documented. As such, this was completed on 01-Feb-2008.*

Response 31B: *Work Order 1415800, dated 09-Sep-2007, has conditional steps to perform a mechanical inspection as well as steps to rebuild the pump. The mechanic reviewed the job plan with the Maintenance Supervisor and determined that steps (b) (4) for rebuilding the pump were not required. After completion of the remaining steps of the mechanical inspection, the mechanic did not identify any deficiencies that would require the pump to be rebuilt. This decision was reviewed with the mechanical supervisor prior to the equipment being placed back in service as documented by the supervisor's initials on the work order. We agree, however, that the rationale should have been documented. As such, this was completed on 01-Feb-2008.*

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32. There is no data to support the (b) (4) post SIP hold for (b) (4) tanks. Specifically, (b) (4) (b) (4) Hold time for Tank / Skid systems in (b) (4), Building (b) (4), Department (b) (4), dated 8/27/07 is inadequate in that media challenges from tanks in (b) (4) used to support (b) (4) SIP hold were not equivalent to the PEDVAX processing tanks. Specifically, the tanks used in barrier operations are (b) (4) (b) (4) (no penetration) and Pedvax tanks are (b) (4) Additionally, the tanks used in Pedvax production include assemblies that are connected to the tank and (b) (4) sterilized in place.

Response 32: *It is important to note that a validation assessment of the (b) (4) hold time was completed in July 2006. It concluded that media challenges from tanks in (b) (4) support a (b) (4) hold for the PedvaxHIB® processing tanks. The assessment and rationale were documented in a memo: (b) (4) (b) (4), Building (b) (4), Department (b) (4), dated 03-Jul-2006. This memo was revised and re-issued 27-Aug-2007 as referenced in the observation. The conclusion supporting the (b) (4) hold time was based on a comparison of the (b) (4) tank systems. In particular, the fact that: 1) the tank designs are similar (b) (4) (b) (4); have similar fittings, and have same materials of construction) and 2) the sterilization and use procedures are similar (both are (b) (4) and are (b) (4)).*

Based upon the feedback from the Investigator, we agree that there are sufficient differences in the details of the (b) (4) systems to warrant a more robust demonstration of the post-SIP hold time for the PedvaxHIB® processing tanks. We will perform a media challenge study in the PedvaxHIB® processing tanks designed to challenge and define a maximum post-SIP hold time. This study will be completed prior to the manufacture of the next commercial batch of bulk PedvaxHIB®. Target completion is expected to occur by 30-Apr-2008.

Although additional data will be generated to support the post-SIP hold times, we believe that the existing hold times are appropriate based upon the following: 1) The (b) (4) tanks are held under (b) (4) following SIP; 2) The tanks are designed for (b) (4) and are (b) (4) (b) (4); 3) The majority of the (b) (4) tanks are used for non-sterile processing or for processing materials that subsequently undergo sterilization (b) (4) in the manufacturing process (e.g., (b) (4)); and 4) As indicated in the July 2006 memo, the tanks are similar to the (b) (4) tanks that have been challenged with a (b) (4) hold time.

In addition to revalidation of the hold time for the PedvaxHIB® tanks, the other (b) (4) tanks will be re-assessed to ensure that the equivalence assessments in the referenced position paper are scientifically sound. The assessments will include a detailed documented comparison of the (b) (4) an itemization of the (b) (4), a comparison of the storage conditions (e.g., (b) (4) and a comparison of materials of construction. All the assessments will be reviewed for technical robustness and completeness by an outside consultant that is an expert in SIP system validation. Action plans will be

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developed, as necessary, to address any enhancements identified. The assessments and action plans, as necessary, will be completed by 30-May-2008.

Additionally, this observation, response, and all key learnings will be directly shared with (b) (4) Validation personnel to emphasize that validation assessments must be robust, scientifically sound, and well documented. This will be fully completed by 14-Mar-2008. An SOP will be developed and implemented governing equivalency assessments so as to assure technical oversight, robust documentation, and consistent principles. This SOP will be implemented by 31-Jul-2008. In addition, an SOP will be developed and implemented providing technical guidance for equivalency of tanks in regard to post-SIP hold times (e.g., (b) (4) This SOP will be implemented by 31-Jul-2008.

33. Single use vent filters (e.g. (b) (4) etc.) used as sterileboundaries across manufacturing areas including bulk bacterial vaccine, bulk viral vaccine and formulation/filling operations are not integrity tested.

Response 33: *With the exception of vent filters, all other process filters at a sterile boundary are integrity tested. Additionally, robust controls are in place for vent filters that include the utilization of pre-use integrity tested redundant series filters. In May 2007, we identified the integrity testing of (b) (4) vent filters as an area for enhancement and implemented a project in September 2007 to ensure that all (b) (4) vent filters will be integrity tested pre-use (by the vendor) and post-use (by Merck). The project plan and progress to date were shared with the Investigator and include the following:*

- *Defined the project requirements and strategy.*
- *Project plan for Phase (b) (4) (b) (4) was approved on 14-Sep-2007.*
- *Project Plan for Phase (b) (4) (b) (4) was approved on 02-Nov-2007.*
- *Implementation is being rolled out in a phased approach targeted to begin no later than 31-Mar-2008 for the first manufacturing facility. The final rollout will include all manufacturing facilities at West Point that use (b) (4) vent filters and is targeted for completion in 12-Dec-2008. The final roll-out will encompass (b) (4) manufacturing facilities, all of Merck's vaccine products manufactured at West Point, and, according to project estimates, in excess of (b) (4) integrity tests (b) (4)*

As detailed above, all other process filters at a sterile boundary are integrity tested. The vent filters had not been tested previously because the controls in place are robust. Manufacturing Operations employs the following controls with respect to vent filters in order to ensure that they are suitable for use:

- (b) (4) *filters* (b) (4) *must be used.*

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- *Filters are pharmaceutical grade with vendor confirmation that filter validation testing was satisfactorily completed.*
- (b) (4) *of the filters undergo pre-use integrity testing.*
- *Life-cycle studies have been performed to demonstrate filter integrity is maintained after repeated sterilization cycles at temperature and time conditions in excess of typical operational conditions.*
- *Monitoring of sterilization temperature and dwell times is performed, and if an Out of Specification occurs with either parameter, the filters will be discarded.*

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.

Response 34: *The primary purpose of the can database (referred to as (b) (4) DB in our procedures) is to document the unique identifier (serial number) for each can, the date tested, and is the repository for (b) (4) test results (pass/fail). For the (b) (4) cans managed within our inventory, each can must undergo a (b) (4) test. The (b) (4) test is conducted after each use of a can in manufacturing and is a requirement for lot release as per SOP 286-304 (b) (4) (b) (4) ;".*

We acknowledge that the can database contained a limited number of inaccurate data associated with can tracking status due to data entry errors. While we have already corrected these inaccuracies, it is important to note that these data are a tracking tool only and not the information used for product release. Furthermore, we have verified that none of the data entry errors impacted the (b) (4) test results or resulted in the incorrect use of cans within our manufacturing areas.

To aid in managing the large inventory of cans, the (b) (4) DB is also used for tracking of the can status. In addition to the (b) (4) DB, we have a series of SOPs that provide procedural controls relating to can status. Specifically, SOP 287-118X (b) (4) (b) (4) " details that every can that satisfactorily completes (b) (4) testing is affixed with a (b) (4) that indicates that a can has passed (b) (4) testing and may be assembled for sterilization and use. At the conclusion of each use, a (b) (4) is physically affixed to the can indicating that the can has completed use in manufacturing and that the can requires cleaning and post-use (b) (4) testing. In addition, each stainless steel can is permanently etched with a unique serial number. The serial number of each can used in a given process is recorded in the batch record as well as in the Can DB per SOP 287-111X (b) (4) – (b) (4) Lastly, SOP 286-304 (b) (4) (b) (4) " requires verification at the time of product release that post-use testing is satisfactory (i.e., (b) (4)) for the harvest and/or dispensed cans used to manufacture a given lot prior to product release.

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A thorough investigation into the root cause for these errors has been completed and corrective actions have been identified to improve the accuracy of the entries into the can database. To ensure our systems are robust, the following corrective actions will be implemented to address the causes of the inaccuracies:

- *SOP 227-150X (b) (4) " and SOP 287-118X (b) (4) " will be updated to clarify roles and responsibilities and to update the administrative functions performed by the can management team. The revision of the procedures and corresponding training of appropriate personnel will be completed by 04-Apr-2008.*
- *The appropriate personnel will be re-trained by 04-Apr-2008 on SOP 287-111X (b) (4) (b) (4) ".*
- *Routine data audits of the database will be conducted for the database. SOP 227-150X (b) (4) " will be updated by 04-Apr-2008 to include database auditing procedures.*

LABORATORY SYSTEM

35. CP 9110.735, (b) (4) Assay for Phenol in Bacterial Vaccines, dated 18 August 2006, uses a (b) (4) . SOP 160-QP-353X, states that it is the responsibility of all laboratories to have an effective system in place to ensure that all prepared reagents, solutions, and media are prepared and labeled properly. The analyst who performed the (b) (4) assay on 14 November 2007 prepared the (b) (4) 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.

Response 35: *We acknowledge that although all West Point Quality Control Laboratories have procedures in place to ensure solutions are labeled appropriately, the analyst failed to follow the instructions within the approved departmental standard operating procedure, SOP 160-QP-353X "Solution Preparation, Expiry and Labeling Procedures". Immediately upon recognition of the observation during the laboratory tour, the analyst corrected the label on the solution to reflect the appropriate preparation date. A process is in place for second person review, and we fully expect that this process would have identified the error. We clearly understand that proper documentation during testing is a cGMP requirement and must be followed. The analyst was disciplined as a result of not following the procedure. In addition, all West Point Quality Control Laboratory personnel that conduct testing and second person review will be provided specific training concerning this particular observation, the response, and the departmental SOP. Training will be completed by 03-Mar-2008.*

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36. CP 9110.718, Molecular Size Analysis of the Pneumococcal Polysaccharide Samples Using (b) (4) dated 22Aug05, was re-validated for serotype 4 on 05Oct99. The validation report contained a commitment to qualify the remaining (b) (4) serotypes. Qualification of serotypes (b) (4) was completed and summarized in a May 2000 report. Observation V.8 from the previous Level 1 inspection (2/7-24/2006) noted that the remaining serotypes (b) (4) were not qualified for use in this assay. Although the firm did provide a report (dated 26May06) summarizing the qualification of serotypes (b) (4) for use in CP 9110.718, serotypes (b) (4) (b) (4) have yet to be qualified.

***Response 36**: We wish to clarify this observation and actions to detail the entire history of actions taken with respect to the method validation and subsequent qualification of the serotypes associated with CP 9110.718 "Molecular Size Analysis of Pneumococcal Polysaccharide Samples Using (b) (4) ". It is important to note that method validation was performed utilizing the (b) (4) in both our research (1996) and QC laboratory (1999) and that a three lot qualification of all serotypes has been performed as of May 2006. (See Table 1.)*

Table 1: Number of Batches of Each Serotype

Serotype	*Qualified in MRL Oct-1996*	*Qualified in MMD May-2000*	*Qualified in MMD May-2006*
(b) (4)			

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It was our understanding that in 2006 the Investigator's concern was with use of only (b) (4) batches for the qualification of Serotypes (b) (4). We committed in our response to the Team Biologics 2006 observation to test a (b) (4) batch for each of these (b) (4) serotypes by 01-Jun-2006 to complete the qualification. The "Report for Supplemental Sample Qualification in Control Procedure 9110.718 for Pneumococcal Powder Types (b) (4)", which was dated 24-May-2006 and approved 25-May-2006, was provided to the Investigators during the 2007 inspection. Therefore, we believed that our written commitment to Team Biologics observation fully addressed the Investigator's concern.

Only during the most recent inspection did we learn from the Investigator that the expectation was to re-qualify any serotype that had been solely qualified in our research laboratory. It is important to note that our research laboratories and the production laboratories utilized the same method validation and qualification requirements. Additionally, system suitability and validity requirements are performed routinely as part of the testing requirements. Therefore, we maintain that the method validation and qualification already performed are appropriate.

However, unrelated to this specific issue, we have initiated an evaluation of enhanced chromatography columns. As such, the (b) (4) will perform a (b) (4) lot qualification of all serotypes utilizing the new column technology no later than 15-Dec-2008.

37. Preservative-free RECOMBIVAX HB® Reference Standard Lot 1571L is stored at (b) (4) in 45A/2504. Each box of 10 single dose, 5 µg/0.5 mL 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 (b) (4) 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.

Response 37: *As part of the (b) (4) review of the performance data for the RECOMBIVAX HB® working reference standard, data are reviewed to determine if they support expiry extension. As part of this review, the performance of the working standard is evaluated as compared to the master standard. During the 2007 analysis, this master standard data point was under investigation and not available for use in the analysis for expiry extension.*

Pending resolution of the investigation into the cause for the invalid four year stability time-point associated with the master standard used for qualifying working standard Lot 1571L, we completed an evaluation of the stability of the working standard using prospectively defined, alternate scientific criteria. Alternate criteria included: a) evaluation of the historical performance of the positive control in the antigen assay (CP 9110.577), b) evaluation of the historical slope and Y-intercept parameters in the antigen assay, c) evaluation of the historical performance of the positive control in the IVRP assay (CP9119.780), and d) evaluation of the historical slope and Y-intercept

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parameters in the (b) (4) assay. The use of these two assays, which are measuring different attributes, allowed us to rigorously assess the stability of the reference standard by two independent means. In all cases, these analyses demonstrated that there is no change in the performance of this material within the previously established control limits. Based on the data from these analyses, we concluded that the reference standard is stable and remains suitable for use. Although the data support expiry extension of greater than six months, a more conservative, interim six month extension was approved based upon this data analysis and in accordance with SOP 129.022 (b) (4) (b) (4) (b) (4) pending completion of our stability investigation.

Although the identified criteria were prospectively defined in this extension, our SOP regarding extension of expiry periods for biological critical reagents is not explicit with regard to this requirement. To further enhance our Quality System, we will update SOP 129.022 (b) (4) (b) (4) to require prospective definition of the extension parameters. Additionally, this SOP will be amended to require a protocol if any reference standard requires a dating extension. Any deviations to this protocol will require the review and approval of (b) (4) senior management and Quality Operations Laboratory senior management. Notification will also be provided to the Vice Presidents of (b) (4) and West Point Quality Operations. The SOP updates, approval, and training will be completed by 06-May-2008.

Further discussion of our evaluation is provided below:

Regression Analysis of (b) (4) in CP9110.780 ((b) (4) Assay)
CP9110.780 positive control data are shown in Figure 1. The solid line indicates the linear regression analysis of the (b) (4). The associated (b) (4) is shown in the table below. These data support the conclusion that the RECOMBIVAX HB® Reference Standard Lot 1571L has been stable and continues to maintain the critical performance characteristics required for use.

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(b) (4)

(b) (4)

Figure 1: Regression Analysis of (b) (4) ***Data in CP9110.780***

Historical Reference Curve (b) (4) ***Values in CP9110.780***

Performance of the RECOMBIVAX HB® Reference Standard Lot 1571L was evaluated by analysis of (b) (4) *data generated by CP9110.780. Regression analysis results shown in Figure 2 indicate that no significant trend over time was observed* (b) (4) *was demonstrated to be* (b) (4) *These data support the conclusion that the RECOMBIVAX HB® Reference Standard Lot 1571L has been stable and continues to maintain the critical performance characteristics required for use.*

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(b) (4)

(b) (4)

Figure 2: Historical Reference Curve (b) (4) Values in CP9110.780

Historical Slope Curve Parameter in CP9110.780

In addition to the evaluation of the (b) (4) and Reference Curve (b) (4) value in CP9110.780, the RECOMBIVAX HB® Reference Standard Lot 1571L performance was also evaluated by trending the reference standard curve (b) (4). Figure 3 shows the regression analysis from this monitoring process with all test data measured through 11-Jan-2008. The slope values are performing within the established (b) (4) (b) (4) Control Limits which are used for release testing to ensure that the test is valid and the material is appropriate for release. We acknowledge that there appears to be a trend in the slope over time. However, by extrapolation of the current slope, it will require approximately (b) (4) before the lower control limit is reached which is beyond the six month interim extension. The current evaluation demonstrates continued stability and acceptable performance of RECOMBIVAX®HB Reference Standard (Lot 1571L).

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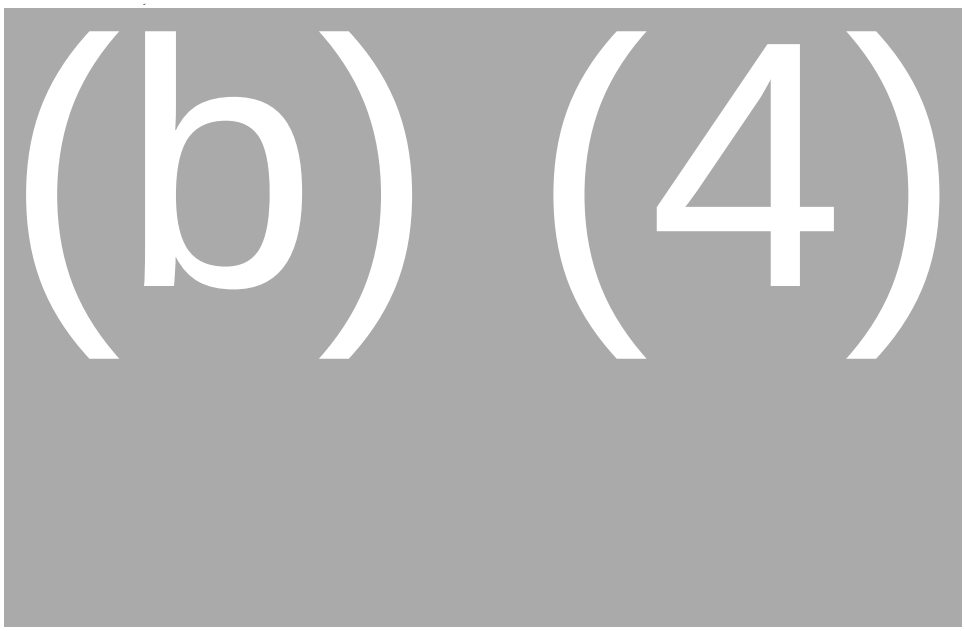

Figure 3: Regression Analysis of Slope Data in CP9110.780 for Data through January 2008

Upon availability of the Master Standard stability data time-point (targeted for 08-Apr-2008), we will conduct a full evaluation by 30-Apr-2008 of the expiry date for Lot 1571L from the November 2006 and November 2007 extensions using the parameters shown below:

38. Pneumo Antiserum Type 11A/758 polyvalent standard is purchased from (b) (4) for use in CP 9110.758, Pneumococcal Polysaccharide Identity and Quantification by Rate Nephelometry with Correction for Residual Concentrations, dated 13 July 2007. No expiration date is assigned to this antiserum.

Response 38: *As part of our Quality Management System, re-evaluation dates have been established for all critical reagents, including PNEUMOVAX® 23 Antiserum Type 11A/758 polyvalent standard. The re-evaluation dates for this antiserum, as well as other PNEUMOVAX® 23 antisera, were assigned based on a literature review of typical storage conditions for polyclonal antisera.*

Based on our discussions with the Investigators, we would like to offer clarity with regard to the terminology used in this observation, specifically, expiration date and re-evaluation

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date. Based on (b) (4) (b) (4) " the term expiration date is used for drug product and cannot be extended through re-test. Re-evaluation or retest date is used for drug substance and can be extended through additional testing. We believe re-evaluation dates are more appropriate for critical reagents unless data demonstrate that the reagent is no longer appropriate for use. In those limited cases, an expiry date is set.

Effective 22-Feb-2008, we will establish the (b) (4) re-evaluation date on Type 11A antiserum based upon the data from (b) (4), which supplies the PNEUMOVAX® 23 antiserum Type 11A, as well as all other PNEUMOVAX® 23 antisera. The supplier has stability data to support (b) (4) dating period at (b) (4) conditions. Furthermore, we will implement (b) (4) re-evaluation dating for all other types of PNEUMOVAX® 23 antiserum by 21-Apr-2008.

39. (b) (4) testing for (b) (4) is performed by MRL. The sample receipt tracking system for MRL is (b) (4). On 26 November 2007, (b) (4) was logged in as Pedvax Protein instead of (b) (4) testing. Pedvax Protein is not performed by MRL.

Response 39: *In this observation, the Investigator noted that a sample of (b) (4) (b) (4) incorrectly was logged in by a technician in the testing laboratories (Merck Research Laboratory).*

It should be noted that this human error did not compromise the integrity or identification of the sample, as it was stored in the appropriate conditions (b) (4) within the correct walk-in refrigerator but was placed in the incorrect testing bin. The technician involved with this error was informed of the observation during the laboratory tour and immediately corrected the log book and sample location.

To address this observation, all technicians involved in logging samples into the central pharmacy area were retrained by 30-Jan-2008 in appropriate log in expectations to increase awareness and prevent recurrence. Additionally, SOP SA-2404 for "Receipt and Registration of Test and Control Articles", will be revised and training completed by 29-Feb-2008 to include additional clarity on interpreting laboratory test sheets and appropriate log in procedures.

40. MRL is responsible for CP 9110.732, (b) (4) (b) (4), dated 02 May 2007. This procedure takes a total of (b) (4) to perform. Three analysts (b) (6), and (b) (6) 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.

Response 40: *Although there is not one single SOP that describes training specifically for Control Procedure (CP) 9110.732 "Haemophilus B Conjugate Vaccine and Haemophilus B Conjugate and Hepatitis B Vaccine" in its entirety, it is important to note that all technicians in question were current in their training on each individual aspect of the testing procedure for this assay (i.e., sample preparation, (b) (4) (b) (4)). Training on these procedures was conducted as per the Safety Assessment SOP for training "Maintaining SOP Training*

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Records and Documenting Training, SA-0005" as well as the Biologics Release Testing & Immunotoxicology Policy for training entitled, "Training Policy and Requirements for (b) (4) *. Training for all employees was documented in their individual training files.*

We acknowledge the Investigator's concern with how training for CP 9110.732 was documented. As part of the transfer of the in-vivo testing from the Manufacturing Division's laboratories to the Research Division's laboratories, the practices regarding training documentation were changed to better align the two laboratories. Historically within the research's laboratories, testing analysts were trained based on specific elements of the assay. To be consistent with the manufacturing laboratories' procedures, the research laboratory introduced a (b) (4) *approach to training in which the testing analysts were now required to sign off indicating that they have done the following:* (b) (4) (b) (4) (b) (4) *a* (b) (4) (b) (4) *. All of these phases are documented individually, and all require some amount of time to complete. The training coordinator considered that since the personnel in question (i.e., with the initials* (b) (6) (b) (6) *had all been previously trained under the historic research laboratory's program, they were considered trained on the control procedure, and the coordinator had them all sign off on the training as of the first day of the* (b) (4) *day assay. In retrospect, this documentation of the training was not appropriate. As a result of this event, we will review all training records associated with the laboratory transfer and to ensuring that all training has been completed and is appropriately documented by 30-Apr-2008.*

While it is accurate that at the time of the inspection, a document describing training specifically for Control Procedure CP 9110.732 was not in place, separate procedures existed which described the individual tasks required to perform CP 9110.732. As a result of alignment with the manufacturing laboratories' procedures, we are enhancing the clarity regarding required training by instituting the following by 31-Mar-2008: a training module that contains detailed background, assay information, a list of SOPs, and other documents to be reviewed, and a training checklist for this control procedure. We will also be instituting similar training modules for other Control Procedures by 15-Dec-2008.

With respect to assessing the competency of individuals trained on (b) (4) *procedures via* (b) (4) *test results, we would like to emphasize that we believe the primary means of assessing an individual's competence is best assured by the following:*

- *The individual must have documented evidence of completion of the required training set forth above.*
- *The technical ability of each individual is evaluated by an experienced trainer.*
- *The trainee is not permitted to conduct a test independently until the experienced individual indicates they are adequately trained.*
- *With each assay performed, a positive control is also prepared that acts as a direct measurement of the acceptability of the* (b) (4) *portion of the assay. Therefore, we*

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have continual monitoring of the overall performance of the testing analysts on a per assay basis.

Based upon the assurances described above, we believe that these controls ensure that our training is effective.

41. MRL is responsible for CP 9110.732, (b) (4) (b) (4), dated 02 May 2007 and CP 9110.003, (b) (4) Test, dated 26 May 2006. Worksheets for these assays are not controlled in that:

A. (b) (4) Test (TT# 07-2007) was initiated on 18 May 2007 using CP 9110.003 Revision #32. Data are recorded on worksheet #003. The analyst crossed out #003 and replaced with #002.

B. Worksheet #002 of CP9110.732 Revision #5 was used for (b) (4) Test (TT#07-2040) initiated 18 July 2007 and (b) (4) Test (TT#TT-2078) initiated 11 September 2007.

***Response 41A and 41B**: It is important to note that in both cases referenced in the observation, all testing was completed accurately and all data were reviewed and found to be acceptable. There were no testing anomalies as a result of the worksheet errors.*

To address the observation, all personnel were retrained in the expectation for proper documentation associated with the control and use of controlled work sheets by 31-Jan-2008. The actions below will be fully documented in SOP SA-0021 by 29-Feb-2008:

- *The person responsible for maintaining the controlled worksheets will (b) (4) (b) (4).*
- *(b) (4) are present and accurate.*
- *The worksheet information will be recorded (b) (4) (b) (4) the date distributed, and the status of the worksheets) on a tracking sheet.*
- *(b) (4) will retrieve pre-printed worksheets for use on a particular test (b) (4) (b) (4) on which the worksheets are to be used on the tracking sheet.*
- *Before the study packet is sent to archives, the (b) (4) will verify which worksheets were used on that study and will record this information on the tracking sheet.*
- *Upon revision of a particular worksheet, all unused worksheets will be returned and destroyed and new worksheet numbers assigned and distributed as above. The numbers of the destroyed worksheets will be recorded and accounted for on the tracking sheet.*

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This procedure, SOP SA-0021, will remain in place until all MRL controlled worksheets utilized for (b) (4) release testing are migrated into either: (1) the current (b) (4) system within the QC Laboratory or (2) a cGMP-validated electronic data capture system.

Both systems are currently being evaluated, and we will have a system chosen by 30-Jun-2008 and implemented by 30-Sep-2008.

42. Pedvax Bulk has Out of Long Term Static Process Capability Limits (LTSPCL) for Aluminum of (b) (4). These limits do not reflect the current manufacturing process. APR 2007-160S-0014 was initiated on 26 February 2007 due to Pedvax Bulk Lots 2118609-7, 2118895-2, 2118895-3, 2118895-4, 2118895-7, 2118895-9, and 2118896-9 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.

***Response 42**: We understand the concern from this observation to be that the current Long Term Static Process Capability Limits (LTSPCLs) for aluminum content in PedvaxHIB® bulk do not represent the current manufacturing process, as identified in investigation APR 2007-160S-0014. The investigation evaluated production data from the (b) (4) lots made after implementation of the changes listed in the observation and determined that a shift in process capability had occurred as a result of these changes.*

LTSPCLs are alert limits that provide an additional level of process control oversight. According to SOP 283-346 "Test Data Analysis for (b) (4) Product Reviews", which was effective at the time of the investigation, at least (b) (4) lots are needed to update LTSPCLs in order to capture process variation. LTSPCLs were not updated at the time of the investigation because data were available from only (b) (4) lots, and therefore, the investigation assigned a Corrective Action / Preventative Action (CAPA) to update the LTSCPLs when sufficient data were available. This CAPA was also documented in the 2007 PedvaxHIB® Annual Product Review.

During the development of our detailed procedure for managing LTSPCLs in August 2007, we identified that an update to LTSPCLs could be delayed if a sufficient number of batches were not available. Our draft procedure from August 2007 was shared with the Investigator during the inspection. The approved version of SOP 240-111X (b) (4) (b) (4), which became effective on 17-Dec-2007, included a provision to implement a temporary Alert Limit when insufficient data are available for statistical calculation of LTSPCLs. In this event, we believe it would be appropriate to implement temporary process control limits. CAPA VAL-2007-0112 was initiated to implement either a LTSPCL or temporary Alert Limit for PedvaxHIB® bulk by 30-Jun-2008. If a temporary Alert Limit is established, an LTSPCL will be established when a sufficient number of lots are available in accordance with our procedures.

It is important to note that no bulk adsorption lots have been manufactured since the approval and closure of the investigation in April 2007.

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43. Packaged Antivenin Lot 0713P 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 0835F 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 0713P was released on 25 August 2004 and Lot 0835F was released on 09 October 2006. Investigation 2007-223B-0068 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 (b) (4). 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 (b) (4).

Response 43: *We fully recognize the seriousness of this event. This observation was identified and reported to the agency via BPDR 07-008 on 05-Oct-2007. The two subject lots were identified as a result of our ongoing Quality Systems enhancements in August 2007 as having been released to market without all required market package identity tests completed. It should be noted that all other product testing had been completed and all results were within specification. Given the seriousness of this event, a comprehensive investigation was conducted. The review included all sterile products and bulk biologics still within expiry. This review encompassed approximately (b) (4) lots and determined that no other lot of any product was released to the market with a test deletion error.*

As documented in the BPDR, the primary root cause for the missed identity tests was insufficient clarity of release requirements as specified in the Merck Quality Standard for the ANTIVENIN market package. The Quality Standard was not clear in specifying that there are multiple separate identity test requirements for each of the (b) (4) individual components of the market package (vials of (b) (4) (b) (4)) defined in other Quality Standards. In this unique case, multiple identity tests are required in order to differentiate between the ANTIVENIN and the Normal Horse Serum. This lack of clarity led the Laboratory Supervisor and Release Coordinator to conclude that some of the identity tests specified in the (b) (4) (b) (4) were redundant and not required. The tests were incorrectly deleted.

The comprehensive investigation and subsequent testing ensured that there was no product quality impact on either lot. As part of investigation 2007-223B-0068 and as documented in BPDR 07-008, multiple corrective actions were put in place, including correction of any systemic issues in order to prevent reoccurrence.

Specifically, the following actions have been completed.

- *Retain samples of Lots 0713P and 0835F were submitted for identity testing in September 2007 to have the missing tests performed. All results were valid and within specification.*
- *A review was conducted of all ANTIVENIN lots manufactured between 1997 and 2007; no additional instances of missed tests were identified.*
- *In support of this investigation, an extensive assessment of (b) (4) test data for all bulk biologics and packaged lots within expiry was conducted to ensure all release tests were performed. This analysis comprised approximately (b) (4) lots. There were no other lots identified in which tests were incorrectly deleted.*

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- *A new and separate ANTIVENIN market package Quality Standard (QS) was created which contains the specific requirements for the three product vials that comprise the market package. The Quality Standard now is fully aligned with* (b) (4)*. The QS was issued on 12-Oct-2007 with an effective date of 12-Nov-2007.*

- *An evaluation of the* (b) (4) *test rejection process was completed in November 2007 with the following further enhancements targeted for completion by 31-Mar-2008:*

  - *Establishment of a procedure to clearly define who has the authority to delete tests in* (b) (4) *and what documented approvals are required prior to deletion of a test. At a minimum, the procedure will define the following:*

    - *A Laboratory Supervisor will have the authority to delete test replicates (i.e.,* (b) (4) *etc) with concurrence from Laboratory Management.*

    - *Only the Laboratory Manager responsible for Sample Log In will have the authority to delete duplicate log in errors with the concurrence of the Director / Associate Director of the Laboratory.*

    - *Deletion of a release or stability test for a production sample can only occur by the formal change control process in accordance with SOP 266-309X* (b) (4) *Automation Change Control".*

  - *Modification of* (b) (4) *user accounts to restrict access for test deletions to only those individuals as specified in the above procedure.*

  - *Establishment of a report which will summarize all deleted tests and 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.*

As a result of this investigation, we have corrected the items that directly contributed to this error, and we are in the process of aggressively implementing enhanced system controls throughout the site regarding test deletion approval and required documentation. Merck personnel involved in this event fully understand the significance of this error. Through the investigation, we have determined that it was unique in occurrence and not representative of the release systems as a whole.

44. Sterility test failure investigation, 2006-223M-0037, for MMR Re-dispensed Bulk, lot 2115177-7B1, and (b) (4), lot (b) (4), 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 that 2-3 ml of sample spilled onto the floor during the final examination for microbial growth.

Response 44: *In order to address this observation accurately, corrections to specific points within the observation are required.*

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First, Test Failure Investigation (TFI) 2006-223M-0037 only included measles re-dispensed bulk Lot 2115177-7B1 and (b) (4) *Lot* (b) (4) *. It did not include M-M-R®II re-dispensed bulk as indicated within the observation.*

Second, Test Failure Investigation 2006-223M-0037 was closed on 17-Nov-2006 and not canceled as noted within the observation. The test investigation was completed with root cause determination as laboratory contamination due to media leakage beyond closure of the test canisters. The investigation concluded with the issuance of a Sterility Investigation Cancellation Memo, which documented the rationale and invalidated the sterility test failure. As per SOP 286-335X (b) (4) *once the testing laboratory has identified a sterility failure, the laboratory issues a memo to all affected areas, including* (b) (4) *then notifies the* (b) (4) *committee of the failure. If the conclusion of the* (b) (4) *Committee is that the sterility failure is invalid based on an unequivocally ascribed laboratory error,* (b) (4) *will document the findings of the* (b) (4) *meeting and the rationale to invalidate the sterility failure in a* (b) (4) *, which is approved by the Vice President of West Point Quality Operations. It was this memorandum that was issued on 07-Nov-2006 and not the cancellation of TFI 2006-223M-0037.*

Third, although there was no documentation noted on the test worksheet, the observation of leaking media from the canister was noted in the TFI when the investigation was initiated on 14-Jun-2006 and specific statements were included as part of the investigation. Specifically, it is documented within the investigation that an improper seal was visually observed by Laboratory Operations supervision and Laboratory Technical Support [LTS (analytical support scientist)] when the reading technician swirled the test canister and 2-3 mL of medium spilled onto the floor. The SI committee convened on 10-Jul-2006 where the findings of the laboratory investigation that included the leaking canister observation were communicated.

Because the invalidation of any sterility result must go through a formal peer review that includes Senior Quality leadership, the laboratory investigation could not be approved until this review was completed. An interim report extension was initiated on 30-Jun-2006 for the lab investigation that included a statement indicating that the out of specification result was due to a laboratory related issue. A subsequent interim report extension was placed on 25-Aug-2006 to allow for the peer review; however, all final conclusions were finalized within the laboratory investigation at this time. While it is true that the leaking canister was not documented as part of the test data packet, it was clearly included as part of the investigation report in June 2006, as part of the discussion that occurred on 10-Jul-2006 with the (b) (4) *committee, and within the final version of the laboratory investigation report that was issued on 25-Aug-2006.*

Although the observation of the media leakage was evident to several laboratory representatives, it was not recorded on the test worksheet for either of the lots at the time that the failure was observed. Since this investigation, SOP 286-335X has already been updated to include a requirement to document evaluation of test canister integrity on the (b) (4) *worksheet which is part of CP9110.517* (b) (4) *The effective date for SOP 286-335X was 06-Aug-2007. Therefore, it is now a requirement to document any container cracks, leakage, or other observations related to test canister integrity, at the time that the contaminated sample is processed.*

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The observation also makes reference to the time frame that existed between issue identification and final investigation close-out. Effective as of 20-Mar-2008, Quality Operations will track all open Sterility Investigations to further ensure timely closure after all investigation elements are completed.

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.

Response 45: *We acknowledge that CP 9110.001 "Sterility Test Methods" does not formally require documentation of any product or sample preparation anomaly experienced during Sterility Testing. It has been our practice, however, that when a product or sample preparation anomaly is observed, the technician, at a minimum, would raise the issue to their supervisor or group leader within the laboratory.*

While the focus of this observation was specific for Sterility Test Methods, anomalies concerning product samples apply to all testing conducted within Laboratory Operations. Therefore, SOP 160-QP-355X "Documentation of Test Information in Laboratory Notebooks and on Testing Data Forms" will be updated to add clarity on the types of anomalies to be documented. This SOP will also be cross referenced to all departments within Laboratory Operations. The SOP update and associated training will be completed by 04-Apr-2008. This SOP will be included as part of each testing technician's training curriculum by 25-Apr-2008.

46. The Control Procedure (CP9110.551) for performing plaque assays to measure Varicella potency in the (b) (4) Laboratory and training of the staff to perform this procedure are deficient. Specifically,

A. There is inadequate monitoring of (b) (4) culture plates prior to inoculation with virus. Up to (b) plates are examined per set of (b) (4) 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 (b) (4) for at least (b) (4) cell confluence and (b) (4) 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 (b) (4) 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.

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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.

i. The (b) (4) estimation for voiding (b) (4) 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.

Response 46: *As a result of this observation, Control Procedure (CP) 9110.551* (b) (4) (b) (4) *" will be revised to include detailed directions to examine a larger sampling of plates selected from across the plating process. To ensure that a sufficient number of plates are examined and provide a comprehensive overview of the entire test, at least* (b) (4) *plates per incubator tray will be examined* (b) (4) *for cell confluence prior to inoculation. This correlates to at least* (b) (4) *of the plates within each assay. Further, the plates observed will be selected from multiple locations across each incubator tray planted for the test to ensure that plates from the beginning, middle, and end of the plating process are evaluated. CP 9110.551 for the Varicella plaque assay potency will be revised and training will be completed by 08-May-2008.*

Response 46Bi: *As was discussed with the Investigator in greater detail after the laboratory tour, the cell sheet destruction, which was evident on plates present in the laboratory waiting to be counted for plaques, was not caused by damage during refeeding or plate manipulations but was caused by a concentrated area of viral infection, resulting in a cytopathic effect on the sample plates. We confirmed that this conclusion was supported by additional plates in which more dilute preparations of this particular sample were plated and shown to be in the countable range.*

Currently, a detailed training program exists which includes specific instruction on how to conduct all upstream procedural steps including the re-feeding process. Although we do not routinely observe disruption within the monolayer caused by the re-feeding process, we agree that disruption of this layer can be caused by several factors throughout the testing process. As stated within the observation, CP 9110.551 does not specify methods to reduce cell sheet disruption caused by the force of media addition or other factors. In order to continue to improve and adopt recommendations for good cell culture practice, CP 9110.551 will be revised by 08-May-2008 to provide specific instruction on dispensing culture media which will improve the current re-feeding process.

Response 46Ci-iii: *A detailed training program currently exists within the laboratory in which technicians are trained to identify atypical plates that may occur within the testing process. This training program is rigorous and documented and ensures that technicians can determine the difference between viral infection and cell monolayer damage.*

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The job skills training for any new trainee is conducted in (b) (4) phases. The (b) (4) begins with the trainee reading through the Control Procedure followed by a (b) (4) (b) (4) The (b) (4) requires the completion of (b) (4) (b) (4) as Standard Operating Procedures, Quality Standards, or other associated Control Procedures. The (b) (4) (b) (4) (b) (4) During this phase, the trainee does not perform any task without assistance from a qualified operator. The (b) (4) is the (b) (4) the trainee by a (b) (4) . The trainee will conduct all aspects of the procedure independently and must satisfactorily demonstrate proficiency. If the trainee does not perform satisfactorily, the qualified personnel would address the deficiencies in detail with the trainee and provide a repeated practice of the training. Re-evaluation of the training is scheduled immediately following the repeated practice. In the event of (b) (4) unsatisfactory evaluations, the trainee will not be permitted to perform the task.

With respect to the (b) (4) estimation of voiding plates, the technicians conducting testing are trained as described above specifically to determine the difference between plates with concentrated viral infection and cell monolayer damage. For each sample tested within the assay, (b) (4) are performed which target the validated countable range. Since (b) (4) plates are tested (b) (4) , it is not uncommon to observe atypical plates caused by concentrated viral infection. Any atypical plates are voided. However, in the event atypical plates are observed (b) (4) within the same sample, current laboratory practice would require the technician to bring the information to the supervisor's attention which would then require additional follow-up.

We wish to clarify the third part of the observation. CP 9110.551 does provide criteria on how to evaluate stained plates. Specifically, the procedure for examining stained plates states that observations of mold, contamination, excessive drying or voiding for any other reason are to be noted on the assay worksheet.

We agree additional information can be included within the procedure to enhance the criteria for evaluating atypical plates. To assist in plate validity assessments and to enhance the current training program, additional training tools and visual references will be developed and implemented by 25-Jun-2008 to provide examples of atypical plate presentation that should be voided. Visual references to distinguishing features of cell layer damage versus (b) (4) effect will also be included in these training tools. In addition, for routine production samples, if large clearings are observed, the plates will be reviewed by a supervisor in order to determine if a microscopic evaluation is necessary. If determined to be related to mechanical damage due to plate handling, the analysts performing that specific test will be retrained on plate preparation and handling procedures. These specific criteria will be added to CP 9110.551 by 08-May-2008.

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MATERIALS SYSTEM

47. SOP 204-200BX, (b) (4) (b) (4), 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 2118473 is a quarantined bulk lot stored in Building (b) (4) Room (b) (4). This quarantined lot was not separated from work in progress material.

Response 47: *The material in question was not physically segregated, as noted in the observation, as required in SOP 204-200BX (b) (4) (b) (4)." Our review revealed that SOP 204-200BX was not fully aligned with other site procedures. Specifically, site procedures SOP 286-206X "Procedure for Control of Material" and SOP 286-215X (b) (4) state that formal control of quarantined material is managed (b) (4) through our validated materials management system. These procedures also require that (b) (4) material is required to be physically segregated. As such, SOP204-200BX was modified and approved on 17-Jan-2008 to align with the site procedures for the control of material, stating that only (b) (4) material requires physical segregation and that quarantined material will be managed (b) (4) through our validated materials management system.*

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 (b) (4) Sterile Supply Department (b) (4) 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 (b) (4) bags prior to the deviations that identified (b) (4) 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.

Response 48A and 48B: *We understand the need to have a procedure for managing first in / first out (FIFO) utilization of materials within those departments that prepare sterile supplies and equipment. In practice, these departments manage supplies by monthly receipts that are consumed between shipments. Upon receipt, component and supplies material are confirmed to be consistent with what was ordered. Materials are then moved to storage in specific locations for immediate use.*

The West Point Site's Senior Management Team previously identified the management of sterile supplies as an area for enhancement and chartered a project team to develop a Standard Operating Procedure for management of product contact components at the West Point site. A comprehensive project plan was shared with the Investigators during the inspection. The new procedure will require all areas to maintain a list of product contact components stored and used within each area and to utilize the product

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component inventory in a FIFO manner, including appropriate documentation. Each shipment of components will be required to undergo an accountability check upon receipt and components will be stored in a manner that ensures clear visibility of material identification. The systematic approach to this project addresses the storage and issuance of material within all departments storing and issuing sterile supplies including the Sterile Supply department in Building (b) (4). The project also includes establishing a comprehensive product contact component list that includes (b) (4) bags, sterilizing filters, vent filters, and tubing etc. as referenced in the observation.

Implementation of this new procedure with training will be completed in the Sterile Supplies departments by 30-Apr-2008. With respect to other manufacturing departments that directly order product contact components, the procedure will be rolled out in a phased approach with full implementation by 26-Sep-2008.

In regard to the (b) (4) bag utilization referenced in the observation and as outlined in Response 28, we have definitively determined the timeframe that this lot of (b) (4) bags was available for use in production. Despite not having a formalized FIFO system, we were able to determine the timeframe through existing systems, as documented in our atypical report. We do agree that the implementation of updated procedural instructions outlined above will allow us to better investigate and operate with more efficient systems.

PACKAGING AND LABELING SYSTEM

49. Validation of the modified packing configurations using (b) (4) focused on preventing the temperature going below the glass transition temperature of the stoppers and did not address the possible link between (b) (4) and container/closure integrity due to filling line defects.

Response 49: *As previously stated in Response 2, there was a detailed evaluation of the impact of container closure defects after shipment related to the potential ingress of CO_2 into vial head space. This evaluation included various vial/stopper combinations, both with and without overseals, during simulated and actual shipments. The study did not indicate a correlation between CO_2 ingress and any of the various seal conditions. As of 31-Jan-2008, we have found no correlation between CO_2 ingress and filling line defects.*

The validation of modified packing configurations using (b) (4) focused on preventing the temperature in shipping containers from going below the glass transition temperature of the stoppers, identified as the root cause of CO_2 ingress. This validation study demonstrated our ability to maintain the required temperature and time requirements of the product during shipment. As a result, we are able to ensue that the glass transition temperature of the stopper is not reached.

As noted in our response to Observation 2, the overall effectiveness of the modified packaging configuration as it relates to over pressurization is demonstrated at (b) (4) reduction in associated complaints since the implementation of the corrective action.

As stated previously in our response to Observation 6, we will enhance our complaint investigations related to vial over pressurization to include an assessment of the vial's container/closure integrity.

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Stanley Booth
Vice President
West Point Operations

Merck & Co., Inc.
WP36M-4
770 Sumneytown Pike
PO Box 4
West Point PA 19486-0004
Tel 215 652 0316
Fax 215 993 0811

MERCK
Manufacturing Division

13 March 2009

By E-mail and Overnight Courier

Jacqueline Little, Ph.D.
Team Leader, Team Biologics Compliance
U.S. Food and Drug Administration
Office of Enforcement
15800 Crabbs Branch Way, HFC-210/Suite 110
Rockville, MD 20855

RE: 2009 Team Biologics Inspection
Merck & Co., Inc. – West Point, PA
27-Jan-2009 to 12-Feb-2009
Form 483 Responses

Dear Dr. Little:

Enclosed with this letter please find our responses to the FDA Form 483 Observations from the Team Biologics Inspection of our West Point, Pennsylvania facility that was conducted from 27 January 2009 to 12 February 2009. We have thoroughly reviewed each Observation, assessed the system that governs each Observation topic, and provided a response and corresponding action plan, as appropriate.

As discussed previously with the FDA, in 2006 we began a multi-year effort to strengthen our internal Quality Systems. Since then, we have been providing regular updates to the Agency on the work we have undertaken, as well as our progress. Through these efforts, we continue to strengthen our Quality Systems. While our work is not yet complete, we remain committed to meeting or exceeding Agency expectations. During the course of the 2009 inspection, we had the opportunity to review much of the progress that we have achieved. We will continue our focus on improving, among other things, supplier management, component management, environmental monitoring, change management, and deviation management.

Merck Senior Management, as well as the West Point site leadership team, remains engaged in these efforts and is very supportive. In addition, we continue to utilize several external consultants, including (b) (4) and (b) (4) to help guide our actions and ensure they are commensurate with industry standards and Agency expectations.

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Please note that many of the target dates for the actions identified in our response to the Observations have been sequenced with the (b) (4) (b) (4) scheduled for 2Q2009 and 3Q2009. This (b) (4) (b) (4) (b) (4) For this reason, many of our target dates are scheduled for early 2Q2009 or 4Q2009.

While we believe that these responses completely address the Form 483 Observations presented to the West Point site, we would appreciate the opportunity to review, either through a teleconference or a face to face meeting, any instances where you feel that additional action may be required. We will follow up with you in approximately two weeks to ensure receipt of the responses and to determine an agreeable course of action, should additional information be required.

Sincerely,

Stanley D. Booth
Vice President
West Point Operations
215-652-0316

Diana C. Gleaton
Executive Director
West Point Quality Operations
215-652-9316

Enclosure

Copies:
U. S. Food and Drug Administration:
R. Ashley, Consumer Safety Officer
D. Feigelstock, Ph.D., Staff Fellow
K. Campbell, Acting District Director, Philadelphia Office
M. Malarkey, Director, Office of Compliance and Biologics Quality
C. Meseda, Ph.D., Microbiologist, Laboratory of DNA Viruses
S. Norris, Staff Scientist, Laboratory of Bacterial Polysaccharides
O. Osunsanmi, MPH, Consumer Safety Officer
W. Vann, Ph.D., Chief, Laboratory of Bacterial Polysaccharides

Merck & Co., Inc.,
M. J. Angelo, Ph.D., Sr. Vice President, Quality and Compliance
R. T. Clark, Chairman, President & CEO
W. A. Deese, Executive Vice President and President, Merck Manufacturing Division
W. J. Mullin, Vice President, Global Vaccine and Sterile Quality Operations
J. T. McCubbins, Ph.D., Sr. Vice President, Global Vaccine and Sterile Operations

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1. SOP 227-154X, Automation Change Control was not followed to ensure proper notification, tracking, and documentation of changes to maintain the automated system's state of control. For example,

   A. (b) (4) Gardasil lots 1704U, 1647U, 1648U, 1694U, 1693U, and Recombivax lots 1556U, 1624U, 1575U, 1646U, and 1425U were impacted by this deviation. The root cause was a Supervisor made a setpoint change outside of Automation Change Control procedures.

   B. (b) (4) . The root cause was (b) (4)

   C. (b) (4)

Response 1: *SOP 227–154X, "Automation Change Control" requires that any change to automated system code must be managed under our change control procedures. For each of the three examples, it is acknowledged that SOP 227–154X was not followed. In each instance, upon our discovery of the incident, an Atypical Process Report (APR) was initiated to investigate the events, and actions were taken to mitigate the chance of recurrence and/or to enhance our detection capability.*

In response to this observation, we have completed a review of all APRs from 30 October 2007 through 28 February 2009 related to automation change control in Barrier (b) (4) *following implementation of the corrective actions identified in the three cited APRs to determine their effectiveness. This review has revealed that there were no new events related to* (b) (4) *It also showed that the corrective action from* (b) (4) *was effective in identifying* (b) (4) *This was the only APR in* (b) (4) *for the time period reviewed and since implementation of the corrective actions.*

The use of SOP 227-154X ensures that there is traceability to the person making a change to (b) (4) *Since this SOP was not followed in the three 2007 APRs noted, there is no direct traceability to the individual involved, as noted in Observation 1, Subparts B and C. In response to the observation and to reinforce the requirement to follow formal change control when any code change is needed for automated equipment, thus ensuring traceability to the person making the change, a Quality Bulletin will be issued to all personnel in West Point Operations by 03 April 2009. The Bulletin will reiterate our requirement to follow change control procedures at all times and will include specific examples of incidents requiring change control. It*

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should be noted that the Quality Bulletin procedure was not in place at the time the referenced deviations occurred, and as such, a broader action across all manufacturing areas was not taken at the time of the investigation. A new SOP 260-302X, "Preparation, Approval, and Communication of Site Quality Alerts, Quality Bulletins and CAPAs", was approved, effective 30 June 2008, and requires consideration of a site wide communication / action to ensure that events or lessons learned from one production area in response to an Atypical Process Report are appropriately applied to other areas. As an additional action, a review of human error related automation APRs generated in other departments from 01 July 2008 to 31 December 2008 will be performed to identify any trends that may require additional action. This review will be completed by 19 June 2009.

As noted in examples in Observation 1B and 1C and as reviewed with the Investigator during the inspection, a listing of all impacted lots was not included in the APR header even though all potentially impacted lots were evaluated as part of the respective investigations described below. SOP 286-125X, "Atypical Process Reports (APRs) in West Point Operations" was updated with an effective date of 14 March 2008 to require that if potentially affected material was not going to be referenced in an APR due to the determination that there was no product impact, a documented rationale for this decision must be approved by a West Point Product Release Director and attached to the APR. This requirement was added to the SOP after the initiation of the subject APRs. As an additional enhancement, SOP 286-125X will be effective by 25 May 2009 to require that all potentially affected lots be identified and included in the APR investigation even if it is determined that there is no product quality impact.

In order to assure all steps are being taken to avoid unintended and unauthorized changes to our automated systems, we will commit to conducting a security and access review for all GMP factory automation systems used in manufacturing and laboratories at West Point.

This assessment will include:

- *Verification that passwords are changed at a documented frequency with rationale for the frequency,*
- *Assurance that the security levels for the systems are appropriate for system use,*
- *Verification that the user access lists are current and are limited to appropriate personnel,*
- *Assurance that sufficient auditing oversight is in place.*

This assessment will be completed by 28 August 2009. The assessment will include action plans and associated timing for any actions identified.

For all systems which require manual password changes, such as those cited in Observation 1, password administration procedures will be effective by 29 August 2009 to require documented evidence that the password for these systems has been updated. For systems with automated password reset capability, the system already requires passwords to be changed at a predefined interval. If the password is not updated, the user is automatically deactivated.

Additional detail on each of the examples cited in Observation 1 is provided below.

Response 1A: *Regarding* (b) (4) *, the investigation indicated that the Operations Supervisor did not follow SOP 227-154X and changed* (b) (4)

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Subsequently, the supervisor (b) (4) *In this case, even though* (b) (4) *. A review of batch records identified that the incorrect set point was in place from 07 October 2007 to 26 October 2007. The impact of the change* (b) (4) *. This review determined that* (b) (4) *. In response to this event, several corrective actions were implemented. We assured* (b) (4) *effective as of 14 December 2007 such that the supervisors did not have access to make changes to the set points. Additionally,* (b) (4)

Response 1B: *Regarding* (b) (4) *. Due to system software limitations, the operator performing the machine set up has access to parameters that are validated as well as those that are configurable, therefore, allowing inadvertent changes to occur.*

All products filled (i.e., (b) *lots) since the validation for each product were considered potentially impacted and evaluated as part of the investigation, and a supplemental validation study with the modified parameters was performed for all impacted products. The supplemental validation study showed that the changes to the program parameters did not affect the inspection machine's capability to detect defects. Additionally, the procedural requirement to conduct acceptable standards challenges on* (b) (4) .

Response 1C: *Regarding* (b) (4)

A review of the event history on the system showed (b) (4) *The* (b) (4) *There* (b) (4) *The corrective action for this event was* (b) (4)

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(b) (4) . *In addition, the automation support staff for the area was re-trained on SOP 227-154X, "Automation Change Control" by 25 May 2007. As a result of this event, the individual responsible for the change was released from the Company.*

The events cited in the observation were raised as deviations, investigated, and addressed through the deviation management process, and resulted in the implementation of additional safeguards to mitigate the chance of recurrence, and/or to enhance our detection capability. As noted previously, we have assessed the effectiveness of the corrective actions deployed in (b) (4) *and have concluded that the corrective actions have been effective. Additional communication to West Point Operations through the Quality Bulletin will reinforce the expectations to adhere to Change Control procedures for automated systems. The review of human error related automation APRs generated in other production areas will allow for us to determine if additional actions above those already specified are warranted. Additionally, our commitment to conduct a security and access review for all of our GMP factory automation systems used in manufacturing and laboratories at West Point will assure all steps are being taken to avoid unintended and unauthorized changes to our automated systems.*

2. The firm observed recurring events of elevated particulate reject rates during automated inspection of lyophilized products. Fifty-three deviation investigations have been initiated since 10/5/06 for stainless steel particles, impacting approximately (b) product lots filled on lines (b) (b) and (b) For example,

i) (b) (4) , Proquad lot 0658584 and lot 0658585.

ii) (b) (4) , Varivax lots 0660941, 0660897, 0660079, 0660563, 0660564, 0660565, 0660566, 0660569, 0660570, 0660571, 0660657, 0660831; rHA M-M-R lots 0660275, 0660581, 0661068; and M-M-R II lots 0660693, 0660694, 0660870.

iii) (b) (4) M-M-R II lot 0662709.

iv) (b) (4) , M-M-R II lots 0660869 and 0661002.

v) (b) (4) , Varivax lot 0661555.

vi) (b) (4) , Black Widow Spider Antivenin lot 0659931.

The firm determined the root cause of (b) (4) The firm rejects vials with particulates that are rejected by the automated inspection systems and which are found to have particulates during (b) (4)

A. There is no assurance (b) (4) The (b) (4) The systems are only (b) (4) There is no assurance (b) (4)

B. There is no assurance (b) (4)

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Response 2: *We understand the importance of* (b) (4) *. To that end, we have in place the following systems to ensure that particulates are identified and/or removed:*

- (b) (4) *We require* (b) (4) *These requirements for visible particulates are aligned with the United States Pharmacopeia (USP) 31 General Requirements Chapter <1> Injections: Foreign and Particle Matter, which require final container inspection of all parenteral preparations to ensure that every lot is essentially free from visible particulates.*

- (b) (4) *: The inspection* (b) (4)

- (b) (4) *For particulate defects, the acceptance criterion is zero in the statistical sample population utilizing ANSI/ASQ Z1.4-2003 tightened sampling plan.*

- (b) (4) *. For particulate defects, the acceptance criterion is zero in the statistical sample population.*

- (b) (4) *: Should a deviation be noted in any of the above described quality control systems, the investigation process ensures thorough investigation for root cause and determination if there is any impact of the event to product quality.*

- (b) (4) *: The* (b) (4) *in alignment with the USP. A review of customer complaints for* (b) (4) *showed that there were no customer complaints in which the analyzed particulate was determined to be stainless steel.*

In addition to the identification and removal of vials containing particulates, numerous corrective actions have been implemented to reduce the generation of stainless steel particulates in the manufacturing environment such as:

- *On Line* (b) *corrective actions, such as* (b) (4)

- *On Line* (b) *a dedicated team was chartered in October 2008 to reduce particulate generation. Corrective actions implemented on Line* (b) *in January 2009 have resulted in zero lots as of 03 March 2009 that have exhibited elevated particulate reject rates following* (b) (4) *.*

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- *On Line* (b) *corrective actions were implemented in January 2009 based on the dedicated team's recommendation. There have been* (b) (4) *Of the lots inspected, none was found to have elevated particulate reject rates.*

The observation notes that investigations initiated since 05 October 2006 involving stainless steel particulates impact (b) (4) *It is important to note that an investigation was conducted for each observation of particulate to investigate root cause and to evaluate the potential impact to product quality of each impacted lot. As part of each investigation cited, characterization of* (b) (4) . (b) (4) *Of the* (b) (4) . *Furthermore, of* (b) (4) . *The fact* (b) (4)

As stated previously, whether the sample particulates were determined to be in the visible range or sub-visible agglomerations, each event was investigated and the potential impact to product quality was assessed. The potential that the particulates are not visually detected and rejected during inspection is considered in each investigation. As such, the documented product impact evaluations of each of the (b) *lots support that there is no adverse impact to product quality. Supporting the determination of impact to product quality are medical assessments that in each case consider sterility assurance, particulate composition, number of particulates, size of the particulates, and method of injection for each potentially impacted product. In each case, the medical assessment determined that the potential risk of medical harm was extremely remote.*

In July 2007, in order to better understand the agglomerates in reconstituted product, a study of M-M-R®II product with stainless steel particulates was initiated (i.e., (b) (4) *Product samples manufactured on Line* (b) (4) *Inspection of the reconstituted vials confirmed that the agglomerates disperse and are no longer visible. The observation that the particulates are* (b) (4) *USP 31 General Requirements Chapter <1>, which requires that lots are essentially free of visible particulates, is consistently met. The absence of visible particulates upon reconstitution meets the USP guidance for demonstrating suitability for reconstituted solutions prior to use.*

A study into the (b) (4) *In a filled product vial, the* (b) (4) *Due t* (b) (4)

As part of our existing quality systems, we will continue to monitor the reject rates associated with particulates and determine whether any additional enhancements to our systems are warranted.

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Response 2A: *We acknowledge that the automated inspection machines used to inspect the final containers of* (b) (4) *. As such, we will develop and implement a procedure to routinely assess reconstituted product for the presence of visible particulates. By reconstituting* (b) (4) *This new procedure will be effective by 13 November 2009 to accommodate updating of site master formulas for* (b) (4)

As part of our overall process enhancement program, West Point Operations is developing the capability to perform (b) (4) *Although* (b) (4)

Response 2B: *There were no stability studies related to the impact of stainless steel particulates provided during the inspection. Following the inspection, an historical stability study from 2001 was identified. We apologize for this oversight.*

Under special stability studies numbered BS0284 and BS0291 for M-M-R®II and VARIVAX® Process Upgrade using lots manufactured in 2001, one lot of each product that was investigated for the presence (b) (4) (b) (4) *Additionally, five of the* (b) *lots indicated in the observation have been placed on stability as part of* (b) (4) *ncluding ANTIVENIN®, VARIVAX®, and ZOSTAVAX®). All tests results are satisfactory through all completed time points. In accordance with SOP 286-125X, "Atypical Process Reports (APRs) in West Point Operations", any future* (b) (4)

Additionally, we have completed (b) (4) *on samples of M-M-R® II and VARIVAX®, (SPTE-P-08-0097 dated 09 December 2008 and* (b) (4) *dated 06 February 2009) that were confirmed to contain* (b) (4) *particulates. Evaluation of these products encompasses each of the viruses (measles, mumps, rubella, and varicella) present in M-M-R®II, VARIVAX®, ProQuad®, and ZOSTAVAX®. All results met the required acceptance criteria, supporting that* (b) (4) *In order to gain additional empirical data, we will place M-M-R® II and VARIVAX® vials which* (b) (4)

3. DIST2005-009, Distribution Performance Qualification on Vial and Syringe Images in the (b) (4) which supports the Gardasil, Recombivax, and Vaqta vial and syringe images. The study for vial images was conducted with (b) (4) packed (b) (4) In practice, the firm ships from (b) (4) . (b) (4)

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(b) (4) . For the shippers (b) (4)

Response 3: *As general background,* (b) (4)

In response to the observational concerns that DIST2005-009 does not support the packaging configuration for (b) (4) *Based on the findings, we will provide additional guidance to the Order Fulfillment Centers concerning the packout of the* (b) (4) *, including additional detail, if required, regarding the combination of the* (b) (4) *Where appropriate, SOPs will be updated at the Order Fulfillment Centers with this detail by 14 July 2009.*

4. Regarding Vaccines Complaint Investigations:

A. The firm's investigations for complaints in which returned samples had cracked vials were insufficient to determine if the cracked vials were associated with vial defects or with vaccine filling, packaging, or shipping operations. The firm observed an increase in complaint rate regarding cracked or broken vials for distributed vaccine products that were manufactured since 10/06. Approximately 152 complaints of cracked or broken vials were received since 1/1/08. No root cause was determined for the increased complaint rate. In the following complaints, customers reported under filled vials and no cracks in the vials were observed by the customer. The firm detected cracks in the returned samples, to include cracks along and behind the label. Multiple complaints of broken or cracked vials had been received against the associated fill lots.

1. Complaint 89473, 6/6/08, the fifth complaint for Gardasil lot 1757U/0659182. The firm observed a crack on the shoulder of the vial, along the top edge of the label. Two vials had thermal stress fracture defects and two of the vials had impact fractures. The firm concluded that these breaks represent the normal random variation of the whole process of providing this product to their customers.

2. The firm did not analyze the following returned products for complaints of under filled vials to determine what type of fracture or failure mode resulted in the cracked vials:

   a. Complaint 68894, 1/7/08, the second complaint for Gardasil lot 1448U/0659653. The firm observed several cracks at the base of the vial.

   b. Complaint 70588, 1/21/08, the third complaint for Gardasil lot 1448U/0659653. The firm observed a small crack in the vial near the bottom of the primary label.

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c. Complaint 73237, 2/14/08, the fourth complaint for Gardasil lot 1446U/0659441. The firm noted a U-shaped crack in the wall of the vial behind the primary label.

d. Complaint 80155, 3/28/08, the third complaint for Gardasil lot 1978U/0659964. The firm observed a crack near the base of the vial.

e. Complaint 82035, 4/14/08, the second complaint for Recombivax HB lot 0627U/0656877. The firm observed solution in the vial and a crack near the heel of the vial.

f. Complaint 83175, 4/18/08, the third complaint for Gardasil lot 1060U/0658556. The firm observed a crack between the heel of the vial and the bottom of the label.

g. Complaint 85577, 5/6/08, the second complaint for Gardasil lot 1757U/0659182. The firm observed a crack on the shoulder of the vial along the top edge of the label.

h. Complaint 97972, 8/4/08, the second complaint for Gardasil lot 0070X/0660553. The firm observed a crack in the vial between the bottom of the label and the heel of the vial.

3. Complaint 102623,9/4/08, the sixth report for Gardasil lot 1978U/0659964. The firm observed a crack between the bottom of the label and the heel of the vial. The firm examined three of the six vials and observed all of the fractures were the result of impact.

B. The Cracked Broken Vials Complaint Reduction Investigation determined that the associated defects were heel and neck fractures, and the majority of the product cartons were in pristine condition. One of the corrective actions implemented (b) (4) The root cause of the cracked and broken vials was not determined to be related to the vial manufacturing process and has not been established to date.

C. Although individual investigations were conducted no formal comprehensive investigation has been opened into 13 complaints received from different healthcare providers in different geographical areas from January 2008 to January 2009 regarding bubble/foaming of Zostavax Vaccine vials upon reconstitution; and for the increase in Zostavax foaming/bubble complaints from (b) (4) versus (b) (4) complaints per Zostavax sold in year 2008. Justification provided for the lack of comprehensive investigation was that the complaints were not considered critical and was not one of the top 5 categories for vials and syringes frequency of complaints received which require that assessments to be performed.

D. Investigations conducted into received complaints of Zostavax vials bubbling/foaming are inadequate and incomplete. For example: The firm stated that the review of the manufacturing documentation revealed no significant observations that were noted during (b) (4) . However, it was noted that (b) (4) The list of the affected

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manufactured bulks and vials lots on the cease release notification included 4 vial lots from the Zostavax received complaints #s 114817, 124960, 127869 and 110320. The (b) (4) noted bubbling, foaming and particulates during manufacture of the Zostavax lot at the following locations:

1. Observations of bubbling particles in the dose check and (b) (4)
2. (b) (4)
3. (b) (4)
4. Observation of particulates (b) (4) .

Response 4A1/A2/A3: *For each cracked or broken vial complaint received by West Point, investigations were performed according to our complaint investigation procedure SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports". As required in this SOP, the following elements were included in the investigations into each of the complaint reports highlighted in Observation 4, Subpart A1, A2, and A3:*

a. *A review and description of the returned complaint sample (when available);*

b. *An examination of all market control retention samples for the packaged lot in question to assess whether a similar defect was present;*

c. *A comprehensive review of supplies inspection, filling, and packaging batch record documentation, release test data, and* (b) (4) *and*

d. *A lot history trend for the final finish (packaged lot) number to determine if there are similar complaints registered against the same package lot.*

Effective 28 March 2008 our procedures were updated to require an expanded lot history trend to assess whether there were complaint reports of cracked or broken vials reported against not only the same packaged lot number, but also the same fill lot. This was implemented as the same fill can be used in multiple packaged lots. Additionally, if our investigation concluded that the broken or cracked vial was attributed to a vendor defect, the lot history trend was further expanded to review any packaged lot that originated from the same vial lot number. This enhancement provided a mechanism to identify trends across product beyond the packaged lot number.

As part of the investigations into broken or cracked vial complaints, the returned complaint (b) (4) *This is required* (b) (4) *For the complaint reports referenced in Observation 4A2, the returned complaint samples were not* (b) (4) *. For the complaint referenced in Observation 4A3, the available returned complaint* (b) (4) *. To address the concerns in Observation 4A in the future,* (b) (4)

To further enhance our investigation into cracked vial complaints and to detect commonalities across the various complaints, a formal protocol for evaluation of cracked vial complaints to

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include the sample analysis above will be developed. This protocol will be incorporated into our complaint investigation procedure SOP 283-316 and effective by 13 May 2009.

Although no specific root cause was determined for the increased broken / cracked vial complaint rate, actions were taken at West Point in response to the level of broken / cracked vial complaints that occurred after October 2006. We convened a team to perform a comprehensive evaluation of broken/cracked vials in 2007, as this was the largest contributor to the overall complaint rate. This investigation (i.e., (b) (4) *"Final Report for Cracked and Broken Vials Complaint Reduction Investigation") included an end-to-end failure mode analysis that included the glass vendor, filling, packaging, and shipping processes. To support this analysis, measurements of force typically experienced by vials during transportation between buildings on the West Point site were taken. Multiple potential failure modes for broken/cracked vials and corrective actions were identified and are summarized in Table 1.*

(b) (4)

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Due to the varying inventories of each specific product, the lag time between implementation of corrective actions in Operations and effect on product in the market place is estimated to be (b) (4) *. The full benefit of these corrective actions is expected to be observed in a reduction of complaints starting in December 2007 and continuing through May 2009* (b) (4) *for broken and cracked vials is performed to assess the dates of manufacture of the complaint lot versus the implementation dates of the corrective actions listed in the table above. Data collected to date demonstrate a gradual decrease in broken/cracked vial complaints. However, a conclusion that the full complement of all actions is sufficiently effective is premature at this time. We will continue* (b) (4) *of complaints for broken and cracked vials. A final effectiveness check will be performed by 17 June 2009 to formally document if the corrective actions implemented to date were effective in reducing complaint rates and if not, to determine next steps to further reduce broken and cracked vials. We will also monitor any new actions implemented that are identified as part of the ongoing broken/cracked vial complaint investigations performed with the enhancements discussed in this response.*

Currently, (b) (4)

Moving forward, (b) (4) *We believe this expanded scope will aid in identifying instances of glass breakage that occur due to specific cause and as a result of normal random variation of the whole process. This system will be developed to aid in: (i)* (b) (4) *This system will be developed and incorporated into the cracked vial protocol discussed above by 21 January 2010.*

Response 4B: *We acknowledge that there was no corrective action implemented at West Point to add the heel defect to our defect sets. While we believe that the manufacturer's in-process controls are the most appropriate place to eliminate the occurrence of such defects (i.e.,* (b) (4)

As indicated in the response to Observation 14, Supplies Inspection will develop a physical defect kit that will be part of the training program for employees performing visual inspection activities of incoming primary packaging components. This kit will include heel cracks.

The container defect sets used for the qualification of the (b) (4) *of filled vials include cracks on the bottom of the vial as well as the vial wall. Based on this, we believe the vial defect sets for* (b) (4) *contain the appropriate defects and no further action is necessary.*

We believe that the implementation of the actions above in Response 4A and Response 4B will enhance the thoroughness of our broken/cracked vial investigations that will aid in the determination of root cause of these complaints.

Response 4C: *As discussed with the Investigator, the West Point Vaccine and Sterile Complaints' Charter was created in 2008 to develop a more robust and structured approach to manage complaint trends. Through this chartered process,* (b) (4) *is reviewed on a* (b) (4) *In*

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2009, the priorities were expanded to include the (b) (4) *complaint types (i.e., approximately* (b) (4) *incoming complaints) and to include emergency complaints. The ZOSTAVAX® foaming complaints did not occur at a frequency to place them in the* (b) (4) *complaint types and are defined as non-emergency complaints in accordance with our procedure.*

As noted in the observation, individual investigations were conducted for each specific complaint report associated with foaming of ZOSTAVAX®. We commit to performing a formal, overarching investigation for all reports of complaints for foaming associated with ZOSTAVAX® by 23 April 2009. As communicated to the Investigator, foaming in ZOSTAVAX® is often observed during vaccine bulk manufacture and is known to be a result of the presence of protein in the medium Phosphate Gelatin Sucrose (PGS) used to manufacture the product. This information will be included in the overarching investigation.

Response 4D: *We wish to clarify that bubbling, foaming, and black particulates were only noted in the* (b) (4) *This skid is used to clean equipment that is used in the manufacture of ZOSTAVAX®.* (b) (4) *was initiated to address this issue and lists the lots associated with the complaint investigations. The* (b) (4) *to ensure that prior to any further distribution of potentially impacted product, the issue was fully understood, the product impact was evaluated, and appropriate controls were in place.*

SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports", requires a review of each APR associated with the complaint lot. This review is currently performed using a report generated from our quarantine system that includes only an abbreviated description of the event. The review of the APRs includes all APRs associated with the lot in the complaint report. If there are no relevant APRs, this is documented in the complaint report. This process was followed for the complaints noted in the Observation.

Our determination that APR 2008-113-0047 was not relevant to the foaming complaints was based on the fact that:

- *The customer did not note any black particulates in the complaint vials, and/or particulates were not visually observed in the returned complaint samples.*
- *The bubbling and particulates in the atypical investigation were only observed in the cleaning solution and not during the actual manufacturing/filling process for the complaint lots in question.*
- *The* (b) (4) *concluded that there was no product quality impact due to the fact that the particulates present in the* (b) (4)

We believe our conclusion remains accurate regarding the lack of relevance of this APR to the ZOSTAVAX® foaming complaint reports. To further enhance the investigation process, SOP 283-316 will be effective by 13 May 2009 to require the use of a report that includes a more comprehensive APR summary taken directly from the deviation investigation tracking system. This report includes a more detailed description of the event as compared to the current report generated from the (b) (4) *. This* (b) (4)

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5. Regarding the firm's Biological Product Deviation Reporting (BPDR) system:

   A. SOP 283-303X, Regulatory Agency Reporting for Biological Products, defines the events that require submission of a Biological Product Deviation Report (BPDR). This procedure identifies significant labeling or package insert error (i.e. information found to be incorrect or missing) including product name/type, lot number, storage temperature, administration route, concentration or volume, or expiration date, as a Biological Deviation. This procedure does not require a BPDR for single reports of missing label events, but requires a BPDR for reports that exceed the labeling/packaging AQL for the complaint product lot. As a result, BPDRs were not submitted for the following complaints in which the complaint modes were confirmed by the firm:

      1. Complaint 91775, Gardasil lot 1968U, the customer reported two vials from a ten-pack did not have the lot number or expiration date stamped on the labels. The returned vials did not have a lot number or expiration date printed on the labels.

      2. Complaint 86657, Gardasil lot 0525U, the customer reported a carton of product contained one vial missing a label. The returned vial was unlabeled and free of glue residue.

      3. Complaint 90049, Varivax lot 1890U, the customer reported two vials in a carton of product were missing labels. The returned vials were unlabeled and free of glue residue.

      4. Complaint 91348, Gardasil lot 1978U, the customer reported one vial in a ten-pack carton was missing a label. The returned vial was unlabeled and free of glue residue.

   B. A deficiency from the 1/08 inspection was no BPDR was submitted concerning leaks in Gardasil syringes. As corrective action, the firm implemented an (b) (4) This (b) (4) is considered for a BPDR. This (b) (4) is deficient as follows:

      1. The (b) (4)

      2. If the firm's review of the complaint product lot history record does not identify that the defect occurred (b) (4) product lot before a BPDR is considered.

      3. The firm did not implement (b) (4) for BPDR events.

Response 5A: *We wish to emphasize that we understand fully the importance of the regulatory reporting requirements and take this obligation seriously. To that end, our existing procedure for Biological Product Deviation Reporting, SOP 283-303X, "Regulatory Agency Reporting for Biological Products", was developed to ensure that events that may have the potential to impact the safety, purity, or potency of marketed product are reported in compliance with the regulations. This SOP contains specific guidance for missing label reports. As described in the observation,*

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SOP 283-303X states that the receipt of a single report for a missing label does not necessitate a Biological Product Deviation Report (BPDR). However, (b) (4) *of a BPDR. This procedure was developed to utilize an established statistical measure of quality to assess if complaint reports for missing labels represent an unexpected (i.e., reportable) event for the lot in question. Further, as defined in our procedure, SOP 315-219, "Packaging Statistical Sampling (PSS) for Products Packaged in West Point Packaging Operations", a missing label is considered an obvious defect and is certain to be noticed by the end user; thus, inhibiting its dispensing and use. This logic applies to a missing lot number and/or expiration date from a label. In the cases noted in this observation, the lots associated with the complaint reports were confirmed to have* (b) (4) *as defined in SOP 315-219. As such, it was determined that a BPDR was not required as (i) the reports did not represent an unexpected event, since the AQL was met and (ii) there was no potential to impact the safety, purity or potency of the product, since the defect is expected to inhibit the use of the product. While a BPDR was not issued in these cases, it is important to note that a comprehensive review and investigation was performed as detailed further in our response below.*

In discussions with the Investigator during the inspection, the Investigator emphasized that a BPDR should be issued after a single confirmed labeling event. As a result, West Point SOP 283-303X will be effective by 24 June 2009 with the requirement for a BPDR to be submitted in response to one confirmed complaint, based upon an examination of returned complaint sample, for (i) a missing primary label and (ii) a missing lot number and/or expiration date from the primary label.

Following the SOP update, we will contact the Agency should a labeling event occur that is not otherwise described in the SOP to confirm that there is alignment as to whether the event should be formally reported. (b) (4) *of the SOP update, and a follow up report will be provided to the Agency by 21 January 2010 to reconfirm that we are reporting labeling events in accordance with the Guidance Document and are meeting the Agency's expectations.*

It is important to note that as part of our complaint trending management process, a comprehensive investigation was performed in 2007 in response to an observed increase of label complaints. Areas of improvement and specific actions to decrease the frequency of missing labels were implemented as a result of this comprehensive investigation between August 2007 and January 2008 including, but not limited to: (i) (b) (4) .

Since implementation of the improvements noted above, there has been a notable reduction of missing label complaints. These complaints were reduced from 74 complaints for lots packaged on Line (b) *in 2007 to two complaints (i.e., one that was confirmed and one that was unconfirmed as the latter vial was not returned for evaluation) for lots packaged on Line* (b) *and distributed between January 2008 through December 2008. During this timeframe (i.e., January 2008 through December 2008), there* (b) (4) *labeled and distributed. The samples associated with the complaints referenced in this observation were all determined to be labeled prior to the implementation of the actions noted above.*

Response 5B: *We acknowledge that* (b) (4) *complaints that was developed should have been formally made part of existing standard operating procedure. However, training of the complaint unit personnel was performed and documented on the use of*

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(b) (4) *. Additionally,* (b) (4) *As this* (b) (4) *in a procedure, SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports" will be revised to include the requirement to utilize this* (b) (4) *by 13 May 2009.*

The (b) (4) *a BPDR if there was a confirmed manufacturing or packaging root cause identified, and to include a* (b) (4) *The section of* (b) (4) *Due to the low level of reports of leak prior to use since implementation of* (b) (4) *we have not had the opportunity* (b) (4) *during complaint investigations. We acknowledge that a revision is required and commit to perform a reassessment as noted below, to improve the clarity and intent of the monitoring tool.*

The memorandum that accompanied the implementation of the (b) (4) *The* (b) (4) *At the time of the inspection, there were only four applicable complaints of leaking "prior to use" syringes received against different lot numbers since the* (b) (4) *was implemented in August 2008. Thus, there has been limited experience with the application of the* (b) (4) *and it was not yet expanded to include leaking vial complaints. As there were no leaking "prior to use" complaints for vials in 2008, the initial implementation of the* (b) (4) *was appropriately focused on the syringe image. In alignment with the implementation memorandum and as a result of this observation, we will reassess the current* (b) (4) *and optimize it based on our experience to date. The* (b) (4) (b) (4) *The* (b) (4) *SOP 283-303X will be* (b) (4)

6. (b) (4) . (b) (4) were directly impacted by the *S. maltophilia* contamination. (b) (4) The firm estimated (based on production process and testing data) that the contamination will not affect the product and therefore no BPDR was filled. However, only one of the twelve affected and released bulks was put on stability. The one bulk placed on stability did not represent the "worse case scenario" for the contaminated bulks.

Response 6: (b) (4) *was initiated in August 2007 upon* (b) (4) *of Stenotrophomonas maltophilia from the VAQTA®* (b) (4)

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All potentially impacted VAQTA® bulk lots (b) (4) *All of the affected lots were under our control during the time of the investigation and no distributed product was affected. Since the initiation and completion of the investigation took place prior to the release of any affected lots and the atypical was considered when making the release decision, the regulations regarding filing a Biologics Product Deviation Report (BPDR) were not applicable, and thus, no BPDR was submitted.*

The VAQTA® (b) (4) .

Our investigation concluded that there was no impact to lots processed using columns that tested positive for S. maltophilia (b) (4) *:*

1. (b) (4)
2. (b) (4)
3. *There was* (b) (4)
4. (b) (4)
5. *S. maltophilia is a Gram negative bacterium with a lipopolysaccharide (LPS) containing outer membrane. LPS is an endotoxin that is able to be measured using the Limulus Amebocyte Lysate (LAL) assay.* (b) (4) .

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Based on these factors, the lots associated with the investigation were determined to be typical of the process. Therefore, the investigation concluded that no stability requirements were warranted.

However, as discussed during the inspection, one VAQTA® bulk lot directly impacted by this investigation and two final container lots sourced from a total of four directly impacted bulk lots have been placed on stability through (b) (4)

Table 2: VAQTA® Bulk Lot 2123433 Stability Data

(b) (4)

Table 3: VAQTA® Final Container Lot 0662532 Stability Data

(b) (4)

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Table 4: VAQTA® Final Container Lot 0929X Stability Data

(b) (4)

In conclusion, the investigation (b) (4) *determined that there was no impact to VAQTA® bulk lots as a result of* (b) (4) .

However, we recognize that the rationale for the lack of stability requirements in this case was not clearly stated in the investigation report. As a result, (b) (4) *has been revised as of 27 February 2009 to document the rationale as to why additional stability studies were not necessary. Additionally, review of the* (b) (4) *procedure identified a lack of:* (b) (4)

As a result, SOP (b) (4)

7. Evaluation of the impact of changes and deviations on PedvaxHIB product does not always take into full consideration the sensitivity of the manufacturing process to changes.

A. The type of (b) (4) This change was not deemed necessary to report to the regulatory agency because the change was thought not to have product impact. This conclusion does not take into consideration that (b) (4)

B. During the manufacture of (b) (4) The firm reviewed the use of the incorrect value and concluded that there was no product impact based on a review of the process manual. The review and basis for the conclusion did not include the results of release test performed on lot 2130375.

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Response 7: *We understand the need to fully evaluate changes and deviations, while taking into account the sensitivity of the manufacturing process. We further understand the need to report changes and deviations in accordance with Agency expectations.*

Response 7A: *During the processing* (b) (4) *. The* (b) (4)

The (b) (4) .

We acknowledge (b) (4) *However, there was no statistically significant difference in batch temperature, batch moisture, or* (b) (4) *We acknowledge that there is a recent ongoing investigation into an out of specification result for* (b) (4) (b) (4) *However, based upon the information available at the time* (b) (4) *, we concluded that no adverse impact on product quality resulted from this change, thus supporting the decision that this change was not a reportable event.*

Our Change Control SOP 298-184X, "Vaccine and Sterile Operations (b) (4) *which governs process related changes,* (b) (4) *. If either of these is required, they are included in the* (b) (4) *The* (b) (4)

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(b) (4) . *In addition,* (b) (4)

Response 7B: *The* (b) (4) . *It is also used to calculate* (b) (4) (b) (4) *An addendum to the investigation was subsequently approved on 05 February 2009, documenting the evaluation of the release test data in the APR.*

We acknowledge that release data should be used for determining product impact for process related investigations. It is important to note that West Point Quality conducts a complete review of all release data, as noted above, in addition to all associated investigations prior to making a release decision on a lot. However, to ensure that relevant release test results are explicitly reviewed as part of the product impact assessment related to an investigation, we will modify SOP 286-125X, "Atypical Process reports (APRs) in West Point Operations" to require that release tests that are directly linked to product impact be explicitly assessed as part of the investigation. The update to SOP 286-125X will be completed by 25 May 2009.

8. Equipment is not always adequately qualified or tested prior to returning to service.

A. During (b) (4) . As described in (b) (4) The (b) (4) As a result during the manufacture of (b) (4)

B. A deviation report, (b) (4) The (b) (4) . The (b) (4) The repair personnel had not properly established that the pump was working properly when it was installed.

C. (b) (4) , an increased amount of broken glass was observed at (b) (4) lots 0661316, 0661273, 0661271 and 0661272. The root cause (b) (4) . The (b) (4) The investigation noted SOP 298-184X, Vaccine and Sterile Operations (b) (4) did not have clear

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procedures on how to determine what type of testing is required for this type of equipment change. Corrective actions have not been implemented to date for the deficient change control procedure.

Response 8: *We acknowledge that the implementation of each of the changes highlighted in Observation 8 would have been better executed with additional testing prior to implementation. Therefore, we will update our procedure(s) to require testing of equipment, following repairs or changes, before returning it to service. In the event that these repairs or changes can only be adequately assessed during routine manufacturing operations (e.g., manufacturing a batch at scale), we will update our procedure(s) to require formal monitoring post implementation.*

To strengthen our work order system that manages repairs and (b) (4) *, an* (b) (4) *. This* (b) (4) *In addition, we will clarify within the applicable procedure the types of equipment and automation changes that should be managed in the work order system versus those which require change control. The appropriate procedure(s) defining the above will be effective by 05 October 2009.*

Response 8A*: With respect to the issue described in* (b) (4) *he APR concluded* (b) (4) *. This would have provided adequate assurance of* (b) (4) *Consequently, we will ensure the work order procedures clarify the definition of* (b) (4) *and clearly explain when to* (b) (4) *Furthermore, we will clarify the requirement for testing prior to returning the equipment to service.*

Response 8B*: With respect to the issue described in* (b) (4) *, we acknowledge that* (b) (4) *to returning it to service would have identified the incorrect wiring of the pump after repair. We will develop* (b) (4) *that will* (b) (4) (b) (4)

Response 8C*: With respect to the issue described in* (b) (4) *, we acknowledge that* (b) (4) *We will clarify our* (b) (4) *with respect to expectations for testing and monitoring of equipment before returning it to service.*

In addition, our (b) (4) *As stated above, thel appropriate procedure(s) will be effective by 05 October 2009.*

Furthermore, a comprehensive training program will be developed for individuals involved with equipment and automation changes (e.g., authors, approvers, mechanics, etc) as further assurance that appropriate testing is executed as part of work orders and change control. The training will be available and implementation will begin by 05 October 2009.

With regard to Observation 8C, we recognize that we have not yet completed the corrective action. However, (b) (4) *esting requirements discussed above will address the system-*

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related actions. The system-based enhancement to address the timeliness of the corrective and preventative actions is addressed in our response to Observation 11.

9. The firm does not trend or otherwise evaluate all vial and syringe glass breaking events during filling operations. Glass breakage events are documented in the batch record or a Glass Breakage Monitoring Logbook form which is placed in each individual batch record. Deviation Alerts/Investigations are only required for unique glass breakage events (events which do not occur at known pinch points on the filling line); improper line clearances in response to a glass breakage event; glass breakage events that require grouping product; and glass fragments in accepted final filled product containers. There is no limit established for the number of glass breakage events which can occur during filling and there is no trending of these events to determine when an investigation should be initiated to evaluate a root cause and implement corrective actions.

Response 9: *As an enhancement to our existing* (b) (4)

(b) (4)

, West Point Operation (b) (4)

- (b) (4)
- (b) (4)
- (b) (4)
- *The appropriate SOPs, including the Glass Breakage Management SOP and batch records will be updated to accommodate these changes.*

We will begin implementation of these enhancements as soon as possible by compiling and assessing the batch record data in order to determine the appropriate limits through our change

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control process. However, we do not expect that these enhancements will be fully implemented until 14 December 2009 after the implementation of (b) (4)
In addition, all appropriate Standard Operating Procedures and batch records (i.e., approximately (b) *will be effective to reflect the identified enhancements and levels by 14 December 2009.*

For the syringe filling line, there are no pinch points as documented in the Glass Breakage Management SOP. As such, all glass breakage events already result in a deviation alert and are tracked using the deviation management trending process. No changes are recommended for the syringe filling line.

10. Investigations for defective vial components that are found during manufacturing were deficient as follows:

A. Vendor complaints and investigations were not initiated for the following events of (b) (4) defect observed in (b) (4) . (b) (4) This defect can critically weaken the vial.

1. (b) (4) , M-M-R II lot 0661676.
2. (b) (4) , M-M-R II lot 0661733.
3. (b) (4) , M-M-R II lot 0662294.

B. (b) (4) . An operator identified seven vials with Spiticule defects (excess string-like glass on the interior vial surface) during (b) (4) of Pneumovax 23 lot 0662018. This critical defect can result in free-floating glass particles in the vaccine product. The root cause of the Spiticules was improper adjustment of the punch out burner during vial manufacturing by the vendor, and the inability of the vendor's (b) (4) system to detect these defects. Seven vial lots and twenty four vaccine product lots were impacted by this deviation. The vendor implemented corrective actions that were effective for vial lots manufactured after to 3/31/08. The firm did not implement corrective actions or controls to address vials in inventory that were manufactured prior to implementation of the vendor's corrective actions. As a result, an additional event of Spiticule defects for filled product was observed. (b) (4) was initiated for 4 Spiticule defects that were identified during (b) (4) of Pneumovax 23 lot 0663429. The associated Merck vial lots S269217 and S269218 were manufactured in 2007.

C. At the time of this inspection, thirteen glass vial lots that were manufactured prior to 3/31/08 remained in the firm's inventory. There is no assurance that the firm's (b) (4) (b) (4) .

1. (b) (4) , 4 vials containing Spiticule defects were identified after (b) (4) . The firm did not evaluate these vials with Spiticule defects with the other (b) (4) in that are used (b) (4) ((b) (4)) and (b) (4) ((b) (4)) vaccine products. There is no assurance that any of the firm's (b) (4) will detect this defect.

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2. Although Spiticule defects in vials have been observed in production, the firm does not utilize vials with Spiticule defects for validations and daily qualification for the (b) (4)

D. The Supplies Inspection department was not notified of the above events of defective vials so that appropriate corrective action could be implemented at incoming inspection, such as a tightened inspection plan.

Response 10: *Our investigation procedure, SOP 286-125X, "Atypical Process Reports (APRs) in West Point Operations", was updated on 08 September 2008 to require a vendor investigation when a Merck West Point investigation determines that the root cause for a component defect may be due to the manufacturing process at the vendor. We acknowledge there is opportunity to further enhance the consistency of investigations related to primary packaging components. As such, we will develop a new procedure by 17 October 2009. The new SOP will detail how to* (b) (4) *This procedural guidance will contain the following requirements for investigation of these primary packaging component defects:*

1. (b) (4)
2. (b) (4) .
3. (b) (4)

In addition to this (b) (4) *This evaluation will be part of the* (b) (4) *The* (b) (4) *Additionally,* (b) (4) *. In the event the defect cannot be detected, the investigation will document the actions taken. The appropriate procedure will be effective by 17 October 2009.*

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Response 10A: *We understand the concern regarding vendor notification for Merck West Point investigations that are related to a vendor quality issue (e.g.,* (b) (4) *. Our investigation procedure SOP 286-125X was effective 08 September 2008, to require a vendor investigation when Merck West Point investigations determine the root cause is due to vendor quality. The investigations referenced did not include vendor investigations as they were closed between 30 May 2008 and 19 June 2008 prior to the updated SOP 286-125X previously mentioned. Our investigations performed after 08 September 2008 include vendor investigations.*

(b) (4)

All of the referenced investigations were initiated as a result of glass breakage on the filling line. We used SOP 285-225, "(b) (4) *, SOP 285-230, "Operation of Filling Rooms* (b) *and* (b) *and SOP 285-279X "Line Cleaning after Mechanical Adjustments" to respond to the event. Impacted material was segregated and discarded.*

(b) (4) *was the root cause of the broken glass. We believe this to be an appropriate conclusion based on* (b) (4) *At the conclusion of the investigation, appropriate employees were trained on the APR conclusions in order to emphasize how handling can cause vial breakage.*

(b) (4)
at West Point. This was based on the description of the glass breakage discovered on the line (i.e., full separation of the top of the vial at the neck) and the input provided by (b) *regarding the failure mode of vials* (b) (4) *The two investigations concluded that there were no other process signals (i.e.* (b) (4) *for the source glass lots that were indicative of a vial integrity concern with final product using these lots of glass.*

In summary, we are confident in our final product disposition decisions.

Response 10B: *We believe it is important to provide additional background for the two investigations referenced in the observation in order to explain the rationale for the product disposition decisions in each. In the case of* (b) (4) *, an investigation was initiated by an operator performing the* (b) (4) *who questioned the level of spiticule defects during inspection. Although the investigation determined that the lot was typical, a vendor investigation was still requested to determine root cause and understand if improvements could be made to their manufacturing process to reduce levels of this defect. The vendor implemented a routine check of their manufacturing equipment as an enhancement to their process in an effort to reduce the occurrence of the spiticule defect. Since the Merck West Point investigation concluded that the initiating event was consistent with normal manufacturing and was not an indication that there was a unique event at the vendor, the material manufactured by the vendor prior to the vendor corrective action was considered acceptable. We acknowledge this disposition decision for components made prior to the vendor corrective action should have been documented in the investigation. As stated above, our procedures will be updated to ensure an*

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evaluation is documented regarding the potential impact to material made by vendors prior to the implementation of their corrective action.

(b) (4) *was initiated in response to identification of three spiticule defects in the statistical sample of filled containers taken post inspection. It concluded the defects were concentrated in the subject filled lot based on the relatively high level of defects observed during the* (b) (4) *as compared to inspection data for filled material using the same vial lot. The investigation considered potential impact to all other filled lots and the remaining inventory of glass from the source vendor lot. The data reviewed for the filled lots indicated there were no elevated levels of defects. Glass lots in inventory associated with the originating vendor lot were discarded as a precaution to eliminate the risk that they may contain elevated levels of the spiticule defect.*

In summary, (b) (4) *determined that the level of spiticule defects in the impacted glass lot was not above the typical level received from the vendor. Therefore, the investigation did not deem material produced by the vendor, before the vendor corrective action, as unacceptable. In contrast,* (b) (4) *determined that the level of spiticules in the vendor lots was atypical, and therefore, the glass in inventory was discarded.*

Response 10C: *We agree that our inspection processes need to provide assurance that defects generated in the manufacturing process can be adequately detected. As stated previously, the vision inspection validation master plan and the investigation process will be enhanced to address this concern.*

The observation specifically addresses inclusion of spiticule defects in the set-up and qualification sets used for the (b) (4) *. At West Point, there are* (b) (4) *for sterile injectable vaccine products, namely* (b) (4) *The Building* (b) (4) *that is referenced in the observation only inspects for* (b) (4) *. It is used in combination with* (b) *For this process,* (b) (4) *.*

For the (b) (4) *designed to detect container defects, the container sets used for the set-up check and the validation challenge sets include cracked containers, containers with marks on the side walls, and containers with glass particulates for liquid products.* (b) (4) *:*

1. *Cracks and spiticule defects both reflect light when front lit and block light when backlit.*

2. *Sidewall marks and spiticule defects both block light when backlit.*

3. *Glass particles in liquid product provide the exact detection challenge that spiticules will present in the event that part of the spiticule breaks off and was to become free floating glass particulate.*

This supports that spiticules would be detected by (b) (4) *in the same manner as cracks and sidewall marks. As is the case for cracks and marks on containers, inspection capability for spiticules will be a function of the extent of the defect. Furthermore, a study was performed on the* (b) (4) *to understand the capability of the system to detect the specific spiticule defects. The study found that by running the three*

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containers with spiticules (b) (4)

Based on the above rationale, we believe our inspection system set-up checks and validations contain defects that are representative of the naturally occurring defects for the manufacturing process. As such, (b) (4)

Response 10D: *We agree with this observation and will implement procedures as described earlier to ensure that Supplies Inspection is notified about investigations related to vendor quality issues. This will ensure that Supplies Inspection evaluates the defects and documents appropriate actions.*

11. Corrective actions are not implemented in a timely manner to prevent the recurrence of manufacturing deviations. For example:

A. The firm has recurring glass breakage events at the (b) (4) in Department (b) (4) . A procedure for setting appropriate (b) (4) . For example,

1. (b) (4) was initiated for glass particles observed (b) (4) lots 0662104, 0662105, 0662106, 0662107, 0662108, and 0662109. The root cause was (b) (4)

2. (b) (4) lot 0663380, an operator identified half a glass vial in position on the (b) (4) . The root cause of the broken vial was a breakage event at (b) (4) .

B. (b) (4) was initiated because partially stoppered vials from VARIVAX (b) (4) lot 0662000 were being (b) (4) Corrective actions from the previous events were not effective to prevent the recurrence of the deviation.

Response 11: *We fully agree that timely and effective corrective actions must be implemented in order to prevent recurrence of manufacturing deviations. We will continue to improve the robustness of our Corrective Action Preventative Action (CAPA) system and will ensure that corrective actions to prevent recurrence are implemented in a timely manner, as more fully described below:*

1. *We will institute a new CAPA* (b) (4) *that will review all open corrective and preventative actions, monthly, and identify those CAPAs targeted to be completed within the* (b) (4) *. The initiation of this CAPA* (b) (4) *will commence as of* (b) (4) (b) (4)

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2. (b) (4) *For all CAPAs identified* (b) (4) (b) (4)

As reviewed with the Investigators during the inspection, the site has begun a major initiative to improve its overall Deviation Management System. As part of this initiative, an enhanced CAPA management system will be put in place for all new CAPAs generated as of 01 July 2009. This improved CAPA management system will include:

- (b) (4)

The optimized CAPA system for new CAPAs, which will be reflected in SOP 286-341X, "Corrective Action / Preventative Action (CAPA) Management Procedures", is targeted to be in place by 01 July 2009.

We believe that the robustness of the West Point Site's CAPA system will be significantly improved by the implementation of these two enhancements: (i) (b) (4)

Response 11A: (b) (4) *was initiated for broken glass particles found at the bottom of* (b) (4) (b) (4) *was initiated for a broken vial found at* (b) (4)

The CAPA stating, '(b) (4) *The cause for this delay was due to* (b) (4) *, which we believe our corrective actions described previously will address. The* (b) (4)

Response 11B: *We wish to clarify the comment in the observation that the investigation of* (b) (4) *did not identify any previous occurrences of this deviation.* (b) (4) *was initiated to investigate the event associated* (b) (4) *This was the first time this deviation was identified and immediate actions were taken at the time of the event to mitigate product impact. The* (b) (4) *, like the one associated with this deviation, occur*

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(b) (4) *As this was the first reported deviation of this type, we performed a look back of the past three-year's validation activities to ensure that this type event had not occurred previously. Investigation* (b) (4) *did not identify any previous occurrences of this same event and concluded that there was no quality impact to any material manufactured during a continuing validation study over the past three years* (b) (4) *. As such, there were no previous CAPAs in place that could have prevented this deviation. In response to* (b) (4) *eight corrective / preventative actions were assigned and completed, and this event has not recurred. We are confident that for this event the corrective and preventative actions will be effective in preventing recurrence.*

12. (b) (4) , Pneumovax 23 lot 0661527, was initiated for broken glass observed on the Line (b) (4) . The root cause was the mechanics were not trained on how to (b) (4) In addition, SOP 115-206, Operating Procedures (b) (4)

Response 12: *We would like to clarify the sequence of events that led to* (b) (4) *The* (b) (4) *functionality was not newly installed on the line in December 2007. Rather, the* (b) (4) *had been removed, reinstalled, and was not adjusted back to an appropriate position in December 2007 as part of routine maintenance activities. As the device is not normally removed and adjusted during routine operation, the mechanics were not aware of the impact that its position would have* (b) (4) *. As part of the investigation, the mechanics in the area were given hands-on training by the area engineer that focused on the appropriate adjustment of the* (b) (4)

As reviewed with the Investigator, we began an in-depth study of line performance in November 2008. At the conclusion of the study, we updated SOP 115-206, "Operating Procedures (b) (4) *," which became effective on 27 February 2009, to include an* (b) (4)

Additionally, in accordance with our site GMP training procedure, SOP PC7598, "MMD West Point GMP Training Program", all affected employees were trained on the update to SOP 115-206.

13. The operation of the (b) (4) and the training level of its operators prior to initiating a production run is deficient. For example,

A. (b) (4) , During the (b) (4) .

B. (b) (4) , A small product leak was discovered due to a pump seal ruptured due to the (b) (4)

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Response 13: *Please note that the two APRs listed in the observation are associated with the same event. As a result of our investigation, we concluded that neither the operation of the* (b) (4) *. Rather, our investigation concluded that the root cause of the atypical event was the result of a simultaneous combination of events that had not been experienced in this operation previously. The rationale for our conclusion is provided within this response, along with the corrective actions that will be implemented to prevent the recurrence of this event. This was a unique event that had not occurred in the* (b) (4) *during which* (b) (4) *ots were manufactured and was not attributed to a training deficiency of our Operators.*

Our investigation of these deviations attributed the primary root cause of the pressure spike that resulted in the (b) (4) *While the* (b) (4) *existed prior to the noted deviations, the simultaneous combination of the* (b) (4) *As noted in* (b) (4) *, the mis-alignment of the positioner was due to the* (b) (4) *. This deficiency was corrected and verified via* (b) (4)

In the current-state design, the (b) (4) *cited in Observation 13A as well as damage to the* (b) (4) *that resulted in the small leak upon restart cited in Observation 13B. The Operators did not have sufficient time to identify the deviation prior to the* (b) (4)

We believe our evaluation of the root cause of the event is accurate and training and qualification of our staff was adequate prior to initiating this production campaign. In preparation for the production runs in Building (b) *(i.e., PNEUMOVAX®23 bulk* (b) (4) *There were some processing steps, including the* (b) (4) *involved in the cited deviations,* (b) (4)

Our Operators (i) participated in the cleaning, sanitization, and sterilization cycles, in addition to the (b) (4) *, to prepare for the production campaign and (ii) completed process evaluation checklists to assess process understanding. The* (b) (4) *The* (b) (4)

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(b) (4) *. Therefore, when this was originally investigated, we concluded that since the root cause was attributed to the variables described above rather than inadequate training, no additional Operator training was required.*

The primary root cause of deficient system design will be addressed by the corrective action generated and tracked in (b) (4) *We will make a change to* (b) (4) (b) (4) *. This modification will be completed by* (b) (4) *.*

As previously stated, a contributing root cause for the (b) (4) *As noted in the commitment to Observation 8, an equipment operability check procedure will be developed for maintenance work orders.*

14. Glass vials item number (b) (4) are used for (b) (4) vaccine products, to include Gardasil, VAQTA (Pediatric & Adult), Recombivax (Pediatric, Adult, Dialysis), M-M-R II, Varivax (Frozen), Varivax III, Zostavax, ProQuad, Pneumovax, Attenuvax, Meruvax, Mumpsvax, and Normal Horse Serum. Regarding incoming inspection of vial component code (b) (4)

A. (b) (4)

Response 14: *We understand and recognize that visual inspection procedures for incoming materials should be well defined to ensure* (b) (4)

Response 14A: *Ambient lighting in the Supplies Inspection incoming inspection room was evaluated in April 2006 and on 11 February 2009. In both cases, the results met our defined lighting requirements for site laboratory lighting standards. To ensure the lighting intensity is appropriate for component inspection, a new standard operating procedure will be implemented to* (b) (4) *requirements for incoming inspection of primary packaging components. The* (b) (4) *. This new procedure will also define* (b) (4) *The results of each evaluation will be documented. This procedure will be effective by 08 June 2009.*

Response 14B: *Supplies Inspection's existing procedures define a consistent approach to visual inspection of vials; however, the visual inspection guidance is not consolidated into a single*

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document. Personnel within the Supplies Inspection organization are trained on all aspects of component inspection. Existing training and procedures ensure consistency of inspections across operators.

As an enhancement to our existing procedures, we will develop a single standard operating procedure for incoming inspection of packaging components, including vials. This new standard operating procedure will consolidate current guidance and provide enhanced procedures that specifically set forth how the visual inspection of components, including vials, should be conducted. Furthermore, component-specific instruction will be included to ensure consistency in application, as needed. This procedure will be effective by 29 June 2009.

***Response 14C:** Although the Supplies Inspection Department does not have a "kit" of physical component defects as a part of the current training program for incoming inspection personnel, the training program uses industry-derived standardized defect classification manuals [i.e., from the Parenteral Drug Association (PDA)] that include definitions and photographs of routine and rare component defects. Use of these classification manuals ensures consistent defect classification by Supplies Inspection personnel during training and normal inspection.*

As an enhancement to our current classification manual, a standardized "kit" of component defects will be developed. A new standard operating procedure will define the requirements for the establishment and maintenance of a standardized kit of physical samples of primary packaging component defects. Additionally, the physical defect kit will be a part of the training program, for employees performing visual inspection activities of incoming packaging components. Standardized kits of physical primary packaging component defects and the new standard operating procedure will be effective by 29 June2009.

15. A single Merck vial lot contains (b) (4)) that typically come from more than one vendor production lot, and is comprised of material made across multiple vendor manufacturing lines. The firm did not determine if other vial lots were impacted by vendor vial lots with known defects.

A. Merck vial lot S270737, vendor lot (b) (4) was rejected during incoming inspection for crack defects. (b) (4) was initiated for this vial lot. This deviation documents that (b vials from lot S270737 had defects in the neck, below the flange. The defective vials were analyzed and determined to have lap mark (or infold) defects from the glass tubing conversion operation, which were severe strength reducing defects that could possibly lead to failure during over-sealing.

B. Merck vial lots S265165 and S265291 (vendor lots (b) (4)) were rejected for top of vial edges which were squared. (b) (4) documents that the lip radius of these vial lots was too sharp. The root cause was (b) (4) on the machine head during vial manufacturing, which resulted in an out of round condition as the soft glass contacted the drop down pad. Merck rejected vial lots S265165 and 2652921.

C. Merck vial lot S267085, vendor lot (b) (4) was rejected at incoming inspection for (b vials with seal imperfections. (b) (4) documents (b) (4) vials from lot S267085 were (b) (4)). The chips were caused during the vial manufacturing process where the (b) (4) was out of position to prevent the vial finish from being pushed into the (b) (4) during the lifting operation.

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Response 15: *We wish to clarify the first sentence of the observation, in that we do not combine vendor production lots into a single Merck West Point vial lot. In the cases cited, the vendor,* (b) (4) *portrayed the vial lot as a single vendor lot, which upon receipt at Merck West Point, was assigned a unique Merck lot number. The tubing vial manufacturing process is essentially a continuous process in which vials are manufactured over multiple days. The* (b) (4) *facility, located in* (b) (4) *historically provided a single vendor lot that was comprised of vials that were manufactured on multiple manufacturing lines. The vendor defined a lot as the number of vials required to fulfill a customer order. A lot did not represent a unique manufacturing event.*

When the investigations were performed, we followed our procedure to assess the deviation's affect on all receipts from the same vendor lot. Based on the lot information provided by the vendor with each order, each shipment was believed to be an independent lot. Through separate discussions between West Point Site Technology and the vendor, it was identified that the vendor lot numbers provided with shipments were not from a single production line; unfortunately, this information was not communicated to Supplies Inspection personnel. As a result, there was no assessment of other potentially affected lots, defined by the vendor as those vials manufactured on the same production line(s) prior to, or subsequent to, the vials shipped to West Point In order to ensure that issues such as this are properly communicated, the following actions have been identified:

- *The improved communications between operations and Supplies Inspection personnel, as discussed in response to Observation 10, will ensure Supplies Inspection (i) has visibility of ongoing issues related to vendor components and (ii) evaluates whether additional corrective actions are required.*

- *As discussed with the Investigator, starting on 01 May 2008,* (b) (4) *agreed that they would not* (b) (4) *ots manufactured on different production lines into a single lot number. This immediately improved our ability to quickly isolate potential issues of incoming glass from this vendor. In addition, we will update our procedure(s) to require the vendor to identify the associated lots of glass (defined by the vendor as vials manufactured on the same production line prior to, or subsequent to, the vials in question) where the investigation concludes a root cause is related to the vendor's manufacturing process. By 30 July 2009, we will ensure we are aligned with the vendor with respect to the rationale for determining associated lots.*

For the vial lots identified in this observation (i.e., S270737, S265165, S265291, S267085), we have since received information from the vendor on all associated lots. We reviewed key data to determine if there was any indication of similar defects in Supplies Inspection or in Manufacturing. Specifically, the data from the Supplies Inspection of the associated vials lots, the (b) (4) *inspection of the filled product, and the statistical sampling* (b) (4) *inspection of filled product were reviewed. This is summarized below.*

a. *With respect to vials in Merck Lot S270737, there were three associated vial lots identified by the vendor. The results from the incoming inspection of the associated vial lots were reviewed and showed no evidence of crack defects in the associated lots. There were* (b) *associated product lots that used vials from one of the four vial lots. The type of defect observed in vial Lot S270737 would manifest during sealing of the product lots as a broken vial or as a container integrity defect. Any vials broken in this manner would be detected by the* (b) (4) *and therefore, would not appear in the accepted population. For the* (b) *product lots, no inspection* (b) (4))

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sampling failures were recorded for container integrity defects in the neck and flange region. In summary, there is no evidence that the deviation investigated for Lot S270737 extended to associated vial lots.

b. *With respect to vials in Merck Lots S265165 and S265291, there were 11 associated lots identified by the vendor. The results from the incoming inspection of the associated vial lots were reviewed and there were no observations of "squared finish". There were (b) associated product lots that used vials from one of the 13 vial lots. Since the seal would be placed over the potentially impacted area of the vial, it is unlikely the defects would be identified during the (b) (4) or the (b) (4) One of the (b) lots had inspection (b) (4) ; however, the root cause was associated with the manufacture of the product lot and not with the manufacturing process of the vials. Additionally, there were no (b) (4) (b) (4) failures for the product lots associated with a "squared finish". In summary, there is no evidence that the deviation investigated for the "squared finish" for Lots S265165 and S265291 was extended to other associated vial lots.*

c. *With respect to vials in Merck Lot S267085, there were three associated lots identified by the vendor. The results from the incoming inspection of the associated vial lots were reviewed and there were no observations of sealing surface imperfections. There were (b associated product lots that used vials from one of the four vial lots. Since the (b) (4) would be placed over the region in question, it is unlikely that these defects would be identified by the (b) (4) of products. For the (b lots, there were no inspection (b) (4) for defects associated with seal surface imperfections. In summary, there is no evidence that the deviation investigated for sealing surface imperfections for Lot S267085 was extended to other associated vial lots.*

16. There are no data to support the 1 year expiration date under the firm's use and storage conditions for raw material (b) (4) used in Gardasil manufacturing. The firm stores the raw material in the original container (b) (4) The firm has not conducted (b) (4) under their use and storage conditions.

Response 16: *Upon receipt and prior to release for use in manufacturing, (b) (4) Although we have not conducted (b) (4) under our use and storage conditions, which include (b) (4) we do have stability data from the supplier of this raw material that support its use under comparable use and storage conditions. Our rationale for using these data to support our expiry is provided below. Additionally, we will describe our proposed corrective actions to ensure our use of this material is consistent with the recommended expiry from the vendor.*

As discussed during the inspection, we currently use an expiry of one year from the date of manufacture for this raw material. This expiry was tighter than the manufacturer's shelf-life recommendation and stability data, which supported a two-year expiry period. The manufacturer's recommendation for partially using a container is to reseal after use and repeat (b) (4) The manufacturer's stability data included satisfactory results from a 36-month study conducted at (b) (4) in original containers (b) (4) . Since the conclusion of the inspection, we have received written

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confirmation from the vendor that over the course of the 36 month stability study, (b) (4) *The repeated* (b) (4)

From the vendor's information, (b) (4) *In addition, the specification applied in the study for* (b) (4) (b) (4) *in GARDASIL® formulation* (b) (4) (b) (4) *of our product GARDASIL®, made with* (b) (4) *To provide additional assurance that our* (b) (4) *is supported by the vendor data for expiry, we will* (b) (4)

In addition, we will update the current SOP 286-408X, "Expiration Dating of Incoming Materials", which governs expiry dating for raw materials. The update to the procedure will require an evaluation, when creating or updating expiry and (b) (4) *, of our usage conditions of the raw materials and a comparison to the conditions used by the vendor to establish expiry. This update will be completed by 28 April 2009. We will also conduct an assessment of West Point raw materials used as excipients to ensure that the data to support material expiry is consistent with our usage conditions of these materials. This assessment will be completed by 09 December 2009.*

17. There is no designated area for storing incoming samples for analysis by (b) (4) The firm (b) (4) (b) (4) . There was no designated place to isolate incoming Lot release samples in the freezer.

Response 17: *We agree that the area within* (b) (4) *As of 13 February 2009, containers designated and labeled for incoming samples only have been placed into* (b) (4)

Although the observation was specific to (b) (4) *we have evaluated the additional laboratories used at the West Point site for release testing of Vaccine Products to ensure that similar conditions are not present. Two additional areas were reviewed: the Merck Research Laboratories – Safety Assessment and Merck Manufacturing Division - Laboratory Operations. Based upon the practices outlined below, no additional actions are required for these areas.*

Merck Research Laboratories – Safety Assessment: *The current process for the storage of biological samples allocated for* (b) (4) *in Merck Research Laboratories -Safety Assessment, is to store all incoming test samples in validated GMP cold temperature units.*

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Incoming samples stored (b) (4) *Those samples* (b) (4) *In this unit, GMP and GLP samples are* (b) (4) *GMP or GLP accordingly. The procedure for storage of release samples can be found in SOP SA-2404, "Receipt and Registration of Test and Control Articles".*

Merck Manufacturing Division - Laboratory Operations: *A review of the organizational and segregation practices for Controlled Temperature Units (CTUs) utilized within Laboratory Operations was also conducted. The use of incoming storage bins designated for samples to be tested by all of Laboratory Operations is utilized throughout each of the testing areas. Samples are segregated by the laboratory testing group and are placed in specific locations within each of the respective testing areas and required CTUs. This process ensures proper organization and segregation for the specific release test to be performed. The procedure for storage of release samples can be found in SOP 028-L102X, "Sample Submission and Flow within Biological and Pharmaceutical Login Areas".*

18. The controls of environmental manufacturing (b) (4) Specifically, several (b) (4) were noted for *Bacillus cereus* (spore forming), gram negative rods and other microbial organisms in the vaccines manufacturing buildings/areas. For example:

A. The corrective/preventive actions in regards to the control of *Bacillus cereus* and other microbial organisms in the (b) (4) , Building (b as the result of *Bacillus cereus* contamination of (b) (4) lot #(b) (4) APR (b) (4) dated October 08, 2007 and the recall of Marketed PedvaxHIB and Comvax lots that were affected by the media challenge failure is inadequate. For example:

   There is no documentation that the (b) (4) for PedvaxHIB has been conducted.

B. Bacillus cereus, penicillium, gram negative and other microbial excursions were isolated (b) (4) Specifically *Bacillus* species were (b) (4) (b) (4) for *Bacillus cereus*/species were (b) (4) . For example:

   1. Six (6) *Bacillus cereus* excursions in the month of February 2008 and three (3) had (b) (4)

   2. Total of 10 action levels bioburden excursions were isolated (b) (4) mostly Bacillus cereus excursion and 3 out of the 9 were Bacillus cereus with microbial result (b) (4)

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and Sample ID #(b) (4) also at (b) (4)

3. Total of five (5) Bacillus cereus excursions as well as other organisms were isolated in (b) (4) and 1 out of the 5 had microbial result of (b) , i.e., Sample ID #(b) (4) dated (b) (4) .

4. Total of six (6) microbial excursions in (b) (4) and two out of the 6 were Bacillus cereus had (b) (4) , Sample ID #(b) (4) dated (b) (4)

5. Total of seven (7) bioburden excursions were noted in (b) (4) most of which were Bacillus cereus/species, Sample ID #(b) (4) dated (b) (4)

C. Twenty-Six (26) action level bioburden excursions including seven (7) (b) results were noted in the (b) (4)) and organisms such as: *Bacillus cereus, Microbacterium* species and gram negative rods were identified.

D. Nineteen (19) action levels bioburden excursions including *Bacillus* species and eleven (11) (b) results were noted in the (b) (4) manufacturing area (b) used in the manufacturing of Gardasil, PedvaxHIB and Recombivax from (b) (4)

E. Seventeen (17) action levels bioburden excursions including eight (8) (b) results were noted in the (b) (4) used in the manufacturing of (b) (4) Recombivax and sterile diluent. Organisms such as: *Baccillus cereus, Baccillus sphaericus, Baccillus pumilus, Baccillus sphaericus Baccillus megateruim* were isolated.

F. Fourteen 14 microbial action level excursions and one result of (b) (4) were noted in the (b) (4) of PedvaxHIB, Recombinax HB, Mumpsvax.

G. Seventeen (17) microbial action level excursions were noted in the (b) (4) of which 10 were (b) (4) The (b) (4) , (b) (4) of i.e.,Gardasil, Vaqta, Recombivax with organisms such as *Bacillus* species, mold, and gram negative rods identified.

H. Twenty-four (24) microbial (b) (4) for gram negative rods were documented and various types of organisms including *Bacillus cereus* were isolated (action limit of<1.0cfu/cu m).

Response 18: *Merck West Point has a sound environmental monitoring program that provides meaningful data on the quality of the manufacturing environments used in the production of our vaccines. This environmental monitoring program includes a robust investigation process,* (b) (4) *performance reviews, and* (b) (4) *that assesses trends and the effectiveness of corrective actions. While we* (b) (4) *assess and make enhancements to bioburden controls, we believe that the environmental monitoring program we have in place is appropriate and effective. We would like to provide some additional information concerning the examples of microbial excursions included in this finding.*

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Excursion Rates: *While multiple microbial excursions are cited throughout the observation, we believe it is important to note that only one of the areas cited in the observation (i.e.,* (b) (4) *) is a Class 100/10,000 area used for aseptic processing. The other areas are primarily Class 100,000 manufacturing areas that employ closed system processing or are used for* (b) (4) *. Additionally, it is important to highlight the number of excursions in the context of the total number of tests taken. The action level rates for these Class 100,000 areas, as well as for our Class 100/10,000 areas, are provided in Table 5. These data are from the period reviewed during the inspection (i.e., 01 January 2008 through 26 January 2009). Also included are total excursion rates (i.e., action and alert levels) for both types of areas.*

Table 5: Microbial Excursion Rates for Classified Areas for 01 January 2008 through 26 January 2009

Classified Areas[1]	No. Action Levels	Total Tests	Action Level Rate	Total Excursion Rate[2]
Class 100/10,000 (Grade A/B)	(b)			%
Class 100,000 (Grade C)	(b)			

[1] Data collected from all Licensed Classified Areas on site
[2] Includes Alert and Action level excursions

As defined in our (b) (4) *procedure,* (b) (4) *Additionally, although there is limited literature and no regulatory guidance on acceptable excursion rates for classified environments, based upon input from our GMP consultant, we believe we are within industry norms with regard to our observed action level excursion rates for classified areas.*

(b) (4) *will be discussed further in the detailed responses to Observations 18A – H. We believe* (b) (4) *data demonstrate an overall state of control of these classified manufacturing areas. This conclusion is further supported by the fact that there have been no sterility failures or media challenge failures during the review period of 01 January 2008 through 26 January 2009 for the departments highlighted in the observation.*

Bacillus and Overall Bioburden Control: *This observation also references several incidences of Bacillus species recovered from the various manufacturing environments. Because Bacillus is a common environmental contaminant, it is probable that Bacillus may be recovered from routine environmental monitoring samples, especially those from Class 100,000 areas, given their adjacency, in many cases, to unclassified areas. Furthermore, in several instances results of* (b) *were noted. In the majority of these instances, the* (b) (4) (b) (4) *in Class 100,000 areas where gloves are not required. The remaining instances of* (b) *were associated with* (b) (4) *in Class 100,000 areas;* (b) (4) *in Class 100,000 areas; and floor samples in one Class 10,000 room. Our historical performance also reinforces that the incident rate of Bacillus, where Bacillus is identified from an action level excursion, significantly decreases for the Class 100/10,000 areas. The incident rate for Bacillus action level excursions was* (b) (4) *in Class 100,000 areas,* (b) (4) *in Class 100/10,000 areas. A review of* (b) (4) *in the observation also confirmed that there were no media challenge failures during the review period.*

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While we have concluded that the incident rate of Bacillus in our classified areas is low overall and our current disinfection program includes use of (b) (4) *that are effective against Bacillus, we recognize the need to* (b) (4) *and improve our microbial controls. In 2008, we evaluated our disinfection procedures utilized for classified areas across the site. From this evaluation, we identified several areas to enhance the effectiveness of our bioburden control of all microorganisms, both vegetative and spore formers. These enhancements will include:*

- *Standardized cleaning and disinfection frequencies for all similar grade areas.*
- *Standardized cleaning and disinfection process for items, such as carts, tanks, etc., transferred into classified rooms at the Class 100,000/unclassified boundary.*
- *Standardized cleaning agents and disinfectants and application methods for all similar grade areas.*
- *Standardization of mandatory event-based triggers for cleaning, disinfection, and sporicidal decontamination for all manufacturing facilities.*

A summary of these planned changes was reviewed with the Investigator. We expect these changes to further enhance the control of Bacillus and other organisms in our classified environments. Preparations for these enhancements to our bioburden control program are well underway and are on target for implementation by 15 April 2009. Following implementation of the enhanced cleaning and disinfection program, we will evaluate routine monitoring data collected (b) (4) *to determine the effectiveness of the new program. This evaluation will be completed by 12 December 2009.*

Addressing Recurring Types of Excursions: *The examples provided in the observation highlighted a few common types of surfaces/ areas where multiple excursions occurred during the period reviewed. Several actions have been taken or are planned as a result of the investigations into these events. They are discussed below.*

Drains: *Multiple action level excursions occurred at sink and floor drain locations in Class 100,000 areas across the site during the review period. Corrective actions taken in response to the excursions included enhancements to cleaning procedures on 19 December 2008 to require* (b) (4) *. Investigations into the* (b) (4) *. As a corrective action,* (b) (4) *with* (b) (4) *. Because these actions were recently implemented, the effectiveness of the actions cannot yet be appropriately assessed. In addition to these local departmental actions, the site wide enhancements to the cleaning and disinfection program planned for 15 April 2009 should also improve bioburden controls for our sink and floor drains across the site. We will continue to manage drain excursions through our normal investigation procedures. However, to assess effectiveness of the recently implemented corrective actions, we will also formally evaluate drain monitoring performance across the site for the period of 01 January 2009 though 31 March 2009. The assessment will be documented by 15 May 2009.*

Bench Tops: *Multiple action level excursions occurred at bench top locations in Class 100,000 areas across the site during the review period. In one of the areas,* (b) (4) *that experienced recurring action levels, the implementation of routine* (b) (4) *proved effective. There were eight excursions from 01 January 2008 to 29 August 2008. As of 28 February 2009, since the implementation of*

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the corrective action on 30 August 2008, there has been one excursion. The other bench top (b) (4) *with no common root causes or trends determined. We anticipate that the site wide enhancements to the cleaning and disinfection program planned for 15 April 2009 should also improve bioburden controls for these bench top surfaces. We will continue to manage bench top excursions through our normal investigation procedures. However, to assess the effectiveness of the enhanced cleaning and disinfection procedure, we will also formally evaluate monitoring performance of Class 100,000 bench top locations across the site for the period of 15 April 2009 though 15 July 2009. The assessment will be documented by 29 August 2009.*

Thaw Baths: (b) (4) *These events are discussed further in the response to Observation 19. This area was among the final areas at the site to deploy standardized* (b) (4) *procedures according to a prioritized implementation plan. Their departmental procedure for* (b) (4) *has now been updated with an effective date of 06 March 2009. Based on the low* (b) (4) *where the standardized procedure has been implemented, we anticipate a significant decrease in the excursion rate for* (b) (4) *. To assess effectiveness of the enhanced cleaning and disinfection procedure, we will also formally evaluate monitoring performance of all* (b) (4) *the site, including* (b) (4) *for the period of 06 March 2009 though 06 June 2009. The assessment will be documented by 18 July 2009.*

In addition to addressing some of the common themes highlighted in the examples provided in this observation, we would also like to respond to each specific item noted.

Response 18A and 18B: *We will address Observation 18A and 18B together as they both refer to controls in the Building* (b) *PedvaxHIB® Chemistry Suite (i.e., Department* (b) (4) *The PedvaxHIB® Chemistry Suite is a Class 100,000 manufacturing suite for processing steps* (b) (4) *of PedvaxHIB®* (b) (4) *. The observation references the failure of* (b) (4) *, which was determined to be due to a change in the* (b) (4) *In addition to correcting the* (b) (b) *numerous other actions were taken to further minimize the risk of microbial contamination. Among these actions was the implementation of a significantly expanded environmental monitoring program in the suite. This enhanced program, which was implemented in February 2008 and included an* (b) (4) *program, was designed to provide an indicator of the level control in the suite and to highlight potential areas of focus for enhanced bioburden control.*

On 10 July 2008, we documented our intent to conduct an evaluation of the expanded monitoring results (b) (4) *to determine if sampling could be reduced back to more routine monitoring levels. We agree that the text in this memo was not adequately reflective of our intent and could be read* (b) (4) *from the date the* (b) (4) *It is important to note that to date, no reduction* (b) (4) *has occurred, and no reduction will occur* (b) (4) *. The evaluation referenced in* (b) (4) *was approved on 11 March 2009. The 11 March 2009 assessment did not support a reduction in the* (b) (4) *. Therefore, a subsequent assessment of* (b) (4) *of data covering February through July 2009 will be completed by 28 August 2009. Once the evaluation supports* (b) (4) *sites identified as potentially problematic will be added to the routine*

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(b) (4) *, while other sites that have demonstrated control will be reduced.*

The (b) (4) *of the PedvaxHIB® Chemistry Suite in February 2008. As noted in the observation, several action level excursions occurred in the subsequent months. The majority of the excursions (i.e.,* (b) *were from floor and drain locations. Each of the excursions was investigated, and several corrective actions were implemented during the course of the year to address the bioburden levels. These actions are summarized in Table 6.*

Table 6: Actions Taken in Response to Microbial Excursions in the PedvaxHIB® Chemistry Suite

Action	Date Implemented
(b) (4)	(b) (4)
Updated SOP 204-608E – "Housekeeping Procedures for D204 – PedvaxHIB® in the (b) to include (b) (4) .	(b) (4)
Updated SOP 204-414X – "(b) Material Movement Into and Between Classified Areas" to require (b) (4) of materials including cart wheels being moved from a lower classed area to a higher classed area.	(b) (4)
Updated SOP204-608E – "Housekeeping Procedures for D204 – PedvaxHIB® in the (b) to clarify requirement to disinfect the interior of cabinets.	(b) (4)

Prior to implementation of the requirement to autoclave hoses, there were (b) (4) *. Subsequent to the implementation of the corrective action, there were* (b) (4) *.*

Prior to implementation of other actions beginning with (b) (4) (b) (4) *discussed in the observation. Corrective actions will be formally documented following the evaluation with a target date of 24 April 2009.*

The overall action level excursion rate for (b) (4) *for the PedvaxHIB® Chemistry Suite was* (b) (4) *The action level rate from* (b) (4) *, the rate from* (b) (4) *This trend indicates that the actions taken have been effective in reducing the number and types of excursions in the PedvaxHIB® Chemistry Suite.*

Due to the location of the majority of the excursions (i.e., floors) and the type of processing that occurs in the areas (i.e., closed system processing), the risk to product as a result of the excursions is extremely low. This is supported, in part, by the fact that six satisfactory media challenges of the PedvaxHIB® Conjugation and (b) (4) *were conducted in the*

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March through May 2008 timeframe. We will continue to utilize our investigation process to further enhance the microbial controls in the area.

Response 18C: *All processing rooms in Building* (b) (4) *area (i.e., Department* (b) (4) *are Class 100,000. As noted in the observation, 26 action level excursions occurred during the period 01 January 2008 through 26 January 2009. A total of 2*(b) (4) *The majority of the excursions (i.e., 19) occurred in* (b) (4) *. The details of the root cause and corrective actions for these excursions are discussed in the response to Observation 19.* (b) (4) *. The excursion rate for* (b) (4) *area, excluding the* (b) (4) *which indicates an adequate level of control of the facility overall.*

Response 18D: *The Building* (b) (4) *area (i.e., Department* (b) (4) *is comprised of Class 100,000 rooms that support* (b) (4) *for GARDASIL® and RECOMBIVAX HB® and rooms that support* (b) (4) *manufacture in Building* (b) *There is no exposure of product or components in either* (b) (4) *A total of 19 action level excursions was reported during the period 01 January 2008 through 26 January 2009. A total o*(b) (4) *The excursions were spread throughout the period, with no more than four excursions occurring in any given month. Fifteen of the 19 excursions occurred on two types of surfaces in the facility. These are discussed below.*

- ***Sink and Floor Drains:*** *Six excursions, four of which were*(b) (4) *were from sink or floor drain samples. Investigation into these excursions determined that* (b) (4) *procedure for the area did not require a response* (b) (4) *SOP 204-400X, "Waste Handling Procedures" was updated on 19 December 2008* (b) (4) *. As previously noted, we will perform* (b) (4)

- ***Bench Tops:*** *Nine excursions, seven of which were* (b) (4) *were from microbial surface samples of bench tops in Class 100,000 rooms in* (b) (4) *. No specific pattern was noted as the excursions occurred on bench tops located in four different rooms, and the excursions occurred sporadically throughout the year. While no definitive root cause has been determined for these excursions, we believe* (b) (4) *will reduce these types of occurrences. We will continue to manage bench top excursions through our normal investigation procedures. However, to assess effectiveness of* (b) (4) *, we will also formally evaluate monitoring performance of Class 100,000 bench top locations across the site for the period of 15 April 2009 though 15 July 2009. The assessment will be documented by 31 August 2009.*

There were no trends noted for the other four excursions from the (b) (4) *as they were from four different sites in four different rooms and were spread throughout the year. Based on the overall* (b) (4) *we believe the facility is in an overall state of*

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environmental control. We also believe the actions taken and planned will further enhance this level of control.

Response 18E: *The Building (b) (4) (i.e., Department (b) (4) is a Class 100,000 facility with one Class 10,000 room containing a Class 100 Bio Safety Cabinet used for non-aseptic dispensing and a Class 10,000 laminar flow hood utilized for cool down of sterilized equipment. The facility also has two Class 10,000 Bio Safety Cabinets (BSC) used for thawing and non-aseptic dispensing operations. We wish to clarify that Building (b) is not used (b) (4) RECOMBIVAX HB® and (b) (4) as was noted in the observation. A total of 17 action level excursions were reported during the period 01 January 2008 through 26 January 2009. A total of (b) (4) These are discussed below.*

- ***Bench Tops:*** *Nine of the excursions that included six (b) occurred on bench top work surfaces in multiple Class 100,000 rooms between February 2008 and October 2008. Eight of the nine excursions occurred prior to implementation of routine (b) (4) in the department on 29 August 2008. This indicated that actions taken have significantly reduced the incidences of bench top excursions in the (b) (4)*

- ***Sinks:*** *Three excursions that included two (b) occurred at sink drains, with the last two occurring in December 2008 and January 2009. As a result of these most recent occurrences, drain cleaning procedures in (b) (4) area are being modified to require documentation (b) (4) in accordance with SOP 262-290X. SOP 305-604, "Maintenance (b) (4) Procedures for (b) (4) " will be effective by 01 May 2009.*

There were no trends noted for the other five excursions from the (b) (4) area as they were from four different sites and were spread throughout the year. Based on the overall action level excursion rate (b) (4) , we believe the facility is in an overall state of environmental control. We also believe the actions taken and planned will further enhance this level of control.

Response 18F: *The Building (b) (4) (i.e., Department (b) (4) contains Class100/Class 10,000 filling rooms for liquid products as well as Class 10,000 and 100,000 support areas. While the observation states that there were 14 microbial action levels during the period from 01 January 2008 through 26 January 2009, our review subsequent to the observation noted 15 microbial action level excursions for (b) (4) . During this period, a total (b) (4)*

Nine of the total 15 microbial action levels were associated (b) (4) . There were no adverse trends noted as the nine excursions were spread throughout the review period at (b) (4) . There were no excursions on product contact equipment. A total of (b) (4)

Four of the total 15 microbial action level excursions for S (b) (4) Room (b) There were no adverse trends noted as the four excursions were spread throughout the review period at (b) (4) . A total of (b) (4)

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samples were taken in Room (b) during the period, (b) (4)

There were no trends noted for the other two excursions from (b) (4) Based on the overall action level excursion rate of (b) (4) we believe the facility is in an overall state of environmental control.

Response 18G: *The Building (b) (b) (4) i.e., Department (b) (4) is a Class 100,000 facility where components and equipment are prepared for sterilization for use in the aseptic filling operations and includes Class 10,000 areas used for the unloading and storage of sterilized components and equipment. All components and equipment (b) (4) A total of (b) (4)*

Twelve of the excursions that included nine (b) were from samples of floor and sink drains. Nine of the drain site excursions occurred at the Room (b) floor drain. Investigations into the repeat excursions identified that (b) (4) and the most likely cause of the microbial excursions. As a corrective action, (b) (4) in Room (b) were replaced with (b) (4) . The two tests taken since replacement of the (b) (4) replacement have yielded results below the alert/action levels. As previously noted, we will perform an assessment of drain monitoring performance across the site for the period of 01 January 2009 though 31 March 2009. The assessment will be documented by 15 May 2009.

The remaining five excursions from (b) (4) were from Class 10,000 area floor site samples. The excursions occurred between February and September 2008. One of the key corrective actions taken in response to the excursions was to ensure proper movement of equipment to facilitate adequate cleaning and disinfection of floors. This corrective action, which was completed on 06 October 2008, proved effective as there were no additional floor excursions (b) (4) samples taken since the last excursion in September 2008.

Based on the overall action (b) (4) , we believe the facility is in an overall state of environmental control. We also believe the actions taken will further enhance this level of control.

Response 18H: *We would like to acknowledge that following the conclusion of the inspection, we realized an oversight in the Compressed Gas data retrieved during the inspection. The results from (b) (4) (i.e., Department (b) (4) were inadvertently omitted from the presented data. A total of (b) compressed gas samples were collected for (b) (4) in the time period with three excursions; bringing the site total to 27 compressed gas excursions, not 24 as previously reported.*

Through our investigation of the 27 compressed gas excursions, we have concluded that the excursion rate is primarily due to bioburden in the environment, where compressed gas systems are sampled for testing and are not representative of the quality of the compressed gas systems themselves. Because the majority of the sampling locations are located in unclassified areas, testing typically requires brief exposure of the (b) (4) . This current limitation in our compressed gas sampling procedure allows for the possibility of microbial contamination of the (b) (4) . As part of a plan to reduce the potential for "false positives", we recently implemented two procedural enhancements that we expect to drive down extrinsic

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environmental contamination events for compressed gases. On 23 January 2009, SOP 262-299X, "(b) (4) " was updated to (b) (4) . Additionally, the use of clean, (b) (4) was also implemented on 23 January 2009. In addition, we will implement another enhancement to further ensure the integrity of compressed gas samples. We will ensure that personnel collecting compressed gas samples in uncontrolled spaces have access to (b) (4) . A detailed project plan identifying the sites that do not currently have a HEPA filtered environment (b) (4) and the appropriate means to achieve this will be approved by 28 June 2009 with action items implemented by 30 November 2009.

We acknowledge the presence of Bacillus cereus in one of the 27 samples and Bacillus species in three other samples. The sampling location where Bacillus cereus was recovered is in an unclassified area. Additionally, two of the three sample sites where Bacillus species was recovered are in unclassified areas, and the third was from a Class 100,000 area. While spore-forming organisms identified in our compressed gas sampling are investigated, their presence is likely due to extrinsic contamination. The lack of system contamination is further supported by the presence of only Staphylococcus or other skin organisms in eight of the 27 excursions and the absence of any significant trends at any of the compressed gas sites. Organisms such as Staphylococcus and other skin organisms are clearly the result of personnel contamination, as they cannot survive in a dry gas system and do not form spores. Our commitment to provide local control or provide a suitable area for (b) (4) will greatly reduce these excursions due to extrinsic contamination.

The 27 excursions are from (b) (4) total compressed gas samples, (b) (4) . The action level for microbial compressed gas samples is (b) compressed gas.

Twenty-two of the 27 excursions, including the (b) (4) , were from samples taken in unclassified mechanical spaces. A breakdown of the 27 excursions revealed that the excursions consisted of 19 samples (b) (4) , seven samples with (b) (4) and one sample of (b) (4) The sample that (b) (4) was collected in the mechanical space of Building (b) Human Papilloma Virus Purification in October 2008. Of the 15 samples collected at this site in 2008, this was the only sample to exhibit any microbial growth. The absence of any microbial growth in the additional samples provides confidence that the compressed gas system is operating in a state of control. All five tests subsequent to the (b) result at this site were below the alert/action levels.

Of the five compressed gas excursions collected within classified areas, two were collected in Building (b in the VAQTA® bulk manufacturing facility. The samples were collected in January and March 2008 and each yielded (b) (4) The root cause was identified as contamination external to the compressed gas system due to either increased activity in the area or collection of a sample near the floor. Corrective actions were implemented on 26 June 2008 to improve the handling of sample tubing. Ten consecutive satisfactory samples have been collected at this site with no microbial growth. The remaining three compressed gas microbial excursions collected in classified areas all occurred in Building (b) (4) Two samples were collected in April 2008 and one in November 2008. The two samples collected in April were collected on two consecutive days and each yielded (b) (4) . The organisms were Micrococcus luteus and Staphylococcus capitis, both of which are skin organisms. The root cause in both cases was determined to be tester contamination due to the types of organisms recovered. Both sites were satisfactorily sampled 13 other times each during review period with no microbial growth. The excursion that occurred in November yielded one CFU of Bacillus species and was

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attributed to (b) (4) being stored in an unclassified area. As discussed above, SOP 262-299X was updated in January 2009 to require (b) (4) . The classified area sample sites associated with the five excursions each support manufacturing operations that are upstream of final product sterilization.

We recognize the Investigator's concern to be that environmental contamination of the sample prevents an accurate assessment of the compressed gas quality. We acknowledge the opportunity and are taking steps to improve our compressed gas sampling procedures; however, we maintain that our compressed gas systems are free of microbial contamination. This is supported by the absence of any significant trends at any of the compressed gas sites as well as by the identification of skin contaminants in a number of samples, which are indicative of extrinsic contamination by the tester. The corrective/preventative actions implemented in January 2009 and the additional controls planned are expected to drive down the incidences of extraneous sample contamination from the environment.

Conclusion: *In conclusion, we are confident that the procedures and controls currently in place ensure a robust and effective program that provides meaningful data on the integrity of our manufacturing environments. This conclusion is supported by the low action level excursion rates highlighted in this response, coupled with the absence of sterility or media challenge failures from these areas. While we believe that the areas and systems addressed in the observations remain in a state of control, the corrective and preventative actions identified in our response will provide further enhancements to our program and control of our classified areas.*

19. Although the (b) (4) vaccine products. Eight (8) out of approximately (b) (4) For example:

    1. (b) (4) of Recombivax bulk had (b) (4) with 10 isolates of *Bacillus cereus*/species, and one *Paenibacillus* species, 4 out of the (b) (4) had results of (b) for Bacillus species.

    2. (b) (4) of Gardasil bulk had 2 action levels microbial contaminations with isolates of *Bacillus cereus* and *Bacillus thuringieneis*.

    3. (b) (4) of Varicella bulk had microbial level of (b) (4) result and isolates of *Bacillus* species, *microbacterium* species, and *Staphylococcus* species.

    B. There is no documentation of cleaning qualification/validations for any of (b) (4) (b) (4) of bulk vaccines.

    C. Although individual investigations were conducted, there is no documentation that formal investigations has been opened to address the high microbial levels including Bacillus cereus noted in these (b) (4) .

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Response 19: *West Point Operations remains fully committed to enhance the microbial control within (b) (4) in vaccine manufacturing. A series of improvements were made throughout 2008 to the disinfection procedures for (b) (4) s the West Point plant site. The rationale for the improved (b) (4) was documented in project plan (b) (4) . This plan was approved 11 July 2008 and included in (b) (4) in vaccine manufacturing. As of 26 January 2009, four of these (b) (4) not yet in service, thus at the time of the inspection there were (b) (4) .*

Given the number of (b) (4) the West Point site, the implementation of the improved (b) (4) , beginning in 2008 and progressing through March 2009. (b) (4) was part of the improved procedures that was implemented for all 41(For (b) (4) where we have implemented (b) (4)) Based on these data, we believe the new procedure is effective at controlling microbial bioburden levels, including spore-forming organisms such as Bacillus species in the thaw baths.

For reference, (b) (4) in Class 100,000 areas, (b) (4) Class 10,000 areas, and (b) (4) Class 100 areas.

We (b) (4) to confirm the effectiveness of these procedural changes. The (b) (4) were fully implemented for all (b) as of 06 March 2009. To assess effectiveness of these enhancements, we will trend all microbial monitoring data for (b) (4) across the site for the period of 06 March 2009 though 06 June 2009. The assessment will be documented by 15 July 2009.

Response 19, Subparts 1, 2, and 3: *To respond specifically to (b) (4) referenced in Observation 19, the noted excursions occurred prior to the implementation of the improved (b) (4) . Procedures were updated on 06 March 2009 for the (b) (4) These (b) (4) located in Class 100,000 areas. Given that the improved (b) (4) has been shown effective against Bacillus species, we anticipate that these improvements will be effective. The third example listed in the finding, thaw bath 1075533, which is located in a Class 100 area, had a single isolated excursion on 20 November 2008. The revised disinfection procedure, including use of (b) (4) was implemented on 15 December 2008. From 15 December 2008 to 23 February 2009, (b) (4) samples were taken on this bath with no excursions.*

Based on the microbial monitoring performance data of the (b) (4) after the implementation of the (b) (4) procedures, we have confidence that the revised procedures are effective at reducing the microbial levels within the thaw baths to acceptable levels. We will monitor the effectiveness of our improved disinfection procedures through the commitments discussed above.

Response 19B: *Based on discussions with the Investigators, we understand the concern in Observation 19B to be the lack of formal documentation to justify the disinfection procedures for the thaw baths used in vaccine manufacturing. While we do not currently have a formal qualification study for the revised disinfection procedures for (b) (4) , the procedures were based on studies that demonstrated disinfectant effectiveness (b) (4) The (b) (4)*

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(b) (4)

To enhance our technical documentation, we commit to qualifying our (b) (4) *procedures by* (b) (4) *. This study will include* (b) (4) *. The effectiveness of the* (b) (4) *We commit that this study will be completed by 28 August 2009.*

Response 19C: *Our procedure SOP 262-221X, "Response to Environmental Excursions", dictates that each microbial excursion is investigated for root cause and for potential impact on product quality. For each of the excursions noted in Observation 19, an investigation was completed per our procedures. As an outcome of the investigation process, we identified several actions, including implementation of a project plan entitled, "Key Requirements for the* (b) (4) *Used in West Point Vaccine Operations," document number SPTE-M-08-0339, approved 11 July 2008 to assess microbial controls for* (b) (4) *including controls effective against Bacillus cereus. We are fully committed to continuous improvement of disinfection procedures for thaw baths across the site as demonstrated by the individual corrective actions associated with each investigation and the project plan described above* (b) (4)

The West Point site now has an improved method for identifying trends in investigations. The (b) (4) *. Per SOP 286-125AX, "Deviation Data Collection and Investigation",* (b) (4) *at West Point. To further enhance our procedures with this* (b) (4) *. Our procedures will be effective by 06 June 2009 to formalize this site-wide review and the response to significant trends.*

20. Regarding Disinfectant Effectiveness Study:

A. There is no documentation that evaluations of the disinfectants effectiveness used in the sanitization of the manufacturing areas were conducted during the investigation into the sterility failure of PedvaxHIB and COMVAX bulk lot #2123254 by *Bacillus cereus* in Chemistry Suite, Building (b) that led to the recall of Marketed PedvaxHIB and COMVAX vials.

B. Although the spread of Bacillus species in the manufacturing areas specifically, (b) for the manufacturing of PedvaxHIB was attributed the spread of the organisms from the floor of one manufacturing areas to others; the disinfectant effectiveness study that was conducted in 2002 failed to include the disinfectants effectiveness on the manufacturing floors.

C. The disinfectant effectiveness study that was conducted in 2002 was only conducted on (b) (4) and there is no disinfectant effectiveness data to support (b) (4) . The firm currently has a

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draft and unsigned disinfectant effectiveness study protocol with no documentation of implementation start date.

Response 20A: *We wish to clarify that Lot 2123254 was the failing media challenge lot from the Building (b Chemistry Suite used for the manufacture of PedvaxHIB® and COMVAX® bulk and not a PedvaxHIB® or COMVAX® lot. During the investigation into the media challenge failure, we did test our* (b) (4) *This testing is documented in the report entitled* (b) (4) *The report, which was provided to the Investigator, shows that* (b) (4) .

This study, in conjunction with the collection of published scientific literature on the effectiveness of sodium hypochlorite against spore-forming organisms, provided us with sufficient data and scientific rationale to conclude that the effectiveness of the disinfectant used was not a contributing factor in the media challenge failure investigation.

Response 20B: *We acknowledge that our disinfectant effectiveness study should be enhanced by including an evaluation of the flooring material (i.e.,* (b) (4) *As a result,* (b) (4) *will be evaluated in* (b) (4) *. The study protocol, a draft of which was shared during the inspection, was approved on 23 February 2009. The study is due to be completed by 11 May 2009. Upon completion of the study, we will evaluate if any changes should be made to our disinfection program and will promptly implement, as applicable.*

In addition, as described previously in our response to Observation 18, we have taken several actions in Building (b over the past year to control Bacillus, and we are in the process of (b) (4) *the revised SOP 262-217X, "Cleaning, Disinfection, and Decontamination of Classified Areas" and the new SOP 262-293X, "Transfer of Materials".*

Response 20C: *We acknowledge that our disinfectant effectiveness study should be enhanced by including an evaluation of* (b) (4) *The study protocol, a draft of which was shared with the Investigator, was approved on 23 February 2009 and is due to be completed by 11 May 2009. Specifically, the* (b) (4) *. These surfaces represent all materials for which* (b) (4) .

Although it is true that there is no specific disinfectant effectiveness data for the use of (b) (4) *Therefore, we concluded that a separate study was not required since* (b) (4) *. We acknowledge, however, that our rationale for the equivalency of these disinfectants should have been better documented and as a result, we will document by 27 March 2009 our rationale as* (b) (4)

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While it is true that no effectiveness studies for (b) (4) *on surfaces were performed, this is because* (b) (4) *has the same active ingredient as* (b) (4) *provides equivalent (or better) disinfection effectiveness compared to* (b) (4) *Furthermore, we have studies, which were shared with the Investigator, showing that* (b) (4) *is effective at disinfecting surfaces.* (b) (4) *In addition,* (b) (4) *Furthermore,* (b) (4) *the B. cereus was exposed to, the faster the population was killed. Nonetheless, we acknowledge that our rationale for the equivalency of these disinfectants should have been better documented and as a result, we will document by 27 March 2009 our rationale as to why they are equivalent.*

21. Particles/impurities such (b) (4) are used in the manufacture of vaccines products. However, the firm continued to manufacture vaccine products with these raw materials with justifications that the use of the raw materials has no impact on product quality in the event that similar particles were present in the materials. No released vaccine lots were placed on stability in regards to these raw materials particles/impurities. For example:

A. Per (b) (4) dated February 27, 2008 after QC release and while dispensing kit from (b) (4) in the container. Identification of (b) (4) concluded that they are (b) (4) The firm continued the use of the component in the manufacturing of vaccine products. Trend analysis from February 26, 2007 to February 26, 2008 indicated that this was the 11th occurrences in the past 12 months of particulate matter in weight and dispensing. In addition, only 2 out of the 7 received (b) (4) per SOP #263-61203X, dated December 15, 2008.

B. On three separate occasions particles/impurities were found (b) (4) . The firm continued the use of the component in the manufacture of vaccine products. Trend analysis from February 26, 2007 to February 26, 2008 indicated this was the 3rd extraneous matter atypical event for the lot (b) (4) received for the same period as follows:

1. Per (b) (4) dated December 01, 2007 during (b) (4) which was identified by (b) (4)

(b) (4)

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2. Per (b) (4) dated February 27, 2008 while dispensing an associate discovered extraneous particle inside a bag of lot of (b) (4). Identification of the particle by (b) (4).

3. Per (b) (4) date January 01, 2008 during dispensing two dark particles were found and were identified by E(b) (4)

C. On three separate occasions particles/impurities were found (b) (4) The firm continued the use of the component in the manufacture of vaccine products. Trend analysis from February 26, 2007 to February 26, 2008 indicated this was the (b) (4)

1. Per (b) (4) dated February 29, 2008: while dispensing of (b) (4), an associate discovered particle matters. Identification of the particle (b) (4)

2. Per (b) (4) dated May 27, 2008 during weighing operation a dark particles identified by (b) (4).

3. Per (b) (4) dated June 05, 2008 a blue gray particle were found towards the bottom of (b) (4)

D. Although the firm continues to document extraneous particles/impurities in the above received manufacturing components, inadequate corrective and preventive actions were instituted. Per the above (b) (4) dated February 29, 2008 the vendor responded to the firm's concerns and stated that it has confirmed through prior investigations that the particles found in the components are inherent to the manufacturing and process train for these materials. As such no additional CAPAs were instituted at the vendor or at the firm.

E. (b) (4) have been conducted. There is no documentation that attempts were made to re-qualify new suppliers that could supply products with no particles/impurities.

F. There are no validation studies to support the firm's claims of no product impacts for vaccine products such as: Pneumovax, Pedvax, Varicella, Zostavax, Mumpsvax and MMR II manufactured using these raw materials. Per Memo #2007-199-007 dated October 31, 2007: filters, i.e.,(b) (4) from the product. Furthermore, that if the particles (b) (4) and (b) (4) Also that (b) (4) ; and per (b) (4)

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G. The firm indicated that the continued used of these lots was based on the lots of (b) (4) that passed USP specifications. (b) (4)

Response 21: *The two materials in question;* (b) (4) *United States Pharmacopeia (USP) and American Chemical Society (ACS)* (b) (4) *, were both fully released by each vendor. Upon receipt at West Point, both lots were tested again and met all pre-defined quality specifications as defined by either USP monographs and/or Merck Quality Standards prior to release by West Point Quality Operations Product Release staff for use in West Point Operations.*

We take seriously the presence of any identified physical matter, including any foreign materials and/or impurities, in our raw materials. In each case, we initiate investigations to determine the identity of the particle, and based on information provided by the vendor, we determine if the particle is inherent or foreign to the manufacturing process. In addition, we evaluate our processes for the ability to remove insoluble material to determine the potential impact on product quality. If there is potential for some of the particulate matter (b) (4) *. In each of the cases identified, the lot in question fully met all of its pre-defined quality specifications. Additionally,* (b) (4) *USP Merck specifications include a test for physical matter with a specification of* (b) (4) *All test results met the required specifications prior to release and use of the respective raw material by West Point Production Operations.*

Because our investigation concluded that the lots highlighted in the Observation met all of their pre-defined quality specifications and represented findings that were orders of magnitude below the USP and/or Merck Quality Specifications, (as described in more detail below), no additional requirement was identified to add these lots into the stability program. However, we note that given the nature of our (b) (4) *that were manufactured using the affected lots of* (b) (4) (b) (4) *in the Observation have been placed on stability. These lots are part of routine stability studies and represent product families that include: ZOSTAVAX®, GARDASIL®, VAQTA®, PNEUMOVAX®23, RECOMBIVAX HB®, and PedvaxHIB®. To date, no Out of Specification or atypical results have been obtained in these stability studies. ProQuad® lots made from the affected raw material will be on stability by 01 June 2009.*

For the specific examples referenced in the Observation, we provide the following detail:

A. (b) (4) ***:*** *During this investigation, the six particulates identified in one container from the lot were submitted to our Analytical laboratories for identification, and the lot was quarantined pending completion of the investigation. The investigation included the identification of the particulates and confirmation by the vendor that these particulates are inherent to their manufacturing and packaging process. Because of the slight possibility that the particulate could be in a soluble form, a Medical/Toxicological assessment was included as part of the product impact evaluation. In addition, the evaluation confirmed that the number of particulates as specified by* (b) (4) *was well within specification levels. The conclusion of no product impact was based on presence* (b) (4) *manufacturing and the Medical/Toxicological assessment that noted the potentially soluble particulate components would not have potential to impact the health of patients. The*

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summary of our investigation concluded that five of the seven containers from the lot had been subdivided for use in operations, and only one was observed to have particulates. Within the one container, a total of six particulates was observed, which (b) (4) *. Since the investigation, the remaining two containers have been utilized in operations and no particulates were observed. Furthermore, we calculated the worst-case weight/weight percent of observed particulates in the lot, which was determined to be* (b) (4) *.*

For trending purposes, the reference to (b) (4) *relates to all cases where a particle was observed during* (b) (4) *and this specific vendor, this is the only occurrence of particulates identified out of the four lots received by this vendor since January 2007. The reference to sampling two out of seven containers is correct and appropriate for* (b) (4) *Per our SOP 263-SI203X, "Chemical Sampling Procedures", a total of two containers was required to be sampled out of the seven containers received in this lot, which is aligned with statistical sampling expectations.*

B. (b) (4) **:** *All three examples referenced in Observation 21, Subpart B, refer to* (b) (4) *21. In each case, the lot of* (b) (4) *and Merck Quality Standard Specifications prior to release by the West Point Quality Operations Product Release group and prior to use in production operations. This includes testing at Merck West Point for physical matter with a specification of* (b *In addition, each event was investigated individually and documented in its respective investigation report. The investigations included the identification of the particulates, confirmation by the vendor that these particulates are inherent to the vendor manufacturing and packaging processes, and confirmation that the particulates are insoluble. Therefore, a Medical/Toxicological assessment was not needed. It was also confirmed that the number of particulates as specified by* (b) (4) *was well within specification levels. Based on all this information, the investigation concluded that the insoluble particulates would be removed by the filtration process during media manufacturing, and therefore, there was no impact to product quality.*

C. (b) (4) **:** *The three examples referenced in Observation 21, Section C, refer to* (b) (4) *. In each case, the lot of* (b) (4) *met all of its pre-defined USP and Merck Quality Standard Specifications prior to release by the West Point Quality Operations Product Release group and prior to use in production operations. This includes testing at Merck West Point for physical matter with a specification of* (b *. Each event was investigated individually and documented in its respective investigation report. The investigations included the identification of the particulates, confirmation that these particulates are inherent to the vendor manufacturing and packaging processes, and confirmation that the particulates are insoluble. Therefore, a Medical/Toxicological assessment was not needed. It was also confirmed that the number of particulates as specified by* (b) (4) *were well within specification levels. Therefore, the investigation concluded that there was no impact to product quality.*

In summary, for the period of time referenced in Observation 21, Subparts B and C, Merck West Point released (b) (4) *Over the course of the use of these containers in manufacturing, a total of 32 particulates were observed and investigated, the majority of which were extremely small (i.e., approximately* (b) (4) *In all cases, the particulates were identified and confirmed to be inherent to the raw material and/or the vendor's manufacturing process. Thirteen of the* (b)

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containers (i.e., approximately (b) were observed to contain some evidence of visible particulates; this affected approximately eight lots in this overall time period. The worst-case (b) (4) and the USP limit of ≤ 0.1% for insoluble matter as defined in the General Notices. Based upon these data and the thorough investigation surrounding each of these events, it was concluded that the insoluble particulates would be removed by the filtration process during media manufacturing and therefore there was no impact to product and that the raw material may be used in production operations.

D. **APR** (b) (4) *met all of its predefined Quality specifications including a test for extraneous matter and since the vendor confirmed that the extraneous matter in question was inherent to their manufacturing process, the investigation accurately concluded that a CAPA was not required. In the event we encounter extraneous matter that is foreign to the vendor's manufacturing process or if the level of extraneous matter results in an OOS, the material will be rejected and an investigation will be conducted which will identify, as appropriate, applicable CAPAs.*

E. ***Requirements for Vendor Audits:*** *The Investigator accurately states that we did not conduct "For-cause" audits of the vendors. Our rationale was that an audit was unnecessary since the vendor had already confirmed that the presence of the particulates was inherent to its manufacturing/packaging processes; the levels observed were orders of magnitude below accepted specifications, and the lots were well within their pre-defined specifications for particulate/insoluble matter. As stated below in the corrective action, we will evaluate if a change in (b) (4) supplier to one that provides USP grade will offer significant improvement in the frequency or level of particulate matter.*

F. ***Validation Studies:*** *Although the presence of particulate matter identified in this observation is well within the USP specifications as well as Merck's specification, it should be noted that each of the cited raw materials also undergoes a (b) (4) This (b) (4) was reviewed as part of our product impact assessments. The (b) (4) Therefore, we believe that the ability of the process using the above described filtration is effective at removing the particulates during filtration and that additional specific validation studies were not warranted.*

G. (b) (4) ***:*** *In the case of (b) (4) and (b) (4), we have had direct experience with each of these suppliers for over 15 and over 5 years, respectively. Since both of these materials have a pre-defined specification for either physical matter or insoluble matter and in each case when particulate matter was observed, levels were orders of magnitude below any specification threshold, we believe based on the information provided above that the quality decision made in each case was appropriate. For the cases discussed with the Investigator, the particulate matter was not observed during initial sampling activities; the particulates were observed during downstream subdivision of the raw material containers, even at the extremely low levels that were present. Due to the observance of the particulates during downstream processing, we have the ability to assess homogeneity of the lot. As mentioned previously and as a result of our discussion with the Investigator, we have identified a CAPA that will be implemented as described above.*

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Corrective Action Applicable to Observations 21, Subparts A, B, C, and G:
With respect to (b) (4) *, we will evaluate alternate suppliers of this chemical to determine if a supplier of USP grade material would be significantly superior in reducing the presence of particulate matter, while continuing to meet pre-determined specifications. This evaluation will be completed by 08 December 2009.*

22. Regarding Compressed Gases Used in Vaccines Manufacturing:

A. Not all sampling of compressed gases sterilizing filters used in vaccines manufacturing processes are representative of use conditions. (b) (4) are not monitored or sampled at the point of use during manufacturing. In addition, there is no documentation in any of the SOPs including SOP# 262-299X dated January 20, 2008 titled: (b) (4) of Compressed Gases that specifically states the location for the testing of compressed gases, i.e., (b) (4) .

B. Not all compressed gases point of (b) (4) used in the manufacture of vaccines have data to justify the number of uses. For example: (b) (4) and the following were noted:

1. There was no documentation of before and (b) (4)

2. There was no documentation of before and (b) (4) of, i.e., Zostavax, Varivax and Pedvax could be used for 6 months.

3. (b) (4) .

C. There are no documentations of deviation and/or investigation as such; no product impact assessment was conducted into (b) (4) . The compressed gas is used to (b) (4) . Deviation Report #208-2008-025 that was signed on February 03, 2009 was provided after the above deficiency was noted during this inspection.

D. There is no documentation of corrective and preventive actions for the following compressed gases excursions:

1. No documentation of CAPA for Investigation #2008-EM220-0038 dated July 25, 2008 regarding (b) (4) in MMR II bulk manufacturing with particulate action level count of (b) (4) . The root cause of the action level particle count was determined to be due to particles generated by (b) (4) There is no documentation of corrective actions to prevent reoccurrence. Per the investigation report: no CAPA is required.

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2. No corrective and preventive action was instituted for production sampled of (b) (4) Per Investigation #2008-EM220-0028 dated June 19, 2008 the root cause was attributed to particulate that were generated by s(b) (4) Per the investigation report: no CAPA was required.

3. Investigation # 2008-EM225-0026 dated August 01, 2008 conducted (b) (4) The investigation failed to include 19 missed tests for various compressed gases used in vaccine manufacturing from November to December 2008.

Response 22: *We fully understand that the proper generation, control, and monitoring of compressed gases are important factors in vaccine manufacturing. As background, there are currently* (b) (4) *compressed gas systems at the Merck West Point manufacturing site. In each system, the compressed gas is* (b) (4)

We acknowledge that each compressed gas location should be further assessed to document its use within manufacturing and its criticality relative to maintaining product quality. These considerations will dictate the level of monitoring required at each specific location. The compressed gas locations can be classified into the following categories, as shown in Table 7. The point-of-use (POU) locations in Observation 22 contain both critical and non-critical locations.

Table 7: Categories for Compressed Gas Locations

Category	Definition	Current Control	Example
Critical	(b) (4)		
Non-Critical (Class 100 and 10,000)	(b) (4)		
Non-Critical (Class 100,000 and unclassfied)	(b) (4)		

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While not documented in a formal plan, we initiated implementation of (b) (4) *) compressed gas monitoring of systems across the West Point site, in* (b) (4) *. Implementation was completed for the first department, that is in* (b) (4) *in August 2008. We acknowledge that our current compressed gas monitoring program does not* (b) (4) *As such, we will take the following actions:*

- *Develop a documented project plan to establish appropriate* (b) (4) *. This plan will be approved by 05 May 2009, with key implementation dates set for all applicable departments across the West Point site.*

- *Update SOP 262-113X, "Environmental Monitoring Plan for Classified Areas and Systems" to include the requirement to perform gas monitoring* (b) (4) *in accordance with the documented project plan by 06 June 2009. As part of this SOP revision, we will ensure that the SOP clearly* (b) (4)

- *Complete implementation of testing at specified* (b) (4) *and obtain initial results by 01 February 2010. The time required to implement this* (b) (4)

While we agree that the assessment and (b) (4) *oss the site will further enhance our program, we believe that our existing testing program provides a high level of assurance that the quality of gas delivered to manufacturing areas is suitable for its intended use. This is based on the fact that (i) any gas used in critical applications (i.e., required to maintain sterility assurance of the product) passes through* (b) (4)

In summary, we believe that our existing compressed gas control and monitoring program provides a high level of assurance that the quality of gas delivered to manufacturing operations is suitable for its intended use. This is supported by (b) (4) *The actions planned as described above will further enhance our compressed gas monitoring program.*

Response 22B: *In response to this observation, we will implement the following phased approach to document our principles and to align our gas filtration procedures to ensure consistency of application across the site.*

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***Phase I** - We will define and document the principles to be employed for each category of compressed gas filters referenced in Response to 22A, Table 7, in vaccine manufacturing at the West Point plant site by 19 May 2009. This plan will document the requirements for* (b) (4) *the determination of the* (b) (4)

(b) (4)
principles by 28 July 2009.

(b) (4)
The project plan will be created by 21 September 2009.

We would like to provide additional information relating to the examples that were specifically noted in the observation.

***Regarding Observations B1 and B2:** The filters identified in Observations B.1 and B.2 are in the third category in Table 7, Non-Critical Applications in a Class 100,000 or unclassified area. The compressed gas locations in Building* (b) *are solely used for the processing of equipment and* (b) (4) *n. These filters are* (b) (4) *at the vendor, as documented on their Certificate of Analysis. These filters are located* (b) (4) *at the compressed gas source, which are post-*(b) (4)

***Regarding Observation B3**: The three filters referenced in Observation 22B3 are utilized in critical applications in* (b) (4) *in Building* (b) *These* (b) (4) *at West Point. Although we acknowledge that we do not have formal studies supporting the number of times that these filters can be sterilized, we do have extensive historical* (b) (4) *These data include* (b) (4) *. Our use data are supported by the information provided on the vendor Certificate of Analysis* (b) (4) *.*

The (b) (4) *. In 2008, there were* (b) (4) *completed in Building* (b) *totaling approximately* (b) (4) *, with zero sterility failures. In addition, during 2008, Building* (b) *completed* (b) (4) *There was one vial from one media challenge that exhibited growth. The root cause of this single alert level event was determined to be inadequate disinfectant of the bag in which the media was received.*

Part of our phased approach to align practices and to provide the enhancements described above will include a documented assessment based on our historical in-process use data that have been documented in (b) (4) *. We will do this* (b) (4)

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(b) (4)

In summary, as committed above, we will review our gas filter management practices and identify areas where these practices should be enhanced in order to ensure that data support the use of these filters and to further ensure that procedures regarding compressed gas filter management are consistent across all manufacturing areas.

Response 22C: *As background to Observation 22C, we want to clarify that we have formal procedures that define our quality systems surrounding Environmental Monitoring investigations. In accordance with SOP 286-125AX, "Deviation Data Collection and Investigation" and SOP 262-221X, "Response To Environmental Excursions", and SOP 286-125X, "Atypical Process Reports (APRs) in West Point Operations", all environmental monitoring action level excursions are required to be investigated in a timely manner. SOP 262-221X requires that a Deviation Alert be submitted within one business day following the action level result appearing on the Environmental Monitoring Out-of-Specification (OOS) report. This OOS report contains all suspect alert and action level results approved within the last 24-hour period.*

We acknowledge that the action level microbial excursion of (b) *for compressed gas sample identification (ID)* (b) (4) *had not been investigated as required by our procedures. This sample was collected on 05 October 2008, and the OOS result appeared on the Environmental Monitoring OOS report on 15 October 2008, following incubation, result reading, and approval of the test. After this event was brought to our attention, we immediately issued two Deviation Alerts on 03 February 2009. The first was to investigate the action level result for sample ID* (b) (4) *The second was to determine why an investigation was not initiated when the action level result occurred.*

The investigation into the microbial level excursion for sample ID (b) (4) *was completed on 23 February 2009 under investigation 2009-EM208-0002. The sample was collected from a* (b) (4) *located in Class 100,000 room in Building* (b) *This gas location is used to complete* (b) (4) *The* (b) (4) *. The excursion was determined to be an isolated event in that there were no excursions in the 12 months prior and that there were also no excursions in the subsequent three months of data at this sampling location. There was no product impact associated with this event given that: (i) this excursion was determined to be an isolated incident, (ii) there are additional* (b) (4)

The investigation into the lack of a timely investigation into the noted excursion was completed on 11 March 2009 under investigation 262-2009-025. The investigation determined that the action level result correctly appeared on the OOS report on 15 October 2008, but the Deviation Alert for this excursion was not initiated due to human error. A Deviation Form was drafted but was not initiated formally into our systems due to a miscommunication between departments. A review of all environmental monitoring samples currently in (b) *from 08 February 2003 to 18 February 2009 was completed and determined that there were no other instances of failure to initiate a Deviation Alert in response to an OOS result. As an immediate CAPA during the investigation, the Environmental Monitoring Specialist was made aware of the error and was re-trained on SOP 286-125AX and SOP 262-221X. All Environmental Monitoring personnel involved in deviation management will be provided awareness training regarding this event by 27 April 2009.*

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Response 22D: *Site procedures governing Environmental Monitoring excursions in SOP 286-125AX, "Deviation Data Collection and Investigation", and SOP 262-221X, "Response to Environmental Excursions" require that an investigation be conducted for all environmental monitoring action level excursions. The investigation should include the identification of a root cause, and when applicable, the identification of CAPAs. CAPAs are implemented to resolve any control issues identified during the investigation and to prevent reoccurrence of the event (i.e., in this case, another excursion).*

After reviewing investigations 2008-EM220-0038 and 2008-EM220-0028 further, we agree that CAPAs should have been implemented to reduce repeat occurrences. As such, we will implement appropriate CAPAs as described below:

1. *Investigation 2008-EM220-0038: A CAPA will be initiated to* (b) (4) *. The CAPA will be completed by 30 April 2009.*

2. *Investigation 2008-EM220-0028: A CAPA will be initiated to update SOP 262-299X,* (b) (4) *", and SOP 262-475,* (b) (4) *The CAPA will be completed by 30 April 2009.*

With regard to Item 3 referencing EM investigation 2008-EM225-0026, the root cause was attributed to human error with multiple contributing factors. We respectfully submit that this investigation did include four CAPAs to address the root cause and contributing factors. These CAPAs provided appropriate (b) *access to the supervisor involved and provided for notification/training across both Operations and Environmental Monitoring personnel on the learnings from the investigation. (Note – additional detail regarding this missed test investigation, is provided in the response to Observation 23 below.)*

Although the missed test event itself was investigated, we agree that the investigation should be supplemented to reconcile the 19 samples noted by the Investigator. Investigation 2008-EM225-0026 was amended to investigate these samples. It was determined that 14 of the 19 samples were not missed, because the sample sites were not active at the time of sampling. The remaining five samples were missed and as such, were included within the revised scope of investigation 2008-EM225-0026. A fifth CAPA was also added to the amended investigation to conduct training for Operations personnel on instructions to not reject routine samples and to contact the Environmental Monitoring group if such an action is required. This training was completed as part of the close-out of the amended investigation.

A separate investigation 262-2009-026 into this omission was completed on 11 March 2009. The root cause was shown to be the result of a human error on the part of the EM Specialist assigned to investigate the missed tests. The EM Specialist, although fully trained, inadvertently entered the wrong date in the (b) (4) *This human error resulted in the 19 samples not showing up in the investigation trends, and subsequently not being listed in the investigation. In addition, the employee classified 14 of these samples as "missed tests", despite being from an inactive location at the time of sampling. In response to this investigation, the status of the tests was updated in* (b) *to reflect the correct status* (b) (4) *The Environmental Utilities team was retrained on SOP 262-NGL100X, "Use of* (b) (4) *for Environmental Monitoring", and a training module will be created to aid in the process of identifying missed tests and when routine samples should be rejected in* (b) *by 30 June 2009.*

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The investigations noted in Observation 22.D occurred between June and August 2008. Since the time of these investigations, the West Point site has made significant enhancements to its deviation management process. As discussed during the inspection, enhancements were implemented in November 2008 to better define what constitutes a deviation, how to investigate a deviation and the minimum requirements for an investigation report. Furthermore, the site has created a dedicated Deviation Management Team. As part of the formation of the Deviation Management Team, all Quality Approvers were trained in February 2009 to ensure that all lots/samples impacted by a deviation event are identified as part of the investigation and that the appropriate source documentation is reviewed prior to approving any investigation.

We believe that the CAPAs instituted in response to this observation coupled with the enhancements instituted as part of the site's deviation management initiative strengthens our quality systems and will prevent future re-occurrence of these gaps.

23. There is no investigation for (b compressed gases missed tests due to (b) (4) and (b) (4) . Per Deviation Alert Report #262-2008-014 dated December 18, 2008 calculation was created in (b) in the particulate compressed gases to calculate the equipment calibration expiration date. The calculation was incorrect and did not work; samples that were previously (b) (4) . The previous samples were not re-logged as such, were documented as missing. (Investigation was initiated during this inspection after the deficiency was noted). In addition, several sampling of compressed gases used in vaccine manufacturing were missed from January 2008 to 2009, for example, (b) (4) for the monitoring of Rotavirus compressed gases were missed.

Response 23: *We fully understand and are committed to the need to adhere to all pre-established compressed gas sampling plans. Our response to this observation is provided in three sections as follows: (i) Our overall performance around missed compressed gas sampling, (ii) Investigation into 34 missed samples due to* (b) (4) *, and (iii) Missed compressed gas samples in the Rotavirus manufacturing area.*

Additionally, we recognize that several of the investigations identify human error as the root cause or a contributing cause to missed tests. We recognize the importance of strict adherence to procedures and are committed to ensuring that all tests are appropriately performed and that we have the necessary oversight of our environmental sampling program. This includes ensuring clarity of roles and responsibilities and accountability of individuals responsible for the scheduling of and collecting of environmental samples. We believe that the actions described in this response ensure that these goals are met.

Overall Performance Regarding Missed Compressed Gas Samples: *We are committed to reliably adhering to our environmental sampling schedule as a means of ensuring adequate control of our classified areas and systems. It is important to note that the cluster of missed samples in the Rotavirus area noted in the observation are not representative of our overall compressed gas sampling performance. Our historical site-wide performance demonstrates that, with the exception noted in the Rotavirus are in 2008, we have consistently been completing samples as intended. Data supporting this are as follows:*

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- *In 2006,* (b) (4) .
- *In 2007,* (b) (4) .
- *In 2008, in all areas* ***excluding Rotavirus****,* (b) (4) *missed.*
- *In 2008, in all areas* ***including Rotavirus****,* (b) (4) *missed.*

Each case of a missed sample was appropriately investigated in accordance with SOP 262-221X, "Response to Environmental Excursions".

While historical data support that we have routinely achieved a low missed test rate, we will strengthen our system by incorporating several enhancements as defined below. This will ensure implementation of a site-wide plan that reduces the potential for missed tests in all classified areas and systems by doing the following:

- *Assessment of missed test root causes across the site and identification of additional holistic CAPAs as appropriate.*
- *Development and implementation of missed sample metrics designed to identify problematic areas and or individuals.*
- *Use of behavioral analysis tools to better assess all root causes related to human related events associated with sample scheduling, collection and, tracking.*
- *Development of simplified and robust systems to track status of scheduled tests.*
- (b) (4) *to ensure samples are not inappropriately rejected. This will be done in alignment with the* (b) (4) *described in Observation 24.*
- *Review of SOPs and revisions as appropriate to ensure completeness and specificity of procedures for* (b) (4)
- *Clarification of roles and responsibilities* (b) (4) .

By 24 April 2009, we will develop a (b) (4) *detailing this systemic approach and the specific actions we will take to reduce missed tests.*

Missed Samples Due to (b) (4) *We would like to clarify that, at the time of the inspection, an investigation into the event of missed samples due to* (b) (4) *was already in progress and was initiated on 18 December 2008. At the time of the inspection, since the investigation was still in progress, a completed investigation report was not available. Because missed tests were reported in multiple departments, a decision was made by West Point Product Release to consolidate the investigation across the individual areas to ensure the investigation included a comprehensive evaluation of all potentially systemic missed test issues. As a result,*

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and as shared with the Investigator, Deviation Alert 262-2008-014 was initiated on 18 December 2008. The deviation alert form included a description of the event, the immediate corrective actions taken, the event trending, and the Quality review and approval of the Deviation Alert. Part of the Quality approval, as defined by SOP 286-125AX, is for the Quality Approver to determine the type of investigation that needs to be performed based on the deviation. In this case, the Quality Approver correctly and appropriately classified this event as a Minor investigation in accordance with event trending procedures in SOP 286-125AX, because trending determined that this event had not occurred previously. The investigation was ultimately closed on 27 February 2009.

We do acknowledge that the minor investigation form does not have a date-initiated field, and thus, it is not possible from the minor investigation form alone to know when the investigation was initiated. The original intent was that the deviation alert form and the minor investigation form would always be reviewed together. We learned during this investigation that our assumption was not correct. As discussed with the Investigator at the time of the inspection, we commit to updating SOP 286-125AX to specify that the minor investigation is initiated at the time of approval of the deviation alert form. We further commit to updating the minor investigation form to include the date the investigation is initiated. We will update SOP 286-125AX and modify the Minor Investigation form by 24 March 2009.

We would also like to clarify the events surrounding the deviation identified in Deviation Report 262-2008-014. In September 2008, a change request to our (b) (4) [redacted] *This* (b) (4) [redacted] *. The* (b) (4) [redacted] *The first phase affected compressed gas* (b) (4) [redacted] *and was implemented on 20 September 2008.*

SOP 027-SL200X (b) (4) [redacted] *," requires that any* (b) (4) [redacted] *Due to human error, the calculation was not entered into* (b) (4) [redacted] *correctly and therefore did not function properly. The procedure* (b) (4) [redacted] *. As a result, the incorrect calculation was placed in service. As a result of the expiry calculation error, samples collected after the change was implemented remained in* (b) (4) [redacted] .

On 20 November 2008, it was identified that compressed gas samples were remaining as (b) (4) [redacted] *prevent other samples from remaining in* (b) (4) [redacted] *In accordance with SOP 262-NGL100X,* (b) (4) [redacted]

A retrospective review of (b) (4) [redacted] *from January 2007 to 03 March 2009 was conducted and identified no other cases in which a change was implemented*

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prior to second person review or automation testing. Therefore, we conclude this was an isolated occurrence. The individual responsible for implementing the erroneous calculation in (b) (4) *was retrained in SOP 027-SL200X, "Template Object Validation and Approval" on 19 February 2009. Furthermore, as a site-wide corrective action, all system administrators will receive additional training on the importance of following approved procedures, using this event as a case study for awareness. This training will take place by 25 April 2009.*

The investigation into these events explicitly identified each missed test site and evaluated the associated potential quality impact. In nineteen of the 34 cases, the compressed gas is used in a (b) (4) *, and therefore, it has no impact on product quality or* (b) (4) *. The remaining 15 compressed gas sites are each used in* (b) (4) *. However, because in each of these 15 cases, the compressed gas was supplied* (b) (4) *again, there was no impact to product quality or* (b) (4) *as our review has shown that* (b) (4) *Additionally, we assessed particulate data from each impacted sample location, bracketing each missed particulate sample (i.e., 10 samples prior to and three samples after the missed sample) to evaluate the state of control of the system. This review found zero excursions out of a total of the* (b) (4) *samples surrounding the 34 missed samples. Additionally, a review of the* (b) (4) *As a result, we concluded that the compressed gas systems were in a state of control and there is no product quality impact as a result of these missed tests.*

Missed Samples in Rotavirus Manufacturing: *The observation states that several samplings of compressed gas samples were missed from January 2008 to 2009 and provides as an example that 57 of* (b) (4) *compressed gas samples were missed in the Rotavirus manufacturing area. We would like to clarify that 57 samples were shown as missed, and* (b) (4) *samples were actually taken.*

The 57 missed Rotavirus samples were associated with four different investigations. Product impact was assessed for each of the four investigations. However, because compressed gas in the Rotavirus area is supplied to use points that are protected by (b) (4) *in each of the four investigations, it was concluded that there was no potential for product impact as* (b) (4)

In addition, we performed an overview of the compressed gas system(s) performance to verify the state of control of the system. A review of the (b) (4) *compressed gas samples collected in Rotavirus manufacturing over the period 01 January 2008 to 26 January 2009 identified four microbial action level excursions and one particle action level excursion. Two of the microbial excursions occurred on 31 July 2008, and yielded results of one and* (b) (4) *. The third and fourth excursions occurred on 04 September 2008 and 06 September 2008; each of these samples* (b) (4) *. All four samples were collected in* (b) (4) *. The root cause for the four microbial excursions was inadequate disinfection of the test equipment that is stored in* (b) (4) *A CAPA* (b) (4) *of the microbial samplers was implemented in December 2008, and an additional CAPA* (b) (4) *was implemented in January 2009. No compressed gas microbial excursions have occurred in Rotavirus manufacturing since September 2008. The action level particle count excursion occurred on 22 January 2009. The root cause for this particle excursion was* (b) (4) *. The site was flushed and sampled again on 23 January 2009 with satisfactory results. All* (b) (4) *compressed* (b) (4) *were taken in* (b) (4) *, and all production points of use are equipped with*

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(b) (4) *, providing assurance of the compressed gas quality in Rotavirus manufacturing. This is further supported by the successful completion of* (b) (4) *one in April and one in December during this same time-period.*

Two of the 57 missed samples discussed in the Rotavirus section of the observation are related to the (b) (4) *. Details of the three additional investigations comprising the remaining 55 missed samples are provided below.*

APR (b) (4) ***:*** *Investigation APR* (b) (4) *was initiated on 01 August 2008 following the discovery of 51 samples with a status of "Missed" in the Rotavirus area. "Missed" samples are those that were appropriately scheduled but were never taken. Our review subsequent to the inspection has revealed that 32 of these samples were inappropriately classified as "Missed". The compressed gas sites for these 32 samples are associated with* (b) (4) *in which only one of two sites is in service at a time, and therefore, only one of the two is to be sampled. Samples are* (b) (4) *at the sites associated with this investigation. Because only the* (b) (4) *which in this case was in Rotavirus manufacturing, should* (b) (4) *rom the schedule in accordance with SOP 262-NGL100X, "Use of S*(b) (4) *. Because these 32 samples were not rejected from the schedule, they were inappropriately classified as "Missed" and included in the 57 highlighted in this observation.*

We do acknowledge that the remaining samples were indeed bona fide missed samples. The identified root causes of the true missed tests investigated in APR (b) (4) *were due to human error involving the scheduling of compressed gas samples and lack of communication when samples were not collected. Corrective actions were implemented in September 2008 as part of this investigation to improve communication and monitoring regarding compressed gas sampling status.*

(b) (4)

Investigation 225-2008-0248: *On 30 November 2008, two routine microbial compressed gas samples were missed and investigated in Minor Investigation 225-2008-0248. The root cause of the investigation was determined to be human error. An evaluation of the manufacturing schedule was completed in February 2009 to assure that all necessary samples are collected.*

As discussed above, we will consider these events fully as we develop our systematic Missed (b) (4) *by 30 April 2009.*

Investigation 2009-EM225-0001: *On 31 December 2008,* (b) (4) *. Trending for the missed test event identified this as the third event, and therefore, per SOP 286-125AX,* (b) (4) *. The investigation determined that the root cause was* (b) (4) (b) (4) *). In this case,* (b) (4) (b) (4) (b) (4) *were collected for the two compressed gas sites on 08 January 2009 with satisfactory results.*

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Our investigation determined that this (b) (4) *A CAPA has been assigned to determine how to eliminate the potential for this scheduling error by 29 May 2009 (i.e., prior to June,* (b) (4) *If the potential for scheduling error cannot be eliminated by 29 May 2009, we will provide documented oversight of the scheduling prior to 01 June 2009 to avoid undetected scheduling errors.*

We recognize that the four events discussed above have highlighted the need to strengthen our scheduling system used to ensure that compressed gas samples are consistently taken and not missed. Our (b) (4) *, as described earlier in this response, will focus on enhancing this system.*

24. The corrective and preventive actions implemented as the result of (b) (4) dated August 04, 2008 regarding missed licensed identity test for the release of (b) (4) for a Rubella Pool lot 2105491 due to the deletion of the missed test by an Analyst (b) (4) Specifically, the Analyst was able to permanently remove the test record for the sampling of (b) (4) . The corrective action instituted to prevent reoccurrence, failed to include addition to the (b) (4) that will prevent approximately (b) Laboratory Analysts with access to the (b) (4) In addition, the corrective and preventive action implemented as the result of Observation #43 from the January 2008 inspection regarding the root cause of a missed test that was attributed to the sample test that was also deleted in (b) (4) .

Response 24: (b) (4) *was submitted as a result of an event that occurred in 2005 in which* (b) (4) *for Rubella Pool Lot 2105491 was erroneously rejected from the* (b) (4) *This error took place prior to several system improvements that were introduced in 2008 as a result of Observation 43 from the November 2007 through January 2008 inspection. These improvements include:*

- *Site procedures were updated in March 2008 to require change control documentation for test rejection. Specifically, any time a test is rejected, a change request documenting the reason for the change must be submitted to the West Point* (b) (4) *The* (b) (4)
- (b) (4) .

These improvements were added as enhancements to the existing requirement to perform a comprehensive review of the (b) (4) *(i.e., Merck's product specification document) by the Release Coordinator to confirm that all required release tests have been completed.*

As a result of this event and to further ensure that no additional required testing was missed, an assessment was completed to look at all the biological lots in inventory at West Point and their corresponding biological family tree lots manufactured since 01 January 1997 through the

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submission of the BPDR on 04 August 2008. All lots were evaluated to confirm (b) (4) *in the product Quality Standard, was completed. Specifically, the assessment reviewed: (i) those Quality Standard test results not reported to CBER per protocol, since these tests are already* (b) (4) *, and (ii) those test results* (b) (4) *additional occurrences of missed testing were identified. In addition to this assessment, access restrictions were implemented to only allow the rejection of samples and tests by Quality Personnel within Laboratory Operations and West Point Product Release. This brought the total number of individuals at the West Point site having the ability to reject samples and tests to* (b) *from approximately* (b) *users.*

Further restrictions to reject tests and samples will be implemented by updating (b) (4) *by 15 June 2009 for a limited group of individuals within the Quality unit. This group will be defined as Senior Level Laboratory and West Point Product Release (WPPR) personnel along with individuals within the* (b) (4) *. This restriction will decrease the overall number of individuals who currently have the ability to reject tests and samples* (b) (4) *. SOP 027-SL115,* (b) (4) *", will also be revised by 15 June 2009 to state that access to reject release samples and tasks is limited to Senior Level Laboratory and WPPR personnel, in addition to the* (b) (4) *. We are confident that this added protection will ensure prevention of re-occurrence of the stated event in the future.*

In addition, a permanent software update to (b) *will be evaluated, which would further restrict the ability to reject a release test and sample to the* (b) (4) *The evaluation will be completed by 03 April 2009 and will include whether the software fix is feasible, along with the timing for implementation.*

25. Corrective and preventive actions implemented to (b) (4) dated May 23, 2008 regarding (b) (4) as follows:

A. The information contained in the BPDR that was sent to CBER did not include the previous and related event of (b) (4)) investigation that was initiated after black particles and oily residue were found in drums of (b) (4) received from a vendor.

B. There are no assurances that one cleaning verification/revalidation run for (b) (4) that was initiated as the result of the black particles and oily residue noted in (b) (4) is adequate and (b) (4) as stated under Observation #25C below should have been conducted as follows:

1. The cleaning verification study (b) (4) dated April 08, 2008 conducted after the corrective action to (b) (4) black particles failed acceptance criteria for conductivity for (b) (4)

2. The Cleaning Verification failed to include (b) (4) samples.

3. The above noted cleaning verification study failure root cause was attributed to residue from (b) (4)

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corrected; only (b) (4)

(b) (4) dated May 19, 2008 run that was conducted and was stated to meet conductivity specification has the notation of "NA" for specification in the documentation of the cleaning validation results for conductivity with result of conductivity noted as (b) (4). In addition, the following deficiencies were noted:

- SOP #207-211 dated December 10, 2008 titled: Operating the Chemical (b) (4), and the (b) (4) print out titled: (b) (4)
- No deviation was documented and no investigation was conducted (b) (4)
- The (b) (4)

C. (b) (4) dated June 2, 2008 (b) (4) The validation had no documentation of deviation and no investigation was conducted. In addition (b) (4)

Response 25: *The Biologic Product Deviation Report (BPDR) was issued to report a cleaning verification failure of* (b) (4) *at the West Point site.* (b) (4) *Our review of the events has concluded that the actions taken in response to the cleaning failure are complete.*

This response is organized to address each subpart of the observation and will address: (i) the completeness of information contained in BPDR 08-005, (ii) the rationale and supporting information for performance of a single validation run, and (iii) specific details within the observation concerning the investigation and revalidation #88733. In each section, we will provide the rationale for our decisions, along with corrective actions we are undertaking, where appropriate.

Completeness of Information Contained in BPDR 08-005: *Upon re-review of the event presented in the BPDR, we have confirmed our original conclusion that the* (b) (4) *was not appropriate for inclusion in the BPDR because it was not causative to the event that was the subject of the BPDR, that is the* (b) (4) *While the* (b) (4)

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For background, the (b) (4) *documented in Atypical Process Report (APR)* (b) (4) *involved bulk cleaning solution that was found to contain a black residue and black particulates. The investigation was closed following a comprehensive series of actions including a risk analysis and extensive inspection and testing of equipment. All fixed equipment that used the cleaning agent was inspected for evidence of the residue and/or particulates according to the* (b) (4) *of Vaccine and Sterile Manufacturing at West Point Following Investigation APR* (b) (4) *These activities did not identify any instances in which the residue or particulates had deposited in the equipment.*

Among the cleaning verification studies that were executed as part of the (b) (4) *was study* (b) (4) *dated 08 April 2008 on* (b) (4) *This is the study that is the subject of this observation. In this study, a failed result was obtained for rinsate conductivity. All other results passed. The investigation of the failed conductivity result established that the result was unrelated to the presence of residue/particulates in the* (b) (4) *. The investigation established a definitive root cause.* (b) (4) *Subsequent studies as discussed below confirmed this root cause conclusion. Therefore, the BPDR addressed the failed cleaning verification results and the associated root cause and corrective actions for the failed results.*

Completeness of the Validation Study: *Observation 25, Subpart B addresses two points: 1) that we performed* (b) (4) *and 2) that specific details of the investigation and validation did not meet expectations.*

1) Rationale and Supporting Information for the Performance of (b) (4) ***Run*** (b) (4) .

- *The following sequence of activities preceded the* (b) (4)
- *Study* (b) (4)
- (b) (4) .
- (b) (4)

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(b) (4)

.

- (b) (4)

.

These above described studies provide (b) (4) *As such, we believe* (b) (4) *is sufficient to confirm that the process continues to meet its originally validated performance criteria.*

2) *Specific Details of the Investigation and Validation Identified in the Observation*

a. *Observation 25B2 correctly notes that the Cleaning Verification did not include* (b) (4) *. Although the controls on the use of this equipment* (b) (4) *. At present,* (b) (4) *SOP 240-310, "Performing Cleaning Validation Testing in Biological and Sterile Manufacturing" will be effective by 29 May 2009 to include a requirement to perform* (b) (4) *. In addition, a new SOP for Cleaning Verification studies is in preparation and will include a requirement for* (b) (4) *The SOP will be effective by 20 May 2009.*

(b) (4) *however, by procedure,* (b) (4) *should have been performed in* (b) (4) *Study* (b) (4) *and* (b) (4) *Study* (b) (4) *. It was an error in the development of these study plans not to include* (b) (4) *. We have initiated an investigation of this deviation, (Deviation Alert 207-2009-034). According to our standard deviation management procedures, we will investigate the root cause for the failure to identify this test and develop corrective actions accordingly.* (b) (4)

b. *Observation 25B includes the statement,* (b) (4) *dated May 19, 2008 run that was conducted and was stated to meet conductivity specification has the notation of "NA" for specification in the documentation of the cleaning validation results for conductivity with result of conductivity noted as* (b) (4)

The notation of "NA" for specification appears in (b) (4) *The line on this sheet that is referenced in the observation is indicated as "NA" because it applies only to an intermediate value that has no specification. The specification for conductivity is indicated in both the study protocol and the final report, as conformance with "USP General Chapter <645> Conductivity". USP <645> contains a multi-stage set of criteria. Accordingly, the* (b) (4)

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presents the results as (b) (4) *. The* (b) (4) *the USP acceptance* (b) (4) *Each of these lines represents an evaluation of the conductivity against a stage in the USP testing. For each of these lines the specification is listed as '*(b) (4) *since the specification is not a simple value. Similarly, the results are listed as '*(b) (4) *or* (b) (4) *The final line in the results summary is labeled as the "Conductivity* (b) (4) *" and is also listed with the* (b) (4) *specification and the final test result. Table 1 below shows the full* (b) (4) *for the conductivity result for this study.*

Table 8: Information Presented for (b) (4)
(b) (4)

c. *We understand a concern noted in Observation 25B to be that SOP 207-211 and the* (b) (4) *However, we would like to clarify that the specification for* (b) (4) (b) (4) *To provide additional assurance that the* (b) (4) *meet the specification, we will add the specification to SOP 207-211, '*(b) (4) *The printout and SOP updates will be completed by 27 June 2009.*

d. *We understand another concern noted in Observation 25B to be that the deviation was neither documented nor was an investigation conducted into the liquid observed at the* (b) (4) *As a result,* (b) (4) *Thus,* (b) (4) *. The validation scientist who executed the study noted on the study record* (b) (4) *. We will update our SOP for cleaning validation studies, 240-310X, and the new SOP for* (b) (4) *As previously stated, SOP 240-310X, and the new SOP will be effective by 20 May 2009.*

e. *Observation 25B includes the statement '*(b) (4)

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(b) (4)

The in-line conductivity probe was determined to be operating correctly. During the investigation of APR (b) (4) *in May 2008, it was discovered that the incorrect* (b) (4) *This* (b) (4) *The change did follow the* (b) (4) *; however, the testing was insufficient in that it did not identify the coding error that resulted in the improper storage and reporting of the* (b) (4) *. The* (b) (4) *subsequently was corrected in May 2008.*

To (b) (4) *in the response to Observation 8.*

Comparability studies between the (b) (4) *are not necessary because the accuracy of each is independently confirmed through routine calibration. The* (b) (4)

f. *Observation 25.C notes the following two concerns previously discussed above: (i)* (b) *(See Response 25B, 2d above) and (ii)* (b) (4) *(See Response 25B, 2e above).*

26. Regarding the (b) (4) :

A. The sampling of (b) is not representative of production/manufacturing operations use conditions and the sampling of (b) (4) are not consistently applied through out the production areas. For example: Per SOP 351-371X, dated April 17, 2006, during the production of (b) (4) nd per SOP #262-113X dated October 20, 2008 (b) (4) Also per SOP 204- 231N dated June 30 2008 (b) (4) for the Pedvax manufacturing process in Chemistry Suite (b) are (b) (4) and per SOP204-210V dated October 29, 2008 (b) (4)

B. Investigations and controls (b) (4) . For example:

(b) (4) rom February 2008-2009.

C. The CAPA instituted as the result of (b) (4) are in adequate, per the root cause investigation, the reasons for the (b) (4) are as follows: APR#(b) ; per APR# 2(b) (4) 4)the contamination was caused by (b) (4) per APR (b) (4) Still. The CAPA

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failed to include the examination of (b) (4) areas to prevent future occurrences similar to the ones noted above. For example:

1. Per APR (b) (4) dated November 30, 2007, (b) (4)

2. Per APR #(b) (4) dated March 26, 2008 (b) (4) .

3. Per APR (b) (4) dated October 22, 2008, (b) (4)

Response 26A: *We are fully committed and understand the importance of ensuring (b) are representative of the conditions under which the (b) (4) n manufacturing operations. As such, we have two governing SOPs that define requirements for (b) (4) : SOP 262-113X, (b) (4) for Classified Areas and Systems", and SOP 262-398X, '(b) (4) ". SOP 262-113X (b) (4) and SOP 262-398X provides general (b) (4) In addition to these (b) (4)*

We acknowledge that our current system of having these site-wide and local procedures to describe the sampling practices should be enhanced as follows.

- *By 06 June 2009, we will revise SOP 262-113X to provide (b) (4)*
- *By 19 September 2009, (b) (4) procedures against the revised procedure SOP 262-113X to confirm that each one is indeed consistent with this document. Modifications to the procedures will be made as needed.*

Sampling at the West Point Site: *We understand that during the inspection, we should have articulated a clear, cohesive summary of how we sample our (b) (4) in a manner that is representative of manufacturing operations use. We would like to take this opportunity to provide a brief overview of our systems, and why we believe that the (b) (4) is indeed representative of production/manufacturing and that consistent principles are widely used at the West Point site.*

We have (b) (4) locations:

1. *(b) (4) These locations are used by manufacturing operations (b) (4) for their operational needs. (b) (4)*

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2. (b) (4) - *These locations are used* (b) (4) *. Note that these locations are usually located* (b) (4)

(b) (4) :

- (b) (4)

Sampling of (b) (4) (b) (4) *All of the WFI systems have been validated to consistently deliver* (b) (4) *For this reason the time at which the sample is taken is not a critical factor. In the special case of* (b) (4) *of a product, which is defined* (b) (4) *SOP 262-113X requires the collection of a sample* (b) (4) *During qualification activities for* (b) (4)

(b) (4) *After reviewing the results of the site* (b) (4) *overview provided to the Investigator during this inspection, it was noted that PedvaxHIB® manufacturing area, Department* (b) *was the only manufacturing department that specifically* (b) (4) *In order to align all manufacturing operations practices, the PedvaxHIB® manufacturing SOP 204-210V, "* (b) (4) *" will be revised by 11 May 2009 to remove the requirement* (b) (4)

Response 26B: *We acknowledge the importance of investigations and controls* (b) (4) *We also acknowledge that* (b) (4) *However, it is not unexpected to find these organisms* (b) (4) *Furthermore, the presence of these organisms, at controlled levels, does not impact the ability of our systems to consistently produce* (b) (4)

We recognize that the design, operation, and monitoring of (b) (4) *of the United States Pharmacopeia.* (b) (4)

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(b) (4) . As (b) (4) In the majority of our systems, there is an addition of (b) (4)

The (b) (4) This method is widely recognized as the (b) (4) . A review of our 2008-2009 (b) (4) still event discussed in Response 26C3 below. These results indicate that (b) (4)

Per site SOP 262-113X, (b) (4) ", all (b) (4) . Typically, the systems are (b) (4) (b) (4) . According to site SOPs 286-125AX, ""Deviation Data Collection and Investigation and SOP 262-221X, "Response to (b) (4) ", (b) (4)

For Building (b and Building (b) the (b) (4) and Building (b has (b) (4) .)All systems have (b) (4) It should be noted that the action levels for Building (b and Building (b were established upon the initial installation of these (b) (4) . Industry standards, as well as available guidance from the World Health Organization (WHO), suggest (b) (4)

(b) (4) the 2008 to 2009 review period was (b) (4) The (b) (4) for Building (b) (4) for Building (b) and (b) for Building (b) These individual and (b) (4) In addition, our data from (b) (4)

Response 26C: We understand this observation to be related to a concern that Corrective Actions/Preventative Actions (CAPA) associated with (b) (4)

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In accordance with site procedures defined in SOP 283-125AX, "Deviation Data and Collection" and SOP 262-221X, "Response to (b) (4) *With each investigation, we attempt to determine a root cause and appropriate corrective actions. For each of the three examples cited in this observation, we conducted thorough investigations that identified definitive root causes for each event. For each event, we also identified and implemented CAPAs that prevented any reoccurrence of endotoxin excursions at the sample sites in question. A brief summary of investigations into the* (b) (4) *are provided below.*

1. *Please note that although referenced in the first sentence of the observation, APR* (b) (4) *related event, so we believe the correct reference is to APR* (b) (4) *, which is addressed below. APR* (b) (4) *in Building* (b) *It should be clarified that the three results were from one sample tested in* (b) (4) *and not from three consecutive samples as noted in the observation. The investigation identified the root cause of this excursion to be* (b) (4) *. The sample* (b) (4) *his incident was discussed with the sampling technician and area supervisors. No additional* (b) (4) *have been noted at this site since the CAPA from this investigation was implemented (i.e., representing 28 additional samples), demonstrating that the corrective action was effective.*

2. *APR* (b) (4) *was for a single, isolated* (b) (4) *. It should be clarified that the three results were from one sample tested in* (b) (4) *and not from three consecutive samples as noted in the observation. The root cause of the* (b) (4) (b) (4) *The CAPA initiated as a result of the investigation included a procedural update to* (b) (4) *There were no further* (b) (4) *(i.e., representing 12 additional samples), demonstrating that the corrective action was effective.*

3. *APR* (b) (4) *was for* (b) (4) *from the Building* (b) (4) *The investigation determined the root cause of the* (b) (4) *to be improper* (b) (4) (b) *The* (b) (4) *. The Building* (b) (4) *In addition,* (b) (4) *The CAPA completed as a result of the investigation was to set the* (b) (4) *Eleven (11) samples have been collected with no excursions since the CAPAs were implemented demonstrating that the CAPAs were effective.*

For the third example above, the Building (b) *still is the only one of its type at the West Point site; therefore, assessment of other systems in response to this event was not necessary.*

For the other two examples, we recognize that a broader assessment of other systems was not conducted. As noted previously, however, these were single isolated excursions. In addition, our data from the review period 01 January 2008 through 26 January 2009 indicate that our (b) (4) *In that period, we experienced* (b) (4)

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(b) (4) *The absence of recurring excursions also indicates that the CAPAs implemented through our investigations have been effective.*

We do agree that some investigations may warrant a broader evaluation of other systems to determine if a more global CAPA is appropriate. As noted in response to Observation 19, to further enhance our procedures, we will include a review of (b) (4) *data across the site on a specified routine frequency. Our procedures will be revised with an effective date of 09 June 2009 to formalize this site-wide review and the procedures to respond to significant trends.*

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Willie A. Deese
President

Merck & Co., Inc.
WS3W-31
Two Merck Drive
P.O. Box 200
Whitehouse Station NJ 08889-0200
E-Mail: willie_deese@merck.com
Tel 908 423 1693
Fax 908 735 1288

MERCK
Manufacturing Division

May 15, 2008

Mr. David K. Elder
Director
U.S. Food and Drug Administration
Office of Regulatory Affairs/Office of Enforcement
Division of Compliance Management and Operations
15800 Crabbs Branch Way, HFC-210
Rockville, MD 20855

Dear Mr. Elder:

This document provides the written response to the April 28, 2008 Warning Letter regarding the U.S. Food and Drug Administration's (FDA) inspection of Merck & Co., Inc.'s (Merck) West Point, Pennsylvania, plant between November 26, 2007 and January 17, 2008.

As the President of the Merck Manufacturing Division and a direct report to Mr. Richard T. Clark, Chairman, President and Chief Executive Officer, Mr. Clark has asked me to become personally involved in this matter. Accordingly, I am not only providing you with Merck's response but I will also be joining the Merck team at the meeting with the Agency on May 23, 2008. I will personally update Mr. Clark on the meeting as well as key actions taken in response to the Warning Letter.

I wish to convey to you that I, Mr. Clark and Merck senior management, take this matter very seriously. Merck has been, and remains committed to complying with current good manufacturing practices (cGMPs) and to ensuring a reliable supply of quality vaccine products.

I also want to express my appreciation for the willingness and agreement by the Agency to meet with Merck representatives on May 23, 2008. You have my commitment that rectifying all issues and meeting the Agency's expectations is our top priority.

To that end, we have reviewed in depth the Form 483 observations and the Warning Letter and have implemented (or are implementing) enhancements throughout West Point Vaccine and Sterile Operations. We are confident that the comprehensive actions noted in our February 15, 2008 response document coupled with the additional actions noted in response to the Warning Letter will address all issues and will enhance our systems to ensure continued and sustained compliance with cGMPs.

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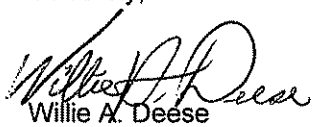
We would like to reaffirm Merck's commitment to quality and compliance. I also assure you that I, and the other senior managers at Merck, will continue to be involved, and we are committed to resolving these issues and working closely with the Agency to ensure a continued supply of quality vaccines.

Sincerely,



Willie A. Deese

Attachment

Copies:

U.S. Food and Drug Administration:

J. Little – Team Biologics Compliance
J. Bringger – Team Biologics Compliance
J. Adamo – Staff Fellow
M. Davis-Lopez – Consumer Safety Officer
J. Diaz-Albertini – Investigator
T. Gardine – District Director, Philadelphia Office
J. Loreng - Investigator
C. Lynch - Biologist
M. Major - Research Microbiologist
R. McElwain – Consumer Safety Officer
M. Malarkey- Director, Office of Compliance & Biologics Quality, CBER
A. Montemurro – Lead Consumer Safety Officer
T. Roecklein – Consumer Safety Officer

Merck & Co., Inc.:

M. J. Angelo – Sr. VP, Quality
R.T. Clark – Chairman, President and CEO
J. Lee – VP, Global Vaccine Technology & Engineering
J. T. McCubbins – Sr. VP, Global Vaccine Manufacturing & West Point Operations
W. J. Mullin – VP, West Point Quality Operations

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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 (b) of Varivax III (b) (4) . This product had been shipped to the Netherlands and then returned to the United States before being place on stability. The product was not licensed in the United States at the time of the deviation. Your investigation concluded that the failure was (b) (4) . Your investigation did not include testing of other potentially affected products (b) (4) , for example, ProQuad®, to determine if there were any detrimental effects on these products.**

Merck Response 1a: *The response to this issue can be found in the Merck & Co., Inc. (Merck) submitted written response to the 2007 Team Biologics Inspection FDA Form 483 Observations dated 15-Feb-2008 (henceforth collectively referred to as Merck's Observation Responses or individually, Merck's Observation Response). These Merck Observation Responses, along with the associated observation number and page number(s), are referenced throughout this document, as needed. In reference to the above cited observation, refer to Merck's Observation Responses 2 and 49, located on pages 14 to 22 and page 100, respectively.*

Testing of Other Potentially Affected Product: *During the investigation (in 2006), the only product samples in our possession (b) (4) VARIVAX®III lots. Due to the fact that there were no other product samples with (b) (4) and that our efforts to (b) (4) VARIVAX®III lots. As a result of our discussion with the Investigator during the Inspection, we agreed to expand the testing on other potentially impacted products, including ProQuad® Frozen, (b) (4) . The status of the (b) (4) on other products is as follows:*

1. *The test plan for (b) (4) The (b) (4) ZOSTAVAX® Frozen, ProQuad® Frozen, VARIVAX®, (b) (4) and (b) (4) See Attachment 1 for a copy (b) (4) In accordance with (b) (4) :*

   a) (b) (4)

[1] *Please note that due to the volume of documentation referenced in this text, only the pertinent pages of any supporting documentation are provided as an attachment to this Warning Letter response. A full copy of any documentation referenced is available upon request.*

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(b) (4)

"Report for VARIVAX® Process Upgrade, M-M-R®II, and M-M-R®II with (b) (4)

b) *Once we were able* (b) (4) *, we developed and approved on 31-Mar-2008, protocols for studies to* (b) (4) *, ProQuad® Frozen, VARIVAX®, and ZOSTAVAX® Frozen products. These protocols define the number of samples to be tested, the procedure f*(b) (4) *The initiation of* (b) (4) *Due to the unavailability of samples of ProQuad® Frozen for testing and in order to* (b) (4) *lot of ProQuad® Frozen* (b) (4) (b) (4) *These data will be submitted to the Agency by 22-Jun-2008. Upon manufacturing of the next campaign of ProQuad® Frozen, this study will be repeated*

c) (b) *ATTENUVAX®, MERUVAX®, MUMPSVAX®, and M-M-VAX® the next time that these products are manufactured.*

Supporting Test Data and Analysis of Product Impact: *During the 2006 investigation and in the absence of additional product samples* (b) (4) *Merck did perform an assessment of product quality in the event that product was* (b) (4) .

1. ***Sterility Assurance:*** *Sterility assurance was assessed by: (i)* (b) (4) *from a lot of VARIVAX®III* (b) (4) *and (ii)* (b) (4) *Of the* (b) (4) *All sterility results from this VARIVAX®III lot were passing. In addition, material analysis of* (b) (4) *VARIVAX®III vials* (b) (4)

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2. *Product Potency:*

i. *The potency assessment for VARIVAX®III included an evaluation of the potential impact to product potency. There was* (b) (4)

ii. (b) (4) *. For* (b) (4) *of M-M-R®II and VARIVAX®III susceptible* (b) (4)

iii. *Potency testing is performed* (b) (4) *for M-M-R®II and VARIVAX®III. All lots* (b) (4) *conditions have exhibited satisfactory results for potency.*

iv. *Testing on Importation was coordinated in Europe by Merck's Haarlem, Netherlands facility for VARIVAX®III and M-M-R®II. All such tests were within specification* (b) (4) *, which were part of the 2006 investigation.*

Based on the sterility assurance and product potency assessment results completed at the time of the investigation, we concluded that the data support the fact that there is no detrimental effect on product potency and/or sterility. As stated in Merck's Observation Response, we are committed to supplementing the existing investigation with the expanded testing described above.

Status of Corrective Actions: *It is important to note that all commitments to date noted in Merck's Observation Response have been completed as planned. In addition to the* (b) (4) *, we committed to three additional actions. The status of these actions is as follows:*

1. *SOP 283-303X, "Biological Product Deviation Reports", renamed "Regulatory Agency Reporting for Biological Products" was updated to include instructions that all products potentially impacted by an event must be clearly indicated in all regulatory communications. The SOP was updated, and training was completed, by 29-Apr-2008. See Attachment 2 for supporting documentation of this update.*

2. *Guideline 108.008, "Guideline for Coordinating Preparation of CMC Regulatory Submissions for Approved Biologics Products" was revised on 22-Feb-2008 to require that information provided in connection with regulatory filings should, where applicable, indicate when a change to a regulatory filing is made in response to a quality investigation. See Attachment 3 for supporting documentation of this revision.*

3. *A formal protocol was developed on 19-Mar-2008* (b) (4) *. The protocol is* (b) (4) *. See Attachment 4 for supporting documentation of the protocol.*

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1b. Numerous customer complaints have been received (b) (4) . For example, Complaints 48891 and 53106 for Zostavax®, lot 0290U, (b) (4) . The investigations (b) (4) . The investigation (b) (4)

Merck Response 1b: *In reference to the above cited observation, see Merck's Observation Response 6, located on pages 43 and 44.*

We acknowledge that the complaint investigations (b) (4) of the ZOSTAVAX® vials. We have (b) (4) . In addition, (b) (4)

Status of Corrective Actions: *A total of (b) (4) were taken (b) (4) . A summary of the actions is as follows:*

1. *(b) (4) including ZOSTAVAX® and ProQuad®) (b) (4) , effective 10-Jan-2008.*

2. *A formal protocol for the evaluation of (b) (4) . This protocol includes (b) (4) . Specifically, the evaluation includes (b) (4) . See Attachment 4 for supporting documentation of the protocol.*

3. *West Point Complaint Unit personnel were re-trained on SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports" on 06-Mar-2008 in order to reinforce the expectation of timely and complete documentation of all aspects of the complaint investigation.*

4. *SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports" was updated to require investigations to include an analysis of shipping method as a potential root cause. The SOP was updated and training completed by 28-Mar-2008. See Attachment 5 for supporting documentation of the update.*

5. *The (b) (4) . The (b) (4) with ProQuad® Frozen and ZOSTAVAX® Frozen, and identified further action to be taken to map out the*

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(b) (4)

6. *In Merck's Observation Responses, we committed* (b) (4) *by 01-May-2008 in order to confirm that the shippers are performing as intended. Please note that the Merck terminology for such studies is* (b) (4) *. SOP* (b) (4) *. The* (b) (4) *The* (b) (4)

7. *An audit has been initiated as of 17-Mar-2008 of the practices and procedures being used by the Building* (b) *West Point distribution department personnel, to assure they are in alignment with the* (b) (4) *. This audit was completed by 14-May-2008 and confirmed that the procedures and practices are aligned with the* (b) (4) *The audit will be extended to the other domestic distribution sites to confirm the procedures and* (b) (4) *The extended audit will be completed by 30-Jun-2008.*

The enhancements to the complaint investigations (b) (4)

1c. Not all lots of product that may have been affected by (b) (4) **Only** (b) (4) **of product,** (b) (4) **. Approximately** (b) (4) **lots of lyophilized product and** (b) (4) **of liquid products were filled during the** (b) (4) **.**

Merck Response 1c: *In reference to the above cited observation, see Merck's Observation Response 1Bi-ii, located on pages 9 to 13.*

As general background, this event was isolated to one specific lot of (b) (4) *A total of* (b) (4) *We wish to clarify that there were several additional* (b) (4) *available for use in this time period. All lots were assessed as part of this investigation, and quarantine decisions specifically determined for the* (b *lots were made based on our investigation which included:* (b) (4)

The summary of lot assessment is as follows:

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- *The* (b) (4) *. Based on our investigation, we concluded* (b) (4) *In addition,* (b) (4)

- *For the* (b) (4)

Status of Corrective Actions: *One of the commitments outlined in Merck's Observation Response 1 included an update to SOP* (b) (4) *" to provide more detailed guidance for timely and detailed documentation of material* (b) (4) *. Specifically, the SOP was updated to* (b) (4) *. The SOP was updated and training of site personnel was completed by 14-Mar-2008. See Attachment 6 for supporting documentation of the update.*

In Merck's Observation Response 1Bi-ii, we committed to three actions. The following summarizes all actions taken or to be taken.

- *The* (b) (4) *was supplemented on 17-Mar-2008 to include the* (b) (4) *. The supplement is consistent with the revisions made to SOP 286-125X as discussed above. While additional detail was added to the investigation, the material potentially impacted was properly* (b) (4) *(June 2007). See Attachment 7 for supporting documentation of the supplemented APR.*

- *SOP 204-186X, "West Point Sterile Supply Component/Equipment Receipt and Management" was implemented as of 30-Apr-2008* (b) *See Attachment 8 for supporting documentation of the SOP.*

- *Our outside cGMP consultant has reviewed all segregation and re-inspection procedures. A report documenting the review was received on 07-May-2008 and included recommendations for further enhancing the clarity of specific departmental*

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procedures. As a result, we will update our current departmental procedures to provide clarity by 07-Aug-2008. In addition, we will establish (b) (4) *Vaccine & Sterile Operations by 07-Aug-2008.*

In summary, while there (b) (4)

1d. Product lots that failed the initial (b) (4) **For example, M-M-R II® lots 0654444 and 0655487 failed the critical defect category for** (b) (4) **and no investigations were performed. These lots were subsequently distributed.**

Merck Response 1d: *In reference to the above cited observation, see Merck's Observation Response 26, located on pages 72 and 73.*

For general background, we previously communicated in Merck's Observation Response that (b) (4) *for M-M-R®II Lots 0654444 and 0655487 were investigated as part* (b) (4) *and* (b) (4) *respectively, and that* (b) (4) *The* (b) (4) *The investigations concluded that* (b) (4) *As part of the investigations, each lot was* (b) (4) *The quality of the two M-M-R®II Lots 0654444 and 0655487 is assured* (b) (4)

Although the two lots were investigated as part of the referenced APRs, we updated our SOPs effective on 15-Oct-2007 (b) (4)

Status of Corrective Actions: *In Merck's Observation Response, we committed to the following enhancement which has been fully implemented. Change Request WP2-08-0105 was implemented on 26-Mar-2008 to ensure that* (b) (4) *The updated procedure requires that* (b) (4) *The SOP was approved and training completed by 26-Mar-2008. See Attachment 9 for supporting documentation of the SOP update.*

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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 "Investigating and Writing West Point Product Quality Complaint Reports" directs that (b) (4) **This** (b) (4) **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.**

Merck Response 2: *In reference to the above cited observation, see Merck's Observation Response 9, located on page 46.*

We acknowledged that an update to our lot history process for complaint investigations will enhance the ability to detect trends in complaints related to bulk lots, fill lots or components. Therefore, we committed to update our procedure to require an enhanced lot history evaluation process.

This enhanced process has been fully implemented as follows:

- *SOP 283-316, "Investigating and Writing West Point Product Quality Complaint Reports" was updated to include guidance for complaint categorization. A flow chart was developed and included in this SOP to provide standard guidance for the categorization process. Following categorization, the SOP now specifies the following:*

  1. *For complaint reports that are associated with the filling operation,* (b) (4)
  2. *For complaint reports that are associated with a component defect,* (b) (4)
  3. *For complaint reports that are associated with the bulk manufacturing process,* (b)

The SOP was updated and training was completed, on 28-Mar-2008. See Attachment 10 for supporting documentation of the SOP update.

We believe the above actions will strengthen the ability to detect and respond to trends.

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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 [21CFR211.100(a)]. For example:**

   a. **The validation performed in December 2006 for (b) (4) is not representative of the (b) (4) . This equipment is used to inspect multiple vaccine products from filling lines (b) and (b)**

Merck Response 3a: *In reference to the above cited observation, see Merck's Observation Response 25A, located on page 71 and 72.*

For general background, the validation of (b) (4) Based on the fact that inspection machines (b) (4) .

The (b) (4)

In addition to the actions specified in Merck's Observation Response, Merck is in the process of (b) (4) To that end, by (b) (4) Merck will develop a Validation Master Plan and a corresponding project plan to review the validation of existing equipment against the requirements of the Validation Master Plan.

Status of Corrective Actions: *In response to this observation, we committed to two actions as follows:*

1. *We are updating our procedures to include the use of non-defect vials during (b) (4) . The SOP updates are on target for completion by 30-May-2008.*

2. *As discussed in Merck's Observation Response 25A, Merck determined on 30-Nov-2007 (b) (4) See Attachment 11 for supporting documentation of the (b) (4) .*

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3b. Process control limits were not evaluated and (b) (4) for Zostavax® as required by SOP 300-103X. The SOP states that the (b) (4) . (b) (4) were inspected by the (b) from February 2006 to September 2007, yet the limits have not been evaluated.

Merck Response 3b: *In reference to the above cited observation, see Merck's Observation Response 24, located on page 70.*

We understand the importance of establishing (b) (4) in order to ensure that the process operates consistently. As stated in our written response to the Observation, the error associated with not (b) (4) for ZOSTAVAX® was associated with a change in our methodology of calculating and evaluating these limits.

We acknowledge that our SOP (b) (4) . The (b) (4) . Subsequently, process capability limits were (b) (4) .

On 19-Dec-2006, the inspection (b) (4) . SOP 300-103X, was updated effective 01-Jan-2007, and stated (b) (4) .

As of 19-Dec-2006, at the time (b) (4) of ZOSTAVAX® Frozen had been inspected and entered into the (b) (4) . Given the transition (b) (4) , there was (b) (4) . We acknowledge that the (b) for ZOSTAVAX® should have been (b) (4) .

As a result and as committed to in Merck's Observation Response, SOP 300-103X was updated (b) (4) . The SOP was updated, and training was completed, by 29-Apr-2008. See Attachment 12 for supporting documentation of the update. As further assurance that (b) (4) . The SOP that governs Vaccine and (b) (4) will be updated to align with SOP 300-103X by 31-Jul-2008.

ZOSTAVAX® Frozen was inspected on the (b) (4) . As of 05-May-2008, a total of four ZOSTAVAX® lots have been inspected on (b) (4) with SOP 300-103X, when (b) (4)

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(b) (4) . *In this interim period,* (b) (4) *by West Point Product Release.*

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 [21 CFR 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** (b) (4) **of known rejects to be accepted by the equipment. In addition,** (b) (4) .

Merck Response 4: *In reference to the above cited observation, see Merck's Observation Response 23, located on pages 67 to 70.*

For general background, the control standards (noted above as control samples and reject set) are used to confirm proper set-up and operation of the inspection system prior to operation. Although our procedures allowed for a lower detection of defective vials (b) (4) . *This supports that there* (b) (4)

Regarding (b) (4) . *Historically, our complaint* (b) (4) *from February 2006 (the date of our last* (b) (4) (b) (4) *to December 2007.*

Status of Corrective Actions: *As stated in Merck's Observation Response, we recognize the importance of continuous improvement of our systems. Accordingly, we committed to take the following three actions, all of which have been completed.*

- *The acceptance criteria for the control standards on the* (b) (4) *inspection systems were updated to reflect actual system performance. All appropriate batch records were updated and associated training was completed, on 21-Mar-2008. These updates require* (b) (4) *See Attachment 13 for supporting documentation of this update.*

- *SOP* (b) (4) . *The updated procedure ensures* (b) (4) . *The SOP was updated, and training was completed, on 25-Mar-2008. See Attachment 14 for supporting documentation of this update.*

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- *To ensure consistency across all manufacturing areas, an assessment of control standards inspection acceptance criteria was performed for* (b) (4) *. At West Point, there are* (b) (4) *. The* (b) (4) *. The assessment recommended* (b) (4) *See Attachment 15 for supporting documentation of this assessment.*

  The results of the assessment including the subsequent actions taken are as follows:

  a. *The acceptance criteria for the* (b) (4) *of control standards, no action was needed.*

  b. *The procedure for creating defective standards for* (b) (4) *was updated to enhance the* (b) (4) *SOP 135-218X, "Creating Standards for* (b) (4) *Inspection" was updated and associated training was completed, on 16-Apr-2008. See Attachment 16 for supporting documentation of this update.*

  c. *The acceptance criteria for the* (b) (4) *of control standards, no action was needed.*

  d. *The procedure for* (b) (4) *SOP 135-343X, "*(b) (4) *Syringe Standard* (b) (4) *" was updated and associated training was completed, on 16-Apr-2008. See Attachment 17 for supporting documentation of this update.*

  e. *The acceptance criteria for the control standards for* (b) (4) *for vials were updated* (b) (4) *All appropriate batch records, as well as SOP* (b) (4) *See Attachment 18 for supporting documentation of this update.*

  f. *The procedure for* (b) (4) *SOP* (b) (4) *See Attachment 18 for supporting documentation of this update.*

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These actions ensure that our created control standards reflect the defects that the system is validated to identify, are properly maintained or replaced as needed, and meet an acceptance criterion of 100% during equipment set-up for (b) (4) *inspection equipment.*

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** (b) (4) **used in the manufacturing of GARDASIL®, Lots 2121579 and 2121693.**

Merck Response 5: *The documentation generated in support of the automation changes needed to correct this error is provided in Attachment 19. See the response to Observation 14, located on page 31 of this document for further information.*

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** (b) (4) **. 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** (b) (4) **These** (b) (4)

Merck Response 6a: *In response to the above cited observation, see Merck's Observation Response 8, located on page 45.*

Status of Corrective Actions: *We committed to update our investigation management SOPs to enhance our atypical event trending process and to provide consistency in trending of all types of atypical events. The following summarizes the corrective actions taken.*

- *SOP 286-125X, "Processing Atypical Process Reports (APR) in Vaccine/Sterile Operations" was updated* (b) (4) *Specifically, the SOP was updated* (b) (4) *. Also, guidance was provided for* (b) (4) *. For example,* (b) (4) *. If, however, a* (b) (4)

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(b) (4)
See Attachment 20 for supporting documentation of this update.

- *The following SOPs were also* (b) (4) *: SOP 262-221X, "Response to Environmental Excursions", SOP 262-137X, "*(b) (4) *Application for Environmental Monitoring Investigations", SOP 262-137AX,* (b) (4) (b) (4) *", SOP 236-378X, "Atypical Process Report", SOP 223-126X, "Investigation Procedure Using* (b) (4) *and SOP 223-307X, "Laboratory Investigation Procedure". The SOPs were updated, and training was completed, on 14-Mar-2008. See Attachment 21 for supporting documentation of these updates.*

While we recognize that our previous practice for handling atypical event trends required updating to ensure consistency of practice for adjusting the number of occurrences, we do not believe that this practice affected the outcome of any of our investigations. With the implemented enhancements, we are confident that our atypical investigation management system will be more effective.

6b. CP 9110.001, "Sterility Test Methods," does not direct that any anomaly concerning the product or sample preparation such (b) (4) **The procedure only addresses** (b) (4)

Merck Response 6b: *In response to the above cited observation, see Merck's Observation Response 45 located on page 96.*

The observation cites that the (b) (4) *. In order to address the documentation of* (b) (4) *including Sterility Testing per CP 9110.001, the SOP updates listed below were implemented.*

Status of Corrective Actions: *In response to this observation, we committed to and completed two actions as follows:*

- *SOP* (b) (4) *. The SOP was updated, and training was completed, by 28-Mar-2008. See Attachment 22 for supporting documentation of this update.*

- *SOP* (b) (4) *on 07-Apr-2008. This* (b) (4)

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(b) (4)
. *See Attachment 23 for supporting documentation of this addition.*

The update to SOP 160-QP-355X and the addition of the SOP to the Laboratory Operations personnel training curricula (b) (4)

6c. There are no data to support (b) (4)

Response 6c: *The response to this observation has been incorporated into the response to the request for additional information for Observation 37, located on page 42 of this document.*

CGMP DEFICIENCIES CONCERNING BULK DRUG SUBSTANCES AND DRUG COMPONENTS

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, "Determination of the** (b) (4) **Measles, Mumps, and Rubella Bulk,"** (b) (4)
   .

Merck Response 1a: *In response to the above cited observation, see Merck's Observation Response 21, located on pages 64 to 65.*

As general background, we confirmed (b) (4)
bulk vaccines for measles, rubella, and rotavirus bulk lots. As noted in the observation, a stability study for the mumps (b) (4)
. *This stability study was initiated on 02-May-2008.*

Status of Corrective Actions: *In response to this observation, we committed to and completed two actions. The actions completed are as follows:*

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- *One lot of mumps bulk that has been subjected to* (b) (4) (b) (4) (b) (4) *The expiry for mumps bulk is currently ten years. See Attachment 24 for supporting documentation of this action.*

- *Merck Divisional Guidance GDL 6.43, "Drug Substance Retest and Expiry Periods and Manufacturing Dates" was updated to ensure* (b) (4) *The revised document was available in the Merck Quality Manual on 23-Apr-2008, and training of impacted West Point personnel (e.g., Technology Groups, West Point Stability Unit) was completed on 07-May-2008. See Attachment 25 for supporting documentation of this update.*

We believe the actions taken and the system enhancements implemented to date will further ensure the robustness of the bulk stability program.

b. There are no data to support (b) (4) **Specifically,** (b) (4) **Additionally,** (b) (4)

Merck Response 1b: *In response to the above cited observation, see Merck's Observation Response 32, located on pages 79 to 80.*

As general background, the assessment previously performed (b) (4) *. As a result of the discussions with the Investigator, we agree that there are* (b) (4)

Status of Corrective Actions: *As committed in Merck's Observation Response, the following is a summary of the status of the five actions.*

- (b) (4) *The final report is pending approval and will be available for review during the next Team Biologics Inspection.*

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- *The other* (b) (4) *. An outside consultant on* (b) (4) *. These* (b) (4) *on target for completion by 30-May-2008.*

- *The FDA observation, the Merck Observation Response, and the key learnings have been shared with our internal* (b) (4) *. This activity was completed on 10-Mar-2008.*

- *We are in the process of developing and implementing an SOP describing the manner by* (b) (4)
  We are on target to meet the 31-Jul-2008 commitment date for this SOP update.

- *We are in the process of developing and implementing an SOP that will provide* (b) (4) *We are on target to meet the 31-Jul-2008 commitment date for this SOP update.*

In addition to the actions specified in the Merck's Observation Response, Merck is taking the following additional actions (b) (4) .

- *Merck* (b) (4) *at West Point to ensure the data are robust and scientifically sound by 28-Nov-2008. Action plans will be developed, as necessary, to address any enhancements identified.*

- *Merck* (b) (4)
  Merck's (b) (4) *This activity includes:*

  - (b) (4)

  - (b) (4)

We believe the comprehensive actions taken and to be taken will improve our systems.

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Failure Investigations

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

a. You failed (b) (4) **. These** (b) (4) **manufacture MMR®II, PedvaxHIB®, VAQTA®, VARIVAX® product lots.**

Merck Response 2a: *In response to the above cited observation, see Merck's Observation Response 1Ai-Av, located on pages 3 to 8.*

All lots associated with these filters were assessed by our investigation, and we respectfully submit that all product disposition decisions were appropriate. Merck and (b) (4) *Merck medical assessment, the Director of West Point Product Release concluded* (b) (4) *. However, as a result of the observation, we fully recognize that more timely documentation of key decisions taken would have improved the rationale and clarity of our decision process.*

Status of Corrective Actions: *The following is a summary of the status of the four corrective actions committed to in Merck's Observation Response:*

- *The Vice President of West Point Quality Operations will issue a directive by 19-May-2008 to all applicable site staff emphasizing the importance of timely, detailed, and well-documented investigations.*
- *SOP 286-125X, "Processing Atypical Process Reports (APR) in Vaccine/Sterile Operations" was enhanced to provide more detailed guidance for timely and detailed documentation of material assessment and* (b) (4) *. In addition, it was updated to require that all* (*. The SOP was updated, and training was completed, on 14-Mar-2008. See Attachment 6 for supporting documentation of the update.*
- *The investigation related* (b) (4) *observations was updated in accordance with the revised SOP 286-125X. See Attachment 26 for supporting documentation of this update.*
- *An update to* (b) (4) *was provided to CBER on 22-Feb-2008.*

We will provide an update to (b) (4) *to summarize the investigation into the reports of* (b) (4) *. In summary, we submit that our actions*

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throughout the course of (b) (4) *demonstrate a rigorous root cause investigation in conjunction with our vendor and a thorough product impact evaluation.*

b. Your investigation (b) (4) **The investigation also concluded there was no impact** (b) (4) **Attached to the investigation was** (b) (4) **This information was** (b) (4) **However, these pages from the notebook are no longer available.**

Merck Response 2b: *In response to the above cited observation, see Merck's Observation Response 4A, located on pages 37 to 38.*

The observation refers to an investigation that contained an attached document that was unsigned and undated, which is an unacceptable practice by our own procedures. Between the time this investigation was completed and its subsequent review during the Team Biologics Inspection, we had already enhanced our investigation procedures to ensure all pertinent information is appropriately documented, signed, and dated in our investigations.

Status of Corrective Actions: *As committed in Merck's Observation Response, the following two actions have been completed as follows:*

- *Detailed training was provided as of 16-Apr-2008 to all operating areas involved in vaccine processing on core requirements for GMP documentation in order to prevent recurrence of the documentation event that occurred during the investigation and approval of APR 2007-204C-0001.*

- *SOP* (b) (4) *The SOP update and associated training for all cross-referenced departments across Operations was completed on 29-Feb-2008. See Attachment 27 for supporting documentation of this update.*

The implemented enhancements provide further assurance that atypical investigations are documented thoroughly and in a timely manner.

2c. (b) (4) **The contaminant was noted as *Bacillus cereus*. The investigation failed to assess a recent change in the** (b) (4) **, implemented in July 2006. The validation of this** (b) (4)

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Merck Response 2c: *In response to the above cited observation, see Merck's Observation Response 3A, located on pages 25 and 26.*

We note the following key aspects of investigation 2006-204C-0034:

- *The change in the* (b) (4) *was, in fact, assessed as part of this investigation. The investigation concluded that this change was not the root cause for the sterility failure. This conclusion was based on data available at the time of the investigation.*
- *The investigation concluded that the most probable root cause for* (b) (4)
- *The* (b) (4) *. In addition,* (b *. Based on the data available at the time, that is the historical* (b) (4) *.*

Merck technical and quality experts identified the root cause for (b) (4) *These results led to our decision to recall the potentially affected lots from the market.*

Status of Corrective Actions: *Merck made* (b) (4) *. These actions are documented in* (b) (4) *that was submitted on* (b) (4) *The key actions documented in the BPDR are summarized below:*

- *The* (b) (4)
- (b) (4) *.*
- (b) (4)

In summary, we believe that the investigation into the (b) (4) *failure in August 2006 was thorough and made sound scientific conclusions based on the information available at the time. Through our investigation into the subsequent media challenge failure, we were able to identify and correct the root cause for the sporadic microbial events. Based on this investigation, additional actions have been identified and are being completed as described above. These actions will further strengthen the* (b) (4)

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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** (b) (4) **in 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.**

Merck Response 3: *In response to the above cited observation, see Merck's Observation Response 3Ci, located on pages 29 to 31.*

As general background, (b) (4) *measles, mumps, and rubella bulk manufacturing. The bulk drug substance is* (b) (4) , (b) (4)

In Merck's Observation Response, we acknowledged that (b) (4) *As per our license,* (b) (4) *As such,* (b) (4)

While we believe that no further action is required at this time, we will review our overall principles for stability with our internal technical experts. We would also like to further discuss this issue with CBER to ensure that our proposed path forward meets Agency expectations.

Buildings 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, "Housekeeping Procedures for the BTMC," does not provide a frequency for performance of the multi-step decontamination with Sodium Hypochlorite.**

Merck Response 4: *In response to the above cited observation, see Merck's Observation Response 30, located on page 77.*

SOP 204-608X, "Housekeeping Procedures for the BTMC", that governs the cleaning and disinfection program for the Biotechnology Manufacturing Complex (BTMC), did not specify a routine frequency for performance of the (b) (4)

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Status of Corrective Actions: *As committed in Merck's Observation Response, we have enhanced or will enhance our cleaning and disinfection program as follows:*

- *SOP 204-608X, "Housekeeping Procedures for the BTMC", was updated to specify a frequency for routine application of* (b) (4) *, in addition to the existing SOPs requirements which require* (b) (4) *The SOP was updated, and training was completed on 20-Feb-2008. See Attachment 28 for supporting documentation of this update.*

- *We are currently in the process of conducting a system review of our other processing areas* (b) (4) *This review is being accelerated and will be completed by 30-May-2008.*

In summary, we have completed our procedural update to require (b) (4) *in the BTMC. Additionally,* (b) (4) *We believe these actions will adequately address the issue raised.*

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 (b) (4) **However, there was no documentation as to why this prescribed action was not completed.**

b. Work order 1415800, dated September 9, 2007, issued for (b) (4) **However, there was no documented reason for the failure to complete these activities.**

Merck Response 5: *In response to the above cited observation, see Merck's Observation Response 31, located on pages 77 and 78.*

We agree that the rationale for placing the "N/A" next to (b) (4) *that were not executed was not explicitly documented in each Work Order.*

Status of Corrective Actions: *As committed in Merck's Observation Response, we have implemented or will implement four actions as follows:*

- *On 01-Feb-2008, management communicated the observation, the findings, and the actions to be taken to all Maintenance personnel. This communication reinforced the*

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principles of cGMP documentation, as well as the need for a documented rationale for decisions surrounding the execution of maintenance work.

- *The rationale for all steps on Work Orders 1400076 and 1415800, where an N/A was placed, was documented on 01-Feb-2008. See Attachment 29 for supporting documentation.*

- *All maintenance personnel were trained on proper cGMP techniques for documenting the rationale for job steps that are conditional. This training was completed by 03-Mar-2008.*

- *A site wide action has been initiated to enhance the instructions in all cGMP Preventative Maintenance Work Orders. Specifically, a team has been formed and has initiated a review and evaluation of our current cGMP preventive maintenance instructions. The enhancements will include a specific decision tree to assist the mechanic in documenting the rationale for not performing conditional work. This team will provide standards for preventive maintenance instructions to thoroughly document the rationale for decisions made in regard to conditional steps. Any required updates to the preventive maintenance work order instructions will be complete by our commitment date of 01-Jul-2009.*

We believe that our enhancements will ensure robust and appropriate execution and documentation of all work orders.

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, "Final Report for the Container Closure Validation of the (b) (4) **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 Alum diluent.**

b. (b) (4) **used in the manufacture of vaccines are stored in** (b) (4) **. Validation studies have not been conducted to** (b) (4) **.**

Merck Response 6: *In response to the above cited observation, see Merck's Observation Response 22, located on pages 65 and 66.*

6a. We note that the (b) (4) *. As a result, we will update the validation of the* (b) (4) ,

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(b) (4)

6b. *With regard to the* (b) (4) *. Historically, we have applied the* (b) (4) *. As noted below,* (b) (4) *.*

Status of Corrective Actions: *As committed in Merck's Observation Response, the following is an update of the actions taken:*

- (b) (4) *. The study will be initiated by 30-Jun-2008.*
- *SOP 240-356X, "Validation Assessment for Filters and Container Closures" and SOP 240-150X, "Standard Procedure for* (b) (4) *" have been updated as of 18-Apr-2008 and 28-Apr-2008,[2] respectively, and training has been completed to specify that validation data are required to support integrity of the closure over all anticipated conditions of storage and* (b) (4) *See Attachment 30 for supporting documentation of these updates.*
- (b) (4) *.*
- *We have further revised SOP 240-356X, "Validation Assessment for Filters and Container Closures" and completed training on the revised SOP on 18-Apr-2008. The scope of the revised SOP 240-356X includes intermediate products and in-process materials, such as the* (b) (4) *referenced above, along with finished and sterile products. See Attachment 30 for supporting documentation of this revision.*
- *A documented risk assessment has been initiated for* (b) (4) *This risk assessment will be completed by 29-Aug-2008.*

In addition to the actions specified in Merck's Observation Response, we are taking the following actions:

[2] *It is important to note that the SOP 240-150X was effective as of 28-Apr-2008. However, the SOP was updated and training was completed by 23-Apr-2008.*

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- (b) (4)

  1. A(b) (4)

  2. (b) (4)

We believe the actions taken or to be taken will provide additional assurance that our vaccine product closure systems remain integral over the maximum allowable storage time and through all anticipated storage conditions. In addition, the risk assessments described above will better define the validation requirements for closure systems associated with in-process materials used in manufacturing.

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.

***Response to Quality Control Unit Comment**: We fully recognize the importance of a robust and mature Quality Control Unit at the West Point Site that has oversight responsibility for all systems within the manufacturing and operations area. We understand that a strong Quality Control Unit assures the identity, strength, quality, and purity of the drug product and drug substance manufactured at the site. The FDA Form 483 Observations and the Warning Letter Observations reinforce our need to further strengthen our Quality System so that the Quality Control Unit functions as intended.*

As previously communicated to the Agency, we independently recognized the need to strengthen our Quality System at the West Point site and as a result, implemented key initiatives as part of our commitment to ensure compliance with Good Manufacturing Practices. These key initiatives not only ensured prospectively that the quality system was enhanced, but in many cases, assessed past performance in order to identify areas that should be strengthened. As noted in Merck's Observation Response, many of the FDA Form 483 Observations were actually self-identified issues that Merck had independently begun to address and for which significant progress was well under-way before the 2007 Team Biologics Inspection.

We recognize that our system enhancements require a multi-year focus by a dedicated senior management team to realize the goal of having a robust and mature Quality System which operates as intended. We are committed to ensuring that this goal is fully realized. We take all FDA Form 483 and Warning Letter Observations seriously and as opportunities to enhance our systems. In addition, as previously communicated, we have engaged outside GMP consultants to help us focus our initiatives and ensure compliance

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with Good Manufacturing Practices. All learnings will be shared throughout the site and Merck, where applicable.

Specifically, examples of some key initiatives to strengthen our West Point Quality Systems include the following:

1. *Site wide initiatives led by the new Quality Systems Director, who reports directly to the Vice President of West Point Quality Operations, include the following:*

   a. (b) (4)

   b. (b) (4)

   c. (b) (4)

   d. (b) (4)

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2. *GMP Facility and Utility assessments against global regulations led by the recently appointed Quality Engineering Director, who reports directly to the Vice President of West Point Quality Operations. This function will assess GMP Facility and Utility related operations, and using a risk based approach, will prioritize areas for enhancement, develop implementation plans, and monitor implementation through completion.*

   (b) (4)
   . This includes refining the corrective action process to ensure all areas affected are properly addressed and actions are consistently applied. Additionally, (b) (4)

3. (b) (4)

4. *The internal West Point* (b) (4)
   , (b) (4)
   We will work closely with our Divisional GMP Auditing department and our external GMP consultant to participate directly in (b) (4) *. The* (b) (4)

5. *Independent third party review of our Deviation and Complaint Management procedures by* (b) (6) *of* (b) (4) *. This review will include a detailed system assessment, including a review of several investigations, including those referenced in the FDA Form 483 Observations. The learnings from this retrospective assessment will be incorporated into training programs or procedures to drive the methodology for identification of root cause(s), to ensure a consistent approach in the evaluation of all potentially affected products, to improve the clarity and structure of the documented investigations, and to ensure and monitor the effectiveness of our corrective actions.*

   Additionally, by 01-Jul-2008, we will establish a Senior Management Steering team consisting of West Point Quality Operations, Global Vaccine Technology and Engineering, Divisional Quality Assurance, and an outside Consultant with expertise in GMP. (b) (4)
   . This team will continue to monitor these activities until we can confirm that corrective actions

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are applied systematically and are robust, comprehensive, and sustainable across the site.

6. *The* (b) *. The focus of this initiative will be to significantly minimize the frequency of deviations, eliminate repeat deviations, improve the thoroughness of the investigations, ensure that any learnings from any one investigation are shared and implemented across all operations areas, and improve the overall timeliness of the investigation reports. This will be performed in close alignment with* (b) (6) *actions as well as the actions performed by Quality Systems Director.*

7. *An initiative to review and* (b) (4) *, with the support and assistance of* (b) *, an independent* (b) *consultant, is underway. With guidance from* (b) (4) *, detailed technical requirements, meeting or exceeding industry standards will be established for the design, operation, and validation of* (b) (4) *. The* (b) (4) *. Action plans, as appropriate, will be developed to ensure compliance with these* (b) (4) *. An additional objective of this initiative is to* (b) (4) *, where necessary, so as to ensure that* (b) (4) *.*

8. (b) (4)

RESPONSES TO WARNING LETTER COMMENTS AND REQUESTS FOR FURTHER INFORMATION

Observation 2: Your response indicates that although (b) (4) **However, your investigation states that** (b) (4) **for MMR can not be** (b) (4) **for the VARIVAX III product. In addition, your investigation states that due to the** (b) (4) **. Please provide an explanation to clarify these statements.**

Response to Observation 2: *In reference to the above cited observation, see Merck's Observation Response 2, located on pages 14 to 22. For additional information on this topic, please refer to our response to the Drug Product 1a, located on page 15 of this document.*

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As committed in Merck's Observation Response, we agree that (b) (4) *. As a result, we have initiated the process* (b) (4) *: ZOSTAVAX® Frozen, ProQuad® Frozen, VARIVAX®, and M-M-R®II. The* (b) (4) (b) (4) *. For MERUVAX®, MUMPSVAX®, M-M-VAX®, and ATTENUVAX®,* (b) (4) *of MERUVAX®, MUMPSVAX®, M-M-VAX®, and ATTENUVAX®.*

We would like to clarify the statements that the (b) (4) *for measles, mumps, rubella* (b) (4) *for the VARIVAX®III product" and* (b) *VARIVAX®III Lot 0265P* (b) (4) *." These statements are focused on the assessment of measles, mumps, and rubella* (b) (4) *. The impact of the varicella virus* (b) (4) *of VARIVAX®III. (See Impact on Varicella Potency below.) The* (b) (4) *.*

Impact on Sterility: (b) (4) *from a lot of VARIVAX®III that exhibited* (b) (4) *. Of the* (b) (4) *. All sterility results from this VARIVAX®III lot were passing. In addition, material analysis of the container closure system was performed, and concluded* (b) (4) *. The* (b) (4) *. Therefore,* (b) (4) *of VARIVAX®III subject* (b) (4) (b) (4)

Impact on Varicella Potency: *The* (b) (4) *of VARIVAX®III supports that* (b) (4) *Varicella* (b) (4) *of VARIVAX®III were* (b) (4) *ProQuad® Frozen, VARIVAX®, and ZOSTAVAX® Frozen* (b) (4) *to VARIVAX®III; therefore,* (b) (4) *VARIVAX®III.*

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Impact on Measles, Mumps, and Rubella Potency *The* (b) (4) *of M-M-R®II to* (b) (4) *measles, mumps, or rubella potency in M-M-R®II, M-M-R®II rHA, MERUVAX®, MUMPSVAX®, and ATTENUVAX®. M-M-R®II* (b) (4) *. It was determined that M-M-R®II* (b) (4) *. Based upon this finding, there was an evaluation of* (b) (4) *, i.e., M-M-R®II, M-M-R®II rHA, MERUVAX®, MUMPSVAX®, and ATTENUVAX®,* (b) (4) *. This supports the conclusion that there would be no detrimental effect on measles, mumps, or rubella potency in these products ir*(b) (4)

(b) (4) *ProQuad® Frozen,* (b) (4) *We are in the process of* (b) (4) *of the measles, mumps, and rubella virus components. The fact that the M-M-R®II* (b) (4) *for ProQuad® Frozen* (b) (4) *that the measles, mumps, and rubella* (b) (4) *. As previously committed* (b) (4) *of ProQuad® Frozen* (b) (4) *y. Preliminary results for ProQuad® Frozen* (b) (4)

Additional Actions: *In addition,* (b) (4) *. Please refer to our commitment regarding Quality Systems on page 27, Item 5 on Deviation and Complaint Management.*

Observation 3: Please note that the investigation report dated December 20, 2007, for MMR Lot 1529U 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 Health Canada." Please explain if this is a final report or a summary of the final report.

Response to Observation 3: *We would like to clarify that Merck, in response to a request from Health Canada, conducted a detailed and thorough investigation in December 2007 of all aspects of manufacturing, packaging, and distribution of the affected M-M-R®II vaccine Lot 1529U and its components. Merck prepared the Final Manufacturing Investigation, dated 20-Dec-2007, which summarized the findings of the in-depth investigation conducted. This document was updated on 21-Dec-2007 due to an error noted in Table 3-1 relating to the European distribution information. No other reports relating to this investigation were prepared by Merck other than this Final Manufacturing Investigation. See Attachment 31 for supporting documentation of the Health Canada close out of this investigation.*

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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 (b) (4)

Response to Observation 14: *As background, on 03-Jul-2007,* (b) (4) *. The control* (b) (4)

Merck (b) (4)

Explanation of the Code: *The condition in the* (b) (4)

Documentation of the Inputs and Outputs: *The inputs and outputs of this system were identified during the investigation, and the scenario could be reproduced demonstrating that the error was well defined and understood. The* (b) (4) *. Specifically,* (b) (4)

The following documentation was generated in support of the automation changes needed to correct this error and is provided in Attachment 19.

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- (b) (4) *). The attachments included with* (b) (4) *are as follows:*
  - (b) (4) *).*
  - (b) (4) *).*
  - (b) (4) *).*
- (b) (4)

We, therefore, conclude that this coding condition was a unique event and was not indicative of a wide spread error. In addition, the implemented corrective actions were comprehensive, fully tested, documented, and addressed the issue appropriately.

Observation 15: In your response you state (b) (4) **This measurement is used to** (b) (4) **As these statements seem to contradict each other, please provide a detailed explanation to clarify these statements.**

Response to Observation 15: *We now understand that our statements referenced above appear to be contradictory; therefore, we wish to provide clarification on our original assessment and to update the Agency on our current progress on the* (b) (4) *Attachment 32 contains a summary of the technical assessment into the underestimation of the* (b) (4) *values.*

When we stated in Merck's Observation Response 15 (pages 53-56) that (b) (4) *This conclusion was based on review of* (b) (4)

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What has changed, however, is that the concentration of (b) (4) *We have determined through* (b) (4) *. When* (b) (4) *The fact that the* (b) (4) *. Therefore,* (b) (4)

With this understanding, we have implemented several corrective actions to ensure that (b) (4) *. These include:*

- *We filed* (b) (4) *Since implementation of* (b) (4) *.*
- (b) (4)

In conclusion, although the performance of the method has (b) (4) *As a corrective action,* (b) (4) *. We respectfully submit that these changes enhance the performance of the assay and ensure reliability and consistency.*

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.

[3] *It is important to note that the* (b) (4) *was effective as of* (b) (4) *. However, per procedure the laboratory* (b) (4) *.*

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Response to Observation 16: *In response to the above cited observation, see Merck's Observation Response 16, located on pages 56 to 58.*

A. Status of Divisional Glass Breakage Initiative:

The Divisional guidance document, "Management of Glass Breakage", requires each impacted Merck site to develop an appropriate plan and associated timeline to comply with the following items:

1. *Training of personnel on the importance of managing breakage during processing and on actions to be taken when breakage occurs.*

2. *Development or enhancement of existing SOPs to clearly state what actions must be taken to manage glass breakage from initial supplier receipt to final product inspection.*

3. *Performance of a Failure Modes and Effect Analysis (FMEA) assessment of Operations areas to determine where enhancements for management of glass breakage are needed. Where feasible,* (b) (4)

4. *Development and implementation of an action plan for closing identified issues.*

To date, each site where the Divisional Guidance is applicable has created its plan to meet the expectations outlined in the guidance document and has either completed the necessary steps or is on target to meet the scheduled milestones. The progress of each Merck site against the above deliverables is tracked on a regular basis by Divisional Quality Assurance and periodically reviewed by MMD senior management.

B. Status of Action Items from Merck's Observation Response:

1. *As stated in Merck's Observation Response, awareness training was completed for all West Point Sterile and Packaging Operations employees by 09-Jan-2008. All employees were trained on how to react to glass breakage events and the proper method for documenting and investigating glass breakage events. The training emphasized the importance of identifying glass breakage events on the manufacturing lines, notifying supervisors of the events, and issuing deviation alerts in response to these events.*

2. *A FMEA was performed in February and March 2008 (approved on 23-Apr-2008) using a cross-functional team to evaluate all possible scenarios within the Sterile Filling and Inspection areas at West Point in which a glass particulate could enter a vial or syringe and/or where a vial or syringe could crack. The scope of the FMEA included all* (b) (4)

   As a result of the FMEA, a comprehensive list of potential glass breakage scenarios across all of the processing areas was assembled. Many of the scenarios were repeated throughout the analysis, since the same risk exists for multiple process steps/multiple pieces of equipment. As a result of this FMEA,

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(b) (4) *were identified to reduce the potential for glass breakage and/or enhance the detection and subsequent clearance of glass breakage events. The corrective actions focused on three common themes:*

(1) Establishment of (b) (4)

(2) (b) (4)

(3) (b) (4)

(b) (4)

3. (b) (4) *The objective of the feasibility evaluation was to determine if* (b) (4) *The scope of the evaluation included all filling lines within West Point Sterile and Packaging Operations (SPO).*

Through a risk based assessment, the (b) (4)

(b) (4)

4. *Status of Additional Action: An additional commitment was included in Merck's Observation Response. West Point Sterile and Packaging Operations, committed to updating SOP 285-230, "Operation of Filling Rooms* (b) *and* (b) *to provide additional details with regard to responding to glass breakage events. Detailed instructions were provided for line clearance from all areas of the filling line. In addition, an inspection of the entire filling line, including the stopper bowl and associated area, is required when glass breakage occurs. The procedure was updated and training was completed, by 31-Mar-2008. The supporting documentation for this SOP update is provided in Attachment 34.*

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 (b) (4) **Also, at two different times during the inspection, your production supervisor was unable to provide any information to explain the cited pressure losses.**

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Response to Observation 18: *We apologize for any confusion provided in Merck's Observation Responses and the discussions held with the Production Supervisor during the inspection.*

During the inspection and in Merck's Observation Response, we detailed that th(b) (4)

We acknowledge that at two different times, the production supervisor was unable to provide information to explain all of the cited pressure losses. However, following the inspection, the root cause for each pressure loss was identified as detailed in Merck's Observation Response, (b) (4) *We agree that our system should be enhanced to ensure that* (b) (4)

Status of Corrective Actions: *As committed in Merck's Observation Response, we have completed the following three actions:*

- (b) (4)
- *PedvaxHIB® production batch,* (b) (4) *, it would be evaluated via the Deviation Alert / Atypical Process Report system.*
- *The procedures within the* (b) (4) *and West Point Product Release were revised, and training was completed, to include instructions* (b) (4)
  - (b) (4) *See Attachment 35 for supporting documentation for this update.*
  - (b) (4) *See Attachment 36 for supporting documentation for this update.*
  - (b) (4) *". See Attachment 37 for supporting documentation for this update.*

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- (b) (4) ". *See Attachment 38 for supporting documentation for this update.*
- (b) (4) . *See Attachment 39 for supporting documentation for this update.*

Additional Action: (b) (4) .

These (b) (4) .

Observation 20C: Your response indicates that no marketed product has been manufactured with measles drug(b) (4) **and that all measles drug components** (b) (4) **. However, your response does not address how** (b) (4) **of measles drug components and vaccine drug products made from these drug components. Please comment.**

Response to Observation 20C: *As background, the Measles bulk drug substance is comprised of measles virus in the* (b) (4) *The drug substance* (b) (4) .

In the manufacturing of M-M-R®II product, the Measles drug substance is(b) (4) .

Hence, the Measles drug substance and the M-M-R®II drug product (b) (4) .

The expiration dating for the Measles drug substance and final drug product was evaluated in terms of the (b) (4) . *Below is a summary of our path forward:*

Measles Bulk (Drug Substance): *Even though the* (b) (4) *Merck has elected to file for* (for *Measles Pooled Clarified Bulk* (b) (4) *The reduced expiry will be submitted to CBER by 30-May-2008.*

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((b)) (

Measles Drug Product: *There is no impact, however, to the current expiry for the vaccine drug products made from the Measles bulks, given that we are controlling expiry of the current inventory of Measles bulk* (b) (4) *. Furthermore,* (b) (4) *Since there is a correlation between actual potency of the Measles drug* (b) (4)

Measles potency testing for final container products M-M-R®II, M-M-R®II rHA, ATTENUVAX®, and ProQuad®, (b) (4)
In addition, all stability data for measles potency have been in alignment with the historical profile for each product, and no atypical trends in the data have been observed.

As further support for the drug product, an evaluation was performed in 1996 on an historical database of stability lots to determine if the stability of M-M-R®II or ATTENUVAX® (b) (4) *. As shown in Figure 1, the results of this evaluation showed that the slopes of the potencies were not negatively affected* (b) (4)

(b) (4)

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To confirm acceptability of a seven-year measles bulk expiry, we reviewed the stability database for measles containing vaccine drug products made since this historical evaluation in 1996, specifically those which were made using measles pooled clarified bulk that was approximately seven years old. An evaluation was performed for four lots of representative M-M-R®II finished product manufactured using two different lots of measles pooled clarified bulk that ranged in age from (b) (4) *The slope of the measles potency for these four lots of finished vaccine drug products was found to be satisfactory throughout the 24-month shelf-life and comparable to the historical data set described above. This ensures that the finished product will maintain the required potency throughout the currently approved expiry period.*

In summary, per our commitment in Merck's Observation Response, an internal control of seven years was instituted on 15-Feb-2008 for Measles Pooled Clarified Bulk in our material control system. This internal control will be maintained in conjunction with filing the reduced expiry. A filing may be submitted to extend the expiry when the out-of-specification investigation has been resolved and as additional bulk stability data becomes available. Currently, (b) (4) *are available for two additional Measles Bulk lots on stability. At such time, a request to extend expiry will be submitted to CBER.*

Observation 25; Your response stated that independent of the validation for (b) (4) **there was no impact to product quality for all lots produced since there is an** (b) (4) **Please provide the procedures(s) in place prior to and after the current inspection covering the** (b) (4) **.**

Response to Observation 25: *The procedures in place prior to and after the 2007 Team Biologics Inspection, covering* (b) (4) *SOPs 174-211, "Visual Inspection Methods and Techniques" and 174-321X, "Sterile Filling and Inspection Acceptable Sampling Plan", effective 29-Oct-2007 and 15-Oct-2007, respectively. These procedures have not changed. These SOPs are provided in Attachment 40 per your request. Additionally, a representative sample of the* (b) (4) *the PNEUMOVAX®23 batch record is included in Attachment 41 to demonstrate the data captured for the* (b) (4) .

Observation 34: Your response states that you have verified that none of the data entry errors impacted (b) (4) **or resulted in the incorrect use of the cans 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 helium leak test results or that no cans 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.**

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Response to Observation 34: *As background, the* (b) (4)

In addition, it is important to note that the type of data inaccuracies noted in Observation 34 did not relate to any inaccuracies associated (b) (4) *. Rather, they were related to the tracking status of a can.*

Verification of Appropriate Can Use in Manufacturing*: As stated in Merck's Observation Response 34, we acknowledge that the* (b) (4) *a limited number of inaccurate data associated with can tracking status* (b) (4)

As a result, we evaluated the use of (b) (4) *manufacturing to ensure* (*. Our focus of the evaluation was to ensure that, with respect to* (b) (4)

We have confidence that the data inaccuracies did not impact these aspects based on the following systems and analyses:

- (b) (4) *. By procedure,* (b) (4) *. Based upon this, we have a high level of confidence in the* (b) (4) *Furthermore, even in the unlikely event that there was an inaccuracy in the data entered into the database related to* (b) (4)

  Specifically, our procedures require the following:

  - (b) (4)
  - (b) ( )

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i. (b) (4)

ii. (b) (4)

iii. (b) (4)

- (b) (4)

  i. (b) (4)

  ii. (b) (4)

  iii. (b) (4)

  iv. (b) (4)

  v. (b) (4)

- (b) (4) (b) (4)

Status of Corrective Actions: *As noted in Merck's Observation Response 34, the following SOPs have been updated to address the causes of the inaccuracies:*

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- *SOP 227-150X (b) (4) " and SOP 287-118X[4] "Management (b) (4) " were updated to clarify roles and responsibilities and the administrative functions performed by the (b) (4) . The SOPs were updated and training was completed, by 01-Apr-2008. See Attachment 42 for supporting documentation of these updates.*

- *The appropriate personnel were re-trained by 04-Apr-2008 on SOP 287-111X[4] "(b) (4) .*

- *SOP 227-150X "(b) (4) " was updated (and personnel were trained) by 01-Apr-2008 to include database auditing procedures. See Attachment 43 for supporting documentation of these updates.*

Conclusions: *We have a high level of confidence that redundant checks ensure the accuracy of the data related to (b) (4) and that such (b) (4) Furthermore, we also have a high level of confidence that redundant checks in the processing and handling (b) (4)*

Observation 37: Your response included the same historical data for two of the markers (Historical Positive Control Performance in CP9110.780 and the Historical Reference Curve ED_{50} Values in CP9110.780) that were reviewed during the inspection. Furthermore, updated data submitted in support of the historical slope curve 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 "Assignment and Extension of Re-Evaluation Periods and Storage Conditions for Biologic Critical Reagents" are noted; however, these do not address the problems with the(b) (4) . Please provide the results from the investigation of (b) (4)

Response to Observation 37: *We completed our investigation of the (b) (4) . A more detailed description of our scientific rationale related to the stability investigation is provided in Attachment 44. The investigation concludes that the (b) (4) . The (b) (4)). (b) (4)*

[4] *Please note that Department 287 referenced in the SOP is now Department 208.*

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These findings do not impact the initial qualification of the Working Standard completed in 2003, (b) (4) *. It is important to note that the* (b) (4) (b) (4) *. It has been demonstrated that alum protects this material from aggregation. Therefore, the aggregation phenomenon observed with the Master Standard does not apply to the Working Standard.*

With respect to the (b) (4) *, as evidenced by the data, the lack of a statistically significant trend in the positive control demonstrates that the assay is performing as expected. The root cause of* (b) (4) *The* (b) (4) *The slight downward trend with respect to the upper and lower control limits is driven by a limited number of elevated values at the initial time points. As evidenced by the data, the slope has flattened out as we continue to collect more data.*

Prior to completing our investigation into the Master Standard stability time point, we prospectively defined alternative scientific criteria for requalification of the Working Standard, referenced in Attachment 44 (See Section III). We respectfully disagree that these data are inadequate to support expiry extension of the Working Standard and believe that these data support its continued use. The parameters continue to be monitored and are the basis of continued use of the Working Standard until a new Master Standard is qualified. As committed to in Merck's Observation Response, SOP 129.022, "Assignment and Extension of Re-evaluation Periods and Storage Conditions for Biologic Critical Reagents" has been modified effective 02-May-2008. See Attachment 45 for supporting documentation of this update.

We would welcome the opportunity to have further technical discussions on this issue with the Agency and will contact the product office to arrange a mutually agreeable time.

Observation 38: Your response indicates that you will establish (b) (4) **If this critical reagent has** (b) (4) **Also, please clarify** (b) (4)

Response to Observation 38:

***Re-evaluation Date**: Effective 21-Apr-2008, we have updated the Certificate of Analyses for* (b) (4)

1. *For* (b) (4) *nd*

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(b) (4)

2. *For the five lots of antisera found* (b) (4)

(b) (4)

Re-evaluation Criteria: *The re-evaluation criteria used to qualify material for continued usage in* (b) (4)

(b) (4)

(b) (4)
(b) (4)

(b) (4)

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(b) (4)

Additionally, there are positive control parameters built into (b) (4)

These are evaluated (b) (4)
The (b) (4)

This assessment determines the (b) (4)

We respectfully submit that the existing available positive control data, the re-evaluation of the material in accordance with our (b) (4) *, and the implementation of* (b) (4)

(b) (4)

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 (b) (4) **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 pharmaceutical products to confirm that all tests were performed. What is the status of that evaluation?**

Response to Observation 43:

*1.) SOP 027-SL108X, "SQL*LIMS – Management of Results and Tasks," has been updated to clearly define which individuals are authorized to reject release or stability*

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(b) (4)

2.) *SOP 027-SL108X was also updated to* (b) (4)

In October 2007, a review of the release process was completed for all pharmaceutical products and raw materials tested and released at the West Point site between 01-Jan-2007 to 30-Oct-2007. This review was performed as part of a corrective action to laboratory investigation 2007-223B-0068, which was provided to the investigation team on 29-Nov-2007. This review was completed on 31-Oct-2007 and found that satisfactory controls were in place to ensure that applicable products had been and continue to be released in accordance with Merck's Quality Standards (i.e., all applicable release tests were performed and all specifications had been met prior to release). The results of this assessment, and the conclusion that no additional action was required, were documented in the corrective action close out memo attached to APR 2007-223B-0068.

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