April 30, 2021

Via Electronic Mail
orabioinspectionalcorrespondence@fda.hhs.gov

Confidential

Attention: Lisa Harlan, Acting Staff Director, Investigations Branch
Office of Biological Products Operations
Office of Regulatory Affairs
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
orabioinspectionalcorrespondence@fda.hhs.gov

Re: Emergent Manufacturing Operations Baltimore, LLC's Initial Response to the Form FDA 483 Issued on April 20, 2021 to the Bayview Facility (FEI: 3015448605) Investigators Debra M. Emerson and Cody Rickman, and Senior Advisor Jeremy Wally

Dear Ms. Harlan:

Enclosed please find Emergent Manufacturing Operations Baltimore, LLC's (Emergent or the company) initial response to the Form FDA 483 (483) issued on April 20, 2021 to its Bayview facility (FEI: 3015448605). Please know that Emergent remains committed to meeting the unprecedented challenge of manufacturing novel Covid-19 vaccines to meet the nation's and the world's needs.

Emergent also knows that it must do everything within its power to ensure appropriate controls are in place to assure product quality. We are doing just that. As described in more detail below, Emergent is establishing a Quality Enhancement Plan that will, among other things:

- Implement ***enhanced contamination controls*** at the Bayview facility prior to initiating new production. These enhanced controls are based on a comprehensive assessment of site operations.

- Institute effective ***interim controls***, including Emergent corporate quality, Johnson & Johnson (J&J), and independent third-party oversight and monitoring, to ensure compliance while longer-term improvements are developed and implemented.

- Guide the development and execution of ***continuous improvement*** initiatives to ensure sustainable compliance.

Emergent believes that the implementation of the activities described below fully addresses the 483 observations and ensures that adequate controls are in place to support resumption of new manufacturing at the Bayview facility and authorization of the Bayview facility to manufacture drug substance for the Janssen Covid-19 vaccine under the existing Janssen EUA.

Emergent's Role in the Fight against Covid-19

Emergent understands the critical role the company is playing in the fight against Covid-19 and takes FDA's observations very seriously. Emergent is uniquely situated to supply critical drug substance for Covid-19 vaccine. The Bayview facility is capable of supporting production of greater than (b) (4) vaccine dose-equivalents per year. Accordingly, the company has been working closely with FDA, other government agencies, and our pharmaceutical clients to deliver on the common goal of expeditiously manufacturing safe and effective Covid-19 vaccines doses.

With the unprecedented challenge of establishing manufacturing processes for novel Covid-19 vaccines and rapidly scaling up production to meet the nation's and world's needs, challenges will inevitably arise.

The recent events at the Bayview facility, including the 483 observations, have given Emergent renewed focus. Emergent is fully aware of its responsibility to public health and has openly and transparently collaborated with FDA and J&J to ensure that appropriate and effective measures are implemented. The company knows that speed is essential to confront the on-going Covid-19 pandemic and that the quality of Covid-19 vaccine drug substance is paramount. Emergent is confident it can pursue and achieve these two objectives simultaneously.

The Quality Enhancement Plan

The April 2021 inspection was triggered by an out-of-specification (OOS) result involving the contamination of a single drug substance lot intended for further drug product manufacturing and use in Janssen's Covid-19 vaccine. Emergent, in close collaboration with J&J, is committed to comprehensively investigating the cause of the contamination event and preventing such events from occurring in the future.

Emergent would like to make clear that, as communicated to FDA during the inspection, the company will implement significant improvements at the Bayview facility before initiating any new manufacturing. Specifically, in collaboration with J&J, Emergent is implementing a Quality Enhancement Plan (QEP). The QEP—developed following a comprehensive assessment of manufacturing operations at the facility by Emergent and J&J—includes immediate actions and interim controls that will assure the safety and quality of drug substance manufactured at the Bayview facility while longer term improvements are implemented. Emergent's interim control strategy includes engaging independent third-party experts to provide continuous oversight of

critical activities and to perform batch certification for all Covid-19 vaccine drug substance batches manufactured at the Bayview facility.

As FDA is aware, the company has ceased manufacturing Covid-19 vaccine drug substance for AstraZeneca and decommissioned the Bayview facility manufacturing suite previously used to manufacture AstraZeneca's product, thereby eliminating the risk of cross-contamination during production going forward. The enhancements detailed in the QEP will further address potential routes of contamination from other sources. These include:

- (b) (4)

Emergent recognizes the need for effective and timely implementation of these improvements and we are working collaboratively to execute the remediation process. Individual workstreams are being jointly led by identified subject matter experts (SMEs) in the Emergent and J&J organizations. Program leaders from Emergent and J&J are meeting (b) (4) to review remediation activities and escalate issues, as necessary. A Steering Committee, comprised of Emergent and J&J quality and operations leadership meet (b) (4) with program leads for further accountability and oversight.

Consistent with Emergent's commitment to continuous improvement, the QEP also includes a Sustainable Compliance Plan, detailing on-going actions to maintain a robust culture of quality at the Bayview facility. The company understands that sustainable compliance is achieved through consistent evaluation and improvement of quality activities. Emergent expects nothing less than the consistent adoption of industry best practices in the company's manufacturing and quality operations.

To that end, in November 2020, Mary Oates, Ph.D., joined the company as Senior Vice President, Global Quality. Dr. Oates brings over 30 years of biopharmaceutical experience in Quality, Manufacturing Operations and Regulatory Affairs, including as head of Global Quality Operations for Pfizer Inc. Dr. Oates reports directly to Emergent's Chief Executive Officer and is firmly in charge of quality operations at the Bayview facility. Under Dr. Oates's leadership,

Emergent has significantly strengthened the Bayview facility quality leadership with external hires in recent months, including:

- Edward Elmore, Senior Director of Quality. Mr. Elmore has over 30 years of experience in pharmaceutical manufacturing and quality, including as Executive Director of Quality Assurance at Elanco and Senior Director of Quality Assurance at Eli Lilly and Company. Mr. Elmore joined Emergent in April 2021.

- James Kirk, Director of Quality Assurance. Mr. Kirk has over 25 years of quality leadership experience and joined Emergent from Janssen Pharmaceuticals in March 2021.

- William Hatcher, Director of Quality Control. Mr. Hatcher has more than 15 years of experience in Quality Control focusing on drug product and drug substance from clinical to commercial manufacturing. Mr. Hatcher joined Emergent in March 2021 after serving as Director of Quality Control for Catalent Pharma Solutions.

Emergent's new corporate and Bayview facility quality leadership are fully engaged in the enhancement efforts underway at the facility and will provide direct oversight of quality operations at the facility.

The QEP targets efficient, effective, verifiable measures that will provide confidence in Emergent's drug substance and lays the foundation for continuous improvement. Emergent is confident that the QEP and associated corrective and preventive actions (CAPA), described in detail in the attached 483 response, will assure that the Bayview facility is continuously operated in a state of control.

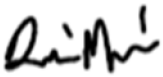
Details regarding the investigation into the OOS contamination event are provided in **Section I** of the enclosed response. The QEP is provided in **Section II** of the enclosed response. The specific responses to the 483 observations are provided in **Section III** of the enclosed response. For ease of reference, the responses are formatted as follows: each response begins with a restatement of FDA's observations in *italic* text. This is followed by Emergent's response to the observations(s). At the conclusion of each observation response, planned CAPAs are detailed with target completion dates, as appropriate.

The company will provide periodic updates to FDA on the status of its ongoing actions and QEP implementation. Emergent will also keep FDA updated of any new actions undertaken.

This document contains confidential commercial and trade secret information that is protected from public disclosure under the Federal Food, Drug, and Cosmetic Act, the Freedom of Information Act, FDA's implementing regulations, and the Trade Secrets Act. Recognizing the need for public information in the context of a global pandemic, Emergent will be submitting a redacted copy of this response reflecting information Emergent believes to be exempt from disclosure. If there are no concerns with those redactions, Emergent consents to the public

disclosure of such redacted version. In accordance with FDA's implementing regulations, if a request for disclosure is received that would exceed the scope of the foregoing consent, or FDA determines for any other reason that it must publicly disclose any of the information that Emergent has designated for redaction, Emergent asks that it be notified and provided an opportunity to address why the information or materials should not be released.

Sincerely,



Dino Muzzin
SVP Manufacturing and Interim General Manager
Emergent Manufacturing Operations Baltimore, LLC's

I. Batch (b) (4) and the Corresponding Investigation

A. Emergent BioSolutions

By way of background, Emergent BioSolutions (Emergent) is one of a limited number of specialty biopharmaceutical companies focused on developing vaccines and other medical countermeasures for biodefense purposes. Founded in 1998, Emergent began as a small anthrax vaccine manufacturing facility that manufactured vaccines primarily and the US military. Since this time, the company's capabilities and expertise has expanded to include numerous other vaccines, including for smallpox and typhoid, antibody therapeutics, and opioid overdose treatments. We are steadfast in our commitment to government service and national security, and are proud to say that we are one of the largest manufacturers of medical countermeasures for the US government.

Emergent's history of collaboration with the US government to develop vaccines to address public health emergencies also includes a long-standing collaboration with the Biomedical Advanced Research and Development Authority (BARDA). In 2012, Emergent's Bayview facility was established as a Center for Innovation in Advanced Development and Manufacturing (CIADM) with the goal of providing a significant domestic infrastructure in the United States capable of producing medical countermeasures to protect Americans from the health impacts of bioterrorism as well as pandemic influenza and other disease in response to public health emergencies.

Following BARDA's designation of the Bayview facility as a CIADM, Emergent invested approximately (b) (4) modernizing manufacturing areas (b) (4) to incorporate flexible, innovative manufacturing platforms that can be used to manufacture multiple products with a focus on medical countermeasure manufacturing. Since 2012, areas (b) (4) have been used in connection with a development-stage influenza vaccine, in response to task orders from the US government related to Ebola and Zika outbreaks, and for development of other clinical-stage drug development manufacturing both for Emergent as well as a limited number of contracted clients.

In addition to modernizing manufacturing areas (b) (4), Emergent also built a (b) (4) manufacturing suite for the sole purpose of manufacturing vaccines in response to a potential pandemic. Following the successful completion of construction activities and the qualification of the clean rooms, area (b) (came on-line for cGMP manufacturing activities in (b) (4) .

Emergent's Bayview facility was constructed to facilitate the use of disposable manufacturing equipment at a very large scale—*i.e.*, batch sizes up to (b) (4). The facility was also designed and constructed to enable live virus vaccine manufacturing. This combination of excess capacity, use of disposable manufacturing equipment at a large scale, and ability to manufacture live virus vaccines makes the Bayview facility (b) (4) .

B. Emergent's Role in Combating the COVID-19 Pandemic

In April 2020, Emergent executed an initial agreement for ramping up drug substance manufacturing for Janssen's Covid-19 vaccine, Ad26.COV2.S, at the Bayview facility, and on July 6, 2020, the companies announced a five-year manufacturing services agreement.

At the time, there was significant uncertainty with regard to which, if any, of the investigational Covid-19 vaccines would successfully demonstrate safety and efficacy to FDA's satisfaction. Accordingly, Emergent was engaged in active negotiations with another vaccine manufacturer to be their drug substance manufacturer. (b) (4) , ended when Emergent received a task order from the US government in early June 2020. The task order requires Emergent to reserve manufacturing capacity (b) (4) . Subsequently, the US government directed Emergent to release the capacity to AstraZeneca for large-scale drug substance manufacturing of its Covid-19 vaccine candidate, AZD1222.

Immediately after entering into drug substance manufacturing agreements, Emergent began working around the clock with its partners to transfer the manufacturing processes and related technologies to the Bayview facility as quickly as possible due to the severity of the pandemic. Given the critical need for Covid-19 vaccine, the decision was made to manufacture both drug substances at full-scale immediately.

C. The Batch (b) (4) Out-of-Specification Result and Initial Laboratory Investigation

(b) (4) , a suspected OOS test result was reported for drug substance Batch (b) (4) for (b) (4) vaccine during in-process and finished product testing. Batch (b) (4) was manufactured at Emergent's Bayview facility between (b) (4) and (b) (4) and sent to (b) (4) for quality control testing. Also, on (b) (4) an (b) (4) agents assay test conducted by (b) (4) ., reported a suspected OOS result for the same drug substance batch.

(b) (4) and (b) (4) immediately initiated laboratory investigations, determining that the OOS results were not due to laboratory error and were valid OOS test results. On (b) (4) and (b) (4) , additional investigational testing on the impacted control cell test sample confirmed the presence of a (b) (4) that was not the (b) (4) . These results indicated a possible contamination with another (b) (4) . At the time of the deviation, drug substance manufacturing for the (b) (4) vaccine was in operation in manufacturing Area (b) (4) and (b) (4) drug substance manufacturing was operating in Area (b) (4) which is independent and separated from Areas (b) (4) However, the manufacturing of drug substance of both vaccine candidates in the same facility raised the possibility that the contaminant was the (b) (4) vector.

(b) (4)
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D. Emergent's Root Cause Analysis and Overall Impact Assessment

(b) (4) (b) (4) in accordance with its standard quality control protocols, Emergent immediately self-initiated a manufacturing investigation, opening deviation 3100012112 on (b) (4) (b) (4). Emergent and (b) (4) approved the investigation plan for the OOS on (b) (4). At all times, Batch (b) (4) remained under Emergent's control and was not sent for further processing into drug product.

Emergent conducted a root cause analysis that included review of Batch (b) (4) in-process testing results and data, finished product data, and a review of the manufacturing campaign timeline with a focus on activities impacting Batch (b) (4). This included a review of potential (b) (4) and (b) (4) and (b) (4) On (b) (4) investigational testing performed by Emergent indicated the presence of a (b) (4) similar to that of the (b) (4). The following day, Emergent contacted (b) (4) to notify (b) (4) of the investigational results of a positive identification of an alternate (b) (4) in the (b) (4) testing article.

An investigation report was issued and provided to FDA on (b) (4) The root cause analysis determined that the (b) (4) (b) (4) (b) (4) Emergent notes that the QEP, described below, is based on a comprehensive review of potential sources of contamination at the Bayview facility, and includes actions to address the most probable root cause identified in deviation 3100012112 as well as other potential sources of contamination, including those identified in the 483 observations.

An impact assessment was also conducted, and (b) (4) testing was performed on all batches manufactured at the Bayview facility. Using (b) (4), the presence of the (b) (4) and (b) (4) were confirmed for all batches within scope of this evaluation. The results of (b) (4) and (b) (4) (b) (4) testing confirmed that the incident had no impact on the other batches tested. FDA has been provided with details of these analyses and all underlying data.

An extended comparability assessment was conducted for the (b) (4) and (b) (4) batches manufactured according to the same manufacturing process variant as Batch (b) (4) Batch (b) (4) was the only batch exhibiting viral contamination.

E. FDA Inspects the Bayview Facility

Subsequent to receipt of the investigation report on (b) (4), FDA conducted an inspection of the Bayview facility from April 12 to April 20, 2021 (the April 2021 inspection). The inspection resulted in the issuance of a Form FDA 483 with nine observations, which is addressed in **Section III** below.

II. Emergent's Quality Enhancement Plan

Emergent fully understands its responsibility to promote public health by assuring the safety, efficacy and quality of the company's critical drug products. Accordingly, Emergent remains steadfastly committed to using its unique manufacturing capacity, expertise in vaccine manufacturing, and technical capability to produce high-quality drug substance for Covid-19 vaccines. Emergent's Bayview facility stands ready to produce drug substance for more than (b) (4) (b) (4) urgently needed Covid-19 vaccines a year to help combat the on-going pandemic.

Emergent is committed to doing so in a way that meets Emergent's and FDA's quality and compliance expectations. To meet the urgent requirements of today, as the world continues to battle resurgent Covid-19 infections, Emergent has initiated a series of immediate actions to address the inspectional observations, enhance operations at the Bayview facility, and minimize the potential for contamination or cross-contamination going forward. These actions, developed and implemented with the support of J&J, address FDA's concerns, as documented on the 483, and will provide assurance of the quality of the Bayview facility's drug substance.

In particular, upon receipt of the 483, Emergent, along with J&J, performed an in-depth analysis of potential sources of contamination and cross-contamination across the Bayview facility. Emergent's comprehensive assessment was organized into three separate workstreams:

- **Establishing a Detailed Process Map to Identify Potential Sources of Contamination.** Emergent created a detailed map identifying every activity performed in the facility relating to the manufacture of (b) (4) bulk drug substance. The map starts with (b) (4) . The purpose was to identify mechanisms by which a contaminant could be introduced and the corresponding controls that must be in place to eliminate the possibility that contamination will occur.

- **Developing and Implementing Actions to Address the Inspectional Observations.** In addition to establishing a detailed process map, Emergent also closely analyzed each of the investigators' inspectional observations and developed an action plan to address them. Based on Emergent's analysis of the 483 and discussions with the FDA investigators, the company has initiated actions in each of the following categories:

  - (b) (4)

- (b) (4) .

Emergent's specific actions within each of these categories are detailed in the company's specific responses to the 483 observations, below.

- **Strengthening the Quality Investigation and Root Cause Analysis.** Emergent also worked closely with J&J to strengthen the quality investigation relating to the OOS. As detailed below in the response to Observation 1(a), this included a detailed and expanded review of over (b) (4) separate elements that could have played a role in the contamination event and the implementation of additional CAPAs. By expanding the scope of the quality investigation, Emergent ensured that additional routes of contamination and cross-contamination have been evaluated, and that appropriate actions to address such routes have been implemented. Emergent is confident that these actions further reduce any potential risk of contamination at the Bayview facility.

The findings were used to create the holistic QEP, set forth in sections A and B below. Emergent's QEP is divided into (b) (4) . (b) (4) .

Emergent is working around the clock with J&J subject matter experts and third-party cGMP consultants to implement the actions required. Emergent is confident that these actions will minimize the chances of contamination in the Bayview facility in a way that meets or exceed industry standard. Emergent is also working with J&J subject matter experts and third-party cGMP consultants to develop and implement actions aimed at continuous improvement and achieving sustainable compliance throughout the Bayview facility.

A. QEP Phase 1: Actions Prior to Initiating New Manufacturing

At the outset, Emergent wishes to emphasize the company's commitment to full transparency with FDA, including throughout the course of its collaboration with the agency to ensure access to critical Covid-19 vaccines.

In order to meet the demand for Covid-19 vaccine drug substance, (b) (4) (b) (4) (4) . With the recent pause of manufacturing activities at the plant, as requested by FDA, Emergent has accelerated corrective and preventive measures and developed additional improvements. Emergent is pleased to report that, in cooperation with J&J, important steps to enhance the Bayview facility are being implemented and verified.

Based on Emergent's detailed process map, the inspectional observations, and Emergent's and J&J's quality investigations, Emergent has included the below actions in Phase 1 of the QEP. Emergent believes that the implementation of these actions ensures that the Bayview facility is

continuously operating in state of control and supports the authorization of the Bayview facility to manufacture drug substance for the J&J vaccine under J&J's existing EUA.

Focus on Janssen Vaccine Drug Substance Production

At the outset, Emergent wishes to emphasize that at the US government's request, on (b) (4) (b) (4) Emergent permanently ceased drug substance manufacturing activities for the AstraZeneca Covid-19 vaccine. The Bayview facility is now dedicated to manufacturing drug substance for Janssen's Covid-19 vaccine.

While Emergent is confident that the Bayview facility's contamination control program together with the enhancements noted below will prevent recurrence of the quality event resulting in the rejection of drug substance batch (b) (4) , the company also believes that by dedicating the Bayview facility to manufacturing drug substance for Janssen's Covid-19 vaccine, any theoretical risk of cross-contamination is eliminated.

Cleaning, Disinfection, and Repairs

Prior to initiating new manufacturing, the facility, including the warehouse, will be repaired, cleaned and disinfected to eliminate conditions that may result in contamination. The following actions have been or will be completed:

- (b) (4) .
- (b) (4)
- (b) (4)

Personnel, Material, and Waste Flow Segregation

Changes are being implemented to ensure that waste does not cross paths with materials or personnel involved in manufacturing operations. In addition to modifying flows, (b) (4)

(b) (4) . Additional gowning and de-gowning requirements will be defined and enforced throughout the facility.

Material Handling Practices

In addition to optimizing material flow, Emergent is significantly enhancing the Bayview facility's practices and procedures for material handling. An assessment was performed of containers (e.g., (b) (4)) used during the manufacturing process. The (b) (4) previously used to contain materials from the (b) (4) area will be replaced with (b) (4) , reducing the potential for contamination. In addition, a visual inspection process will be broadened to ensure that containers and (b) (4) are clean and in a good state of repair before use. This will be described in SOP001518.

Additionally, the (b) (4) (b) (4) (b) (4) preventing the need to move materials across the floor. These enhancements, which will be in place prior to initiating new manufacturing, will ensure that material handling does not introduce a risk of contamination.

Waste Handling Practices

Emergent is committed to ensuring that waste can be removed from the facility in a way that does not introduce contamination. To accomplish this, the decontamination(b) (4) have been functionally qualified and (b) (4) are being established. These will be clearly described in the governing SOP. Emergent is also establishing additional controls relating to the removal of biowaste from the facility that has not gone through (b) (4) decontamination. These will be defined in SOPs. Employees will be trained on these waste removal procedures prior to initiating new manufacturing.

Procedural Updates and Expanding Training and Skill Development for Site Personnel

As described above, Emergent is implementing significant enhancements to the requirements in Bayview's procedures.

The above-described procedural enhancements will ensure that the facility continuously meets FDA's and Emergent's own expectations for quality compliance. In order to assure that the strengthened facility procedures are correctly and consistently executed, Emergent is using the current pause in new production to deliver comprehensive training to facility personnel.

This training will be instructor-led and will be provided to cross-functional cohorts of employees, ensuring that those who execute, verify, review, and/or oversee the activities are fully knowledgeable regarding both the requirements and why the expectations are critical to quality. In addition, the training materials will be approved by a subject matter expert and there will be oversight of both the training delivery and the execution of the activities to ensure training effectiveness.

Upon completion, and prior to initiating new manufacturing, Emergent personnel will be fully prepared to execute their responsibilities correctly and consistently.

Enhanced Oversight

Prior to initiating new manufacturing at the Bayview facility, Emergent is also enhancing the facility's quality oversight. As an immediate measure, Emergent is leveraging corporate and third-party resources and expertise to provide additional quality resources and oversight. This includes oversight of critical activities, a quality-on-the-floor initiative, and enhanced Emergent corporate quality.

Emergent is working in close collaboration with J&J on all aspects of Phase 1 of the QEP. Each party has identified SMEs from their respective organizations to serve as leads for project workstreams. These SMEs report into the (b) (4) , comprised of (b) (4) who meet (b) (4) to oversee implementation effectiveness and project status. A Steering Committee, comprised of (b) (4) , join (b) (4) meetings with the Project Leads to provide additional accountability and ensure oversight, and to ensure that appropriate resources are available to meet project goals.

In addition to the above meetings, J&J will now to provide 24/7 oversight of all production areas in addition to the suites in which their vaccine is manufactured. Further, J&J will now provide full oversight of change controls, qualifications, and process items, including final approval. Emergent has also engaged (b) (4)) to provide independent oversight and re-enforcement of new procedural and process revisions for material and people flow through the facility (e.g., airlocks and waste flow). In addition, (b) (4) will ensure that there is proper documentation and training for these activities.

(b) (4) is also supporting the implementation of interim controls. (b) (4) personnel will be on-site at the Bayview facility to observe the following activities and ensure compliance with site procedures:

- (b) (4)

Additionally, as described in more detail in the response to Observation 7, below, (b) (4) will review and approve training materials and observe training sessions to ensure training effectiveness. (b) (4) will also observe and enforce gowning requirements, documentation requirements, cleaning, cleanliness, and the state of repair and maintenance across the facility.

Emergent believes that the above-described enhancements significantly strengthen operations at the Bayview facility. Through the implementation of facility-wide enhancements, interim controls and independent oversight, Emergent is confident that the Bayview facility will be continuously operating in a state of control.

B. <u>QEP Phase 2: Sustainable Compliance Plan</u>

Emergent recognizes the importance of continuous quality improvement to achieving sustainable compliance and will be using information and learnings from Phase 1 of the QEP to drive sustainable compliance initiatives. The Sustainable Compliance Plan will ensure a robust culture of quality at all levels of the Bayview facility through:

- **Facility leadership engagement.** Emergent understands that consistent, visible support from site leadership is critical to ensuring quality and compliance across the facility. Emergent notes that the site currently has open positions for (b) (4) and (b) (4) . The company is committed to filling these roles with individuals who share Emergent's commitment to quality, including holding individuals accountable for consistently following site policies and procedures.

  Demonstrating the company's commitment to oversight at the Bayview facility, the Interim General Manager position is being filled by Dino Muzzin, Senior Vice President for Manufacturing Operations. Emergent will continue to fill leadership positions with individuals with a strong quality mindset. In particular, Emergent has communicated its expectation that site leadership will be routinely present in the manufacturing area, including performing routine facility walks to observe manufacturing operations and facility maintenance. Leadership engagement will also be demonstrated through accountability for personnel who fail to adhere to site policies and procedures, up to and including termination.

- **Quality culture initiative.** Emergent understands the importance of instilling a robust culture of quality at the Bayview facility at all levels of the organization. To enhance site quality culture maturity, Emergent is reinforcing the foundation of compliance at the site, through skill building, increasing technical and quality expertise, quality and oversight on the floor, and implementing best practices by leveraging third-party expertise. For example, (b) (4) To increase quality culture maturity, these supervisors will be provided enhanced training on all aspects of their responsibilities, including technical skills, compliance, and viral containment, among other subjects.

The site has rapidly evolved and grown, and Emergent recognizes the need to ensure that Bayview facility personnel understand and share the company's commitment to quality. Emergent also understands the need to give personnel the resources they need to consistently and effectively perform their responsibilities. The Bayview facility is currently engaging the expertise of third-party experts (b) (4) to oversee implementation of interim controls. The company will leverage these third-party resources to raise the understanding of site personnel and enable them to assume responsibility for quality at the site long term.

- **Quality unit assessment.** Emergent is committed to ensuring an effective and efficient quality unit at the Bayview facility. As described above, the company has recently brought on new facility and corporate quality leaders to lead the transformation of the Bayview quality unit. In addition, the quality unit has grown rapidly as site operations have expanded to meet the need for Covid-19 vaccine production. The company recognizes the opportunity to evaluate the performance of the quality unit and identify areas for improvement, including areas to develop subject matter expertise. This initiative will be led by the new site quality leader with support from Emergent corporate quality.

- **Skill development initiative.** Emergent recognizes the need for personnel to have the technical and procedural skills to effectively carry out their responsibilities. The company will develop and implement skill building training, to ensure that site personnel have a holistic understanding of the manufacturing process and key elements that impact product safety and quality. This will include developing and implementing a technical skill tutorial for the manufacturing process in collaboration with J&J SMEs.

- **Facility maintenance.** To ensure the site is consistently maintained in a good state of repair, Emergent will continue to emphasize detecting, escalating, and addressing facility maintenance issues as well as implementing industry best practices for cleaning and disinfecting. The site will also develop and implement a new site master plan to assess and document facility upgrade and construction needs.

- **Enhanced investigations program.** As planned prior to FDA's April 2021 inspection, the Bayview facility will adopt Emergent's new corporate quality procedure on deviation investigations, ensuring appropriately documented investigations with scientifically justified conclusions, including for root cause determinations. Bayview personnel will receive instructor-led training on the new procedure, with modules on root cause analysis techniques and investigation skills. The new procedure includes additional clarity regarding what is and what is not a deviation and more clearly defines escalation requirements, the escalation process, and QA's responsibilities for review and approval of the deviation investigation. Emergent notes that the Bayview facility is scheduled to implement the new corporate investigation procedure no later than (b) (4) .

- **CAPA effectiveness verification.** To ensure that the CAPA undertaken in response to the 483 are appropriately implemented and effective, and sustainable, Emergent will verify CAPA effectiveness based on defined criteria, as described in the company's global procedure on GxP CAPA management. In addition, Emergent will leverage independent third-party expertise, including from J&J, to verify CAPA implementation, as appropriate.

III. Emergent's Specific Responses to the 483 Observations

OBSERVATION 1

Failure to conduct thorough investigations into unexplained discrepancies.

Specifically,

a. *The cross-contamination of client* (b) (4) *viral vaccine drug substance batch* (b) (4) *which was manufactured between* (b) (4) *and* (b) (4) *, with the virus from client* (b) (4) *as described in deviation 3100012112 initiated on 3/17/2021 has not been thoroughly investigated. Specifically,*

   i. *The deviation did not include consideration of operator* (b) (6) *who is recorded on the batch record as weighing and dispensing the raw materials for media batch* (b) (4) *used in the manufacture of* (b) (4) *batch* (b) (4) *on* (b) (4) *. This batch of media is implicated by your firm in the deviation as the most probable cause of the cross-contamination event. Operator* (b) (6) *also entered both manufacturing areas where client* (b) (4) *viral vaccine drug substance and client* (b) (4) *viral vaccine drug substance are respectively manufactured on* (b) (4) ,(b) (4) (b) (4) *these raw materials based upon badge access data and video surveillance. Operator* (b) (6) *was observed on the security camera footage dated* (b) (4) *wearing protective gowning and foot protection in the controlled not classified hallway outside the* (b) (4) *room before entering the* (b) (4) *room through the* (b) (4)

   ii. *The deviation investigation did not include a thorough review of personnel movements in and around the facility as a potential source of contamination.*

   iii. *The deviation did not include consideration of the potential impact of the continued use of* (b) (4) *to store raw materials used to manufacture* (b) (4) *used in the manufacture of client* (b) (4) *viral vaccine drug substance and client* (b) (4) *viral vaccine drug substance. These* (b) (4) *were identified in the deviation as being not designed to allow for proper decontamination.*

   iv. *It is not known how long client* (b) (4) *virus will remain viable on a surface. There was no additional cleaning performed other than the routine cleaning in response to this deviation.*

   v. *There is no assurance that other batches have not been subject to cross-contamination.*

b. *On* (b) (4) *, during the filling of batch* (b) (4) *bulk drug substance for client* (b) (4) *released on* (b) (4) *, a* (b) (4) *leak was observed by the operator. The fill*

recipe was paused and (b) (4) *was* (b) (4) *, then the recipe was aborted, and a new recipe was initiated. The practice for aborting a fill is not described within a written procedure and is not a procedural step in the master batch record. Your firm failed to investigate how the operators were trained to perform this recipe abort and initiate a new recipe technique. Your firm also failed to investigate what impact utilizing this technique has on the product during filling operations.*

c. *On 1/19/2021,* (b) (4) *room ID#* (b) (4) *and* (b) (4) *corridor ID* (b) (4) *had logbook entries "fix* (b) (4) *" and "*(b) (4)(b) (4) *". The bulk drug substance batch* (b) (4) *for client* (b) (4) *,released on* (b) (4) *was in the* (b) (4) *at the time of these logbook entries. Your firm failed to initiate a deviation and failed to conduct an investigation to evaluate what impact a* (b) (4) *had on bulk drug substance batch* (b) (4) *or what corrective actions were initiated.*

Response to Observation 1

Emergent understands the importance of thoroughly investigating deviations, including identifying attributable root causes, where possible. The Bayview facility's investigation SOP, SOP000261, *Deviation Investigation Process*, requires that any unexplained discrepancies is thoroughly investigated, root cause(s) determined, where possible, and effective corrective and preventive action (CAPA) implemented. Specifically, SOP000261 requires that deviation investigations include, as applicable:

- (b) (4)

SOP000261 also requires QA to perform the initial assessment of event details to determine the deviation criticality. Deviations considered to be major or critical with respect to potential product quality impact must be investigated in accordance with SOP001881 using the root cause analysis tools set forth in that SOP. In addition, any critical deviations are escalated to the Site Head of Quality for review and final approval.

Bayview facility investigations are performed by subject matter experts with QA oversight and approval. All site investigators are trained on SOP000261 and SOP001881, *Root Cause Analysis.*

As described above, Emergent is in the process of a company-wide investigation enhancement initiative. Prior to the cross-contamination deviation that triggered the April 2021 inspection, Emergent had developed and began implementing enhanced global corporate procedures SOP044111, *Global GMP Deviation Management Procedure*, and SOP044112, *Investigation and Root Cause Analysis Procedure for GMP Deviations*, at all Emergent sites, including the Bayview facility. SOP044112 and SOP044111 include detailed instructions for conducting investigations, including the use of robust root cause analysis tools. Under the new procedures, only qualified investigators who have completed the Emergent corporate quality-developed training can lead deviation investigations, ensuring quality and consistency across investigations.

Emergent has also developed and is implementing a global procedure relating to GxP CAPA management: SOP044131, *CAPA Management Procedure*. This global SOP will enhance processes for implementing and ensuring effectiveness of CAPAs across the company.

The Bayview facility is scheduled to receive instructor-led training on SOP044111, SOP04112, and SOP044131 no later than (b) (4) including modules on (b) (4) and (b) (4). Emergent is confident that these procedures and accompanying training will strengthen site investigation practices, including root cause analysis.

Pending the implementation and verification of effectiveness of these procedural and training enhancements, all newly initiated J&J drug substance batches will undergo independent third-party certification prior to release. This will include a review of any associated Bayview facility investigation to confirm the adequacy of the investigation, including the root cause analysis, and that conclusions are scientifically sound. (b) (4)

With respect to Observation 1(a), Emergent would like to reiterate that it takes the contamination event extremely seriously. As described in detail in Section I.D, above, immediately upon notification by J&J of the OOS result, Emergent self-initiated a manufacturing investigation, opening deviation 3100012112 on (b) (4). Deviation 3100012112 was performed in accordance with SOP00261 and SOP001881. Emergent's initial root cause analysis considered, among other things, (b) (4) and (b) (4) (b) (4), and a (b) (4) (b) (4) Although SOP00261 provides for critical deviation investigations to be completed within (b) (4) days to ensure a thorough investigation and full consideration of potential root causes, due to the critical nature of the deviation, a report for deviation 3100012112 was issued on (b) (4) days after the company became aware of the contamination OOS.

Emergent recognizes the opportunity to further strengthen the root cause analysis for deviation 3100012112 and, on (b) (4), initiated a new deviation to document the enhanced investigation. Emergent's new investigation included a detailed and expanded review of over twenty separate elements that could have played a role in the contamination event and the implementation of additional CAPAs. These include but are not limited to the following:

- (b) (4)

Emergent notes that as part of the investigation, the companies reviewed badge access records, video recordings, and interviewed operators, among other investigation activities. Based on the additional investigation, the following contamination prevention controls were identified:

- The contamination control plan will be updated to ensure that flow paths of raw materials, including (b) (4), prevent crossover with materials designated for other products
- Methods and controls will be identified for introduction of (b) (4), including amending the contamination control in the production envelope procedure SOP000390, *Cleanroom Behaviors and Contamination Control* (b) (4), to include specific instructions on (b) (4) and not from (b) (4)
- The use of (b) (4) will be eliminated through the implementation of (b) (4)
- (b) (4) used for handling the viral stock material will be replaced with new ones
- Updating the personnel gowning procedure SOP001516, *Personnel Flow and Gowning Procedure for* (b) (4), to state that (b) (4) will be required when handling viral material, which will be (b) (4) and (b) (4) before performing any additional activities

CAPAs identified in the prior assessments were reinforced through the additional investigation, including but not limited to:

- (b) (4)

By expanding the scope of the quality investigation, Emergent is confident that potential routes of contamination and cross-contamination have been evaluated and appropriate actions to address such routes are being implemented. Emergent is confident that these actions further reduce any potential risk of contamination at the Bayview facility.

Emergent also notes that, as described in detail in Section II, above, independent of deviation (b) (4), Emergent and J&J collaborated on a comprehensive review of potential sources of contamination at the Bayview facility. Based on the results of this review, Emergent is implementing the QEP to address potential sources of contamination.

With respect to product impact, an impact assessment of the OOS result was conducted, and (b) (4) testing was performed on all batches manufactured at the Bayview facility. Using (b) (4)), the presence and identity of only the (b) (4) and (b) (4) were confirmed for all batches within scope of this evaluation. The results of (b) (4) and (b) (4) testing confirmed that the incident had no impact on the other batches tested. FDA has been provided with details of these analyses and all underlying data.

An extended comparability assessment was conducted for the (b) (4) and (b) (4) batches manufactured according to the same manufacturing process variant as Batch (b) (4). Batch (b) (4) was the only batch exhibiting viral contamination.

(b) (4) *leak*

Regarding Observation 1(b), Emergent recognizes the importance of describing manufacturing steps in site procedures and/or master batch records, as appropriate. For context, the (b) (4) noted in the observation is a (b) (4). Due to the critical need for Covid-19 vaccine drug substance, this piece of

equipment was implemented in an accelerated fashion. Observation 1(b) relates to abortion of the fill process that was initiated to (b) (4) (b) (4) in the event of a (b) (4) in the (b) (4) and (b) (4). Emergent wishes to clarify that the Bayview facility initiated a deviation to investigate (b) (4) leaks.

Aborting the filling process due to a (b) (4) leak was taken based on discussions with the (b) (4) and (b) (4) Specifically, this cross-functional group determined that the operators should abort the process to (b) (4) of the (b) (4) (b) (4).

Additionally, in (b) (4) Emergent requested that the equipment vendor evaluate whether it would be possible (b) (4) (b) (4) (b) (4). The vendor performed (b) (4) testing under Emergent's operating conditions, confirming that there would not be (b) (4) or (b) (4) Accordingly, Emergent determined that the impact to product was low. In light of the observation, Emergent will re-open the deviation investigation to include this additional information.

Emergent also understands the importance of fully documenting all process steps. With respect to the lack of a specific procedure detailing how to abort a fill recipe and initiate a new recipe, Emergent is revising SOP044115, *Setup and Operation of the* (b) (4) (b) (4), and creating a Work Instruction WI042057, *Work Instruction for* (b) (4) (b) (4), to detail the process for aborting and documenting abortion of a batch process in the batch record. Relevant site personnel will be trained on the revised SOP and Work Instruction prior to implementation.

Emergent notes that, as described above, corporate procedures SOP044112, SOP044111, and SOP044131 include details regarding the appropriate identification and reporting of deviations. Site personnel will be trained on the procedures, including when to initiate a deviation.

(b) (4) *bulk drug substance* (b) (4)

With respect to Observation 1(c), Emergent would like to clarify that a deviation was in fact opened at the time of the event on (b) (4)—deviation (b) (4). Unfortunately, the existence of this deviation was not identified during the inspection.

The bulk drug substance is filled into (b) (4) upon completion of the manufacturing process. The individual (b) (4) are then (b) (4) (b) (4) (b) (4) (b) (4). The (b) (4) noted in Observation 1(c) was one of the (b) (4) into which the (b) (4) had been placed. These (b) (4) are not nor are they intended to be a (b) (4). Further, because the (b) (4) inside the (b) (4) was confirmed to be integral during the deviation investigation, it was determined that the (b) (4) had no impact on the bulk drug substance in the closed (b) (4).

Observation 1 Corrective and Preventive Actions

1.1 Emergent has developed global corporate procedures SOP044112, SOP044111, and SOP044131, with detailed instructions for conducting investigations, including the use of robust root cause analysis tools and providing structured approach for identifying, investigating, assessing, and addressing deviations.

Target Completion Date (TCD): Complete

1.2 Emergent will implement and conduct instructor-led training on corporate procedures SOP044112, SOP044111, and SOP044131 at the Bayview facility.

TCD: (b) (4)

1.3 Newly initiated J&J drug substance batches will undergo independent third-party certification by (b) (4) prior to release, including a review of any site investigation to confirm adequacy of the investigation and root cause analysis.

TCD: On-going upon resumption of new J&J drug substance manufacturing

1.4 Emergent has initiated a new deviation (b) (4) to document an additional comprehensive investigation of the OOS result originally investigated under deviation (b) (4) Additional CAPAs with associated target dates will be initiated upon completion of this investigation.

TCD: (b) (4) for completion of investigation (prior to resuming new manufacturing)

1.5 Emergent will revise SOP044115, *Setup and Operation of the* (b) (4) and creating a Work Instruction WI042057, *Work Instruction for* (b) (4) to detail the process for aborting and documenting abortion of a batch process in the batch record. Emergent will train appropriate site personnel on the revised procedure and work instruction on abortion of a batch process and documentation.

TCD: (b) (4)

1.6 Emergent will re-open the (b) (4) leak deviation investigation to include the vendor's impact assessment.

TCD: (b) (4)

OBSERVATION 2

The building used for the manufacture of the client (b) (4) *viral vaccine drug substance and client* (b) (4) *viral vaccine drug substance is not maintained in a clean and sanitary condition.*

Specifically,

a. *Waste generated during the manufacture of the client* (b) (4) *vaccine drug substance and client* (b) (4) *viral vaccine drug substance is not decontaminated using* (b) (4) *that have been qualified for use of a* (b) (4) *qualified for actual use. Such waste is transported through the warehouse before disposal and has the potential to contaminate the warehouse and adjacent areas*

b. *The manufacturing rooms and corridors are not cleaned with a* (b) (4) .

c. *The painted floors in the warehouse were observed to be peeling on multiple days during the inspection. Large areas of the painted surface are missing in front of the* (b) (4) (b) (4) *and* (b) (4) *sampling rooms. The damaged floors and rough surfaces do not allow for adequate cleaning and sanitization.*

d. *On 4/14/2021, the paint on the walls of the controlled not classified corridors surrounding the manufacturing rooms for Areas* (b) (4) *and* (b) (4) *were observed to be peeling in multiple areas. Paint flecks were observed on the floor all along the sides of these walls. Damage to the wall boards was also observed approximately 6 inches above the floor and approximately 3 feet above the floor. This peeling paint and wall damage impacts the firms' ability to adequately clean and disinfect the area.*

e. *On 4/14/2021, the following items were observed inside room* (b) (4)*, a Grade* (b) (4) *room, during the filling of client* (b) (4) *viral vaccine drug substance batch* (b) (4)

    i. *Paint flecks, loose particles/debris, and a washer were observed on the floor along the sides of the wall*

    ii. *Brown residue was observed on the wall*

    iii. *Black residue was observed on the wall*

    iv. *Black residue from a* (b) (4) *was observed on the floor*

    v. *Blue peeling paint was observed along the door jam into room* (b) (4)

Response to Observation 2

Waste Decontamination

Viral containment is of paramount importance, and the Bayview facility's viral containment program includes the use of (b) (4) to decontaminate biowaste before removing it from the facility.

In light of Observation 2(a), Emergent is implementing significant enhancements to its (b) (4) validation and the practice and procedures related to the use of (b) (4) to decontaminate waste from the drug substance manufacturing process. Specifically, Emergent will:

- (b) (4)
- .

Emergent notes that the company has also performed facility walkthroughs to identify ways in which waste flow can be enhanced, facility modifications to improve the flow of waste, training on proper waste handling, increased documentation for each step in the waste handling process, and second-person verification for each step in the waste handling process.

Facility Cleaning and Maintenance

Emergent understands the importance of keeping manufacturing areas in clean and sanitary conditions and maintaining the Bayview facility in a good state of repair. Emergent notes that the facility maintenance program is designed to ensure that drug substances are manufactured in a clean and sanitary environment. Specifically, the Bayview facility has established procedures for cleaning Areas (b) (4) and (b) (4) SOP000392, *EMOB Cleaning Program for* (b) (4) (b) (4) *and* (b) (4) and the warehouse, SOP044245, *Warehouse Cleaning Procedure*, among others. Emergent would like to clarify that all cleaning procedures, including SOP000392, require (b) (4) floor cleaning with (b) (4) .

In light of Observations 2(b)-(e), Emergent is further strengthening the facility maintenance program by revising SOP027886, *Quality on the Floor Program*, to include routine checks throughout the facility. This includes checks of the (b) (4) by the (b) (4) at the (b) (4) checks by the manufacturing manager, and (b) (4) checks by site leadership team members. This also includes (b) (4) checks of the QC laboratory and the warehouse by the area manager and (b) (4) checks by site leadership team members. These checks will be performed using a checklist to ensure appropriate assessments are performed. Depending on the nature of any identified issue, repairs will be performed prior to initiating or resuming manufacturing activities or a work order will be initiated. Repairs will be tracked in logbooks and verified by site QA. In addition, site leadership will perform routine checks to ensure accountability and oversight.

Further, as part of the QEP, Emergent is upgrading the physical facility and site maintenance and cleaning practices and procedures. Quality and maintenance personnel, in collaboration with J&J, have completed a review of all areas used in drug substance manufacturing and assessed each area for cleaning, sanitization, maintenance and repair needs. In particular, Emergent has completed a comprehensive gap assessment of Bayview's cleaning and sanitization procedures, including for classified and non-classified areas.

Based on the results of the assessment, the Bayview facility will implement enhanced cleaning procedures, including specific procedures for (b) (4), and (b) (4) (b) (4) areas. Emergent notes that as part of the revised procedures, the warehouse area will be cleaned on a (b) (4) basis and (b) (4) at regular intervals. Further, to ensure that cleaning procedures are consistently followed, Emergent will provide on-the-job training to relevant personnel on performing cleaning. The effectiveness of these enhancements will be routinely monitored through increased oversight, including by Emergent QA, J&J SMEs, and (b) (4).

Additional QEP Phase 1 activities, which will be completed prior to initiating new manufacturing, include prioritizing (b) (4) to ensure that walls and floors throughout the facility are of appropriate construction to allow appropriate cleaning and prevent contamination. These include:

- (b) (4)

Emergent is confident that the facility is maintained in an adequate state of control and does not present a risk of product contamination.

Observation 2 Corrective and Preventive Actions

2.1 Emergent completed a comprehensive gap assessment of the site's cleaning and sanitization procedures.

TCD: Complete

2.2 Emergent will implement enhanced cleaning procedures that detail the performance of cleaning manufacturing areas. Emergent will provide training to relevant site personnel on the enhanced cleaning procedures.

TCD: (b) (4) (prior to resuming new manufacturing)

2.3 Emergent will revise SOP027886, *Quality on the Floor Program*, to include routine checks throughout the facility. This includes checks of the (b) (4) by the (b) (4) at the (b) (4), (b) (4) checks by the manufacturing manager, and (b) (4) checks by site leadership team members. This also includes (b) (4) checks of the QC laboratory and the warehouse by the area manager and (b) (4) checks by site leadership team members. These checks will be performed using a checklist to ensure appropriate assessments are performed.

TCD: (b) (4)

2.4 Emergent will (b) (4) (b) (4) including (b) (4), (b) (4), and (b) (4).

TCD: (b) (4) (prior to resuming new manufacturing)

2.5 Emergent will (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing in the impacted areas)

2.6 Emergent will (b) (4) .

TCD: (b) (4) (prior to resuming new manufacturing)

2.7 Emergent will install pre-made panels in the (b) (4) supporting (b) (4), warehouse (b) (4), and (b) (4).

TCD: (b) (4) (prior to resuming new manufacturing in the impacted areas)

2.8 Emergent will (b) (4) and (b) (4) and the (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing)

2.9 Emergent will demonstrate the functionality of the (b) (4) in accordance with a written protocol.

TCD: Complete

2.10 Emergent will optimize and qualify the (b) (4) using (b) (4) (b) (4) to demonstrate (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing)

2.11 Emergent will revise the (b) (4) SOP000388, (b) (4) and will train operators on the revised procedure.

TCD: (b) (4) (prior to resuming new manufacturing)

OBSERVATION 3

The building used for the manufacture of the client (b) (4) viral vaccine drug substance and client (b) (4) viral vaccine drug substance is not of suitable size, design, and location to facilitate cleaning, maintenance, and proper operations.

Specifically,

a. *The number and size of decontamination (b) (4) used to decontaminate waste generated during the manufacture of client (b) (4) viral vaccine drug substance or client (b) (4) viral vaccine drug substance are inadequate to ensure that such waste is decontaminated in a timely manner. In addition, an assessment of the building's capacity to decontaminate waste was not performed as part of the incoming process gap assessment prior to introduction of the manufacturing of client (b) (4) viral vaccine drug substance into the facility. The inadequacy of waste handling is underscored by planned deviation 3100012410 that was opened on 4/9/2021 to change the path of waste out of the building for Areas (b) (4) and (b) (4) and due to an increase in waste from Areas (b) (4) and (b) (4) this waste will not be (b) (4) , but it will be (b) (4) bagged and the exterior of the bag will be (b) (4) with (b) (4) prior to transport through the warehouse and out of the building for a limited number of days.*

b. *The warehouse was observed on 1/27/2021, 2/3/2021 and 2/4/2021 through security camera footage, and on 4/12/2021 and 4/13/2021 through direct observation, to be overcrowded with materials staged for entry into manufacturing as well as material staged for QC sampling.*

c. *On 4/14/2021, the Area (b) (4) , room (b) (4) was observed to be congested with (b) (4) and (b) (4) containers used to hold (b) (4) .*

d. *On 4/14/2021, the Area (b) (4) room (b) (4) was observed to be congested with carts, transport racks for (b) (4) drug substance, (b) (4) containers used to hold (b) (4) (b) (4) and drug substance, and various other pieces of equipment. The congestion made it difficult to move without bumping into equipment or (b) (4)*

e. *The doors into and out of the (b) (4) into the (b) (4) area and into the (b) (4) area are too small as operators are unable to use a pallet jack for pallets to move material in large containers. On 4/12 and 4/13/2021, operators were observed pushing and pulling large containers along the floor to move them from (b) (4) room and (b) (4) room into the warehouse.*

Response to Observation 3

The Emergent Bayview facility is designed to have adequate space for the orderly placement of equipment and materials to prevent mix-ups between different components, drug product

containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. Due to the rapid scale up in order to produce critically necessary drug substance for use in Covid-19 vaccines, the facility experienced a dramatic increase in storage and staging demands as the facility operated at full capacity for the first time. In addition, going to full capacity increased waste production with the full impact beginning in the latter part of December 2020. Accordingly, Emergent implemented an alternative biowaste removal process, which is noted in Observation 3(a).

In light of the investigators' observation and Emergent's investigation, the company will strengthen the Bayview facility's biowaste handling process. Specifically, under SOP044335, *Removal of Special Medical Waste from Manufacturing Areas*, when (b) (4) requires waste to be bagged and removed without decontamination, site personnel must (b) (4) (b) (4) and follow a defined exit pathway to remove the waste from the facility, with cleaning and (b) (4) performed along the exit route immediately following waste removal. Documentation of the removal process will be required at every step, including verification by a second person witnessing the activity. As noted above, as an interim control (b) (4) personnel will monitor and verify any waste removal activity.

With respect to the deviation referenced in Observation 3(a), Emergent wishes to clarify that the planned deviation was initiated to document the waste removal process while a procedure for waste removal without (b) (4) decontamination was developed and implemented. This process will now be performed in accordance with SOP 044335. With the optimization of (b) (4) allowing for more material to be decontaminated, (b) (4) is available to support decontamination of biowaste.

With respect to Observations 3(b)-(d), as part of Emergent's and J&J's comprehensive review of the manufacturing facility, described in Section 2, above, the companies collaborated on corrective and preventive actions to alleviate congestion and overcrowding at the facility. These include:

- (b) (4)

With respect to Observation 3(e), Emergent has (b) (4) (b) (4) to allow for entry of materials on pallets or dollies, avoiding contact with floor surfaces.

Observation 3 Corrective and Preventive Actions

3.1 Emergent will strengthen the Bayview facility's biowaste handling process. Specifically, under SOP044335, *Removal of Special Medical Waste from Manufacturing Areas*, when (b) (4) requires waste to be bagged and removed without decontamination, site personnel must (b) (4) of the bag and follow a defined exit pathway to remove

the waste from the facility, with cleaning and (b) (4) performed along the exit route immediately following waste removal.

TCD: (b) (4) (prior to resuming new manufacturing)

3.2 Emergent will evaluate alternatives to (b) (4) in the warehouse.

TCD: (b) (4) (for the evaluation)

3.3 Emergent will ensure that materials and supplies only enter rooms (b) (4) and (b) (4) when needed for production, to avoid congestion with staged materials. This will be verified during (b) (4) area walkthroughs.

TCD: (b) (4) (prior to resuming new manufacturing)

3.4 Emergent has (b) (4) (b) (4) to allow for entry of materials on pallets or dollies, avoiding contact with floor surfaces.

TCD: Complete

OBSERVATION 4

Written production and process control procedures to prevent cross-contamination are not followed in the execution of production and process control functions and are not documented at the time of performance.

Specifically,

a. *According to security camera footage from 1/27/2021 and 2/3/2021, employees handling special medical waste from manufacturing Area* (b) (4) *where bulk drug substance for client* (b) (4) *is manufactured, failed to follow SOP041888 v 3.0 (effective 8/21/2020) regarding handling nondisinfected and non-decontaminated special medical waste.*

    i. *On 1/27/2021 and 2/3/2021, employees in manufacturing Area* (b) (4) *where bulk drug substance for client* (b) (4) *is manufactured, were observed throwing unsealed bags of special medical waste into the service elevator accessing the warehouse corridor.*

    ii. *On 1/27/2021 and 2/3/2021, employees in manufacturing Area* (b) (4) *where bulk drug substance for client* (b) (4) *is manufactured, failed to* (b) (4) *all special medical waste with* (b) (4) *.*

    iii. *On 1/27/2021 and 2/3/2021, employees were observed carrying unsealed bags of special medical waste from manufacturing Area* (b) (4) *The unsealed bags were observed contacting containers of staged manufacturing materials, walls, and fence barriers in the* (b) (4) *corridor of the warehouse.*

    iv. *On 1/27/2021 and 2/3/2021, employees were observed dragging used materials containers and unsealed bags of special medical waste from manufacturing Area* (b) (*across the floor of the* (b) (4) *corridor of the warehouse.*

    v. *On 2/3/2021, employees were observed compacting, using their gloved hands, unsealed bags of special medical waste from manufacturing Area* (b) (*in the warehouse where raw materials were staged for manufacturing in Area* (b) (4) *for client* (b) (4)

    vi. *On 2/3/2021, employees were observed removing their outer protective garments onto the warehouse floor where raw materials were staged for manufacturing in Area* (b) (4) *for client* (b) (4) *and placing the garments in open garbage containers.*

b. *According to direct observation and security camera footage from 2/4/2021 and 4/12/2021, employees handling raw materials intended for the use in manufacturing Area* (b) (4) *where bulk drug substance for client* (b) (4) *failed to follow SOP001518 v 15.0 (effective 4/9/2021)*

and SOP001518 v 14.0 (effective 9/3/2020) regarding the handling of materials into the (b) (4) *room and the* (b) (4) *sampling room.*

i. *On 2/4/2021, employees were observed dragging containers of raw materials across the floor of the* (b) (4) *warehouse corridor failing to apply* (b) (4) *to the bottom of the container.*

ii. *On 4/12/2021, employees were observed dragging containers of raw materials across the floor of the* (b) (4) *warehouse corridor floor failing to apply* (b) (4) *to the bottom of the container.*

iii. *On 4/12/2021, employees were observed dragging containers of raw materials across the floor of the* (b) (4) *corridor failing to apply* (b) (4) *to the bottom of the container.*

c. *According to security badge access logs, shower logs, and security camera footage from 1/19/2021 to 2/21/2021, employees were observed entering manufacturing Area* (b) (4) *where bulk drug substance for client* (b) (4) *and Area* (b) (4) *where bulk drug substance for client* (b) (4) *in the same day failing to document de-gowning, showering, and gowning activities according to SOP001516 v 23.0 (effective 2/5/2021) and SOP001516 v 22.0 (effective 9/2/2019).*

i. *According to the security badge access log, security camera footage, and batch record* (b) (4) *on* (b) (4)*, a manufacturing associate (Operator upstream MFG) was observed entering manufacturing Area* (b) (4) *when manufacturing for client* (b) (4) *was taking place, then* (b) (4) *for raw materials for client* (b) (4)*, and then loading of materials into the* (b) (4) *in manufacturing Area* (b) (4) *for client* (b) (4) *without documenting de-gowning and showering.*

ii. *According to security badge access logs between 1/19/21 — 2/21/21, one MFG Bioprocess Associate entered manufacturing Area* (b) (4) *and manufacturing Area* (b) (4) *on the same day, during 19 different days, only documenting once in shower logbook on 2/21/21.*

iii. *According to security badge access logs between 1/19/21 — 2/21/21, one engineer entered manufacturing Area* (b) (4) *and Area* (b) (4) *on the same day, during 4 different days, not documenting in shower logbook for any of the days.*

iv. *According to firm management between 1/19/21 — 1/31/21, approximately 14 different personnel entered manufacturing Area* (b) (4) *and manufacturing Area* (b) (4) *on the same day, there was no documentation of a shower.*

v. *According to firm management between 2/1/21 — 2/11/21, approximately 13 different personnel entered manufacturing Area (b) (4) and manufacturing Area (b) (4) on the same day, there was only one documented in the shower logbook.*

vi. *According to firm management between 2/12/21 — 2/21/21, approximately 13 different personnel entered manufacturing Area (b) (4) and manufacturing Area (b) (4) on the same day, there were only two documented in the shower logbook.*

d. *According to direct observation and security camera footage from 1/27/2021 to 4/12/2021, employees were observed entering the materials airlock for manufacturing Area (b) (4) where bulk drug substance for client (b) (4) is manufactured, warehouse, (b) (4) room, and (b) (4) room failing to adhere designated gowning zones according to SOP001516 v 23.0 (effective 2/5/2021) and SOP001516 v 22.0 (effective 9/2/2019).*

i. *According to security camera footage on 1/27/2021, employees were observed removing gloves and booties into waste containers located in the warehouse with staged raw materials present after handling special medical waste from manufacturing Area (b) (4)*

ii. *According to security camera footage on 2/3/2021, employees were observed removing protective gowns onto the floor of the warehouse and into waste containers located in the warehouse with staged raw materials present after handling special medical waste from manufacturing Area (b) (4)*

iii. *Per direct observation on 4/12/21, employees were observed wearing protective gowns and booties into the warehouse and warehouse corridor while conducting activities in the Area (b) (4) materials airlock, (b) (4) room, and (b) (4) (b) (4) room.*

Response to Observation 4

Emergent understands the importance of following and documenting adherence to written production and process control procedures to prevent cross-contamination in the execution of production and process control functions. In this regard, Emergent has established robust requirements relating to the flow of personnel and personnel gowning practices to prevent contamination and cross-contamination. From a personnel flow perspective, operators enter the (b) (4) through (b) (4) entrance for each manufacturing area. Once inside the (b) (4), movement through the suites is (b) (4), and operators (b) (4) (b) (4) through (b) (4) exit for each area.

With respect to operator movement between Areas (b) (4) and (b) (4) and Area (b) (4) specifically, Emergent wishes to clarify that, at the time of the inspection, the requirement to shower when moving between Areas (b) (4) and (b) (4) and Area (b) (4) was based on whether an operator had been exposed to a "viral" area within the manufacturing suite. In this context, a "viral" area is one where, based on the

process flow, the operator could have been exposed to live virus. Emergent notes that with the decommissioning of Area (b) (4) and focus on production of drug substance for the J&J vaccine, the Bayview facility is eliminating showering requirements, as they are no longer necessary to prevent cross-contamination. Emergent is also confident that the decommissioning of Area (b) (4) will prevent recurrence of the observations noted in Observation 4(c).

In addition, Emergent has identified a number of procedural, training, and process flow enhancements to prevent contamination. These include:

- Identifying, confirming, and strengthening the process and waste flows across the facility. Specifically, Emergent has conducted a comprehensive assessment to identify changes needed to ensure segregation of flows. As a result of this assessment, Emergent is implementing revised flows that ensure that waste does not cross paths with materials or personnel involved in manufacturing operations. Specifically, SOP001516 will be revised to define relevant requirements, which will be enforced through third-party oversight. Additionally, (b) (4) .
  At an operator level, Emergent will define and enforce gowning and de-gowning requirements that will mitigate the risk of contamination.

  Emergent is confident that these actions will prevent recurrence of the observations noted in Observation 4(a).

- Emergent has also (b) (4) (b) (4) under Change Control 2100006389 to allow for entry of materials on pallets or dollies, thereby avoiding contact with floor surfaces. This includes training on how to transport raw materials.

  In conjunction with this Change Control, Emergent amended SOP1516 for the (b) (4) area to reflect the enhanced flow and to more clearly describe operator gowning requirements.

  Emergent is confident that these actions will prevent recurrence of the observations noted in Observation 4(b).

Emergent will not resume new batch starts until these enhancements have been implemented.

Emergent is also using this voluntary shutdown period to provide training to operators across the facility, as discussed below in the response to Observation 7. These trainings include role-specific training modules to ensure that operators engaged in similar critical manufacturing activities—*e.g.*, waste handling—have received the same training. Emergent is confident that this enhanced training program will prevent recurrence of the observations noted in Observation 4(d), as well several of the investigators' other inspectional observations.

The effectiveness of these numerous enhancements will be continuously monitored through Emergent's enhanced QA on the floor program and through the company's implementation of third-party oversight. These CAPAs will also be evaluated through periodic effectiveness checks.

Observation 4 Corrective and Preventive Actions

4.1 Emergent has discontinued production of AstraZeneca Covid-19 vaccine drug substance in Area (b) (4) which will eliminate the risk of cross-contamination presented by movement between Areas (b) (4) and Area (b) (4

TCD: Complete

4.2 Emergent is implementing revised flows that ensure that waste does not cross paths with materials or personnel involved in manufacturing operations.

TCD: (b) (4) (prior to resuming new manufacturing)

4.3 Emergent has installed an (b) (4) .

TCD: Complete

4.4 Emergent will define and enforce gowning and de-gowning requirements that will mitigate the risk of contamination. Specifically, SOP001516 will be revised to define relevant requirements, which will be enforced through third-party oversight.

TCD: (b) (4) (prior to resuming new manufacturing)

4.5 Emergent has (b) (4) under Change Control 2100006389 to allow for entry of materials on pallets or dollies, avoiding contact with floor surfaces.

TCD: Complete

4.6 The effectiveness of these enhancements will be continuously monitored through Emergent's enhanced QA on the floor program and through the company's implementation of third-party oversight.

TCD: On-going

OBSERVATION 5

The components, product containers and/or closures were not handled and/or stored in a manner to prevent contamination.

Specifically,

Product components, containers, and closures involved in manufacturing operations, quality control sampling, weigh and dispense operations are not handled and stored to prevent cross contamination of viral bulk drug substances created for client (b) (4) *and client* (b) (4)

a. *On 3/16/2021, the firm was notified by client* (b) (4) *that bulk drug substance batch* (b) (4) *manufactured between* (b) (4) *and* (b) (4) *was contaminated with a* (b) (4) *used in the manufacture of bulk drug substance for client* (b) (4) *Review of security camera footage found:*

   i. *On 1/27/2021 and 2/3/2021, employees were observed carrying unsealed bags of special medical waste from manufacturing Area* (b) (4) *The unsealed bags contacted containers of staged manufacturing materials, walls, and fence barriers in the* (b) (4) *corridor of the warehouse.*

   ii. *On 1/27/2021 and 2/3/2021, employees were observed dragging used materials containers and unsealed bags of special medical waste from manufacturing Area* (b) (*across the floor of the* (b) (4) *corridor of the warehouse.*

   iii. *On 2/3/2021, employees were observed compacting unsealed bags of special medical waste from manufacturing Area* (b) (4 *in the warehouse where raw materials were staged for manufacturing in Area* (b) (4 *for client* (b) (4)*.*

   iv. *On 2/3/2021, employees were observed removing outer protective garments onto the warehouse floor and placing them in open garbage containers where raw materials were staged for manufacturing in Area* (*for client*

   v. *On [1/27/2021], an employee was observed putting* (b) (4) *material bucket containers on a table in the service elevator accessing manufacturing Area* (b) (4 *amongst unsealed special medical waste from manufacturing Area* (b) (4) *then bringing the* (b) (4) *material bucket containers into the* (b) (4) *room without decontaminating or disinfecting the* (b) (4) *materials bucket containers.*

   vi. *On 2/4/2021, employees were observed dragging containers of raw materials across the floor of the* (b) (4) *warehouse corridor failing to apply* (b) (4) *to the bottom of the container.*

b. On 4/12/2021, employees were observed dragging containers of raw materials across the floor of the (b) (4) *and* (b) (4) *warehouse corridor floor failing to apply* (b) (4) *to the bottom of the container.*

c. On 4/12/2021, we observed (b) (4) *material bucket containers with cracked or opened closures in the raw materials staging area of the warehouse staged for manufacturing in Area* (b) (4) *for client* (b) (4)

d. On 4/14/2021, we observed employees lifting containers of (b) (4) *onto a platform, opening the container, and then using a scoop to add the* (b) (4) *into the* (b) (4) *of a* (b) (4) *for* (b) (4) *batch* (b) (4) *in manufacturing in Area* (b) (4) *We observed the employees failing to remove or sanitize their gloves after grabbing the bottom of the container.*

Response to Observation 5

Emergent recognizes the importance of handling and storing components, product containers, and closures in a manner to prevent contamination. With respect to Observation 5(a) and as detailed above, Emergent has decided to permanently cease drug substance manufacturing activities for the AstraZeneca Covid-19 vaccine and is in the process of decommissioning Area (b) (4) which is where drug substance manufacturing activities for the AstraZeneca Covid-19 vaccine were performed. Emergent's decommissioning activities are being carried out pursuant to a written decontamination protocol. Emergent's Bayview facility is now dedicated to the manufacture of drug substance for Janssen's Covid-19 vaccine, thereby eliminating the risk of cross-contamination going forward.

In addition to permanently ceasing drug substance manufacturing activities for AstraZeneca's Covid-19 vaccine, Emergent has also completed a comprehensive assessment of the Bayview facility's material handling practices. Based on this assessment, Emergent has initiated several additional actions that address Observations 5(b) and (c). These include segregating raw material and waste flows; strengthening procedures and practices around waste decontamination and removal; replacing the (b) (4) material bucket containers with (b) (4) (b) (4) and revising SOP001518 to require visual inspection of material (b) (4) before each use and to require documentation of this visual inspection in the equipment logbook.

Further, materials in the facility will be evaluated according to an approved protocol to determine if they must be discarded based upon a risk of exposure to contamination (e.g., opened containers of raw materials) or if they can be cleaned and decontaminated ((b) (4) (b) (4)). Only those materials that can be cleaned and decontaminated and pose no risk of contamination will be used in future production.

At the operator level, Emergent has also initiated several actions to strengthen material handling practices at the Bayview facility. As discussed below in the response to Observation 7, this includes role-specific training modules to ensure that operators engaged in similar critical manufacturing activities—*e.g.*, raw material handling—have received appropriate training to

perform such activity. Emergent is confident that this enhanced training program will prevent recurrence of the observations noted in Observation 5(d), as well as several of the investigators' other inspectional observations.

The effectiveness of these numerous enhancements will be continuously monitored through Emergent's enhanced QA on the floor program and through the company's implementation of third-party oversight. These CAPAs will also be evaluated through periodic effectiveness checks.

Emergent is confident that the above actions will broadly strengthen materials handling practices across the facility and prevent recurrence of the observations noted in Observation 5.

Observation 5 Corrective and Preventive Actions

5.1 Emergent has discontinued production of AstraZeneca Covid-19 vaccine drug substance in Area (b) (4) which will eliminate the risk of cross-contamination presented by movement between Areas (b) (4) and Area (b) (4)

TCD: Complete

5.2 Emergent has implemented revised flows that ensure that waste does not cross paths with materials or personnel involved in manufacturing operations.

TCD: Complete

5.3 Emergent will replace the (b) (4) material bucket containers with (b) (4) (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing)

5.4 Emergent will revise the individual media preparation batch records regarding the use of (b) (4) and train personnel on the revised batch records.

TCD: (b) (4) (prior to resuming new manufacturing)

5.5 Emergent will revise SOP001518 to require visual inspection of material (b) (4) before each use and to require documentation of this visual inspection in the equipment logbook.

TCD: (b) (4) (prior to resuming new manufacturing)

5.6 Emergent will evaluate materials in the Bayview facility according to an approved protocol to determine if they must be discarded based on risk of exposure to contamination, or if they can be cleaned and decontaminated.

TCD: (b) (4) (prior to resuming new manufacturing)

5.7 Emergent will implement enhanced Quality Assurance on the floor and third-party oversight to continuously monitor the effectiveness of the implemented enhancements.

TCD: On-going

OBSERVATION 6

Written procedures designed to assure that the drug substances manufactured in the facility have the identity, strength, quality, and purity they purport or are represented to possess are inadequate.

Specifically,

a. *The procedure for decontamination of waste generated during the manufacture of the client* (b) (4) *viral vaccine drug substance and client* (b) (4) *viral vaccine drug substance described in SOP040195 does not include a description of how the bags containing the waste are to be placed into the* (b) (4) *to ensure that there is adequate* (b) (4) *into these bags to decontaminate the waste. Such waste is transported through the warehouse, where raw materials are received and staged, prior to disposal.*

b. *The procedure used for the periodic monitoring of decontamination* (b) (4) *effectiveness described in BOP040102 and documented on FRM042531 does not include a requirement for placement of the* (b) (4) *or* (b) (4) *in a* (b) (4) *location inside the* (b) (4) *to support that all of the waste is decontaminated. Such waste is transported through the warehouse, where raw materials are received and staged, prior to disposal.*

c. *The procedure for cleaning and decontamination of* (b) (4) *used to store and transport raw materials described in SOP001518 does not include a requirement for cleaning the* (b) (4) *or to remove residual* (b) (4) *onto the* (b) (4) *prior to placing* (b) (4) *used to store the raw materials inside the* (b) (4) *Such* (b) (4) *were identified in deviation 3100012112 as being able to introduce material on the outside of the* (b) (4) *into a* (b) (4) *in which* (b) (4) *used to manufacture the client* (b) (4) *viral vaccine drug substance are formulated.*

d. *The procedure "Material and Waste Flow for Area* (b) (4) *SOP041888, version 3.0, effective 21 Aug 2020 does not reflect current operations for the movement of contaminated waste. The procedure states* (b) (4) *all potentially contaminated waste", however staff in Area* (b) (4) *were allowed to dispose of potentially contaminated waste without first using the* (b) (4) .

Response to Observation 6

Emergent understands the need for establishing and following robust written procedures designed to assure that the drug substances manufactured in the facility have the identity, strength, quality, and purity they purport or are represented to possess. Due to the nature of the drug substance manufacturing activities performed at the Bayview facility, such written procedures include a robust cross-contamination risk mitigation plan that describes the flow of processes, people, and

materials into and out of the facility and defines the risk mitigation steps required to reduce the risk of cross-contamination at each step.

Emergent also recognizes that the rapid ramp-up of full-scale manufacturing activities for two live virus Covid-19 vaccine drug substances revealed several areas for further strengthening with respect to the Bayview facility's cross-contamination control procedures. For example, going to full capacity increased waste production with the full impact beginning in the latter part of December 2020. Accordingly, Emergent implemented an alternative biowaste removal process.

In light of the investigators' observations and Emergent's investigation, Emergent is strengthening the Bayview facility's waste management and decontamination procedures. In particular, prior to resuming new batch starts, Emergent will:

- Demonstrate the functionality of the (b) (4) in accordance with a written protocol; and
- Optimize and qualify the (b) (4) to demonstrate appropriate viral log reduction.

To address Observation 6(a), Emergent will revise the (b) (4) decontamination SOP000388, *Operation of the Decontamination* (b) (4), based on the (b) (4) qualification to describe how the (b) (4) containing the waste are to be placed into the (b) (4) (b) (4) to ensure that there is adequate (b) (4) into these (b) (4) to decontaminate the waste.

With respect to Observation 6(b), Emergent will revise BOP040102, (b) (4) (b) (4), to include a requirement for placement of the (b) (4) or (b) (4) in a (b) (4) location inside the (b) (4) to support that all waste is decontaminated. This activity will be documented in revised FRM042531, *Decontamination* (b) (4) *Testing Form*.

To address Observation 6(d) and as detailed above, Emergent will strengthen the Bayview facility's biowaste handling process. Specifically, under SOP044335, *Removal of Special Medical Waste from Manufacturing Areas*, when (b) (4) requires waste to be (b) (4) and removed without (b) (4) decontamination, site personnel must (b) (4) and follow a defined exit pathway to remove the waste from the facility, with cleaning and (b) (4) performed along the exit route immediately following waste removal. Documentation of the removal process will be required at every step, including a second person verification by someone who actually witnessed the step. As noted in Section II, above, as an interim control (b) (4) personnel will monitor and verify any waste removal activity.

Emergent's waste management plan also incorporates facility modifications and materials and process flow changes to facilitate the segregation of waste from (b) (4) and finished drug substance, training on proper waste handling, increased documentation for each step in the waste handling process, and second-person verification for each step in the waste handling process.

Adherence to the strengthened decontamination SOPs will be monitored through Emergent's enhanced quality oversight program, including Emergent QA on the floor and third-party oversight.

With respect to the Bayview facility's use of (b) (4) to store and transport (b) (4) (Observation 6(c)), as detailed above in the response to Observation 5, Emergent has moved to (b) (4)) to address the risk of contamination from a previously-used (b) (4) This will be documented in the revised individual media preparation batch records. Emergent is confident that replacing the raw material (b) (4) with (b) (4) addresses the observation noted in Observation 6(c) and also reduces the risk of contamination.

Observation 6 Corrective and Preventive Actions

6.1 Emergent will demonstrate the functionality of the (b) (4) in accordance with a written protocol.

TCD: Complete

6.2 Emergent will optimize and qualify the (b) (4) (b) (4) to demonstrate appropriate viral log reduction.

TCD: (b) (4) (prior to resuming new manufacturing)

6.3 Emergent will revise the (b) (4) decontamination SOP000388, *Operation of the* (b) (4) , to describe how the bags containing the waste are to be placed into the (b) (4) to ensure that there is adequate (b) (4) into these (b) (4) to decontaminate the waste.

TCD: (b) (4) (prior to resuming new manufacturing)

6.4 Emergent will revise BOP040102, *Decontamination* (b) (4) *Testing Program*, to include a requirement for placement of the (b) (4) or (b) (4) in a (b) (4) location inside the (b) (4) to support that all of the waste is decontaminated.

TCD: (b) (4)

6.5 Emergent will implement SOP044335, *Removal of Special Medical Waste from Manufacturing Areas*, to establish robust controls relating to the disposal of (b) (4) biowaste.

TCD: (b) (4) (prior to resuming new manufacturing)

6.6 Emergent will revise the individual media preparation batch records regarding the use of (b) (4) and train personnel on the revised batch records.

TCD: (b) (4) (prior to resuming new manufacturing)

6.7 Emergent will implement enhanced QA on the floor and third-party oversight to continuously monitor the effectiveness of the implemented enhancements.

TCD: On-going

OBSERVATION 7

Employees were not trained in the particular operation that they performed and/or in CGMPs related to their job function.

Specifically,

The firm has failed to adequately train personnel involved in manufacturing operations, quality control sampling, weigh and dispense, and engineering operations to prevent cross contamination of bulk drug substances created for client (b) (4) *and client* (b) (4).

Review of security camera footage found:

a. *Personnel involved in manufacturing operations entered manufacturing Area* (b) (*while processing of client* (b) (4) *bulk drug substance was taking place, then entered* (b) (4) (b) (4) *rooms where operations for client* (b) (4) *bulk drug substance was taking place without properly adhering to gowning procedures.*

b. *Personnel involved in manufacturing operations and engineering entered manufacturing Area* (b) (4) *while processing of client* (b) (4) *bulk drug substance was taking place, then entered manufacturing Area* (b) (4 *while processing for client* (b) (4) *bulk drug substance was taking place without properly adhering to gowning procedures.*

c. *Personnel involved in manufacturing operations dragged non-disinfected and non-decontaminated special medical waste from manufacturing Area* (b) (*across the warehouse corridor,* (b) (4) *corridor, and* (b) (4) *corridor floors, failing to adhere to materials and waste handling procedures.*

d. *Personnel involved in manufacturing operations collided with walls, warehouse barriers,* (b) (4) *doors,* (b) (4) *doors, and staged raw material containers with nondisinfected and non-decontaminated special medical waste from manufacturing Area* (b) (4 *failing to adhere to materials and waste handling procedures.*

e. *Personnel involved in manufacturing operations removed protective gowns and foot covers worn in manufacturing Area* (b) (4) *and handling non-disinfected and non-decontaminated special medical waste from manufacturing Area* (b) (4) *in the warehouse with staged raw materials, failing to adhere to gowning procedures.*

The following was directly observed during the inspection:

f. *Personnel involved with* (b) (4) *, and* (b) (4) *operations were observed dragging raw material containers used in manufacturing Area* (b) (*across the* (b) (4) (b) (4) *and* (b) (4) *corridor, failing to adhere to materials and waste handling procedures.*

Response to Observation 7

Emergent understands the critical importance of having appropriate training for GMP personnel and of ensuring that operators are trained on the necessity of fully understanding and adhering to established procedures. Emergent will enhance training opportunities and requirements for site personnel, with a focus on ensuring employees' understanding of contamination containment. Emergent is using the pause in new manufacturing to provide comprehensive training to facility personnel, to ensure that, upon resumption of operation, site personnel will be prepared to execute their roles in a consistently GMP-compliant manner. Emergent has conducted a comprehensive review and evaluation of its training program and, in light of the 483 observations, is further strengthening the program as described below.

In the immediate term, Emergent will conduct specific training to support one-time changes associated with the resumption of manufacturing of new drug substance lots for the Janssen Covid-19 vaccine, such as activities associated with decontamination of Area (b) (4) Emergent will identify personnel who need to be trained, create training materials reviewed and approved by subject matter experts (SMEs), provide training to site personnel, and implement oversight of the training process to ensure the delivery of the training is effective.

Prior to resuming initiation of new Janssen Covid-19 vaccine drug substance lots, Emergent will develop and deliver integrated and instructor-led training related to routine activities, such as (b) (4), and (b) (4) activities. Emergent will develop *role-based* training curricula, again created and approved by SMEs, and train cohorts of cross-functional employees who require knowledge of that curriculum. For example, operators, engineers, QA personnel, and others involved in waste handling will be trained comprehensively on the waste handling curriculum. Moreover, as part of Emergent's interim controls, a third-party will provide oversight of the delivery of training to ensure its effectiveness, including execution of critical activities after training.

To address the observations in the 483, the curricula will include training on GMP principles, microbial contamination prevention, and viral containment. This program will provide specialized additional training specific to the issues identified in the 483 and will include examples from the April 2021 inspection. Education on viral containment will be included in annual training for site personnel.

Observation 7 Corrective and Preventive Actions

7.1 Emergent will conduct specific training to support one-time changes associated with the resumption of manufacturing of new drug substance lots for the Janssen Covid-19 vaccine, such as activities associated with decontamination of Area (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing)

7.2 Emergent will develop and deliver integrated and instructor-led training related to routine activities, such as (b) (4), and (b) (4) activities.

TCD: (b) (4) (prior to resuming new manufacturing)

7.3 As part of Emergent's interim controls, a third-party will provide oversight of the delivery of training to ensure its effectiveness, including execution of critical activities after training

TCD: On-going

OBSERVATION 8

Equipment used is not of adequate size to facilitate operations for its intended use or for cleaning and maintenance.

Specifically,

a. *On 4/13/2021,* (b) (4) *dating back to 2/22/2021 were observed in and on top of a plastic container in the* (b) (4) *inside the microbiology laboratory that is used for testing of client* (b) (4) *viral drug substance. These* (b) (4) *included environmental monitoring* (b) (4) *raw material* (b) (4) *, and microbial limit testing for client* (b) (4) *that are to be sent for microbial identification. This* (b) (4) *was overcrowded, and a cleanout had occurred on 4/12/2021.*

b. *On 4/14/2021, the* (b) (4) *inside the* (b) (4) *lab* (b) (4) *room* (b) (4) *was observed to be overcrowded. Inside this* (b) (4) *the analysts store* (b) (4) *awaiting send out for identification,* (b) (4) *, retains for client* (b) (4) (b) (4) (b) (4) *of inprocess and final drug substance samples, and laboratory supplies and* (b) (4) *needing storage under* (b) (4)

Response to Observation 8

Emergent fully recognizes the importance of ensuring that equipment is of adequate size to facilitate operations for its intended use or for cleaning and maintenance. The sudden scale-up to full-scale manufacturing activities for two different Covid-19 vaccine drug substances strained the capacity of Emergent's existing (b) (4) described in the observation. As an interim measure, Emergent has taken immediate actions to clean and organize these (b) (4) In addition, the cessation of manufacturing activities in Area (b) (4) will reduce the strain on the capacity of the existing (b) (4)

Emergent will purchase and qualify (b) (4) unit for the Area (b) (and (b) (4) (b) (4) to facilitate sample storage. This action is being performed under Change Control 210006400. Emergent will also purchase and qualify (b) (4) for the (b) (4) . This action is being performed under Change Control 2100006142.

Beyond these measures, which will significantly increase (b) (4) storage capacity, Emergent will implement measures to prevent future overcrowding and to segregate materials stored in the (b) (4) To that end, Emergent will revise SOP000336, *Operation and Cleaning of* (b) (4) , to include:

- (b) (4)

Emergent is confident that the addition of (b) (4) in the (b) (4) and the revision of SOP000336 will address the overcrowding issues noted in Observation 8.

Observation 8 Corrective and Preventive Actions

8.1 Emergent will purchase and qualify (b) (4).

TCD: (b) (4)

8.2 Emergent will revise SOP000336, *Operation and Cleaning of* (b) (4), to provide for visual inspection (b) (4) for overcrowding and sample segregation.

TCD: (b) (4)

OBSERVATION 9

Equipment and/or utensils are not cleaned and maintained at appropriate intervals to prevent contamination that would alter the safety, identity, strength, quality or purity of the drug substance.

Specifically,

a. *The non-dedicated* (b) (4) *used to hold* (b) (4) *raw materials are not required by written procedure to be cleaned after each use. The procedure as described in SOP001518 (version 14) requires that they are* (b) (4) *with* (b) (4) *when travelling through the* (b) (4) .

b. *I observed residue on the bottom of a* (b) (4) *inside the Area* (b) (4) *suite. Rouging was observed on the metal screws that attach the* (b) (4) *to the* (b) (4) *below in many of the* (b) (4) *seen in the hallway. These* (b) (4) *are used to transport material in Area* (b) (4)

General Response to Observation 9

Emergent recognizes the importance of cleaning and maintaining equipment and utensils at appropriate intervals to prevent contamination that could alter the safety, identity, strength, quality or purity of a drug substance. Equipment and utensils in Areas (b) (4) and (b) (4) are maintained in accordance with SOP1518.

Emergent recognizes the opportunity to strengthen its equipment and utensil maintenance practices and procedures. Emergent quality and maintenance personnel will review and revise SOP001518. This will include, but not be limited to:

- For the (b) (4) , Emergent will replace the (b) (4) with (b) (4) (b) (4) . This enhanced practice will be documented in the revised individual media preparation batch records.

- For (b) (4) Emergent has clarified the process for inspecting, cleaning, and, if needed, disposal of the (b) (4) prior to each use. This process is described in SOP001518. The inspection, cleaning, and disposal of the (b) (4) must be documented in the material transfer logbooks, FRM045355, FRM045353, and FRM045354. Emergent will also revise SOP001518 to state that the (b) (4) must be visually inspected prior to each use, and that this visual inspection must also be documented in the material transfer logbooks, FRM045355, FRM045353, and FRM045354.

Emergent is confident that the CAPAs described above will strengthen the site's cleaning and contamination mitigation program and will prevent recurrence of the inspectional observations noted in Observation 9. Adherence to the strengthened requirements will be monitored through

Emergent's enhanced quality oversight program, including Emergent QA on the floor and third-party oversight of (b) (4) and movement of material into the (b) (4).

Observation 9 Corrective and Preventive Actions

9.1 Emergent will replace the (b) (4) with (b) (4) that will be (b) (4)

TCD: (b) (4) (prior to resuming new manufacturing)

9.2 Emergent will revise SOP001518 to state that the (b) (4) must be visually inspected prior to each use, and that this visual inspection must also be documented in the material transfer logbooks, FRM045355, FRM045353, and FRM045354

TCD: (b) (4) (prior to resuming new manufacturing)

9.3 Adherence to the revised procedures will be monitored through Emergent's enhanced quality oversight program, including Emergent QA on the floor and third-party oversight of (b) (4) and movement of material into the (b) (4)

TCD: On-going