SUMMARY

(MSL)

This inspection of Merck Sharp & Dohme Corp. located at 770 Sumneytown Pike, West Point, PA 19486-0004 was conducted in accordance with CPGM 7345.848 "Inspection of Biological Drug Products (CBER) and CPGM 7356.002 "Drug Manufacturing Inspections" (eNSpect Operation Id: 55619). The inspection was a Level II inspection per CPGM 7345.848 with a focus on the Quality System and the Packaging and Labeling System (including visual inspection). Limited coverage was also given to the Facilities and Equipment System, Materials System, Production System, and Laboratory Control System. The coverage that was provided under CPGM 7356.002 is described in the Small Molecule Program Summary at the end of this section. The inspected site continues as a licensed manufacturer of vaccines, antivenin, and normal horse serum. The site also conducts some limited activities related to other drugs as well.

The last Team Biologics inspection of the site (conducted 3/12-4/02 & 4/16-4/17, 2015) resulted in the issuance of a Form FDA 483 containing 16 observations. Observations included: Testing procedures relative to appropriate laboratory testing for sterility were not followed.; The accuracy, sensitivity, specificity, and reproducibility of test methods employed by the firm were not established and/or documented. The amendment titled "Final Report-Amendment –Sterility Test Sample Storage Evaluation Project for In-Process Virus Vaccine Samples" dated March 14, 2002 initiated to extend the evaluation of the frozen storage time of virus vaccine bulks from 7 to 16 weeks and an evaluation of the time the samples remain at room temperature after thawing and prior to testing was inadequate.; Aseptic processing could not be assured as controls for equipment and facilities were inadequate. There was no requirement to initiate a quality notification (QN) investigation for HEPA filter failures and incursions (leaks) into classified rooms.; Aseptic processing areas were deficient regarding the system for monitoring environmental conditions.; The failure of a batch or any of its components to meet specifications whether or not the batch was distributed did not always extend to other products with the associated discrepancies.; Certain products that failed to meet established standards or specifications and any other relevant quality control criteria were not rejected.; Failure to report any event associated with the manufacturing, including testing, processing, packing, labeling, or storage, or with the holding or distribution of a licensed biological product, which may affect the safety, purity, or potency of a distributed licensed product.; The suitability of the testing methods was not verified under actual conditions of use. Specifically, the visual inspection program was not adequate to eliminate defects from product.; Equipment was not cleaned, maintained, and sanitized at appropriate intervals to prevent malfunctions or contamination. Specifically, contamination from occluded surfaces and cross contamination of sterility test samples had been cited as the root cause for sterility test failures.; Laboratory controls did not include certain scientifically sound and appropriate specifications, standards, sampling plans, and test procedures designed to assure components and products conformed to appropriate standards of identity, strength, quality, and purity.; Examination and testing

of certain samples was not done to assure that in-process materials conformed to specifications.; Written procedures for cleaning and maintenance failed to include description in sufficient detail of the methods of disassembling and reassembling equipment as necessary to assure proper cleaning and maintenance. Specifically, the October 2014 replacement of copper cooling coils in the Building (b) (4) tunnel generated copper particles which were not properly cleaned.; The flow of certain components and in-process material through the building was not designed to prevent contamination.; The antigen content specification for the stability of Hepatitis A Vaccine (VAQTA) drug product had not been revised since implementation of a new analytical assay for potency (b) (4) . The then current antigen content specification for drug product stability ((b) (4) Units/mL) had not been approved by the Agency for use with the new assay. Records were not maintained so that data therein could be reviewed at least annually to evaluate the quality standards of each drug product to determine the need for changes in specifications or manufacturing or control procedures. Specifically, late environmental monitoring annual performance evaluations; The number of qualified personnel was inadequate to perform certain laboratory testing. Corrective actions related to these observations were reviewed during the current inspection.

A CBER PAI regarding a new area for the manufacturing of VAQTA drug substance (conducted 6/22-26, 2015) resulted in the issuance of a Form FDA 483 containing 3 observations. Observations included: Cleaning issues for purification skids and columns; Written procedures for preventing contamination as described in SOP B83 VAQTA: Shower Log (Document Number (b) (4)) were not strictly followed.; Labeling of certain containers was not performed in accordance with established procedures. Corrective actions related to these observations were reviewed during the current inspection.

The current inspection resulted in the issuance of a Form FDA 483 containing 16 observations. Observations included: Written records of investigations into unexplained discrepancies of a batch or any of its components to meet specifications do not always include the conclusions and follow-up. Specifically, Investigations are not always conducted in a timely manner into vaccines manufacturing and equipment non-conformances, and corrective and preventive actions are not always instituted in a timely manner to prevent reoccurrences. Apart from manufacturing "Events" that are not required to be documented as deviations but are documented in the batch records and are not investigated per SOP #06-QUA-125AX Version 13.0, various documented manufacturing non-conformances/deviations since the last inspection of March 2015 were not always corrected in a timely manner. There are no documentation that formal investigations are opened and no documented justifications are provided.; Input to and output from the computer or related system of formulas or other records or data were not adequately checked for accuracy. Specifically, the validations of the (b) (4) vials inspection machines(b) (4) and(b) (4) as corrective actions to previous 2015 FDA-483 Observations 5B, 8A, 8B, 10A, 11A and 11B regarding Recombivax HB Adult batch # 0672446 that was recalled in June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch is

inadequate.; The corrective actions to previous 2015 FDA-483 Observations 1A and 2B regarding the freezing and thawing of sterility samples before performing sterility testing for virus vaccine samples that have been frozen for 16 weeks and thawed for one day prior to performing sterility test is inadequate.; Observation #3 from the 2015 Pre-approval Inspection (PAI) regarding labeling of containers that are not performed according to established procedures has not been adequately corrected.; The Quality Control Unit failed to conduct an adequate annual review of production records so that data therein can be used for evaluating the quality standards of each product to determine the need for change in product specifications, manufacturing and/or control procedure.; The responsibility and procedure applicable to the Quality Unit are not fully established and/or followed. Specifically, The Quality Unit oversight of the Production Unit for vials/syringe defects inspections, labeling and packaging operations are inadequate.; Batch production and control records are not adequately prepared for each batch of production and do not include complete information relating to the production and control of each batch. For example, the batch record for labeled and packaged vials failed to include certain information.; Certain employees are not adequately trained in the particular area that they perform.; Vaccines syringes, vials and tubes collected for retention samples for yearly inspections and for complaints investigations are not representative of the released batches.; Failure to submit Biological Product Deviation Reports; There is a lack of rotation so that the oldest approved stock of components is used first in that there are no written procedures stating that vaccine bulk drug substance should be used (when possible) on a First In First Out or First Expired First Out basis.; There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed with regard to OOS test results for pyrogen in PedvaxHIB samples.; Biological Laboratory Procedure 052650232GEN.004 entitled "Bioburden" does not require bioburden recoveries that are identified to be assessed as to whether the identified microorganisms (other than USP indicator organisms) are objectionable.; Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product in that discoloration presumed to be rouging was observed on the CIP/SIP manifold located inside of the barrier (aseptic filling isolator) located in Building 38 Room 1323 during the aseptic filling of Pneumovax Batch 0000702018.; Since 2015 a low bias has been observed for hepatitis A antigen content in VAQTA final container batches from the manufacturing target of 61 U/mL. The corrective action involved the application of a correction factor to the Alum Adsorbed Bulk prior to final formulation. The investigation is ongoing and the root cause has not yet been identified.; The endotoxin in-process alert limit of 500 EU/mL for the final retentate of each individual polysaccharide used in the Pneumovax 23 vaccine is not representative of historical data.

No samples were collected and there were no refusals.

Small Molecule Program Summary

(CDZ)

This GMP inspection of a small molecule drug manufacturer and biologics manufacturer was performed under Op ID 55619 in accordance with Compliance Program Guidance Manual (CP) 7356.002 Drug Manufacturing Inspections.

The previous GMP inspection was conducted on 9/02/2014 through 09/12/2014 was classified as VAI and resulted in the issuance of a 3 item Form FDA 483 for: 1) inadequate testing of incoming raw materials; 2) use of apparatus not meeting established specifications; and 3) failure to verify suitability of testing methods. Corrective actions from the previous 483 items were evaluated. All corrective actions were found to be adequate.

The current inspection revealed that the firm has discontinued the manufacture of small molecule pharmaceuticals. A stability program for small molecule products previously produced on site as well as a limited number of small molecule products produced offsite is maintained. Inspectional systems covered included Quality, Laboratory and Facilities and Equipment as well as Field Alert Reporting.

ADMINISTRATIVE DATA

Inspected Firm:	Merck Sharp & Dohme Corp.
Location:	770 Sumneytown Pike West Point, PA 19486-0004
Phone:	215-652-0855
Mailing Address:	same as location address
Dates of Inspection:	04/18/17, 04/19/17, 04/20/17, 04/21/17, 04/24/17, 04/25/17, 04/26/17, 04/27/17, 04/28/17
Days in the facility:	9
Participants:	Mihaly S. Ligmond, CSO, Team Biologics (MSL) Omotunde O. Osunsanmi, CSO, Team Biologics (OOO) Marian Major, Ph.D., Supervisory Research Microbiologist, OVRR/DVP (MEM) Craig D. Zagata, CSO, PHI-DO (CDZ)

(MSL)

At an opening meeting on 4-18-17, we (MSL, OOO, and CDZ) issued a Form FDA 482 Notice of Inspection dated 4-18-17, and presented our credentials to Martin R. Kuhn, Vice President, Plant Management, Plant Manager, West Point. Mr. Kuhn identified

himself as the most responsible person for the site. During this opening meeting I explained that the purpose of the inspection was a GMP inspection. The firm made an opening presentation as well.

On the first day of the inspection, prior to entering any manufacturing or testing areas Valerie Godzieba, Associate Director, Safety & Environment reviewed my titer and PPD test results. See the ADDITIONAL INFORMATION section of this Establishment Inspection Report (EIR) for the entry requirements for manufacturing and testing areas. I allowed her to photocopy my PPD test results record. I was granted medical clearance to enter the manufacturing and testing facilities.

Dr. Major arrived on 4-19-17 and Form FDA 482 Notice of Inspection dated 4-19-17 was issued to Mr. Kuhn upon her arrival. She also presented her credentials to Mr. Kuhn.

On 4-19-17 the firm presented an overview of gowning practices relevant to the site which I attended prior to entering any manufacturing or laboratory areas.

A Form FDA 483 Inspectional Observations dated 04/28/2017 containing 16 observations was issued to Mr. Kuhn during a final closeout meeting on 4-28-17.

This was a team inspection including the FDA representatives noted above. The sections of this Establishment Inspection Report (EIR) written by each FDA representative are denoted by the initials of the FDA representative. CSO Ligmond and CSO Osunsanmi were present for the entire inspection. Dr. Major was present on 04/19/17, 04/20/17, and 04/21/17. She also had telephonic communication with the firm after her departure but during the inspection. CSO Zagata was present on 04/18/17, 04/19/17, and 04/20/17. Only CSO Ligmond and CSO Osunsanmi were present for the final closeout meeting and issuance of the Form FDA 483. As such only CSO Ligmond and CSO Osunsanmi signed the Form FDA 483.

HISTORY

General History

(MSL)

This Merck Sharp & Dohme Corp. site located at 770 Sumneytown Pike, West Point, PA 19486-0004 is a subsidiary of Merck & Co., Inc. with corporate headquarters at 2000 Galloping Hill Road, Kenilworth, NJ 07033. Exhibit MSL1 contains some corporate information. The company's Annual Report can be found at:
http://investors.merck.com/financials/annual-reports-and-proxy/default.aspx

The West Point site continues as a licensed manufacturer of vaccines, antivenin, and normal horse serum. The site also conducts some limited activities related to other drugs as well. The following Merck Divisions are located at the West Point site: Global Human

Health, Merck Manufacturing, and Merck Research Laboratories. The site contains approximately(b) (4) buildings (not all of which are used for vaccine/antivenin/normal horse serum manufacturing or testing). With regard to vaccine/antivenin/normal horse serum the site activities include warehousing, manufacturing, testing, and shipping.

Exhibit MSL2 contains some information on recent regulatory agency inspections of the site.

Exhibit MSL3 contains portions of the Site Master File West Point Manufacturing Operations Version 7.0 Effective Date: 31 October 2016. Appendix 2 (on pages 27-30 of the exhibit) shows what is manufactured at the site and the buildings used except that Sterile Diluent is not currently manufactured at this site. Appendix 3 (on pages 31-34 of the exhibit) shows recent GMP inspections and GMP certificates. Appendix 4 (on pages 35-38 of the exhibit) shows contract laboratories used by the site. Appendix 5 (on pages 39-43 of the exhibit) contains organizational charts as of 31 Oct 2016. Appendix 6A1 (on pages 44-45 of the exhibit) contains a site map.

Exhibit MSL4 contains information regarding major personnel and facility changes at the West Point site. As can be seen on pages (b) (4) of the exhibit, facility changes (Major Facility Renovations (2015 to Apr 2017)) include: (b) (4) (2014-2015, Complete),(b) (4) (b) (4) (2015-2017, Complete). (b) (4) (2014-2016, Complete) (b) (4) (b) (4) (2016-2017, in Execution phase), (b) (4) (2016-2017, in Execution (b) (4) (2017-2019, in Execution phase), (b) (4) (b) (4) (2016-2017, in Execution phase), (b) (4) (2017-2019, in Execution phase), (b) (4) , (b) (4) , Process Simulations) (2015-2016, Complete). (b) (4) (b) (4) (2017, in Execution phase), (b) (4) (2015-2016, Complete), B62 New In-coming Supplies Inspection Area (2016-2017, in Execution phase), (b) (4) (b) (4) (2016-2017, in Execution phase), (b) (4) (b) (4) (2015-2016, Complete), (b) (4) (2016-2017, in Execution phase).

As per Exhibit MSL5 key site activities include:

Effective 31 October 2016, Dr. Timothy Bassler was appointed Executive Director, West Point Quality Lead, replacing Mark Stannard.

GLIMS Migration: Upgrade current GMP system for managing environmental and analytical data.

(b) (4)

Capital Projects: Several large capital projects expanding capacity and installing new capability.

(b) (4)
(b) (4)

Exhibit MSL6 contains some information regarding investigational vaccines that have been manufactured at the West Point site.

No recalls have been initiated for products manufactured at this site since the last Team Biologics inspection.

Operations at the site are conducted (b) (4).

I verified that the site's registration is current.

All correspondence regarding this inspection should be sent to:

Martin R. Kuhn, Vice President, Plant Management, Plant Manager, West Point
at
Merck Sharp & Dohme Corp.
Merck Manufacturing Division
WP36M-4
770 Sumneytown Pike
PO Box 4
West Point PA 19486-0004
Tel.: 215 652 0855

Small Molecule Program History

(CDZ)

According to Todd Williams, Quality Director, Shared Services, the firm has ceased production of small molecule pharmaceutical products. Mr. Williams provided an internal memo detailing the declassification of the pharmaceutical manufacturing GMP areas on December 19, 2014(**Exhibit CDZ 1**). He also provided a table that detailed the final production and packaging dates for small molecule pharmaceuticals by the firm (**Exhibit CDZ 2**).

Mr. Williams stated that the firm has transitioned to a biologics manufacturing site and has no plans in the future to resume production of small molecule pharmaceuticals. The firm continues to maintain a stability program for manufactured pharmaceutical products.

The final products produced on site are projected to complete their stability studies in 2017.

INTERSTATE COMMERCE

(MSL)

Exhibit MSL7 contains some recent interstate shipping related documents for products manufactured at this site.

Exhibit MSL8 contains a list of Vaccine, Antivenin, and Normal Horse Serum Batches Manufactured 01Mar2015 – 19Apr2017 including the usage decision and distribution date. As per Jason Johnson, Associate Director, Quality Systems & Compliance the distribution date means the date shipped to another Merck site or to a customer.

JURISDICTION

(MSL)

With regard to licensed products the site operates under US License No. 0002.

The following vaccine/antivenin/normal horse serum products are manufactured at this site:

ANTIVENIN (*LATRODECTUS MACTANS*) (Black Widow Spider Antivenin) Equine Origin

Normal Horse Serum (Supplied with the ANTIVENIN)

GARDASIL [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant] Suspension for intramuscular injection

GARDASIL 9 (Human Papillomavirus 9-valent Vaccine, Recombinant) Suspension for intramuscular injection

RECOMBIVAX HB Hepatitis B Vaccine (Recombinant) Suspension for intramuscular injection

M-M-R II (MEASLES, MUMPS, and RUBELLA VIRUS VACCINE LIVE)

Liquid PedvaxHIB [Haemophilus b Conjugate Vaccine (Meningococcal Protein Conjugate)]

PNEUMOVAX 23 (pneumococcal vaccine polyvalent) Sterile, Liquid Vaccine for Intramuscular or Subcutaneous Injection

ProQuad Measles, Mumps, Rubella and Varicella Virus Vaccine Live Suspension for subcutaneous injection

RotaTeq (Rotavirus Vaccine, Live, Oral, Pentavalent) Oral Solution

VAQTA (Hepatitis A Vaccine, Inactivated) Suspension for Intramuscular Injection

VARIVAX Varicella Virus Vaccine Live Suspension for subcutaneous injection

ZOSTAVAX (Zoster Vaccine Live) Suspension for subcutaneous injection

The firm also manufactures refrigerated storage versions (vs. frozen storage) of ProQuad, VARIVAX, and ZOSTAVAX for distribution outside of the US (See Exhibit MSL11).

Exhibit MSL9 contains information on the worldwide authorization status of the vaccines listed above.

INSPECTIONAL COVERAGE/NOTE

(MSL)

Our coverage was limited to commercial vaccine and antivenin/normal horse serum product operations and the other limited drug product operations conducted at this site as discussed in this EIR.

My coverage focused solely on activities related to vaccines and antivenin/normal horse serum, primarily focusing on vaccine related activities.

(OOO)

I covered portions of the Quality System and Labeling and Packaging System discussed below as well as other topics discussed under the FDA-483 Inspectional Observations of this EIR.

(MEM)

I was present at the inspection from April 19 to 21, 2017.

During this inspection I evaluated the firm's practices and procedures as they relate mainly to the manufacture of VAQTA (Hepatitis A Vaccine, Inactivated) although I also reviewed items related to other viral vaccine products and manufacturing in general. I reviewed the stability program, rejected batches since the last FDA inspection; selected Out of Specification results since the last inspection; selected deviations and selected 483

items from the last inspection. I took part in inspections of selected manufacturing facilities as they relate to the above products.

A list of the people I interviewed during the inspection is included in Exhibit MEM-1.

INDIVIDUAL RESPONSIBILITY AND PERSONS INTERVIEWED

(MSL)

We interacted with various company personnel during the inspection. Not all personnel we interacted with are based at this site.

Two key personnel at the firm are:

Martin R. Kuhn, Vice President, Plant Management, Plant Manager, West Point; Mr. Kuhn is the most responsible person for the site. We issued the Form FDA 482s and the Form FDA 483 to Mr. Kuhn. As per Mr. Kuhn he has been in his current role since 22 August 2016. Previously he was the Associate Vice President, Deputy Plant Manager, West Point. He stated that he has no lot release authority. He stated that he has hire/fire authority for all operations that report to him. He stated that Quality does not report to him. As per Mr. Kuhn, he reports to Jacks Lee, Senior Vice President Global Vaccine Operations who is based at the West Point site.

Brian Timothy Bassler, Ph.D., Executive Director, West Point Quality Operations; Dr. Bassler is the top Quality official for the site. As per Dr. Bassler he has been in his current position since 31 October 2016. He stated that he has the final word on lot release but that duty is typically delegated to members of his staff. He stated that he does not report to Mr. Kuhn. He stated that he has hire/fire authority within the Quality Unit. As per Dr. Bassler he reports to Joseph Perez, Vice President Vaccines Quality who is based at the West Point site.

Exhibit MSL10 contains various organizational charts and the address of Kenneth C. Frazier, President & Chief Executive Officer of Merck & Co., Inc. Appendix 5 of Exhibit MSL3 (pages 39-43) also contains some organizational charts.

As of 1/31/17 the West Point site employed (b) (4) employees excluding contractors/temps, interns, and co-ops.

We held regular meetings with Management throughout the inspection to keep them informed as to our findings.

FIRM'S TRAINING PROGRAM

(MSL)

I briefly reviewed the firm's training program regarding data integrity and general GMPs and noted no significant deficiencies.

See Observation 8 of the current Form FDA 483 for an issue that was observed during the current inspection regarding training.

(CDZ)

According to Hardeep K. Sembhi, Associate Director of Learning and Development, employees associated with production receive (b) (4) GMP training as well as training on any revised SOPs. New employees receive introductory GMP training as well as (b) (4) training. I reviewed SOP 11-T&D-003X, MMD West Point GMP Training Program without objection.

I reviewed 2016 training records for the following firm employees without objection: (b) (6) (Sr. Specialist, Complaints), (b) (6) (Specialist, Complaints), (b) (6) (Material Associate II) and (b) (6) (Material Associate I).

MANUFACTURING/DESIGN OPERATIONS

General Information

(MSL)

The West Point site does not solely conduct all activities related to all the vaccines that are manufactured at this site. For example, besides being manufactured at the West Point site human papillomavirus (HPV) monovalent bulk drug substances are also manufactured at a Merck site in Elkton, VA; besides being manufactured at the West Point site varicella drug substance is also manufactured at a Merck site in Durham, NC, besides being conducted at the West Point site MMR II drug product filling is also conducted the Durham, NC site. Most VARIVAX Frozen drug product (the drug substance for this product is made at the West Point site) is manufactured at the Durham, NC site. Labeling and packaging and distribution activities for some vaccines filled at the West Point site are conducted at a Merck site in Wilson, NC. Packaging and distribution activities for certain vaccines are also conducted at a Merck sites in Haarlem, The Netherlands and Brazil.

The West Point site conducts vaccine and antivenin/normal horse serum drug substance manufacturing, final drug product manufacturing and filling, labeling and packaging, and related testing activities.

Certain of the vaccine drug substances (for example for MMR II) are manufactured aseptically. All of the vaccine and the antivenin/normal horse serum drug products are

filled aseptically. The site has (b) (4) filling lines, some of which are (b) (4) filling lines.

Exhibit MSL11 contains a document showing for each vaccine, antivenin, and normal horse serum product the packaging configuration and the (b) (4) filling line (with the building number in which the line is located) used to fill the product.

Reprocessed, Reworked and Returned Vaccines:

(OOO)

My review of the list of reprocess, reworked and returned vaccine products that was provided during the inspection disclosed no objectionable conditions.

Quality System

(MSL)

Aside from what is discussed elsewhere in this EIR my coverage of this system included: verification that the firm has various written procedures applicable to the Quality Unit; a review of selected deviations (called Investigational Quality Notifications (iQNs)) including, but not limited to: iQNs related to data integrity, an overview review of potency type deviations related to measles, mumps, rubella, and varicella containing vaccines, and an overview review of absence of intact cell (AIC) assay deviations with regard to varicella; a review of the 2016 MMR II Product Review General Section; and a review of the 2016 ProQuad Product Review General Section.

See Observations 10 and 12 of the current Form FDA 483 for issues I observed regarding this system during the current inspection.

Deviations:

(OOO)

The inspection disclosed the firm has approximately (b) (4) non-conformances/deviations with three (3) classifications of: (b) (4) (b) (4) that were provided for review during this inspection. I reviewed a selected number of all the eleven manufactured vaccines non-conformances with major concentrations on the vaccines final container defect inspections, labeling and packaging. Furthermore, selected numbers of the following two manufactured vaccines batches non-conformances were also reviewed in-depth:

Rotateq:

(OOO)

My review of the Rotateq vaccine manufacturing non-conformances since the inspection of April 2015, revealed some significant observations in the final containers inspection non-conformances, i.e., fill volumes Process Control Limits (PCL) exceeded and particulates noted in the filled batches, which are discussed further under **Observation #1 & 2** of this EIR.

Pneumovax:

(OOO)

My review of the manufactured Pneumovax vaccine non-conformances since the last inspection of April 2015, disclosed several batches that exceeded the fill volumes, dirty vials, vials with cracked and breakages, stoppers seal defects and particulate process control limits. Please see additional discussion for vials defect under **Observation #1&2** discussions of this EIR.

Corrective and Preventive Actions (CAPAs):

(OOO)

This inspection disclosed that approximately (b) (4) CAPAs were opened since the inspection of April 2015. Furthermore, it was noted that there was no specific time frame for closure of CAPAs as stated in CAPA SOP #06-QUA-341X , Version 7.0 page #6 section E4, which under the heading action required of the SOP, states that if, "More than (b) (4) are required to complete a preventive action" that quality must approve the action and timing. As such, I was told by Hillary McLaughlin, Associate Director Quality that the time frame for closure of a CAPA is (b) (4) days. However several CAPAs were observed opened for over (b) (4) days, **(Exhibit #OOO4).** In addition, per the information I requested and provided during this inspection, (b) (4) of all the (b) (4) CAPAs that were opened were not closed within (b) (4) days (b) (4) However, it was noted that (b) (4) of all CAPAs were not closed if based on (b) (4) calendar days, **(Exhibit #OOO5).**

Annual Product Review

(CDZ)

I reviewed SOP 01-QUA-340X, Authoring Approving and Revising Annual Product Reviews without objection. I reviewed the 2016 and 2017 APR for Emend capsules, the 2016 APR for Emend IV, the 2016 and 2017 APR for Janumet tablets and the 2016 APR Singulair oral granules without objection.

Change Control

(CDZ)

I reviewed SOP 03-QUA-326X, West Point Change Management procedure without objection. Alice Vento, Sr. QA Specialist provided a listing of change controls related to small molecule operations at the firm. I reviewed Change Control records (b) (4) (b) (4) without objection.

Deviation Investigations

(MEM)

I was given an overview of the site deviation management program by Hilary McLaughlin (Associate Director for Quality). This described the process for determining the level of seriousness of the event and whether an event requires an investigation. I reviewed SOP 06-QUA-125X (Performing Investigations). This described the responsibilities, requirements and procedures for performing investigations at the West Point facility. When an event or deviation occurs it is assessed against SOP 06-QUA-125AX (b) (4) Investigative Quality Notifications (iQNs) are initiated in SAP and assigned due dates of (b) (4) business days from the discovery date. Trending is performed to assess repeat events and evaluated to determine recurrence or events that are related. **I asked how the opening and closing of events are tracked to assess the timeliness of closure. I was told that this is included in the Annual Product Review (see Annual Product Review Discussions and 483 Observation #5B).** Investigations are classified as (b) (4) at the completion of the investigation. However, not all events are placed into one of these classifications and therefore would not be investigated or tracked.

I reviewed a select number of deviations and out of specifications from a list provided to me by management.

Investigation iQN (b) (4) **.** I reviewed this investigation with Irene Liao (Assoc. Dir. Engineering), William Ahlmark (Dir. Engineering), Kevin McLaughlin (Assoc. Dir. Quality). This investigation consisted of several combined events that indicated the same route cause. At the time of the event there had been notifications for high protein and antigen concentration values for hepatitis A (VAQTA) bulk material in (b) (4) samples tested. The values were exceeding the long-term process capability limits established for the manufacturing process. These high values were for seen for different laboratory results (protein content, antigen content, high performance size exclusion

chromatography for hepatitis A) and for samples tested from different points in both VAQTA bulk manufacturing buildings (b) (4) The investigation concluded that the root cause of the high protein and high antigen concentrations indicated a system change in the upstream process from July 2015. The investigation determined that the high protein and antigen concentrations were associated with the use of fetal bovine serum (FBS) from a specific manufacturer. Analysis of data from April 2015 to November 2015 found that the introduction of FBS produced at (b) (4) corresponded to elevated protein and antigen values. The corrective action was to recalculate the antigen and protein performance limits.

I asked to see the new limits compared to the previous in-process limits and the report detailing the calculation of these new limits. This recalculation was detailed in the Technical Summary (b) (4) (*Technical Summary,* (b) (4) (b) (4) (b) (4) New limits were calculated based on data for between (b) (4) and (b) (4) bulk VAQTA batches produced from 14 October 2010 to 18 December 2015. The new process limit values were based on (b) (4) limits as calculated via (b) (4) software.

I noted from the summary that the new process control limits for (b) (4) were broader than those in place previously. The limits in the new (b) (4) were narrower than those previously set using data from (b) (4), as (b) (4) has only been in production for a short time. I told the Merck representatives that I found this a concern as the manufacturing process should be more consistent than it was several years ago, not less consistent. Therefore, the process control limits would be expected to be narrower upon recalculation not broader.

Investigations iQNs (b) (4) . I reviewed several investigations with Kevin McLaughlin (Assoc. Dir. Quality) and April Fultz (Dir. Quality) into issues with the temperature chart recorders connected to the (b) (4) bioreactors used for hepatitis A bulk production. In each case during processing of different VAQTA batches it was discovered that the temperature for the incubators containing the bioreactors was not being recorded due to issues with the temperature charts. The paper had jammed (iQN (b) (4)), the temperature charts were missing from the batch record (iQN (b) (4) the temperature chart was not recording the temperature because the technician had failed to confirm the pen was engaged (iQN (b) (4) , during batch review the temperature chart was found to be missing data for 2 days for a specific incubator ((b) (4) The corrective action is ongoing and will install temperature probes that are connected to the (b) (4) monitoring system. I reviewed the change control memo to initiate installation of the (b) (4) in (b) (4) controlled temperature units in

the (b) (4) VAQTA manufacturing facility. The temperature charts will be maintained but the temperature data will be recorded electronically and backed up so data can be obtained in the event that the paper chart data is unavailable. The investigation and corrective actions is acceptable.

Investigation iQNs (b) (4). I reviewed several investigations with James Bukoski (Sr. Spclst. Engineering) into failed recirculation pumps used for the (b) (4) bioreactors during hepatitis A bulk production. The bioreactors used for manufacture of the hepatitis A bulk in (b) (4) consist of (b) (4), (b) (4) (bioreactors). These reside inside an incubator which is temperature controlled. Media recirculates through the bioreactor and oxygenator vessel continuously during processing. Each bioreactor has (b) (4) (b) (4). This system is used (b) (4) to the system and (b) (4).
iQN (b) (4): The (b) (4) failed and the (b) (4) stopped. This was discovered when the bioreactor product temperature was observed to be out of range. The (b) (4) could not be restarted. It was determined that the (b) (4) had failed to (b) (4) through the bioreactor for approximately (b) (4) hours. It was determined the lost time was minimal compared to the (b) (4) days of total time that media circulates in the bioreactor. Corrective action was to replace with a new pump.
iQN (b) (4) The (b) (4) stopped due to an unplanned power failure. The pump is configured to restart following loss of power but in this case it did not restart. The (b) (4) off for (b) (4) hours before it was restarted (b) (4). It was determined the lost time was minimal compared to the 21 days of total time that media circulates in the bioreactor. There was no corrective action as subsequent tests showed the pump restarted following loss of power with no issues.
iQN (b) (4): The recirculation pump was found to be frozen and had stopped recirculating media. This was discovered when the bioreactor product temperature was observed to be out of range. It was determined that the pump had failed to recirculate media through the bioreactor for a maximum of 6 hours. It was determined the lost time was minimal compared to the 21 days of total time that media circulates in the bioreactor. Corrective action was to replace with a new pump.

Investigations and corrective actions were appropriate. However, there was a trend for events involving failed equipment in the (b) (4) hepatitis A bulk manufacturing facility. See Discussions with Management.

Root Cause Investigation into VAQTA Low Antigen Level in Final Fill

(MEM)

I reviewed the current investigation into the root cause of low hepatitis A antigen in final containers of VAQTA. Current hepatitis A drug product release antigen data has been exhibiting a low bias compared to the target antigen level of (b) (4) U/mL since 2015. In order to resolve this issue in the short term the sponsor submitted a prior approval supplement for approval to introduce a revised dilution model. This was approved by CBER on March 10, 2017 under STN (b) (4). However, the root cause for the low antigen bias had not been identified at the time of the supplement approval.

I discussed with Tim Knapp (Sr. Spclst. Engineering), William Ahlmark (Dir. Engineering), Joseph Bernardo (Assoc. Dir. Quality Control) and Irene Liao (Assoc. Dir. Engineering) the most recent investigations to determine the root cause. I reviewed a Continuing Process Report issued 29 November, 2016 (b) (4) (b) (4) (b) (4) (Exhibit MEM-6) which covered VAQTA formulation and filling batches in (b) (4) The report found that the VAQTA filling and formulation processes were in a state of control. I also reviewed a Technical Summary ((b) (4) (b) (4) (Exhibit MEM-7). This Technical Summary described the potential root causes identified and the actions taken to investigate the potential contribution to the low antigen bias. These potential root causes included the age of the bulk used for formulation of the final product (bulk antigen results may decrease during storage prior to final formulation), bulk antigen concentration (bulk antigen measurements may only be accurate within a certain range), and formulation (variability in the formulation process could lead to lower than expected antigen levels post-dilution). The report found that antigen concentration decreases as the bulk ages but this does not account entirely for the low antigen bias. This age of the bulk was incorporated into the dilution model approved under STN (b) (4). The report stated that further work into the other potential root causes would include evaluating samples collected directly from the alum vessels versus sub aliquoted samples, evaluation of initial sample dilution in the antigen test method (b) (4) (b) (4)) and a lab scale dilution comparison to full-scale experimental formulation. A laboratory assay analysis was performed to determine if there were issues with assay 061000112GEN, this investigation did not identify an assignable laboratory root cause. I was provided with a draft Technical Protocol (b) (4) (b) (4)). (Exhibit MEM-8). At the time of the inspection this had not been finalized for implementation. See 483 Observation #15.

Annual Product Review

(MEM)

I received an overview of the Annual Product Review (APR) from Jason Johnson (Ass. Dir. Quality Systems & Compliance) and Kristin Costello (Sr. Specialist, Quality Assurance). I also reviewed SOP 01-QUA-340X (b) (4) (b) (4)). The information compiled during the APR process is trended and summarized to determine if manufacturing/packaging procedures and corresponding quality systems are in control. The APRs for each product includes an Executive Summary, production batches, process flow diagrams, change requests deviation summaries, complaints and adverse events, equipment qualification summaries, environmental monitoring summaries, stability summary, market actions (recalls, returns, regulatory notifications) and product specific data sections. I reviewed the section summarizing deviations for the VAQTA 2016 APR. Section III.E. (Deviation Investigations) reports investigations that were closed during the current review period as well as Significant deviations that remained open at the close of the review period. There was no assessment or reporting in the APR of the total number of deviations opened at the end of the current review period or total deviations that remain open (see 483 Observation #5B. I requested an explanation of how all deviations are tracked to monitor the proportion still open at the end of the year, not just those classed as Significant.

An overview of the information submitted to the Quality Review Council was provided by Tim McHugh and Hilary McLaughlin. This showed the tracking of open deviations and updates on the numbers of deviations that had been open for more than 30 days. This was acceptable but I informed management that the APR did not adequately reflect all deviations associated with any specific product.

Facilities and Equipment System

(MSL)

My coverage of this system included: a walkthrough inspection of a portion the area where VAQTA drug substance is manufactured in Building (b) (4); visual inspection of various pieces of equipment used in the manufacturing of VAQTA drug substance in Building (b) (4); a review of the packing controls over chromatography columns used in the manufacturing of VAQTA drug substance in Building (b) (4); confirmation of the presence of pest control devices in relevant areas of the buildings I inspected; visual inspection of equipment located on aseptic Filling Line (b) (4) located in Building (b) (4) (a (b) (4) type filling line); a review of environmental monitoring positions and practices for Line (b) (4); a

review of environmental and personnel microbiological monitoring procedures (brief), microbiological limits, and microbiological trend data focusing on Grade (b) (4) areas; a review of Grade (b) (4) area HEPA filter testing practices; a walkthrough inspection of portions of Building (b) (4); visual inspection of equipment located in the (b) (4) (b) (4) located in Building (b) (4) Room (b) (4) a review of environmental monitoring positions for air in the (b) (4) located in Building (b) (4), Room (b) (4); and a review of active viable air sampling practices.

See Observation 14 of the current Form FDA 483 for an issue I observed regarding this system during the current inspection.

Materials System

(MSL)

My coverage of this system included: a review of WFI monitoring (for bioburden and endotoxin) trending; a brief review of examples of Certificates of Analysis for syringe barrels and certain stoppers; a brief review of raw material kitting practices; a brief review of product shipping practices; and a review of the rotation of approved vaccine drug substances.

See Observation 11 of the current Form FDA 483 for an issue I observed regarding this system during the current inspection.

Production System

(MSL)

My coverage of this system included: a brief review of the depyrogenation practices conducted on-site for empty final product containers and stoppers washed on-site used for vaccines and antivenin/normal horse serum; a review of selected Building (b) (4) VAQTA drug substance manufacturing practices; viewing a portion of the aseptic filling of PNEUMOVAX 23 Batch 0000702051 on aseptic Filling Line (b) (4) located in Building (b) (4) (a (b) (4) type filling line); a review of aseptic production practices related to Line (b) (4); a review of aseptic operator gowning related to Line (b) (4); a review of master and/or stock (working) virus seeds for varicella, measles, mumps, and rubella; viewing a portion of the aseptic filling of PNEUMOVAX 23 Batch 0000702018 on the (b) (4) (b) (4) located in Building (b) (4), Room (b) (4); a review of aseptic production practices related to the (b) (4) located in Building (b) (4), Room (b) (4) a review of bioburden and endotoxin trend data (if relevant) related to: RotaTeq, MMR II, ProQuad, VARIVAX, ZOSTAVAX, ANTIVENIN, Normal Horse Serum, VAQTA, RECOMBIVAX HB, GARDASIL, PNEUMOVAX 23, and Liquid PedvaxHIB; a review of the use of paper batch records in Grade (b) (4) areas; a review of the batch record hand stamping process for interim changes to a batch record; and a review of the endotoxin in-process alert limit for the final retentate of each individual polysaccharide used in PNEUMOVAX 23.

See Observation 16 of the current Form FDA 483 for an issue I observed regarding this system during the current inspection.

Bulk Manufacturing

(MEM)

On April 19, 2017 I underwent gowning training with Carole Gruber (Associate Director, Learning and Development) and (b) (6) (Specialist, Learning and Development) who demonstrated the gowning process required for access to the vaccine bulk manufacturing suites. I was supplied with the SOPs for gowning 15-QUE-292X (b) (4)) 24-QUE-365X (b) (4)) and 24-QUA-117X (*General Uniforms and Hygiene for Vaccine and Sterile Operations*). The training and SOPs were found to be appropriate.

VAQTA B28 Manufacturing

(MEM)

I was provided with an overview of the hepatitis A (VAQTA) drug substance manufacturing procedure in (b) (4) by April Fultz (Dir. Quality), Kevin McLaughlin (Assoc. Dir, Quality), Michelle Paquette (Sr. Spclst, Engineering) and Craig McGee (Assoc. Dir, Operations). The process consists of (b) (4) (b) (4) (b) (4) , (b) (4) to produce the purified virus bulk. This purified virus bulk (b) (4) (b) (4) (b) (4) (b) (4) . This results in the alum adsorbed bulk which is dispensed and stored for up to (b) (4) months at (b) (4) All of these procedures take place within the (b) (4) facility. (b) (4) (b) (4)

On April 19 I visited the (b) (4) hepatitis A manufacturing suite with April Fultz (Dir. Quality), Craig McGee (Assoc. Dir, Operations), Kevin McLaughlin (Assoc. Dir, Quality), (b) (6) (Bio-Technician Level 3), (b) (6) (Bio-Technician Level 2). In room (b) (4) I observed cell seeding into Bioreactors (b) and (b) (4) for infection the following week for Batch number 0000689853. Bioreactors (b) and (b) (4) in the same room had

already been seeded for Batch number 0000681155. I also viewed rooms (b) (4) and (b) (4), which also contained Bioreactors for cell culture and virus propagation. Room (b) (4) contained Batch number 0000686051 which was planted with cells on April 12, 2017 and infected on April 18, 2017. Room (b) (4) contained Batch number 0000686048, planted on April 5, 2017 and infected with virus on April 12, 2017. The cell plant dates were written on the cell cube together with the cube assembly dates. The plant dates and infection dates were written on the doors of the incubators containing the Bioreactors together with the Batch number. I viewed Room (b) (4) which contained the ion exchange column processing batch number 0000681153, and Room (b) (4) used for inactivation. There was no inactivation occurring at this time.

I observed the setting up of the alum co-precipitation in Room (b) (4) for batch # 0000673959. This involves the transfer of the inactivated virus bulk into vessels containing the alum adjuvant.

No objectionable circumstances were observed during this tour.

Batches Manufactured and Disposition

(MEM)

I reviewed the list of batches manufactured and disposition of all batches with (b) (6) (b) (6) (Spclst, Quality). A list for all batches manufactured from March 1, 2015 to April 19, 2017 was provided, which included stock seeds, bulks and final product for all products. The batches were listed in numerical order by material number. The list included batch numbers, the date of manufacture and the batch shelf life expiration. A code was included under (b) (4) ". I requested a copy of the SOP for batch disposition, SOP 07-QUR-254X (b) (4) (b) (4), in order to interpret the different codes. This was provided. There were a number of batches that showed no disposition despite having been manufactured in 2016. I asked to see an update in the usage of (b) (4) batches of hepatitis A bulk. This list was provided (Exhibit MEM-9) and discussed with April Fultz (Dir. Quality) and Kevin McLaughlin (Assoc. Dir. Quality). The batches were abandoned during processing due to issues with the equipment or lack of resources. All equipment related issues were investigated under iQNs.

Packaging and Labeling System

(MSL)

My coverage of this system included: an inspection of label and labeling material storage areas in Building (b) (4) and a review of label issue, label return, and label and labeling material storage and control practices in this building; and an inspection of the area where labeling material is stored in Building (b) (4) and a review of labeling material storage and control practices in this building.

(OOO)

During the current inspection, I reviewed all of the eleven CBER licensed and manufactured vaccines final product containers non-conformance defects. The decision to cover the packaging and labeling system was based on the risk assessments and data mining of the vaccines manufacturing non-conformance classifications of: Significant, Deviation, Minor Deviations and customers' complaints of the vaccines final container defects such as: cracks, leaks, under fills/over fills and particulates that were reviewed.

See **Exhibit #OOO1,** for a list of final vaccine containers that are currently manufactured, inspected and packaged at this inspected Merck, WP facility including the vaccines packaging configurations, building locations for inspection and packaging, inspection methods and equipment/machines used in the inspection and packaging operations. It should be noted that not all of the vials and syringes filled and inspected at this inspected Merck facility are labeled and packaged for distribution. Unlabeled final containers are sent to other Merck facilities for labeling and packaging and distributions into the US and ROW, i.e., Wilson, North Carolina, US facility.

Examples of the inspection of sterile vaccines vials and syringes after the filling process provided by the firm's personnel are discussed below:

<u>West Point Syringe Filling Line – Inspection Room Process Flow Narrative</u>

(OOO)

The SFL Inspection is located in Room (b) (4) of Building (b) (4). (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

The (b) (4) Inspection Machine (b) (4) (Model (b) (4) is used to inspect filled and unlabeled 1.5 mL syringes for attribute (e.g. cracks, broken flange, missing tip cap, liquid in plunger stopper ribs, etc.) and particulate (e.g. glass, stainless steel, fiber, etc.) defects prior to labeling and bulk packaging. The machine utilizes a combination of (b) (4)

(b) (4). Each syringe enters as a (b) (4) and must receive a passing signal from (b) (4) to be classified as (b) (4). (b) (4) to each production batch, the (b) (4) machine is first confirmed to have been cleaned. A (b) (4) is then performed to ensure that each (b) (4) is setup within the defined ranges. A (b) (4), comprised of known defects and known acceptable syringes, is then run through the machine. All acceptance criteria must be met before a production batch is started.

Syringes are conveyed to the (b) (4) (b) (4) (b) (4). The inspections at these stations are intended to remove defects that could cause handling problems once syringes are inverted and run through the rest of the machine. Rejects are directed to (b) (4) The syringes (b) (4) (b) (4) (b) (4) (b) (4) (b) (4). The syringes (b) (4) syringes (b) (4) while accepted syringes (b) (4). If a syringe is rejected for both (b) (4) In the event of a (b) (4)" (b) (4)

Accepted syringes (b) (4) (b) (4) Syringes (b) (4). The Syringe ID Labeler is used to apply a (b) (4) label to the outside of the syringe barrels, which contains a (b) (4). The label is applied to products that require identification by downstream packaging operations. The label is for internal use only, for identification of the batch number. The Syringe ID Labeler inspects each syringe for presence of the label and correct (b) (4) code.

Following the Syringe ID Labeler, inspected and labeled (if necessary) syringes proceed into the (b) (4) Machine. The (b) (4) Machine (b) (4) (b) (4) (b) (4) (b) (4). Syringes for Acceptable Quality Level testing are sampled from (b) (4) at this time. Additionally, (b) (4) samples are taken at this location. (b) (4) (b) (4) until needed for further processing.

During inspection of a production batch, statistical sampling is performed on both the accepted and rejected syringes. Accepted syringes, containers are sampled from (b) (4) (b) (4) inspected during the batch as part of the Acceptable

Quality Level (AQL) testing. The numbers of detects are counted and compared to an AQL for each defect classification ((b) (4) For rejected syringes, containers are sampled throughout the batch from the (b) (4) of the (b) (4) and (b) (4) inspected at the conclusion of the batch. Any syringes with true defects are (b) (4) (b) (4) (b) (4) . If the inspection data (b) (4) , an investigation will be initiated.

West Point Vial Filling Line – Inspection Room Process Flow Narrative

(OOO)

The VFL Inspection Room is located in Room (b) (4) of Building (b) (4) Capped and sealed vials (b) (4) (b) (4) Samples required for release testing are (b) (4) (b) (4) (b) (4) The release samples are (b) (4) inspected and processed per procedure. Samples are also taken here for (b) (4) testing. (b) (4) testing is performed to confirm proper operation of the (b) (4) samples are taken (b) (4) (b) (4) (depending on batch size), and (b) (4) .

Vials (b) (4) : (b) (4) The (b) (4) Inspection Machines are used to inspect filled and unlabeled 3mL vials for attribute (e.g. cracks, dirty container, protruding stopper, missing flip-off cap, damaged seal) and particulate (e.g. glass, stainless steel, hair) defects prior to labeling and bulk packaging. The machines utilize a combination of (b) (4) during inspection. Each vial (b) (4) (b) (4) to be classified as (b) (4) each production batch, the (b) (4) machines are first confirmed to have been cleaned. (b) (4) (b) (4) . (b) (4) (b) (4) . All acceptance criteria must be met on each machine before a production batch is started.

Vials are fed into the (b) (4) . In the (b) (4) (b) (4) The vials are (b) (4) (b) (4) . Vials (b) (4) inspected for bottom defects (b) (4) where they are inspected for particulates by the (b) (4) (b) (4) (b) (4) Vials (b) (4) Vials (b) (4) (b) (4) If a vial is rejected for (b) (4) (b) (4) , (b) (4) Acceptable material is sent to

(b) (4). In the event of a machine alarm, a predetermined number of vials are diverted to (b) (4)

Accepted vials exit the (b) (4) Inspection Machines and (b) (4) (b) (4) for storage. Once a tray is full, the operator inspects the tray for cap/seal color defects. Samples are taken here for Acceptable Quality Level (AQL) testing and retention samples. Then the operator places (b) (4) (b) (4). (b) (4) (b) (4) until needed for further processing.

During inspection of a production batch, statistical sampling is performed on both the accepted and rejected vials. Accepted vials, containers are sampled and (b) (4) inspected during the batch as part of the Acceptable Quality Level (AQL) testing. The numbers of defects are counted and compared to an AQL for each defect classification (b) (4). For rejected vials, containers are sampled from the (b) (4) (b) (4) throughout the batch and (b) (4) inspected at the conclusion of the batch. Any vials with true defects are recorded, and the rates for critical defects are compared against (b) (4) (b) (4) from the (b) (4) is also compared to (b) (4) If the inspection data exceeds (b) (4), an investigation will be initiated.

Laboratory Control System

(MSL)

My coverage of this system included: walkthrough inspections of a portion of the Environmental Monitoring Laboratory located in Building (b) (4) (new since the last Team Biologics inspection); a physical inspection of selected active viable air monitoring plates in the Environmental Monitoring Laboratory located in Building (b) (4) a review of active viable air monitoring practices for environmental monitoring of Grade (b) (4) areas; and a review of Biological Laboratory Procedure (b) (4) entitled "Bioburden".

See Observation 13 of the current Form FDA 483 for an issue I observed regarding this system during the current inspection.

Stability Program

(MEM)

I reviewed general stability protocols with Don Monkovic (Dir. Quality) and a stability protocol for Measles, Mumps and Rubella Live Virus vaccine (MMR II). These were found to be acceptable. I was informed that one lot of each bulk and final container is selected for stability testing each year plus any additional lots that need to be followed

due to manufacturing changes. These are not selected as the first batches made for each product each year as this could potentially place a burden on the testing labs to test many samples at the same time point. Instead the selection is made based on the predicted workload or on the number of batches made during the year. I asked how the decision is made to select final container or bulk samples for stability testing. The quality control department informs the staff in the barrier fill operations area that they will place vials from this fill on stability, this information is entered into the batch record and the number of vials pulled from the beginning, middle and end of production are noted in the batch record. The collection of samples for release testing and any additional testing is documented in SOP 24-LYO-325X (b) (4) (Exhibit MEM-2) which I reviewed with Tim Cooper (Assoc. Dir. Operations), Michael Nuzzolo (Dir. Quality) and Don Monkovic (Dir. Quality). I was provided with a copy of a page from the batch record for VAQTA final container filling which indicated the removal of stability samples at the time of filling (Exhibit MEM-3).

Failed Stability Test Results

(MEM)

I requested a list of all failed stability results since the last inspection. (b) (4) samples had failed stability between March 1, 2015 and April 18, 2017 (Exhibit MEM-4). (b) (4) e for human papilloma virus (HPV) vaccine (iQN200415162), (b) for Pedvax Hib (iQN200415687), (b) for VAQTA (iQN200495475 and iQN200491853) and (b) for Proquad (iQN200492978). The HPV result was designated as a lab error and not approved as a failed stability result. The Proquad and VAQTA results were still under investigation at the time of the inspection. The Proquad stability failure was due to a pH value out of specification. The preliminary root cause was attributed to transcription error. BPDRs had been submitted to CBER for the Pedvax HIB and VAQTA failed results. I reviewed the BPDR (BPDR 2017-005) for the (b) (4) failed VAQTA results which were associated with hepatitis A antigen content (Exhibit MEM-5). The investigation and proposed follow-up was found to be appropriate.

Small Molecule Stability Program

(CDZ)

I reviewed SOP 30-STB-311, Stability Program Management without objection.

According to Don Monkovic, Director of Large Molecule Stability, the firm is still conducting stability studies for small molecule products produced on site that have not

yet reached expiry. Currently this consists of only Emend. Janumet stability studies for products produced at West Point are conducted at the firm's Wilson, NC facility.

I reviewed stability protocols for the following products without objection: Emend 40mg, Emend 125 mg, IV Emend 115mg, IV Emend 150 mg, Emend 40mg capsules, Emend 80mg capsules, Emend 125mg capsules, Emend 165mg capsules, Cancidas 50 mg and Cancidas 70 mg.

I reviewed the following small molecule pharmaceutical stability failure investigations without objection (identified by Quality Notification number):

(b) (4)

MANUFACTURING CODES

(MSL)

Exhibit MSL12 contains a memorandum describing the site's batch numbering procedure.

COMPLAINTS

Complaints

(MSL)

The intake of complaints from the US market is conducted by the Merck National Service Center which is not located at this site.

The West Point site conducts investigations related to complaints that are relevant to the West Point site. During a discussion I had with Lynn DeHaven, Senior Quality Specialist on 4-24-17 she stated that all West Point product quality complaints are investigated regarding West Point products.

(OOO)

My reviews all of the eleven manufactured vaccines release products quality complaints during this inspection disclosed that the firm received approximately (b) (4) complaints **(Exhibit #OOO2)** all of which were for defective vaccines: vials, syringes and tubes including complaints of vials labeling, low/high fill volumes, cracks and leaks since the

inspection of April 2015. For a list of vaccine products reviewed during this inspection and the packaging configurations, see **Exhibit #OOO1.** Furthermore, (b) (4) of all received complaints were for vaccines in final container vials. For percentage breakdowns of the received complaints into vials, syringes and tubes, see **(Exhibit #OOO2).** For a list provided on the ten (10) top final vaccine containers product quality complaints from March 01, 2015-April 17, 2017 see **Exhibit #OOO3.**

I was unable to review the adequacies of the firm's investigations, identifications of the correct root causes and the instituted corrective and preventive actions to prevent reoccurrences into the received complaints during my reviews of the manufacturing non-conformances of the (b) (4) vaccine received complaints since the inspection of April 2015. This was because the released vaccine vials, syringes and tubes batch numbers are different from the manufacturing vaccines batch numbers that are documented on the list of the manufacturing non-conformances provided for review during the inspection. For example, Rotateq batch numbers provided for manufacturing non-conformances/deviations **(Exhibit #OOO6)** are the batch numbers of the sterile aseptic filled batches some of which exceeded the process control limits. However, the Rotateq batch numbers on the received list of complaints provided for review during the inspection **Exhibit #OOO7** are the final packaged batch numbers. As such, there was no way of knowing if the reported and received complaint batches had similar non-conformances during the labeling and packaging process as those reported in the complaint list.

The need to have the same batch numbers for the filled and packaged vaccine batches or to include the fill batches on the complaint list was discussed with the firm's personnel and management, during the inspection and close-out FDA-483 discussions. There were no comments on this issue from either the firm's personnel or management.

(CDZ)

I reviewed SOP 04-QUC-316X, (b) (4) and SOP 04-QUC-323X, (b) (4) (b) (4) without objection.

According to Lynn DeHaven, Sr. Quality Specialist, complaints are received at Merck National Service Center where they are entered into (b) (4) and assigned an owner. There have been (b) (4) complaints regarding small molecule pharmaceuticals since the previous inspection. I reviewed the (b) (4) records (b) (4) (b) (4) without objection.

Adverse Event Reports

(MSL)

During a discussion I had with the firm on 4-25-17 which included Angela Pufko, Executive Director, Drug Safety and Jane Toscano, Associate Director in Regulatory Affairs Department, Quality and Compliance Ms. Pufko stated that she is based at the Merck Upper Gwynedd site. She stated that pharmacovigilance is part of Merck Research Laboratories and the Upper Gwynedd site is the headquarters for her group, which manages oversight of the quality and compliance of the case processing of Adverse Experiences. I was told that the address of the site is 351 N. Sumneytown Pike, North Wales, PA 19454. I was also told that the site was inspected by FDA from 8/29-9/20, 2016 and a Form FDA 483 was issued for late reports. I verified that a Form FDA 483 dated 9/20/2016 covering an FDA inspection that was performed 8/29/2016-9/20/2016 was issued to Walter L. Straus, M.D., Associate Vice-President, Clinical Safety & Risk Management for the Merck & Co Inc, site located at 351 N Sumneytown Pike, North Wales, PA 19454-2505. As such, I did not review AE reporting in depth during the current inspection. I did briefly review reporting (to FDA) timeliness compliance rate graphs with regard to products manufactured at the West Point site from 01-January 2015 through 31-March-2017.

RECALL PROCEDURES

Recalls

(MSL)

The recall procedure applicable to this site is SOP Document Number: 21-QUA-353 Version: 1.0 entitled (b) (4) ".

Exhibit MSL13 contains the closure letter for Recall (b) (4) for GARDASIL Lot J007354. This recall was initiated prior to the last team Biologics inspection of this site.

Exhibit MSL14 contains a memorandum with the subject "Recalls and Market Withdrawals Initiated for Products Manufactured at Merck, West Point Between 01-Mar-2015 and 20-Apr-2017". The memo states the following in part:

"...There were zero (0) recalls or market withdrawals initiated or executed by Merck Sharp & Dohme Corp., West Point, PA for products the West Point site has responsibility for between 01-Mar-2015 and 20-Apr-2017. However, there was one open recall during that time as noted below....

...This letter only pertains to product recalls and market withdrawals overseen by Merck's West Point facility...."

The open recall noted in the memo was (as per the memo) initiated on 19-Dec-2013 for GARDASIL Lot J007354. The reason stated in the memo is "Voluntary recall due to the

potential for a limited number of vials to contain glass particles in the lot." As stated in the memo the termination date was 02-Mar-2015.

BPDRs

(MSL)

The BPDR procedure applicable to this site is SOP Document Number: 08-QUA-303X Version: 11.0 entitled (b) (4) " (See Exhibit MSL15).

The site submitted numerous BPDRs since the last Team Biologics inspection. I reviewed selected BPDRs during the current inspection.

See Observations 1B, 10, and 12 of the current Form FDA 483 for issues that were observed during the current inspection regarding BPDRs.

(OOO)

I reviewed the adequacies of the investigations of BPDs that were reported to CBER specifically, for vials, syringes and tubes defect including labeling issues. It was noted that (b) (4) of all the (b) (4) BPDRs submitted to CBER since the last inspection were for vials, syringes and tubes potential non-conformances, **(Exhibit #OOO8).** My reviews of the investigations conducted into approximately (b) (4) out of the (b) (4) BPDRs that were reported since the inspection of April 2015 disclosed, inadequate investigations were conducted. The inadequate identifications of the correct root causes and the instituted corrective and preventive actions to prevent reoccurrences are discussed below in **Observation #1B, Observation 2** and under the title of "Complaints" above.

Examples of reviewed BPDRs that are related to vials, syringes and tubes defects in regards to the labeling and packaging system covered during the inspection are as follows:

1. BPDR (b) (4) regarding customer complaint for a mix-up of labeled syringes from two different batch numbers within a single carton of Pneumovax.

2. BPDR #2015-010 Investigation (b) (4), reported from the Merck Wilson, NC facility regarding customer complaints of (b) (4) Gardasil vials that contained particles in each vial.

3. BPDR (b) (4), regarding (b) customer complaints of Pneumovax broken syringe tips.

4. BPDR # (b) (4), regarding customer complaints of two leaking Pneumovax 23 syringes.

5. BPDR (b) (4) regarding customer complaint of one leaking Gardasil syringe.

6. BPDR (b) (4) Investigation (b) (4), reported by the Merck Wilson, NC facility regarding customer complaint of a vial of Gardasil containing a black particle.

7. BPDR (b) (4) investigation (b) (4), reported by the Merck Wilson, NC facility regarding customer complaint of one syringe of Pneumovax that contains a black particle.

8. BPDR (b) (4) investigation (b) (4) reported by the Merck Wilson, NC facility regarding customer complaint of one vial of Gardasil that contained black particle.

9. BPDR (b) (4) regarding a black particle that was found in Barrier Operation filling line during AQL sampling.

For the list of BPDRs submitted to CBER since the inspection of April 2015, see **Exhibit #OOO9.**

Field Alert Reports

(CDZ)

I reviewed SOP 08-QUA-392X, Regulatory Reporting for Pharmaceutical Products and SOP 8.02, Regulatory Agency Reporting, which detail the process for submitting Field Alert Reports to the FDA without objection.

According to Todd Williams, Quality Director the firm has had one Field Alert Notification regarding small molecule pharmaceuticals since the previous inspection. I reviewed the FAR for Aprepitant Lot V2437 regarding an empty blister pack, submitted on 8/15/2014**(Attachment CDZ 1)** and associated investigation without objection. The FAR was submitted late due to a misclassification by a Merck Australia site. I reviewed the associated investigation into the late submission and the associated corrective action document 08-QUA-312XF3 without objection.

According to Mr. Williams the firm acts as a reporting site for FARs. This function is administrative in nature and responsibility for quality oversight of international FARs is contained on a regional level. I reviewed without objection the timeliness of reporting of the following FARs that listed Merck Sharpe & Dohme Corp West Point, PA as the reporting establishment:

- FAR – CELESTONE SOLUSPAN Injectable Suspension USP, Lot 073102, submitted 11/03/2014 **(Attachment CDZ 2)**

- FAR -ELOCON Cream, Lot 5RJDA96003, submitted 12/06/2016 **(Attachment CDZ 3)**
- FAR – NASONEX Nasal Spray, Lot 15MAA520A, submitted 11/28/2016 **(Attachment CDZ 4)**
- FAR - ELOCON, Lot 4RJDA29001, submitted 9/28/2015 **(Attachment CDZ 5)**
- FAR - ELOCON Cream, Lot 5RJDA04001, submitted 3/30/2016 **(Attachment CDZ 6)**
- FAR – EMEND for Injection, Lot L911300, submitted 10/08/2015 **(Attachment CDZ 7)**
- FAR – EMEND for Injection, Lot K022850, submitted 6/11/2015 **(Attachment CDZ 8)**
- FAR - INVANZ, Lot 2200440, submitted 04/08/2016 **(Attachment CDZ 9)**
- FAR – INVANZ ADD-Vantage, Lot 2171140, submitted 08/18/2015 **(Attachment CDZ 10)**
- FAR - INVANZ ADD-Vantage, Lot 2149130, submitted 04/09/2015 **(Attachment CDZ 11)**
- FAR - INVANZ, Lot M013569, submitted 08/02/2016 **(Attachment CDZ 12)**
- FAR - INVANZ, Lot M031748, submitted 12/13/2016 **(Attachment CDZ 13)**
- FAR – COSOFT PF, Lot MK13N002, submitted 09/25/2014 **(Attachment CDZ 14)**
- FAR – LOTRISONE Cream 1%/0.05%(15g) , Lot 5-NBN-02 to 5-NBN-23, submitted 05/26/2015 **(Attachment CDZ 15)**
- FAR – LOTRISONE Cream 1%/0.05%(15g), Lot 4NBN52, submitted 09/28/2015 **(Attachment CDZ 16)**
- FAR –CANCIDAS I.V. 70mg, LotMCB068, submitted 11/23/2015 **(Attachment CDZ 17)**
- FAR – CANCIDAS INFUSION 50mg, Lot 2180890, submitted 03/18/2016 **(Attachment CDZ 18)**

- FAR – CELESTONE SOLUSPAN Injectable Solution USP, Lot 014126, submitted 11/19/2014 **(Attachment CDZ 19)**
- FAR - CELESTONE SOLUSPAN Injectable Solution USP, Lot 085567 submitted 05/13/2016 **(Attachment CDZ 20)**
- FAR - CELESTONE SOLUSPAN Injectable Solution USP, Lot 112698, submitted 05/12/2015 **(Attachment CDZ 21)**
- FAR - CANCIDAS INFUSION 50mg, Lot 2186080, submitted 05/09/2017 **(Attachment CDZ 22)**

DRUG SHORTAGE INFORMATION

(MSL)

Exhibit MSL42 contains Regulatory Conversation documents and associated information regarding drug shortage issues the firm reportedly discussed with FDA. The documents include shortage discussions regarding: TICE BCG, vaccines in syringes, Hepatitis A Vaccine (VAQTA), and Hepatitis B Vaccine (RECOMBIVAX HB). These documents contain certain details not discussed below.

During a discussion I had with the firm on 4-20-17 which included Kimberly Duffy, Executive Director, Regulatory Affairs - CMC and Michael Nuzzolo, Director, Quality, I was told that with regard to VAQTA and RECOMBIVAX HB an increase in global demand overcame their capacity to produce the products. I was also told that with regard to VAQTA and RECOMBIVAX HB the firm has also had production issues. With regard to RECOMBIVAX HB Mr. Nuzzolo stated that an area of the bulk facility was shut down for a period of time due to mold (early October to early December 2016).

Ms. Duffy stated that with regard to VAQTA the firm has distributed product from the CDC stockpile with approval from the CDC. She stated that with regard to Hepatitis B Vaccine the firm is borrowing pediatric doses from the CDC stockpile with CDC approval. I was told that with regard to both of these vaccines that this was done to fulfill market demand.

Ms. Duffy stated that the firm will run out of adult Hepatitis B Vaccine next month and the firm will not have more until the third quarter of 2018. She stated that the firm is prioritizing the fill of pediatric doses.

I was told that the firm is moving more filling (of other products) to a site in Ireland to add capacity and this will therefore free space at the West Point site to fill more product at the West Point site. I was told that filling capacity at the West Point site is at its maximum.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

(MSL)

At a final closeout meeting on 4-28-17 we (MSL and OOO) issued a Form FDA 483 Inspectional Observations containing 16 observations to Mr. Kuhn. The names of all 4 FDA representatives are on the Form FDA 483 however since only CSO Ligmond and CSO Osunsanmi were present for the closeout meeting only these 2 FDA representatives signed the Form FDA 483.

During this meeting I stated that the Form FDA 483 only represents our observations and is not a final Agency determination of the firm's compliance. I stated that sanctions available to the Agency for a biologics firm found to be noncompliant include: a Regulatory Meeting; issuance of a Warning Letter; issuance of a Notice of Intent to Revoke; biologics license revocation; Seizure; Injunction; and/or Prosecution. I stated that if the firm wants their written response to be considered by the Agency prior to the Agency taking an action against the firm that the response needs to be received by the Agency in NMT 15 working days from the close of the inspection. I did not state that an action would, or would not, be taken against the firm. Mr. Kuhn stated that the firm planned a written response. I stated that the firm's response should be made to the attention of Colleen Hoyt, Branch Director.

We did not read the Form FDA 483 aloud but we allowed time for those present to read each observation and provide comments.

Below (in bold type) is each observation as listed on the Form FDA 483. Following each observation is a discussion of the observation including the supporting evidence, relevance, and a summary of any relevant discussions with Management.

(OOO)

Prior to the discussion of each FDA-483 item, the firm's management was told to take their time in reviewing the FDA-483 that was issued and if needed to have personnel familiar with the FDA-483 that was issued review the observations to assure that the FDA-483 observations are factual and that, i.e., the dates, CAPAs, deviations, non-conformances and batch numbers are accurately stated.

1. Written records of investigations into unexplained discrepancies of a batch or any of its components to meet specifications do not always include the conclusions and follow-up. Specifically:

Investigations are not always conducted in a timely manner into vaccines manufacturing and equipment non-conformances, and corrective and preventive actions are not always instituted in a timely manner to prevent reoccurrences. Apart from manufacturing "Events" that are not required to be documented as deviations

but are documented in the batch records and are not investigated per SOP #06-QUA-125AX Version 13.0, the following documented manufacturing non-conformances/deviations since the last inspection of March 2015 were not always corrected in a timely manner. There are no documentation that formal investigations are opened and no documented justifications are provided:

(OOO)

The observations were mostly discussed with Hilary McLaughlin, Associate Director, Quality and Timothy McHugh, Associate Director, Quality.

This inspection disclosed that vaccines products and equipment manufacturing non-conformances and deviations that are referred to as Quality Notifications (QN) that are opened since the last inspection of April 2015 are not always corrected in a timely manner. Furthermore, it was noted that corrective and preventive actions are not always instituted in a timely manner to prevent reoccurrences of non-conforming products. Although individual QN is opened into some of these non-conformances, however, there are no documentation that formal investigations are opened into clusters of these non-conformances and no documented justifications are provided. In addition, the inspection revealed that manufacturing non-conformances that are classified as "Events" are not required to be documented as deviations but are documented in the batch records. As such, these non-conformances are not investigated per SOP #06-QUA-125AX Version 13.0 **(Exhibit #OOO11 page #2, 15 & 21).**

For a list provided by the firm showing the total numbers of manufactured and equipment non-conformances indicated in Observation #s1A-1H below, see **Exhibit #OOO10.**

A) There have been (b) (4) **System Integrity/leaks non-conformances at, i.e., the** (b) (4) **vaccine manufacturing steps that include:** (b) (4) **product tanks,** (b) (4) **, pumps,** (b) (4) **bioreactor, water leaking from ceilings, product containers leaking and in some cases resulted in the rejections of manufactured products.**

(OOO)

This inspection disclosed approximately (b) (4) occurrences of system integrity leaks non-conformances **(Exhibit #OOO12)** that occurred during the vaccines manufacturing operations since the inspection of April 2015. The reviews of the deviation sorts for leaks disclosed the lack of timely corrective and prevent actions to prevent future reoccurrences of these leaks. For example, there was no documentation that a formal investigation was opened to address these leaks as a whole, per equipment leaks, etc. Furthermore, this inspection noted that apart from the integrity and equipment leaks on the list provided as **Exhibit #OOO12** above, there have been (b) (4) maintenance work orders **(Exhibit #OOO13)** for roof leaks in the vaccines manufacturing buildings (MMD) in a one year period, from April 18, 2016 to April 18, 2017.

The review of the (b) (4) System Integrity/leaks non-conformances some of which occurred during the manufacturing processes of most of the 11 manufactured vaccines, occurred at the (b) (4) vaccine manufacturing process steps, and include equipment such as: (b) (4) product tanks, (b) (4), pumps, (b) (4) bioreactor, water leaking from ceilings, product containers leaking and in some instances resulted in the rejections of manufactured products. Examples of some of the documented system integrity leaks non-conformances are provided below:

- QN (b) (4) dated January 24, 2016 **(Exhibit #OOO14),** documented that water was leaking into Room (b) (4) cold vault (b) (4) and Room (b) (4) from the 2nd floor mezzanine located above the subject rooms. As a result of the leak, the Laminar Flow Hood Filters in the ceiling Room (b) (4) had signs of water damage and subsequently (b) (4) filters failed for media leaks. (b) (4) ProQuad 4C batches (b) (4) AUS batch, (b) (4) VARIVAX and (b) (4) frozen Zostavax batches that were stored inside cabinets were affected and had to be unloaded and the cabinet decontaminated.

- QN (b) (4), dated June 16, 2015 **(Exhibit #OOO15),** documented that approximately (b) (4) of propylene glycol was observed on the floor underneath Tank (b) (4) on June 17, 2015. On the following day glycol was found on a (b) (4) (b) (4) clamp on the glycol supply line hose (b) (4) and on July 02, the second shift noted a slow drip of glycol from the glycol supply hose (b) (4) with approximately 10ml of glycol on the floor. It was noted that no corrective action to prevent reoccurrences was initiated on the glycol tank leaks of June 16, June 17 and July 02, 2015. Per page #2 of the QN "no Corrective Action Preventive Action (CAPA) is required".

- QN (b) (4) dated May 29, 2017 **(Exhibit #OOO16),** documented that prior to the transfer of the MMR intermediate for ProQuad Frozen batch 0000690554 a cut was identified on the (b) (4) tubing on the PGS bottle. The transfer assembly was located in the Grade (b) (area during the leak event.

B) There have been (b) (4) non-conformances of vials, syringe defects, i.e., low/high product fill volumes, stopper defects, cracked vials and vials seal defects. In addition, approximately (b) (4), of all BPDR submitted to the agency are vials and syringe defects related. Furthermore (b) (4) complaints were received for vials, syringes and tubes defects.

(OOO)

My reviews of vials, syringes and tubes defects, disclosed there have been (b) (4) non-conformances **(Exhibit #OOO17)** for example: low and high product fill volumes, stopper defects, cracked vials and vials seal defects. However, no formal investigation has been opened to adequately identify root causes and address reductions in the numbers of these final containers vials defects non-conformances. In addition, this inspection

disclosed approximately a total of (b) (4) of all (b) (4) BPDR submitted to the agency since the last inspection of April 2015 are vials and syringe defects related **(Exhibit #OOO8).** Furthermore, the inspection noted that (b) (4) complaints were received for vials, syringes and tubes defects **(Exhibit #OOO2).**

Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences and the final containers defects non-conformances that continue to occur as the result of lack of timely corrective and preventive action per the above observation is provided and discussed below:

- Per QN (b) (4) dated July 22, 2016 Gardasil batch 0000602103 **(Exhibit #OOO19)** had a total reject rate of (b) (4) and batch 0000602101 had a total reject rate of (b) (4) both of which were above the Process Control Limit (PCL) of (b) (4) for total reject rate. The batches were not re-inspected per SOP 24-INS-103X Version 21.0 page #5, **(Exhibit #OOO20).** The high reject rates per the QNs were due to elevated (b) (4) inspection (b) (4) which remains uncorrected and continues into 2017. See additional discussions below on the (b) (4) (b) (4) under Observation #2.

- Per QN (b) (4) dated February 09, 2016 **(Exhibit #OOO21)** a total reject rate was exceeded with result of (b) (4) with limit of (b) (4) and (b) (4) of the rejects were attributed to the (b) (4) for heel crack defects detection on the Eisai inspection machine. The batch was not re-inspected per SOP 24-INS-103X Version 21.0 page #5.

- Per QN (b) (4) dated February 06, 2017 PCL total reject rate was exceeded for three (3) Gardasil batches as follows: **(Exhibit #OOO22).**

  - HPV NONA batch 0000668361, total reject rate of (b) (4) with PCL limit of (b) (4) and the rejects attributed to the (b) (4) for heel crack defect detection on the (b) (4) inspection machine.

  - Gardasil batch 0000 679685, total reject rate of (b) (4) with PCL limit of (b) (4) and the rejects attributed to the (b) (4) for heel crack defect detection on the Eisai inspection machine.

  - Gardasil batch #0000691148 had a total reject rate of (b) (4) with PCL limit of (b) (4) and the rejects attributed to the (b) (4) for heel crack defect detection on the (b) (4) inspection machine.

- Per QN (b) (4) dated January 20, 2017, **(Exhibit #OOO52)** the (b) (4) heel crack defects detection (b) (4) were responsible for the following Gardasil false total reject rates:

  - Batch 0000660967 rejects of (b) (4) of the (b) (4) total vials rejected.

- Batch 0000660980 rejects of (b) (4) of the (b) (4) total vials rejected.
- Batch 0000662803 rejects of (b) (4) of the (b) (4) total vials rejected.

All of the above Gardasil batches that exceeded total reject rates were determined to be caused by the (b) (4) and (b) (4) of the (b) (4) inspection machine. Per SOP 24-INS-103X Version 21.0 page #5, (b) (4) (b) (4) as per SOP-06-QUA-125AX. …PCL exceedances where the root cause is considered to be false rejects do not require re-inspection regardless of PCL category". As such, these batches and several other batches that were above the total reject rates were not re-inspected.

Furthermore, although the firm is aware of the inadequate qualification of the (b) (4) machine final containers inspections since 2013 that Recombivax HB batch #0672446 was recalled in June 2013 due to vials heel defects, the (b) (4) machine was only re-qualified for crack vials in May 2016. In addition, it was noted that the firm was aware of the inadequate re-qualification of the (b) (4) inspection machine in May 2016 for crack vials. However, CAPA TW (b) (4) **(Exhibit #OOO58)** to validate the (b) (4) machine was not opened until April 18, 2017. Also, the validation "Target Date" of the (b) (4) machine per the CAPA is not until June 2017. As such, the firm failed to adequately identify root causes and institute adequate corrective and preventive actions in a timely manner to prevent reoccurrences.

C) There have been (b) (4) particulates and foreign matters non-conformances, i.e., in filled vaccine product tubes, syringes, vials, stopper bowl, production tanks, manufacturing components and solutions.

(OOO)

See **Exhibit #OOO24**, for the (b) (4) particulates and foreign matters non-conformances, i.e., in filled vaccine product tubes, syringes, vials, stopper bowl, production tanks, manufacturing components and solutions.

Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences into the particulates and foreign matters non-conformances that continue to occur as the result of lack of timely corrective and preventive action is provided and discussed below:

QN (b) (4) dated February 11, 2015 was combined with QN (b) (4) dated February 02, 2015. In addition, (b) (4) batches of Rotateq for particulate matter were combined with QN (b) (4) for investigation.

Per QN# (b) (4) particulate reject rates of (b) (4) Rotateq batches exceeded the established PCL from January 26, 2015 to April 08, 2015 (**Exhibit #OOO25 Page #2**).

The non-conformance trend that was performed per page #2 of QN (b) (4) identified two prior PCL excursions in January 26, 2014 and May 27, 2015 due to embedded charred/degraded LDPE in the Rotateq tubes received batches from the supplier. This inspection disclosed that the root cause of the particulates was identified as embedded charred/degraded LDPE in (b) (4) received Rotateq tubes batches. As such, the most resent reoccurrences were identified as the (b) (4) occurrence of received tubes from the vendor with charred LDPE.

This inspection disclosed inadequate corrective and preventive actions were not instituted in a timely manner after the first and second occurrences in 2014/2015 to prevent the (b) (4) (b) (4) reoccurrences. Per the information provided by the firm's personnel, the (b) (4) batches of Rotateq were released for distribution into the US and ROW market due to the lack of product impact **(Exhibit #OOO25 page #2)** and no BPDR was reported to the Agency.

D) There have been (b) (4) glass breakage non-conformances for, i.e., vials, syringes, glass particles found in (b) (4) freezer, several broken vials as the result of shipped vaccine batches, broken glass in lyophilizer and glass breakages in product vials and vials (b) (4).

(OOO)

See **Exhibit #OOO26**, for the (b) (4) glass breakages non-conformances for vials, syringes, glass particles found in (b) (4) freezer, several broken vials as the result of shipped vaccine batches, broken glass in lyophilizer, glass breakages in product vials and vials (b) (4)

Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences and the final containers glass breakages non-conformances that continue to occur per the above observation are provided and discussed below:

QN (b) (4) date February 01, 2017 was combined with QN (b) (4) **(Exhibit #OOO27),** due to share root cause. This inspection disclosed that as the result of inadequate maintenance of the (b) (4) final containers packaging machine there were several machine malfunction occurrences that resulted in glass breakages on the inspection line that exceeded of glass breakage PCL. See page #17 of the exhibit for the list of (b) (4) vaccine batches and number of broken glass breakages that were due to the lack of adequate maintenance of the machine to prevent the reoccurrences of glass breakages of final containers by the (b) (4) machine as discussed below.

See **Exhibit #OOO27 page #16** for the (b) (4) customer representative comments, which states as follows: (b) (4)
(b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4) . Also see page #15 of the exhibit for the additional (b) (4) packaging machine maintenance recommendations by the (b) (4) customer representative.

For QN (b) (4) in regards to the glass fragments that were found underneath the (b) (4) (vial screen) of the (b) (4) line (b) (4) Freezer (b) (4) noted in the above observation, see **Exhibit #OOO28.**

The above Observation 1D disclosed inadequate corrective and preventive actions to prevent reoccurrences. Per **Exhibit #OOO27, page #17:** titled: (b) (4) (b) (4) ", there have been approximately (b) (4) previous occurrences of glass breakages affecting different vaccine batches on the (b) (4) inspection machine at the same (b) (4) labeler. However, no adequate corrective and preventive actions have been implemented and the glass breakages continue into 2017. For example, the list of glass breakages provided as **Exhibit #OOO26 page #3-4** disclosed, documentation of approximately (b) (4) different vaccines batches with glass breakages since January 2017 and as recently as March and April 2017, **Exhibit #OOO29 & Exhibit #OOO30.**

E) There have been (b) (4) non-conformances for, i.e., expired equipment, manufacturing components and solutions used in the manufacture of vaccine products.

(OOO)

See **Exhibit #OOO31** for the (b) (4) non-conformances that include the use of expired equipment, manufacturing components and solutions during the manufacture of vaccine products. My review of the list non-conformances disclosed several instances that expired equipment, components and solutions were used in the vaccines manufacturing processes and no adequate corrective and preventive actions have been instituted to address the issues and no justifications are provided. Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences of the use of expired equipment, components and solutions, per the above observation are provided and discussed below:

- Per QN (b) (4) dated December 12, 2016 **(Exhibit #OOO32)** a batch of (b) (4) (b) (4) equipment was used 14 days beyond its expiration date.

- Per QN (b) (4) dated November 02, 2016 **(Exhibit #OOO33),** it was discovered that NAOH batch that was charged into TA-503 on November 2016 has expired on September 02, 2016. The expired NAOH was used to charge five (5) bulk powder batches used in the sanitization of (b) (4) filters.

- QN (b) (4) dated February 14, 2017 **(Exhibit #OOO34)** disclosed that one of two L-Glutamine batches used in the formulation of maintenance media batch for Varicella bulk exceeded thawing time.

F) There have been(b) (4) VARIVAX vaccine(b) (4) filters integrity failures, including, sterilizing filters, primary and secondary filters.

(OOO)

See **Exhibit #OOO35** for the (b) (4) VARIVAX vaccine (b) (4) filters integrity failures including, sterilizing filters, primary and secondary filters. My review of the non-conformance disclosed lack of adequate corrective and preventive actions in a timely manner to prevent reoccurrences as discussed in the examples below:

Per QN (b) (4) and QN (b) (4) dated April 05, 2016 **(Exhibit #OOO36)** from February 08 to July 20, 2016 there were (b) (4) primary and secondary double (b) (4) (b) (4) Filters for a total of (b) (4) filters that had filters integrity failures. Per the QN (b) (4), page (b) (4), the failures of these filters affected (b) (4) Varicella Harvested Viral Fluid batches of which (b) (4) batches out of the (b) (4) batches were accepted and (b) (4) (b) (4) batches were recommended for discard due to the following reasons: (b) (4) of the batches were discarded due to sterility assurance and (b) (4) of the batches were conservatively discarded due to sequencing of testing and defining sterility assurance criteria.

During the inspection and discussions on the filters integrity failures, I stated that I was concerned about the lack of corrective and prevent actions in a timely manner, which could have prevented less number of filter failures and could have affected less number of vaccine batches. I asked the firm's personnel why it took five (5) months, (b) (4) filter failures affecting (b) (4) Varicella Harvested Viral Fluid batches before the root cause of the filters integrity failure was determined. I stated that the first filter integrity failure should have resulted in opening of an investigation and the firm contacting the filters manufacturer. During the inspection and as the result of my questions regarding the lack of timely corrective actions to the filters failure occurrences; Ms. McLaughlin provided me with a written explanation on the time line of the filters integrity failures that was put together during the inspection and was not part of the original QN (b) (4) document **(Exhibit #OOO37).**

Furthermore, per QN (b) (4) /QN (b) (4) **(Exhibit #OOO38)** From February 26, 2015 to May 26, 2015 a total of (b) (4) filters used in the maintenance media sterile filtration failed post use filter integrity testing.

G) There have been(b) (4) vaccine products related labeling non-conformances, including missing labels on syringes, laboratory samples missing labels and miss-labeled product retention samples.

(OOO)

See **Exhibit #OOO39** for the (b) (4) vaccine products related labeling non-conformances, including missing labels on syringes, missing labels on laboratory samples and miss-labeled products retention samples.

Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences of labeling non-conformances, which continue to occur are provided and discussed below:

- Per QN (b) (4) dated January 25, 2017 **(Exhibit #OOO40)** during the initial submission of retention sample, it was identified that retention samples from ProQuad Frozen batch 0000643041 and ProQuad 4C batch 0000651461 were incorrectly labeled. It was noted that retention sample from the middle of batch 0000643041 had the correct label on the outside of the box but a different label associated with batch 0000643038 inside the box. The end of the batch samples contained labels from the associated batch as well, both inside and outside the box. Furthermore, the retention samples from the beginning and middle of batch 000065146 had correct label on the outside of the box but, label from associated batch 000065162, inside the box.

- Per QN (b) (4) dated February 15, 2017 **(Exhibit #OOO41)** bioburden sample 0000667680 was labeled as product (b) (4) on both of the testing worksheet and the sample bottle. As such, the sample was tested per the Qualified Sample List for Product (b) (4). The error was found when an attempt was made to enter the result into (b) (4).

- Per QN (b) (4) dated November 02, 2015 **(Exhibit #OOO42),** an inter-site investigation was received from (b) (4) packaging operations at (b) (4) (b) (4) for (b) (4) syringes that were filled and packaged at this inspected facility for missing the (b) (4) identification label during packaging of Gardasil 0.5 ml.

H) There have been (b) (4) vaccines product related glycol leaks non-conformances, i.e., leaks from ceiling onto manufacturing areas, glycol leaks from equipment during manufacturing process.

(OOO)

See **Exhibit #OOO43** for the (b) (4) vaccines product related glycol leaks that were documented as non-conformances, which resulted in leaks from the ceiling onto manufacturing areas and glycol leaks from equipment during the manufacturing process.

Examples of the several instances that corrective and preventive actions were not conducted in a timely manner to prevent reoccurrences of, i.e., glycol leaks non-conformances, which continue to occur, are provided and discussed below:

- QN (b) (4) dated November 08, 2016 **(Exhibit #OOO44)** disclosed drops of glycol of approximately 2 liters were observed leaking from the ceiling through the HEPA screens of cold room (b) (4) which house the (b) (4) (b) (4) Per page (b) (4) of QN (b) (4) the leak was first observed in the cold room during processing of HPV purification batch. Also, per page (b) (4) of the QN, there had been four (4) previous other leaks unrelated to this event within the last one year that glycol leaks have been observed.

- Per QN (b) (4) dated November 25, 2016 **(Exhibit #OOO45),** approximately 0.5L of glycol spilled from the (b) (4) docking station in room (b) (4). The glycol sprayed from the glycol return hose and associated quick connect on the tank docking station.

- Per QN (b) (4) dated January 14, 2017 **(Exhibit #OOO46)** after formulation of bulk product in portable tank (b) (4) and while performing the (b) (4) (b) (4), the air vents overflowed through the air vents to the top of the chiller. Approximately one liter of glycol spilled onto the floor and into the pit scale in room (b) (4).

During the inspection I requested to see any formal investigations that have been opened as corrected actions that were previously opened before the start of the current inspection into the above listed non-conformances of Observation #s: 1A to 1H to prevent reoccurrences of these events, and none could be provided by the firm's personnel and management.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

2. Input to and output from the computer or related system of formulas or other records or data were not adequately checked for accuracy. Specifically: the validations of the (b) (4) vials inspection machines (b) (4) and (b) (4) as corrective actions to previous 2015 FDA-483 Observations 5B, 8A, 8B, 10A, 11A and 11B regarding Recombivax HB Adult batch # 0672446 that was recalled in June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch is inadequate. For example:

A) There is no documentation of Process Qualification study of the (b) (4) machines capabilities to detect vials heel crack defects. The Performance Qualification study (b) (4) dated May 18, 2016 for (b) (4) machine (b) (4), titled: (b) (4) (b) (4) (b) (4) acceptance rate of (b) (4), is inadequate as follows:

(OOO)

The observations were mostly discussed with Arthur Keoseyan, Associate Director Engineering; Emily Buschmeier, Senior Specialist Engineer and Chad Slate, Associate Director Engineering.
This inspection disclosed that the performance qualification conducted into (b) (4) vials and syringes inspection machines (b) (4) in regard to heel crack detections is inadequate. For example (b) (4) machine (b) (4) was qualified in May 2016 as corrective actions to previous April 2015 FDA-483 Observations 5B, 8A, 8B, 10A, 11A and 11B. The 2015 observations were issued as the result of Recombivax HB Adult batch # 0672446 that was recalled in June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch.

The review of the Performance Qualification Study Report (b) (4) dated May 18, 2016 for (b) (4) machine (b) (4), titled: (b) (4) (b) (4) **(Exhibit #OOO48)** and Protocol (b) (4) dated May 13, 2016 titled: Vision Inspection Performance Qualification Protocol for Gardasil **(Exhibit #OOO50)** disclosed the qualification of the Eisai machine capability for acceptance rate of (b) (4) failed to include the (b) (4) machines ability to detect vials heel crack defects similar to those in the recalled Recombivax HB Adult batch # 0672446 as discussed below.

i) The capability of the (b) (4) machines to detect vials with vials heel crack defects has not been conducted. The performance qualification for cracked vials conducted was not based on real crack defects from the recalled batch or rejected vial defects during the (b) (4) machine Performance Qualification study (b) (4) to determine the capability as compared to the current (b) (4) acceptance criteria for the (b) (4) machines. The qualification was conducted using (b) (4) to make a diagonal line to simulated defective cracked vials. The uses of (b) (4) to make a diagonal line to simulated crack vials defects have been discussed with the firm's management during previous inspections as inadequate). In addition, not all of the (b) (4) machine vials defect cameras were turned on during the qualification.

(OOO)

This inspection disclosed that the capability of the (b) (4) machines to detect vials heel crack defects has not been conducted. Furthermore, the review of the Performance Qualification Study Report (b) (4) to determine the capability of the current (b) (4) acceptance criteria for the (b) (4) machines was not based on real crack defects from the recalled batch or rejected vial defects that were culled out during the vials defect inspections. Per the above Qualification Protocol (b) (4), page #8, the descriptions of the methods used to create the known defective vials in the characterized challenge sets for the qualification is documented in SOP #17-INS-110X: (b) (4) (b) (4) **(Exhibit #OOO49).** My review of the

SOP 17-INS-110X page (b) (4) disclosed, it allows for the use of (b) (4) to make a diagonal line to simulated different variations and sizes of defective cracked vials.

Although the use of (b) (4) to make a diagonal line to simulated crack vial defects have been discussed with the firm's management during previous inspections of 2013 and April 2015 as inadequate to qualify the (b) (4) machines; this inspection revealed that the (b) (4) machine qualifications were conducted again in 2016 using (b) (4) to make a diagonal line to simulate defective cracked vials. In addition, this inspection disclosed that during the performance qualification, i.e., (b) (4) not the entire (b) (4) machine vials defect detection cameras were turned on. It was noted that the cracked vial defects cameras were turned on while the other vial defects detection cameras were turned off, **Exhibit #OOO50 page #10**, titled: Inspection Validation Test Procedure. For a list of (b) (4) Machines (b) (4) inspection machines vials and syringes inspection cameras, see **Exhibit #OOO47.** For the (b) (4) machine camera and sensor grouping table, which list the vials inspection cameras that were turned on and/off during the qualification, see **Exhibit #OOO50 page #4**. As such, the actual capabilities of the (b) (4) machines to detect defective vials were not adequately conducted. Furthermore, there was no documentation that (b) (4) inspection machine process validation with a statistically determined number of vials that is representative of the up to (b) (4) final containers per vaccine batch has been conducted as discussed below.

ii) The number of vials selected for use in the performance qualification to determine the percent capability of the (b) (4) machine to detect vials with cracked defects was not based on an acceptable statistical sampling plan. For example: Although total vials per vaccine batch ranges from (b) (4), the qualification was conducted with three (3) simulated cracked vials that were created by the use of (b) (4) to make a diagonal line with approximately (b) (4) non-defective vials that were ran (b) (4) times through the (b) (4) machine.

(OOO)

The review of the (b) (4) machine, i.e. (b) (4) performance qualification protocol **(Exhibit #OOO50 page #10)** disclosed the number of vials selected for use in the performance qualification to determine the percent capability of the (b) (4) machine to detect vials with cracked defects was not based on an acceptable statistical sampling plan. Although total vials per vaccine batch ranges from (b) (4), **(Exhibit #OOO51)**, per page (b) (4) of the (b) (4) machine performance qualification protocol, the qualification was conducted with three simulated cracked vials that were created by the use of (b) (4) (b) (4) to make a diagonal line with approximately (b) (4) non-defective vials that were ran seven times through the Eisai machine.

B) Although the recall of Recombivax HB Adult batch # 0672446 was in June 2013, not all corrective and preventive actions to prevent similar reoccurrences of the 2013 vials heel crack defects have been instituted. For example:

i) The (b) (4) machines continue to reject high percentages of inspected vials in several vaccine product batches, which the firm classified as false rejects as such, these batches were not re-inspected. The high reject rates were attributed to the new cameras (b) (4) installed on the (b) (4) machine for cracked vials detection. As the result of the (b) (4) machines high vials reject rate, CAPA (b) (4) datcd April 18, 2017 was opened to re-validate and retune the (b) (4) inspection machines (b) (4) For example:

(OOO)

(The above observation should state to validate)

ii) Per QN (b) (4) dated January 20, 2017, the (b) (4) heel crack defects detection cameras were responsible for Gardasil:

a) Batch 0000660967 rejects of (b) (4) of the (b) (4) total vials rejected.

b) Batch 0000660980 rejects of (b) (4) of the (b) (4) total vials rejected.

c) Batch 0000662803 rejects of (b) (4) of the (b) (4) total vials rejected.

(OOO)

The current inspection disclosed that corrective and preventive actions as the result of the recalled Recombivax HB Adult batch # 0672446 of June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch have not been adequately corrected to prevent similar reoccurrences. For examples, high vial defects reject rates were documented in the three batches noted in the above Observations #2Bii (a-c), see **(Exhibit #OOO52 page #2)** for QN (b) (4) that listed these high reject rates for the three above noted Gardasil batches. For the batch records of the three batches showing the total number of filled vials and total number of "falsely" rejected vials, see **Exhibit #OOO53, 54 & 55.**

My review of the investigation conducted into the high number of rejected Gardasil vials by the Eisai machines, disclosed that these batches were not re-inspected since the vials were classified as false rejects. Per QN (b) (4), page #2, the entire high vials reject rates were attributed to the new cameras (b) (4) installed on the (b) (4) machines for cracked vials detection. Furthermore, previous 12 months occurrences with same root cause trending in SAP disclosed (b) (4) previous events with similar root cause. As such, per page #2 of QN (b) (4) the recent non-conformances of false vials rejects were classified as the (b) (4) occurrence in the past 12 months.

As the result of the (b) (4) machines high final containers reject rates, which was ongoing during this inspection, I was informed that CAPA (b) (4) **(Exhibit #OOO58)** has been opened to validate and retune the (b) (4) inspection machines (b) (4)

and(b) (4) However, CAPA (b) (4) to validate the (b) (4) machine was not opened until April 18, 2017. Also, the validation of the (b) (4) machine "Target Date" per the CAPA is June 2017.

iii) There is no documentation that vial/syringe defects inspection personnel that conduct re-inspections of vials heel crack defects have been qualified to re-inspect.

(OOO)

Per the information provided to me during the inspection by the above firm's noted personnel, the vial/syringe defects inspection personnel that conduct re-inspections of vials heel crack defects have not been trained and/or qualified to re-inspect vials with this type of defect. Furthermore, my review of SOP #17-INS-110X: (b) (4) (b) (4) **(Exhibit #OOO49 page #19)** that is also used in the training of vials inspection personnel disclosed that it contains no information and/or photographs of simulated or actual vials with cracked heel defects.

iv) No actual cracked heel vials are used in the training of the vial inspection personnel. Only simulated vials are used.

v) SOP #17-INS-110X Version 3.0, titled: (b) (4) (b) (4) used in the training of the vial inspection personnel and for (b) (4) machine challenge set up did not contain photographs of examples of vials with crack heels similar to the undetected ones found in the recalled product batch.

(OOO)

In addition, this inspection disclosed that the firm has no library of defective vials that contains all of the defective vials, i.e., particles; different types of vial cracks including cracked heel vials that were (b) (4) culled out during vial inspections and similar to the (b) (4) machine undetected ones that were found during the (b) (4) vials inspection of the recalled product batch for use in the training of the vial inspection personnel. Furthermore, this inspection disclosed that only photographs of simulated vials, (no cracked vials heel defects) are included in the training SOP #17-INS-110X Version 3.0, titled: (b) (4) **(Exhibit #OOO49)** and the video used in the training of vials defect inspection personnel.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

3. The corrective actions to previous 2015 FDA-483 Observations 1A and 2B regarding the freezing and thawing of sterility samples before performing sterility testing for virus vaccine samples that have been frozen for (b) (4) weeks and thawed for (b) (4) to performing sterility test is inadequate. For example:

A) The acceptance criteria for study (b) (4), dated January 19, 2017 titled: (b) (4) (b) (4), failed to include the percentages of recoveries of the <100cfu/ml inoculum per challenged organisms used for the study. The study acceptance criterion only requires that: (b) (4) (b) (4)

(OOO)

The observation was mostly discussed with Joseph Vido, Associate Director Quality Control and Jennifer Holub, Senior Specialist Quality Control.
The corrective actions to the previous April 2015 FDA-483 Observations 1A and 2B regarding the freezing and thawing of sterility samples before performing sterility test for virus vaccine samples that have been frozen for (b) (4) and thawed for (b) (4) to performing sterility test was found to be inadequate. My review of the acceptance criteria/protocol of the study, titled: (b) (4) (b) (4) **(Exhibit #OOO18)** for validation study (b) (4) dated January 19, 2017 and study report, titled: (b) (4) (b) (4) (b) (4) **(Exhibit #OOO23):** disclosed that the acceptance criteria failed to include the percentages of recoveries of the <100cfu/ml inoculum per challenged organisms used for the study.

I informed Joseph Vido, Associate Quality Director, Quality Control that the study acceptance criterion, Attachment 1, to the validation study titled: (b) (4) (b) (4) (b) (4), page (b) (4) only requires that: (b) (4) (b) (4) is inadequate. I stated that the acceptance criteria to the study should have included additional requirements for the percentages of recoveries for the <100cfu/ml inoculum per challenged organisms used for the study.

I was informed by Mr. Vido that the sterility test is qualitative and not quantitative and that the study was to show if there was growth or no growth, which will indicate if organisms are present or not. I again stated that the acceptance criteria in the attachment to the validation study should have included the percentages of recoveries for the <100cfu/ml inoculum per challenged organisms. Furthermore, I stated that the sample was frozen under the assumption that all of the organisms or majority of the organisms present in the original samples will still be present after freezing for (b) (4) week and the study should have included recovery rates for the inoculum organisms at the end of (b) (4) week in order to be credible. I was informed by Mr. Vido that the study team did not consider the inclusion of the challenged organisms' recovery rates in the acceptance criteria of the study and in hindsight; it should have been included in the acceptance criteria.

During the inspection, I was informed that the firm had additional explanations to present to me on the freezing and thawing of sterility samples before performing sterility test for virus vaccine samples study. I stated that I will be willing to review the additional information only if it includes the recovery rates per challenged organisms used for the study. I further stated that I have spent enough time with the firm's personnel reviewing the corrective actions to the previous April 2015 observations (almost a week) and needed to move on to other topics.

4. Observation #3 from the 2015 Pre-approval Inspection (PAI) regarding labeling of containers that are not performed according to established procedures has not been adequately corrected. The current inspection revealed several instance of vaccine products labeling issues that could result in product mix-up, the use of the wrong products and equipment.

(OOO)

The observation was mostly discussed with April Fultz, Director of Quality.
This inspection disclosed that the specific corrective actions to Observation #3 from the June 2015 Pre-approval Inspection regarding labeling of containers that are not performed according to established procedures have been corrected. However, the current inspection revealed several instance of vaccine products labeling issues that could result in product mix-ups, the use of the wrong products and equipment. As such, I informed the firm's personnel that although correction actions specific to the previous FDA-483 Observation #3 have been corrected, however, that the observations was in regards to labeling of containers that are not performed according to established procedures, which during this inspection I noted as still present. I further stated that the Agency expects across the board corrective actions of cited observations. For example, this inspection disclosed,(b) (4) vaccine products related labeling non-conformances, including missing labels on syringes, missing labels on laboratory samples and miss-labeled product retention samples, **(Exhibit #OOO39, 40, 41 &42).** See additional discussion under **Observation #1G** of this EIR.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

5. The Quality Control Unit failed to conduct an annual review of production records so that data therein can be used for evaluating the quality standards of each product to determine the need for change in product specifications, manufacturing and/or control procedure. For example:

A) Manufacturing non-conformances/deviations classified as (b) (4) are documented in the batch records are not investigated and are not included in the review and trending of manufacturing non-conformances/deviations. For example, the following deviations during vaccine manufacturing process can be documented

as event in the batch records per SOP #06-QUA-125AX, titled: (b) (4) (b) (4) **:**

(OOO)

The observations were mostly discussed with Hilary McLaughlin, Associate Director Quality.

This inspection disclosed deficiencies in the firm's quality controls over the vaccines manufacturing and the production unit. Furthermore, this inspection disclosed manufacturing non-conformances and/or deviations that are classified as (b) (4) and per SOP #06-QUA-125AX, Version 13.0 titled: (b) (4) **(Exhibit #OOO11)** in all cases are documented in the batch records. As such, the non-conformances classified as (b) (4) are not investigated and are not included in the review and trending of manufacturing non-conformances and deviations.

i) Equipment calibration expires prior to preventive maintenance because the equipment is in use.

ii) (b) (4) **filter failure when a** (b) (4) **filter is in place and has satisfactory results.**

iii) Isolated missed routine room cleaning.

(OOO)

For examples of the above listed observation #5(Ai), 5A(ii) and 5A(iii) see additional examples listed in SOP #06-QUA-125AX **Exhibit #OOO11 page #21, Appendix #4.**

During the FDA-483 discussion before the close-out discussion, Ms. McLaughlin informed me that the above Observation #5(i) should have included the additional wording as stated in the SOP. I informed her that I will include it in the EIR as follows: Equipment calibration expires prior to preventive maintenance because the equipment is in use; *however, the unit is calibrated satisfactorily as soon as the unit is available and extension approved prior to expiration.*

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

B) The Annual Product Reviews (APRs) do not reflect the status of deviations observed or remaining open for each product. The APR reports the number of deviation investigations closed for the specific APR time frame and the number of Significant deviations remaining open at the close of the review period. It does not reflect the total number of deviations opened that year or that remain open.

(MEM)

I received an overview of the Annual Product Review (APR) from Jason Johnson (Ass. Dir. Quality Systems & Compliance) and Kristin Costello (Sr. Specialist, Quality Assurance). I also reviewed SOP 01-QUA-340X (b) (4) (b) (4) The information compiled during the APR process is trended and summarized to determine if manufacturing/packaging procedures and corresponding quality systems are in control. The APRs for each product includes (b) (4) (b) (4) , (b) (4) , (b) (4) sections. I reviewed the section summarizing deviations for the VAQTA 2016 APR. Section III.E. (Deviation Investigations) reports investigations that were closed during the current review period as well as Significant deviations that remained open at the close of the review period. There was no assessment or reporting in the APR of the total number of deviations opened at the end of the current review period or total deviations that remain open. I requested an explanation of how all deviations are tracked to monitor the proportion still open at the end of the year, not just those classed as Significant.

An overview of the information submitted to the Quality Review Council was provided by Tim McHugh and Hilary McLaughlin. This showed the tracking of open deviations and updates on the numbers of deviations that had been open for more than 30 days. This was acceptable but I informed management that the APR did not adequately reflect all deviations associated with any specific product.

6. The responsibility and procedure applicable to the Quality Unit are not fully established and/or followed. Specifically, The Quality Unit oversight of the Production Unit for vials/syringe defects inspections, labeling and packaging operations are inadequate. For example:

A) Manufacturing deviations/non-conformances are not closed in timely manner and the firm failed to follow SOP #06-QUA-120X, Version 5.0 titled: Sitewide-Quality Notification Management at West Point that requires the completions and closures of manufacturing non-conformances in (b) (4) days in that (b) (4) out of (b) (4) of manufacturing non-conformance/deviations since the inspection of March 2015 were not closed within the deviation SOP time frame.

(OOO)

The observations were mostly discussed with Timothy Cooper, Associate Director Operations; Kimberly Bittman-Long, Associate Director, Quality; Helen Julia Lothian, Associate Director, Quality and Arthur Keoseyan, Associate Director, Engineering.
My review of the manufacturing deviations and non-conformances (QNs) disclosed in most instances that they are not closed in timely manner. Furthermore, my review disclosed that the firm failed to follow SOP #06-QUA-120X, Version 5.0 titled: Sitewide-Quality Notification Management at West Point **(Exhibit #OOO56 page #3)** that requires the completions and closures of manufacturing non-conformances in (b) (4) (b) (4) days. Per the information requested and provided to me during the inspection titled: Number of iQNs **(Exhibit #OOO10)** since the last inspection of April 2015, the firm had approximately of 9,464 documented non-conformances, which did not include non-conformance that are documented in the vaccine batch records as (b) (4) . My review of the provided non-conformance list disclosed that (b) (4) out of (b) (4) (closed IQNs) of the non-conformances, which is approximately (b) (4) of all manufacturing non-conformance and deviations were not closed within the deviation SOP time frame of (b) (4) days.

My further review of the list of documented (b) (4) non-conformances and deviations disclosed inadequate justifications for the classifications of (b) (4) of all the vaccines manufacturing non-conformances and deviations (QNs) as "Minor Deviations", **(Exhibit #OOO59).** For example, the above cited Observation #1F regarding (b) (4) VARIVAX, vaccine (b) (4) filters integrity failures, including, sterilizing filters, primary and secondary filters were mostly classified as minor deviations **(Exhibit #OOO35).**

During the inspection, the inspection team was informed by the firm's management that classifications and documentation of manufacturing non-conformances was in the process of been revaluated.

Furthermore the current inspection disclosed inadequate Quality Unit oversight of the Production Unit in regards to vials, syringes and tubes defect inspections and labeling and packaging, examples of which are discussed below.

B) There is no documentation that the vials/syringe line clearance inspections are verified and released for use by the Quality Unit. The (b) (4) machines, i.e., (b) (4) machines line clearance are conducted by the firm's Mechanics Department personnel and the Production Unit operators and verified by a second Production Unit Operator.

(OOO)

My inspection of the (b) (4) machine vials, syringes and tubes line clearance disclosed the lack of verification and release of the line clearance conducted by the Production Unit by the Quality Unit. For example, the (b) (4) machines vaccines final containers line clearance inspection is conducted by the firm's Mechanics Department personnel and the Production Unit operators per SOP 24-Bar-344, Version 8.0 titled: (b) (4)

(b) (4) **(Exhibit #OOO60).** The line clearance is also verified by a second Production Unit Operator per SOP #27-PAC-202 titled: (b) (4) (b) (4) **(Exhibit #OOO61)** and not by the Quality Unit.

See **Exhibit #OOO62** for the vials, syringes and tubes inspection operator job descriptions that include the setup of vials, labeling and packaging lines, inspection of the (b) (4) and (b) (4) labeling machines.

C) The line clearance inspections performed by the Production Unit operators for the (b) (4) vial/syringe defects inspection machine, i.e., (b) (4) machine, and the labeling and packaging machine are inadequate. For example, there are no assurances and/or documentation that all of the required areas in the SOPs and/or that were initially inspected by the first operator were actually inspected and verified by the second Production Unit operator.

(OOO)

During the inspection the (b) (4) machine for the (b) (4) vials, syringes and tube defects inspection line clearance Document (b) (4) Version #6, titled: Line (b) (4) Pre-Operational Checklist **(Exhibit #OOO63),** which includes the requirements for line clearance to be performed and documented by the Production Unit operators could not be provided during the inspection for the most recent completed and released vaccine batch. Also, the comparison of Document (b) (4) inspection requirements to the actual documented inspection performed by the operators on the (b) (4) machine, titled: (b) (4) Pre-Operational Checklist **(Exhibit #OOO64)** disclosed that not all of the required areas of the document **Exhibit #OOO64** were inspected by the operators. In addition, per the signature of the second operator on page 3 of **Exhibit #OOO64**, there was no documentation that the second (b) (4) inspection machine verifying operator actually re-inspected and verified the listed areas initially inspected by the first operator per the documentation in **Exhibit #OOO64**. The only verification is the second operator's electronic signature on page #3 of document-**Exhibit #OOO64.** Similar concerns as described above for the (b) (4) inspection machine were also noted for the (b) (4) labeling and packaging machine.

As such, there are no assurances and/or documentation that all of the required areas in the checklists that were initially inspected by the first operator were actually inspected and verified by the second Production Unit operator.

D) There is no documentation that the labeling and packaging line clearance inspections are verified and released by the Quality Unit. The labeling and packaging line clearance inspection are conducted and verified by the production unit operators.

(OOO)

This inspection also disclosed that the syringe labeling and packaging line- (b) (4) (b) (4) line clearance is not verified and release by the quality unit but is conducted by the operators per SOP #27-PAC-R001 Version 1.0 titled: Clean and Inspection Job Aid for Line (b) (4) **(Exhibit #OOO65)** and verified by a second operator per SOP #27-PAC-202 titled: Equipment and Line Clearance: Completing Pre-Op Checklist **(Exhibit #OOO61)**.

E) The vials and syringe samples selected from the (b) (4) inspection machines for the Acceptable Quality Limits (AQL) sampling Level II inspections are collected and inspected by the Production Unit personnel and not by the Quality Unit.

(OOO)

See SOP 23-BAR-318X Version 11.0 titled: (b) (4) (b) (4) **(Exhibit #OOO66 page # 1)** section 4, titled: (b) (4) (b) (4), which disclosed that the vials and syringe samples selected from the (b) (4) inspection machines for the Acceptable Quality Limits (AQL) sampling Level II inspection are collected and inspected by the "Inspector"/Production Unit personnel and not by the Quality Unit.

F) Although SOP #24-INS-243X Version 6.0 titled: (b) (4) (b) (4), Section (b) states as follows: (b) (4) (b) (4), however, the SOP failed to state the maximum number of times that a vaccine batch can be inspected for vials/syringes defects and the final disposition of the subject batch.

(OOO)

For the above noted SOP #24-INS-243X Version 6.0 titled: (b) (4) (b) (4) see **Exhibit #OOO57 page (b) (4) section (b)** which failed to state the maximum number of times that a vaccine batch can be inspected for vials/syringes defects and the final disposition of the subject batch.

G) Vials, syringes and tubes that are rejected during the AQL inspections are not added to the total rejects of the batch. In addition the evaluation of a batch for release is not based on the accumulative total of the defective vials culled out as the result the re-inspections of the batch.

(OOO)

This inspection disclosed the lack of procedure in place that specifically states that vials, syringes and tubes that are rejected during the AQL inspection of a batch are to be added to the total rejects of the vaccine batch. Furthermore, the review of the vaccine batch records disclosed that rejected vials, syringes and tubes are not included in the total

number of final product containers, rejects that were culled out as the result the re-inspections of the batch. This was also confirmed by the above noted firm's personnel. As such, the evaluation of a batch for released is not based on the accumulative total defects reject rate.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

7. Batch production and control records are not adequately prepared for each batch of production and do not include complete information relating to the production and control of each batch. For example, the batch record for labeled and packaged vials failed to include:

A) The documentation of total number of inspected vials, syringes and tubes received for labeling/packaging and total number that were labeled.

(OOO)

The observations were discussed with Helen Julia Lothian, Associate Director, Quality and Linwood Gatewood, Manager Quality.
My review of the labeling and packaging production batch records disclosed inadequate documentation of the information relating to the labeling and packaging the vaccine batches. For example, Pneumovax 23.0 0.5ml Syringe US, batch #N005096 page #5 of the batch record indicated the quantity of material issued, material yield, sampled and waste but did not define the "material" **Exhibit #OOO67.** There was no documentation in the batch records of the total number of Pneumovax syringes received for labeling and packaging, total number of syringes that were actually inspected and packaged.

B) There is no documentation of the reasons for the rejected vials, syringes and tubes that are recorded in the batch record.

(OOO)

This inspection disclosed the lack of documentation of the reasons for the final material or waste noted in the vials, syringes and tubes batch records. For example, the batch record for Rotateq 2ml 1 Dose ESP Private Batch #N011598 **(Exhibit #OOO68)** noted (b) (4) under Final Material as waste. However, there was no explanation as to the type of the "Waste" of final material on the Final Material Accountability Range table in the batch record. Per Helen Julia Lothian, Associate Director, the (b) (4) is the number of rejected tubes. However, no reasons for the rejected (b) (4) tubes were documented in the batch record.

C) There is no documentation of the labels received for the labeling operations and the return of unused labels in the batch record.

(OOO)

Furthermore, the inspection disclosed the lack of documentation of the labels received for the labeling operations and the return of the unused labels in the batch record, **(Exhibit #OOO68 & 69).** During the discussion on the documentation of number of received labels in the batch record, Helen Lothian, Associate Director, Operations informed me that there is no labeling information such as the number of vials and syringe labels received in the batch record, since there are label inspection cameras on the labeling line, which accounts for 100% inspection of labels. She provided me with portions of Rotateq 2ml 25X 1 Dose Tube USA, Batch #N009963 batch record as an example of labeling documentation in the batch record, **(Exhibit #OOO69 page #6)**, which only indicated (b) (4) full boxes, (b) (4) partial boxes and (b) (4) return, in the table titled: "Bulk Material Issued". I informed her that I was not asking her to conduct complete label accountability that include the number of labels received, rejected and investigation in cases of significant discrepancies. I started that the batch record should at least contain the number/weight of labels received for the labeling operations and the number/weight of the return unused labels in the batch record.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

8. Employees are not adequately trained in the particular area that they perform. For example:

A) The training and qualifications of the Production Unit personnel for vials/syringe defects inspection is inadequate. Although there are (b) (4) vials/syringe defects culled out, i.e. (b) (4) machine inspection of a vaccine batch, however, the firm continues the use vials/syringe defects made from (b) (4) to make simulated defective vials/syringes for the personnel training and qualifications. Furthermore, there are no library of defects from culled out vial/syringe defects during product batch inspections for use in the training of vials and syringes inspection personnel.

(OOO)

The observation was mostly discussed with Arthur Keoseyan, Associate Director, Engineering and Emily Buschmeier, Senior Specialist Engineering.
As discussed in Observation #2A (ii), 2A(iv) and 2A(v) above, the firm has no library of defects that are from culled out vials, syringes and tubes for use in the training and qualifications of the Production Unit Vaccine final containers inspection personnel. Per the information provided during the inspection (b) (4) vials/syringe defects are culled out during an inspection of a vaccine batch **(Exhibit #OOO71).** However, these defects are not used in the training and qualifications of the final containers inspection personnel. This inspection disclosed that the training and qualifications of the Production Unit personnel for vials and syringes defects inspection are conducted by the use of

defective vials and syringes made from (b) (4) to make simulated defective vials and syringes per SOP #17-INS-110X: (b) (4) (b) (4) **(Exhibit #OOO49).** The same simulated defect product containers were also used in the qualifications of the inspection machines, i.e., (b) (4) machine. During the inspection, I was informed that the photographs in the Production Unit Training SOP #17-INS-110X titled: (b) (4) (b) (4) **(Exhibit #OOO49 page #19)** and one of the SOPs used in the training of final vaccine containers inspection personnel also contains no information and/or photographs of culled out final vaccine defective containers, but defects created by the use (b) (4) . See additional discussion under **Observation #2A** of this EIR.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

9. Vaccines syringes, vials and tubes collected for retention samples for yearly inspections and for complaints investigations are not representative of the released batches.

A) Retentions samples are collected after inspection by the (b) (4) machine, but before the vials, syringes and tubes labeling and packaging operations. It was noted that vials/syringes can be stored for up to (b) (4) after inspection before labeling and packaging. For example,

(OOO)

The observations were mostly discussed with Don Monkovic, Director Quality and Tim Cooper, Associate Director Operations.
This inspection disclosed that vaccines final containers, i.e., vials, syringes and tubes collected for retention samples for yearly inspections and for complaint investigations are not representative of the released batches. Per the batch documentation of collections of samples provided during the inspection, i.e., retention, LAL, volume fill, CBER/FDA and sterility, are collected after inspection of the naked vaccine containers by the (b) (4) machine and before the vials, syringes and tubes labeling and packaging operations, **(Exhibit #OOO70).**

I informed the firm's management and personnel that from the information provided during the inspection that vaccine vials and syringes can be stored for over (b) (4) after inspection and before the containers are labeled and packaged. Furthermore, I stated that the retention samples are required to be inspected periodically and are also inspected and tested as the result of customer complaints. For example, I stated that vaccine batches after the collections of the retention samples as currently practiced could be subjected to handling and storage conditions that could later result in complaints. This I stated will not be evident in the yearly inspection and complaint testing of the retention samples in the final containers that were collected after the inspection of the vials and before labeling,

packaging, transportation to the storage areas where the batch could be stored for over (b) (4) (b) (4)

See **Exhibit #OOO71,** titled: West Point Packaged Gardasil batches with date filled, inspection date, rejects data, packaged date and date the batch was shipped. The document indicated the time frames of a vaccine batch from the time the naked vials were inspected to when the batch was labeled, packaged (if labeled and packaged at Merck, PA) or shipped to other Merck locations for labeling and packaging. Also, see examples below for the time period that a batch was inspected before it was labeled, packaged or shipped to be labeled and packaged at another Merck facility:

i) Gardasil batch L010587, 0.5ml was inspected on November 04, 2013 and was labeled and packaged on April 06, 2015.

(OOO)

See **Exhibit #OOO71 page #1,** for Gardasil batch L010587, 0.5ml that was inspected on November 04, 2013 and was labeled and packaged on April 06, 2015.

ii) Mumps Measles and Rubella (MMR) fill batch 0000545580 was inspected on January 22, 2016 and as of April 27, 2017 has not been labeled and packaged.

(OOO)

See **Exhibit #OOO71 page #2,** for Mumps Measles and Rubella (MMR) fill batch 0000545580 that was inspected on January 22, 2016 and as of April 27, 2017 has not been labeled and packaged.

B) The documentation of the collections of product release test samples, stability and retention samples in the batch record is inadequate. There are no procedures in place that specifically explains the locations during the manufacturing process that the retentions and stability samples are collected.

(OOO)

This inspection disclosed the lack of a procedure in place that specifically describes the locations during the manufacturing process that the retentions and stability samples are collected with the exceptions of Live Virus Vaccines (LVV). The portion of the batch record that listed the samples to be collected and provided for review, titled: Barrier Operations Sampling Form for the collections of release test samples, stability and retention samples is inadequate, **(Exhibit #OOO70).** During the inspection, I was provided several documents including Document # GDL 29.13 Revision 2.0 titled: Retention, File, and Legal Samples **(Exhibit #OOO72)** and referenced pages 4 and 6, which provides no answers to the observation in regards to the manufacturing locations that the retention and stability samples are collected during the manufacturing process.

During the FDA-483 close-out discussion, none of the firm's management that was present objected to the observations.

10. Failure to submit a Biological Product Deviation Report. Specifically,

A) A BPDR was not submitted with regard to QN (b) (4) . This deviation was opened due to data integrity issues in the Laboratory Operations Microbiology and Sterility Assurance (LOMSA) department where sterility testing, media fill evaluation, and environmental monitoring plate reading are conducted.

(MSL)

I was shown no documentation that a BPDR was submitted with regard to QN (b) (4) .

Exhibit MSL19 contains Quality Notification Report Notification: (b) (4) and a memo to the QN (b) (4) File dated 13May2016 with the subject of "Final Investigation Report –Revision 1.0[1]". This deviation was opened due to data integrity issues in the Laboratory Operations Microbiology and Sterility Assurance (LOMSA) department.

As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: 200374252) the "**Date Atypical Identified**" is stated as "07-May-2015". As can be seen on pages 2-4 of the exhibit (in the Quality Notification Report Notification: (b) (4)) under "**Description of Event**" the following is stated in part:

"In Feb 2015, Laboratory Manager E1-YM signed a worksheet for receiving a bulk process simulation sample, reading the sample and reviewing self-generated data. The subject event was found on 07May2015 during review of a worksheet in support of an unrelated investigation. This occurrence is a direct violation of Standard Operating Procedures 22-LQA-355X Documentation of Test Information and 22-PTL-377X Second Person Review of Laboratory Documentation and investigation 200374252 was initiated.

In response to this event from May 2015 through Oct 2015, retrospective worksheet reviews for general GMP documentation errors were conducted in accordance SOP 06-QUA-125X "Investigation Procedure" and subsequently "West Point Operations – Microbiology and Sterility Assurance Investigation and Corrective/Preventive Action Operating Plan" approved on 05Jul2015 –attachment 1. During the retrospective review, it was identified that documentation review errors that have the highest risk to impact product release and/or stability decisions were associated with the laboratory manager in question (b) (6)) as well as two other individuals performing the laboratory manager review activity (b) (6) Two of the affected employees (b) (6) have already been removed from Merck employment due to the nature and extent of their GMP errors. The third employee (b) (6) was suspended from performing GMP

activities pending execution of a Performance Expectation plan and formal reinstatement. CAPA (b) (4) was initiated to document actions taken to retrain and reinstate (b) (6) and to document additional actions required to assess the ongoing effectiveness of (b) (6) in performing worksheet reviews.

West Point Operations – Microbiology and Sterility Assurance Investigation and Corrective/Preventive Action Operating Plan version 1.0 was approved on 15Oct2015 to include definitions for error categories based on risk to release and/or stability decisions – attachment 6. Retrospective data reviews were halted in Oct2015 while a risk based approach for data review was approved to ensure identification of errors that have the highest risk to product release and/or stability decisions. These errors are documented in "Investigation (b) (4) Protocol for Data Review" approved 01Dec2015 – attachment 2 (referred to as the protocol for data review). On 02Dec2015, retrospective data review restarted using the updated strategy documented in the protocol to include this risk based approach.

According to the risk based strategy, worksheets were assessed for the following category of errors: (1) The Laboratory Operations Microbiology Sterility Assurance (LOMSA) lab manager performing a primary data generation function and then reviewing the same entry as an independent second person reviewer; (2) Approving a laboratory worksheet that had an empty space for a required lab result; or (3) Reviewing and approving a laboratory worksheet with a reported test value that was outside the pre-defined test limit range or specification or critical parameter (e.g. incubation time).

Information obtained from retrospective data reviews conducted during the course of the investigation was used to assist in root cause analysis. The root cause analysis was performed via an independent team in mid Oct2015 and focused on the lab manager worksheet review process. Preliminary root cause conclusions were documented in "Justification for Continued Testing in Quality Control Laboratory Operations at West Point", approved on 11Dec2015 – attachment 3. The final root cause report is documented in "Methodology Used to Perform Root Cause and Root Cause Conclusion for Investigation for QN 200374252" approved on 04Jan2016 – attachment 4. Root cause conclusions were assessed regarding their relevance to other Quality Control Laboratories at West Point. The investigation team determined the other West Point Quality Control Laboratories were out of scope.

Additionally, in Jan and Feb 2016, the current LOMSA staff who review worksheets were evaluated to confirm the hypothesis that these other employees did not review worksheets with errors that rise to the level as the errors identified in (b) (6) and (b) (6) s work. The evaluation concluded the other LOMSA employees remained out of scope of the subject investigation.

Also, in Feb2016, during reconciliation of worksheets for reviews associated with the three subject employees, errors as defined by the protocol for data review were found in two worksheets approved by a fourth employee (b) (6). This employee was therefore

assessed via an approved protocol and determined to be an employee associated with systemic errors. All errors however, were committed prior to implementation of high priority actions taken in response to investigation (b) (4). Since initiation of these actions, no errors per the protocol for the data review were found in (b) (6) work.

All errors identified as part of the retrospective reviews were assessed for impact by Quality as per SOP 06-QUA-125AX (b) (4)" at time the error was found. The conclusion of all assessments for errors found as part of investigation (b) (4) was that there is no potential product impact.

"Investigation Operating Plan" revision 2.0 was approved on 10Dec2015 (attachment 5) and details the work streams required to close this investigation. The work streams include: (1) Retrospective review of worksheets reviewed by the subject employees of investigation (b) (4), (2) Evaluation of other LOMSA employees who perform worksheet review to confirm the hypothesis that worksheets approved by the current staff do not contain errors that rise to the level of errors found in the subject employees' work, and (3) Implementation of a compliance plan to enhance our current systems and controls to prevent recurrence. All work streams are completed as documented in the associated work stream final report.

The subject investigation was originally approved on 15Mar2016. The investigation was revised in accordance with the revision report listed as dir link (b) (4).

The following revised dir links were attached in accordance with the aforementioned revision report:
1. Investigation (b) (4) final investigation report version 0.0 is listed in dir link (b) (4). The revised Investigation (b) (4) final investigation report version 1.0 is listed in dir link 1 (b) (4).
2. (b) (4) Attachments 1 to 16 version 0.0 is listed in dir link (b) (4). Attachment 16 was revised per the subject investigation's revision report. As a result, version 1.0 which includes the updated attachment 16 is attached in dir link (b) (4).
3. (b) (4) Technical Assessment version 0.0 is listed in dir link (b) (4). Two revisions were made to this attachment as per the subject investigations revision report. The updated version 1.0 is attached in dir link – (b) (4) 1.
4. A new dir link was attached to include a complete listing of all investigation team members to include both core and support members as indicated in the investigations revision report. The investigation team list is attached in dir link (b) (4) ...."

As can be seen in Exhibit MSL20 LOMSA department duties are stated as "Responsible for executing Microbiology Testing, Environmental Monitoring Evaluations & Sample Testing, Process Simulation Evaluations, HEPA Filter Certifications & Testing and Airflow Visualization Studies."

During a discussion I had with the firm on 4-20-17 I was told that no BPDR was needed because they (the firm) assessed each event and there was no impact to the validity of the results.

B) A BPDR was not submitted with regard to QN (b) (4) . This deviation was opened due to data integrity issues in the VAQTA manufacturing area of Building (b) (4)

(MSL)

I was shown no documentation that a BPDR was submitted with regard to QN (b) (4)

Exhibit MSL21 contains Quality Notification Report Notification: (b) (4) and an Investigation Report for: Hepatitis A Purified Vaccine, Parallel Inactivated Material (b) (4) QN (b) (4) dated 15-Apr-2016. This deviation was opened due to data integrity issues in the VAQTA manufacturing area of Building (b) (4)

As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: (b) (4)) the "**Date Atypical Identified**" is stated as "19-May-2015". As can be seen on page 2 of the exhibit (in the Quality Notification Report Notification: (b) (4) under "**Description of Event**" the following is stated in part:

"On 05Mar2015, in-process contamination was identified in batch 0000461142 HepA Parallel Inactivated Purified Bulk (material (b) (4)), manufactured in Building (b) (4) Department (b) (4) . This event is investigated in Sterility Investigation SI (b) (4) (QN (b) (4)). As part of SI (b) (4) process and support activities were reviewed in detail to aid in root cause identification. This review included, but was not limited to: batch records, cleaning and equipment logs, and environmental and facility data. During review of the data associated with batch 0000461142, documentation discrepancies were identified for two process activities completed on 15Feb2015. Specifically, the documentation for a laminar flow hood (LFH) pre-use cleaning and a Microscopic and Macroscopic Observation (MO) task did not align with room entry times as evidenced by differential pressure and/or card reader data.

Following employee interviews and confirmation of the differential pressure data used to ascertain room entry times, the two documentation discrepancies were concluded to be the result of intentional document falsification. The subject investigation, QN (b) (4) was initiated on 19May2015 to evaluate the scope, root cause, and potential product impact associated with the identified document integrity events. The two bio-technicians associated with the falsified tasks were subsequently terminated on 19May2015.

The investigation scope included a review of both batch records and cleaning logs for more than (b) (4) bulk batches manufactured between October 2014 and May 2015, and

encompassed (b) (4) different employees in Department (b) (4). The review identified (b) (4) discrete occurrences of document falsification, associated with (b) (4) bio-technicians and (b) (4) bulk production batches.

The root cause for all (b) (4) document integrity (DI) events was determined through a behavioral assessment. All events were concluded to be the result of Personal Benefit Violations, enabled by a decision gap. Specifically, all (b) (4) employees involved in the events consciously falsified documentation for one of two tasks - Microscopic and Macroscopic Observations (MO) or hood cleaning. All (b) (4) employees associated with the falsification events were terminated, the first (b) (4) on (b) (4), (b) (4) on (b) (4), and (b) (4) on (b) (4). The final employee was notified later because they had been out of work on medical leave since (b) (4).

(b) (4) affected batches were discarded as a result of the above referenced Sterility Investigation, SI (b) (4) / QN (b) (4) 4. (b) (4) batches had been discarded for an unrelated event that had occurred prior to identification of either the in-process contamination of document integrity events. As such, (b) (4) batches were evaluated for product quality impact. The investigation concludes the document integrity violations had no product quality impact on the four affected batches."

Exhibit MSL22 contains a timeline of events related to both of the QNs that are the subject of this observation.

During a discussion I had with the firm on 4-27-17 Kevin Monroe, Director, West Point Quality Assurance confirmed that the firm did not file BPDRs for QN (b) (4) or QN (b) (4). He explained a gap that had existed in SOP Document Number 06-QUA-125AX entitled (b) (4)". Exhibit MSL23 contains Versions 10.0, 11.0, 12.0, and 13.0 of this SOP. I was told that Version 10.0 was in effect in May 2015 and Version 13.0 is the current version. He stated that these instances (QN (b) (4) and QN (b) (4)) occurred prior to revisions to SOP 06-QUA-125AX in November 2015 and May 2016. He stated that if these issues happened today they would be evaluated differently. I stated that when changes are made sometimes retrospective assessments of previous decisions may be necessary.

Exhibit MSL24 contains flow charts which show the differences between the regulatory notification assessment process for deviations from the June 2015 process (previous process) and the process effective as of 27-May-2016 (current process). The exhibit contains other information regarding regulatory notification assessments, including changes that were made in November 2015 and May 2016, as well. As per Mr. Monroe the gap in the June 2015 process is described in the flow chart box that states:

(b) (4)
(b) (4)".

Management voiced no objections to either part of this observation at the final closeout meeting.

11. There is a lack of rotation so that the oldest approved stock of components is used first. Specifically, there are no written procedures stating that vaccine bulk drug substance should be used (when possible) on a First In First Out or First Expired First Out basis.

(MSL)

I was shown no written procedures stating that vaccine bulk drug substance should be used (when possible) on a First In First Out or First Expired First Out basis.

As examples, Exhibit MSL25 contains charts showing the ages of the inventory of varicella and MMR bulks.

Exhibit MSL26 contains SOP Document Number: 24-PLN-189X Version 2.0 entitled (b) (4) Note on pages(b) (4) of the document under Section(b) (4) "Procedure" FIFO and/or FEFO are mentioned however this SOP does not apply to vaccine bulks such as those noted in Exhibit MSL25.

Exhibit MSL27 contains documents showing the registered drug substance storage conditions and expiry for Measles Pooled Clarified Bulk/Dispensed/Redispensed with Recombinant Human Albumin; Mumps Pooled Clarified Bulk/Dispensed/Redispensed with Human Serum Albumin; Rubella Pooled Clarified Bulk/Dispensed/Redispensed with Recombinant Human Albumin; and Varicella Bulk. As can be seen from these documents the Measles Drug Substance has an expiry of up to 12 years, the Mumps Drug Substance has an expiry of up to 12 years, the Rubella Drug Substance has an expiry of up to 12 years, and the Varicella Drug Substance has an expiry of up to 6 years.

During a discussion I had with the firm on 4-26-17 Hillary McLaughlin, Associate Director, Quality stated that dilution models cannot go in a strictly First In First Out (FIFO) manner for all products. She stated that there was no procedure explicitly stated to use the oldest bulk first when possible but that is the practice.

On 4-27-17, as a corrective action to this issue, Tara Tagmyer, Ph.D., Director, Quality Operations provided me with Quality Notification Report Notification: (b) (4) which is a CAPA to "...Update appropriate dilution model SOPs to include guidance on FIFO use of bulks when appropriate and possible for all products...." (See Exhibit MSL28). Dr. Tagmyer also stated that SOP 24-PLN-189X does not apply to vaccine bulk.

Management voiced no objections to this observation at the final closeout meeting.

12. There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed. Specifically, since December 2015 there

have been (b) documented confirmed OOS test results for pyrogen in PedvaxHIB release (the batches were rejected) or stability samples for the following batches: Batch 000344131, Batch 0000578232, and Batch 0000636946. In all (b) cases test method variability was assessed as the most likely or one of the most likely root causes. The investigations conducted as a result of the OOSs did not also consider whether method variability could create false negative (passing) results.

(MSL)

Note: Batch 000344131 stated in the observation above is incorrect and should actually be Batch 0000344131.

Since December 2015 there have been (b) documented confirmed OOS test results for pyrogen in PedvaxHIB release (the batches were rejected) or stability samples for the following batches: Batch 0000344131, Batch 0000578232, and Batch 0000636946 as documented in the following Quality Notification Reports and associated information:

Quality Notification Report Notification: (b) (4) and associated information (Exhibit MSL29)

As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: (b) (4)) the "**Date Atypical Identified**" is stated as "15-Dec-2015". As can be seen on pages 2-3 of the exhibit (in the Quality Notification Report Notification: (b) (4)) under "**Description of Event**" the following is stated in part:

"A stability sample from PedvaxHIB batch 0000344131 was Out of Specification (OOS) on 15-Dec-2015 upon completion (b) (4) pyrogen testing due to (b) (4) (b) (4) exhibiting a temperature rise of (b) (4). A maximum of (b) (4) may exhibit a temperature rise of (b) (4) in the USP test method.

(b) (4) pyrogen stability testing per the USP method in 052790168GEN for batch 0000344131 was initiated on 08-Dec-2015 in (b) (4) of the (b) (4) exhibited a temperature rise of (b) (4), not meeting the criterion that all (b) (4) must have a temperature rise of (b) (4). Therefore, expanded testing was performed in (b) (4) additional (b) (4) on 15-Dec-2015 per BLP 052790168GEN, Pyrogens. (b) (4) of the (b) (4) (b) (4) tested on 15-Dec-2015 exhibited temperature rises (b) (4) , generating the OOS result with (b) (4) total (b) (4) exhibiting a temperature rise (b) (4) .
The total temperature rise of (b) (4) for all (b) (4) met the total rise specification of (b) (4)

Batch 0000344131 was manufactured on 04-Dec-2013 and was placed on stability study to support a process change request for the use of an alternate glass supplier (b) (4) for filling of PedvaxHIB into vials at West Point, PA. All other stability test results through (b) (4) for Batch 0000344131 are in conformance. The pyrogen test results from the

previous study intervals were as follows (individual temperature increases shown in parentheses):

- (b) (4) Satisfactory; (b) (4) required ((b) (4) (b) (4))
- (b) (4) Satisfactory; (b) (4) required (b) (4)
- (b) (4) : Satisfactory; (b) (4) required (b) (4)

No definitive root cause for the OOS results of the subject batch was found in manufacturing or the testing laboratory. The most likely root cause for the subject OOS was inherent pyrogen assay variability. Animal testing is inherently sensitive as each animal used for pyrogen testing is unique. In addition, the tolerance of the temperature probes (b) (4) The magnitude of the tolerance represents (b) (4) of the maximum allowable temperature increase for each measurement (b) (4) and (b) (4) individual rabbit temperature increases that were observed above the (b) (4) temperature limit were within (b) (4) probe tolerance.
Trending was completed from 15-Dec-2014 to 10-Feb-2016 with the cause code levels of (b) (4) Product/Process and (b) (4) Laboratory Method and no filters, with no related events identified.

The subject event was the only occurrence of a pyrogen test OOS, resulting in a (b) (4) reocurrence rate, below the (b) (4) recommended for a preventive action per SOP 06-QUA-341X. Therefore, a preventive action was not assigned.

No atypical event with potential to cause the subject OOS result was identified during the investigation. Pyrogen testing was performed correctly per BLP 052790168GEN. PedvaxHIB pyrogen data from the subject batch was determined to be valid. The subject batch was manufactured and tested in a validated manner and met all critical process parameters.

A review of bulk, formulation, filling, and laboratory testing did not identify any events that would affect pyrogen results. A review of the stability data did not indicate any concerns with the subject bulk batch, the use of the (b) (4) vials or any trends with the product. A review of complaints for PedVaxHIB batches filled in 2013 and their associated package batches was performed, there were no complaints related to this OOS event.

An Adverse Event (AE) review was conducted for any adverse experience reports received through January 11, 2016 for all 2013 PedvaxHIB filled/package batches, including the subject batch. The AE review concluded that there was not enough information in the reports to determine whether or not any of the events could be related to the potential presence of pyrogenic substances from microbial contamination or other sources.

Furthermore, additional pyrogen testing (b) (4) to the current stability protocol for the subject batch as confirmation of the root cause conclusion was conducted. This testing produced conforming results in (b) (4), with a total temperature rise of (b) (4). The conforming result at the additional stability time point supports the root cause conclusion of inherent assay variability as this result is consistent with the (b) (4) (b) (4) passing pyrogen stability testing for this batch. Since the OOS result at (b) (4) (b) (4) was most likely due to overall inherent test method variability, the quality of the batch is assured. Pyrogen testing will occur as scheduled as scheduled at the final stability interval of (b) (4).

Due to the above rationale there are no indications that the OOS pyrogen result is representative of the quality of the batch."

The firm submitted BPDR Tracking Number: BPD 2016-002 (Report Confirmation #: (b) (4)) regarding this issue (See Exhibit MSL32).

Quality Notification Report Notification: (b) (4) and associated information (Exhibit MSL30)

As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: (b) (4)) the "**Date Atypical Identified**" is stated as "04-May-2016". As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification (b) (4)) under "**Description of Event**" the following is stated in part:

"PedvaxHIB product 0496110.F1BF batch 40000185824.0000578232 was Out of Specification (OOS) on 03-May-2016 upon completion of pyrogen testing due to a total temperature rise of (b) (4). Per the USP test method and 052790168GEN Pyrogens, to generate passing results in (b) (4), no more than (b) (4) may exhibit a temperature rise of (b) (4) and the sum of the (b) (4) temperature rise must be (b) (4) No definitive root cause for the OOS result of the subject batch was found in manufacturing or the testing laboratory. The most likely root cause for the subject OOS was inherent pyrogen assay and process variability.
Animal testing is inherently sensitive as each animal used for pyrogen testing is unique. In addition, the tolerance of the temperature probes (b) (4) the magnitude of which is (b) (4) of the allowable temperature increase for each measurement.

PedvaxHIB Batch 0000578232 is the only batch within scope of this investigation. For pyrogen testing, the cumulative sum of the (b) (4) temperature rise is a Critical Quality Attribute for the product.
(b) (4) and human threshold pyrogenic responses are similar; therefore, a sum of temperature rise responses that exceeds the acceptance criteria indicates that the subject batch would be likely to cause fever when injected into patients. This risk to patient safety is deemed unacceptable and Batch 0000578232 will be discarded."

Quality Notification Report Notification: (b) (4) and associated information (Exhibit MSL31)

As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: 200472099) the "**Date Atypical Identified**" is stated as "08-Nov-2016". As can be seen on page 2 of the exhibit (in the Quality Notification Report Notification: (b) (4) under "**Description of Event**" the following is stated in part:

"PedvaxHIB product (b) (4) Batch 40000210922.0000636946 was Out of Specification (OOS) on 08-Nov-2016 upon completion of pyrogen testing due to a total temperature rise of(b) (4). Per the USP test method and 052790168GEN Pyrogens, to generate passing results in (b) (4), no more than (b) (4) of the (b) (4) may exhibit a temperature rise of(b) (4) and the sum of the (b) (4) temperature rise must be (b) (4). No definitive root cause for the OOS result of the subject batch was found in manufacturing or the testing laboratory. The most likely root cause for the subject OOS was inherent pyrogen assay variability; however, process variability could not be definitively ruled out as a potential root cause for the subject event. Animal testing is inherently sensitive as each animal used for pyrogen testing is unique. In addition, the tolerance of the temperature probes (b) (4), the magnitude of which is (b) (4) of the allowable temperature increase for each measurement.

The occurrence rate is (b) (4) for the subject event. As such, a CAPA was initiated as part of this investigation in order to evaluate the PedvaxHIB sample matrix qualification to determine if the appropriate concentration and volume are being used for pyrogen testing, and determine if changes are required. Pending results of evaluation of the PedvaxHIB sample matrix qualification, additional corrective action may be required in order to evaluate alternative methods of pyrogenicity testing for PedvaxHIB batches. The need for an Effectiveness Check will be evaluated per SOP 06-QUA-341X upon completion of this CAPA.

PedvaxHIB Batch 0000636946 is the only batch within scope of this investigation. Each PedvaxHIB batch is tested for pyrogens; if the test results for a batch exceed specifications an investigation is initiated for the batch. No other OOS pyrogen test results for PedvaxHIB have occurred around the time of this event. Additionally, PedvaxHIB Batch 0000636946 was not used in downstream processing of any additional batches. The risk to patient safety is deemed unacceptable; therefore PedvaxHIB Batch 0000636946 will be reject tagged and discarded per SOP 07-QUR-201X. (reference Z4 QN (b) (4)."

As can be seen in the discussions above, in all 3 cases test method variability was assessed as the most likely or one of the most likely root causes for the OOS results.

I was not shown that any of the investigations conducted as a result of the OOSs also considered whether method variability could create false negative (passing) results.

Additionally, as of the date of the current inspection there was an open investigation for an OOS pyrogen test for PedvaxHIB Batch 0000681879 (See Exhibit MSL33 for open Quality Notification Report Notification: (b) (4) and associated information). As can be seen on page 1 of the exhibit (in the Quality Notification Report Notification: (b) (4)) the "**Date Atypical Identified**" is stated as "24-Mar-2017".

Exhibit MSL34 contains the Quality Standard for Haemophilus b Conjugate Vaccine QS Edition Date 30-APR-2016 Revision #: 33. This exhibit contains various information including specifications and Biological Laboratory Procedure Method Number: 052790168GEN.003, Method Name: Pyrogens.

During a discussion I had with the firm on 4-27-17 which included Kelley Progin, Associate Director, Engineering and David Ulmer, Associate Director, Quality, Ms. Progin stated there is a bias in the pyrogen test due to the nature of the product; there is a known amount of (b) (4) which is part of the product. I was told that they know there is endogenous endotoxin. I was told that (b) (4) is consistent with historical data. I was told that a combination of inherent bias and tightened specifications for pyrogen in the USP increase the statistical probability that they (the firm) exceed the specification for Pedvax. I was told that Document 56221-2013-MISC-0022-REV03 shows that the nature of the product is pyrogenic (See Exhibit MSL35 for a portion of this document and note Section 8.2.2.4 " (b) (4) . Mr. Ulmer stated that they will include a memo as additional information to address the open Quality Notification (QN). See pages 6-9 of Exhibit MSL33 for a memorandum dated 26-Apr-2017 with a "SUBJECT:" of "PedvaxHIB Pyrogen OOS Investigation". I did not verify if this is the memo to which he referred.

Management voiced no objections to this observation at the final closeout meeting.

13. Biological Laboratory Procedure 052650232GEN.004 entitled "Bioburden" does not require bioburden recoveries that are identified to be assessed as to whether the identified microorganisms (other than USP indicator organisms) are objectionable. This procedure applies to all bioburden testing conducted at the site.

(MSL)

Exhibit MSL36 contains Biological Laboratory Procedure Method Number: 052650232GEN.004 Method Name: "Bioburden". I was not shown that this method requires bioburden recoveries that are identified to be assessed as to whether the identified microorganisms (other than USP indicator or specified organisms) are objectionable. This procedure applies to all bioburden testing conducted at the site.

As can be seen on page 10 of Exhibit MSL36 under Section II "**Acceptance Criteria**" Subsection C "Identification Tests" the following is stated:

"**Note:**(b) (4) (b) (4)

1. Identify all representative colony types with a (b) (4), if possible. Identify all isolates.
2. If a USP indicator organism (i.e. *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Salmonella* species, *Escherichia coli*, or *Burkholderia cepacia* a specified organism) is identified from any bioburden sample, that sample will be considered unsatisfactory. Investigate according to site-specific procedures."

During a discussion I had with the firm on 4-27-17 which included Katie Ellis, Manager, Quality Control and Joseph Vido, Associate Director, Quality Control Ms. Ellis stated that BLP 052650232GEN.004 applies to all bioburden testing done on site. She stated that all representative growth in bioburden samples is identified. Ms. Ellis and Mr. Vido stated that microbial limits testing is done on raw materials. They stated that that is where objectionable organism assessment is made.

Management voiced no objections to this observation at the final closeout meeting.

14. Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, discoloration presumed to be rouging was observed on the CIP/SIP manifold located inside of the barrier (b) (4) located in Building (b) (4) Room (b) (4) during the aseptic filling of Pneumovax Batch 0000702018.

(MSL)

I made the above observation while viewing a portion of the aseptic filling of PNEUMOVAX 23 Batch 0000702018 on 4-25-17.

Exhibit MSL37 contains a photograph (taken by the firm) of the equipment that is the subject of this observation.

During a discussion I had with the firm on 4-27-17 Justin Nace, Senior Specialist, Engineering stated that they believe the discoloration is (b) (4) rouging. He stated that no analysis was done on the discoloration and there was no written evaluation of it. He agreed that the location of this discoloration is in a Grade (b) (4) area.

Management voiced no objections to this observation at the final closeout meeting.

15. Since 2015 a low bias has been observed for hepatitis A antigen content in VAQTA final container batches from the manufacturing target of (b) (4) U/mL. The corrective action involved the application of a correction factor to the Alum Adsorbed Bulk prior to final formulation. The investigation is ongoing and the root cause has not yet been identified.

(MEM)

I reviewed the current investigation into the root cause of low hepatitis A antigen in final containers of VAQTA. Current hepatitis A drug product release antigen data has been exhibiting a low bias compared to the target antigen level of (b) (4) U/mL since 2015. In order to resolve this issue in the short term the sponsor submitted a prior approval supplement for approval to introduce a revised dilution model. This was approved by CBER on March 10, 2017 under STN 103606/5826. However, the root cause for the low antigen bias had not been identified at the time of the supplement approval.

I discussed with Tim Knapp (Sr. Spclst. Engineering), William Ahlmark (Dir. Engineering), Joseph Bernardo (Assoc. Dir. Quality Control) and Irene Liao (Assoc. Dir. Engineering) the most recent investigations to determine the root cause. I reviewed a Continuing Process Report issued 29 November, 2016 (b) (4) (b) (4) (b) (4)) (Exhibit MEM-6) which covered VAQTA formulation and filling batches in (b) (4) The report found that the VAQTA filling and formulation processes were in a state of control. I also reviewed a Technical Summary ((b) (4) (b) (4) *, December 2016*) (Exhibit MEM-7). This Technical Summary described the potential root causes identified and the actions taken to investigate the potential contribution to the low antigen bias. These potential root causes included the age of the bulk used for formulation of the final product (bulk antigen results may decrease during storage prior to final formulation), bulk antigen concentration (bulk antigen measurements may only be accurate within a certain range), and formulation (variability in the formulation process could lead to lower than expected antigen levels post-dilution). The report found that antigen concentration decreases as the bulk ages but this does not account entirely for the low antigen bias. This age of the bulk was incorporated into the dilution model approved under STN 103606/5826. The report stated that further work into the other potential root causes would include evaluating samples collected directly from the alum vessels versus sub aliquoted samples, evaluation of initial sample dilution in the antigen test method (b) (4) (b) (4) and a lab scale dilution comparison to full-scale experimental formulation. A laboratory assay analysis was performed to determine if there were issues with assay 061000112GEN, this investigation did not identify an assignable laboratory root cause. I was provided with a draft Technical Protocol (*Technical Protocol for the Comparison of VAQTA Alum Adsorbed Bulk Samples* (b) (4)

and (b) (4)*, March 2017*). (Exhibit MEM-8). At the time of the inspection this had not been finalized for implementation.

16. The endotoxin in-process alert limit of (b) (4) /mL for the final retentate of each individual polysaccharide used in the Pneumovax 23 vaccine is not representative of historical data. From January 1, 2015 to April 26, 2017 the highest result obtained for any of the polysaccharides tested in this timeframe was (b) (4) /mL.

(MSL)

Exhibit MSL38 contains SOP Document Number: 01-QUA-340X Version 12.0 entitled "Authoring, Approving and Revising Annual Product Reviews".

As can be seen on page 17 of the exhibit in "ATTACHMENT A – In-Process Tests" for the "**Product Name**" "Pneumovax Recovery" "**Test Name**" (b) (4) " the "**Specification**" is stated as (b) (4) /mL". This is the endotoxin in-process alert limit (of (b) (4) /mL) for the Final Retentate of each individual polysaccharide used in PNEUMOVAX 23.

Exhibit MSL39 contains endotoxin results trend data for this sample point (and others) from 01JA2015 – 26APR2017. As can be seen from the exhibit the highest result obtained for any of the polysaccharides Final Retentates tested in this timeframe was (b) (4) (b) (4) /mL. As such, the limit is not representative of recent historical data.

During a discussion I had with the firm on 4-27-17 I was told that the (b) (4) /mL limit is an in-process alert limit.

Exhibit MSL40 contains a memo dated 31-Oct-06 with the "SUBJECT:" of "PDMA Regulatory Commitment 675-1-1 Close-out" and associated information. As can be seen on page 1 of the exhibit the memo states the following in part:

"**Summary**

During the PDMA inspection for PNEUMOVAX NP, a commitment was made by Merck and Co. to re-initiate in-process testing for bioburden and endotoxin at the Final Retentate step and bioburden at the Phenol Inactivated Broth step. In addition, a commitment was made to establish alert limits for these tests. See Attachment 1 for the written commitment.

This memo summarizes the activities which support the close-out of this commitment.

Sampling Commitment:

Change request (b) (4)) was approved and implemented on 31-Oct-2006 for the addition of the samples discussed above (Attachment 2).

Alert Limit Commitment:

A document was written and approved by Technology, Operations, and Product Release to support the selection of alert limits for these tests (Attachment 3). In addition, an automation change request was initiated to implement these alert limits in (b) (4) (Attachment 4)...."

As can be seen on page 22 of the exhibit in Attachment 3 the following is stated in part:

"...The following alert limits are recommended based on the ability of the downstream process to clear bioburden and endotoxin balanced by the intention to investigate high results and implement improvements where possible.

- Bioburden at Phenol Inactivated Broth: (b) (4) CFU/mL
- Bioburden at Final Retentate: (b) (4) CFU/mL
- Endotoxin at Final Retentate: (b) (4) EU/mL..."

Management voiced no objections to this observation at the final closeout meeting.

REFUSALS

(MSL)

We encountered no refusals during the current inspection.

GENERAL DISCUSSION WITH MANAGEMENT

(OOO)

1. The lack of the same vaccine batch numbers for complaints and the manufacturing non-conformances, especially for filled container vaccine batches with non-conformance, i.e., final container defects was discussed with the firm's management. See additional discussion in this EIR under the titled: Complaints.

2. Corrective and preventive Actions (CAPAs) are not closed in a timely manner to prevent reoccurrences. In addition, there is no specific time frame for the closures of CAPAs in the CAPA SOP. See additional discussion in this EIR under the title: Corrective and Preventive Actions (CAPAs).

3. Not all batches that failed the defect process control limits are re-inspected per the SOP, for example: vaccines batches with cracked vials and syringes are not always re-inspected.

4. Inadequate justifications for the classifications of (b) (4) of all drug products manufacturing non-conformances/deviations as (b) (4) Deviations" per the firm's Deviation SOP # 06-QUA-125X Version 16.0. For example, QN (b) (4) dated April 05, 2015 noted that on February 08 to July 20, 2016, there were (b) (4) (double filters, (b) (4) total) primary and secondary (b) (4) filters used in the harvesting of Varicella Viral Fluid that failed to meet post-use filter integrity tests specification. The filters failures affected (b) (4) harvested viral fluid batches and were classified as (b) (4) Deviation".

5. Sample vaccine unit selected for identification test are removed from the packaging line and not from the final packaged box that are inspected before the batch is released.

6. The destruction of the inspection machine, i.e. (b) (4) machine rejected vials, syringes and tubes are not documented. The firm provided a revision to an unsigned SOP and revision to one of the vaccine batch records for the documentation of the destruction of rejected vials. The compliance of the firm with the SOP should be reviewed during the next inspection of the firm.

(MSL)

I discussed the following issues with Management during the inspection and again briefly during the final closeout meeting after the issuance of the Form FDA 483.

1. Nonsterile paper batch records are used in Grade (b) (4) areas of Building (b) (4) where MMR II bulk is produced and also in a Grade (b) (4) area of Building (b) (4) where RotaTeq bulk is produced.

The firm has an ongoing Project Plan to implement the use of electronic batch records in areas of the site including these areas (See Exhibit MSL43). Mitigations to the current practice are discussed in SOP Document Number: 24-MMR-112X Version 3.0 (See Exhibit MSL44).

2. Exhibit MSL45 contains a Measles, Mumps, and Rubella Sock Seeds Overview. As can be seen on page 3 of the exhibit with regard to Mumps Stock Seed Lineage the following is stated in part:

"...SS Pool Lot 69000 Filled to Lot 86300 on 06May1980

*Current Mumps HVF Manufacturing Uses Vials of Batch 86300 Only"

As can be seen on page 13 of the exhibit (which is an excerpt from the BLA) "...FROZEN REDISPENSED STOCK SEED LOT 69000..." is referenced. During a discussion I had with the firm on 4-26-17 Victor Johnston, Senior Specialist, Engineering stated that the BLA contains an error in the redispensed lot number . He stated that it should be Lot 86300 not 69000. I stated that the firm should consider updating the BLA.

Exhibit MSL46 contains a portion of the batch record for Mumps RHA Harvested Virus Fluids Batch Number: 0000686017. As can be seen on the first page of this exhibit the following is stated in part:

"...4.18.2 Use mumps seed virus lot #69000 fill no. 86300 and inoculate based on the following formula:..."

As can be seen on the second page of the exhibit "MUMPS STOCK SEED FILL NO. 86300..." was documented as used.

I did not mention the following issue at the final closeout meeting:

1. Based on a comment I made, during the inspection the firm updated SOP Document Number: 15-QUE-214X entitled (b) (4) " from Version: 10.0 to Version: 11.0. Changes were made to with regard to HEPA filter leak testing to indicate that a leakage rate (b) (4) of the (b) (4) constitutes a failure. Version 10.0 of the SOP indicated that a leakage rate (b) (4) constituted a failure. See Exhibit MSL47 for Version: 10.0 of the SOP and Exhibit MSL48 for Version: 11.0 of the SOP.

Exhibit MSL49 contains SOP Document Number: 06-QUA-125X Version 16.0 entitled "Performing Investigations". This SOP also mentions (on page 36) HEPA filter failure events in Critical Grade (b) (4) areas but indicates that an example of an event includes HEPA filter leaks (b) (4) This SOP may need to be updated to align with SOP 15-QUE-214X Version: 11.0. I did not discuss this specific issue with the firm during the inspection.

At the end of the closeout meeting Mr. Kuhn made some final closing comments including that they will give the observations full consideration.

(MEM)

VAQTA Bioreactor Events. I discussed with April Fultz (Dir. Quality) the high number of events involving bioreactor equipment in the (b) (4) hepatitis A bulk manufacturing

facility. I was provided with an overview of the trends for bioreactor events for 2015, 2016 and 2017. There was a large increase in events in 2016 from (b) (4) in 2015 to (b) (4) in 2016. Currently in 2017 there have been (b) (4) events. These events have involved pump malfunction, bioreactor leaks, dissolved oxygen events and temperature charts. A systematic approach to resolving these issues has been established to deal with each of these areas. For bioreactor leaks SOPs have been revised with valve checks and testing. For the dissolved oxygen, glucose and lactate issues diodes have been installed to improve functionality. For the pump failures new pump heads have been installed and for the incubator charts a change request is in place to replace the (b) (4) with (b) (4) (b) (4) system, similar to that currently used in the new (b) (4) hepatitis A bulk manufacturing facility. In my further discussions with Martin Kuhn, Tim Bassler and John Schettini I informed management that although the corrective actions were appropriate the events seen in (b) (4) were associated with having an aging system. I suggested that they should either move all hepatitis A bulk manufacturing to the new suite in (b) (4) or invest in updating their equipment in (b) (4)

ADDITIONAL INFORMATION

(MSL)

Exhibit MSL16 contains a list of West Point Inter-Site Quality Agreements.

Exhibit MSL41 contains a document entitled (b) (4) (b) (4) This document also contains information regarding the ANTIVENIN.

Exhibit MSL17 contains information regarding entry requirements for various areas of the facility. In summary, in order (for a CSO) to enter all relevant manufacturing areas at the site s/he must have demonstration of immunity (b) (4), (b) (4). In order (for a CSO) to enter animal testing facilities s/he must have (b) (4).

During a discussion I had with the firm on 4-26-17 which included Todd Stamp, Director, Quality and Tara Tagmyer, Ph.D., Director, Quality Operations I was informed that an in-process Mumps Harvest batch had been confirmed contaminated the previous day. I was told that this was not via a sterility test but rather that a technician noticed an anomaly and an investigational sample was sent to the laboratory. I was told that they have changed the production schedule and won't start any new production until they have sufficient information from the investigation. I was told that the preliminary scope indicates that no marketed material is impacted but they need to finish the investigation to determine the final impact. I was told that there was no indication that they may need to shut down the facility. I was told that infected cell slurry suspension is the material

involved and that a gram negative rod was found. I was told that a supervisor saw the material as turbid and this is what started this event.

SAMPLES COLLECTED

(MSL)

We collected no samples during the current inspection.

VOLUNTARY CORRECTIONS

(MSL)

Corrective actions the firm took during the current inspection with regard to Form FDA 483 observations or discussion items I wrote for the current inspection are discussed under the observations or discussion items to which they pertain.

I followed up on the following observations from the Form FDA 483 dated 17 April 2015 that was issued as a result of the last Team Biologics inspection. My comments regarding the firm's actions related to these observations are also below.

Observation 3: Corrective actions are generally adequate however, see Observations 1A and 1E of the current Form FDA 483 for related issues. Also see my Discussion Item regarding HEPA filters.

Observation 4: Corrective actions are adequate.

Observation 7: Specific corrective actions are adequate however see Observation 10 of the current Form FDA 483 for other failures to submit BPDRs that were observed during the current inspection.

Observation 9: Specific corrective actions are adequate however see Observation 14 of the current Form FDA 483 for a different issue regarding equipment maintenance. Also, with regard to corrective actions related to Observation 9A the firm has plans to install (b) (4) devices on certain laboratory isolators but as of the date of the current inspection the installations had not yet been performed.

Observation 12: Response is adequate.

Observation 13: Corrective actions are adequate however see Observation 13 of the current form FDA 483 for an issue I observed regarding bioburden testing in general.

Observation 15: Specific corrective actions are adequate however see Observation 5 of the current Form FDA 483 for issues regarding annual reviews.

Observation 16: Corrective actions are adequate.

I also followed up on the following observations from the Form FDA 483 dated 06/26/2015 that was issued as a result of a PAI inspection. My comments regarding the firm's actions related to these observations are also below.

Observation 1: I did not follow-up on this observation, however I collected documentation regarding the firm's actions related to this observation, which are submitted as Exhibit MSL18.

Observation 2: Corrective actions are adequate.

(OOO)

Review of corrective actions CGMP inspection of April 2015:

This inspection disclosed the following observations from the CGMP inspection of 2015 have been adequately corrected:

Observation #s: 1A(iii),1B, 5A, 6A, 6B, 10B, 10C, 10D, 10E, 10F

The following Observations have not been adequately corrected:

Observation #1A and 2B, regarding the freezing and thawing of sterility samples before performing sterility test for virus vaccine samples that have been frozen for up to (b) (4) weeks and thawed for (b) (4) prior to performing sterility test was found to be inadequate. See additional discussion under Observation #3 of this EIR.

Observation #5B, 8A, 8B, 10A, 11A &11B, corrective actions of May 2016 performance qualifications into the (b) (4) vials and syringes inspection machines (b) (4) and (b) (4) was found to be inadequate. The above 2015 observations were issued as the result of Recombivax HB Adult batch # 0672446 that was recalled in June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch. See additional discussion under Observation #2 of this EIR.

Review of Corrective Actions to PAI of June 2015:

Observation #3: My review of the corrective action to the observation from the June 2015 PAI regarding labeling of containers that are not performed according to established procedures have been corrected. However, the current inspection revealed several instance of vaccine products labeling issues that could result in product mix-ups, the use of the wrong products and equipment. See additional discussion under Observation #4 of this EIR.

Review of Corrective Actions to Form FDA 483 dated 17 April 2015

(MEM)

I followed up on Form 483 Observation #14, from the previous FDA inspection with Tim Knapp (Senior Specialist, VAQTA Formulation and Filling). This observation concerned the antigen content specification for the stability of hepatitis A vaccine (VAQTA) drug product. At the time of the previous inspection the stability specification for the drug product had not been revised since the implementation of a new analytical assay for potency. The antigen content specification in use at the time (b) (4) U/mL) had not been approved by CBER for use with the new assay. A complete response letter was issued on 23 April, 2014 for a CBE 30 supplement describing a proposed, revised stability specification for drug product potency. Following the issuance of Form 483 in 2015 Merck committed to submit an amendment to CBER requesting a change to the stability expiry to bring it in line with the release specification for potency. This was completed by Merck under STN# 103606/5690 in which they requested to include an antigen content expiry specification of (b) (4) U/mL and a shelf life of 24 months for the drug product. This supplement was approved by CBER on October 13, 2015. This new stability specification is consistent with the release specification of (b) (4) mL. The issue relating to this observation has been addressed satisfactorily.

(CDZ)

The previous GMP Pharmaceutical inspection ending on 9/14/2014 resulted in the issuance of a three item FDA-483 for the following deficiencies:

1. Laboratory controls do not include determination of conformance to appropriate written specifications for the acceptance of each lot within each shipment of components and in-process materials used in the manufacture, processing, packing, or holding of drug products.

   Specifically, incoming raw materials for the manufacturing of Janumet® are not tested adequately to ensure components are free of extraneous matters for Janumet® product lines. The firm does not have adequate QC testing requirements to capture incoming raw materials are free of contaminants.

   I reviewed the firm's investigation and executive summary based on Quality notifications (b) (4) *in regards to the extraneous matter in raw materials. Corrections were verified. Product is no longer produced at the site.*

2. The use of apparatus not meeting established specifications was observed.

   Specifically, firm's routine calibration program for dissolution apparatus does not include the Performance Verification Testing (PVT), using the Prednisone calibration tablets. Dissolution apparatus is required to undergo both the mechanical calibration and PVT on a periodic basis. However, the suitability of the apparatus is demonstrated by the PVT, as indicated by the harmonized USP <711>. SOP No. 160-T-117, Calibration of Dissolution Equipment (effective 10Feb2012) and SAT #164 Dissolution (rev# 4, effective 30Oct2009) states the use of mechanical testing only for routine (b) (4) calibration.

   Corrections verified, calibration process is in agreement with FDA GFI: The Use of Mechanical Calibration of Dissolution Apparatus 1 and 2. Product is no longer produced at the site.

3. The suitability of all testing methods is not verified under actual conditions of use.

   Specifically, compendial microbiological testing methods require verification of method suitability with the manufactured product to ensure products itself do not interfere with the microbiological methods. Firm failed to perform microbiological suitability testing on replicate lots to ensure the method is suitable for detection of microbial organism. Single lot of each manufactured product was used to perform method suitability testing. Review of firm's SOP 29-MSA-102, (ver. 1.0, effective 27 Aug2014) specifies three lots of products used for microbial suitability testing.

   I reviewed SOP 29-MSA-354, (b) (4) *without objection. The firm now requires* (b) (4) *batches of product for microbial suitability testing. Corrections verified. Product is no longer produced at the site.*

EXHIBITS COLLECTED

MSL's Exhibits

MSL1. Corporate Information
MSL2. List of Recent Regulatory Agency Inspections
MSL3. Portions of Site Master File Version 7.0
MSL4. List of Major Personnel and Facility Changes
MSL5. List of Key Site Activities
MSL6. Investigational Vaccine Information
MSL7. Shipping Documents
MSL8. List of Vaccine, Antivenin, and Normal Horse Serum Batches Manufactured 01Mar2015 – 19Apr2017
MSL9. Information on the Worldwide Authorization Status of Vaccines

MSL10. Organizational Charts and Address of Kenneth C. Frazier, President & Chief Executive Officer of Merck & Co., Inc.
MSL11. Packaging Configuration and Product Filling Locations/Lines Information
MSL12. Memorandum Dated 1/16/2013
MSL13. Recall Number B-0996-14 Closeout Letter
MSL14. Memorandum Dated 21-Apr-2017
MSL15. SOP Document Number: 08-QUA-303X Version: 11.0
MSL16. List of West Point Inter-Site Quality Agreements
MSL17. SOP Containing Area Entry Requirements Information
MSL18. Information Regarding Corrective Actions to Observation 1 of the PAI Form FDA 483 Dated 06/26/2015
MSL19. Quality Notification Report Notification: (b) (4) and a Memo to the QN (b) (4) File dated 13May2016 with the subject of "Final Investigation Report – Revision 1.0[1]"
MSL20. Description of Duties of LOMSA Department
MSL21. Quality Notification Report Notification: (b) (4) and Investigation Report for: Hepatitis A Purified Vaccine, Parallel Inactivated Material 2000655 QN (b) (4) dated 15-Apr-2016
MSL22. Timeline of Events
MSL23. SOP Document Number: 06-QUA-125AX Versions 10.0, 11.0, 12.0, and 13.0
MSL24. Regulatory Notification Assessment Process for Deviations Information
MSL25. Charts Showing the Ages of the Inventory of Varicella and MMR Bulks
MSL26. SOP Document Number: 24-PLN-189X Version: 2.0
MSL27. Registered Drug Substance Storage Conditions and Expiry Information for Measles Pooled Clarified Bulk/Dispensed/Redispensed with Recombinant Human Albumin; Mumps Pooled Clarified Bulk/Dispensed/Redispensed/ with Human Serum Albumin; Rubella Pooled Clarified Bulk/Dispensed/Redispensed with Recombinant Human Albumin; and Varicella Bulk
MSL28. Quality Notification Report Notification: (b) (4)
MSL29. Quality Notification Report Notification: (b) (4) and Associated Information
MSL30. Quality Notification Report Notification: (b) (4) and Associated Information
MSL31. Quality Notification Report Notification: (b) (4) and Associated Information
MSL32. Electronic Biological Product Deviation Receipt Confirmation, Report Confirmation #: (b) (4)
MSL33. Quality Notification Report Notification: (b) (4) and Associated Information
MSL34. Quality Standard for Haemophilus b Conjugate Vaccine QS Edition Date 30-APR-2016 Revision #: 33
MSL35. Portion of Document (b) (4)
MSL36. Biological Laboratory Procedure Method Number: 052650232GEN.004
MSL37. Photograph
MSL38. SOP Document Number: 01-QUA-340X Version 12.0

MSL39. Endotoxin Results
MSL40. Memo Dated 31-Oct-2016 and Associated Information
MSL41. Document Entitled (b) (4)
(b) (4)
MSL42. Drug Shortage Information
MSL43. Project Plan Document Number: (b) (4)
MSL44. SOP Document Number: 24-MMR-112X Version: 3.0
MSL45. Measles, Mumps, and Rubella Stock Seeds Overview
MSL46. Portion of Batch Record for Mumps RHA Harvested Virus Fluids Batch Number: 0000686017
MSL47. SOP Document Number: 15-QUE-214X Version: 10.0
MSL48. SOP Document Number: 15-QUE-214X Version: 11.0
MSL49. SOP Document Number: 06-QUA-125X Version: 16.0

OOO's Exhibits

Exhibit #OOO1: Vaccine Final Containers Inspection Methods for West Point, 2 pages

Exhibit #OOO2: Total complaints received, 1 page

Exhibit #OOO3: Top (b) (4) product quality complaints, 4 pages

Exhibit #OOO4: CAPA List from March 2015- April 2017, 8 pages

Exhibit #OOO5: iQN CAPA closure timing, 1 page

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Exhibit #OOO7: List of Rotateq product quality complaints from March 2015-April 2017, 3 pages

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Exhibit #OOO9: List of BPDRs from March 2015 to April 2017, 6 pages

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Exhibit #OOO48: Validation Report TW (b) (4) , 10 pages

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Exhibit #OOO52: QN (b) (4) , 5 pages

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Exhibit #OOO70: Barrier operations sampling for batch 0000699082, 3 pages

Exhibit #OOO71: WP packaged Gardasil /MMR with date filled, manufactured, etc., 2 pages

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MEM's Exhibits

MEM-1: List of people interviewed during the inspection
MEM-2: SOP 24-LYO-325X Release Testing Sample Selection and Preparation
MEM-3: Page 37 of 43 from VAQTA Batch Record (Batch 0000629184). Barrier Operations Sampling Form
MEM-4: List of Out of Specification Results for Stability Tests from March 1, 2015 to April 18, 2017
MEM-5: BPDR 2017-005
MEM-6: (b) (4)
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(b) (4)
MEM-7: (b) (4)
(b) (4) *, December 2016*
MEM-8: (b) (4)
(b) (4), March 2017
MEM-9: List of abandoned hepatitis A bulk batches and reasons for no usage decision
MEM-10: Executive Summary from VAQTA 2016 Annual Product Review

CDZ's Exhibits

CDZ 1	Memo regarding declassification of B69/69D Pharma OPS, 1 page
CDZ 2	Table of last small molecule production lots, 1 page

ATTACHMENTS

Form FDA 482 Notice of Inspection Dated 4-18-17
Form FDA 482 Notice of Inspection Dated 4-19-17

Form FDA 483 Inspectional Observations Dated 04/28/2017

CDZ 1 FAR - Aprepitant, Lot V2437 , submitted 8/15/2014, 16 pages
CDZ 2 FAR – CELESTONE SOLUSPAN Injectable Suspension USP, Lot 073102, submitted 11/03/2014, 8 pages
CDZ 3 FAR -ELOCON Cream, Lot 5RJDA96003, submitted 12/06/2016, 6 pages
CDZ 4 FAR – NASONEX Nasal Spray, Lot 15MAA520A, submitted 11/28/2016, 6 pages
CDZ 5 FAR - ELOCON, Lot 4RJDA29001, submitted 9/28/2015, 10 pages
CDZ 6 FAR - ELOCON Cream, Lot 5RJDA04001, submitted 3/30/2016, 6 pages
CDZ 7 FAR – EMEND for Injection, Lot L911300, submitted 10/08/2015, 8 pages
CDZ 8 FAR – EMEND for Injection, Lot K022850, submitted 6/11/2015, 6 pages
CDZ 9 FAR - INVANZ, Lot 2200440, submitted 04/08/2016, 6 pages
CDZ 10 FAR – INVANZ ADD-Vantage, Lot 2171140, submitted 08/18/2015, 12 pages
CDZ 11 FAR - INVANZ ADD-Vantage, Lot 2149130, submitted 04/09/2015, 6 pages
CDZ 12 FAR - INVANZ, Lot M013569, submitted 08/02/2016, 8 pages
CDZ 13 FAR - INVANZ, Lot M031748, submitted 12/13/2016, 8 pages
CDZ 14 FAR – COSOFT PF, Lot MK13N002, submitted 09/25/2014, 12 pages
CDZ 15 FAR – LOTRISONE Cream 1%/0.05%(15g) , Lot 5-NBN-02 to 5-NBN-23, submitted 05/26/2015, 6 pages
CDZ 16 FAR – LOTRISONE Cream 1%/0.05%(15g), Lot 4NBN52, submitted 09/28/2015, 10 pages
CDZ 17 FAR –CANCIDAS I.V. 70mg, LotMCB068, submitted 11/23/2015, 6 pages
CDZ 18 FAR – CANCIDAS INFUSION 50mg, Lot 2180890, submitted 03/18/2016, 8 pages
CDZ 19 FAR – CELESTONE SOLUSPAN Injectable Solution USP, Lot 014126, submitted 11/19/2014, 8 pages
CDZ 20 FAR - CELESTONE SOLUSPAN Injectable Solution USP, Lot 085567 submitted 05/13/2016, 8 pages
CDZ 21 FAR - CELESTONE SOLUSPAN Injectable Solution USP, Lot 112698, submitted 05/12/2015, 10 pages
CDZ 22 FAR - CANCIDAS INFUSION 50mg, Lot 2186080, submitted 05/09/2017, 8 pages

Mihaly S. Ligmond -S

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
DMPTPO/OMPTO/USFDA 12420 Parklawn Drive, ELEM-2142 Rockville, MD 20857 Tel.: (301) 796-2720 Industry Information: www.fda.gov/oc/industry	04/18-28/2017
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Martin R. Kuhn, Vice President, Plant Management, Plant Manager, West Point

FIRM NAME	STREET ADDRESS
Merck Sharp & Dohme Corp.	770 Sumneytown Pike
CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-0004	Manufacturer

THIS DOCUMENT LISTS OBSERVATIONS MADE BY THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OF YOUR FACILITY. THEY ARE INSPECTIONAL OBSERVATIONS; AND DO NOT REPRESENT A FINAL AGENCY DETERMINATION REGARDING YOUR COMPLIANCE. IF YOU HAVE AN OBJECTION REGARDING AN OBSERVATION, OR HAVE IMPLEMENTED, OR PLAN TO IMPLEMENT CORRECTIVE ACTION IN RESPONSE TO AN OBSERVATION, YOU MAY DISCUSS THE OBJECTION OR ACTION WITH THE FDA REPRESENTATIVE(S) DURING THE INSPECTION OR SUBMIT THIS INFORMATION TO FDA AT THE ADDRESS ABOVE. IF YOU HAVE ANY QUESTIONS, PLEASE CONTACT FDA AT THE PHONE NUMBER AND ADDRESS ABOVE.

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

1. Written records of investigations into unexplained discrepancies of a batch or any of its components to meet specifications do not always include the conclusions and follow-up. Specifically:

Investigations are not always conducted in a timely manner into vaccines manufacturing and equipment non-conformances, and corrective and preventive actions are not always instituted in a timely manner to prevent reoccurrences. Apart from manufacturing "Events" that are not required to be documented as deviations but are documented in the batch records and are not investigated per SOP #06-QUA-125AX Version 13.0, the following documented manufacturing non-conformances/deviations since the last inspection of March 2015 were not always corrected in a timely manner. There are no documentation that formal investigations are opened and no documented justifications are provided:

A) There have been (b) (4) System Integrity/leaks non-conformances at, i.e., the (b) (4) vaccine manufacturing steps that include: (b) (4), product tanks, (b) (4), pumps, (b) (4), bioreactor, water leaking from ceilings, product containers leaking and in some cases resulted in the rejections of manufactured products.

B) There have been (b) (4) non-conformances of vials, syringe defects, i.e., low/high product fill volumes, stopper defects, cracked vials and vials seal defects. In addition, approximately (b) (4) of all BPDR submitted to the agency are vials and syringe defects related. Furthermore (b) (4) complaints were received for vials, syringes and tubes defects.

C) There have been (b) (4) particulates and foreign matters non-conformances, i.e., in filled vaccine product tubes, syringes, vials, stopper bowl, production tanks, manufacturing components and solutions.

D) There have been (b) (4) glass breakage non-conformances for, i.e., vials, syringes, glass particles found in (b) (4) freezer, several broken vials as the result of shipped vaccine batches, broken glass in lyophilizer and glass breakages in product vials and vials (b) (4).

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	O. Osunsanmi	Mihaly S. Ligmond,CSO;Omotunde O. Osunsanmi, CSO;Marian Major,Supervisory Research Microbiologist;Craig D. Zagata,CSO	04/28/2017

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E) There have been (b) (4) non-conformances for, i.e., expired equipment, manufacturing components and solutions used in the manufacture of vaccine products.

F) There have been (b) (4) VARIVAX vaccine 0.2µm filters integrity failures, including, sterilizing filters, primary and secondary filters.

G) There have been (b) (4) vaccine products related labeling non-conformances, including missing labels on syringes, laboratory samples missing labels and miss-labeled product retention samples.

H) There have been (b) (4) vaccines product related glycol leaks non-conformances, i.e., leaks from ceiling onto manufacturing areas, glycol leaks from equipment during manufacturing process.

2. Input to and output from the computer or related system of formulas or other records or data were not adequately checked for accuracy. Specifically: the validations of the (b) (4) vials inspection machines (b) (4) and (b) (4) as corrective actions to previous 2015 FDA-483 Observations 5B, 8A, 8B, 10A, 11A and 11B regarding Recombivax HB Adult batch # 0672446 that was recalled in June 2013 due to potential presence of vials heel crack defects that could impact the integrity and sterility of the vaccine product batch is inadequate. For example:

A) There is no documentation of Process Qualification study of the (b) (4) machines capabilities to detect vials heel crack defects. The Performance Qualification study TW (b) (4) dated May 18, 2016 for (b) (4) machine (b) (4) titled: (b) (4) that determined the (b) (4) machine capability for crack vials defects acceptance rate of (b) (4) is inadequate as follows:

i) The capability of the (b) (4) machines to detect vials with vials heel crack defects has not been conducted. The performance qualification for cracked vials conducted was not based on real crack defects from the recalled batch or rejected vial defects during the (b) (4) machine Performance Qualification study TW (b) (4) to determine the capability as compared to the current (b) (4) acceptance criteria for the (b) (4) machines. The qualification was conducted using (b) (4) to make a diagonal line to simulated defective cracked vials. The uses of (b) (4) (b) (4) to make a diagonal line to simulated crack vials defects have been discussed with the firm's management during previous inspections as inadequate). In addition, not all of the (b) (4) machine vials defect cameras were

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turned on during the qualification.

ii) The number of vials selected for use in the performance qualification to determine the percent capability of the (b) (4) machine to detect vials with cracked defects was not based on an acceptable statistical sampling plan. For example: Although total vials per vaccine batch ranges from (b) (4), the qualification was conducted with (b) (4) cracked vials that were created by the use of (b) (4) to make a diagonal line with approximately (b) (4) non-defective vials that were ran (b) (4) times through the (b) (4) machine.

B) Although the recall of Recombivax HB Adult batch # 0672446 was in June 2013, not all corrective and preventive actions to prevent similar reoccurrences of the 2013 vials heel crack defects have been instituted. For example:

i) The (b) (4) machines continue to reject high percentages of inspected vials in several vaccine product batches, which the firm classified as false rejects as such, these batches were not re-inspected. The high reject rates were attributed to the new cameras (b) (4) installed on the (b) (4) machine for cracked vials detection. As the result of the (b) (4) machines high vials reject rate, CAPA TW (b) (4) dated April 18, 2017 was opened to re-validate and retune the (b) (4) automated inspection machines D778 and D779. For example:

ii) Per QN (b) (4) dated January 20, 2017, the (b) (4) heel crack defects detection cameras were responsible for Gardasil:

a) Batch 0000660967 rejects of (b) (4) of the (b) (4) total vials rejected.

b) Batch 0000660980 rejects of (b) (4) of the (b) (4) total vials rejected.

c) Batch 0000662803 rejects of (b) (4) of the (b) (4) total vials rejected.

iii) There is no documentation that vial/syringe defects inspection personnel that conduct re-inspections of vials heel crack defects have been qualified to re-inspect.

iv) No actual cracked heel vials are used in the training of the vial inspection personnel. Only simulated vials are

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used.

v) SOP #17-INS-110X Version 3.0, titled: (b) (4) used in the training of the vial inspection personnel and for (b) (4) machine challenge set up did not contain photographs of examples of vials with crack heels similar to the undetected ones found in the recalled product batch.

3. The corrective actions to previous 2015 FDA-483 Observations 1A and 2B regarding the freezing and thawing of sterility samples before performing sterility testing for virus vaccine samples that have been frozen for (b) (4) weeks and thawed for (b) (4) to performing sterility test is inadequate. For example:

A) The acceptance criteria for study QUA-2016-198, dated January 19, 2017 titled: (b) (4) (b) (4), failed to include the percentages of recoveries of the <100cfu/ml inoculum per challenged organisms used for the study. The study acceptance criterion only requires that: (b) (4) (b) (4)

4. Observation #3 from the 2015 Pre-approval Inspection (PAI) regarding labeling of containers that are not performed according to established procedures has not been adequately corrected. The current inspection revealed several instance of vaccine products labeling issues that could result in product mix-up, the use of the wrong products and equipment.

5. The Quality Control Unit failed to conduct (b) (4) review of production records so that data therein can be used for evaluating the quality standards of each product to determine the need for change in product specifications, manufacturing and/or control procedure. For example:

A) Manufacturing non-conformances/deviations classified as "Event" (s) are documented in the batch records are not investigated and are not included in the review and trending of manufacturing non-conformances/deviations. For example, the following deviations during vaccine manufacturing process can be documented as event in the batch records per SOP #06-QUA-125AX, titled: (b) (4):

i) Equipment calibration expires prior to preventive maintenance because the equipment is in use.

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ii) (b) (4) filter failure when a (b) (4) filter is in place and has satisfactory results.

iii) Isolated missed routine room cleaning.

B) The Annual Product Reviews (APRs) do not reflect the status of deviations observed or remaining open for each product. The APR reports the number of deviation investigations closed for the specific APR time frame and the number of Significant deviations remaining open at the close of the review period. It does not reflect the total number of deviations opened that year or that remain open.

6. The responsibility and procedure applicable to the Quality Unit are not fully established and/or followed. Specifically, The Quality Unit oversight of the Production Unit for vials/syringe defects inspections, labeling and packaging operations are inadequate. For example:

A) Manufacturing deviations/non-conformances are not closed in timely manner and the firm failed to follow SOP #06-QUA-120X, Version 5.0 titled: (b) (4) that requires the completions and closures of manufacturing non-conformances in (b) (4) days in that (b) (4) out of (b) (4) (b) (4) of manufacturing non-conformance/deviations since the inspection of March 2015 were not closed within the deviation SOP time frame.

B) There is no documentation that the vials/syringe line clearance inspections are verified and released for use by the Quality Unit. The automated machines, i.e., (b) (4) machines line clearance are conducted by the firm's Mechanics Department personnel and the Production Unit operators and verified by a second Production Unit Operator.

C) The line clearance inspections performed by the Production Unit operators for the automated vial/syringe defects inspection machine, i.e., (b) (4) machine, and the labeling and packaging machine are inadequate. For example, there are no assurances and/or documentation that all of the required areas in the SOPs and/or that were initially inspected by the first operator were actually inspected and verified by the second Production Unit operator.

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D) There is no documentation that the labeling and packaging line clearance inspections are verified and released by the Quality Unit. The labeling and packaging line clearance inspection are conducted and verified by the production unit operators.

E) The vials and syringe samples selected from the automated inspection machines for the Acceptable Quality Limits (AQL) sampling Level II inspections are collected and inspected by the Production Unit personnel and not by the Quality Unit.

F) Although SOP #24-INS-243X Version 6.0 titled: (b) (4) (b) (4), Section 3 states as follows: "There can be no more than (b) (4) re-inspections completed for any batch", however, the SOP failed to state the maximum number of times that a vaccine batch can be inspected for vials/syringes defects and the final disposition of the subject batch.

G) Vials, syringes and tubes that are rejected during the AQL inspections are not added to the total rejects of the batch. In addition the evaluation of a batch for release is not based on the accumulative total of the defective vials culled out as the result the re-inspections of the batch.

7. Batch production and control records are not adequately prepared for each batch of production and do not include complete information relating to the production and control of each batch. For example, the batch record for labeled and packaged vials failed to include:

A) The documentation of total number of inspected vials, syringes and tubes received for labeling/packaging and total number that were labeled.

B) There is no documentation of the reasons for the rejected vials, syringes and tubes that are recorded in the batch record.

C) There is no documentation of the labels received for the labeling operations and the return of unused labels in the batch record.

8. Employees are not adequately trained in the particular area that they perform. For example:

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CITY, STATE AND ZIP CODE	TYPE OF ESTABLISHMENT INSPECTED
West Point, PA 19486-0004	Manufacturer

A) The training and qualifications of the Production Unit personnel for vials/syringe defects inspection is inadequate. Although there are (b) (4) vials/syringe defects culled out, i.e., (b) (4) machine inspection of a vaccine batch, however, the firm continues the use vials/syringe defects made from (b) (4) to make simulated defective vials/syringes for the personnel training and qualifications. Furthermore, there are no library of defects from culled out vial/syringe defects during product batch inspections for use in the training of vials and syringes inspection personnel.

9. Vaccines syringes, vials and tubes collected for retention samples for (b) (4) inspections and for complaints investigations are not representative of the released batches.

A) Retentions samples are collected after inspection by the (b) (4) machine, but before the vials, syringes and tubes labeling and packaging operations. It was noted that vials/syringes can be stored for up to (b) (4) months after inspection before labeling and packaging. For example,

i) Gardasil batch L010587, 0.5ml was inspected on November 04, 2013 and was labeled and packaged on April 06, 2015.

ii) Mumps Measles and Rubella (MMR) fill batch 0000545580 was inspected on January 22, 2016 and as of April 27, 2017 has not been labeled and packaged.

B) The documentation of the collections of product release test samples, stability and retention samples in the batch record is inadequate. There are no procedures in place that specifically explains the locations during the manufacturing process that the retentions and stability samples are collected.

10. Failure to submit a Biological Product Deviation Report. Specifically,

A) A BPDR was not submitted with regard to QN (b) (4). This deviation was opened due to data integrity issues in the (b) (4) department where sterility testing, media fill evaluation, and environmental monitoring plate reading are conducted.

SEE REVERSE OF THIS PAGE	EMPLOYEE(S) SIGNATURE	EMPLOYEE(S) NAME AND TITLE (*Print or Type*)	DATE ISSUED
	O. Osunsanmi	Mihaly S. Ligmond,CSO;Omotunde O. Osunsanmi, CSO;Marian Major,Supervisory Research Microbiologist;Craig D. Zagata,CSO	04/28/2017

DISTRICT OFFICE ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
DMPTPO/OMPTO/USFDA 12420 Parklawn Drive, ELEM-2142 Rockville, MD 20857 Tel.: (301) 796-2720 Industry Information: www.fda.gov/oc/industry	04/18-28/2017
	FEI NUMBER 2510592

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT IS ISSUED

TO: Martin R. Kuhn, Vice President, Plant Management, Plant Manager, West Point

FIRM NAME	STREET ADDRESS
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West Point, PA 19486-0004	Manufacturer

B) A BPDR was not submitted with regard to QN (b) (4) . This deviation was opened due to data integrity issues in the VAQTA manufacturing area of Building(b) (4)

11. There is a lack of rotation so that the oldest approved stock of components is used first. Specifically, there are no written procedures stating that vaccine bulk drug substance should be used (when possible) on a First In First Out or First Expired First Out basis.

12. There is a failure to thoroughly review any unexplained discrepancy whether or not the batch has been already distributed. Specifically, since December 2015 there have been (b) documented confirmed OOS test results for pyrogen in PedvaxHIB release (the batches were rejected) or stability samples for the following batches: Batch 000344131, Batch 0000578232, and Batch 0000636946. In all (b) cases test method variability was assessed as the most likely or one of the most likely root causes. The investigations conducted as a result of the OOSs did not also consider whether method variability could create false negative (passing) results.

13. Biological Laboratory Procedure 052650232GEN.004 entitled "Bioburden" does not require bioburden recoveries that are identified to be assessed as to whether the identified microorganisms (other than USP indicator organisms) are objectionable. This procedure applies to all bioburden testing conducted at the site.

14. Equipment and utensils are not maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug product. Specifically, discoloration presumed to be rouging was observed on the CIP/SIP manifold located inside of the barrier (b) (4) located in Building(b) (4) Room (b) (4) during the aseptic filling of Pneumovax Batch 0000702018.

15. Since 2015 a low bias has been observed for hepatitis A antigen content in VAQTA final container batches from the manufacturing target of(b) (4) U/mL. The corrective action involved the application of a correction factor to the Alum Adsorbed Bulk prior to final formulation. The investigation is ongoing and the root cause has not yet been identified.

16. The endotoxin in-process alert limit of(b) (4) EU/mL for the final retentate of each individual polysaccharide used in the Pneumovax 23 vaccine is not representative of historical data. From January 1, 2015 to April 26, 2017 the highest result obtained for any of the polysaccharides tested in this timeframe was (b) (4) EU/mL.

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	S. O. Osunsanmi	Mihaly S. Ligmond,CSO;Omotunde O. Osunsanmi, CSO;Marian Major,Supervisory Research Microbiologist;Craig D. Zagata,CSO	04/28/2017