RESPONSE TO THE FDA FORM 483 OBSERVATION RECEIVED 16 OCTOBER 2020

Product Name: **JCAR017 (lisocabtagene maraleucel)**

Application Number: **BLA** (b) (4)

Sponsor: **Juno Therapeutics, Inc, a Celgene Company**

Reference is made to the FDA Form 483 dated 16 October 2020 regarding the Pre-License Inspection of Juno (JuMP) manufacturing site located in Bothell, WA (FEI: 3011834594) conducted over seven days: October 7-9, and 13-16, 2020.

Sponsor's Response to the FDA Form 483 observation is provided in Attachment 1.

JUNO | Bristol Myers Squibb Company

November 05, 2020

Attention: Jay Eltermann
FDA/CBER/OCBQ/Division of Manufacturing and Product Quality
10903 New Hampshire Avenue
Silver Spring, MD 20993
Building 71, Room 6038

Dear Mr. Eltermann,

Enclosed you will find the Juno Therapeutics a wholly owned subsidiary of Bristol Myers Squibb ("Juno-BMS") response to the FDA Form 483 observation received on October 16, 2020. Investigators, Prabhu P. Raju and Eileen Liu conducted the Pre-License Inspection for JCAR017 (lisocabtagene maraleucel) over seven days: October 7-9, and 13-16, 2020. We would like to thank them for their insights and professional manner in which they conducted the inspection.

Juno-BMS, is committed to manufacturing quality products in compliance with cGMP requirements and FDA expectations. As shown in our response to the inspection observations, we have considered the events discussed in the observation individually and from a holistic perspective and trust that we have addressed the observations in a satisfactory manner.

If you have questions about our response or would like to discuss, please contact me at snehal.patel@bms.com (650) 303-9668 or Jeffrey Masten, Vice President and Head of Quality at jeffrey.masten@bms.com (415) 481-2180.

Sincerely,

(b) (6)

Snehal Patel
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Cc:
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Executive Summary:

Juno-BMS understands that patients and the Agency rely on us to manufacture safe and effective life saving products in conformance with current good manufacturing practices. Juno-BMS takes these observations very seriously and is committed to providing high quality drug products to our patients.

Juno-BMS has fully evaluated each inspectional observation and associated events from an individual and holistic perspective, identified immediate actions to address the observations and confirmed we continue to operate in a state of control.

A Juno-BMS response containing the following sections has been prepared for each observation:

- Executive summary, including immediate actions to address the deficiency, impact statement and applicable corrective actions
- Overview of the process that was the subject of the observation
- Details of the response to the observation
- Summary of commitments to address the observation
- Conclusion

Although Juno-BMS remains highly confident in our systems, processes, and quality decisions, as part of its on-going commitment to continuous improvement, certain actions have been identified to further enhance our processes and controls and improve the overall effectiveness of our operations and quality system. These actions are described in detail as part of the specific response to each observation within this document.

Observation #1:
There is a failure to thoroughly review any unexplained discrepancy, the failure of a batch or any of its components to meet any of its specifications, whether or not the batch has already been distributed. Specifically,

DEV-2019-03442 (Critical Classification), created on 10DEC2019, reported a (b) (4)

(b) (4)

(b) (4) *. DEV-2019-03442 Root Cause Analysis, Final Impact Analysis, and Corrective Actions were deficient for the following reasons:*

a. *The reliability of CoA from the vendor supplying* (b) (4) *Lots was not established and therefore the quality of previously supplied* (b) (4) *lots, which were released based on the vendor CoA* (b) (4) *negative results, was not determined.*

b. *A clinical impact analysis was requested to understand the potential clinical risk of* (b) (4) *exposure to patients treated with JCAR017 where* (b) (4) *was used in the* (b) (4) *. The clinical impact analysis stated there was no known transmission of* (b) (4) *to humans. The clinical impact analysis did not include an assessment of adverse events for patients treated with JCAR017 where* (b) (4) *was used in the* (b) (4) *.*

c. *A CAPA with Effectiveness Checks, per SOP-01151, Global CAPA Management, dated 17Dec2018, was not opened specifically for DEV-2019-03442, to address the inconsistency between the OOS results from the contract testing lab for Juno Lot* (b) (4) *(Vendor Lot* (b) (4) *) and the vendor CoA negative* (b) (4) *results. CAPA effectiveness checks were not conducted for the implemented corrections involving the* (b) (4) *, for the purpose of* (b) (4) *, and the cleaning of QC/Microbiology locations where* (b) (4) *Juno Lot* (b) (4) *was used.*

d. *The contract test lab, that reported the positive* (b) (4) *results, conducted an OOS Investigation (Record ID:* (b) (4) *, dated 07NOV2019) and concluded that the assay controls performed as expected and the assay is valid. The* (b) (4) *assay for* (b) (4) *was positive from the contract laboratory that tested* (b) (4) *Lot* (b) (4) *, and negative from the vendor that supplied* (b) (4) *Lot* (b) (4) *. DEV-2019-03442 did not include an OOS investigation conducted by the* (b) (4) *vendor (Material Supplier), as per Attachment C (GMP Material Supplier Investigations) of the Global Deviation SOP, SOP-001145, dated 07JUN2019,*

to determine if their assay produced a valid result, and the assay controls performed as expected.

Response:

I. Response Summary

Juno-BMS understands the importance of thoroughly investigating any unexplained discrepancy including the failure of a batch or any of its components to meet specifications. We are committed to ensuring that a robust investigation is performed for each deviating event as required by our procedures; thereby ensuring the safety and quality of our products for our patients. With respect to deviation DEV-2019-03442, we will supplement the record to include information regarding:

- Impact to (b) (4) material received prior to the failed lot, Vendor Lot (b) (4)
- The assessment of Adverse Events for patients treated with JCAR017 using material from (b) (4) lots,
- Documentation of the root cause analysis related to the discrepancy between the contract lab and vendor (b) (4) test result for the same material lot tested and
- The effectiveness check of the corrective action to change from (b) (4) to (b) (4) .

Immediate actions to address the observation were taken including reopening deviation DEV-2019-03442 to add the required documentation, specifically:

a. Documentation of a Health Hazard Evaluation (HHE) which includes an assessment of Adverse Events for patients treated w/JCAR017 using (b) (4) . This documentation along with the previously completed clinical impact analysis expands the scope of potentially affected material beyond the one vendor lot, (b) (4) , with the failed (b) (4) result.
b. Documentation from the (b) (4) vendor to demonstrate their assay produced a valid result, and the assay controls performed as expected and to complete the causal analysis.
c. Initiation of a CAPA to track effectiveness monitoring for the implementation of (b) (4) to (b) (4) (b) (4) failed results/opportunity for inconsistent results.

These actions will be completed by 30 November 2020.

With respect to the investigation of DEV-2019-03442, Juno-BMS wishes to emphasize at the outset that as a result of the investigation, finished product manufactured using (b) (4) Juno Lot (b) (4) (Vendor Parent Lot (b) (4)) was rejected and no product manufactured with that (b) (4) lot was distributed. After completion of the HHE, the impact analysis for DEV-2019-03442 was updated and concludes that previously released material produced with potentially affected (b) (4) lots is not impacted by this deviation. This conclusion is supported by the previous assessment that (b) (4) if present, has no known transmission to humans and the HHE which concludes that there is insufficient evidence to suggest that (b) (4) in (b) (4) played a role in causing adverse events in JCAR017 treated subjects. Previous product quality impact assessments remain unchanged and the investigation fully supports that patient safety is not impacted.

Juno-BMS is now using (b) (4) method shown to be highly effective in the (b) (4) . (b) (4) lot of (b) (4) received at Juno-BMS is tested by the vendor and a contract lab until qualification of the material is complete, and (b) (4) manufacturer lot will continue to be tested upon (b) (4) receipt thereafter; Qualification of the (b) (4) will consist of a minimum of testing (b) (4) lots of material by both the vendor and the contract lab.

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Deviation and Raw Material Qualification Processes

Deviation Process

As described in the procedure reviewed during the inspection, SOP-001145, *Global Deviation* Management, v10.0, each deviation investigation performed at Juno-BMS requires an assessment of root cause, product, process, equipment, and systems impact, a historical review for the same or similar events, and identification and implementation of corrective and preventive actions, as appropriate. If the event is determined to be a repeat occurrence, an assessment of any actions taken in response to the prior event is required as part of the investigation. If a previous corrective or preventive action is determined to be ineffective as part of this review, a new CAPA with a novel mechanism to address the failure will be required. Any deviating event classified as Minor, Major, or Critical requires documentation of the root cause analysis performed in support of the investigation. As part of the investigation phase, the documentation must include scope, impact, root cause, and CAPA determination with associated effectiveness checks. The Quality organization oversees and approves all deviation investigations prior to closure. To further ensure the adequate oversight and appropriate response to deviating events across the Juno-BMS site, SOP-001216, *Deviation Trending Program*, v3.0, requires deviation trending at least (b) (4) . Deviation trending includes an assessment of all events, during (b) (4) to identify whether a trend of the same failure mode with the same cause or causal factors is emerging. If a trend is identified, a trend investigation is conducted to determine if further investigation is warranted and/or if additional corrective actions are needed. The effectiveness of previously implemented CAPAs and the need for additional CAPAs with novel mechanisms to address the identified failures are part of this assessment. Each of the three aspects of the deviation program; historical review, effectiveness checks and deviation trending, will identify if a corrective or preventive action had the intended effect to address the failure.

Raw Material Qualification Process

The process to introduce a raw material is governed by SOP-001066, *Material Introduction, Revision and Withdrawal,* v3.0. A change control is required to introduce a new raw material to the Juno-BMS manufacturing site. Management of a vendor throughout its lifecycle is outlined in SOP-002673, *Global GMP/GDP Material Suppliers Quality Status Life-Cycle*, v1.0. The risk-based approach outlined in this document requires that (b) (4) be conducted for (b) (4) as it is used as (b) (4) JCAR017 process. Quality agreements are also required to be in place with raw material providers and third-party testing labs as outlined in SOP-001445, *Global Quality Agreement Process*. These agreements define the quality roles and responsibilities that are shared between Juno-BMS and the service/material provider.

Further, our procedures for qualification of raw materials, governed by SOP-001048, *Raw Material Qualification and Classification*, v2.0, include establishing the reliability of the manufacturer's certificate of analysis (CoA) through validation of test attributes listed on the CoA. A risk-based approach is used to determine the number of lots (i.e. (b) (4)) required for qualification (b) (4) testing). The qualification process is initiated for (b) (4) . Each raw material specification defines the sampling plan (including (b) (4) testing requirements), acceptance criteria, and methods being used to validate CoA test attributes. Test methods for validating CoA test attributes are performed using a

combination of in-house and contract testing labs. To meet CoA validation requirements, each lot tested must meet (b)(4) testing requirements. Following the successful completion of CoA validation testing, the raw material is then eligible to move to (b) (4) testing where test results are accepted based on the manufacturers CoA along with (b) (4) as required by the individual raw material specification. Eligibility for (b) (4) testing also requires the raw material manufacturer to be in good standing (no significant audit findings and/or deviation events reported to BMS-Juno as required by the Quality Agreement, that could call into question the integrity of their release testing on the CoA). Raw materials that are approved for (b) (4) testing also require (b) (4) (b) (4).

We have addressed each of the specific sections of this observation below and are committed to taking the appropriate corrective actions in any of the areas that did not meet the high standard established within our processes and procedures. We appreciate the feedback and the opportunity it provides to continuously improve.

Response (a):
The reliability of the vendor CoA was in the process of being established as part of our qualification process for (b) (4) processes per SOP-001048, *Raw Material Qualification and Classification Procedure*, when the positive (b) (4) result was returned by the contract lab ((b) (4)) conducting the (b) (4) testing. As stated in deviation, DEV-2019-03442, no positive results had been detected for any lot of (b) (4) that had been used for previous production when tested by the Manufacturer ((b) (4)) as this would result in the rejection of that lot. Review of the assay results conducted at the time of the event and further actions required are summarized in section (d) of this response. The lot that returned the positive result for (b) (4) per (b) (4) testing was the (b) (4) lot tested during the (b) (4) (b) (4) qualification process. The (b)(4) Manufacturer lot tested, (b) (4) Lot (b) (4), passed all (b) (4) testing, including the (b)(4) test for the presence of (b) (4)

The patient lots produced using the impacted lot of (b) (4) were rejected and never distributed to patients as indicated in DEV-2019-03442. The clinical risk of utilizing (b) (4) from lots previously released using only the vendor's CoA was addressed within the deviation investigation through a clinical impact assessment. This assessment concluded that (b) (4) has no known transmission to humans. As discussed in section (b) of this response, a Health Hazard Evaluation (HHE) has now been conducted in addition to the initial clinical impact assessment. The HHE concluded that there is insufficient evidence to suggest that (b) (4) played a role in causing adverse events in JCAR017 treated subjects. Previous product quality impact assessments remain unchanged and the investigation fully supports that patient safety is not impacted.

(b) (4) has not been used in production of JCAR017 since this result was received from the contract testing lab and will not be used in JCAR017 production in the future. (b) (4) (b) (4) has been implemented in the JCAR017 production process per Change Control DCR-2019-10831. This provides an additional measure of safety to patient supply as this method of (b) (4) (b) (4) treatment has been shown to be effective in (b) (4) (b) (4) Validation Summary demonstrates (b) (4) (b) (4)

The (b) (4) raw material is undergoing qualification (utilizing the system outlined in the introduction to this response and reviewed during the inspection) for use in the JCAR017 process per SOP-001048, including establishing reliability of the CoA from the vendor. As required by our raw material qualification and

certification processes, (b) (4) manufacturer lots of (b) (4) are required to undergo (b) (4) release testing before (b) (4) testing can be approved. To date, (b) (4) manufacturer lots have been received at the Juno-BMS manufacturing site and have undergone (b) (4) qualification testing. This testing included (b) (4) (b) (4) testing conducted by (b) (4) All results have passed, confirming the results reported on the (b) (4) CofA. In addition, any significant deviations related to (b) (4) manufacturer) will be considered before the (b) (4) testing level can be approved by Supplier Quality as outlined within the qualification procedures.

Finally, the specification for (b) (4) (Specification (b) (4) (b) (4)) requires that all new manufacturer lots of (b) (4) received at the Juno-BMS facility (b) (4) have (b) (4) testing completed (including (b) (4) testing for (b) (4)). This requirement applies to (b) (4) testing phases of qualification for (b) (4) . This will continue to ensure that the material supply remains suitable for use in the JCAR017 process. As stated above, (b) (4) manufacturer lots of (b) (4) have been received and tested with passing results that included the (b) (4) testing.

In order to explicitly relate the completion of the qualification process to this event, CAPA-2020-01113 has been opened to track the completion of the (b) (4) qualification process. The CAPA will remain open until the initial qualification process is completed (b) (4) manufacturer's lots received at the Juno-BMS manufacturing site and approval by Supplier Quality as outlined within the qualification procedures). The target for completion of this CAPA will be (b) (4) in order to allow for (b) (4) manufacturer lots to be received at the Juno-BMS site (based on (b) (4)). This CAPA, along with the continued requirement to perform (b) (4) testing (including (b) (4) testing) for (b) (4) will ensure that the quality of (b) (4) utilized in JCAR017 production has been and will continue to be confirmed. This CAPA has been added to the original deviation, DEV-2019-03442.

Response (b):

Juno-BMS acknowledges that the clinical impact assessment included in the deviation did not explicitly assess the adverse event database. This exercise should have been performed to determine if there were any adverse events from previously undetected (b) (4) that may have been used in JCAR017 production. Further, we have reviewed our internal processes and procedures and determined that a Health Hazard Evaluation, as outlined in SOP-001133, *Health Hazard Evaluation/Medical Assessment*, v6.0, should have been completed, which includes assessment of adverse events, in conjunction with the Clinical Assessment that was provided at the time of the deviation. As the patient lots impacted by this event were rejected and never distributed to patients, it was determined at the time of the event that the requirements as outlined in this SOP did not apply. As a result of this observation and the review of our processes and procedures, we have now completed a Health Hazard Evaluation (HHE). After both case level and population level analyses, there is insufficient evidence to suggest that (b) (4) in (b) (4) played a role in causing adverse events in JCAR017 treated subjects. This assessment will be added to DEV-2019-03442. Previous product quality impact assessments remain unchanged and the investigation fully supports that patient safety is not impacted.

Further, CAPA-2020-01113 has been created to add training on the requirements outlined within SOP-001133, *Health Hazard Evaluation/Medical Assessment*, to ensure that the circumstances under which an

HHE is required is clear to all investigators and Quality Assurance deviation approvers. This training will be added to the curriculum associated with the *Health Hazard Evaluation* procedure to ensure that the need to conduct an HHE is clearly understood by all investigators and Quality Assurance deviation approvers in the future. This CAPA will be completed by (b) (4) .

Finally, CAPA-2020-01113 has been created to perform a retrospective review of critical deviations since SOP-001133, *Health Hazard Evaluation/Medical Assessment,* became applicable to Juno-BMS, after acquisition by Celgene Corporation to confirm that no additional HHEs should have been performed. This CAPA will be completed by 30NOV2020.

Response (c):
The failure to establish the reliability of the vendor's Certificate of Analysis was discovered during the execution of the raw material qualification process per SOP-001048 *Raw Material Qualification and Classification Procedure*, v2.0. As required by the qualification procedures, DEV-2019-03442 was opened to investigate the failure and determine the appropriate corrective and preventive actions. We acknowledge that an effectiveness check should have been included for this deviation that specifically confirmed the (b) (4) .

As documented within the deviation investigation and reviewed during the inspection, (b) (4) (b) (4) is known to be (b) (4) . The investigation concluded that the inconsistency between the results was explained by (b) (4) (b) (4) . To further ensure that no elements of the laboratory testing as conducted at (b) (4) have been overlooked (including the execution of (b) (4) testing) that may have contributed to the inconsistency, CAPA-2020-01113 has been opened to add a specific lab practices review (including those related to (b) (4) testing) during the next scheduled audit of (b) (4) This will be completed by (b) (4) . This timeline takes into account the following considerations:

- Current COVID-19 travel restrictions hamper the ability to rapidly schedule vendor on-site audit activities
    - In the event that COVID restrictions prevent travel, (b) (4) (b) (4)
- (b) (4)

A Change Control (DCR-2019-10831) to introduce (b) (4) to the JCAR017 process was implemented on 19DEC2019 to (b) (4) . Testing by (b) (4) of all manufacturer parent lots received at the Juno-BMS production site was added as part of the introduction of (b) (4) . Subsequent to the implementation of (b) (4) , we have received (b) (4) manufacturer lots and have not obtained any positive results for (b) (4) As this continues to be a requirement for each receipt of a new parent lot, the effectiveness of this correction will continue to be monitored. The requirement for effectiveness checks for CAPAs is clearly outlined within our CAPA procedure (SOP-001151). We acknowledge that an effectiveness check should have been included for this deviation that specifically confirmed the (b) (4) . As

documented in the response to Part (a) of this observation, we have opened CAPA-2020-01113 to document the effectiveness of the (b) (4) in confirming the reliability of the vendor C of A and (b) (4) in the production of JCAR017. The due date for this CAPA will be (b) (4) in order to allow for (b) (4) manufacturer lots to be received at the Juno-BMS site (based on (b) (4)).

Regarding the observation related to the effectiveness of the cleaning of the QC/Microbiology locations that may have come in contact with (b) (4) Juno Lot (b) (4) response memos were generated and attached to the deviation (DEV-2019-03442). These memos documented the assessment of risk associated with potential contact and the requirement for additional cleaning/disinfection that was completed in response to this event. Additionally, the assessments documented that all assays are conducted with (b) (4) (b) (4) per SOP-000166. Out of an abundance of caution, all QC (b) (4) were disinfected (b) (4) (b) (4) This cleaning was also documented within our electronic work order system ((b) (4)). Juno-BMS has completed a (b) (4) effectiveness study as documented within RPT-000291 that indicates that (b) (4) are effective in (b) (4) (b) (4) As a result of this assessment and the demonstration of the effectiveness of the disinfectants used in response, no further effectiveness check for the cleaning is required.

Although appropriate actions were taken and documented during this event, the requirement to consider the QC areas potentially impacted by an event of this nature are not explicitly spelled out within the SOP that outlines the response to (b) (4) within the Juno-BMS facility (SOP-000236 (b) (4) *Response)*. CAPA-2020-01113 has been opened to revise SOP-000236 to include specific requirements regarding the need to consider QC areas that may be impacted during a (b) (4) event due to handling/testing of samples/material related to the event. In addition, this CAPA will also make it clear that SOP-000236 applies to potential (b) (4) of all types, including (b) (4) . The due date for this CAPA is (b) (4) .

Response (d):
A cross-functional meeting was held between Juno-BMS and (b) (4) on 16JAN2020 to determine and understand the cause for the (b) (4) test results. A review of the testing records was conducted as a result of this meeting and a statement provided by (b) (4) indicated that no anomalies had been noted related to (b) (4) testing and that all testing for (b) (4) had passed. In addition, they noted that no inquiries or complaints related to (b) (4) or testing for (b) (4) had been received related to (b) (4) of material besides the inquiry received from Juno-BMS. We acknowledge, however, that the documentation of the assay review that was conducted by (b) (4) at the time of this event, in alignment with Attachment C (*Additional Celgene Investigation Decision Tree*) of SOP-001145, could have been more robust.

In order to supplement the assay review documentation previously provided by (b) (4) related to this event, we have requested a detailed review of the (b) (4) testing of (b) (4) Lot (b) (4) by (b) (4) and will provide written documentation of the review of the validity of this assay and the performance of the assay controls used. This assessment will be tracked via CAPA-2020-01113 and attached to the deviation (DEV-2019-03442) related to this event. Further, CAPA-2020-01113 has been opened to provide clarification within SOP-001048 *Raw Material Qualification and Classification Procedure* that a laboratory investigation

for any failure that occurs during qualification will include input from both the testing lab and the vendor. The due date for this CAPA will be (b) (4) .

III. Summary of Commitments to Address the Observation

In response to the subject observation, and as previously stated within the response to each specific observation above, Juno-BMS commits to the following:

- Complete CAPA-2020-01113 to track the completion of the (b) (4) qualification process. This action will be completed by (b) (4) .
- Complete CAPA-2020-01113 to perform training on the requirements outlined within SOP-001133 *Health Hazard Evaluation* to ensure that the circumstances under which a Health Hazard Evaluation (HHE) is required is clear to all investigators and Quality Assurance deviation approvers. This action will be completed by (b) (4) .
- Complete CAPA-2020-01113 to add a specific lab practices review (including those related to (b) (4) (b) (4) testing) during the next scheduled audit of (b) (4) This action will be completed by (b) (4) .
- Complete CAPA-2020-01113 to revise SOP-000236 (b) (4) *Response* to include specific requirements regarding the need to consider QC areas that may be impacted during a (b) (4) event due to handling/testing of samples/material related to the event. This action will be completed by (b) (4) .
- Complete CAPA-2020-01113 to provide clarification within SOP-001048 *Raw Material Qualification and Classification Procedure* that a laboratory investigation for any failure that occurs during qualification will be required by both the testing lab and the vendor. This action will be completed by (b) (4) .
- Complete CAPA-2020-01113 to perform a retrospective review of critical deviations since SOP-001133 *Health Hazard Evaluation* became applicable to Juno-BMS operations (after acquisition by Celgene Corporation) to confirm that no additional HHEs should have been performed. This action will be completed by (b) (4) .
- Emphasize the points made within the inspection observation by adding the observation and responses to the training curriculum assigned to deviation investigators, reviewers, and approvers. This action will be completed by (b) (4) .

IV. Conclusion

As outlined above, Juno-BMS has processes and procedures in place to ensure deviation root cause analysis, final impact analysis, corrective actions with effectiveness checks and raw material qualifications are completed. These systems and the related governing documents are based on scientifically sound justifications as outlined within this response as well as the associated quality system documentation. Nonetheless, in response to the learnings from this inspection, we have reviewed the procedures involved in these activities and are committing to enhancing them for breadth and clarity as outlined in our response and in alignment with our commitment to continuously improve.

Observation #2:
Written records of investigations into unexplained discrepancies, the failure of a batch or any of its components to meet specifications, do not always include the appropriate conclusions and follow-up. The following Notice of Events (NOEs) were not classified as Deviations.

a. *DEV-2020-02527, dated 29AUG2020, NOE Classification, reported Suspected* (b) (4) (b) (4) *during* (b) (4) *of Lot* (b) (4) *. The Deviation was classified NOE only since there was no impact to product. The* (b) (4) *Material* (b) (4) (b) (4) *Lot* (b) (4) *had a* (b) (4) *.* (b) (4) *typically has a* (b) (4) *. SOP-000236,* (b) (4) *Response, dated 02APR2020, requires a deviation be initiated in the event of suspected* (b) (4)

b. *DEV-2020-02599, dated 04SEP2020, NOE Classification, reported* (b) (4) *Pipette* (b) (4) *found to be Out of Process Tolerance during On Demand Calibration. This Event was classified NOE only since there was no impact to product quality. However, the description section of this deviation stated the potential impact from out of tolerance pipettes would result in invalid test results and failure to meet assay and sample acceptance criteria. Approximately* (b) (4) *JCAR017 lots had invalid test results and were identified as lots that were potentially affected by the pipettes out of tolerance failure.*

c. *DEV-2020-02726, dated 17SEP2020, NOE Classification, reported Operators inadvertently* (b) (4) *during* (b) (4) *for Lot* (b) (4) *. The cause was determined to be personnel inattention and DEV-2020-02726 was classified NOE-only. Management counseling of the manufacturing operators was completed but a CAPA, per SOP-00151 (Global CAPA Management, dated 17DEC2018), with Effectiveness Checks for the management counseling corrective action was not implemented.*

Response:
I. Response Summary
Juno-BMS understands the importance of investigating unexplained discrepancies, or the failure of a batch or any of its components to meet specifications, to ensure appropriate root cause is determined, impact is adequately assessed, scientifically sound conclusions are reached, and appropriate corrective and preventative actions with effectiveness checks are implemented and documented.

Juno-BMS wishes to clarify that, as described in detail below, Notice of Events (NOE) are classified as deviations under SOP-001145, Global Deviation Management, v10.0, which also specifies the investigational requirements. We included the outcome of the review of the specific events cited in Section II and describe the immediate and corrective actions to identify opportunities in the way we classify deviations to ensure that the appropriate investigation is conducted based upon the severity of each deviation with documented root cause, impact assessment and corrective and preventative actions.

Immediate action was taken to review the three deviations, DEV-2020-02527, DEV-2020-02599 and DEV-2020-02726, to identify the additional documentation needed to complete the records and to revise the classification in accordance with SOP-001145, *Global Deviation Management*, v10.0. Details of the

individual records reviewed are described in the Response sections below. Preliminary review of procedures for both the deviation and CAPA system, SOP-001145 and SOP-001151, respectively, indicate that the requirements for classifying, investigating and documenting deviations and CAPAs are clearly defined. Although Investigators and approvers of deviation records are qualified and proficient in performing investigations and approving these records in accordance with the deviation and CAPA procedures, we will update existing training materials and instructions to improve consistency in the classification and documentation of the deviations at Juno-BMS.

The impact of the misclassification of these NOE Only deviations has been fully evaluated. Based on the evaluation, we conclude that the previous assessments of impact with respect to each deviating event remain valid based on the following:

- Product impact assessment and batch disposition status remains unaffected by the change in classification of these records as the conclusions within these records remain unchanged.
- Product test results remain unaffected by the reclassification of these records as the conclusions within these records remain unchanged.

To fully evaluate the scope of the misclassification events, a retrospective analysis of a representative sample of closed deviations will be performed to further identify any impacted records and to better understand any potential inconsistencies in application of the deviation and CAPA system requirements. A new requirement to perform periodic checks on closed deviations to confirm classification and consistent application of documentation requirements in deviation records will be added to the deviation trending procedure, SOP-001216, *Deviation Trending Program*.

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Deviation Classification and Documentation Process

SOP-001145, *Global Deviation Management*, v10.0, describes the global process for evaluating, recording, tracking, and investigating Good Manufacturing Practices (GMP) and Good Distribution Practices (GDP) deviations related to commercial and investigational products, materials, systems, and processes. Per SOP-001145, a deviation is an event that is determined to be a failure, non-conformance, or departure from approved procedures, established standards, processes, or regulation which may affect the safety, quality, identity, purity, or potency of product, have regulatory implications and/or an impact on a critical system. Detailed instruction for the management of deviations at the Cell Therapy Development and Operation (CTDO) sites is provided in WP-010024, *CTDO Deviation Management*, v3.0.

To clarify the observation statement, "The following Notice of Events (NOEs) were not classified as Deviations", SOP-001145, *Global Deviation Management*, describes (b) (4) severity classifications for deviations and includes NOE Only as a deviation class. NOE Only events are those in which the event has no impact on materials, product, process, systems or equipment and the root cause of the event is known. Because the impact and cause are known, no further investigation is performed and all relevant information for impact and cause is documented in the deviation record.

SOP-001145 defines the (b) (4) Deviation Severity Classifications as follows:

(b) (4)

Per SOP-001145, each deviation requires, at minimum, documentation of the following:

- (b) (4)

In addition to the requirements above, any deviating event classified as Minor, Major, or Critical requires documentation of the root cause analysis performed in support of the investigation. As part of the investigation phase, the documentation must include scope, impact, root cause, and CAPA determination with associated effectiveness checks.

If the deviating event is classified as NOE Only, the record is approved for closure by the record owner/investigator and Quality Operations. If the deviating event is classified as Minor, Major, or Critical, the record is approved for closure by the record owner, SME/Functional Area Management, and Quality Operations. For any deviating event classified as Critical, a Director level or above is required for the SME/Functional Area Management approval and the site Quality Head or Global Quality Head is required for the Quality approval.

To further ensure the adequate oversight and appropriate response to deviating events across the Juno-BMS site, SOP-001216, *Deviation Trending Program*, v3.0, requires deviation trending at least (b) (4) . Deviation trending includes an assessment of all events, including those classified as NOE Only, during the (b) (4) to identify whether a trend of the same failure mode with the same cause or causal factors is emerging. If a trend is identified, a trend investigation may be initiated to complete further investigation or root cause analysis and CAPA determination.

Response (a):
Juno-BMS will reclassify DEV-2020-02527 since the root cause of the event was not known at the time of initiation and investigational sample testing was required in support of the causal analysis.

Per SOP-000236, (b) (4) *Response*, v6.0, processing was able to proceed as the triage team was unable to confirm the material was (b) (4) In parallel to forward processing, investigational samples were taken and submitted to QC Microbiology for (b) (4) and (b) (4) investigational testing. The investigational testing revealed no evidence of (b) (4) and there were no additional signals of (b) (4) during downstream processing or testing. In addition, a review of the Certificate of Analysis (CoA) for the product lot, (b) (4) , revealed all QC release testing of the final drug product met specification. Following the investigational testing, a decision was made to close the deviation record with the classification of NOE Only since the suspected (b) (4) event was not confirmed.

Juno-BMS recognizes the importance of thoroughly investigating suspected (b) (4) and has performed a retrospective review from June 2019 (implementation of deviation classification system which includes NOE Only) to October 2020 for any prior suspected (b) (4) events which may have been misclassified or closed without a full investigation. The review revealed two prior events of suspected (b) (4) which were closed with a NOE Only classification.

The two prior events, DEV-2019-03253 and DEV-2019-03269, were initiated due to an observation of an abnormal background of a (b) (4) . At the time of the two prior events, the site was conducting a trend investigation for (b) (4) across multiple lots, DEV-2019-03089. The (b) (4) for the two prior events were obtained following in-process testing for (b) (4) . Investigational sampling and testing were performed in support of both events. The testing revealed no evidence of (b) (4) and a decision was made to close the deviation with the classification of NOE Only since the suspected (b) (4) event was not confirmed. The lots in scope of DEV-2019-03253 and DEV-2019-03269 were rejected due to DEV-2019-03089.
In response to the subject observation, Juno-BMS commits to the following:

- Reopen DEV-2020-02527 to reclassify the event and further investigate potential causes of the abnormal (b) (4) of the (b) (4) . Target closure of the record is (b) (4) from reopening; 27NOV2020
- Reopen DEV-2019-03253 and DEV-2019-03269 to appropriately classify each event. Target closure of each record is (b) (4) from reopening; 27NOV2020

- Revise SOP-000236 to provide clear instruction that any suspected (b) (4) event cannot be closed as NOE Only when investigational testing is required or a definitive root cause for the observation of suspected (b) (4) is unknown and update the appropriate training curriculums to include information developed. CAPA-2020-01117 has been initiated to track the revision of SOP-000236 and will be completed by17DEC2020

Response (b):
Juno-BMS wishes to clarify the observation statement that, "Approximately (b) (4) JCAR017 lots had invalid test results and were identified as lots that were potentially affected by the pipettes out of tolerance failure." In accordance with SOP-001145, when (b) (4)

As documented in the Interim Disposition Assessment (IDA) for the subject record, DEV-2020-02599-IDA-00004, Juno-BMS comprehensively evaluated affected lots for potential impact. The affected lots for the subject event were determined by reviewing any lots tested in Room (b) (4)
(b) (4)
. The assessment then focused on (b) (4)
(b) (4) , to assess the potential impact from the subject event. The assessment determined there were (b) (4) lots which had an invalid assay result during the timeframe evaluated, none of which were determined to have used the subject pipette. The remaining (b) (4) ots in scope of the subject event were reviewed and each lot met the sample and assay acceptance criteria for %CV with no impact from the deviating event as documented in DEV-2020-02599-IDA-00004.

The root cause determination and historical review performed for DEV-2020-02599 revealed the event required further investigation as documented in the Initial Impact Assessment field of the subject record. Prior to the initiation of DEV-2020-02599, an investigation was underway for a trend of QC pipettes found out of process tolerance during calibration, DEV-2020-01860. A review of the event description for DEV-2020-02599 revealed the event met the criteria used to identify the scope of the trend investigation. Therefore, the subject deviation was closed as NOE Only, due to the ongoing trend investigation, DEV-2020-01860, for cause analysis and CAPA determination.

Juno-BMS recognizes the opportunity to strengthen the investigation report for DEV-2020-02599.

In response to the subject observation, Juno-BMS commits to the following:

- Reopen DEV-2020-02599 to re-classify and summarize the findings of the trend investigation into the subject record. The target closure of the record is (b) (4) from reopening: 27NOV2020

Response (c):
Juno-BMS wishes to clarify the observation statement that, "Management counseling of the manufacturing operators was completed but a CAPA, per SOP-001151, with Effectiveness Checks for the management counseling corrective action, was not implemented," SOP-001145, *Global Deviation Management,* states that if a CAPA is not required a justification indicating why a CAPA will not be initiated must be documented. For each deviation record, (b) (4) , our electronic deviation management system, requires the record owner to answer the question "Is CAPA Required?" to advance the deviation workflow to closure. If the answer is 'No',

(b) (4) requires the record owner to document a justification for the decision before advancing the workflow. The justification is then reviewed and approved by Quality as part of the record closure. With respect to the subject event, the action of personnel counseling was performed during the course of the investigation and documented within the deviation record.

For the subject deviation, the failure of (b) (4) was an isolated event caused by operator error. As an immediate action to the observed event, the product was isolated from the process flow and new materials were obtained to forward process. After setting up with the new materials, the product was forward processed with the correct (b) (4) . The product impact was determined through a review of (b) (4)
(b) (4)
(b) (4) therefore there is no product impact due to this event. Based on this information, the decision was made for area management to counsel the involved personnel on the importance of maintaining focus during execution of GMP activities. As detailed in the investigation report, the personnel counseling was completed prior to the closure of the deviation record. Therefore, a CAPA record was not initiated to track the completion of the counseling.

The current practice at Juno-BMS for measuring effectiveness of personnel counseling completed during the course of an investigation is through event historical review and/or the deviation trending program. Each event requires a historical review to determine if the event is a repeat occurrence. If the event is determined to be a repeat occurrence, an assessment of any actions taken in response to the prior event is required as part of the investigation. Therefore, if a previous corrective or preventive action is determined to be ineffective, a new CAPA with a novel mechanism to address the failure will be required. For the subject event, the personnel counseling is documented within the deviation record. So, if a subsequent event with the same failure mode was to occur the historical review would identify the prior event and the effectiveness of prior counseling would be assessed as part of the subsequent event investigation. A query of the Juno-BMS deviations revealed that the subject event is an isolated incident which has not occurred outside of DEV-2020-02726.

In addition to the historical review, SOP-001216, *Deviation Trending Program*, requires deviation trending at least (b) (4) . Deviation trending includes an assessment of all events, including those classified as NOE-Only, during (b) (4) . If a negative trend is identified, a trend investigation may be initiated to complete further investigation or root cause analysis and CAPA determination. Each of the (b) (4) aspects of the deviation program, (b) (4) , will identify if a corrective or preventive action had the intended effect to address the failure.

In response to the subject observation, Juno-BMS commits to the following:

- Develop a procedure to ensure a consistent response process and documentation practices for human error related events. This action will be tracked in CAPA-2020-01117 and will be completed by (b) (4)
- Revise WP-010024 to provide instruction for managing corrective actions and corresponding effectiveness checks, which are implemented during an open investigation. This action will be tracked in CAPA-2020-01117 and will be completed by (b) (4)

III. Summary of Commitments to Address the Observation

In response to the subject observation, and as previously stated within the response to each specific observation above, Juno-BMS commits to the following:

- Four deviation records will be reopened to address reclassification and to document relevant information as described in this response. Target closure of each record is (b) (4) from reopening 27NOV2020:
  a. DEV-2020-02527
  b. DEV-2019-03253
  c. DEV-2019-03269
  d. DEV-2020-02599
- Complete CAPA-2020-01117 to track the revision of SOP-000236 to provide clear instruction that any suspected (b) (4) event cannot be closed as NOE Only when (b) (4) (b) (4) . Target completion date: (b) (4)
- Complete CAPA-2020-01117 to develop a procedure to ensure a consistent response process and documentation practices for human error related events. Target completion date: (b) (4)
- Complete CAPA-2020-01117 to track revision of WP-010024 to provide instruction for managing corrective actions and corresponding effective checks, which are implemented during an open investigation. Target completion date: (b) (4)

Additionally, to ensure a holistic assessment of the deviation classification process, Juno-BMS commits to the following:

- Complete CAPA-2020-01117 to review training materials specific to deviation classification and revise as necessary to ensure comprehensive and clear training is delivered for classifying deviating events. Target completion date: (b) (4)
- Complete CAPA-2020-01117 to perform a retrospective review of a representative sampling of deviation records completed between the period of June 2019 to October 2020, to evaluate deviation records are appropriately classified, and conclusions are complete and justified. June 2019 marks the start of the current deviation classification scheme at Juno-BMS. Target Completion Date: (b) (4)
- Complete CAPA-2020-01117 to track the revision to SOP-001216 to require a periodic review of a representative sampling of deviation records to ensure each event is appropriately classified. Target Completion Date: (b) (4)

IV. Conclusion

Juno-BMS is confident in the effectiveness of our deviation management system. Nonetheless, in response to the learnings from this inspection, we are committed to reviewing our deviations management program to identify enhancement opportunities. The assessment of our training materials and update of our procedures will further enhance our investigations into deviating events and ensure that our deviation records are appropriately classified, thorough, timely, unbiased, well-documented, and scientifically sound, consistent with the FDA's guidance.

Observation #3:

The written procedure for Manufacturing Material Visual Inspection, SOP-000512, dated 20Jun2020, defines the method used to inspect raw, intermediate and Formulated Drug Product (FDP) materials for foreign particulates and defects, and applies to the visual inspection of GMP materials used throughout the manufacturing process. SOP-000512 does not specify when in the manufacturing process (b) (4) *intermediate materials,* (b) (4) *, and their immediate containers are inspected for* (b) (4)*. Specifically,*

a. (b) (4)

b. (b) (4)

Response

I. Response Summary

Juno-BMS understands the importance of clear written procedures to ensure production and process controls are established, executed and documented concurrently.

We acknowledge that SOP-000512, *Manufacturing Material Visual Inspection*, v5.0, provides instructions for performing container (b) (4) inspections and documenting in the Electronic Batch Record (EBR) at (b) (4) of the process. However, we agree that SOP-000512 and the EBR should be strengthened to provide specific instructions regarding inspection of intermediate containers during the (b) (4) steps of the JCAR017 manufacturing process.

As an immediate action, SOP-000512 was reviewed and will be revised by (b) (4) to include the specific instructions on how to perform the inspection process during (b) (4) steps. In addition, the EBR will be revised to enable operators to document the inspection results directly into the EBR (b) (4) and this will be completed by (b) (4) .

Operators perform and document inspection of containers per SOP-000512 at (b) (4) of the process and are trained to inspect raw materials and intermediates using SOP-000512 prior to use of the material. Any material failures such as (b) (4) are required to be investigated per WP-010024 CTDO Deviation Management, therefore there is no impact on product quality due to the lack of specificity in the current procedure.

Corrective actions will be taken as defined in section IV to revise SOP-000512 and the associated electronic batch record to provide specific instructions on when to perform the inspection and to enable the documentation of the inspection results. Other manufacturing processes will also be evaluated to ensure we meet the same standards for documenting the performance of steps in the manufacturing process. These actions will be tracked in CAPA-2020-1089 and CAPA-2020-1090.

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Manufacturing Material Visual Inspection Process

Visual inspection of product containers occurs and is documented in the (b) (4) Electronic Batch Record (EBR) during the following unit operations:

- (b) (4)

In addition to these inspections of product containers which are documented in the (b) (4) EBR, SOP-000512 governs the general pre-use inspection of raw, intermediate, and in-process materials used throughout the manufacturing process. Operators are trained to inspect raw materials and intermediates using SOP-000512 (b) (4) per WP-010024 CTDO Deviation Management. RPT-000591, (b) (4) *Risk Assessment*, is used when a deviation for (b) (4) is initiated to understand risk factors and mitigation for (b) (4).

Response (a) and (b):

The existing visual inspection steps at (b) (4) coupled with the execution of SOP-000512 requirements to inspect raw materials and intermediates at (b) (4) (b) (4) ensures high detectability of any (b) (4) and that appropriate actions are subsequently taken. Juno-BMS recognizes the opportunity for improvement of the procedures and documentation related to the visual inspections and will revise, SOP-000512 and the (b) (4) electronic batch record will be revised to provide instructions governing the inspection of (b) (4) containers and capture the documented evidence of the inspection at each of the following manufacturing steps:

- (b) (4)

The revision to SOP-000512 and updates to the (b) (4) to collect the documented evidence of the inspections on the JCAR017 commercial EBR will be implemented by (b) (4).

It is important to note that Juno-BMS has taken a holistic approach in evaluating SOP-000512 and how visual inspections are documented in the (b) (4) electronic batch records. As a part of this response, Juno-BMS has identified that the visual inspection of product containing materials can be further enhanced through the addition of an additional check to the list above:

- SOP-000211 (b) (4) Operation and Maintenance will be revised to add (b) (4) check to the (b) (4) sampling block and a check (b) (4). This change will be completed by (b) (4)

Additionally, as a post implementation activity related to changing the JCAR017 commercial EBR, all JCAR017 clinical EBR records will be aligned to collect the documented evidence of visual inspection described in SOP-000512. The update to JCAR017 clinical EBR records will be completed by (b) (4).

III. Summary of Commitments to Address the Observation

In response to the subject observation, and as previously stated within the response to the observation above, Juno-BMS commits to the following:

- Revise SOP-000512 to provide specific instructions for the inspection of (b) (4) containers in (b) (4). This action will be tracked in CAPA-2020-1089 and will be completed by (b) (4)
- Revise SOP-000211 (b) (4) Operation and Maintenance to add (b) (4) check to the (b) (4) sampling block and a check (b) (4). This action will be tracked in CAPA-2020-1090 and will be completed by (b) (4)
- Revise the JCAR017 commercial EBR to enable the concurrent documentation of the inspection outcomes described in SOP-000512. This action will be tracked in CAPA-2020-1089 and will be completed by (b) (4)
- Revise the JCAR017 clinical EBR records to enable the concurrent documentation of the inspection outcomes described in SOP-000512. This action will be tracked in CAPA-2020-1089 and will be completed by (b) (4)

IV. Conclusion

Visual inspection of materials utilized during the manufacturing process is currently conducted to ensure detection of (b) (4) prior to use and that appropriate action is taken in response to any detected (b) (4) Operators are trained to inspect raw materials and intermediates using SOP-000512 prior to use and escalate any material failures such as (b) (4) per WP-010024, *CTDO Deviation Management*. Revisions to SOP-000512 and the (b) (4) electronic batch record described in Section III and Section IV of this response will be executed to more clearly specify when the visual inspections are conducted and to require documentation in the EBR. We believe that these enhancements will strengthen our procedures to ensure that raw and intermediate materials are free of defects.

Observation #4:
Procedures designed to prevent microbiological contamination of drug products purporting to be sterile are not established or followed. Specifically,

On 08OCT2020, we observed the aseptic filling of drug product (DP) Lot (b) (4) *the ISO* (b) (4) (b) (4) *in the* (b) (4) *; Rm* (b) (4) *We observed the following deficient aseptic practice.*

a. *We observed an aseptic verifier* (b) (4) *his gloves with sterile* (b) (4) *before performing personnel monitoring (PM) of his gloves, SOP-000567, entitled "ISO* (b) (4) *Environmental Monitoring and ISO* (b) (4) *Personnel Monitoring", VP10.0, section 15.2 states* (b) (4) (b) (4) *.*

b. *We also observed an aseptic operator performing viable surface monitoring of the* (b) (4) *For each sample collected, the operator* (b) (4) *. After completing the surface monitoring, he proceeded to perform PM of his gloves. SOP-000567, entitled, "ISO* (b) (4) *Environmental Monitoring and ISO* (b) (4) *Personnel Monitoring", V10.0, section 13.6 states* (b) (4)
(b) (4)

Response:
I. Response Summary
Juno-BMS understands the importance of personnel consistently following established procedures for environmental and personnel monitoring, including SOP-000567, ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring, v10.0. In accordance with SOP-001145, *Global Deviation Management*, a deviation DEV-2020-03108 was initiated on 15OCT2020 to investigate the observed failures to appropriately perform personnel monitoring.

Immediate action was taken to investigate this observation and to correct the contributing factors and known root cause.

- A deviation DEV-2020-03108 was initiated to fully investigate both observations. Preliminary analysis indicates that the sequence of steps defined in SOP-000567 was the root cause of the observation related to the verifier (b) (4) their hands prior to personnel monitoring and was a contributing cause of the performer (b) (4) prior to performing environmental monitoring. SOP-000567 will be revised by 15DEC2020 to clarify sampling steps to ensure personnel (b) (4) (b) (4)
- The operators involved with cleaning the (b) (4) after surface monitoring were counselled on the requirement in SOP-000567 to perform (b) (4) (b) (4) . Awareness training will be delivered in November to all operators performing personnel monitoring in ISO (b) (4) as an interim measure until the SOP and training material revisions are complete.

Based on review of ISO (b) (4) EM data and finished product test data, there is no impact to product test results or product quality. This analysis is based on the evaluation of the history of ISO (b) (4) environmental data in total and finished product sterility test results.

1. The following environmental data from ISO [(b) (4)] was included in the impact analysis:

(b) (4)

2. Finished product testing, specifically review of finished product sterility testing from the time period of (b) (4) through (b) (4), indicates all results have met specifications, further supporting control of the ISO [(b) (4)] environment.

As mentioned, immediate actions have been taken to revise the affected procedures and training materials related to personnel monitoring. Upon completion of DEV-2020-03108, the root cause will be further assessed to identify any additional corrective actions. The target date for closure of DEV-2020-03108 and initiation of CAPAs to document correction actions is 14NOV2020.

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Deviation Investigation and Personnel/Environmental Monitoring Process

Personnel and Environmental Monitoring Process

SOP-000567, *ISO [(b) (4)] Environmental Monitoring and ISO [(b) (4)] Personnel Monitoring*, governs the set-up, collection, submission, plate management and results analysis of environmental monitoring data collected during ISO [(b) (4)] operations.

The ISO [(b) (4)] Environmental Monitoring program is an important laboratory control. This program provides meaningful information on the quality of the aseptic processing environment. Monitoring the quality of the ISO [(b) (4)] environment includes the following:

- (b) (4)

The EM program is designed to assess the quality of the ISO [(b) (4)] environment to ensure it meets all requirements defined in our procedures.

Deviation Investigation
The observation of an aseptic verifier (non-performer) (b) (4) gloves with sterile (b) (4) before performing personnel monitoring (PM) resulted in the initiation of investigation DEV-2020-03108 (Procedure Misalignment for ISO (b) (4) Between SOP-001094 and SOP-000567) on 15OCT2020, during the inspection. The additional observation of the operator (performer) performing personnel monitoring after sanitizing the viable surface monitoring site with sterile (b) (4) has been included in the scope of DEV-2020-03108. In this event, the operator cleaned (b) (4) after taking the surface sample. Although the surface sample was correctly collected, the operator handled an (b) (4) prior to personnel monitoring. SOP-000567 requires that personnel monitoring be completed (b) (4) (b) (4) .

Response (a):
During the inspection, a verifier, during (b) (4) operation, was observed performing personnel monitoring (b) (4) . Although instructions in SOP-000567 require that operators (b) (4) performing personnel monitoring, it is acknowledged that the procedure should be clarified to more clearly state the sequence of actions that should be taken.

The following sequence is currently defined in SOP-000567:

(b) (4)

Although a subsequent instruction in SOP-000567 requires that (b) (4) (b) (4) , the sequence above requires sanitization of gloves and (b) (4) . This sequence of steps creates the condition where the verifier's (b) (4)).

To address this observation, SOP-000567 (ISO (b) (4) Environmental Monitoring and ISO (b) (4) Personnel Monitoring) will be modified to ensure that verifier (non-performer) personnel monitoring occurs (b) (4) (b) (4)). This will ensure that verifier personnel monitoring does not occur (b) (4) (b) (4) . More specifically, SOP-000567 will be modified to require that personnel monitoring of the verifier occurs in the following, revised sequence:

(b) (4)

Response (b):
During the inspection an aseptic performer, during (b) (4) operation, was observed to sanitize a sampling site with sterile (b) (4) . SOP-000567, step (b) (4) states to (b) (4) (b) (4) .

It should be noted that the operator did not (b) (4) . The (b) (4) samples were correctly collected.

The concern raised during the inspection was that since the operator handled the (b) (4) (b) (4) , the subsequent personnel monitoring would not be representative of the aseptic manipulation activities performed within the ISO (b) (4) environment since the operator's glove (b) (4) (b) (4) .

To address the observation, SOP-000567 will be modified to ensure that the ISO (b) (4) performer personnel monitoring occurs (b) (4) . In the current state, SOP-000567 provides instructions to the operator to collect EM samples in the following sequence:

(b) (4)

Juno-BMS notes a review of the SOP found that the process could be enhanced by implementing the following, revised sequence:

(b) (4)

By executing the sequence of EM sample collection in the revised order, the personnel monitoring samples are (b) (4) and the potential failure mode of inappropriately (b) (4) (b) (4) is eliminated from the process. Juno-BMS wishes to reiterate that historical EM results demonstrate that the site's-controlled environments have been maintained in a state of control. Therefore, there is no product impact associated with the existing SOP-000567 cleaning process.

III. Summary of Commitments to Address the Observation

In response to the observation and as previously stated within the response, Juno-BMS commits to the following:

- SOP-000567 will be modified to ensure that the ISO (b) (4) performer personnel monitoring does not occur (b) (4) . This action will be tracked in CAPA-2020-01077 and will be completed by 15DEC2020
- SOP-000567 will be modified to ensure that the verifier (non-performer) personnel monitoring occurs (b) (4) to ensure that personnel monitoring is not performed (b) (4) (b) (4) . This action will be tracked in CAPA-2020-01077 and will be complete by 15DEC2020
- As a part of the 15DEC2020 updates to SOP-000567, training will be provided to SOP users including operators, aseptic trainers and SOP authors on the following topics:
    - The specific procedural changes implemented to correct the observations 4(a) and 4(b)

- The microbiological and quality rationale for the changes as they apply to the observations of (b) (4)
- A comprehensive review of procedures for environmental and personnel monitoring defined in SOP-000567 will be performed.

The comprehensive review of SOP-000567 will be completed by (b) (4) .

IV. Conclusion

To reduce the possibility for operator error, Juno-BMS will implement a revised SOP-000567 through CAPA-2020-01077; which will change the procedural flow to prevent recurrence of both subject observations. In addition, a holistic review of the procedure will be conducted under CAPA-2020-01077 to ensure that the requirements in SOP-000567 meet the environmental monitoring standards and provide tools for effectiveness evaluation.

As previously stated, the disinfection of performer or verifier (non-performer) gloves (b) (4) (b) (4) does not affect the following ISO[(b) (4)] EM samples:

(b) (4)

The environmental monitoring data collected from the ISO[(b) (4)] environment provides a high degree of assurance that the environmental quality of the ISO[(b) (4)] environment was not affected by the subject observations. The proposed scope of CAPA-01077 defines the appropriate steps to improve the process and prevent recurrence of the subject observations.

Observation #5:

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

a. *MET-000054, entitled, "Bacterial Endotoxin Test Method", V8.0 is deficient in that it fails to specify the minimum time required for the adequate* (b) (4) (b) (4) .

b. *On 13OCT2020, we observed* (b) (4) *DP lots* (b) (4) *assessments in the Analytical Chemistry RM* (b) (4) *We observed the analyst did not* (b) (4) *reference standards for* (b) (4) *assessment; she also did not* (b) (4) *test sample for* (b) (4) *assessment. MET-001013, entitled "Appearance by Visual Inspection", V6.0, section 11.6 states* (b) (4) (b) (4) . *Additionally, section 11.7.1 states to* (b) (4) (b) (4) .

Response:

I. Response Summary

Juno-BMS understands that laboratory controls must include the establishment of scientifically sound and appropriate test procedures and specifications designed to confirm identity, strength, quality, and purity.

The company's qualification and validation program assures the accuracy and reliability of testing performed in quality control laboratories, as described in Section II. Immediate actions were taken to investigate the discrepancies and correct potential contributing factors until corrective actions are completed:

1. Interviews were conducted with QC Microbiology trainers and laboratory analysts to determine the (b) (4) practices of the endotoxin samples when performing the endotoxin tests.
2. Awareness training for all QC Microbiology analysts will be conducted, as an interim measure, to ensure continued consistent practice for minimum (b) (4) (b) (4) . The awareness training will be completed by 13NOV2020.
3. DEV-2020-03113 was initiated to investigate the deviation from MET-001013, *Appearance by Visual Inspection*, v6.0.
4. Awareness training was provided to all QC associates who are qualified on MET-001013 on 16OCT2020, to ensure the following:
    - The (b) (4) reference standard is (b) (4) (b) (4) .
    - The test samples are (b) (4) .

Potential impact to product quality has been evaluated. Based on this assessment, we conclude that the (b) (4) discrepancies have no impact to product test results.

- Although the current method lacks the specificity on sample (b) (4) for endotoxin testing, the performance of the test in practice is (b) (4) (b) (4) . A study to further evaluate (b) (4) (b) (4) will be conducted to further substantiate the minimum (b) (4) .

- A review of the source for the Appearance Test Method, MET-001013, (b) (4) – (b) (4)) concluded that (b) (4) is not required when assessing for (b) (4)

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Laboratory Controls

SOP-000237, *Analytical Method Qualification and Validation*, v3.0, provides guidance for performing qualification and validation of test methods in compliance with current Good Manufacturing Practice requirements. As per this SOP, compendial methods are verified to demonstrate that the analytical laboratory can replicate the standard method with an acceptable level of performance and that the method is suitable under actual conditions of use. Successful implementation of the bacterial endotoxin test method is documented in RPT-000396, *Method Verification Report: JCAR017 Bacterial Endotoxin Test Method (TM-0054)* and successful implementation of the Appearance test method is documented in RPT-001222, *Method Transfer Report of MET-001013 Appearance by Visual Inspection*. SOP-000237 ensures alignment between the validation/verification outcome and the test procedures that govern routine testing.

Response (a):

The test procedure, MET-000054, *Bacterial Endotoxin Test Method*, v8.0, is confirmed to be in alignment with the method verification report (RPT-000396); however, neither document contains specific detail regarding the minimum length of time required for (b) (4) .
A study will be conducted to establish (b) (4) will subsequently be incorporated into MET-000054, *Bacterial Endotoxin Test Method*, through the change control process per SOP-002081, *Global Change Management in* (b) (4) ; v10.0. CAPA-2020-01059 has been initiated to track this action and will be completed by (b) (4) .

Response (b):

On 15OCT2020, DEV-2020-03113 was initiated to investigate the deviation from MET-001013, *Appearance by Visual Inspection*, v6.0 described in the observation. In addition, on 16OCT2020, an awareness training was provided to all QC associates who are qualified on MET-001013, to ensure the following:

a. (b) (4) reference standard is (b) (4) assessment and
b. the test samples are (b) (4)

MET-001013 is a compendial method that describes the procedure for determining (b) (4) (b) (4) . A summary of the test method execution procedure is as follows:

(b) (4)

(b) (4)

During the investigator's observation on 13OCT2020, the QC analyst was observed performing the assessment for (b) (4) which are described in sections 11.6 and 11.7 of MET-001013. Through interview with the QC analyst conducted as part of the investigation for DEV-2020-03113, the QC analyst indicated that the (b) (4) standards described in the note above step 11.6.1 was performed during step 11.4 of the method as part of the system suitability assessment and prior to (b) (4) assessment section 11.6. Juno-BMS will revise the test method requires revision to ensure that the reference standard is (b) (4) . The deviation did not have an impact to the reported results as the test results are (b) (4) (b) (4) per section 12.0 of the method. During the deviation investigation interview, the data verifier confirmed that the results were verified by (b) (4) (b) (4) per section 11.6.1. The results of the verifier match those (b) (4) (b) (4)

Investigation DEV-2020-03113 also addresses the observation that the QC analyst did not (b) (4) (b) (4) assessment as required in section 11.7 of MET-001013, instead, the QC analyst (b) (4) . A review of the source for the test method ((b) (4) (b) (4)) concluded that (b) (4) (b) (4) was originally included in the method because it is part of the (b) (4) (b) (4) method for visual inspection designed to assess (b) (4) (b) (4) . MET-001013 is not used to assess for (b) (4) is unnecessary. (b) (4) of the test sample is performed as part of sample preparation and (b) (4) assessment in test method sections 11.4 and 11.5. An investigation is initiated if the sample is not (b) (4) . Juno-BMS acknowledges that the test method requires revision to remove the requirement for (b) (4) assessment. The deviation did not have an impact on the test result as the test sample was (b) (4) assessment in test method section 11.5 and (b) (4) would have an impact on (b) (4) as the test sample (b) (4) .

An evaluation of the MET-001013 training program, along with interviews of all qualified QC analysts and trainers of the test method indicates QC analysts understood the requirement for (b) (4) standard (b) (4) to test samples.

Based on the findings from the deviation investigation, MET-001013, *Appearance by Visual Inspection*, v6.0, will be revised to clarify when to (b) (4) reference standard and to remove the requirement of (b) (4) . Revisions will be managed through the change control process per SOP-002081, *Global Change Management in* (b) (4) v10.0. CAPA-2020-01073 has been initiated to track the method and relevant training document revisions and will be completed by (b) (4) .

III. Summary of Commitments to Address the Observation

In response to the subject observation, and as previously stated within the response to each specific observation above, Juno-BMS commits to the following:

- A study will be conducted to establish (b) (4) will subsequently be incorporated into MET-000054, *Bacterial Endotoxin Test Method*, through the change control process per SOP-002081, *Global Change Management in* (b) (4) , v10.0. CAPA-2020-01059 has been initiated to track this action and will be completed by (b) (4) . Awareness training for all QC Microbiology analysts will be conducted by 13NOV2020, as an interim measure, to ensure continued consistent practice for minimum (b) (4) .
- Revise MET-001013, *Appearance by Visual Inspection*, v6.0, to clarify (b) (4) reference standard and to remove the requirement of (b) (4) (b) (4) This action will be tracked in CAPA-2020-01073 and will be completed by (b) (4) .

Additionally, to ensure a holistic assessment of the release test methods, Juno-BMS commits to the following:

- Perform a comprehensive review of release test methods to verify that the required level of clarity is provided for each method. Opportunities to provide clearer instructions will be tracked and the appropriate change notice will be performed. This action will be tracked in CAPA-2020-01114 and will be completed by (b) (4) .

IV. Conclusion

Laboratory controls include the establishment of scientifically sound and appropriate specifications and test procedures designed to assure that drug products conform to appropriate standards of identity, strength, quality and purity. SOP-000237 "Analytical Method Qualification and Validation" provides requirements for validation and verification of analytical methods and ensures alignment between the protocol outcome and the test procedures. Juno-BMS is committed to continuous improvement of its test methods and validation process, as defined in the response.

Observation #6:
Deviations from written test procedures are not justified to assure compliance with established specifications and standards.

On 07OCT2020 in the Environmental Monitoring Laboratory Rm (b) (4) we randomly selected and inspected EM plates that had been enumerated, counts verified by a second verifier, and results recorded in LIMS earlier the same day. We observed (b) (4) of the inspected EM plates showed discrepant enumeration results. The observed discrepancies were confirmed by the firm's management.

Response:
I. Response Summary
Juno-BMS understands the importance of compliance with established specifications and standards. We acknowledge the discrepancy detected during the inspection where (b) (4) of the inspected EM plates showed discrepant enumeration results after the plates had been read, verified by a second verifier and recorded in LIMS.

Immediate action was taken to investigate the discrepancy and correct potential contributing factors in the interim until a comprehensive root cause analysis and corrective actions are completed.

- A deviation DEV-2020-02989 was initiated to fully investigate the discrepancy. Preliminary analysis indicates that factors such as (b) (4) may have contributed to the enumeration discrepancies. Through interviews and review of training records and training material it was determined that the involved personnel are qualified and proficient in enumeration of colonies and were following procedures during the enumeration and verification activity
- (b) (4) was installed to facilitate detection of colonies
- Awareness training for QC Associates regarding the discrepancies was conducted, highlighting the detection challenges such as (b) (4) on the plates, and (b) (4) which may (b) (4) (b) (4). QC Associates are also required to escalate issues or inadequacies when identified

The impact of the EM plate enumeration discrepancies has been fully evaluated. Based on this assessment, we conclude these discrepancies have no impact on the product test results or product quality based on the following: (b) (4) plates described in the observation were (b) (4) and remained below the Alert Level and Action Limit upon correction of the result. Therefore, there was no impact to the final EM sample results due to the enumeration discrepancy.

We are confident that our EM data continues to accurately reflect the environmental state of our facility. The impact assessment of this event takes into account the purpose and nature of environmental monitoring, the level of the discrepancy and information provided in (b) (4) (b) (4), which acknowledges the (b) (4) (b) (4) (b) (4). It states: "(b) (4) (b) (4) ."
However, it is recognized that continuous improvement of our EM program including ensuring the accuracy of our plate enumeration and verification method is required.

- EM data is reviewed on (b) (4) basis to assess for trends in our controlled areas. Review of our (b) (4) EM trend reports indicates the environment is operating in a state of control
- An initial assessment concluding low impact to our EM data is supported based on review of the observed EM plate count enumeration discrepancy, and review of our (b) (4) EM trend reports supporting that the environment continues to operate in a state of control

Section III summarizes corrective actions to address the observations as described in the body of the response.

II. Overview of Enumeration Process

SOP-000229, *Colony Counting*, v6.0, describes the method for colony enumeration. GED-001207, *Trainer Job Aid – Microbial ID and Plate Processing*, v1.0, provides instruction and requirements for the qualification of all QC Associates on this activity. The task of colony enumeration is performed on plates obtained from the environmental monitoring program. The procedure requires an initial count be performed by a trained QC Associate. This QC Associate enters the initial plate counts into LIMS. The same plates are then evaluated by a second QC Associate, who performs verification of each of the documented counts that are recorded in LIMS. Discrepant results that are identified by the verifier must be corrected as per SOP-000431 *General Use of LIMS EM Module*, v5.0.

Response:

The environmental monitoring plates in scope of this observation were all sampled from the ISC (b) (4) environment. The alert levels for this environment classification at the facility vary from (b) (4) CFU to (b) (4) CFU (b) (4) CFU to (b) (4) CFU for surface monitoring, depending on the room. For each of the (b) (4) plates, the enumeration was discrepant by (b) (4) As illustrated in Table 1, both the original plate count and the corrected plate count were below the alert limit for the sample. A detailed review of each of the (b) (4) plates was performed in conjunction with a QC Associate interview. The morphological characteristics of each of the missed colony-forming units were assessed and documented. This assessment revealed that factors such as (b) (4) , and other attributes may present a detection challenge. See Table 2. A holistic summary of potential detection challenge factors was compiled. During the associate interview and review of the plates, it was noted that each of the (b) (4) colonies presented some level of detection challenge, and (b) (4) of the (b) (4) missed colonies exhibited more than one of the detection challenge factors. (See Table 1).

Table 1: Assessment of EM plates from DEV-2020-02989

Sample ID	ISO Class	Sample type	Limits*	Original colony count	Corrected colony count	Description of Missed Colony
(b) (4)						

*Alert and Action Limits defined in SOP-000078, Environmental Monitoring Program, v19.0

Table 2: Colony Detection Challenge Assessment

Potential Detection Challenge	Assessment
(b) (4)	

In accordance with SOP-000168, *CTDO GxP Training Program, v.11.0*, laboratory associates are required to demonstrate proficiency on this task prior to being permitted to perform the task independently. As per GED-001207 *Trainer Job Aid – Microbial ID and Plate Processing*, v.1.0, the demonstration of proficiency for this task includes (b) (4) . The QC Associates who were engaged in the performance and verification of colony counting tasks on 07OCT2020 were qualified to perform the task independently.

Upon discovery of the deviation on 07OCT2020, immediate actions were taken, including installation of (b) (4) to facilitate detection of colonies during plate enumeration and awareness training for QC Associates, which includes the associates performing the initial plate counts, as well as the verifiers. DEV-2020-02989 will drive CAPA for further enhancements as applicable. A comprehensive review of the current enumeration practices, result verification practices, and training program is being conducted in conjunction with a root cause analysis under DEV-2020-02989. The initial review of the current practices for plate enumeration and training of associates and verifiers indicates improvement opportunities with regard to (b) (4) and clear accuracy requirements. Following the conclusion of the root cause analysis, CAPA will be initiated to remediate the areas identified.

Improvements (b) (4)
difficult to detect colonies and inclusion of detection challenge factors (for example, (b) (4)
(b) (4) , and so forth) in the test procedure, implementation of an accuracy requirement within the method as well as within the qualification program, improvement of verification practices to eliminate the potential for confirmation bias.

III. Summary of Commitments to Address the Observation

In response to the subject observation, and as previously stated within the response, Juno-BMS commits to the following:

- Closure of DEV-2020-02989 which will require initiation of a CAPA based on the final root cause analysis. Initial corrective actions will include revision to the colony counting procedure and related training materials. The target date for closure of DEV-2020-02989 and initiation of CAPAs to document corrective actions is 20NOV2020.

IV. Conclusion

Based on evaluation of the deviation that occurred on 07OCT2020 involving inaccurate enumeration of EM plates, it is determined that a comprehensive investigation and root cause analysis is required to identify process and training improvements. Immediate corrective actions have been implemented in the interim. The initial impact assessment of this event takes into account the purpose and nature of environmental monitoring, the level of the discrepancy and information provided in (b) (4) (b) (4) . This supports an initial assessment of low impact to our EM data based on review of the observed EM plate count enumeration discrepancy, and review of our (b) (4) EM trend reports supporting that the environment continues to operate in a state of control.

We remain committed to continuous improvement of our environmental monitoring program and associated training as defined in the response.