September 15, 2020

Siri Glimstad
Allison Lucas, Esquire
200 Park Avenue, 17th Floor
New York, NY 10166
foia@sirillp.com

Dear Attorney Allison Lucas

The attached record(s) are being provided by the Office of Regulatory Affairs (ORA) Division of Information Disclosure Policy (DIDP) - [Freedom of Information Act (FOIA) FOIA Branch East] in response to your request **#2020-2335** for record(s) from the Food and Drug Administration pursuant to the Freedom of Information Act regarding:

MERCK COMPANY, INC, WEST POINT, PA – FIRM RESPONSE DATED 10/07/2019

Your request is granted in part.

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

- Exemption (b)(4) permits the withholding of trade secrets and commercial or financial information obtained from a person that is privileged or confidential. We have determined that portions of the enclosed records satisfy these criteria.

DIDP [FOIA Branch East] response to this request is considered closed. If you have any questions about this response, you may contact Michele Beckett at 215-717-3073 or michele.beckett@fda.hhs.gov.

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

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

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

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

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

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

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

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

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(Note: C and O type requestors are charged a $5.75 administrative fee. This fee does not apply to N type requestors.)

Sincerely

9/15/2020

X Michele Beckett

Signed by: PIV

Michele Beckett
Government Information Specialist
U.S. Food and Drug Administration
Office of Strategic Planning and Operational Policy
Division of Information Disclosure Policy
Freedom of Information Act Branch East
Michele.beckett@fda.hhs.gov

[Enclosures: WL Response]

Joseph Perez
Vice President, Vaccines Operations
West Point Plant Manager

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MERCK

07 Oct 2019

Ms. Julie Bringger
Director of Compliance Branch
Office of Biological Products Operations
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Jacksonville, FL 32202
Julie.Bringger@fda.hhs.gov

Subject: Response to Form 483 issued to Merck Sharp & Dohme Corp. (FEI Number 2510592) at West Point, PA site for inspection held 09 - 20 September 2019.

On behalf of Merck Sharp & Dohme Corp., we enclose our responses to the Form 483 issued during the referenced inspection of its manufacturing facility in West Point, Pennsylvania.

Merck is dedicated to ensuring the safety and quality of the vaccine products we supply in support of public health. To this end, we are resolute in our efforts to continuously improve the robustness and effectiveness of our facilities and quality systems as evidenced by the multiple examples shown to the Investigators of our self-identified improvement plans. We fully understand the importance of continuous improvement in all facets of cGMPs, and we are committed, at the highest levels of our management, to deliver ongoing enhancements in compliance.

We appreciate the interactions and discussions with the Investigators during their inspection of Merck West Point as we continuously learn from the input. The Form 483 issued (Attachment 1 of the enclosed response) primarily focused on investigation processes (including deviation management and complaints), cold storage practices (including monitoring of cold temperature units and our seed storage), the environmental monitoring program (including methods and monitoring practices) and laboratory practices (including reference standards and test instrument monitoring). Enclosed is a holistic response to the Form 483. We have committed to 40 actions, both specific and comprehensive -- to address the observations as well as to improve more broadly across our Quality Systems.

We are confident that these responses and actions address the observations we received. Should you require any additional information, please feel free to contact either of us directly at joseph.perez@merck.com /(215) 652-1653 or timothy_bassler@merck.com /(215) 652-6057.

Sincerely,

Joseph Perez
Vice President, Vaccines Operations
West Point Plant Manager

B. Timothy Bassler, Ph.D.
Associate Vice President
West Point Quality Operations

cc: Lynn Bottone, Vice President, Vaccines Quality
Jacks Lee, Senior Vice President, Global Vaccines Operations

Responses to FDA Form 483

Following the
Inspection of Merck Sharp & Dohme Corp.,
a Subsidiary of Merck & Co., Inc.
West Point, PA
FEI Number: 2510592

09 - 20 September 2019

07 October 2019

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Observation 1:

Failure to thoroughly investigate any unexplained discrepancy or failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. Specifically,

Pyrogen test OOS results were observed in PedvaxHIB® release batch (b) (4) and stability batch (b) (4) . Furthermore, stage1 test OOS results were observed in two additional release batches (b) (4) and (b) (4) (the latter batch OOS result was determined un-related to this observation).

PedvaxHIB® release batches (b) (4) and (b) (4) were not distributed. Stability batch (b) (4) manufactured in 2016 has unexpired doses currently on the market. A BPDR was submitted to the FDA on 06May2019.

QN 200679070 combined investigation determined no laboratory errors had occurred. The investigation further identified and determined a change in the rabbit feed regimen from 3/4/2019 to 5/8/2019 had resulted in metabolic response which led to rabbit temperature elevation causing pyrogen test to fail, thus invalidating OOS results.

Review of QN 200679070 combined investigation shows all test procedures were followed, no laboratory errors had occurred, healthy rabbits that had passed the (b) (4) (screen) test and had acceptable baseline control temperature were selected for pyrogen test. Additionally, a total of (b) (4) PedvaxHIB® batches (including (b) (4) release batches and (b) (4) stability batches) impacted by the feed regimen change between 3/4/2019 and 5/8/2019 were subject to pyrogen testing, and (b) (4) release batches and (b) (4) stability batch) out of the (b) (4) batches had observed OOS results.

Your firm invalided the OOS results based on the observed feed regimen change. However, you lack adequate justification to conclude that the feed change had caused pyrogen test to fail because only healthy rabbits that had passed the (b) (4) (screen) test and had acceptable baseline control temperature were selected for testing per SOP 29-IRT-004, "(b) (4) ", version 3.0 and Method Number (b) (4) , "Pyrogens", Method Edition Date 4/30/2016. Your firm lacked justification to invalidate pyrogen OOS results and to allow re-test.

Response 1:

We understand this observation to relate to whether the root cause we identified at the conclusion of our investigation into Quality Notification (QN) 200679070 was adequate justification for invalidating the out-of-specification (OOS) results of the pyrogen testing on PedvaxHIB® batch (b) (4) and batch (b) (4) , and for retesting the product. Merck West Point submitted Biological Process Deviation Report (BPDR) BPDR-2019-010 in connection with this event on 20Jun2019. As documented in the investigation and as detailed below, the root cause we identified, informed by a veterinary assessment and a rigorous statistical analysis, justifies the invalidation of the OOS results, the retesting of the product and, most importantly, confirmed the quality of the affected batches.

At Merck West Point, PedvaxHIB® final container samples are tested on live New Zealand White rabbits to determine whether the vaccines contain pyrogenic (fever-inducing) agents. This testing, which is governed by biological laboratory procedure (b) (4) *Pyrogens*, follows United States Pharmacopoeia (USP) Chapter <151> *Pyrogen Test*. When a pyrogenic agent is present, a rabbit will exhibit an increase

in temperature of (b) (4). During a pyrogen test, the rabbits are restrained on a table and injected with a sample of PedvaxHIB®. Their body temperatures are then monitored for (b) (4) hours and evaluated against the method specifications. Prior to each pyrogen test, rabbits are screened through both a (b) (4) test and test-day selection, to reduce the potential for a false-positive test response – a test failure due to something other than a contaminating pyrogenic agent and unrelated to the quality of the batch. The (b) (4) test and test-day selection process are explained below:

> (b) (4) Test: The (b) (4) test is a selection test designed to screen from testing rabbits temperamentally unsuited to pyrogen testing. It does not serve as an "assay control" for the pyrogen test. Test rabbits are exposed to the same conditions as in the pyrogen test itself except that they are not injected with PedvaxHIB®. They are acclimated to the room, the table, the physical restraints, and the placement of the temperature probe for a period of (b) (4) hours. A rabbit that proves overly excitable, stressed, or otherwise temperamentally unsuitable to undergo pyrogen testing is deemed to have failed the (b) (4) test and culled from the test population, as is any rabbit that exhibits either an individual temperature (b) (4) (normal range (b) (4) for purposes of this test) or an increase in temperature of (b) (4) during the (b) (4) test. The rabbits that pass the (b) (4) test may be used in pyrogen testing from (b) (4) after passing the (b) (4) test.
>
> Test-Day Selection: In addition to the (b) (4) test, each rabbit on the day of pyrogen testing must have an initial temperature between (b) (4) and its temperature may not vary by more than (b) (4) from the other rabbits' temperatures. Any rabbit which does not satisfy these criteria on the day of the test is not used in testing.

Before and during testing, the testing environment, including the ambient temperature, lighting conditions, as well as the care and feeding of the rabbits, is controlled as much as possible. For example, curtains are placed over windows in the test room, technicians do not enter the room unless it is necessary, and hallway noise is kept to a minimum. The feeding regimen is also controlled to minimize the impact of each rabbit's metabolism on its body temperature during testing, an impact which our investigation, described below, demonstrated to be significant. During initial testing, the vaccine is injected into (b) (4) rabbits, and their temperatures are monitored (b) (4) over the course of the next (b) (4). If none of the rabbits exhibits a temperature increase of (b) (4) then the test is complete, and the batch is considered free of contaminating pyrogenic agents and the test results are considered passing. If any of the rabbits exhibits an increase in temperature (b) (4) during that period, extended testing is required per procedure. Extended testing calls for (b) (4) additional rabbits to be tested. The results of extended testing are considered passing if no more than (b) (4) rabbits tested exhibit a temperature increase of (b) (4) and the cumulative temperature increase of all (b) (4) rabbits is (b) (4)

Variability in the results obtained during pyrogen testing on live rabbits is expected and may be due to one or more factors. These factors include the care and feeding of the rabbits prior to testing, the test environment in which the rabbits that continue into testing are kept, and the inherent pyrogenic nature of the PedvaxHIB® sample matrix**.** The PedvaxHIB® product matrix consists of two components: outer membrane protein complex (OMPC), derived from meningococcal bacteria, and polyribosylribitol phosphate (PRP); the two components are conjugated to form the bulk drug substance. The components are purified from gram-negative bacteria and therefore contain inherent endotoxins (pyrogenic components) that will induce an immune response. This describes a known, inherent pyrogenic response associated with PedvaxHIB® that may result in elevated temperatures in the rabbits which undergo pyrogen testing with that product, but an increase in temperature is expected to be small. The inherent pyrogenic response to PedvaxHIB® increases the sensitivity of the assay to other variables that influence the temperature response, including environment. While there is inherent variability in the testing as a result of the animal assay and the product matrix, the assay design ensures that any temperatures that drop during the testing

(b) (4)

are recorded as zeros, rather than as a negative number, in order to ensure that negative temperature changes will not affect results. Therefore, a negative temperature change would not affect a passing result.

Pyrogen Testing of Batches (b) (4) and (b) (4)

On 04Mar2019, we changed the feeding regimen for the rabbits used in pyrogen testing. Prior to that date, rabbits under Merck West Point control slated for (b) (4) or pyrogen testing received their normal feed ration up to (b) (4) before the execution of the test. The change in the feed regimen, which applied to the rabbits used in both the (b) (4) and pyrogen tests, was to provide the rabbits (b) (4) and to allow the rabbits to eat right up until a test was started. This change was made at the direction of a veterinarian on the staff of Merck Research Laboratories responsible for overseeing the care of the Merck West Point colony, in order to stimulate the rabbits' appetites, as a result of the failure to thrive of one rabbit which had recently been added to the Merck West Point rabbit colony.

From 04Mar2019 through 16Apr2019, we tested (b) (4) batches of PedvaxHIB® for pyrogens. (b) (4) of those batches tested within specification. On 16Apr2019, one OOS result was reported for PedvaxHIB® release batch (b) (4). The extended testing results reported for this batch, (b) (4) exceeded the allowable cumulative response of (b) (4) QN 200679070 was therefore initiated in accordance with our deviation management procedures. On 30Apr2019, two batches (b) (4)) underwent initial testing. These batches were not placed on extended testing, as through the course of the investigation, these batches were added to the scope of the investigation and pyrogens testing was paused. Subsequently, on 06May2019, an additional OOS result was obtained for PedvaxHIB® stability batch (b) (4). This was the first pyrogen OOS identified for this batch; the test results at all other timepoints, time zero, 6 months, 12 months, and 24 months, conformed to specifications. The extended testing result of (b) (4) exceeded the allowable cumulative response of (b) (4) At this point, the ongoing investigation found a five-fold increase in the rate of rabbits failing the (b) (4) test and an increased incidence of rabbits requiring extended pyrogen testing. As a result of the OOS results, the (b) (4) test failures, and the number of initial pyrogen tests requiring extended pyrogen testing in so short a period, we suspended (b) (4) and pyrogen testing on 07May2019. Because our investigation determined the probable root cause to be a change in the feed regimen, as described in detail below, on 08May2019, we subsequently reverted to the original feeding regimen to prepare for investigational testing.

Investigation (QN 200679070 – identified 16Apr2019) Pyrogen Failures for batches (b) (4)

All investigations related to deviations in the manufacture and testing of vaccines at Merck West Point are conducted in accordance with Merck's global deviation management procedures. These procedures require us to determine the root cause of each deviation, develop corrective and preventive actions as needed, and assess product impact. Specifically:

- GP 3.50.4 *Investigation Process and Report* requires us to document the root cause of the deviation, as well as an assessment of the impact of the deviation on the product and or relevant process.
- GP 3.50.5 *Management of Corrective and Preventive Actions (CAPAs)* governs the development of CAPAs.

As detailed in the report of our investigation into QN 200679070, and as discussed with the Investigator during the inspection, we concluded that the OOS results generated by the tests described above were the result of a change in the test rabbits' feeding regimen.

During our investigation, we hypothesized and assessed (b) (4) different possible causal categories for the OOS results. (b) (4) of these were ruled out. The (b) (4), animal husbandry practices, specifically the change in feeding regimen, was determined to be the root cause.

1. Product Sample Handling (Ruled Out) – There were no changes in how the samples were handled during the test at issue. All samples were appropriately stored, prepared, and confirmed to be integral and to have the correct product appearance prior to use.
2. Test Equipment/Components (Ruled Out) – There were no changes to the test equipment or components. All test components were within expiry, and all testing equipment was properly calibrated and free from alarms or errors.
3. Diluent Reagent (Ruled Out) – There were no changes to the preservative-free alum diluent reagent used to prepare the samples (dilution); the reagent was stored appropriately, released for use, and within expiry.
4. Testing Personnel (Ruled Out) – The analysts were trained and experienced in the pyrogen test method and in rabbit handling. No change in personnel occurred during the period in which the OOS occurred.
5. Animal Source (Ruled Out) – Two different groups of rabbits, all supplied by the same vendor, exhibited OOS test results. Statistical analysis demonstrated that the source of the OOS was not attributable to the rabbit groupings.
6. Manufacturing (Ruled Out) – Our review of the equipment, sterilization, and depyrogenation records, the environmental control data, and manufacturing deviations associated with batches (b) (4) and (b) (4) did not reveal anything that would have resulted in an OOS.
7. Animal Husbandry Practices (Including animal environment, care, and feeding - Root Cause) – As described above, the rabbits used in the pyrogen test at issue underwent a change in their feeding regimen. Following the change, a five-fold increase in the number of (b) (4) failures was observed. Additionally, there was a significant increase in the number of pyrogen tests that were required to proceed to extended testing.

Once the changes in the feeding regimen were identified, we sought to understand whether these changes could have resulted in a corresponding temperature increase in the rabbits observed during testing and if there was any empirical evidence of the impact of the change in the feeding regimen.

A Merck staff veterinarian, through documented correspondence included within the investigation, indicated that a change in the rabbits' feeding regimen may have elevated their body temperatures, as food stimulates metabolism and other physiologic processes, which lead to increased body temperature. The Merck Center for Mathematical Sciences (CMS) completed a quantitative analysis of the rabbit temperature data, which identified a statistically significant change in the rabbits' individual temperatures after the feeding regimen was changed. The difference in results between the two groups (pre and post feed change) was statistically significant, with a p-value of p(b) (4). A p-value(b) (4) indicates that the significant increase in the individual rabbit temperature responses was attributable to the change in the feed regimen.

Based upon the data obtained through the course of the investigation, the veterinary assessment, and the statistical evidence that a shift in rabbit temperatures had occurred, investigational testing was executed through a Quality-approved protocol, in accordance with our investigational procedures. Prior to initiating the investigational testing, the original feeding regimen was reinstated (i.e., the rabbits were made to fast for at least (b) (4) before being tested) on 08May2019. Between 17May2019 and 22May2019, investigational testing of t(b) (4) preparations of PedvaxHIB® stability batch (b) (4) was performed. These investigational tests showed that the rabbits did not exhibit an increase in temperature outside the specified range, which supported the conclusion, based on our investigation, the assessment of the Merck veterinarian, and Merck CMS's statistical data analysis, that the root cause was the feed change implemented on 04Mar2019.

With the investigational testing confirming the change in the feeding regimen as the root cause, in accordance with the above-referenced GPs, the OOS result for PedvaxHIB® stability batch (b) (4) was invalidated and the batch was retested in accordance with a Quality-approved protocol on 24May2019. The results of the initial retesting were within specification (all (b) (4) (b) (4) In addition, also in accordance with SOP above-referenced GPs, the OOS results for PedvaxHIB® release batch (b) (4)) were invalidated and the batch was retested in

accordance with a Quality-approved protocol on 11Jun2019. The results of the initial retesting were within specification (all (b) (4) No extended testing was required for either retested batch.

As described above, we determined the root cause of the OOS to be the change in the rabbit feeding regimen, from a controlled fast to the ability to eat food right up until testing. Rabbits which consume food up to the start of the testing were shown to have temperature increases of up to (b) (4) and lasting up to (b) (4) (b) (4). This increase would not have been detected by the (b) (4) test, as the test only removes behavioral outliers, not rabbits with shifted baselines or increased variability within the acceptance criteria from the day of the test. Furthermore, the rabbits were used in pyrogen testing between 24 hours and 7 days after the (b) (4) test and were allowed to eat up until the test initiation. As such, the increased variability would have carried into the pyrogen testing, which may or may not have been observed in the (b) (4) test, as the effects of eating is temporal.

Additional Supporting Data

During the discussion with the Investigator, we reviewed existing data to further support the feed change as the root cause of the event. This data, presented below, will be added to the report of the investigation into QN 200679070.

As illustrated below in Table 1-1. Percent of Batches Requiring Extended Testing, temperature data collected before the change in the feeding regimen was made, during the period when the change in the feeding regiment was in place, and after the feeding regimen was returned to its original state were analyzed. All samples, tested between 01Jan2018 and 03Sep2019, were evaluated for the percentage of tests that proceeded to extended testing as a result of higher individual temperatures (one or more rabbits exceeding a temperature increase of (b) (4)

Table 1-1. Percent of batches requiring extended testing

Data Set	Total Batches Tested	Batches Requiring Extended Testing (%)	Batches Requiring Extended Testing
Original Regimen (01Jan2018-03Mar2019)	(b) (4)		
Changed Regimen (04Mar2019-07May2019)			
Revert to Original Regimen (08May2019-03Sep2019)			

Figure 1-1. Cumulative Rise of Rabbit Temperature Increases For Release Batches was normalized to show (b) (4) batches completed prior to the “Changed Regimen,” (b) (4) batches completed during the “Changed Regimen,” and (b) (4) batches completed after the “Revert to Original Changed Regimen.” This allows for an equivalent data set to be evaluated. The results lead to the same conclusion demonstrated in Table 1-1, above, in that it shows that rabbits which fasted before being tested exhibited less temperature variability than those that were allowed to eat right up until the time they were tested.

Both the extended testing data and cumulative temperature increase data confirm statistically significant differences between the original feeding regimen and the changed feeding regimen. The feeding change resulted in a baseline temperature and variability increase in the rabbits, and when the original feeding regimen was reinstated, the baseline temperatures and variability returned to that observed prior to the feeding change.

(b) (4)

In conclusion, we are confident that, in accordance with our deviation management procedures, we thoroughly investigated the OOS results associated with the pyrogen testing of PedvaxHIB®. As a result of systematic root cause analysis, we identified the most likely root cause and completed investigational testing that confirmed the root cause as the feed change. Based upon investigational testing results, which confirmed root cause, we invalidated the OOS results, in accordance with our SOPs. Subsequently, we retested PedvaxHIB® release batch (b) (4) and PedvaxHIB® stability batch (b) (4) As a result of the investigation, BPDR-2019-010 was filed with the agency on 20June2019. PedvaxHIB® stability batch (b) (4) was placed on stability to support the 2016 annual requirement for PedvaxHIB® batches manufactured and is considered representative of US marketed material within expiry (36 months). A review of customer complaints and adverse events associated with PedvaxHIB® was completed, and there is no signal of product quality or patient safety issues related to the product since 01Jan2016. Although we are confident that we thoroughly investigated the issue and confirmed that there was no effect on product quality, we acknowledge that we can enhance the documentation contained within the investigation.

Actions: The following actions will be taken to address this observation.

Action 1–1: Update of QN to include the additional data included within this response.
Due Date: (b) (4)

Observation 2

Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications do not always include the conclusions and follow-up and did not extend to other vaccine bulk substances that may have been associated with the specific failure or discrepancy. Specifically,

a) Performing Investigations-Root Cause Table, Quality Notification Report #200557839, dated 29Nov2017, reported that during calibration of Pressure Indicator (PI) (b) (4) , which is located on the Clean in Place (CIP) tank (b) (4) in Building (b) (4) , it was identified that the stainless steel diaphragm of the pressure transmitter was damaged and pieces of the diaphragm were missing. Recombivax®(Hepatitis B) Bulk Product manufacturing occurs at this (b) (4) site. The CIP tank (b) (4) services Recombivax® (Hepatitis B) purification tanks: (b) (4) . (b) (4) production tanks are in the sterile barrier ((b) (4)). The final Bulk Alum Product (BAP) manufactured in (b) (4) is dispensed into bottles for long term storage. All material manufactured in the previously mentioned tanks and within expiry from dated identified, approximately (b) (4) Recombivax HB® bulk batches were in scope. BPDR 2018-003, submitted on 1/12/2018 reported an adverse event review for the affected batches was not required. An adverse event review for the affected batches was not documented in the Performing Investigations-Root Cause Table, Quality Notification Report #200557839, closed on 12Apr2018. The impact on stability for any Recombivax® (Hepatitis B) final container lots processed from the 86 Recombivax HB® bulk batches was not assessed.

b) Investigation Report, Quality Notification Report #200657572, dated 31Jan2019, (b) (4) , Dispensing Room (b) (4) Recombivax® HB, reported that residual product was held up in the vent filter line of the dispensing skid (b) (4) The biotechnician performing the testing observed what appeared to be residual product on the vent filter. The root cause of the event was a human related design issue associated with incorrect valve position coding during implantation of the Sterile Boundary upgrade in 2012. Following a common drain of (b) (4) air blow is performed. Due to an error in valve positioning, the air blow pushed residual product into the vent filter line. The Summary of Impact assessment did not include a Plant-wide scope retrospective review of vent filter contamination deviations/events and automation coding errors to identify the number of deviations/events that share a similar root cause. BPDR 2019-007, dated 3/15/2019, was reported for this event.

c) Investigation Report, QN#: 200651804, dated 07Jan2019, reported a piece of plastic was found in the chemical dosing line of the Building (b) (4)), Room (b) (4) (b) (4) during a (b) (4) gasket replacement preventive maintenance (PM #65393) under work order (WO) #2459176. The piece of plastic was found at an orifice restriction where the chemical dosing line connects back into (b) (4) recirculation line on (b) (4) Analytical identity testing concluded that the material was composed of (b) (4) The point of occurrence for this event is that part of a (b) (4) process filter casing broke, resulting in a piece of plastic entering the (b) (4) . The last Preventive Maintenance (PM) was performed on 14Dec2015 (WO 2208362). A total of (b) (4) Clarified Varicella Bulk batches, which are inputs to Varicella containing products, were manufactured in (b) (4) during 14Dec2015 and 29Dec2018. The Impact Assessment did not include rationale for why any existing stability data for any in-scope Varicella clarified bulk or finished product on Annual Product Stability was not assessed, or any medical assessment was not conducted. BPDR 2019-001 was submitted by the MSD Packaging site on 2/21/19.

Response 2:

All investigations related to deviations in the manufacture and testing of vaccines at Merck West Point are conducted in accordance with Merck's global deviation management procedures. These procedures

require us to determine the root cause of each investigation, develop corrective and preventive actions as needed, and assess product impact. Specifically:

- GP 3.50.2 *Deviation Notification and Classification* governs how to determine the scope of the investigation, considering both the type of event and the root cause.
- GP 3.50.4 *Investigation Process and Report* requires a documented decision on the following:
    - Root cause trending, across the Merck West Point site, in connection with each investigation, to determine whether the root cause identified has recurred elsewhere.
    - A determination of whether any batches in scope of the investigation should be put on stability.
    - A determination of whether a medical assessment is required when there is a product safety or contamination issue associated with batches in scope of the investigation.
- SOP CSRM-SOP-232-PV002 *Medical Assessments for MMD Quality* requires an adverse event review as part of the medical assessment if impacted batches were released to the market.
- GP 3.50.5 *Management of Corrective and Preventive Actions (CAPAs)* governs the development of CAPAs for investigations as well as how to perform (b) (4) analysis, to identify whether the CAPAs should be extended to other areas or processes at Merck West Point.
- GP 3.50.6 *Incident and Deviation Trending* requires deviations to be trended, (b) (4) across the site and (b) (4) at the departmental level, to determine whether there are systemic issues that require holistic action.

We are confident that our current procedures holistically guide us to manage each investigation appropriately. All three investigations identified in this observation, the details of which are accurately summarized, followed the procedures outlined above and concluded, with robust, scientifically sound rationales, that there was no product impact from the events. We acknowledge, however, that we could enhance our deviation management procedures, to include the following:

- Personnel will document their rationale for determining whether a medical assessment is required.
- Personnel will document their rationale for determining whether to put a batch on stability.
- Personnel will assess impact to existing stability studies (batches already on stability) and will document their rationale.

Actions: The following action(s) will be taken to address this observation.

Action 2-1: Enhance procedures to require documented rationale in the investigation report for determining whether a medical assessment is required.
Due Date: (b) (4)

Action 2-2: Enhance procedures to require documented rationale in the investigation report for determining whether to put a batch on stability.
Due Date: (b) (4)

Action 2-3: Enhance procedures to require an assessment of existing stability studies (batches already on stability) and documented rationale in the investigation report as part of the product impact assessment.
Due Date: (b) (4)

Subpart a:
Subpart (a) relates to whether an adverse event review and an impact assessment on existing stability studies should have been conducted as part of the investigation into QN 200557839. This investigation was initiated when a damaged diaphragm was identified on a pressure transmitter for clean-in-place (CIP) tank

(b) (4), resulting in the potential for stainless steel particles to be present in Recombivax HB® final containers.

As reported in BDPR 2018-003 and documented in the investigation report, the potential for (b) (4) particles introduced from the drug substance CIP skid to be present in final drug product was unlikely. In this instance, they would have been rinsed to drain during cleaning and sterilization cycles. Additionally, a medical assessment concluded that the risk of associated medical harm is extremely remote. In accordance with our procedures, the medical assessment did not include an adverse event review, as the investigation concluded that the presence of metal particles in the final drug product was unlikely. However, as a continuous improvement, deviation management procedures will be updated to specify that medical assessments for investigations associated with marketed material will require an adverse event review.

As part of our investigation, and per our procedures, we documented that there was no impact to the stability of the product within the scope of the investigation. However, we acknowledge that the investigation did not include the rationale for whether to put a batch on stability or to conduct an assessment of the impact to existing stability studies.

In alignment with the pending actions for procedural updates, we will update QN 200557839 and BPDR 2018-003.

Actions: The following action(s) will be taken to address this observation.

Action 2-4: Enhance our procedures to clarify that medical assessments for investigations associated with marketed material will require an adverse event review.
Due Date: (b) (4)

Action 2-5: Update QN 200557839 to include an adverse event review for marketed batches, the stability impact rationale, and an impact assessment to existing stability studies.
Due Date: (b) (4)

Action 2-6: Update and resubmit BPDR 2018-003 to include an adverse event review and impact to the stability of the product for marketed batches in scope.
Due Date: (b) (4)

Subpart b:
Subpart (b) relates to whether the scope of QN 200657572 was correctly determined and whether site-wide event and root-cause trending were completed. This investigation was initiated when residual product was observed on a compressed air vent filter associated with skid (b) (4).

As reported in BPDR 2019-007 and determined during our investigation:

- A valve position for the air-blow of the vent filter was coded incorrectly in the automation during implementation of the sterile boundary upgrade on 08Nov2012.
- All batches manufactured from 08Nov2012 to 31Jan2019 (date of discovery) were in scope of the investigation.
- There was no impact to product safety, purity, or potency, as the skids are product-dedicated, the validated (b) (4) cycles ensure product sterility, and any potential residual product would have been negligible.

Our completed investigation determined that the high-level cause of the event was that a valve on (b) (4) was incorrectly coded to be in an open position when it should have been coded to be in a closed position. Since (b) (4) and (b) (4) are identical skids used in the dispensing of Recombivax HB® and share the same automation code, we expanded the scope of our investigation to include both skids. The automation code is unique to (b) (4) and (b) (4) and is not shared with other systems or products at Merck West

Point; therefore, the scope of the investigation was limited to (b) (4) and (b) (4) Root-cause trending spanning (b) (4) was performed on a site-wide basis and was documented in the investigation. This activity revealed no deviations sharing the same root cause. Likewise, (b) (4) event trend reports for the Recombivax HB® manufacturing department were completed, and the trend reports did not identify any other instances of residual product deviations related to valve positioning or sequencing. Notwithstanding this observation, we are confident that the scope of the investigation was assessed appropriately across Merck West Point and included all equipment which could have been impacted by the event and root cause.

As we are confident in both the correctness of our determination of the scope of this investigation and the trending we completed, we believe no further actions are necessary with regard to subpart (b).

Subpart c:
Subpart (c) relates to whether the impact assessment associated with QN 200651804 should have included the rationale for not performing a medical assessment and should have extended to existing stability studies. This investigation was initiated when a piece of (b) (4) from our product contact filter casing was found in the chemical dosing line of the Building (b) (4) .

As reported in BPDR 2019-001 and documented in the investigation report, the potential for (b) (4) particles introduced from the drug substance (b) (4) to be present in the final drug product was extremely remote. The piece of (b) (4) was unlikely to generate particles; however, if they had been generated, the particles would have been rinsed to drain during the cleaning and sterilization cycles. For this reason, in accordance with our SOP, no medical assessment was required. However, we acknowledge that the rationale for not requesting a medical assessment was not documented in our investigation, and we will update QN 200651804 in alignment with the pending actions for procedural updates.

As part of our investigation, and per our procedures, we documented the decision of no impact to the stability of the product within the scope of the investigation. However, we acknowledge that the investigation did not include a rationale for whether to put a batch on stability or to conduct an assessment of impact to existing stability studies, and we will update QN 200651804 and BPDR 2019-001 in alignment with the pending actions for procedural updates.

Actions: The following action(s) will be taken to address this observation.

Action 2-7: Update QN 200651804 to include the stability impact rationale (determining whether to put a batch on stability), an impact assessment to existing stability studies, and rationale for the medical assessment decision.
Due Date: (b) (4)

Action 2-8: Update and resubmit BPDR 2019-001 to include impact to the stability of the product for marketed batches in scope.
Due Date: (b) (4)

Observation 3:

Deficiencies were observed in the handling of deviations in the production of VAQTA® drug substance bulk. Specifically,

a. (b) (4) recurrent deviations related to the disconnected agitator from stator during the inactivation of the hepatitis A drug substance intermediate material from June 2017 to April 2019.

i. The number of impacted drug substance batches are (b) (4) To rescue this impacted material, they were transferred to a (b) (4) tank with the (b) (4) . This additional transfer was deviated from the current licensed process; however, no impacted batches were placed on stability to ensure that there was no impact on the product quality under long-term storage.

ii. The first CAPA of updating SOP for the instructions of (b) (4) assembling was implemented in October 2017. No effectiveness study of the CAPA was performed and 8 similar deviations recurred from November 2017 to April 2018.

iii. The second CAPA of further updating the SOPs to include additional instructions on the (b) (4) and the wear of the (b) (4) were implemented in April 2018. No effectiveness study was performed after the CAPA and (b) (4) deviations recurred from July 2018 to April 2019.

b. (b) (4) recurrent deviations related to the Out-of-Process Capability Limit (OOPCL) of formaldehyde during the inactivation process of the Hepatitis A drug substance from May 2017 to December 2018.

i. The number of impacted drug substance batches were (b) (4) The firm concluded that the deviation was caused by a (b) (4) variability of the assay used for the quantitation of formaldehyde content. Therefore, the firm decided that no investigation and CAPA were needed. Based on the assay validation, the assay demonstrated a (b) (4) variability.

Response 3:

We understand this observation to be related to how recurrent deviations are handled, specifically in terms of how CAPAs are implemented and their effectiveness checked, as well as the use of an additional vessel transfer process during VAQTA® drug substance bulk manufacturing**.** We understand the importance of a robust deviation management system and are committed to performing high-quality investigations with effective CAPAs.

VAQTA® bulk processing comprises cell expansion, bioreactor processing, downstream purification, formaldehyde inactivation, sterile filtration, and alum adsorption (co-precipitation). The deviations described in observation 3 are related to the inactivation process. The key steps in the inactivation process are listed below, and a schematic diagram of the routine inactivation process and the additional transfer is shown in Figure 1:

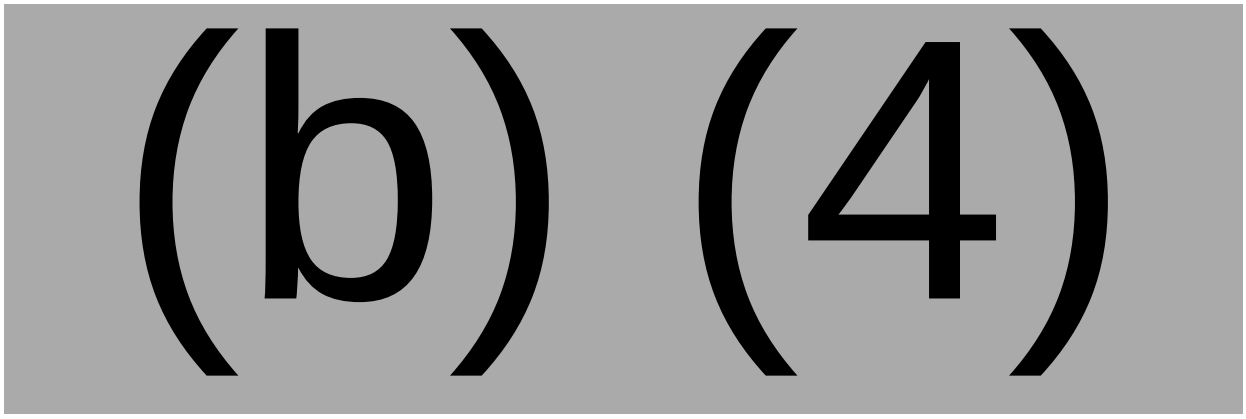
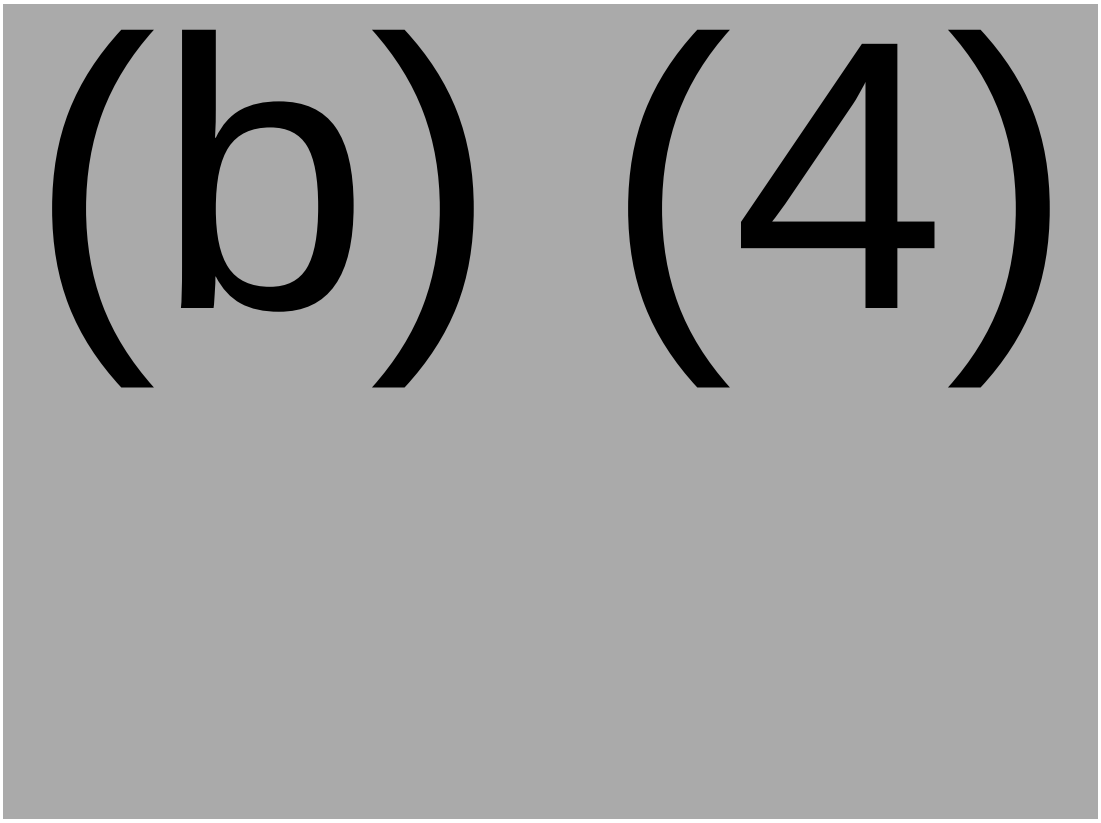


Figure1, below, depicts an example of the process flow of inactivation, including (b) (4) (b) (4)r. In this example, (b) (4) (b) (4) . This (b) (4) transfer process can also be applied in the case of agitator detachment from the mixing vessel or (b) (4) vessel.



Between May 2017 and September 2019, VAQTA® bulk was manufactured in two facilities at Merck West Point: Building (b) (4) an older facility for which Merck submitted an application for deregistration in the United States in January 2019 (STN 103606 / 5875), and Building (b) (4) a newer facility which was first approved for manufacturing in August 2015 (STN 103606 / 5763). The majority (b) (4) of the deviations referenced in this observation are related to manufacturing activities which took place in Building (b) (4) The process improvements to the VAQTA® manufacturing process made during the transition from Building (b) (4) to Building (b) (4) have markedly reduced the occurrence of these deviations. Table 1, below, shows the number of the two deviation types in each facility from 01May2017 to 20Sep2019. We will continue to implement process improvements, as necessary, to further reduce the occurrence of these deviations.

Table 1: Number of Agitator and Formaldehyde OOPCL Deviations in (b) (4) from 01May2017 to 20Sep2019

Deviation Type	Building (b) (4)	Building (b) (4)
Agitator Detachment	(b) (4)	
Formaldehyde OOPCL		

Note: Additional QN trends were run after the inspection and confirmed a total of (b) (4) agitator detachment and (b) (4) formaldehyde OOPCL deviations, respectively, as listed in Table 1. These numbers differ from the (b) (4) agitator detachment and (b) (4) formaldehyde OOPCL deviations cited in observation 3.

The responses to observation subparts 3.a.i, 3.a.ii, 3.a.iii, and 3.b.i and the corresponding actions are presented below.

Observation 3.a.i:

a. (b) (4) recurrent deviations related to the disconnected agitator from stator during the inactivation of the hepatitis A drug substance intermediate material from June 2017 to April 2019.

i. The number of impacted drug substance batches are (b) (4) To rescue this impacted material, they were transferred to a (b) (4) tank with the intact agitator. This additional transfer was deviated from the current licensed process; however, no impacted batches were placed on stability to ensure that there was no impact on the product quality under long-term storage.

Response 3.a.i:
We understand subpart 3.a.i of this observation to be related to a concern over our use of an additional transfer process when an agitator became detached and prevented us from following the established inactivation process, which is (b) (4) This additional transfer process is not described in the license and has not been demonstrated on stability.

As documented in the investigations into these deviations, conducted per SOP 06-QUA-125X *Performing Investigations* and SOP 06-QUA-125AX *Deviation Management at West Point*, none of these deviations was determined to have product quality impact. The additional transfers were carried out (b) (4) (b) (4) that are validated for VAQTA® bulk processing. The vessels that were used in the additional process were connected (b) (4) used in the filed process. Sterility is maintained by (b) (4) , and any particles of product-contact surfaces introduced by the detachment of the agitator would be removed during these filtration steps. In addition, all critical quality attributes for inactivation were met, including completeness of inactivation testing, which ensures that inactivation of the product was successful.

Notwithstanding the above discussion, we do acknowledge that the additional transfer process is not described in the VAQTA® bulk license. We will therefore initiate a change request to formally document the use of the additional transfer process. A BPDR will be filed to inform the agency of this event. We also acknowledge that a batch using this process has not been placed on stability testing. We will therefore place on stability, in accordance with an approved protocol, a VAQTA® drug substance batch manufactured pursuant to the additional transfer process.

Actions: The following action(s) will be taken to address subpart 3.a.i of this observation.

Action 3-1: File BPDR for (b) (4)
Due Date: (b) (4)

Action 3-2: Initiate the change control to enable the additional transfer during the inactivation process step in (b) (4) VAQTA® bulk facility
Due Date: (b) (4)

Action 3-3: Place on stability a drug substance batch that has executed the additional transfer during the VAQTA® inactivation step per an approved protocol.
Due Date: (b) (4)

Observation 3.a.ii and 3.a.iii:

ii. The first CAPA of updating SOP for the instructions of agitator assembling was implemented in October 2017. No effectiveness study of the CAPA was performed and (b) (4) deviations recurred from November 2017 to April 2018.

iii. The second CAPA of further updating the SOPs to include additional instructions on the pre-check of agitator and the wear of the agitator were implemented in April 2018. No effectiveness study was performed after the CAPA and (b) (4) deviations recurred from July 2018 to April 2019.

Response 3.a.ii and 3.a.iii:
We understand subparts 3.a.ii and 3.a.iii of this observation to be related to whether formal effectiveness checks were performed after certain CAPAs were implemented in October 2017 and April 2018.

We acknowledge that an effectiveness check could have been completed for actions taken to address the detachment of the agitator, per SOP 06-QUA-341X *Management of Site Internal Commitments and Corrective Action/Preventive Actions (CA/PA)*. However, the occurrence rate was reduced by the actions taken, as shown in Table 2, below. Additionally, enhancements were made to the deviation management process in September 2018 to require an effectiveness check and an approved CAPA plan for each CAPA.

The root causes of the agitator detachment events were determined to be equipment wear and incorrect assembly of the equipment. Between January 2016 and June 2017, there were zero deviations related to agitator detachment. Between June 2017 and October 2017, (b) (4) agitator detachment deviations occurred in Building (b) (4) of the agitators used), triggering a series of corrective actions. Deviations occurred after the implementation of the first CAPA in October 2017. Therefore, an additional CAPA was implemented in April 2018 to continue addressing the root causes. Table 2, below, presents a timeline of the completed actions which addressed the agitator detachments. The rate of occurrence, as defined by agitator deviations versus total number of agitators used in manufactured batches, has been sharply reduced by these actions.

Table 2: Actions taken to reduce occurrence of agitator deviations

Action Date	Action Description	Resulting Rate of Occurrence (%)
October 2017	CAPA completed to update SOP to address the incorrect assembly.	(b) (4) (25Oct2017 – 02May2018)
April 2018	CAPA completed to inspect all agitators for wear and update SOPs to incorporate the pre-use check for agitator wear	(b) (4) (02May2018 – 31Dec2018)
December 2018	Manufacturing operations ceased in the (b) (4) facility. Operations continued in the (b) (4) facility with newer equipment.	(b) (4) (01Jan2019- 09Sep2019)

To drive further improvement, an additional study was conducted in July 2019, successfully demonstrating a new (b) (4) connection between (b) (4) of the agitator assembly under TW 1010840-BBM-TR-2019 *Technical Report for Evaluation of* (b) (4) *Agitator used in VAQTA® Bulk Manufacturing, WP38, Aug-2019*. The new design allows the agitator to self-tighten during processing, in the event that the assembled agitator becomes loose. This change will be incorporated, starting on 22Jan2020, for all new inactivation vessel assemblies in Building (b) (4) VAQTA® bulk processing. Additionally, an effectiveness check will be initiated for this action, as required by SOP 08-QUA-312X *Creation, Tracking, and Closeout of Commitments (version 9.0)*

Actions: The following actions will be taken to address subpart 3.a.ii and 3.a. iii of this observation.

Action 3-4: Implement (b) (4) agitator design in all new inactivation vessel preparations in Building (b) (4) VAQTA® facility.
Due Date: (b) (4)

Observation 3.b.i:

b. (b) (4) recurrent deviations related to the Out-of-Process Capability Limit (OOPCL) of formaldehyde during the inactivation process of the Hepatitis A drug substance from May 2017 to December 2018.

i. The number of impacted drug substance batches were (b) (4) The firm concluded that the deviation was caused by a (b) (4) variability of the assay used for the quantitation of formaldehyde content.

Therefore, the firm decided that no investigation and CAPA were needed. Based on the assay validation, the assay demonstrated a (b) (4) variability.

Response 3.b.i:
We understand subpart 3.b.i of this observation to be related to the identification, between May 2017 and December 2018, of out-of-process capability limits (OOPCL) deviations concerning formaldehyde and the decisions made concerning whether investigations were required and CAPAs needed. We would like to clarify that all formaldehyde OOPCL events generated within the referenced time period were assessed per SOP 06-QUA-125X *Performing Investigations* and SOP 06-QUA-125AX *Deviation Management at West Point*. These concluded that the root cause/point of occurrence was a combination of process and assay variability. Process and assay variability can come from materials, technicians, equipment, and manual techniques employed both in the formaldehyde solution preparation and addition process and in the testing laboratory.

Formaldehyde is used to achieve completeness of viral inactivation in the VAQTA® process. While the results of the tests on these batches for formaldehyde concentration were OOPCL, all release results, including completeness of inactivation (COI) results, were nonetheless within specification, supporting no impact to product quality. Although no formal CAPAs were developed in connection with any of these deviations, there were no confirmed out-of-specification (OOS) results from testing for formaldehyde concentration. Additionally, routine continued process verification, performed according to SOP 25-BSV-108X *Preparation of Stage 3 Continued Process Verification Plans and Reports*, concluded that collectively these events did not impact product quality and required no further actions.

We acknowledge the discrepancy of the representation of formaldehyde assay variability between the investigations and assay validation. The variability of the validated formaldehyde assay is (b) (4). The (b) (4) value was identified as a variability criterion for investigational testing only and was incorrectly referenced in the investigations. Despite this inconsistency, the root cause/point of occurrence of the associated OOPCL Quality Notifications (QNs) were reassessed and remain the combination of process and assay variability.

During the transition of VAQTA® bulk manufacturing from Building (b) (4) to Building (b) (4) several enhancements were made to the manufacturing process and sample plan. These improvements included an increase in batch size, the addition of automation controls, and the elimination of a non-critical formaldehyde concentration testing point. These changes resulted in a reduced rate of occurrence of OOPCLs for formaldehyde, from 36.8% of batches manufactured in Building (b) (4) out of (b) (4)) to 2.5% of batches manufactured in Building (b) (4) out of (b) (4) batches) since May 2017. Formaldehyde concentrations will continue to be evaluated as part of routine continued process verification, as outlined in SOP 25-BSV-108X, and additional CAPAs will be implemented as appropriate.

Observation 4:

Written records of investigations for the following Product Quality Complaints (PQCs) and Adverse Event Quality Investigation Reports (QIRs) do not include the complete findings of the investigation and follow-up. Specifically,

a) Product Quality Complaint (PQC) PR ID: 223372, dated 19Feb2019, VAQTA (b) (4) reported a vial of VAQTA®-Pediatric form Package Batch N019750 was empty. Package Batch N019750 was sourced from Fill Batch (b) (4) This complaint was classified as High Risk but no regulatory statement was included in the Executive Summary, as per Document Number: 04-QUA-102X, West Point Product Quality Complaint/Adverse Event Processing, dated 23Aug2018 and Document Number: 04-QUA-300X, Performing and Documenting West Point Product Quality Complaint Investigations, dated 17Sep2018.

b) Product Quality Complaint (PQC) PR ID: 158893, dated 26Oct2017, (Pneumovax 23, (b) (4), 1 Dose Vial, FRA) reported one vial of Pneumovax®23 from Final Package Batch N025096 (Fill Batch (b) (4) was filled with only powder upon opening the carton. The nurse reportedly observed a lyophilizate and proceeded to inject physiological serum into the subject vial. The nurse did not administer the vaccine to the patient. A definite root cause could not be determined for the reported powder/malformed appearance, and user technique/manipulation was not confirmed as a root cause. Potential occurrence at the manufacturer (this site) also was not eliminated. A BPDR was not reported for this Product Quality Complaint (PQC).

c) The following AE QIRs did not include the Level of Investigation: 1, 2, or 3 as specified in SOP 04-QUA-322x, Performing Adverse Event Quality Investigations, dated 29May2019. Specifically,

i) AE QIR Parent Record: PR ID: 208791, dated 02Nov2018
ii) AE QIR Parent Record: PR ID: 228095, dated 12Mar2019
iii) AE QIR Parent Record: PR ID: 146494, dated 03Aug2017

Response 4:

We understand this observation to be concerned with the documentation associated with the regulatory assessments and reporting requirements of the investigations into two product quality complaints (PQCs) and with the reports of the investigations into three adverse event quality investigation reports (AEQIRs) which did not reflect the specified investigation levels.

We acknowledge the importance of thorough PQC and AEQIR investigations and the requirement to report appropriate deviations to the FDA in accordance with the CFR § 600.14 *Reporting of biological product deviations by licensed manufacturers*. We believe that our current procedures for PQC and AEQIR investigations are effective to ensure that thorough investigations occur. Those procedures are:

- SOP 04-QUA-102X *West Point Product Quality Complaint/Adverse Event Processing*, which requires complaints to be classified as high, medium, or low risk. High-risk complaints are those that may present risk to patient safety (e.g., missing label). Medium-risk complaints render the product unfit for use and are easily noticed by the customer (e.g., an empty vial). Low-risk complaints do not impact the usability of the product (e.g. secondary package physical damage).
- SOP 04-QUA-300X *Performing and Documenting West Point Product Quality Complaint Investigations*, which governs the performance and documentation of complaint investigations.
- SOP 04-QUA-322X *Performing Adverse Event Quality Investigations*, which governs the performance and documentation of Level 1, 2, and 3 adverse event investigations.

All high-risk PQC investigations prompt an evaluation of whether a regulatory notification is required. The decision whether a regulatory notification is required, along with the rationale for the decision, is documented in the investigation report, in accordance with the above-referenced procedures and with SOP 08-QUA-303X *Regulatory Agency Reporting for Biological Products*. Medium and low risk complaints do not require regulatory assessments under SOP 04-QUA-102X. Our current procedures that ensure the investigations are thorough and that the need for regulatory notification pursuant to CFR § 600.14 is evaluated and documented, where appropriate.

Observation 4a:

a) Product Quality Complaint (PQC) PR ID: 223372, dated 19Feb2019, VAQTA (b) (4) reported a vial of VAQTA®-Pediatric form Package Batch N019750 was empty. Package Batch N019750 was sourced from Fill Batch (b) (4) This complaint was classified as High Risk but no regulatory statement was included in the Executive Summary, as per Document Number: 04-QUA-102X, West Point Product Quality Complaint/Adverse Event Processing, dated 23Aug2018 and

Document Number: 04-QUA-300X, Performing and Documenting West Point Product Quality Complaint Investigations, dated 17Sep2018.

Response 4a:
SOP 04-QUA-102X *West Point Product Quality Complaint/Adverse Event Processing* assigns a risk level to all complaint investigations. For all complaints categorized as high risk, regulatory notification is evaluated, and the decision is documented in the complaint investigation record.

Upon receipt of a complaint, a (b) (4) record is opened in our complaint database. If several complaints related to the same product specimen are reported at the same time by the same complainant, (b) (4) record documents the risk level of each reported defect; (b) (4) is assigned the highest risk level of the reported defects. (b) (4) investigation record is then created for each of the defects reported and is investigated by the appropriate manufacturing site. The printed report for each (b) (4) investigation record includes the (b) (4) record, with the (b) (4) risk level noted, as a cover page. The risk level of the individual reported defects is not presented on the printed report for the (b) (4) record. During the inspection, the Investigator was provided the (b) (4) investigation reports that included the (b) (4) cover page.

PQC 223372 was initiated by (b) (4) in response to a complaint of one VAQTA® pediatric vial that was reported to be missing a label and empty of product. The complaint vial came from a batch that was filled at Merck West Point, secondary packaged at (b) (4), and fully distributed to (b) (4) PQC 223372 was opened as a (b) (4) record for the two issues. Two (b) (4) investigation records (223728 and 223826) were generated under the (b) (4) record, one for each issue, each of which was classified and investigated by the appropriate manufacturing site:

1. (b) (4), the secondary packaging site, investigated missing label PQC investigation (223728) as a high-risk complaint.
2. Merck West Point, the filling site, investigated empty vial PQC investigation (223826) as a medium-risk complaint.

(b) (4) evaluated the missing label complaint to determine if regulatory notification was needed and documented the decision in the executive summary of PQC investigation 223728. (b) (4) determined per SOP 8.02 *Regulatory Agency Reporting*, that no regulatory notification was needed in the distributed markets. (b) (4) report summarized the conclusions of the separate investigations conducted by (b) (4) and Merck West Point. A complaint trend confirmed that, to date, there have been no additional complaints of either empty vials or missing labels related to the batch filled at Merck West Point and the batch packaged at (b) (4). Merck West Point documented the medium-risk investigation into the empty vial in PQC investigation 223826. Because this was a medium-risk complaint, no regulatory assessment was needed per SOP 04-QUA-102X. While a regulatory assessment was not included in the executive summary of Merck West Point's investigation into medium-risk PQC 223826, a regulatory assessment was appropriately documented in the executive summary of the report of (b) (4) (b) (4) investigation into high-risk PQC 223728. Therefore, no additional actions are required.

Observation 4b:

b) Product Quality Complaint (PQC) PR ID: 158893, dated 26Oct2017, (Pneumovax 23, (b) (4) 1 Dose Vial, FRA) reported one vial of Pneumovax®23 from Final Package Batch N025096 (Fill Batch (b) (4) was filled with only powder upon opening the carton. The nurse reportedly observed a lyophilizate and proceeded to inject physiological serum into the subject vial. The nurse did not administer the vaccine to the patient. A definite root cause could not be determined for the reported powder/malformed appearance, and user technique/manipulation was not confirmed as a root cause. Potential occurrence at the manufacturer (this site) also was not eliminated. A BPDR was not reported for this Product Quality Complaint (PQC).

Response 4b:
We understand subpart (b) of this observation to be related to the root cause and regulatory notification conclusions of PQC 158893. PQC 158893 was initiated in response to a report of one Pneumovax®23 vial, belonging to package batch (b) (4) , that was reported to have a powder/lyophilizate appearance. The complaint originated from a batch that was filled at Merck West Point, packaged at (b) (4) , the (b) (4) , and fully distributed to (b) (4)

Upon examination of the returned sample, Merck West Point was not able to confirm the reported defect. The stopper had been punctured multiple times, and the customer indicated they had injected a physiological serum into the vial. While the investigation did not identify a definitive root cause, the investigation considered and eliminated all potential root causes associated with the manufacturing process:

1. Compromised container integrity, resulting in dried residue – Upon return of the complaint sample, vacuum decay testing was performed on the stoppered vial and confirmed the integrity of the vial. Therefore, the potential of product leaking or evaporating from a non-integral vial, resulting in dried residue that would appear as a powder or lyophilizate, was eliminated as a root cause.
2. Other manufacturing signals – No other signals were identified during a review of i) (b) (4) retention samples for the fill batch (b) (4) and ii) in-process statistical samples taken during filling of the batch (b) (4) . No related changes or deviations related to the fill batch were identified, and there were no other malformed appearance complaints for the fill batch.
3. Product mix in packaging –
   a. (b) (4) completed an investigation into a potential product mix and confirmed that the (b) (4) batches packaged prior to batch (b) (4) were also liquid products, not lyophilized products. Further, (b) (4) packaging includes 100% inspection of the flip cap color for each batch; flip cap color is unique to each product type. The investigation concluded that there was nothing identified at (b) (4) that could have resulted in the complaint.
   b. Upon return of the complaint sample to Merck West Point, the components were confirmed to be consistent with those used for Pneumovax®23, and the stopper in the complaint sample was confirmed to be a liquid fill stopper and not a stopper used for lyophilized products.
4. Freezing of the product outside of Merck control – Freezing of the Pneumovax23® product could have resulted in a powder/lyophilizate appearance in the vial. However, handling conditions outside of Merck's control are unable to be confirmed and the injection of serum into the vial by the complainant prevented further evaluation of this potential cause.

Because it concerned a report of malformed product appearance, this complaint was considered high risk, and the need for regulatory notification was assessed. It was determined that no BPDR was required because 1) the defect could not be substantiated from the photos or sample received, 2) the sample was manipulated by the user, 3) all potential manufacturing-related root causes were eliminated, and 4) there were no signals of additional related defects in the batch data, complaint and investigation trending, or retention samples. This regulatory assessment was documented in the supporting investigation and included in the executive summary of the lead investigation.

Based on the discussion above, we maintain the investigation conclusions are appropriate and support the assessment that no BPDR was required.

Observation 4c:

c) The following AE QIRs did not include the Level of Investigation: 1, 2, or 3 as specified in SOP 04-QUA-322x, Performing Adverse Event Quality Investigations, dated 29May2019. Specifically,

i) AE QIR Parent Record: PR ID: 208791, dated 02Nov2018

ii) AE QIR Parent Record: PR ID: 228095, dated 12Mar2019
iii) AE QIR Parent Record: PR ID: 146494, dated 03Aug2017

Response 4c:
We understand subpart (c) of this observation to be related to documentation of the investigation level in three AEQIR reports. SOP 04-QUA-322X *Performing Adverse Event Quality Investigations* requires AEQIR reports to be investigated as Level (b) (4) review), Level (b) (4) review), or Level (b) (4) review), based on the details of the event in the report. All three AEQIRs referenced in this observation were performed and documented as Level (b) (4) .

While these AEQIR reports were investigated according to our current procedures, we recognize that SOP 04-QUA-322X does not require the investigation level to be documented in the investigation report content or in the AEQIR database. Prior to the inspection, Merck had self-identified enhancements to Global Procedure (GP) 8.30.3 *Complaint Investigations*, which had been approved, but not yet implemented. GP 8.30.3 was subsequently implemented on 30Sep2019. In the updated procedure, the investigation levels and types are required to be documented in the AEQIR record.

Actions: The following action was taken to address subpart (c) of this observation:

Action 4-1: Update complaint investigation procedure GP 8.30.3, *Complaint Investigations*, to explicitly require that the investigation type (formerly investigation level) must be specified in each investigation report
Due Date: (b) (4)

Observation 5:

Monitoring and responding to excursions and alarms of controlled temperature devices is not adequate. Significant temperature excursions and communication failures are not investigated per SOP 23-38A-500, Monitoring and Addressing Excursions and Alarms of Controlled Temperature Units. There is no long-term quality control of the controlled temperature units.

a. Specifically, there were (b) (4) significant temperature excursions for freezer (b) (4) in Building (b) (4) between September 16, 2017 and September 16, 2019 that were not rated as significant and investigated accordingly.

b. Freezer (b) (4) in Building (b) (4) which contains pneumococcal Master Cell Bank (MCB), Working Cell Bank (WCB) and retain samples experienced a communication failure with Command Center from May 5 – 9, 2018. The incident was not investigated.

c. Freezer (b) (4) in Building (b) (4) was taken out of service due to a temperature deviation on August 13, 2019. Command Center was notified of the excursion, and the (b) (4) contents were moved to (b) (4) On August 19, 2019, (b) (4) was returned to service, but Command Center was not notified of the service status of the freezer. (b) (4) batch (b) (4) was placed in (b) (4) on August 22, 2019. Freezer (b) (4) temperature went out of range and warmed to room temperature on August 23, 2019. There was no response to the temperature excursion until August 26, 2019, at which point (b) (4) batch (b) (4) was removed from (b) (4) and secured in a different freezer.

Response 5:

We acknowledge the importance of proper responses to temperature excursions in controlled temperature units (CTUs) and recognize that, with respect to the events described in observation 5, we did not respond in complete accord with the relevant SOP, SOP 23-38A-500, *Monitoring and Addressing Excursions and Alarms of Controlled Temperature Units*. Moreover, although this observation was specific to freezers in

Building (b) (4) we recognize the importance of taking a holistic, site-wide approach to addressing the concern identified in this observation. We are committed to enhancing our procedures governing the real-time response, evaluation, and documentation of CTU temperature excursions.

More specifically, in response to the observation, the following actions will be taken:

- Merck West Point will conduct a site-wide assessment of our current procedures for responding to CTU alarms, to confirm that they include instructions for identifying, documenting, and remediating temperature excursions.
- Merck West Point will establish a site procedure that defines the principles governing the monitoring of CTU temperatures, the review of that temperature data, the responses to temperature excursion alarms, and the requirements necessary to ensure that all data are documented.
- Merck West Point will implement CTU temperature trend reporting, to be completed on a defined frequency, for temperature alarm response and equipment performance.

Until the holistic, site-wide approach is defined and implemented, the following near term actions will be or have been completed:

- SOP 23-38A-500 will be updated to include specific guidance concerning how to respond in real-time to alarms. An alarm response log to record (b) (4) (b) (4) will be created.
- SOP 12-38A-500A will also be updated to tag the CTU out of service and require the placement of (b) (4) on freezers to prevent storage of material during any out of service period.
- SOP 23-38A-500 was updated during the inspection to require quality personnel to conduct an (b) (4) .

Freezers (b) (4) are (b) (4) CTUs located in Building (b) (4) at Merck West Point. They are used to store master seed, working seed, purified bulk powder, and samples for the pneumococcal franchise products. Each of these CTUs is connected to the (b) (4) distributed control system, which provides real-time monitoring, recording, and storage of temperature data and generates alarms when a freezer begins to exceed its established temperature limits. The process information system enables the historical trending and review of these data.

CTU temperatures are also monitored by the (b) (4) The (b) (4) actively monitors CTUs and notifies Command Center staff when a temperature alarm is generated. The Command Center is a centrally located station at Merck West Point, handling security, emergency response, and the monitoring of critical assets such as CTUs. When a CTU temperature alarm is generated, Command Center staff notify local management of the alarm, as required by SOP 12-UTS-110X *Procedure of the Dispatch and Recording of* (b) (4) *Alarms*. If response to the temperature excursion is not already in progress according to SOP 23-38A-500, area personnel will then respond.

In addition to the monitoring systems described above, SOP 23-38A-500 requires that the temperature data of all freezers within Building (b) (4) must be reviewed (b) (4) using the process information system and recorded in electronic log 23-38A-500EL1 *PI Data Tracking Checklist eLog*. The SOP classifies excursions based upon temperature and duration and requires actions that are commensurate with each classification level. A significant temperature excursion for bulk polysaccharide powders is defined as one that lasts more than (b) (4) hours or in which the temperature deviates more than (b) (4) from the defined temperature range. Excursions must be evaluated in accordance with SOP 23-38A-500 and site deviation management procedures. In order to assess potential impact to product quality, we consider the extent and duration of the temperature excursion and supporting product technical data.

In the event that a freezer is approaching a significant temperature excursion, SOP 12-38A-500A *Defrosting Reach-In Freezers in* (b) (4) requires personnel to (b) (4) (b) (4) . Operations personnel are required to notify the Command Center staff to

(b) (4) (b) (4) ," because it is being addressed on the floor while the appropriate actions are underway. (b) (4) (b) (4) (b) (4) (b) (4) .

During the inspection, a two-year temperature trend for (b) (4) was requested by, and reviewed with, the Investigator. We identified, during our review of the trend, that there were temperature excursions that could not be immediately explained. This resulted in the initiation of two investigations, which are the subject of observations 5a and 5b. Additionally, an open investigation into a significant temperature excursion for (b) (4) was reviewed with the Investigator and is the subject of observation 5c.

With respect to subpart 5a, QN 200723353 was initiated on 17Sep2019 to investigate eleven events where a significant temperature excursion occurred in connection with (b) (4) is located in the formulation suite of Building (b) (4) and is used to store redispensed bulk (b) (4) r. Through the course of our investigation, it was determined that (b) (4) of the significant temperature excursions were due to the movement of material during routine redispensing and formulation operations. The (b) (4) remaining events were due to freezer maintenance in which the material transfer was not documented appropriately. The root cause of all (b) (4) events was improper documentation of the response to temperature excursions. Specifically, we recognize that SOP 23-38A-500 does not set forth, with an appropriate level of detail, how to document remedial actions taken when responding to temperature excursions as a result of routine operations.

As a near-term action to address the root cause, SOP 23-38A-500 and eLog 23-38A-500EL1 for (b) (4) review tracking will be updated to include the following:

- Specific guidance for real-time response and actions, including response during routine operations.
- Instructions to record temperature alarm response into the tracking log of the CTU and the associated remediation action.
- Instructions on how to respond to when excursions are identified during (b) (4) data review.

Based upon the maximum duration and temperature of these events, there is no impact to product quality. The temperature excursions for the events are supported by data from the study (b) (4) (b) (4) *06Apr2011.* The study concluded that stability of (b) (4) is not affected by exposure to temperatures (b) (4) .

With respect to subpart 5b, QN 200723324 was initiated on 17Sep2019 to investigate a gap in the data recorded for (b) (4) which could not be immediately explained. (b) (4) stores (b) (4) for the pneumococcal franchise products. During the inspection, we communicated that a planned (b) (4) shutdown had been scheduled through change request TR 498639 *Standard, Migration of Building* (b) (4) (b) (4) *System to* (b) (4) *Server, Auto*. Temperature monitoring was completed during the shutdown in accordance with TW 960103 *Technical Protocol for CTU Temperature Monitoring During May 2018 B38A Shutdown*. We would like to clarify that this resulted in an expected communication failure between (b) (4) and (b) (4) from 02May2018 to 09May2018 (not 05May2018 to 09May2018 as noted in the observation), as (b) (4) could not receive the temperature data transmitted by (b) (4) . This event was not documented in the temperature data (b) (4) review logs, which was a gap, and therefore was not immediately available during the inspection.

SOP 23-38A-500 will be updated to ensure that during the (b) (4) review of CTU temperature data, planned outages are documented in the freezer review logs. No investigation was required at the time of the event, as the freezer remained operational during the shutdown, temperature monitoring was performed pursuant to TW 960103 and the (b) (4) temperature alarm point was continuously monitored by the Command Center for the duration of the planned outage. As a result, QN 200723324 concluded that there was no

impact to the material stored in the freezer, as it was confirmed to be operating within the qualified state for the duration of the (b) (4) outage.

With respect to subpart 5c, QN 200716154 was initiated on 26Aug2019 to investigate the significant temperature excursion that occurred in connection with (b) (4) on 23Aug2019. Freezer (b) (4) is located in Building (b) (4) and is used to store (b) (4) bulk powder. The following sequence of events occurred:

- On 13Aug2019, as a result of an increasing temperature trend due to a mechanical issue, the following actions were taken:
    - The contents of (b) (4) were transferred to (b) (4), a temporary holding freezer, as required by SOP 12-38A-500A.
    - A sign designating the status of the freezer was placed on (b) (4) as required by SOP 12-38A-500A.
    - The Command Center was notified to place (b) (4) in disregard status and (b) (4) was defrosted in accordance with SOP 12-38A-500A.
- From 14Aug2019 to 19Aug2019, (b) (4) was defrosted and remained at room temperature.
- On 20Aug2019, temperature control was reestablished for (b) (4); however, the original contents of (b) (4) were not moved back to (b) (4) from (b) (4). At this time, since the contents of (b) (4) were not returned to (b) (4), the Command Center was not notified to return the temperature alarm to active status.
- On 22Aug2019, following completion of processing, (b) (4) (b) (4) batch (b) (4) was placed into (b) (4)
- On 23Aug2019, a significant temperature excursion occurred on (b) (4)
- On 26Aug2019, batch 0001014662 was transferred into (b) (4), and an investigation was initiated.

The investigation determined that the root cause of the event was a gap in SOP 12-38A-500A. The procedure instructs personnel to affix the freezer designation sign on the door of a temporary holding freezer. However, the procedure does not instruct personnel to affix a designation sign to the freezer experiencing a temperature excursion whose contents have been transferred to a temporary holding freezer. In this instance, this oversight led to the (b) (4) bulk powder being placed into (b) (4) storage on 22Aug2019, as the freezer appeared to be operational. In addition, a contributing factor was that SOP 12-38A-500A requires that the (b) (4) temperature alarm point may be returned to active status only when the original material is transferred back. Since the original material was not returned to (b) (4), the alarm point remained in disregard status. Thus, there was no response to the significant temperature excursion, as the individuals assigned to return (b) (4) to service were not aware that the (b) (4) (b) (4) batch was placed into the freezer. Operations personnel thought the freezer was still empty and in disregard status. SOP 12-38A-500A and the associated electronic log will therefore be enhanced to include:

- An instruction to place (b) (4) locks on empty freezers that are not actively monitored, to prevent material from being stored in them.
- An instruction to tag the equipment out of service affected by a temperature excursion to visually indicate the status of the freezer.
- An instruction to place the (b) (4) alarm point, from disregard, back to active status when the freezer is back to the operational temperature range, regardless of when the material is returned to the freezer.

At the time of the significant temperature excursion, (b) (4) batch (b) (4) was the only batch in (b) (4) and was restricted from use by quality on 03Sep2019. Disposition of the affected batch will be determined upon completion of the investigation.

Actions: The following action(s) will be taken to address this observation:

Action 5-1: Perform site-wide assessment of CTU alarm procedures to confirm instructions are included for identifying, documenting, and remediating temperature excursions.
Due Date: (b) (4)

Action 5-2: Develop a procedure for Merck West Point that defines principles for CTU temperature monitoring, data review, alarm response, and documentation requirements.
Due Date: (b) (4)

Action 5-3: Implement CTU temperature trend reporting for Merck West Point CTUs used for cold storage of material intended for commercial use. Trending will be completed on a defined frequency and will include a review of temperature alarm response and equipment performance.
Due Date: 30Apr2020

Action 5-4: As an immediate action taken during the inspection, SOP 23-38A-500 was updated to include a (b) (4) Quality check of the data review.
Due Date: (b) (4)

Action 5-5: Update 23-38A-500 *Monitoring and Addressing Excursions and Alarms of Controlled Temperature Units* and 23-38A-500EL1 *PI Data Tracking Checklist eLog* to enhance real-time temperature excursion response, documentation of planned outages, and weekly monitoring instructions.
Due Date: (b) (4)

Action 5-6: Update SOP 12-38A-500A (b) (4) to include instructions on tagging out-of-service CTUs and on the placement of (b) (4) locks on freezers to prevent storage of material. In addition, instructions will be added to place the (b) (4) alarm point back to active status when the freezer is back to the operational temperature range, regardless of when the material is returned to the freezer.
Due Date: (b) (4)

Observation 6:

Freezers containing MCB, WCB, Master Seed, Viral Seed, and in-process material are not appropriately organized or secured.

a. Freezer (b) (4) in Building (b) (4) contains (b) (4). Other material such as (b) (4), retain samples and "CBER box 1 and 2 are also stored in this freezer. The technician was not able to locate designated items from shelf (b) (4) in a timely manner.

b. Logbook 21-38A-402-F1-0005 for freezer (b) (4) is a paper binder with entries that do not indicate where they are located in the freezer, and there is no electronic back-up. Additionally, the contents of freezer (b) (4) are not accurately documented in the logbook.

c. Freezer (b) (4) in Building (b) (4) contains pneumococcal Master Cell Bank (MCB), Working Cell Bank (WCB) and retain samples that are not segregated.

d. Freezer (b) (4) in Building (b) (4) contains pneumococcal MCB, WCB and retain samples that are not segregated.

e. Keyed access to freezers containing MCB is available to (b) (4) badge holders in Building (b) (4) and (b) (4) badge holders in Building (b) (4) Additionally, the lock box in Building (b) (4) is in a (b) (4) room but is not locked.

f. The HPV Type 6 Master Seed, HPV Type 6 Working Seed, and HPV Type 6 Intermediate Frozen Cell Slurry are stored in Building (b) (4) °C Walk-In Freezer (b) (4), ((b) (4) °C, (b) (4) , "(b) (4) "), (b) (4) . The HPV Type 6 Master and HPV Type 6 Working Seed are not stored separately from the HPV Type 6 Intermediate Frozen Cell Slurry.

g. The HPV Master Seed in Freezer (b) (4) inventory paper logbook does not include what box of the Master Seed Container HPV Type 6 Master Seed containers ((b) (4) are stored. The inventory log sheets only specify that for HPV Type 6 Master Seed there are approximately (b) (4) Master Seed vials of HPV Type 6 Master Seed #(b) (4) in Building (b) (4) ", but not the actual box/container identity. HPV Type 6 Master Seed can be stored in more than one container in the (b) (4) °C (b) (4) . Master Seed Lots (Types (b) (4)) are stored in separate boxes in a Master Seed (b) (4) container but there is no classification of a unique box # for each Master Seed Type. Only the Master Seed Type and Lot# is listed on the box label. Master Seed Types can be stored in multiple boxes.

h. The SAP Inventory Management Tracking system for Building (b) (4) °C Walk-In Freezer (b) (4) ") does not include the shelf location of the HPV Type 6 Master Seed lot(s), HPV Type 6 Viral Seed lot(s), and intermediate HPV Type 6 frozen cell slurry lots.

i. The SAP tracking system for HPV Type 6 Master Seed (Lot (b) (4) does not correlate to actual itemized number of containers (vials) in the paper-based inventory log sheets. Only the quantity, (b) (4) mL, of the Master Seed Lot, Lot (b) (4) is listed.

j. The SAP tracking system for Mumps stock seeds (Lot (b) (4) is recorded as double entries of a total of (b) (4) L and does not accurately reflect the (b) (4) vials ((b) (4) mL) kept in freezer (b) (4) in Building (b) (4)

Response 6:

This observation identifies concerns with how we organize and secure our master cell bank (MCB), working cell bank (WCB), master seed, viral seed, and in-process materials. Specifically, subparts a, b, h, i, and j concern how we document our inventory of these materials; subparts c, d, and f concern how we segregate these materials; subpart g concerns both how we document our inventory of and segregate these materials; and subpart e concerns how we control access to these materials. We understand the fundamental importance of these concerns and, while remaining confident in the level of organization, inventory documentation, and security currently afforded these materials, we acknowledge that our existing procedures could be enhanced.

Background

With respect to this observation and response, the following will provide context to the definition to the material listed within this observation:

- Master (seed or cell bank) – is the starting material (or input) for stock or working material. This material is used less often than all other material in the manufacturing process.

- Working (seed or cell bank) – expanded material made from the master material, which is subsequently used in routine drug substance manufacturing. This material is used with greater frequency than the master material ((b) (4) per drug substance lot).
- In-process – can refer to the (b) (4) , (b) (4) manufacturing.

SOP 21-FRZ-343X *West Point Vaccine Seed and Cell Bank Management* governs how seed and cell banks are manufactured and stored at Merck West Point. The SOP requires seed and cell bank material to be (b) (4) . However, there is no defined segregation guidance regarding material segregation by type (seed, cell bank, in-process, etc.). All seed and cell bank inventory stored at Merck MMD West Point is tracked and accounted for within (b) (4), our electronic inventory management system. However, inventory quantities may reflect only the total aggregate quantity, not the number of units. Inventory control down to the unit level (b) (4) is tracked, however, either in (b) (4) . The locations of all materials are confirmed and tracked through (b) (4). SOP 21-FIN-103X *Inventory Control Procedures* and (b) (4) SOP 21.03 *Physical Inventory Cycle Counts* govern inventory control, but not always to the unit level. The referenced procedures require that a physical inventory of all material (including seed and master cell banks) tracked within (b) (4) be conducted at least (b) (4) . SOP 14-SPR-106X *Restricted Area Access Control* governs personnel access to freezers in which seed and cell banks are stored. All requests for access must be made using (b) (4) . (b) (4) station at Merck West Point, handling security, emergency response, and the monitoring of critical assets, which grants (b) (4) to the area.

Response

With respect to the specific concerns with how we document our inventory of MCB, WCB, master seed, viral seed, and in-process materials (subparts a, b, h, i and j), directions for how to store these materials are contained in the individual product batch records and/or local SOPs. In these records, the storage location within the freezer is identified, but the records do not indicate the level of specificity highlighted in the observation, such as identifying the freezer, freezer sub-section, and shelf. We acknowledge that directions could be updated to enhance the level of specificity. We also acknowledge that our recordkeeping, whether paper or electronic, could be updated to enable personnel to locate and retrieve materials in a prompt manner. Improvements to the specificity of our recordkeeping will be addressed as part of the holistic review discussed below.

With respect to the specific concerns regarding how we segregate the materials discussed (subparts c, d, f and g), SOP 21-FRZ-343X currently does not specify how these materials must be segregated within freezers. We agree that the SOP could be updated with guiding principles regarding material segregation. We will update the SOP to include segregation principles which will specify how these materials are to be stored and segregated within freezers.

With respect to concerns regarding access to these materials discussed (subpart e), the personnel identified in the observation as having access to MCB in Building (b) (4) and Building (b) (4) were granted such access pursuant to SOP 14-SPR-106X. As an immediate action, we have limited access to only those personnel who require routine access to perform their job responsibilities. With respect to the lock box, we wish to clarify that there is no lock box in Building (b) (4) We believe that the lock box mentioned in the observation is in fact in Building (b) (4) The lock box in Building (b) (4) has been locked and the key has been retained by Operations management, who will provide access only to those who require it. We will update the procedure to require that access to freezers is periodically reviewed and provide guidance for further procedural controls and guidance regarding key control and access through the holistic plan described below.

In addition to the specific actions noted above, we will comprehensively address the issues identified within this observation through development of a holistic plan to include enhanced elements of inventory documentation; segregation of the materials, discussed; and controlled access across all freezers containing MCB, WCB, master seed, viral seed, and in-process material.

Actions: The following action(s) will be taken to address this observation:

Action 6-1: Access revocation for Building(b) (4) and Building(b) (4)
Due Date: (b) (4)

Action 6-2: Key removal and retention.
Due Date: (b) (4)

Action 6-3: SOP 21-FRZ-343X *West Point Vaccine Seed and Cell Bank Management* will be updated to add clarity when performing the appropriate storage and segregation of MCB, WCB, master seed, viral seed, and in-process material.
Due Date: (b) (4)

Action 6-4: Approved project plan to incorporate organization, enhanced principles around security, inventory management consistency and resolution and a segregation strategy for MCB, WCB, master seed, viral seed, and in-process material stored in freezers.
Due Date: (b) (4)

Observation 7:

Aseptic processing areas are deficient regarding the system for monitoring environmental conditions. Specifically,

a. Colony growth on test plates are not always enumerated for the media growth promotion (GP) testing. Specifically, growth on the (b) (4) plates and (b) (4) plates are not enumerated compared to the inoculum control for Staphylococcus epidermidis incubated at (b) (4) ºC, Candida albicans and Aspergillus brasiliensis at (b) (4) ºC and for selected in-house isolates incubated at (b) (4) ºC. Your firm lacks adequate justification for not enumerating colony growth to demonstrate the ability of the media to support growth of environmental microorganisms.

b. Personnel monitoring (PM) alert and action level specifications are inadequate. For example, even though filling lines (b) (4) inside the barriers and surrounding areas outside the barriers are both classified as Grade A, only the mechanics' fingertips from both gloved hands are monitored to Grade A (b) (4) cfu action level), the rest of their PM locations; forearms (b) (4)) and chests (b) (4)) are held to Grade B limits. The PM data would fail if held to Grade A limits.

Response 7:

We understand this observation to be related to our environmental monitoring program requirements for colony growth enumeration and personnel monitoring specifications. Specifically, subpart (a) concerns whether our growth promotion criteria is sufficient to confirm that the media will support the growth of non USP specific microorganisms and house isolates, while subpart (b) concerns the adequacy of the specifications we use for personnel monitoring in Grade A processing areas in Building (b) (4) We are

committed to sustaining a comprehensive environmental monitoring program that will ensure all classified areas remain in a state of environmental control.

Response 7a:
Our growth promotion testing program for environmental monitoring (b) (4)) plates and replicate organism detection and counting (b) (4) plates is grounded in our biological laboratory procedure (BLP) (b) (4) *Growth Promotion: Microbiological Culture Media and Raw Materials* and biological analytical technique (BAT) (b) (4) *Growth Promotion: West Point Laboratory Operations Microbiology*. The BLP and BAT are based on USP <61> *Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests* and USP <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments.*

Our (b) (4) and (b) (4) plates use (b) (4) , a microbiological growth medium referenced in USP <61>, which is suitable for environmental monitoring because it supports growth of a wide range of bacteria, yeast, and molds, as noted in USP <1116>. In alignment with USP <61>, media and control plates are inoculated with challenge microorganisms at low levels, (b) (4) CFU, and incubated at (b) (4) for (b) (4). Following incubation, the plates are assessed for growth using a quantitative method of counting, or enumerating, the number of microbial colonies. Media plates assessed for growth using the quantitative method of enumeration are compared against the growth on the control plates. Media plates are considered acceptable if the recovery is between (b) (4) of the growth of the control plate. Each lot of environmental monitoring plates is required to be tested for growth promotion before being released per SOP 15-QUE-400X *Receipt Control and Release of Environmental Monitoring Media*. The release criteria include all USP <61>-required microorganisms for (b) (4) and their corresponding USP acceptance criteria as well as supplemental testing performed on Merck West Point's environmental isolates and additional organisms/incubation temperatures. The USP <61> microorganisms and conditions, as well as those included in Merck's supplemental testing, are detailed below in Tables 7-1 and 7-2, respectively.

Table 7-1: USP <61> Growth Promotion

USP <61> Microorganism	USP <61> Growth Promotion Conditions	USP <61> Requirement (Yes/No)
Bacillus subtilis	Incubation Temperature: 30-35 ºC Incubation Duration: ≤ 3 days	Yes
Staphylococcus aureus	Incubation Temperature: 30-35 ºC Incubation Duration: ≤ 3 days	Yes
Pseudomonas aeruginosa	Incubation Temperature: 30-35 ºC Incubation Duration: ≤ 3 days	Yes[1]
Candida albicans	Incubation Temperature: 30-35 ºC Incubation Duration: ≤ 5 days	Yes
Aspergillus brasiliensis	Incubation Temperature: 30-35 ºC Incubation Duration: ≤ 5 days	Yes

[1] *Escherichia coli* is used, in accordance with USP <61>, as a gram-negative rod indicator organism substitute for *P. aeruginosa.*

In addition to satisfying the requirements in USP <61>, our BLP and BAT require growth promotion testing of environmental isolates as well as testing of additional microorganisms and incubation temperatures for (b) (4) plates, as detailed below in Table 7-2.

Table 7-2: Merck West Point		
Merck West Point Organism	**Merck West Point Growth Promotion Condition**	**Required by USP <61> (Yes/No)**
Environmental Isolates	(b) (4)	No
Candida albicans		No
Aspergillus brasiliensis		No
Staphylococcus epidermidis		No

Merck West Point's environmental isolates are included in our (b) (4) plate growth promotion program, in alignment with the guidance in USP <1116>. We also include additional microorganisms and incubation temperatures beyond those listed in USP <61> and USP <1116>, specifically, *S. epidermidis* and additional incubation temperatures for *C. albic*ans and *A. brasiliensis.* Because environmental isolates are not as well characterized as the reference microorganisms, their growth performance is unpredictable once they are cultured on nutrient media. For both *A. brasiliensis* and *C. albicans*, growth is slower at the additional incubation temperature of (b) (4) Therefore, a qualitative evaluation (growth/no growth) is used to demonstrate the ability of the media to support the growth of these microorganisms.

We acknowledge that the supplemental growth promotion testing, beyond the USP <61> requirements, that is performed to release the (b) (4) plates and (b) (4) plates are not enumerated and compared to the inoculum control. As such, we will develop a project plan to define the requirements for the growth promotion program for (b) (4) plates for any additional microorganisms, including Merck West Point environmental isolates, which are not detailed in USP <61>. The project plan may require us to add or subtract microorganisms and/or incubation temperatures that are currently in our program to fully align with USP <61> and USP <1116> or other compendia. Given that these are additional microorganisms and incubation temperatures outside of USP <61> and that the balance of our program is fully aligned to USP requirements, we are confident in our environmental monitoring growth promotion program and the ability of the media we use to support growth.

Actions: The following action(s) will be taken to address subpart 7a of this observation:

Action 7-1: Create and approve a project plan to define the requirements for the growth promotion program for (b) (4) plates of any additional microorganisms, including Merck West Point environmental isolates, which are not detailed in USP <61>. The project plan may require us to add or subtract microorganisms and/or incubation temperatures that are currently in our program to fully align with USP <61> and USP <1116> or other compendia.
Due Date: (b) (4)

Response 7b:
We acknowledge the importance of a robust environmental monitoring (EM) program for personnel. In May 2019, Merck West Point self-identified that all personnel sampling locations associated with Grade A manufacturing should be aligned with the action level specification of less than (b) (4). As discussed with the Investigator, we were actively working on implementing those limits at the time of the inspection.

Our environmental monitoring program is detailed in SOP 15-QUE-113X *Environmental Monitoring Plan for Classified Areas and Systems*. SOP 15-QUE-113X also describes our personnel monitoring program, which

is based on a risk-based approach to the selection of all personnel sampling locations as well as of the associated alert and action-level specifications. There are (b) (4) personnel sampling locations associated with batch manufacturing: (b) (4), (b) (4) These (b) (4) sites represent the locations on personnel gowning in the closest proximity to exposed product with the highest risk of introducing bioburden into aseptic processing areas and possibly contaminating product. As the (b) (4) are closest to the product, these are assigned a limit of (b) (4), as required by regulatory requirements. The (b) (4) and then (b) (4) are the next closest locations to the product and, therefore, are currently assigned an action level of less than or equal to (b) (4), respectively.

Although our current specifications for (b) (4) are greater than (b) (4), our current recoveries at or above (b) (4) for those locations demonstrate a recovery rate of 0.01%. Table 7-3, below, shows the personnel microbial recoveries, for the (b) (4) locations as well as all personnel sampling locations associated with batch processing, for filling lines (b) (4) in Building (b) (4). These results show that the microbial recovery rates for both sets of data are below the USP <1116> suggested recovery rates for Grade A and, therefore, demonstrate a state of environmental control.

Table 7-3: Filling Line (b) (4) personnel recovery rates

Data Trend	Date Range	Total # of Recoveries (≥ 1 CFU)	Total # of Personnel Samples	Microbial Recovery Rate	USP <1116> Suggested Recovery Rate (ISO 5/Grade A)
Personnel (b) (4) (b) (4)	01Jan2018 to 12Jul2019	(b) (4)	(b) (4)	0.01%	1.0%
Personnel Recoveries (b) (4)	01Jan2018 to 12Jul2019	(b) (4)	(b) (4)	0.02%	1.0%

As discussed, we had already recognized that enhancements to our personnel monitoring specifications could be made; therefore, we are updating our personnel monitoring program by aligning all personnel sampling locations associated with Grade A manufacturing to the (b) (4) specification level. In the meantime, based on our demonstrated recovery rates, which are well below the USP <1116> suggested recovery rate, we are confident in Merck West Point's Grade A personnel monitoring program and state of environmental control in our Grade A manufacturing areas.

Actions: The following action(s) will be taken to address subpart 7b of this observation:

Action 7-2: Apply Grade A specification limit of less than (b) (4) to personnel samples associated with Grade A drug substance and drug product manufacturing.
Due Date: (b) (4)

Observation 8:

Your firm has not sufficiently established the efficacy of disinfectants used in the aseptic process areas. Specifically, Disinfectant Effectiveness Study; Environmental Monitoring Special Study (b) (4) conducted in 2009 is deficient.

a. Study (b) (4) did not adequately demonstrate 3 Log reductions of bacteria and 2 Log reductions of viable spores. Your firm lacks scientific justification for determining disinfectant effectiveness based on the reduction of (b) (4) cfus for each challenge microorganisms regardless of positive control recovery.

b. Study (b) (4) did not include an assessment of neutralizer efficacy. Specifically, after exposure of test coupons to the test disinfectants, the antimicrobial activity of disinfectants applied must be neutralized. Therefore, the efficacy of the (b) (4) for their ability to recover inoculated microorganisms from the test coupons should be demonstrated.

c.(b) (4) are currently used as sporicide (b) (4). Study (b) (4) showed (b) (4) % is not an effective sporicide on some of the test surfaces. Additionally, (b) (4) (b) (4) is not an effective sporicide on all test surfaces tested.

d. Not all representative surface materials from the manufacturing environment were adequately challenged. For example, HDPE used for vial guides, (b) (4) used for outfeed (b) (4), and (b) (4) used for (b) (4) (b) (4) in the vial filling Line (b) (4) were not challenged for disinfectant effectiveness.

Response 8:

We understand the importance of disinfectant efficacy to support microbial control in the aseptic processing areas. While we are confident that our current disinfection program ensures that we remain in a state of environmental control, as evidenced by our low recovery rates in our classified environment (see Table 8-1), we acknowledge that the 2009 study supporting our program, Disinfectant Effectiveness Study; Environmental Monitoring Special Study (b) (4) ("2009 Disinfectant Study"), could be updated. We self-identified the need to update this study and initiated a new study on 19Feb2019, Disinfectant Effectiveness Study (b) (4), which is currently ongoing and set to be completed by (b) (4). Further, SOP 03-QUA-326X *West Point Change Management Procedure* (V18.0) requires that any new materials of construction for non-product contact surfaces introduced into the aseptic manufacturing areas are assessed for disinfectant efficacy prior to implementation.

SOP 15-QUE-217X *Cleaning, Disinfection and Decontamination of Classified Areas* (v.19.0) requires that chemical agents used in the aseptic processing areas must undergo an effectiveness assessment prior to use. The 2009 Disinfectant Study, our current study, evaluated the effectiveness of (b) (4) chemical agents on (b) (4) different surface materials used within the aseptic processing areas at Merck West Point. The data this study generated are the foundation of our current cleaning and disinfection program, which is designed to maintain the aseptic processing areas in accordance with USP <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments.* The materials studied were grouped according to their composition similarity (e.g., metal with metal, plastic with plastic). Materials from each grouping were selected based on their prevalence in the cleanrooms, the uniqueness of their material of construction, and their proximity to product. The acceptance criterion for sporicidal agents was a reduction of viable spores of at least (b) (4) colony forming units (CFUs). This criterion was based on the reduction of CFUs many times greater than the bioburden present in Merck West Point cleanrooms taking into consideration that the targeted surfaces have been previously sterilized, decontaminated, or disinfected as procedurally required. The negative controls, positive carrier controls, and neutralization controls met the validity criteria for the study.

Furthermore, environmental monitoring (EM) data is used to demonstrate the efficacy of our cleaning and disinfection program. EM is performed as part of all manufacturing processes, and is also performed on a routine basis in our classified areas per SOP 15-QUE-113X *Environmental Monitoring Plan for Classified Areas and Systems* (V.26.0). The EM data for all classified areas is reviewed (b) (4) for out-of- specification results, (b) (4) for excursion rates, (b) (4) for isolate trends, (b) (4) by building and is also evaluated on (b) (4). In addition, we have a deviation management program governing the handling of EM out-of-specification results. Based on the data reviews and/or deviation conclusions, applicable CAPAs may be taken. The evaluation of EM data trends ensures that the environmental control is maintained. Our review of the EM data provides assurance that our cleaning and disinfection program is effective.

As shown in Table 8-1, below, the EM recovery rates of the aseptic processing areas in the Merck West Point manufacturing facilities are lower than the contamination recovery rate recommended in USP <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments.* The contamination recovery rate is determined for aseptic processing area based on the EM data trends. These data demonstrate that the aseptic processing areas are in a state of environmental control and highlight the efficacy of our current disinfection program.

Table 8-1: Recovery Rate in the aseptic processing area in Merck West Point facilities

Classifications	Recovery Rate	Suggested Recovery Rate per USP <1116>
Grade A (ISO 5)	0.05%	<1%
Grade B (ISO 7)	0.7%	<5%
Grade C (ISO 8)	5%	<10%
Grade D	15%	N/A

With respect to subparts 8a, b, and d, we acknowledge that the acceptance criteria listed in the 2009 Disinfectant Study were not aligned with USP <1072> *Disinfectants and Antiseptics*, and that a neutralizer efficacy study was not performed as part of the study, as recommended in USP <1227> *Validation of Microbial Recovery*. Furthermore, not all representative surface materials from the manufacturing environment were challenged. As noted, we previously recognized that the 2009 Disinfectant Study needed to be enhanced. The new Disinfectant Effectiveness Study (b) (4) includes the following:

- Sample acceptance criteria of (b) (4) Log reduction for viable spores and (b) (4) reduction for bacteria.
- Neutralized efficacy testing among assay validity criteria.
- Chemical agents challenged on representative surface materials from the manufacturing environment.

With respect to subpart 8c, the Investigator requested a USP<1072> log reduction analysis of the sporicidal data from the 2009 Disinfectant Study. We agree with the Investigator that we did not meet the USP <1072> requirement for the viable spore reduction for sporicidal agents. However, the recovery rate data presented in Table 8-1 demonstrates the efficacy of our environmental control program's ability to maintain a state of environmental performance, in accordance with expectation set forth in USP <1116>.

In conclusion, we acknowledge that the 2009 Disinfectant Study was not fully aligned with USP <1072>. A new Disinfectant Effectiveness Study (b) (4) of the approved chemical agents listed in SOP 15-QUE-217X and as well as of additional sporicidal agents for future consideration is in progress. We will implement any required changes to our disinfection program in response to the findings of Disinfectant Effectiveness Study (b) (4).

Actions: The following actions will be taken to address this observation:

Action 8-1: Complete Disinfectant Effectiveness Study (b) (4)
Due Date: (b) (4)

Action 8-2: Based on the outcome of Disinfectant Effectiveness Study (b) (4) determine if any disinfectant program changes are needed.
Due Date: (b) (4)

Action 8-3: Implement any disinfectant changes identified in response to Disinfectant Effectiveness Study (b) (4).
Due Date: (b) (4)

Observation 9:

Laboratory controls do not include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. Specifically,

a. BAT # (b) (4) **, "Bacterial Endotoxins", Rev 26 and Method Number:** (b) (4) **, "Bacterial Endotoxins", 5/25/2011, that describe the** (b) (4) **endotoxin test method are deficient in that they fail to specify the minimum time required for the adequate mixing or vortexing of sample containers and sample dilutions to ensure the release of endotoxins may have adhered to the surface of the containers.**

b. SOP 15-QUE-398X, "Water Sampling and Delivery", Version 8.0 requires water samples for microbial testing to be delivered to the Environmental Monitoring (EM) Laboratory (b) (4) **ºC cold vault within** (b) (4) **of sample collection. Your firm did not perform a hold time study to demonstrate that the** (b) (4) **hold time does not affect microbial recovery from the water samples.**

c. SOP 15-QUE-398X, "Water Sampling and Delivery", Version 8.0 requires the initiation of a Quality Notification if the samples are not delivered to the EM Laboratory within (b) (4) **. However, your firm does not track the** (b) (4) **delivery time for water samples microbial testing.**

Response 9:

We understand this observation to relate to certain laboratory procedures governing endotoxin sample preparation and water sample tracking. We acknowledge the importance of robust and well-founded testing procedures.

With respect to subpart a, biological laboratory procedures (BLPs) are multi-site documents that specify how to conduct testing. Biological analytical techniques (BATs) are documents that set forth Merck West Point site-specific procedures to carry out the testing. An analyst uses a test record to document the results of a test required by the associated BLP and BAT. BLP (b) (4) *Bacterial Endotoxins* (referred to as "Method Number" in the observation) and BAT (b) (4) *Bacterial Endotoxins* govern bacterial endotoxin testing in our laboratory. These processes are qualified, and our release testing is performed, in alignment with current USP <85> *Bacterial Endotoxins Test*.

As discussed with the Investigator, our current practice is to mix all samples, associated with bacterial endotoxin testing, for (b) (4) , in accordance with the reference standard mix time. The (b) (4) mixing time for drug product is supported by a technical literature assessment. Based on the reviewed literature, a minimum vortex time of (b) (4) is recommended by FDA Guidance for Industry and vendors that supply control endotoxin standards and other materials required for testing. This should be applied to sample containers and sample dilutions. Therefore, our practice meets the industry standards for endotoxin testing.

We acknowledge that mixing time requirements are not reflected in our procedures and agree that our test record template and BAT could be updated accordingly. As such, the test record template was updated, and the BAT will be updated, to require that samples must be mixed for a minimum of (b) (4) .

Regarding subparts b and c, SOP 15-QUE-398X *Water Sampling and Delivery* (v. 8.0) states that, after being collected, samples are stored at (b) (4) (b) (4) . In addition, delivery to the environmental monitoring cold vault (b) (4) is required. In addition, a peer-reviewed study demonstrated that microorganisms consistent with those recovered from our (b) (4) (b) (4) system would survive for periods longer than our current (b) (4) hold time in sterile (b) (4)

(b) (4)

The Merck West Point (b) (4) system meets USP requirements and is tightly controlled with online controls and alarming systems to ensure there is continuous recirculation, a temperature set point of (b) (4) return to every (b) (4) storage and distribution tank, and (b) (4) monitoring. These controls provide assurance that the system is self-sanitizing, stagnation is minimized, and that biofilm formation is prevented.

The state of control of the (b) (4) system has been further demonstrated by our (b) (4) microbial recovery rate from May2017 to Aug2019. We are confident in the microbiological quality of our (b) (4) due to the robustness of the (b) (4) system controls and our monitoring procedures.

We acknowledge the opportunity to further enhance the robustness of water sample management. To this end, SOP 15-QUE-398X *Water Sampling and Delivery* (v.8.0) was updated to specify the water sample time to refrigeration, in alignment with the two-hour requirement in USP <1231> *Water for Pharmaceutical Purposes.* Additionally, a process to track the delivery time for water samples, from the time of sample collection to refrigeration, will be developed and implemented.

Actions: The following actions will be taken to address this observation:

Action 9-1: Update bacterial endotoxins test record to record mixing of samples equivalent to the mix time of the reference standard dilution.
Due Date: (b) (4)

Action 9-2: Update BAT (b) (4) *Bacterial Endotoxins* to include a defined mixing time.
Due Date: (b) (4)

Action 9-3: Update SOP 15-QUE-398X to require microbial water samples to be delivered to the environmental monitoring laboratory cold vault within (b) (4) of sample collection.
Due Date: (b) (4)

Action 9-4: Develop and implement a process to track the delivery time of water samples for microbial testing (i.e., time from sample collection to refrigeration).
Due Date: (b) (4)

Observation 10:

Laboratory records do not include complete data derived from all tests, examinations, and assay necessary to assure compliance with established specifications and standards. Not all laboratory data were appropriately reviewed. On 9/11/2019 in the EM Laboratory located in (b) (4) ºC bin was inspected, containing EM plates that had been counted, reviewed by a second person, and results approved in (b) (4) The following was observed.

-The firm recorded 7 cfus for Sample ID – 219040609 (b) (4) Varicella – SR DPP). 8 cfus were observed. The count was verified by management.

-The firm recorded 1 cfu for Sample ID – 219037845 ((b) (4) PVX – SR table). 2 cfus were observed. The count was verified by management.

-The firm recorded 1 cfu of bacteria for Sample ID – 218920457 ((b) (4) Vaqta – SR DPP). 1 cfu of mold was observed. The appearance of mold colony was verified by management.

-The firm recorded 29 cfus for Sample ID – 219006796 ((b) (4)– Pre-treatment Water). 48 cfus were observed. The count was verified by management

-The firm recorded 1 cfu for Sample ID – 219041362 (b) (4) Vaqta – SR Table). 3 cfus were observed. The count was verified by management.

Response 10:

We understand this observation to related to a concern with the completeness of certain records of the testing of environmental monitoring (EM) samples generated in our EM laboratory located in Building (b) (4) and the appropriateness of the review that those records received.

The handling and testing of EM samples at Merck West Point are governed by SOP 29-MSA-437X *Sample Handling in the Environmental Monitoring Laboratory* (v. 16.0) and SOP 28-MSA-483, *Microbial Testing of Water and Swab Samples* (v. 10.0). These SOPs describe a rigorous, qualified process which is aligned with USP <1116> *Microbiological Control and Monitoring of Aseptic Processing Environments* and USP <1231> *Water for Pharmaceutical Purposes.* Personnel who execute these procedures are required to have a science degree before they may join the department. They receive competency-based training and are assessed annually in accordance with SOP 11-LAB-712X *Training in Laboratory Operations* (v. 2.0). The qualified EM process performed by these personnel is as follows:

- EM surface, air, and (b) (4) samples are taken from various buildings across the Merck West Point site.
    - Surface and air samples are plated, (b) (4) (b) (4)
    - (b) (4) samples are collected in sterile bottles and sealed.
- The samples are then delivered to the EM laboratory.
    - Surface and air samples remain (b) (4) and are incubated for a minimum of (b) (4) at (b) (4) and then a minimum of (b) (4) at (b) (4).
    - (b) (4) samples are processed onto plated test media, (b) (4) by EM laboratory personnel, and then incubated for, at minimum, (b) (4)
- After the plates have been incubated for the required amount of time, they are removed from the incubator.
- After being removed from the incubator and within a period of (b) (4), surface and air sample plates are (b) (4) the lids of those samples, as well as the (b) (4) samples, are opened in an unclassified environment, and all samples are read by qualified EM laboratory personnel. This is in accordance with our study, *Evaluation of Environmental Monitoring Test Plates Following Extended Hold Time at Room Temperature* (Approved 30Oct2015).
- The plates without growth are approved, placed in (b) (4), and discarded per SOP 29-MSA-437X.
- All plates with growth are (b) (4) and staged for second-person review.
- The (b) (4) all plates with growth and the plates are opened a second time in an unclassified environment for second-person review. This typically occurs within (b) (4) business days of the initial review. Final results are then approved in the (b) (4) (b) (4)
- The plates with growth that require identification per SOP 29-MSA-437X, are (b) (4) (b) (4) and sent to another laboratory so that the microorganisms they contain can be identified.

- The plates with growth that do not require microorganism identification (b) (4) (b) (4) and are staged for discard in a (b) (4) refrigerator, marked "Approved Samples Pending Discard," in the EM laboratory.

On 11Sep2019, the Investigator toured the EM laboratory in Building (b) (4) at Merck West Point. During the tour, the Investigator read 64 plates removed from the (b) (4) refrigerator labeled "Approved Samples, Pending Discard" which had already been processed in accordance with the procedures described above. The Investigator's readings of (b) (4) approved, pending-discard plates matched those previously recorded by laboratory analysts and second-person reviewed. Five readings by the Investigator differed from those recorded by laboratory analysts, resulting in this observation. (We note that Merck West Point personnel accompanying the Investigator on her tour did agree with the counts the Investigator made in those five instances reflected in this observation. Merck West Point personnel did not agree with the Investigator that sample ID 218920457 (b) (4) Vaqta® – SR DPP) showed mold as stated in the observation.)

The readings during the inspections of plates in the (b) (4) refrigerator labeled "Approved Samples, Pending Discard" were performed from (b) (4) days after approval of the plates. At this point, the plates were exposed to the unclassified environment and the controls (b) (4) were no longer in place. Refrigerated microorganisms will continue to grow and can change in appearance. In addition, many bacterial organisms take on the appearance of mold after extended periods of incubation (e.g., actinomycetes), resulting in the varied interpretation (b) (4) days after Sample ID 218920457 was approved. As a result, Merck West Point concludes the readings observed during the inspection by the Investigator are not representative of the approved (b) (4) results. The (b) (4) results were obtained and documented by (b) (4) independent trained personnel using the qualified plate reading process.

For the reasons described above, we remain confident that the laboratory records cited in this observation do in fact include complete data derived from all tests, examinations, and assays necessary to ensure that they comply with established specifications and standards. Moreover, we are confident that the data in those records were appropriately reviewed.

Observation 11:

Procedure for deactivating or discarding a reference standard is inadequate.

a. The Chemistry Laboratory in (b) (4) lacks adequate documentation to show that the (b) (4) stockroom checks for expired USP and EP standards per SOP 21-LAB-214X, "Laboratory Reference Standard Program", Version 5.0, have been appropriately performed. The only document available for review was Logbook # 2014-133 which only contains log entries for the months review occurred.

b. SOP 21-LAB-214X, "Laboratory Reference Standard Program", Version 5.0 lacks necessary requirement and details to assure only the current USP and EP reference standards are available for use, and the expired standards are either discarded or deactivated.

Response 11:

We understand this observation to be related to the level of detail included in our current procedures for the management of compendial reference standards.

The United States Pharmacopeia (USP) and the European Pharmacopoeia (EP) do not assign an expiration date to a current reference standard lot until it is superseded by a new lot. When the new lot is available for use, an expiry date is assigned to the previous lot, typically (b) (4) months from the date the new lot is issued. Therefore, in accordance with SOP 21-LAB-214X *Laboratory Reference Standard Program*, we check all USP and EP reference standards in our inventory (b) (4) to confirm that no expired lots are available for use. Specifically:

- Laboratory personnel physically confirm that the lot number on each reference standard label matches the current lot number in the USP or EP standard catalog.
- If the lot numbers do not match, the expiry date must be checked before it can continue to be used.
- When a new lot is received from USP or EP, the prior lot is discarded.
- Completion of the standard review is documented in logbook #2014-133 *USP/EP Expiry Review*.

As evidenced during the inspection, our logbook documentation demonstrates that the required checks of the standard lot numbers are performed (b) (4). Specifically, logbook #2014-133, which was reviewed with the Investigator, includes documentation of completed reviews performed each (b) (4) since 2015.

We acknowledge, however, that our procedure and logbook could be enhanced to include additional detail regarding how the standard check must be performed and how to document the findings in the associated logbook. Therefore, we have updated SOP 21-LAB-214X to increase the frequency of the checks to (b) (4) (b) (4) to improve our detection capability and to provide detailed instructions on how to complete the checks. A new logbook has also been created to document the findings of each individual standard and will include a second-person check.

Actions: The following action(s) were taken to address this observation:

Action 11-1: Updated SOP 21-LAB-214X *Laboratory Reference Standard Program* to include detailed instructions for how to perform the assessment of compendial standards and to require the checks to be performed (b) (4).
Due Date: (b) (4)

Action 11-2: Created new logbook for USP and EP reference standard checks to document the findings of each reference standard review in accordance with the updated instructions in SOP 21-LAB-214X.
Due Date: (b) (4)

Observation 12:

QA unit lacks the responsibility and authority to approve or reject GMP supplies to assure that errors have not occurred. Specifically,

The QA unit lacks written procedures on how the incoming sterile garments and sterile gloves are accepted and rejected for use. For example, currently no testing is conducted and no Certificate of Analysis (COA) is reviewed upon receipt of new lots. Sterile garments and sterile gloves are used in the classified Grade A/B areas where sterile vaccine products are manufactured.

Response 12:

We understand this observation to be related to the lack of written procedures governing the acceptance or rejection of incoming sterile garments and sterile gloves by the Quality Unit.

We recognize the importance of sterile garments and sterile gloves in maintaining the environmental control in our Grade A/B areas. SOP 15-QUE-292X *Grade A/B Gowning Procedure* requires that the integrity and expiry dating of sterile garments and sterile gloves are checked before they are donned. Any package that is expired, torn, or improperly sealed must be discarded. Sterile garments and sterile gloves used at Merck West Point are processed through validated (b) (4) processes and sourced from qualified vendors which are routinely audited by Merck. The personnel monitoring data sampled from sterile garments and sterile gloves in our Grade A/B manufacturing areas over the last 12 months (01Sep2018 – 31Aug2019) shows a microbial recovery rate of 0.19% on (b) (4) samples collected. As such, we have confidence that our sterile garments and sterile gloves are appropriate for use in manufacturing.

As we discussed with the Investigator, Merck West Point had previously identified opportunities to enhance our procedures to incorporate the acceptance or rejection of sterile gloves through an approved project plan, TW 1010143 *Project Plan for Implementation of Identified GMP Supplies to Supplier Transparency (per QUA-57266-2019-015).* We acknowledged that the project plan did not include sterile garments and initiated a CAPA during the inspection to update the project plan to include them. As part of this updated project plan, we will develop and implement a process for the Quality Unit to accept or reject sterile garments and sterile gloves prior to use in manufacturing.

Actions: The following action(s) will be taken to address this observation:

Action 12-1: Develop and implement process for acceptance or rejection of sterile garments prior to use in manufacturing by the Quality Unit.
Due Date: (b) (4)

Action 12-2: Develop and implement process for acceptance or rejection of sterile gloves prior to use in manufacturing by the Quality Unit.
Due Date: (b) (4)

Observation 13:

Test devices are deficient in that instruments lack established specifications are used. Specifically,

On 9/11/2019, LAL Laboratory located in (b) (4) was inspected. Water bath ID (b) (4) was observed not having a secondary temperature monitoring device, for example, a (b) (4) calibrated thermometer. The lab relies on the (b) (4) for temperature monitoring. Water bath ID (b) (4) is used for the release testing of residual bovine serum albumin in bulk live virus of Measles, Mumps, Rubella, Varicella, Rota, and Vaqta. Water bath ID (b) (4) in (b) (4) used for release testing also lacks secondary temperature monitoring.

Response 13:

We understand this observation to be related to a concern over our lack of use of a secondary temperature monitoring device in two water baths – (b) (4) – in the (b) (4) laboratory, located in Building (b) (4)

We are confident in the accuracy of the temperature monitoring devices used in water baths (b) (4) (b) (4) Each device consists of a sensor, calibrated to a (b) (4) (b) (4) standard, and a (b) (4) display showing the current temperature and temperature set point of each water bath. As described in SOP 18-MUC-302X *Instrumentation Calibration and Criticality Procedure*, each sensor is calibrated every (b) (4) . Any out-of-tolerance (OOT) result observed during (b) (4) calibration must be assessed in accordance with SOP 18-MUC-107X *Calibration Alert Investigation Process*. If an OOT were to occur, the scope of each such assessment would date from the OOT to the date the water bath last received a passing calibration result. In addition, SOP 28-PTL-169X *Operation of Temperature Controlled Water Baths* requires users of these water baths to ensure, prior to use, that the baths have been calibrated and that the calibration has not expired. In fact, a review of the calibration records for each of these water baths showed that each unit has remained within tolerance since it was installed. (Water bath (b) (4) was installed 31May2006; water bath (b) (4) was 28Oct2018.)

Based on the accuracy of the temperature monitoring devices used in water baths (b) (4) , given that they are calibrated to (b) (4) standard, their calibration is checked every (b) (4) , and neither device has recorded an OOT result since it was installed, Merck has confidence in the current method for the temperature monitoring of our water baths. As a result, we do not believe a secondary temperature monitoring device is required and no further action will be taken.

Observation 14:

There was a failure to perform qualification validations of the (b) (4) Room in Building (b) (4) (Room (b) (4) and Building (b) (4) (Room (b) (4) and Room (b) (4) used for retaining the following reserve sample products (i.e. Gardasil®, Gardasil® 9, Pneumovax®, Zostavax®, ProQuad®, MMR® II, Varivax®, Recombivax HB®, VAQTA®, Heptavax, PedvaxHIB®, and Rota Taq® etc.) and for storing laboratory critical biological reagents (i.e. HIB Alum Conjugated reference standards, HPV Quad Positive Control, Aluminum Positive Control, and critical reagent stability studies etc.). You failed to ensure that the cold rooms are operating within the specified temperature parameters. For example:

a. The temperature mapping profile validation for (b) (4) Cold Room (b) (4) (Room (b) (4) that is used for retaining reserve samples has not been validated under full load test for routine operation conditions. Only an initial IQ/OQ for this cold room was validated and approved on 8/4/2006.

b. The temperature mapping profile validation for the (b) (4) Cold Room (b) (4) (Room (b) (4) ID (b) (4) that is used for retaining reserve samples has not been revalidated under full load test for routine operation conditions. The IQ/OQ/PQ was last validated and approved on 02/1/2011.

c. The temperature mapping profile validation for the (b) (4) Cold Room (b) (4) to (b) (4) (Room (b) (4) ID (b) (4) that is used for storing laboratory critical reagents has not been revalidated under full load test for routine operation conditions. The IQ/OQ/PQ was last validated and approved on 02/1/2011.

Response 14:

We understand this observation to be related to full load performance qualification (subpart a) and full load requalification for controlled temperature units (CTUs) (subparts b and c) located in Building (b) (4) (Room (b) (4) and Building (b) (4) (Room (b) (4) and Room (b) (4) in West Point Laboratory Operations.

As discussed during review of the documents with the Investigator, we would like to clarify that, with respect to subpart (a), performance qualification (PQ) testing was completed on 04Aug2006 and included an empty chamber study which was documented in the Operational Qualification (OQ) for the CTU. At the time that this qualification was completed, only an empty chamber study was required. In 2009, *Controlled Temperature Unit* (*CTU) Installation/Operational/Performance Qualification Protocol* was implemented, which required an empty and a full chamber study to be performed. With respect to subpart (b), installation qualification (IQ), OQ, and PQ were completed on 26Aug2011, not 01Feb2011; and with respect to subpart (c), IQ, OQ, and PQ were approved on 26Aug2011, not 01Feb2011, and a full load chamber study was approved as part of the initial PQ.

We are committed to ensuring that our CTU system life-cycle management program ensures that the units are properly functioning and that the temperature specifications for each unit are maintained. This program is governed by SOP 28-ESG-218X *CTU System Lifecycle Requirements*. Deviations are investigated in accordance with global deviation management procedures.

CTUs are monitored and maintained on an ongoing basis through the following measures:

- Continuous data acquisition systems are used to monitor critical parameters, with audible alarms, as needed, (b) (4)
- Each alarm is evaluated per SOP 06-VIR-131X *Procedure For Maintaining and Managing Controlled Storage Unit Charts and Temperature Excursions* and investigated in accordance with global deviation management procedures.
- Temperature sensor probes are calibrated at least (b) (4) and any out-of-tolerance result is investigated in accordance with 18-MUC-107X *Calibration Alert Investigation Process*.

In addition to the monitoring described above, a review of temperature trends and calibration records for CTUs (b) (4) was completed for the past two years. All calibrations were within tolerance, and there were no significant temperature excursions, as described in SOP 06-VIR-131X, which confirms that all CTUs were operating within a qualified state of control.

As discussed with the Investigator, we had previously identified opportunities to enhance our existing Laboratory CTU life-cycle management program. Technical Communication TW1004985-BSV-TC-2019 *Controlled Temperature Unit (CTU)* (b) (4) *Periodic Requalification* was issued and approved on 08Jul2019. This communication describes the technical justification, preventive maintenance, equipment life expectancy, and historical performance supporting a program to requalify CTUs every (b) (4). SOP 28-ESG-218X was recently updated, effective 28Aug2019, to require laboratory CTUs to be requalified every (b) (4). An assessment is currently underway to develop a timeline to ensure laboratory CTUs meet this requirement. This assessment will be documented in a project plan to track requalification of all laboratory CTUs to completion. For CTUs (b) (4) noted in this observation, full load chamber requalification testing will be completed by (b) (4).

The enhancements to our CTU life-cycle management program, combined with our current program controls, will continue to ensure that laboratory CTUs remain within a qualified state of control.

Actions: The following action(s) will be taken to address this observation:

Action 14-1: Complete project plan for requalification of Laboratory CTUs.
Due Date: (b) (4)

Action 14-2: Complete requalification testing for (b) (4) in accordance SOP 28-ESG-218X.
Due Date: (b) (4)

Observation 15:

Your reserve sample program that is governed under the following procedures GDL 29.12, (b) (4) Examination of Retention Samples, Rev. 1.0, GDL 29.13, Retention, File, and Legal Samples, Rev. 3.0, and SOP No. 29- LAB-313X, (b) (4) Examination of Retention Samples, Rev. 9.0 is not adequate. For example:

A representative reserve sample is taken from each filled lot prior to labeling (the quantity for required release testing (b) (4) including sterility and pyrogen); however, the (b) (4) visual examination is only conducted based on a (b) (4) sampling plan. For example, a representative reserve sample of (b) (4) syringes for Gardasil ® 9 (Lot # (b) (4) are reserved, but only (b) (4) syringes are pulled for (b) (4) visual inspection. These same syringes will be visually inspected (b) (4) but the remaining (b) (4) syringes will never be visually inspected for the retention period of this reserve sample.

Response 15:

We understand this observation to be related to the adequacy of our site's (b) (4) reserve sample examination program. Specifically, the (b) (4) examination is performed on a (b) (4) of the reserve samples (vials, syringes, or tubes) from each drug product batch, rather than on all reserve samples from (b) (4) number of drug product batches. We believe that our current (b) (4) sample examination program is appropriate to identify any evidence of deterioration, but acknowledge that it can be enhanced.

CFR § 211.170 *Reserve Samples* states that "reserve samples from representative sample lots or batches selected by acceptable (b) (4) shall be examined visually at least (b) (4) for evidence of deterioration unless visual examination would affect the integrity of the reserve sample." Our (b) (4) examination of reserve, or retention, samples is governed by the following procedures:

Merck Global Procedure:

- GDL 29.12 (b) (4) Examination of Retention Samples provides global guidance for Merck sites for conducting (b) (4) visual examination of retention samples of finished dosage biologic and pharmaceutical products.

Merck West Point procedures:

- SOP 29-QUR-255 *Retention Sample Examination* governs performing and documenting the initial retention visual examination.
- SOP 29-LAB-313X (b) (4) *Examination of Retention Samples* governs performing and documenting the (b) (4) examination of retention samples.
- SOP 04-QUA-343X *Market Control Retention Sample Examination* governs the process for handing defects found during the examination of retention samples.

In accordance with the above-referenced procedures, reserve samples are taken from each drug product batch in a quantity sufficient to perform all release testing (b) (4) Prior to release of each drug product batch, all associated reserve samples are fully inspected for defects, in accordance with SOP 29-QUA-255. After this initial 100% examination, a (b) (4) of each reserve sample batch is allocated for (b) (4) examination using (b) (4) *Sampling Procedures and Tables for Inspection by* (b) (4) published by the (b) (4) . These (b) (4) samples are then used for each (b) (4) examination through product expiry. Defects identified in (b) (4) examination are assessed, according to SOP 04-QUA-343X, and investigated, where required, according to site deviation management procedures.

We acknowledge, however, that in accordance with CFR § 211.170, the statistical selection should be applied to a representative sample of drug product batches, rather than to the samples within each batch. All sample units (vials, syringes, or tubes) from the (b) (4) drug product batches should be visually examined at least (b) (4) . Therefore, we will update our (b) (4) reserve sample examination procedures accordingly.

Actions: The following action(s) will be taken to address this observation:

Action 15–1: Implement procedures to perform (b) (4) inspection on 100% of the reserve samples from a (b) (4) number of drug product batches.
Due Date: (b) (4)