



U.S. FOOD & DRUG
ADMINISTRATION

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To: Administrative File STN 125685/0

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Through: Anthony Lorenzo, Branch Chief, OCBQ/DMPQ/MRBII
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Applicant: Enzyvant Therapeutics GmbH, Lic.# 2100

Facility: (b) (4)

Product: Allogeneic Processed Thymus Tissue – agdc (RETHYMIC)

Indication: For the immune reconstitution of pediatric patients with congenital athymia.

Subject: Review memo - Responses to Complete Response Letter issued on December 4, 2019

ADD: October 6, 2021

REVIEW RECOMENDATION

I recommend approval with the recommendation for the Inspectional Follow-up at the next biennial inspection. CBER understands that the recommendation may or may not be taken (based on risk and available resources), and is not requesting documentation to be submitted as evidence of completion for the following items:

- *Please verify the validation/data integrity status of each (b) (4) computerized system. Additionally, please specifically evaluate the following:*
 - (b) (4) *Imaging software, for which multiple data integrity deviations were noted during PPQ.*
 - (b) (4) *environmental monitoring/alarm software, for which numerous “Check Network” and “Check Link” communication error are being investigated under*

DEV-1195. Please verify that the deviation is successfully resolved and that no data is being lost due to communication errors.

- *Please verify that differential pressure sensor on the emergency exit between Access Corridor (b) (4) and non-controlled non-classified area is replaced with (b) (4) compatible sensor that can measure (b) (4)*

EXECUTIVE SUMMARY

Enzyvant provided responses to the Complete Response (CR) letter issued on December 4, 2019 detailing 12 CMC deficiencies. DMPQ related deficiencies included: unresolved Pre-License Inspection (PLI) issues, Drug Product (DP) transport study (Corning culture dishes), DP shipper validation, (b) (4) container decontamination, (b) (4) validation of the (b) (4) container (source material transport and (b) (4) storage), (b) (4) system qualification, and personnel flows. In response, the firm performed new DP shipper qualification and new DP transport studies (transporting cell culture dishes as the primary DP container closure system), a new secondary container system (b) (4) disinfection study, a new (b) (4) system qualification study, as well as new EMPQ, APS, and PPQ studies after facility design modifications were implemented to allow (b) (4) process flows. Initial response to the CRL was received in STN125685/0.58 on April 09, 2021.

Information requests to Enzyvant and their responses related to DMPQ were as follows:

Date of IR or Telecon	Date of Response (for IRs)	Amendment Number (for IRs)
09/03/2021	09/13/2021	125685/0.70
	09/23/2021	125685/0.77
09/16/2021	09/21/2021	125685/0.75

Background

RETHYMIC was developed in Dr. Louise Markert's lab at Duke University. Enzyvant acquired the licensing rights for RETHYMIC from Duke University in December 2016. A rolling BLA (STN 125685/0) was submitted in completion on April 5, 2019 (DMPQ Reviewer: Ekaterina Allen). The PLI was conducted on (b) (4) at the (b) (4)

Inspectors: Randa Melhem, Lily Koo, Ekaterina Allen, Tom Finn, Sukhanya Jayachandra, Prabhu Raju). A Form 483 with 11 Observations was issued at the conclusion of the PLI. A CR letter was issued on December 4, 2019 detailing 12 CMC deficiencies, followed by a Type A meeting on March 19, 2020 to provide feedback on firm's proposed responses.

Review Narratives

Response to each DMPQ related CR deficiency (#1, #7-12) is reviewed below.

Deficiency #1

Outstanding issues identified during the pre-license inspection (PLI) at your contract

manufacturing facility conducted (b) (4), as detailed in Form FDA 483, have yet to be resolved. Please submit documentation that demonstrates that all outstanding inspectional issues identified during the PLI have been resolved.

Review Summary

Observation 1

Corrective actions and preventive actions (CAPA) implemented are not always being documented per the CAPA SOP COMM-QA-076. For example,

- a. **Deviation IR-0111 is regarding failures in the sterile packaging of (b) (4) sterilized critical supplies, which resulted in modified packaging configurations as captured in Change Controls (b) (4)-CCR-434. However, no CAPA was initiated.**
- b. **Deviation DEV-0602 is regarding personnel monitoring samples being discovered by the contract lab in the sample receipt area (i.e., “garage of disposed materials” per contract lab deviation DEV2018_0042) one week after receipt. As a corrective action, the contract lab tested the samples and found negative growth on any of the plates, including the control plates. No growth promotion testing results, if performed on these plates, was reported. No CAPA was initiated to capture the corrective action taken and no additional corrective and/or preventive action was deemed necessary.**
- c. **Deviation DEV-0556 is regarding incorrect lot number of fetal bovine serum (FBS) being recorded on Thymus Organ Medium (TOM) Batch Record due to failure in secondary verification by the operators. The error was not detected during QA review but was discovered 25 days later by the operator who initially reported the incorrect number. As a corrective action, the operator determined the correct lot of FBS and the batch record was corrected and re-reviewed. All staff were reminded of the importance of GDP entries. No CAPA was initiated to capture the corrective action taken and no additional corrective and/or preventive action was deemed necessary.**

Response Summary

To address the Observation, significant revisions to Quality System SOPs were proposed during the March 19, 2020 Type A Meeting. The Agency agreed to the proposed changes, provided that they are properly executed and enforced. In addition, the firm was asked to 1) open deviations for not following existing CAPA SOP to document implemented CAPA and effectiveness evaluation, 2) conduct a re-evaluation of all previous deviations and CAPAs to identify and address deficiencies, and 3) open CAPAs based on the gap analysis results.

In response, an overall evaluation and risk assessment of the Deviation, Investigation, Risk Assessment, and CAPA processes was performed in Q4 2019 to investigate the three cited deviations and the overall failure to initiate CAPAs following deviations. The investigation was documented in Reports QA-2019-010-P and QA-2019-011-P, and determined that the root cause was inadequate and unclear procedures governing the

deviation, risk assessment, and CAPA processes. Based on the review, a new risk matrix including three scoring parameters (severity, probability, and detectability) was implemented in COMM-QA-077 (also implemented in COMM-QA-080 and COMM-QA-042 FRM4), an improved linkage between the CAPA and Change Control processes was established, and the scope of risk assessment was expanded beyond the specific event. Some of the procedural changes included:

- Replacing “deviation report” and “IR report” with one Deviations and Investigation Report (DIR) template
- Adding a section in the DIR and the CAPA report to inquire if external reporting is required
- Adding a section in the DIR for the initiator to provide an overview of CAPAs if applicable
- Specifying a 30-day target timeframe for deviation and investigation resolution
- Clarifying roles and responsibilities in the CAPA report lifecycle
- Requiring the initiator to propose projected completion dates and responsible parties upon initial routing of the CAPA plan, as well to include timelines for effectiveness checks in the CAPA report
- Adding a section to the CAPA report to require the initiator to summarize the CAPA outcome upon the final routing of the CAPA report
- Requiring the initiator to provide an explanation for failure to meet the effectiveness check timeline upon final routing of the CAPA report

In February 2021, Enzyvant (b) (4) completed a retrospective review of all deviations documented (80 deviations and 34 associated CAPA reports) since the transfer of RVT-802 manufacturing to (b) (4) (May 2016 – October 2020). The review was summarized in report QA-2020-001 and showed that 45% of the 80 deviations resulted in CAPAs, though the corrective actions were determined using inconsistent approaches. In addition, CAPAs should have been opened for the 30% corrective actions that were documented in the deviation reports or change control reports. It was also noted that CAPAs were opened 100% of the time when the risk assessment required it, thereby excluding non-adherence to SOP as a root-cause. Finally, no adverse impact was detected in all the reviewed cases as the correction actions were implemented and deemed appropriate. Based on the review, 1) CAPA 0218 was initiated to generate new job aids for investigation using root cause analysis (RCA) tools and vendor deviation, and to improve deviation/CAPA trending processes, and 2) CAPA 0217 was initiated to conduct training on technical writing and RCA tools. The percentage of deviations with associated CAPAs has increased since the retrospective review study.

Based on the evaluation, SOP revisions were made and included the following:

COMM-QA-080 Quality Risk Management: Instructions and examples of risk assessment tools have been included. Risk assessment now included “detectability” as an additional component. Actions that are defined as part of risk control plans are tracked and linked to CAPAs.

COMM-QA-077 Risk Assessment: The risk management requirements are now implemented through COMM-QA-077, which brings together the Change Control, Deviation and Investigation, and CAPA processes through a common risk process and provides a risk-score based guidance for CAPA and Change Control requirements/execution. Risk of harm to the patient is now the primary consideration in risk evaluation. Risk assessment has also been expanded to include worst-case scenarios of related and potential outcomes to develop more robust CAPAs.

COMM-QA-042 Deviations and Investigations: The process now includes a target deviation/investigation resolution time of ≤ 30 days. The Quality Unit is involved early in the deviation process to provide greater oversight.

COMM-QA-076 CAPA: The process is now linked with risk assessments. Risk score specific instructions and examples are provided to guide when and what types of CAPA may be required. CAPA timelines have been added. An effectiveness check risk assessment by the CAPA initiator is now required to assess risk mitigation as a result of the implemented CAPA.

COMM-QA-019 Change Control: COMM-QA-019 is now linked to COMM-QA-077. Instructions are additionally provided to help determining when effectiveness checks are required.

In addition, Enzyvant and (b) (4) implemented quarterly Joint Management Review, beginning in February 2020 to trend quality and processes data, including an evaluation of the implementation of the updated quality processes which determined acceptable execution and enforcement with demonstrated improvement (e.g., deviation and investigation resolution time).

Reviewer Comment: *The response is acceptable. Observation 1 is adequately resolved.*

Observation 2

Report # DEV-0723 019 documented a deviation for (b) (4) lots (b) (4) where final product mycoplasma test results provided by contract testing lab were determined by the contract lab to be invalid. (b) (4) lots (b) (4) were transplanted into the intended patients on April 12, April 15 and April 9, respectively. Repeat testing on (b) (4) samples of all (b) (4) lots

were negative for the presence of Mycoplasma. Root cause was determined to be an error on the part of the contract testing lab.

- a. No investigation was performed as to whether appropriate corrective actions were taken by the contract lab to prevent the problem from reoccurring. No CAPA was initiated to capture the corrective action taken and no additional corrective and/or preventive action was deemed necessary.
- b. The likelihood of repeat occurrence was deemed improbable due to the fact that this event has not occurred in the past, though three individual lots were affected.

Reviewer Comment: *Defer to PO. This observation was made by Thomas Finn (TF).*

Observation 3

The environmental monitoring program is deficient in ensuring that the cleanrooms are operating in a state of environmental control. For example,

- a. The 2017 EMPQ performed following the modifications to the HVAC system is inadequate as it was limited in the number of samples collected and the type of sampling performed: (b) (4) sampling was limited to (b) (4) per location for (b) (4); however, only (b) (4) sampling was performed (b) (4) for (b) (4) conditions.
- b. The routine environmental monitoring program does not include (b) (4) monitoring for (b) (4) in the ISO^{(b) (4)} and ISO^{(b) (4)} areas.
- c. A single (b) (4) sample (b) (4) is collected during the aseptic processing in the (b) (4) ISO^{(b) (4)} during the manufacturing process, which can take up to (b) (4).
- d. Routine (b) (4) sampling for (b) (4) is not performed for the ISO^{(b) (4)} manufacturing area and the associated passthroughs under (b) (4) conditions.
- e. There is no (b) (4) sampling (post operations) in the (b) (4) ISO^{(b) (4)} used for the aseptic manufacturing of the product.
- f. There is no (b) (4) sampling, or sampling of the (b) (4) in the incubator after the manufacturing of a lot. The incubator is located in manufacturing room (b) (4) ISO^{(b) (4)} and used for the in- process incubation of the product up to 21 days.
- g. The differential pressure between the ISO^{(b) (4)} and ISO^{(b) (4)} cleanrooms and between the ISO^{(b) (4)} and the CNC areas is not alarmed or recorded to ensure compliance with the established settings.
- h. The settings for humidity (b) (4) and temperature (b) (4) are too wide.

Response Summary

To address the Observation and additional CBER feedback provided during Type A meeting, the firm revised their routine EM program as well as performed two additional EMPQ studies.

First EM risk assessment (b) (4)-2019-045-P; provided as part of 483 responses, and found deficient, with multiple inconsistencies) was followed by EMPQ performed in October 2019. In early 2020 risk assessments to evaluate the cleaning program (b) (4) 2020-029), aseptic processing (b) (4)-2020-032-P) and cross-contamination risks (b) (4) 2020-065-P) were also executed based on existing SOPs and 2019 EMPQ data.

In May/June 2020 facility was modified to address Deficiency #12. HVAC was rebalanced and pressure differentials are now (b) (4) monitored and alarmed on all doors except Gown Out to Receiving/Supply (see Deficiency #12 for more details). Alarm ranges for temperature and humidity were also updated prior to 2020 EMPQ to (b) (4) (Observation 3h).

Reviewer Comment: Revised humidity and temperature settings are acceptable (see also verification during EMPQ below). Observation 3h is adequately addressed.

Upon recertification of the facility the EM risk assessment was revised (b) (4)-2019-045.1-P), and procedures for cleaning, gowning, and materials transfer/personnel flow were updated. Another aseptic process validation (APV; June 2020), 2020 EMPQ (06/29-08/01/2020), and 2020 process validation (PV) studies were conducted. Following the 2020 EMPQ data review by (b) (4) EM Committee and a multifunctional team, another EM risk assessment was conducted (b) (4)-2019-045.2-P) to develop a routine EM program and (b) (4)-SOP-008 (EM Program for the (b) (4)) was amended accordingly. Below is a summary of provided risk assessments and study reports:

(b) (4)-2019-043-P EMPQ protocol (but not the final report) approved October 4, 2019 was provided. This EMPQ was performed prior to the facility remodeling and rebalancing of the HVAC, and as such had to be repeated. However, 2020 EMPQ design no longer included bioburden sampling of (b) (4) incubators and their (b) (4) which sought to address Observation 3f and would be still applicable post-modifications.

(b) (4)

Additionally, per the info provided elsewhere, the results from 2019 EMPQ indicated that gowning and cleaning improvements as well as facility modifications were needed to

improve personnel and material flows and reduce EM excursions in ISO^{(b) (4)} areas. The cleaning risk assessment ^{(b) (4)}-2020-029-P was performed as a result (not provided).

Reviewer Comment: The firm should provide 2019 EMPQ report, ^{(b) (4)}-SOP-031 FRM 14, and ^{(b) (4)}-2020-029-P for evaluation of the ^{(b) (4)} incubator and ^{(b) (4)} testing results and related updates to routine sampling procedures (incubator/^{(b) (4)} sampling is not covered by ^{(b) (4)}-SOP-008 for routine EM) and to ensure that all gaps in cleaning and disinfection program identified in ^{(b) (4)}-2020-029-P were addressed.

On September 13, 2021 the firm provided the missing documents in the amendment STN 125685/0.70 (response to Q.1 and 2).
^{(b) (4)}-2019-043-P EMPQ Final report approved 06/11/2020.

Reviewer Comment: This EMPQ was performed prior to facility modifications and changes in cleaning procedures. As such, only ^{(b) (4)} incubator and ^{(b) (4)} testing results that were still applicable after the changes were reviewed and summarized below.

^{(b) (4)}

^{(b) (4)}-SOP-031 FRM 14 Preparation of Final Drug Product rev. 07 effective May 14, 2021. Step ^{(b) (4)} of this manufacturing batch record instructs to ^{(b) (4)}

The firm provided result for ^{(b) (4)} DP batches, three PPQ batches and ^{(b) (4)}, that were incubated for 12-21 days. No growth was detected in any ^{(b) (4)} samples. Trending SOP was revised to include ^{(b) (4)} bioburden data.

Reviewer Comment: The firm has implemented routine bioburden testing of the (b) (4). This partially addresses Observation 3f. See the inspectional follow up recommendation for verification of incubator (b) (4) sampling (b) (4) (below).

(b) (4)-2020-029-P Risk assessment (RA) of facility cleaning and disinfection procedures approved May 27, 2020. This is the initial RA based on 2019 EMPQ outcomes and SOP analysis and was performed as described below in updated (b) (4)-2020-0.29.1-P. High and medium risk items were proposed for mitigation. Overall, the proposed cleaning program revisions were related to increase of frequency and areas of sporicide use, increase cleaning/sanitization frequency and expand scope of cleaning (CNC areas, (b) (4), equipment, frequently touched items), proceduralize existing cleaning practices and cleaning of new equipment (pass throughs), sink drains, facility shoes. Use of (b) (4) throughout the facility was significantly expanded, use of (b) (4) was minimized. Sampling of EM equipment and pipet aid was recommended for inclusion into 2020 EMPQ. Stronger sporicide use in response to EM excursion and for (b) (4) cleaning.

Reviewer Comment: The risks identified during the initial risk assessment were largely addressed. (b) (4) did not demonstrate sporicidal efficacy and was later replaced with (b) (4) (see below for more details). Current cleaning program is further supported by 2020 EMPQ outcomes (see below).

(b) (4)-2020-029.1-P Risk assessment of facility cleaning and disinfection procedures approved January 22, 2021. Initial risk assessment (b) (4)-2020-029-P (not provided) identified gaps in cleaning and disinfection program, resulting in several CAPAs and implementation of an updated cleaning program in June 2020, execution of a disinfectant effectiveness (DE) study (b) (4)-2019-051.4-P, EMPQ (b) (4)-2020-034-P. DE study, and 2020 EMPQ indicated a need for cleaning program updates, which prompted an update to the initial risk assessment executed in December 2020. RA was performed using Failure Mode and Effects Analysis (FMEA) to identify potential gaps in cleaning and recommend mitigating actions. Each failure mode was scored for severity (remained the same as in the initial RA), occurrence and detectability (score of (b) (4)) RA assigned numerical Risk Priority Number (RPN; (b) (4)) based on multiplied scores (high risk RPN (b) (4); medium RPN (b) (4); low risk RPN (b) (4)). All (b) (4) high-risk items, several medium and few low risk items were proposed for mitigation as follows:

- General cleaning: implement (b) (4) sporicide cleaning. (b) (4) is replaced with (b) (4).
- ISO (b) (4) All high-risk equipment [pipet aid, (b) (4) and EM equipment (concurrent)] is cleaned with (b) (4) during (b) (4). Post use (b) (4) cleaning with (b) (4) (horizontal (b) (4)), followed by (b) (4).
- ISO (b) (4) clean sink/eyewash after safety checks.
- ISO (b) (4) use of (b) (4) followed by (b) (4) to clean up spills, impact assessment of ISO (b) (4) spills, add sampling of drawer interior to (b) (4) EM sampling

plan, clean interior of gowning bin (b) (4) and when bins are transferred into facility); proceduralize (b) (4) cleaning of dedicated plant shoes and inspection of the shoes at time of use, (b) (4) cleaning of hard to clean equipment (e.g. keyboards, iPhones, etc.)

- CNC: (b) (4) wipe of materials removed from cart passthrough and placed into Clean Storage.

(b) (4) -2020-032-P Risk assessment (RA) of the aseptic processing of RVT-802 approved on June 19, 2020 was performed using Failure Mode and Effects Analysis (FMEA) to inform APV (including interventions) and establish risk mitigation plans. 2020 EMPQ sampling plan for ISO (b) (4) and ISO (b) (4) areas was also within the scope. Each failure mode was scored for severity, occurrence, and detectability (b) (4) (opposite for detectability). RA assigned numerical Risk Priority Number (RPN) based on multiplied scores (high risk RPN (b) (4) medium RPN (b) (4) low risk RPN (b) (4)). No high-risk items were identified, and the following actions and SOP modifications were proposed to mitigate medium risk items:

- Common aseptic technique: use of clean (b) (4) wiped Petri dish racks, incubator cleaning/disinfection/interior (b) (4) monitoring evaluation; packaging toolbox in ISO (b) (4) in ISO (b) (4) Receiving/Supply room, with recorded disinfectant contact time; proceduralize gloves/sleeves disinfection, define aseptic core vs. material transfer zone of (b) (4), restrict (b) (4) from entering aseptic core. Proceduralize histology in-process sampling, discarding product if slicer blade becomes loose while slicing. Have backup slicer available.
- Process: proceduralize slicer handling during setup and use, proper use of forceps and scissors, (b) (4) gloves disinfection, instrument/TOM/dish replacement if suspect contamination, eliminate blocking of first air during slicing and pipetting, new specimen cup handling, sponge handling; ensure disinfectant contact time, (b) (4) monitoring of pipet aid (2020 EMPQ).

Long-term proposed mitigation items included developing petri dish disinfection program, use of an (b) (4) incubator, substitute container closure system with the one amenable to disinfection, use of a different slicer design, sterile wipes for holding/placing of the slicer, longer scissors and forceps; sterility testing for media from bioassay dish; different TOM container, separate Petri dish for filter wetting, dedicated ISO (b) (4) operator, material handoff at the interface, without ISO (b) (4) operator reaching into the (b) (4).

(b) (4) -2020-065-P Risk assessment of the multi-product facility potential for cross-contamination completed in June-July 2020 (post-modifications) and approved on 01/22/2021. The scope included cross-contamination between different products, lots of RVT-802, and via reagents/materials/personnel/equipment transfer between manufacturing rooms or common spaces. Facility, procedures and controls were assessed with Preliminary Hazard Analysis (PHA), and RPN was determined by multiplying severity and occurrence scores (b) (4). (b) (4) detectability was not included as there are no detection controls in place. Occurrence in the facility and in the product was scored and assessed

separately. Potential cross-contamination risks were scored as high (RPN^{(b) (4)}), medium (RPN^{(b) (4)}), and low (RPN^{(b) (4)}). No high-risk items were identified, and the following actions and SOP modifications were proposed to mitigate medium risk items:

- EM Equipment and personnel (apply to all facility): equipment wipe down ^{(b) (4)}, dedicated EM equipment for each ISO area; contractor sampling using non-dedicated equipment to be done in ^{(b) (4)} last (highest risk area). EM personnel to change gloves/sleeves after sampling each room; if room is in use during sampling, EM personnel to exit and re-gown prior to sampling next room.
- ^{(b) (4)} products and Reagent/Media prep: ^{(b) (4)}


Secondary packaging of reagents inside ^{(b) (4)} (remains when passing reagents to ^{(b) (4)})

Long term ensure that all reagents are certified virus and contaminant-free.

- Contractors/maintenance: ^{(b) (4)} entering facility, exiting a manufacturing room. ^{(b) (4)} cleaning (or evaluation) of room post-contractor work. ^{(b) (4)} line clearance to include cleaning/wiping of equipment after calibration/maintenance. Equipment/materials are not to be transferred from room to room, "especially during processing".
- ^{(b) (4)} (RVT-802 dedicated): wiping of containers/materials prior to transfer out of the ^{(b) (4)} room clean (line clearance). If multiple lots are processed on same day, materials are passed for ^{(b) (4)} only except cleaned ^{(b) (4)} and reagents/wipes required for cleaning. Excepted materials are wiped between lots. Product risk assessment and ^{(b) (4)} cleaning in case of positive tissue/product screening result
- ^{(b) (4)} products: ^{(b) (4)} cleaning, product risk assessment in case of positive tissue screening result, wiping of containers/materials prior to transfer out of the ^{(b) (4)} room clean (line clearance); ^{(b) (4)} wipe downs of vials and tubes before and after use in centrifuge and vortexer.

^{(b) (4)}-2019-045.1-P EM program risk assessment report approved 06/19/2020. The RA is an update to the previous EM RA based on 2019 EMPQ outcomes (report not provided), facility modifications, and procedure (cleaning, gowning, material and equipment transfer, personnel flow) changes. The RA goal was to identify sampling sites for 2020 EMPQ. FMEA scoring was limited to severity ^{(b) (4)} only and was largely based on use for/proximity to open processing. Flows, surfaces, and mitigating controls in place (gowning, cleaning) were considered. No failure modes were identified, no risk ranking was performed, no mitigations were recommended. Instead, procedures were reviewed to identify representative sampling sites.

Sampling frequency for EMPQ was also determined (ISO^{(b) (4)} at time of use, ISO^{(b) (4)} supporting ISO^{(b) (4)} during manufacture in ^{(b) (4)} in other suites; other ISO^{(b) (4)} ISO^{(b) (4)} and CNC ^{(b) (4)} during ^{(b) (4)} EMPQ). Reduced frequency (in some locations) Interim EM will be used post-EMPQ until new routine EM is proceduralized. Changes were recommended (vs. 2019 EMPQ) and the sampling required for EMPQ will be as follows:

- ^{(b) (4)}
- 

Reviewer Comment: *No evidence of incubator interior sampling or results of such sampling were provided. I recommend inspectional follow-up to verify sampling of the incubator interior as part of line clearance at the end of each batch.*

- Access corridors ^{(b) (4)} ^{(b) (4)} sampling of highest ingress risk areas: doors, floor and walls along corridor, cart surface, passthrough doors ^{(b) (4)} sites per corridor). ^{(b) (4)} ^{(b) (4)} sampling along corridor ^{(b) (4)} sites each per corridor)
- HEPA Passthroughs: ^{(b) (4)} ^{(b) (4)} [cart (cart pass through only), interior door and bottom/floor) and ^{(b) (4)} ^{(b) (4)} sampling. ^{(b) (4)} ^{(b) (4)} sampling in cart pass through only. ^{(b) (4)} EM to be performed to evaluate the use of pass throughs.

Reviewer Comment: ^{(b) (4)} ^{(b) (4)} *sampling of active pass throughs was not included into EMPQ. This is further discussed in Deficiency 12 below.*

- Changing rooms, Gown-In, Gown-Out, Clean Storage, and Janitor Closet: sampling of areas most frequently touched and/or pose highest risk for materials and equipment that will be later transferred to the manufacturing rooms. ^{(b) (4)}

- (b) (4) sampling of shelves, gowning bin, benches, lockers, eyewash bowl, floor drain, floor, doors, and walls (b) (4) sites per room). (b) (4) sampling (b) (4) sites each per room). In Gowning In room all types of samples are collected on both “clean” and “dirty” sides of the room.
- *Receiving Supply:* Same sampling site rationale was used as for gowning/clean storage above. (b) (4) sampling of sink, shelves, work benches, floor, doors (including pass through), and walls (b) (4) sites). (b) (4) sampling (b) (4) sites each).
 - (b) (4) EM will be performed for (b) (4) throughout the facility
 - Additional sampling of ISO (b) (4) and supporting ISO (b) (4) areas to be described in batch records and other execution documents.

Reviewer Comment: *The monitoring sites and duration proposed for 2020 EMPQ appear acceptable.*

(b) (4) -2020-034-P 2020 EMPQ final report was approved on March 02, 2021. The study was performed under (b) (4) conditions. The latter included RVT-802 APV and routine processing. Manufacture was performed in multiple suites of the facility during (b) (4) days of the study. Sampling of non-production areas in the presence of manufacturing personnel was performed at least once; activities included staff entering/exiting facility, toolbox prep, pass-through transfer/simulated use, and prep for training. Whenever sampling could not be performed concurrently with an activity, it was performed upon completion, later in the day. Sampling sites were as described above in (b) (4) -2019-045.1-P EM Program Risk Assessment.

The (b) (4) sampling was performed either by (b) (4) staff or by (b) (4), a qualified contractor and a subsidiary of (b) (4). All (b) (4) sampling was performed by (b) (4). EMPQ and subsequent interim EM sampling were performed per EMPQ protocol (b) (4) 2020-034-P.

(b) (4) staff used (b) (4) and (b) (4) particle counters (b) (4) provided their own equipment. All equipment was verified by (b) (4) QU to be within their calibration dates. All (b) (4) sampling (b) (4) air and surface) used (b) (4) places with (b) (4).

Reviewer Comment: *The final report does not specify the volume and duration of air sample collected during EMPQ (see Observation 3a above).*

On September 13, 2021 the firm explained in the amendment STN 125685/0.70 (response to Q.3) that (b) (4) were measured (b) (4) throughout setup and processing (b) (4) air samples that covered the initial setup and processing were collected during 2020 EMPQ. A new (b) (4) was used for each (b) (4) sample.

Reviewer Comment: *The response is acceptable. Observation 3a is adequately addressed.*

Upon completion of facility construction and equipment installation, facility was triple cleaned (June 12, 2020), followed by a (b) (4) cleaning (06/27/2020) prior to start of EMPQ. (b) (4) cleaning was also performed on 07/11/2020 (partial, following (b) (4) (b) (4) check) and 07/27/2020 (entire facility) prior to (b) (4) sampling. Other than that, cleaning was performed on a (b) (4).

During EMPQ ISO (b) (4) and ISO (b) (4) LAF were monitored for (b) (4) days under (b) (4) conditions and for (b) (4) days under dynamic conditions, with the following exceptions:

- (b) (4) day (b) (4) sampling of (b) (4), and (b) (4) in Receiving/Supply;
- (b) (4) day (b) (4) sampling of (b) (4)
- No (b) (4) sampling of (b) (4) in the Materials Prep (not used for (b) (4) manufacture)

All other areas except Janitor's closet were monitored for (b) (4) days under (b) (4) conditions (July 30-August 01, 2020) and (b) (4) days under (b) (4) conditions. Janitor's closet was sampled for (b) (4) days under (b) (4) conditions only.

Sampling included active (b) (4) (both (b) (4) conditions); (b) (4) (ISO (b) (4) and personnel monitoring (b) (4) only). Differential pressure, temperature, and humidity were measured and monitored via the (b) (4) system throughout 2020 EMPQ.

(b) (4)

Reviewer Comment: The applicant should confirm ISO (b) (4) and ISO (b) (4) (b) (4) limits. The limits provided in (b) (4) -SOP-008 are acceptable, however it is not clear whether they are applied to (b) (4), or both types of samples.

On September 13, 2021 the firm explained in the amendment STN 125685/0.70 (response to Q.4 and Q.5) that ISO (b) (4) action limit should read (b) (4)

Regarding (b) (4) action limits for ISO^{(b) (4)} areas, the firm explained that those were set at (b) (4) during 2019 EMPQ and subsequent interim EM, which are also the current limits per (b) (4)-SOP-008 (note that the SOP was revised per CBER request to clearly state that same limits apply to (b) (4) sampling). However, during 2020 EMPQ and subsequent interim EM the limits were set as (b) (4) for both ISO^{(b) (4)} and ISO^{(b) (4)} areas.

Reviewer Comment: No clear explanation was provided for using inadequate limits for ISO(b) (4) monitoring during 2020 EMPQ. The firm should reassess (b) (4) ISO^{(b) (4)} air EMPQ results using the appropriate action limits.

On September 21, 2021 the firm clarified in the amendment STN 125685/0.75 (response to Q.1) that all (b) (4) collected during (b) (4) monitoring during the 2020 EMPQ and subsequent interim period were below the ISO^{(b) (4)} criterion of (b) (4).

Reviewer Comment: The response is acceptable.

The acceptance criteria for room controls were set as follows:

- Temperature (b) (4)
- Relative humidity (b) (4)
- Average differential pressure for each (b) (4) acceptance criterion.

The EMPQ (b) (4) sampling results were assessed for contamination incidence rate (b) (4) which was (b) (4) for ISO^{(b) (4)} ISO^{(b) (4)} and CNC areas, respectively. Excursion recovery rates (% samples above alert and action limits, includes (b) (4) samples) were also determined (b) (4), respectively). Majority of recoveries were in Changing room, Receiving/Supply, Gown Out, and “dirty” side of Gown In.

The following action limit excursions occurred during (b) (4) sampling (with follow up, where applicable):

- (b) (4) : ISO(b) (4) (Materials Prep) on 07/08/2020 (b) (4) sampler, (b) (4) and on 07/09/2020 (b) (4) Root cause determined to be improper cleaning and handling of equipment; EM were counseled on equipment wipedown.
- (b) (4) : ISO(b) (4) on 7/10/2020 (b) (4) sampler; (b) (4)
- (b) (4) : ISO(b) (4) (Materials Prep) on 07/13/2020 (center work (b) (4) mold, species not determined). Investigation did not reveal mold trends in the facility.

- (b) (4) : Gown In, clean side ISO (b) (4) on one of the days. Clear root cause not identified.

The following action limit excursions occurred during (b) (4) sampling:

- (b) (4) : ISO (b) (4) on 06/29/2020 (b) (4) chair; (b) (4) . No root cause identified. Isolated incident.
- (b) (4) : ISO (b) (4) Gown Out on 07/08/2020 (eyewash bowl; (b) (4) and on 07/10/2020 (eyewash bowl; (b) (4) . Root cause determined to be (b) (4) eyewash check without subsequent cleaning. SOP updated to require cleaning of the sink, drain and trap after each eyewash check and use.
- Personnel: (b) (4) ISO (b) (4) excursions, both identified as (b) (4)
- (b) (4) ISO (b) (4) on 07/28/2020 ((b) (4) . Clear root cause not determined; ruled an isolated event.
- (b) (4) alert level excursion trend was identified (in front of lockers, CNC changing room; (b) (4) days between (b) (4) . Possible root cause was either improper daily cleaning or “timing of usage/cleaning with respect to sampling”. No excursions (alert or action limit) in the adjacent ISO (b) (4) room were identified.

Colonies of unique morphology were identified visually, by (b) (4) . Among the total of (b) (4) identifications, (b) (4) were (b) (4) (trended separately due to showing stronger disinfectant resistance than other cocci), (b) (4) were spore-forming rods (mostly Bacillus), (b) (4) were mold/fungus, (b) (4) were (b) (4) . The subset of ISO (b) (4) /ISO (b) (4) identifications (b) (4) was also analyzed for prevalence, which was similar to the whole dataset except no (b) (4) bacteria were identified and proportion of mold/fungus was higher (b) (4) . A single colony of a (b) (4) bacteria) was found during the EMPQ (b) (4) Changing Room, 07/15/2020]. No other objectionable organisms were identified.

None of the excursions occurred when the maximum number of personnel were present, therefore the applicant set maximum occupancy levels to maximum number personnel present during (b) (4) sampling.

Reviewer Comment: For several rooms (Receiving/Supply; Gown In, Clean Storage, and Access Corridors 1 and 2) maximum occupancy is supported by only (b) (4) sampling, which is insufficient. Also refer to Deficiency 12 for discussion of green/red light system and operators serving as “hallway monitors”.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.6) that maximum occupancy was based on both 2019 and 2020 EMPQ outcomes. As there were facility design and procedural improvements following

2019 EMPQ, the firm considers 2019 EMPQ the worst-case scenario, which justifies use of its data for maximum occupancy determination.

There are (b) (4) areas where less than (b) (4) days of (b) (4) monitoring at maximum occupancy were performed during 2020 EMPQ: Receiving /Supply (ISO (b) (4) day at NLT (b) (4) people), Gown-In (ISO (b) (4) day at NLT (b) (4) people), Clean Storage (ISO (b) (4) day at NLT (b) (4) people), Access Corridor (b) (4) (ISO (b) (4) days at NLT (b) (4) people), and Access Corridor 2 (ISO (b) (4) days at NLT (b) (4) people).

Reviewer Comment: Though I agree with the firm's rationale, it cannot be applied to all rooms in question. Specifically, the footprint of Receiving/Supply was reduced at a result of remodel to enlarge Changing room and install a cart pass through. Remodeled Gown-Out is the worst-case comparing to the 2019 facility due to an additional door to non-controlled non-classified area (vs. to ISC (b) (4) in 2019). It is therefore inappropriate to leverage 2019 data for these rooms.

On 9/21/2021 the firm explained in the amendment STN 125685/0.75 (response to Q.2) that the maximum occupancy in Gown Out (b) (4) people) is supported by three days of monitoring during EMPQ 2020. The firm revised the maximum occupancy for Receiving/Supply to (b) (4) people based on the CBER feedback. (b) (4)-SOP-003 was amended to reflect this change.

Reviewer Comment: The response is acceptable.

Room controls during EMPQ were assessed via continuous monitoring by (b) (4) sensors and daily monitoring by (b) (4)-traceable instruments used by (b) (4) staff on EM sampling days. All pressure differential, temperature, and humidity data acquired by (b) (4) (except one pressure differential datapoint) met acceptance criteria outlined above. Multiple issues related to (b) (4) sensors were observed: some sensors and collection devices were malfunctioning and had to be repaired, some sensors were not reading accurately throughout EMPQ, short periods of data loss due to connectivity also occurred. Post-EMPQ recalibration found several sensors to be out of tolerance. Temperature sensors in (b) (4) located (b) (4) were relocated post-EMPQ.

DP fluctuations outside of alarm range were mainly related to HVAC shutdown (pressure, temperature) or door opening. Pressure reversal was observed on Gown Out to Receiving door. The root cause was determined to be opening of both Gown Out doors, which was remediated by (b) (4) system. Post-EMPQ data analysis showed no instances of pressure reversal. Temperature as measured by (b) (4) was corrected for the difference with (b) (4)-traceable instrument and was found within (except for brief excursions) the acceptable range, albeit close to its upper limit. (b) (4) was adjusted to lower room temperature closer to the targeted (b) (4)

Reviewer Comment: Though pressure differential EMPQ data was provided for (b) (4) relative to entry and exit corridors only, based on the firm's statement and as supported by information in (b) (4) -SOP-094 (Appendix A), differential pressure is continuously monitored and alarmed on all doors of the facility. However, alarm limits on most doors are wide (b) (4) from Changing room to outside of the facility) and should be justified. Limits for Receiving/Supply to Gown In are positive (b) (4) though per the floor plan air flows from Gown In to Receiving/Supply.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.8) that alarm limits for majority of sensors were established to ensure "the correct direction of differential pressure" (i.e. either positive or negative) given the (b) (4) sensor tolerance and upper/lower limit of the sensor operating range (i.e. (b) (4)). The rationale for alternative alarm ranges was as follows:

- To avoid nuisance alarms (b) (4) on locked door from Gown Out to Receiving/Supply; (b) (4) on frequently used door from Changing room to outside of the facility)
- To ensure robust pressure differentials on emergency exits between access corridors and office areas (b) (4) Access Corridor (b) (4) to office area; (b) (4) Access Corridor (b) (4) to office area). The upper limit outside of sensor's operating range was set to avoid nuisance alarms as the pressure reads (b) (4) on this door (albeit not within the expected tolerance of calibration). The firm has not yet identified an (b) (4)-compatible sensor that can measure (b) (4) (b) (4) does not sell sensors that operate in this range.

The firm explained that Receiving/Supply to Gown In limits should be Gown-In to Receiving/Supply limits. The sensor will be relabeled accordingly.

Reviewer Comment: The response is acceptable. Facility data for differential pressure is (b) (4) recorded and reviewed on the (b) (4) Observation 3g is adequately resolved. Though sensor use outside of its operating range might damage the sensor, the door is not routinely used, and the firm is in the process of resolving the issue. I recommend inspectional follow-up for sensor replacement.

Additional outcomes of the EMPQ include Implementation of (b) (4) -SOP-099 EM Data Trending in the (b) (4) (not provided), which proceduralizes data trending and review (type of data and analysis, review frequency). The data is analyzed (b) (4) and trended (b) (4). Routine EM (frequency, sampling sites, and alert limits) will be reassessed (b) (4). Both (b) (4) reports are reviewed by QU. EM committee (expanded to include third-party SMEs and Enzyvant representative) reviews (b) (4) analyses.

Reviewer Comment: In Type A meeting preliminary response CBER request a trending report for the classified areas to be submitted in response to Observation 3. None was provided in the submission.

On September 13, 2021 the firm provided (b) (4) (Q3 2020, Q4 2020, Q1 2021) and (b) (4) (April-June 2021) EM trending reports in the amendment STN 125685/0.70 (response to Q.7). Q3 2020 covered 2020 EMPQ and interim EM that followed. Q2 2020 EM trending report is in progress; the firm committed to submit it to CBER by 09/23/2021.

Reviewer Comment: The report was provided in amendment STN 125685/0.75 on September 21, 2021. Based on the data provided in the report, facility is in the state of environmental control. The response is acceptable.

The report contained trending of (b) (4) “Check Network” and “Check Link” communication errors (October 2020 – June 2021), which varied from (b) (4) and from (b) (4), respectively. The firm is investigating link errors under DEV-1195.

I recommend inspectional follow-up to verify that the deviation is successfully resolved, and that no data is being lost due to communication errors, as the firm stated.

Trending program includes assessment of facility use, cleaning, EM data, sterility failures (if applicable) as well as evaluation of facility parameters (differential pressure, humidity, and temperature) and alarms.

It appears that although EM OOS occur only occasionally, target contamination incidence rates of (b) (4) for ISO^(b) and CNC areas respectively are routinely exceeded (though values are similar (b) (4) due to recoveries in Changing, Gown-Out and/or Receiving/Supply. This correlates with the facility use. No other trends and no objectionable organisms were identified since Q3 of 2020.

There appears to be a decrease in number of isolates/OOS and proportion of spore-formers and micrococcus-like species since April 2021, when new cleaning program was implemented.

Reviewer Comment: New cleaning program appears to be effective. Trending program is adequate and includes assessment of facility use, cleaning, EM data, sterility failures (if applicable) as well as evaluation of facility parameters (differential pressure, humidity, and temperature) and alarms. The response is acceptable.

(b) (4)-2019-045.2-P EM Program Risk Assessment Final Report approved on 03/05/2021 is an update to the previous risk assessment to incorporate 2020 EMPQ outcomes and establish frequency and locations for routine EM. Typical FMEA approach was used (see risk assessment above for the approach description); scoring of occurrences (b) (4) based on excursion recovery rate/contamination incidence rate) and detectability (b) (4) based on contamination incidence rate and proposed routine EM site analysis) were added. Risk was assessed for each facility area as high (RPN (b) (4) areas), medium (RPN (b) (4) areas) or low (RPN (b) (4) areas). Previous severity scores were reviewed for accuracy (reduced for (b) (4) in Materials Prep and CNC cart pass through).

Sampling sites for routine EM were selected in areas that had the most frequent hits during EMPQ, the most frequent usage, and/or posed the highest risk of ingress (i.e. near doors) or to the product (i.e. close to (b) (4) sampling sites remained the same except ISO (b) (4) HEPA passthroughs and CNC Janitor Closet, where only routine (b) (4) sampling will be performed. (b) (4) sampling remained the same (except frequency – see below). Number of (b) (4) sites was reduced for all other areas (to (b) (4) sites in ISO (b) (4) suites, (b) (4) in other ISO (b) (4) areas, (b) (4) in ISO (b) (4) areas, (b) (4) ISO (b) (4) pass throughs, (b) (4) in CNC areas), except CNC Changing Room. The sampling frequency was reduced to align with (b) (4) guidelines. (b) (4) to be sampled (b) (4), but at least (b) (4) if idle, except (b) (4) is sampled (b) (4) is sampled (b) (4) ISO (b) (4) manufacturing rooms are sampled on the days of use, at least (b) (4) if idle. Other ISO (b) (4) areas and ISO (b) (4) HEPA pass throughs are to be sampled (b) (4). ISO (b) (4) and CNC areas are to be sampled every (b) (4), except Janitor's Closet that is to be sampled (b) (4).

Microbial identification approach proposed by the risk assessment is to genotype all contaminants from ISO (b) (4) ISO (b) (4) and ISO (b) (4) entry areas (including associated pass through); (b) (4) of all contaminants in ISO (b) (4) exit areas (including pass through) and top 5 most prevalent morphologies on each above-alert level plate from CNC areas.

(b) (4)-SOP-008 EM Program for the (b) (4) ver. 13 effective 03/30/2021 proceduralizes the outcomes of EMPQ and EM risk assessments described above. It addresses Observation 3 as follows:

Observation 3b and 3d: (b) (4) monitoring for (b) (4) (at the end of the day) and active (b) (4), adjacent to (b) (4) and (b) (4) (continuous, adjacent to (b) (4) of ISO (b) (4) manufacturing suites included in routine EM program.

Other ISO (b) (4) areas (including passthroughs) and ISO (b) (4) areas are monitored routinely under (b) (4) rather than (b) (4) conditions, as supported by EMPQ and EM risk assessment outcomes above.

- **Observation 3c:** (b) (4) sampling of (b) (4) in operation was added during setup and processing. (b) (4) sampling is “per manufacturing batch record” (every (b) (4)), “larger volumes/longer times” than routine (b) (4) min routine sample could be used.

Observation 3e: (b) (4) are sampled for (b) (4) viables post-operations (per batch record).

Reviewer Comment: Per batch record (b) (4), ISO^{(b) (4)} manufacturing suite air monitoring is performed upon completion of operations only. Per MBR (b) (4) sampling of (b) (4) is repeated every (b) (4) and requires (b) (4). This was simulated during (b) (4) and is acceptable. It is not clear whether the same method (or (b) (4) method as described in the EM risk assessment above) was used during EMPQ.

On September 13, 2021 the firm explained in the amendment STN 125685/0.70 (response to Q.3) that multiple (b) (4) samples that covered the initial setup and processing were collected during 2020 EMPQ. A (b) (4) was used for each (b) (4) sample.

Reviewer Comment: The response is acceptable. Observations 3b-e are adequately resolved.

Observation 4

The current cleaning procedures used in the cleanroom have not been qualified.

a. Disinfectant effectiveness studies have not been performed for the sanitizing agents routinely utilized in the manufacturing facility.

b. The procedures established and followed for cleaning the facility are inadequate; for example

i. Procedure (b) (4)-SOP-060 is deficient in that it does not describe in detail the process for cleaning the (b) (4); specifically, during observation of the simulated manufacturing operations, we noted the following:

(b) (4)

ii. Procedure (b) (4)-SOP-066, includes (b) (4) different procedures for cleaning the (b) (4) incubator even though only one procedure is used at the facility.

iii. Procedure (b) (4)-SOP-006 states that (b) (4) cleaning is required for the cleanrooms (floors and surfaces) even though the production room and supportive areas are used (b) (4) for manufacturing product lots.

iv. The cleaning of the passthroughs is not performed before or after use. It is cleaned once a (b) (4).

Response Summary

As described above, a set of risk assessments (EM, cleaning, cross-contamination, aseptic processing) was performed by the firm following 2019 EMPQ. In 2020 after the

facility modifications, recertification, associated changes to gowning, cleaning, and flow procedures, and (b) (4)
(b) (4) 2020 EMPQ (no clinical material was manufactured under IND 9836 during this timeframe).

The following SOP changes were implemented prior to 2020 EMPQ and DE study:

(b) (4) -SOP-060 Operation and Maintenance of the (b) (4)
(b) (4) effective 03/17/2021: (b) (4) cleaning
described in more detail, including use of wipes (b) (4)
(b) (4) and reapplying disinfectant to maintain required contact
time.

Reviewer Comment: The SOP revision adequately addresses Observation 4b(i) (a) and (b), provided it is properly executed and enforced.

(b) (4) -SOP-006 Cleaning and Sanitization of the Classified Areas in the (b) (4)
(b) (4) ver. 11 effective 03/24/2021: details added regarding disinfectants and
cleaning supplies used in the facility (usage and storage); new section detailing cleaning
procedures performed by (b) (4) personnel [line clearance expanded to include (b) (4)
cleaning of ISO (b) (4) suites, use of (b) (4) instead of (b) (4) for specific
surfaces/equipment, first use (b) (4) cleaning, documentation of (b) (4) contact time for
equipment transferred into (b) (4) cleaning of all pass throughs (cart
pass through is cleaned (b) (4), expanded spill cleanup procedures; (b) (4) cleaning of
Changing Room], updated section detailing cleaning procedures performed by
contracted cleaners (b) (4) disinfectant changed to (b) (4) followed by (b) (4)
(b) (4) cleaning to be followed with (b) (4) cleaning of
sinks/eyewashes with bleach at the time of use added).

Reviewer Comment: The SOP revision adequately addresses Observation 4b(iii) and (iv), provided it is properly executed and enforced.

(b) (4) -SOP-004 Gowning Procedures for the (b) (4) ver. 09
effective 06/25/2020: added shoe covers over street shoes (upon Changing room entry)
and over dedicated shoes (upon Changing room exit).

(b) (4) -SOP-009 Personnel Flow and Material Transfer in the (b) (4)
ver. 09 effective 03/11/2021: changes are described below in Deficiency#12. The firm
stated that operators were retrained to more frequently change wipes used for transfer
of materials into (b) (4)

Reviewer Comment: This SOP (section 8.6) refers to (b) (4) -SOP-060 as the document proceduralizing wiping of items being transferred into the (b) (4). I was not able to locate this information in (b) (4) -SOP-060. (b) (4) -SOP-006 only appears to cover disinfection of equipment transferred into (b) (4).

Observation 4b (ii) regarding (b) (4) -SOP-066 was not addressed.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.9 and Q.10) that wiping and disinfecting materials for (b) (4) transfer is covered in (b) (4)-SOP-009, Rev 9 (Section 8.6), (b) (4)-GEN-011, Rev 2 (Sections 8.2.5 and 8.3.3.7-8), and within the individual manufacturing batch records and associated forms (most detailed). RETHYMIC operators were retrained on the manufacturing forms and demonstrated proficiency via training batches and media fills. Additionally, (b) (4)-SOP-009 was revised to require frequent change of wiping materials and ensuring wipes are saturated with disinfectant. Current version of (b) (4)-SOP-066 Operation and Maintenance of the (b) (4) Incubator ver. 06 effective 03/24/2021 was provided. The SOP clearly delineates cleaning and other procedures specific to each model of the incubator.

Reviewer Comment: The response is acceptable. Observations 4b (i)(c) and 4b (ii) are adequately addressed.

(b) (4)-2019-051.4-P Disinfectant Efficacy Final Report approved 03//25/2021 was provided. The scope of the initial study was expanded based on Type A meeting feedback in March 2020. The protocol was further revised during execution to remove test conditions no longer necessary based on the preliminary data review. Supplemental study was executed in Jan 2021 to support use of (b) (4) under additional conditions of use as it was deemed beneficial to expand its use based on the DE study data review.

The initial study was performed by two qualified vendors that prepared internal protocols based on the master protocol supplied by the firm. Internal protocols were reviewed and approved by (b) (4) and Enzyvant, which also reviewed vendor methods.

The study included microbial arm (b) (4) and facility (b) (4) isolates: (b) (4) and viral arms [porcine parvovirus (PVV, non-enveloped) and pseudorabies virus (PRV, enveloped)].

The firm stated that potential virus sources (donor tissue) and WHO guidelines outlined in Technical Report No.924, 2004, which recommends testing non-enveloped and enveloped viruses, HIV and a model hepatitis virus were considered. HIV was excluded from the study as it is readily inactivated by common disinfectants, PRV is a model for Hepatitis B virus with moderate resistance to disinfectants, and PPV (model for Parvovirus B19) was chosen based on high resistance to disinfectants.

Disinfectants evaluated included (b) (4)

All disinfectants were opened and stored capped for (b) (4) days prior to testing. Historical and new uses (i.e., disinfectant/surface combinations) of each disinfectant were evaluated. Mode of application (i.e., wiping or rubbing) was not evaluated.

Total of (b) (4) representative (b) (4) materials were selected (either most common or worst case of a particular surface type):

- (b) (4)

(b) (4)/disinfectant combinations tested were based on use of a particular disinfectant. The impact of soiling the (b) (4) [with Thymus Organ Medium (TOM) for viruses and (b) (4) Fetal Bovine Serum (FBS) for microbes] was evaluated with (b) (4) (historically used for spill clean-up) and with (b) (4) (supplemental study) on (b) (4) surfaces (excluding walls and equipment exterior), depending on disinfectant used.




(b) (4)

In most cases, (b) (4) contact times were evaluated (b) (4). Acceptance criteria were (b) (4) are not sporicidals and therefore were not tested against (b) (4). Additionally, (b) (4) was not tested against PPV and (b) (4) was not tested against PRV. (b) (4) was tested against viruses only under unsoiled conditions.

(b) (4) were effective on all (b) (4) against all microorganisms / viruses at respective maximum contact times at all tested conditions. Effectiveness of other disinfectants varied depending on surface/organism combination. Most of them were found less effective than indicated in manufacturers' claims, particularly against sporeformers and (b) (4).

The most challenging organisms were (b) (4)

(b) (4)



Based on DE study, the cleaning program was revised. Initial cleaning program in 2020 relied on (b) (4) as sporicidal in addition to (b) (4) cleaning with (b) (4). However, (b) (4) did not show sporicidal activity in DE study, therefore (b) (4) cleaning of facility was increased to (b) (4) was replaced with (b) (4) for the first use daily (b) (4) cleaning, material/bin sanitization prior to facility transfer via cart pass through, and spill cleanup; additional (b) (4) sanitization of (b) (4) post-use was implemented.

Reviewer Comment: Observation 4a is adequately resolved.

Observation 5

The existing alarm system and its implementation are deficient. Specifically,

- a. Temperature probe in (b) (4) used to store released critical reagent, (b) (4), is not placed in the worst-case location as determined during equipment qualification.**
- b. The firm did not perform IQ/OQ of the (b) (4) alarms and probes installed after 2014, including those installed in (b) (4) incubators (b) (4) instrument. The equipment is used for manufacture and release sterility testing of RVT-802 and storage of critical reagents and source material.**

- c. The firm failed to provide records of preventive maintenance for any of (b) (4) alarms used for monitoring of differential pressure, temperature, and humidity within the facility, (b) (4) system, as well as the following critical equipment: (b) (4) incubators (b) (4) levels and temperature), (b) (4) used for storage of critical reagents, source material, and (b) (4) samples, and (b) (4) instrument used for release sterility testing of the product.
- d. The alarm notification and response are not adequate. Per deviation IR-0114 dated December 5, 2017 and a corresponding (b) (4) log for events #7285 and 7286: On December 3, 2019 temperature within the incubator was out of range between 12:35 and 15:12 and (b) (4) was out of range between 12:03 and 14:46. No alarm notification was received until 12:30, and notified employee failed to immediately respond to the alarm. The incubator contained (b) (4) lot of thymus tissue, which was implanted on December 19, 2017.

Response Summary

To address this observation and Type A meeting comments, the firm submitted (b) (4) 2020-011-P (b) (4) Sensor Assessment Report approved 05/05/2020 and its addendum (b) (4)-2020-011.1-P approved 10/16/2020. The assessment evaluated presence and functionality of all sensors and their locations within the system as well as all alarmed equipment/sensors with respect to sensor placement, calibration and operation status; alarm values, appropriate response to alarms, process/frequency for data and system function review and handling of excursions. Both (b) (4) (mostly) and (b) (4) systems were assessed. (b) (4) sensor master list was created, and criticality level was assigned to each based on impact to product quality in case of failure. Several deficiencies were identified, mostly similar to the issues brought up during the inspection, 483 response review and Type A meeting. The firm stated that the gaps were mitigated via SOP (b) (4)-LAB-010 and (b) (4)-SOP-094 revisions (see details below).

The firm stated that IQ/OQ procedures of sensors include verification of calibration and verification of functionality of the Collection Point and Access Point for each sensor (verification of signal in (b) (4)). Any additional IOQ requirements will be defined in the Change Control Request for installation of the new sensors (required for initial installations and replacements per (b) (4)-SOP-094). In May 2020 the new software (b) (4); see below) was added to the (b) (4) system, functionality of all sensors was confirmed, including verification of calibration, and verification of functionality of representative Collection Points and Access Points throughout the facility and in all equipment. As calibration procedures were revised (and due to several sensors showing significant measurement differences from (b) (4)-traceable instrument during 2020 EMPQ), all (b) (4) sensors were re-calibrated in August-September 2020, completing the required IQ/OQ activities. Recalibration was documented in (b) (4)-2020-049-E Final Summary Report for (b) (4) System Sensor Calibrations (provided).

Reviewer Comment: Observation 5b is resolved.

The firm performed additional temperature mapping (b) (4) of multiple (b) (4) throughout the (b) (4) facility to identify worst-case locations (selected based on worst impact to the load) for sensor placement. The temperature mapping results and recommended worst-case sensor locations for all pieces of RVT-802 equipment (i.e. incubators, (b) (4)) were outlined in report (b) (4)-2020-070-E (b) (4) Probe Relocation Report approved 10/16/2020 and the probes were relocated accordingly.

Reviewer Comment: *Though temperature mapping data was provided, it was not specified whether it was acquired for empty or loaded equipment (loads not described) or whether there was any difference in hot/cold spots between the two conditions and if so, how it was reconciled.*

On September 13, 2021 the firm provided (I)OPQ reports for temperature-controlled chambers (b) (4) in the amendment STN 125685/0.70 (response to Q.11). (b) (4)

Reviewer Comment: Though load placement in (b) (4) during temperature mapping did not match that during production, this is acceptable due to the narrow temperature range observed in this incubator (b) (4).

(b) (4)

(b) (4)

Reviewer Comment: (b) (4)

(b) (4)

Reviewer Comment: The response is acceptable. Observation 5a is adequately resolved.

The firm stated in the response that (b) (4)-SOP-094 Temperature and Environmental Monitoring Systems for (b) (4) was revised to include the following additional information:

1. Descriptions of sensor locations for each piece of equipment, both existing and newly installed (Appendix A) and a sensor map showing the general locations (Appendix E)
2. Requirement to perform Installation/Operation Qualification (IQ/OQ) of sensors at time of installation
3. Preventive maintenance procedures (performed concurrently with (b) (4) calibration) of all sensors includes checking physical condition of sensors and components, cleaning of the sensors, and (b) (4) battery change out in the collection and access points. Existing and new (b) (4) sensors are included in the preventative maintenance program.
4. Modified calibration procedures for the (b) (4) sensors
5. Expanded procedures for handling excursions/events,
6. Data review procedures, including frequency and scope
7. Procedures for acknowledging alarms and expected response times. The firm stated that "staff are expected to respond to alarms as soon as possible and, per SOP, must acknowledge the alarm within one business day".

8. Updated alarm ranges based on 2020 RVT-802 Process Risk Assessment (b) (4)-2020-009.1-P, rev.1 approved 03/25/2021)
9. Changes due to addition of (b) (4) software (see details below) to (b) (4) system (sensor addition, daily checkpoints, generation of reports)
10. Appendices specifying details of alarm response (who is responsible, how to respond, and appropriate timing). Alarm delays were set based on historical performance, PQ data, potential product impact, and current alarm frequency.

The firm provided copy of (b) (4)-SOP-094 ver. 06 effective 02/16/2021 and its red-lined version.

Reviewer Comment: The SOP does not have all of the updates listed in the firm's response. Specifically (number correspond to those in the list above),
(1) Appendix A does not include descriptions of sensor locations; Appendix E is not present,
(2) no IQ/OQ requirement for new sensors
(3) PM lacks clarity. It is stated to be performed (b) (4) (8.19.1) and at each calibration (8.19.6), appears to apply to pressure sensors only; requires (b) (4) (8.19.4) and an (b) (4) assessment of need for replacement (8.19.3). It is not clear if all sensors (existing and installed in the future) will be included in PM program or how PM will be documented.
(7, 10) Required alarm response times are not proceduralized.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.12) that the obsolete version (ver. 06) of the (b) (4)-SOP-094 was inadvertently submitted. The SOP was further amended and a redlined version of current ver.10 was provided for review. The SOP updates include items/procedures not previously found/proceduralized (see the list above). Preventive maintenance procedure was clarified. Additionally, the SOP includes Appendix F detailing specifications of various (b) (4) sensors used.

Reviewer Comment: The response is acceptable. Observations 5c and 5d are resolved.

The firm stated that (b) (4)-LAB-010 was modified to include:

1. Detailed procedures for data review, including frequency and scope. Data to be monitored by (b) (4) and reviewed (b) (4) by Quality. (b) (4) QSU director to be notified of alarms. Timing of notification and documentation of responses was included.
2. Product impact assessment in case of excursions, alerting management/quality of potential product quality impact
3. Optional (b) (4) data backup to an external hard drive

The firm provided copy of (b) (4)-LAB-010 ver. 11 effective 02/22/2021 and its red-lined version.

Reviewer Comment: *The firm's response to Type A comment #4 is incomplete as the SOP revisions proceduralizing relaying information from (b) (4) to (b) (4) QSU only apply to (b) (4) alarms, but not to any issues related to system functionality encountered during (b) (4) data review by (b) (4).*

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.13) that (b) (4) Quality System Unit (QSU) supports both (b) (4) and (b) (4). Section 8.7 of (b) (4)-LAB-010 states that QSU performs (b) (4) review of system records. The section was further revised to include system functionality issues, associated alarms, and comment logs in the scope of the review (redlined version of the revised SOP was provided for review).

Reviewer Comment: *The response is acceptable.*

The following reports were provided to support implementation (b) (4) software for (b) (4) (b) (4)-2020-025-E (b) (4) Software Upgrade and System Qualification Final Summary Report approved 05/29/2020. The report summarized IQ and OQ of (b) (4) software at (b) (4) at (b) (4). The (b) (4) is a vendor managed / installed system. Verifications for computer hardware and network configuration and software training were performed by the vendor. Validation was executed by (b) (4) OQ consisted of SOP verification and a set of test modules to verify backup and recovery, system start up and login, access point and zone configuration, security access, security policy configuration and functionality, checkpoint functionality, reporting, and signal loss. All acceptance criteria were met. There were (b) (4) non-conformances during the protocol execution, mostly protocol generation errors. None had impact on system functionality or to product quality.

Reviewer Comment: *Though it is not clear whether (b) (4) software is compliant with 21 CFR Part 11 based on the provided information; the firm provided a statement to that effect in their response to Observation 10 (see below for inspectional recommendation for verification of computer system compliance).*

Observation 6

The Quality Unit oversight of batch record review is deficient. Specifically,

- a. A review of the (b) (4) batch record, Preparation of Final Product (b) (4) SOP-031, FRM14, dated 19Apr2019) and the Room (b) (4) incubator use log form does not include: 1) verification or periodic recording of (b) (4) and temperature during this time period, and/or 2) inclusion of the (b) (4) graph printout, which shows (b) (4) monitoring of (b) (4) and temperature over the (b) (4) day time period, 3/26/2019-4/19/2019. The manufacturing process requires (b) (4) to be

maintained between (b) (4) and the temperature (b) (4) during the incubation period.

- b. Not all time limits for the completion of each process step follow limits defined by process validation, and batch record review does not confirm adherence to step times.

Response Summary

Revisions were made to the manufacturing SOPs related to batch record review. The updated SOPs were reviewed by the Agency (Seq 0050) and deemed "acceptable if properly executed and enforced".

Reviewer Comment: The response to Observation 6a is acceptable. Observation 6b is deferred to PO, as it was made by TF.

Observation 7

Procedures and process control designed to prevent microbiological contamination of drug product are not established with appropriate acceptance criteria. Specifically,

- a. (b) (4)-SOP-060, "Operation and Maintenance of the (b) (4)", dated July 29, 2019, states certification is performed every (b) (4) for every (b) (4) Section 8.11.3 of (b) (4)-SOP-060, states the (b) (4) are certified using standards traceable to the (b) (4), but does not include the acceptance criteria. Additionally, the acceptance criteria for (b) (4) (b) (4) was not specified but was calculated in the most recent (b) (4) certification, dated April 16, 2019.
- b. The (b) (4) System Qualification Summary Report (b) (4)-2019-025-E, dated March 25, 2019, Ongoing Monitoring, did not include acceptance criteria for (b) (4), which were calculated in the supporting (b) (4) Testing Results from October 2018.

Response Summary

The firm stated that to address the Observation, (b) (4)-SOP-060 and (b) (4)-2020-025.1-E were revised to include the acceptance criteria for (b) (4) certification and operational/performance qualification of the (b) (4)-2020-025.1-E is (b) (4) software final qualification report and must have been referred to in error. (b) (4) Qualification Summary Report REP-019 approved 12/03/2020 was also provided in the submission is summarized below.

The acceptance criteria are summarized below and were verified through the new APV, EMPQ, and (b) (4) studies related to the RVT-802 manufacturing processing.

(b) (4)

(b) (4)

In response to FDA's request at the Type A meeting, (b) (4)-SOP-060 now includes information to limit HEPA filter repair to (b) (4) of the total area and (b) (4) maximum width before complete filter replacement becomes a requirement. In addition, the firm updated all critical equipment SOPs to ensure appropriate acceptance criteria were established for calibration. Procedure (b) (4)-EQUIP-003 was updated to describe the acceptance criteria for calibration of all equipment.

(b) (4) Qualification Summary Report REP-019 approved 12/03/2020 for (b) (4) (in (b) (4); DP manufacture) and (b) (4); TOM and other reagent preparation) was provided in 3.2.A.1. Both (b) (4) are (b) (4) ISO (b) (4) environments. IOQ was performed in 07/2011 and 09/2020 for (b) (4), respectively. IQ for both included verification of equipment identification, materials of construction, documentation (purchase order, manuals, technical bulletins, SOPs, installer/vendor documentation), component functionality, and preventive maintenance; calibration was also performed. OQ included (b) (4) checks (or review of such data in the most recent certification. Additionally, (b) (4) test was conducted for (b) (4). PQ consisted of (b) (4) studies under (b) (4) conditions, simulating routine operating processes. Several PQ were performed for (b) (4) to evaluate typical activities and "worst-case" load during slicing (10/2018, 03/2018, and 05/2020) and one for (b) (4) (10/2017). All airflow was found acceptable. The report includes (b) (4) recertification acceptance criteria.

Reviewer Comment: The response is acceptable. Observation 7 is resolved.

Observation 8

The Quality Unit does not have adequate control over critical materials. For example:

- a. A new container closure was implemented before approval by (b) (4) Quality Assurance for use in the (b) (4) facility on July 27, 2019. It was used for the manufacturing of (b) (4) lots (b) (4) initiated beginning on April 27, 2019.
- b. Sterility of critical product-contact equipment sterilized by external vendors (i.e., sterile (b) (4) specimen final container closure system, tissue slicer, blades, blade handles, forceps, filter papers) is not being verified through periodic sampling of incoming lots.
- c. The firm does not have controls in place to ensure that critical product contact supplies, such as support filters included in final product formulation, dissection instrument, and tissue culture implements are sterile and (b) (4)
- d. Identity tests are not in place for critical raw materials used in the manufacture of TOM media. These include (b) (4) filter, and surgical sponge.
- e. No expiration dates exist for critical materials for the final drug product container closure system or secondary sterile overlap for the final product. Materials that do not have an expiration date assigned by the vendor are to be assigned by (b) (4) according to SOP GEN-009. Expiration for these materials is currently designated "Not Applicable". For other critical supplies that are sterile with direct product contact, such as tissue slicers, scissors, and forceps, expiration dates were not provided.

Response Summary

Only responses to Observation 8b, c, and e are reviewed below. Review of other responses is deferred to OTAT as these observations were made by TF and Sukhanya Jayachandra.

To address the Observation 8b and c the firm implemented sterility and endotoxin testing of all lots of sterile incoming critical product contact supplies, including the (b) (4) container. Slicer blades, blade handles, curved forceps, tissue slicers and filter packs are tested for sterility (b) (4) after (b) (4) sterilization at (b) (4). The firm clarified that slicer blades, blade handles, and curved forceps will be released based on sterility results for tissue slicer and filter packs as all of these materials are sterilized using (b) (4) and are (b) (4)

To additionally address Type A meeting comments, the firm provided (b) (4)-2021-006-P Report on Bacterial Endotoxin Impact to RVT-802 Drug Product: Risk Assessment and Development of an Endotoxin Risk Control Program approved 1/31/2021. The risk assessment evaluated individual and cumulative amount of endotoxin (b) (4) to the final drug product and developed a remediation / control plan as appropriate.

(b) (4)

(b) (4)

Reviewer Comment: The response is acceptable.

To address Observation 8e, the firm reviewed all materials to ensure expiry dates were assigned. The SOP (b) (4)-GEN-009 Assigning Lot Numbers and Expiration Dates to

Reagents and Materials ver. 05 effective 03/03/2021 was updated with a requirement to assign expiry dates for all supplies used in manufacture of licensed products.

Reviewer Comment: The SOP includes sections 8.10 Assigning Expiration Dates to Reagents and 8.11 Assigning Lot Numbers and Expiration Dates to Consumables. However, neither section proceduralizes assigning expiration dates for sterile materials despite Type A request to update the SOP with such procedures. It should be clarified if this is covered by another SOP, which should be provided for CBER review.

On 9/13/2021 the firm provided a red-lined revised SOP (b) (4)-GEN-009 in the amendment STN 125685/0.70 (response to Q.14). Expiration dates are required for all supplies, including sterile materials and are either based of manufacturer data (if provided) or is assigned per material specification instructions based on data available in documentation received with the material. Data and/or appropriate documentation will be required to support a defined expiry period.

Reviewer Comment: The response is acceptable.

For all materials provided sterile by supplier, the expiry data will be assigned based on suppliers' assigned shelf life. Shelf life of (b) (4) containers (b) (4) and that of materials packaged at (b) (4) and sterilized by (b) (4) is based on the completed aging/seal integrity studies summarized below.

(b) (4)-2019-052-A (b) (4) Shelf Life, Accelerated and Real Time Aging Studies for (b) (4)

- Create SOPs (b) (4)-EQUIP-045 JA1 and (b) (4)-EQUIP-045 JA2 for operation, maintenance, and use of (b) (4)


- Update SOP (b) (4)-CCR-1072 with new packaging process
- Update material specification for sterilized materials from (b) (4).

Reviewer Comment: *It appears that the packaging configuration has changed comparing to that previously used (i.e., additional pouching) to accommodate for the use of (b) (4). No equipment qualification for the (b) (4) (new equipment) was provided. The details regarding system suitability, positive/negative controls used for (b) (4) test should be provided.*

On 9/13/2021 the firm clarified in the amendment STN 125685/0.70 (response to Q.15) that implementation of (b) (4) required minimal changes to packaging configuration. Specifically, (b) (4) was replaced with (b) (4). The items, quantities of each that were packaged, the dimensions of each inner and outer bag used for packaging each item for (b) (4) sterilization and all packaging materials and item groupings remained the same.

Reviewer Comment: *The response is acceptable. The changes to packaging do not require revalidation of sterilization cycle.*

(b) (4)



Reviewer Comment: *The response is acceptable.*

Regarding the (b) (4) test system suitability controls and method validation, the firm explained that the (b) (4)

The firm stated that the test method has been validated; operators performing the test are trained and training involves comparisons between operators with defined failure modes to ensure that operators can distinguish between passing and failing packages. Operators must also maintain continuous competency on this method every (b) (4).

Reviewer Comment: The response is acceptable.

(b) (4)-2019-048.2-A Establishment of Expiry Date based on Accelerated and Real-Time Aging of the (b) (4) Specimen Container approved on 03/12/2021. (b) (4) container is supplied sterilized by (b) (4), individually packaged in a (b) (4). The study was performed at (b) (4) containers (both study arms). Accelerated aging arm ((b) (4))

prior to the study. For real-time aging arm, (b) (4)

All (b) (4) passed the acceptance criteria (see (b) (4)-2019-052-A study above) except for (b) (4) from real time aging arm. Root cause was determined to be handling and/or transport (the tear in polyethylene film followed a seam or wrinkle). No past sterility failures were associated with (b) (4) container. The expiry date was set to (b) (4) based on the accelerated aging data and material specification was updated accordingly.

Additionally, to address Type A meeting comment, the firm revised vendor qualification questionnaire COMM-QA-002 FRM1 (not provided) to ask if shelf life studies have been conducted for the product/material being supplied, and a copy of the report is requested, if applicable. This answer and any associated documentation are now reviewed as part of the standard vendor qualification process.

Reviewer Comment: The link was provided to COMM-QA-002 Supplier Qualifications ver.12 effective 01/08/2021. The document does not include referenced form or any information regarding revision of FRM1. Review of Observations 8a and 8d is deferred to OTAT. The response to Observation 8b, c, and e is acceptable (see also comments above).

On 9/13/2021 in the amendment STN 125685/0.75 the firm provided COMM-QA-002 FRM1 ver. 07 effective 03/08/2021 in the amendment STN 125685/0.70

(response to Q.16). The document requests that a report supporting shelf life of the product being supplied is provided for review, if available.

Reviewer Comment: The response is acceptable.

Observation 9

The inventory control of raw materials is deficient. Specifically,

- a. Per deviation DEV-0455 dated August 22, 2016: thymus organ media lot TOM-(b) (4) was conditionally released without sterility testing results due to insufficient volume of released TOM available to complete manufacture of lot (b) (4).
- b. Expired supplies were used in manufacture of thymus lots (b) (4) (per deviation DEV-0667 dated February 4, 2019).
- c. The control system to prevent mix-ups for materials, components, samples, and containers, intended for use in the RVT-802 manufacturing process does not include inventory records that show the current real-time inventory for (b) (4) used for storage of critical reagents, source material, (b) (4) and QC samples.
- d. Materials are not being properly segregated. (b) (4) used to store RVT-802 (b) (4) samples is also used to store (b) (4) samples for other products manufactured in the facility, along with research materials. Aside from the RVT-802 mycoplasma (b) (4) sample log on the front of the (b) (4), there is no log of the contents of the (b) (4).

Response Summary

Only responses to Observation 9a-c are reviewed below. Review of the response to Observation 9d is deferred to OTAT as these observations were made by Thomas Finn.

The firm implemented the planned inventory control changes (i.e., procedures related to inventory logs, tracking, restocking, reconciliation, storage, and segregation of materials) that were detailed in eCTD Seq 0050 and previously reviewed and found acceptable by CBER.

In response to Type A comments the firm provided:

- Clean and red-lined versions of SOPs (b) (4)-QA-002 (b) (4) Supply Management ver.04 effective 03/12/21, (b) (4)-SOP-027 Operation and Maintenance of the (b) (4) Temperature (b) (4) and relevant new inventory forms, with all planned changes implemented.
- Description of (b) (4) Storage Current Inventory form use (inventory forms are a printout of inventory as determined during (b) (4) reconciliation, whereas check in/supply logs are updatable inventory logs)

- Clarification of the discrepancy between room temperature and (b) (4) storage logs. Need for separate check in and check out logs for ambient but not (b) (4) storage is due to the vastly different number of items being removed at once.
- Additional (b) (4)-QA-002 FRM4 Unacceptable Supply Corrective Action Log was implemented for situations where discovery of an unacceptable material was made.

Reviewer Comment: Response to Observation 9a-c is acceptable. Response to Observation 9d is deferred to OTAT.

Observation 10

A means of assuring data protection has not been established for the following computerized system. There is failure to maintain a backup file that is assured as secure from alteration, erasure or loss through keeping hard copy or alternate systems. Specifically, the current (b) (4)-EQUIP-021, Operation, Maintenance and Sterility Culture using the (b) (4), dated September 27, 2018, does not include criteria for back up of data from (b) (4), a (b) (4) based data management software application used for the (b) (4) System, to removable (b) (4) and verification of back up to a networked path.

Response Summary

To address the Observation, the firm backs up the (b) (4) files to a removable (b) (4) device, which is then transferred to a secure network drive location. In addition, Procedure (b) (4)-EQUIP-021 "Operation, Maintenance and Sterility Culture using the (b) (4)" has been revised to include the criteria for data back-up from the (b) (4) system, including requirements for audit trail review and the use of updated computer equipment/operating system/application software. Based on the Agency's feedback during the Type A meeting, the firm has also accomplished the following:

1. The (b) (4) data backup schedule has been increased from (b) (4) to (b) (4) during normal working periods and minimally every (b) (4) days.
2. (b) (4) tests confirmed that the audit trail is indelible and Part 11 compliant. SOP-EQUIP-021 was updated to include the audit trail review process.
3. The use and security of the (b) (4) drives were verified to ensure appropriate data protection. SOP-EQUIP-021 was updated to include proper use of (b) (4).
4. The PDF report of the sterility data and associated metadata were verified to represent a true copy of the original data and in a format compatible with the original format to allow data recovery. SOP-EQUIP-021 was updated to include PDF recovery procedures.

Verification of the audit trail functionality and controlled data backup was documented in (b) (4)-2020-067-E "Performance Verification form Audit Trail and (b) (4) of the (b) (4)" (provided in the submission). The

(b) (4) computer operating system and (b) (4) had since been upgraded to the latest version with validation activities managed under CAPA-0149.

To address data integrity at a systemic level, SOP (b) (4)-QA-002 “Computerized System Access and Administration” was developed to implement system access control for all laboratory and manufacturing computerized systems, granting access and user privileges to pre-approved staff members only. Table 9 of the response summarized the software used in manufacturing and testing of RVT-802, types of digital files used, personnel access, and backup method. The (b) (4) software systems included (b) (4)

and user access is limited to the administrator(s) and approved users. Table 8 of the response summarized the data integrity remediation status of each software system. Per the brief status summary, each Part 11 compliant system has been upgraded to the latest software with relevant SOPs updated to include regular data backups and audit trail review requirements. For systems which are not Part 11 compliant, paper records are maintained as the (b) (4) documents with upgrades to Part 11 compliant version planned.

Reviewer Comment: The response addressing the (b) (4) data integrity observation and the data integrity remediation status for each (b) (4) computerized system appears to be acceptable. (b) (4)-2020-067-E performance verification report was reviewed and found acceptable. I recommend inspectional follow-up to verify the validation status of each (b) (4) computerized system.

Observation 11

Performance qualification (PQ) of numerous critical equipment was not completed prior to conducting process performance qualification runs (November 16, 2018 – January 17, 2019) and aseptic processing runs (August 2018). Specifically,

- a. PQ of the (b) (4) incubators, (b) (4), used to incubate the thymus tissue slices, was approved in March 2019.
- b. PQ of the (b) (4) system, used to maintain (b) (4) level inside the incubators, was approved in March 2019.
- c. PQ of (b) (4), used during the processing of RVT-802, was approved in March 2019.

Response Summary

To address the Observation, the firm opened DEV-0829 to investigate the impact of the delayed equipment qualification on the 2018/2019 PPQ and identify root cause. The review confirmed that equipment performance qualifications assessed the same operating conditions that were used during the PPQ/APV batches and the equipment units were up-to-date on calibration and maintenance at the time of the original PPQ.

The root cause was that COMM-QA-044 “Approaches to Validation”, which stated the requirement to performed validations and qualifications in a specific order, was not followed. Under CAPA 0094, COMM-QA-044 has been updated to ensure that critical equipment PQ is always completed prior to PPQ. In accordance, the firm prepared a “PV Readiness Report” (b) (4)-2020-068-P) to evaluate the qualification and calibration status of each piece of critical equipment, including the (b) (4) system, prior to conducting the 2020 PPQ. (b) (4) equipment management program was also improved under CAPA 0184 to update (b) (4)-EQUIP-003 “Equipment Management SOP” to define qualification requirements for new equipment, establishing equipment decommissioning procedures, updating the list of critical equipment for RVT-802, clarifying procedures for (b) (4) qualification assessments, and defining more clearly the calibration and preventative maintenance program. Individual equipment SOP was updated to include preventative maintenance and calibration criteria tasks and frequencies. In addition, COMM-QA-044 now includes a “Post-Execution Requirements” section to ensure that the validated parameters are applied to the routine manufacturing process and incorporated into relevant SOPs. Relevant change controls will be listed in the qualification/validation reports to ensure that the validated parameters/processes are incorporated into applicable SOPs/batch records. Using this process, the RVT-802 batch records have been updated to reflect the validated acceptable ranges, hold times, and processing times per the latest PPQ.

Reviewer Comment: The response is acceptable. Refer to firm’s response to CRL Deficiency #11 for updates on the (b) (4) system. The performance of the relevant (b) (4) and incubators are reassessed through the new PPQ, APV, and/or EMPQ studies, which are reviewed elsewhere in this memo. See also Deficiency 12 for updated (b) (4) incubator and (b) (4) qualification.

Deficiency #7


Transport study (b) (4)-2019-050-A failed to demonstrate microbial protection of DP during packaging, transportation to the OR, and hold in the OR in the (b) (4) culture dish and (b) (4) container. If you intend to proceed with commercialization of the (b) (4) final DP container, please investigate the media growth promotion failures and take appropriate corrective actions prior to conducting a new study demonstrating that the final DP container adequately maintains a sterile environment. Please submit the summary reports.

Response Summary

Each (b) (4) culture dish houses up to four tissue slices on sponge and filter membrane. They are used during tissue culture and for transporting the final DP from (b) (4) to the OR room since the initial IND. The culture dishes are not integral containers; therefore, a transport study (b) (4)-2019-050.1-A) was performed during the initial BLA submission in place of a (b) (4) to demonstrate adequate physical and microbial protection. The study simulated the packing, transport, and holding conditions in (b) (4) runs using (b) (4) dishes containing (b) (4). Post-simulation (b) (4) medium from each dish was shipped to

(b) (4) testing, followed by (b) (4) period. While the sterility testing results were conforming, not all samples passed the growth promotion test. The sporadic growth promotion failures were unexpected since growth promotion had always passed in previous APV runs where the DP container closure system was the (b) (4) containers. Other differences between the APS study and the DP transport study included number of media change, material/reagent lots, sample tube, sample storage conditions, and the use of (b) (4) container. The investigation searching for potential growth inhibitory substance or nutrient depletion yielded inconclusive answers. (b) (4) tests were performed to evaluate the growth promotion of (b) (4), which were the (b) (4) organisms that failed to grow in the initial transport study. (b) (4) lots of (b) (4) were used, and growth media were subjected to worst-case exposure from materials (i.e., sponge, filter, dish) and secondary container (i.e., (b) (4)). All samples underwent the (b) (4) sterility testing prior to being inoculated with (b) (4) of the challenge organism with (b) (4) culture. All samples passed sterility testing and growth promotion testing. No root-cause was identified.

A second confirmatory re-test (b) (4)-2019-057.1-A) was performed with new samples and larger sample sizes (b) (4) to evaluate potential impact of the (b) (4) sample storage tube, leachables from media-contacting materials, and (b) (4). All samples passed growth promotion testing; therefore, the study did not identify a definitive or new root-cause. Other attributable root-causes may be related to the third-party testing lab (e.g., inaccuracy related to small inoculum, cross-contamination, etc.). As no conclusive root-cause could be identified, the DP transport study was repeated as a component of the new APV study, which is summarized in the APV report (b) (4)-2020-017-P, approved on October 21, 2020). The study design and results are briefly summarized and reviewed below.



- (b) (4)
- 

Reviewer Comment: According to Table 3 not all sampling was simulated during APV (e.g., (b) (4) samples on Day (b) (4) and Day (b) (4) mycoplasma sample on Day (b) (4) endotoxin sample on Day (b) (4)). Though incubation of such samples is not required, the action of sample collection needs to be included in the simulation.

On 9/13/2021 the firm clarified in the amendment STN 125685/0.70 (response to Q.17) that all samplings were simulated during APS. "N/A" in Table 3 referred to discarding of the samples (i.e., sampling was performed, but collected samples were not tested for endotoxin and mycoplasma).

Reviewer Comment: The response is acceptable.

(b) (4)



Reviewer Comment: The EM excursion noted on Operator (b) (4) appears to be an isolated event and is acceptable as the Operator was not performing aseptic processing directly and was in contact with the ISO (b) (4) environment and surfaces.

The EM alert/action levels in Figure 1 requires further clarification as the action level for (b) (4) inside the ISO (b) (4) is stated as (b) (4)

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.4 and Q.5) that (b) (4) action limits for ISO (b) (4) areas were set at (b) (4) during 2020 EMPQ and subsequent interim EM.

Reviewer Comment: See ISO (b) (4) limit discussion in the EMPQ section above. Given that APS purpose is to assess (b) (4) rather than (b) (4)

(b) (4) the inadequate limit has no impact on APS validity and/or outcome. Furthermore, current EM limits are acceptable.

There were (b) (4) protocol deviations, as well as (b) (4) deviations related to equipment/sensor issues, (b) (4) data loss due to control point interruption during data upload, and the EM excursion noted previously. I reviewed the deviations and determined they have no impact on the APS study validity or conclusions.

Reviewer Comment: Additional details about the DP packaging and transport should be provided as the APS is leveraged to validate the transport process inside the (b) (4) culture dish, the (b) (4) container, and the shipper. The information should include temperature tracking as well.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.18) that for each APV run DP packaging and transport mirrored the Process used during routine manufacture, including temperature tracking. Specifically, culture dishes were (b) (4)

(batch record (b) (4) 2020-017-P FRM8). Packaging and transport were performed per (b) (4)-2020-017-P FRM22 and is described in detail elsewhere in this review memo. The only difference between these operations is that for APV the product is transported to the operating room and back to (b) (4) to simulate a worst-case transport time. The firm stated that all temperature met specification for the duration of transport.

Reviewer Comment: The temperature tracking data for APS and the subsequent (b) (4) media fills was provided on 9/21/2021 in amendment STN 125685/0.75 (response to Q.3). Results (b) (4) met the acceptance criterion of (b) (4). The response is acceptable.

Deficiency #8

You failed to assure sterility of direct product contact materials. Specifically, (b) (4) validation of the (b) (4) container used for source material transport and (b) (4) storage was deficient. The study was performed on a different container, and (b) (4) was not performed. Please provide the summary report for sterilization validation of the (b) (4) container.

Response Summary

The CBER conclusion upon review of initial and updated 483 responses that was communicated to the firm during Type A meeting was that the proposed sterility testing approach (combination of supplier qualification and routine sterility testing of incoming lots) for (b) (4) container would be acceptable provided it was supported by an adequately validated sterilization cycle. To address additional Type A comments the firm explained that a master product approach was used to validate the sterilization process

for the (b) (4) container. (b) (4) is a member of (b) (4) for sterilization purposes, which consists of the following products

- (b) (4)

All (b) (4) containers meet ISO (b) (4) grouping criteria as they are made of the same materials (vial, cap, and packaging) using the same manufacturing and packaging processes and environment; all containers have similar size, same opening diameter and secondary packaging (individual blister pack; (b) (4) Presterilization bioburden action limit and sterilization cycle and processing are also the same across the family.

Additionally, the following document was provided:

(b) (4)

Reviewer Comment: Though (b) (4) is an acceptable surrogate for (b) (4) container, the (b) (4) study appears deficient. Specifically, the following should be addressed:

- 1. Number of (b) (4) runs performed, with justification***
- 2. (b) (4) placement for each run, with justification***
- 3. A side-by-side comparison of routine and PQ (b) (4) process parameters (including (b) (4) and load description.***
- 4. There is a discrepancy between the number of units per box [i.e. (b) (4) the PQ report and (b) (4) CRL response (Table 12)]***
- 5. Actual (b) (4) during PQ exceeded specified (b) (4) note – no (b) (4) units were provided) and (b) (4) which appear to be ranges suggested by container manufacturer based on material properties and biological (b) (4) setting. The pass/fail status of the PQ was not assessed.***

6. ***It has been previously stated that (b) (4) is the maximum achievable due to (b) (4), which would require a minimum (b) (4). It appears that a much higher (b) (4) was used during (b) (4)***

On September 13, 2021 the firm clarified in the amendment STN 125685/0.70 (response to Q.19) that a total of (b) (4) runs were performed:

- Product (b) (4) run on 07/03/2007 described in the (b) (4) report summarized above)
- Product (b) (4) run on 07/03/2007 (see (b) (4) report summarized below) and (b) (4) PQ runs on 06/05/2008, 09/18/2008, 09/29/2008 (see validation summary report summarized below)].

Per the memorandum provided by (b) (4), the units per case were incorrectly stated in the PQ report (should be (b) (4) the validation summary for sterilization (i.e incorrectly states the product code (should be (b) (4) were (b) (4) with similar outcomes, hence the (b) (4) PQ was performed on worst case product only, (b) (4) (see summary below). (b) (4) supplied during initial (b) (4) was (b) (4), which was later updated to (b) (4) for sterilization validation. The (b) (4) units are reported in (b) (4) (initial (b) (4) (sterilization validation).

(b) (4)

(b) (4)

Reviewer Comment: The response is acceptable.

The firm stated that there were no changes to the product configuration or package orientation, the equipment used, or number of (b) (4) between 2007 (b) (4) study) and 2017 (sterilization validation study). The (b) (4) facility is ISO (b) (4) certified since 06/30/2010 to perform contract (b) (4) using (b) (4) per ISO (b) (4) (b) (4) (expiry date of 03/16/2022). The (b) (4) receives routine maintenance, including (b) (4) calibrations of the (b) (4) as well as preventive maintenance at predetermined frequencies. The (b) (4) is requalified (b) (4). No changes that would require requalification, such as changes of the conveyor or elements of the (b) (4), dimensions of the (b) (4) container, repair or replacement of (b) (4) occurred since 2007.

The firm re-submitted sterilization validation final report (study 949836-S01) performed by (b) (4) container and previously reviewed. The study determined that minimum sterilization dose for sterility assurance level of (b) (4). The firm explained that the containers in this study were (b) (4) to ensure all receive same (b) (4). They state that

(b) (4)

Reviewer Comment: The container used for the sterilization validation study (b) (4) is not one of the (b) (4) master product containers and no explanation for its use as a surrogate was provided. It is not clear whether specified (b) (4) is recommended by the container manufacturer, as it appears based on the (b) (4) report, or the (b) (4) to be delivered during routine cycle. The minimum (b) (4) to be delivered should be based on sterilization validation, whereas the maximum should not exceed supplier's upper limit unless it has been demonstrated that it has no impact on the item being sterilized.

On 9/13/2021 in the amendment STN 125685/0.70 (response to Q.20) the firm provided a memorandum from (b) (4), supplier of (b) (4) containers, dated 09/09/2021. The memorandum states that (b) (4) products are identical with only difference being the cap color (b) (4). The caps are made of the same plastic and have the same design.

Reviewer Comment: The response is acceptable. Container (b) (4) is an acceptable surrogate for (b) (4) container. Deficiency #8 is resolved.


Deficiency #9

Adopting the (b) (4) culture dish as your primary DP container changed your DP packaging and configuration of the shipping container used for DP transport to the OR. Therefore, the validation of this shipping container to maintain the appropriate temperature is no longer valid. Please revalidate and provide the summary report.


Response Summary

The firm revalidated DP shipping container using the adopted packaging configuration. The transport container is an insulated (b) (4) which is packaged as follows: (b) (4) polystyrene culture dishes, each containing up to 4 processed tissue slices and 5 ml media and closed with a lid are packaged in racks inside the sealable polycarbonate (b) (4) container, which is placed inside a cooler; (b) (4) are placed on top of (b) (4). Final validation report (b) (4)-2019-063-E approved 06/19/2020 was provided. The study validated typical handling/distribution during worst case delivery time (simulated (b) (4) and temperature throughout transport. Simulated transport, low and high temperature stress were each evaluated in (b) (4) transport containers.

Simulated transport was performed using maximum load (b) (4) culture dishes, containing
(b) (4)



(b) (4)



Reviewer Comment: The response is acceptable. Deficiency #9 is resolved.

Deficiency #10

Due to the nature of your primary DP container, the environment inside your secondary (b) (4) container becomes more critical to ensure microbial protection of the product. We recommend cleaning and/or sterilization validation of the secondary container and packing of the (b) (4) container in the ISO (b) (4) environment. Additionally, please implement and provide procedures and lot disposition for spill incidents in transport.

Response Summary

To address the deficiency, a cleaning validation was performed to demonstrate effective cleaning of the (b) (4) secondary container used to hold the RVT-803 DP in culture dish during transportation from (b) (4) to the OR. Each (b) (4) container, with an internal (b) (4) DP container was implemented and was re-introduced when the culture dishes were re-implemented as the DP containers. While the (b) (4) have historically been reusable with manual cleaning prior to use, it became single use starting in 2020. New (b) (4) are ordered separately from (b) (4). All components are received non-sterile and are stored in plastic bins. (b) (4)

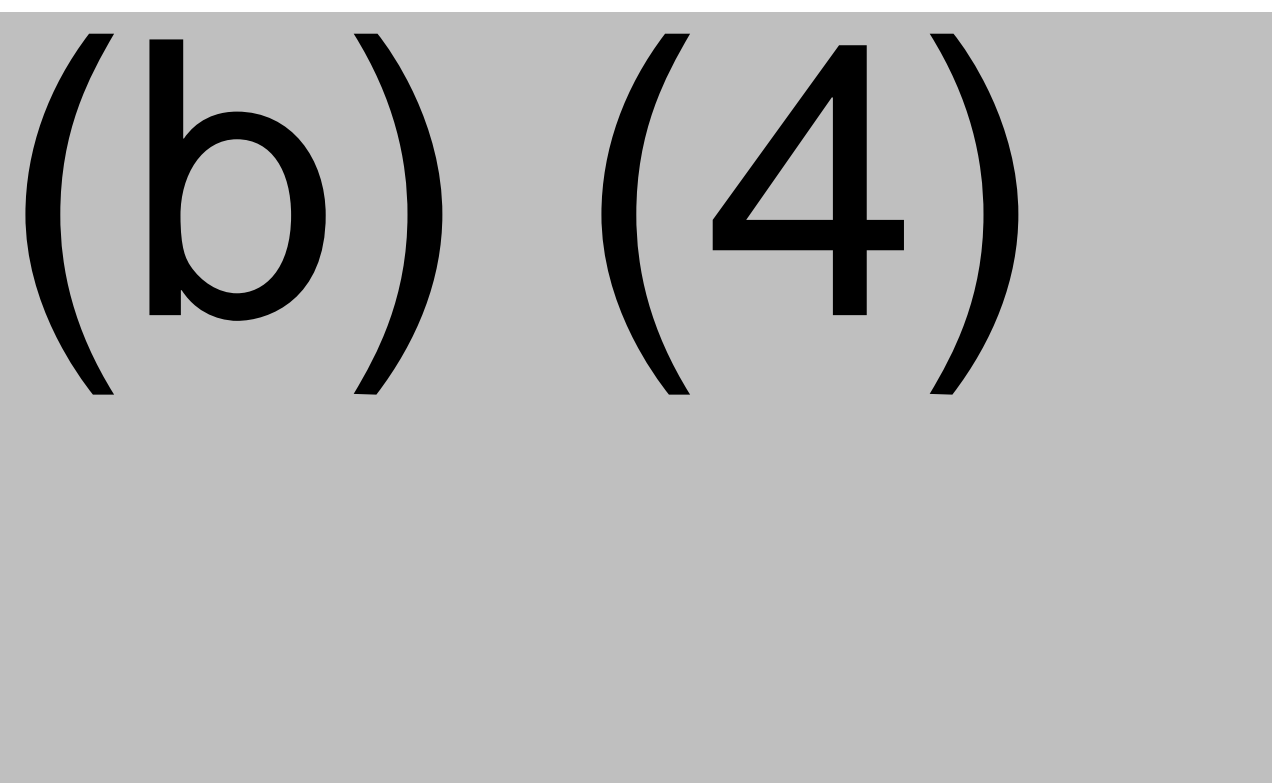

(b) (4)

(b) (4)

(b) (4)

(b) (4)


(b) (4)



Reviewer Comment: The firm needs to clarify the following: 1) Will the (b) (4) be reusable going forward? 2) Verify the cleaning procedures. 3) How is it stored after cleaning? If the plan is to reuse, more information may be required on cleaning spills and dirty hold time. Overall, the cleaning validation study design and post-cleaning results are acceptable for a secondary container with no product-contact, especially with the newly implemented lot disposition related to spills and leaks.

On September 13, 2021 in the amendment STN 125685/0.70 (response to Q.21) the firm clarified that (b) (4) is single use, is discarded upon return from operating room and will not be reused going forward.

(b) (4)



Reviewer Comment: The response is acceptable. Deficiency #10 is resolved. Please note that Enzyvant has committed to developing and validating an integral primary DP container (see OTAT Post-Marketing Commitments).

Deficiency #11

Regarding your (b) (4) system:


- a. Qualification of your (b) (4) system is deficient in scope and duration. Specifically, it did not include monitoring of (b) (4) quality over a period of time, and only a limited number of locations were sampled. (b) (4) sampling did not demonstrate that (b) (4) is within ISO (b) (4) acceptance limits.
- b. Your strategy and schedule for routine (b) (4) sampling is unclear, as not all testing is performed (b) (4), and locations vary for different dates and types of tests. The sampling procedure description is inconsistent (e.g., use of (b) (4) and vague about (b) (4) use during sampling, which could interfere with (b) (4) testing.

Please provide information and/or data to address these issues.

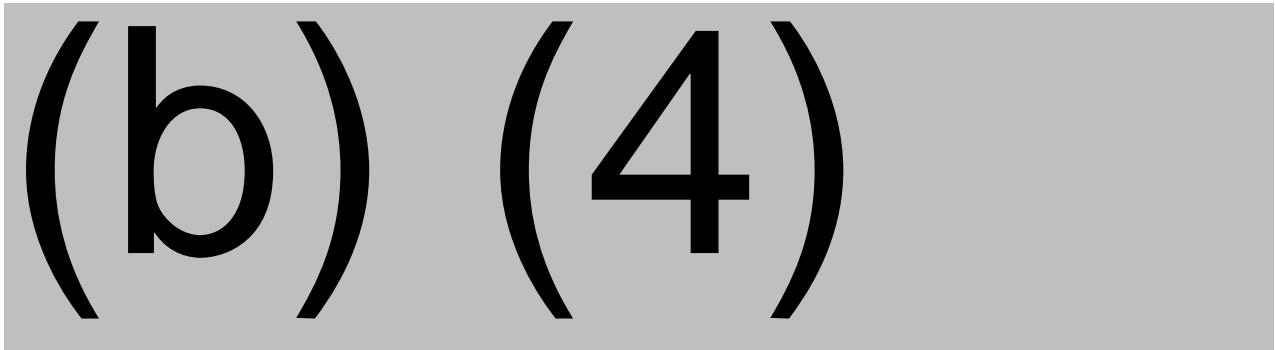
Response Summary

The firm performed requalification of (b) (4) system; summary report of all qualification activities (REP-20) was provided. IQ and OQ of the system were performed in 07/2011. IQ verified equipment identification, system components, materials of construction, reviewed documentation (SOP, manuals, technical bulletins, installer documentation) and preventive maintenance, and inspected piping (component/layout accuracy). OQ included (b) (4), verification of automatic changeover function, system capacity (b) (4), and analytical testing (b) (4). PQ was performed in 01-02/2019 was found deficient and another PQ was performed in 05-08/2020 (detailed in the provided (b) (4)-2020-031.1-E IOPQ Report for the (b) (4) System approved 10/20/2020).


(b) (4)



(b) (4)



(b) (4)



Reviewer Comment: The response addresses both the deficiency and additional Type A meeting comments. It is acceptable. Deficiency #11 is resolved.

Deficiency #12

The personnel flows at your multi-product facility create an increased risk of product contamination and cross-contamination. Specifically,

- a. You allow (b) (4) [REDACTED]
[REDACTED] of your facility. This allows simultaneous presence of personnel working on different products in (b) (4) [REDACTED].
- b. Additionally, personnel enter Gown-In Room (b) (4) [REDACTED] and exit Gown-Out Room (b) (4) [REDACTED] of the facility through the same Receiving/Supply Room (b) (4) [REDACTED]. This allows simultaneous presence of personnel entering and exiting the manufacturing areas in Room (b) (4) [REDACTED].

Please provide a description of procedural and/or engineering controls in place to ensure appropriate personnel flows, to prevent exceeding the maximum number of allowed personnel in Rooms (b) (4) [REDACTED], and to mitigate risk of product contamination and cross-contamination due to personnel flows described above.

Response Summary

To address this deficiency as well as additional Type A meeting comments, the firm implemented several facility modifications along with a wide range of procedural and engineering controls.

The modifications included installation of several active and passive pass throughs (pass through to clean storage was removed), new walls and doors to increase the footprint of Gown In (ISO (b) (4) [REDACTED] Gown Out (ISO (b) (4) [REDACTED] and Changing rooms (reclassified as CNC), and implementation of new exit from Gown Out (ISO (b) (4) [REDACTED] to non-controlled corridor. These changes allowed for implementation of (b) (4) [REDACTED] personnel flow (procedurally controlled) through the facility (to address Deficiency 12a) and for complete segregation of in and out flow of personnel that no longer returns from Gown Out (ISO (b) (4) [REDACTED] to Receiving/Supply (ISO (b) (4) [REDACTED] to address Deficiency 12b). Outer gowning is removed in Gown Out, inner gloves are disinfected with (b) (4) [REDACTED] prior to exit to non-controlled space. Use of the remaining door between Gown Out (ISO (b) (4) [REDACTED] and Receiving/Supply (ISO (b) (4) [REDACTED] is restricted (the door is locked) to cleaning and EM staff on (b) (4) [REDACTED] basis and other contracted personnel with QA approval. However, it cannot be used if such personnel previously entered any suite where manufacturing was ongoing.

Additionally, (b) (4) [REDACTED]
[REDACTED]

(b) (4) [REDACTED] The firm clarified that the (b) (4) [REDACTED] is not utilized to ensure that personnel have exited the dirty corridor (or any other room/corridor) before additional personnel enter that area as due to unidirectional personnel flow the risk of cross-contamination is very low.

Reviewer Comment: Although the risk of cross-contamination is low, to ensure that the facility operates in the state of environmental control the maximum occupancy of the corridor established during EMPQ should not be exceeded. The firm should clarify whether the lights are on a delay and whether it is sufficient to ensure the maximum occupancy in Access Corridor is not exceeded. It is also not clear whether the lights are installed in all manufacturing rooms.

On September 13, 2021 in the amendment STN 125685/0.70 (response to Q.22) the firm clarified that (b) (4) in the facility where personnel can transit through, including those not used by operators (i.e., door to Janitor Closet and between Receiving/Supply and Gown Out) and excluding emergency exits. Opening a door between two facility areas activates (b) (4)

(b) (4) SOP-003 (lists maximum occupancy for rooms) and (b) (4) -SOP-009 (personnel flow and (b) (4) verification prior to entering access corridors).

Reviewer Comment: The response is acceptable.

Material/sample/product flows were also modified. Updated (b) (4) -SOP-009 Personnel Flow and Material Transfer in the (b) (4) ver. 09 effective 03/11/2021 was provided for review. Biological and cell-based materials enter/exit the facility via new active pass throughs (ISO (b) (4) between non-controlled space and ISO (b) (4) (b) (4)

Reviewer Comment: Per the provided floor plan and updated 3.2.A.1 section samples and product can exit manufacturing suites together with personnel, through Gown Out. The firm should clarify if this flow is used and if so, whether product is temporally segregated from waste, as it uses the same flow path.

On 9/13/2021 in the amendment STN 125685/0.70 (response to Q.23) the firm clarified that DP, samples, and unused materials can exit the facility via pass throughs or carried out with exiting personnel. The passthroughs are used for DP and time-sensitive samples (b) (4) -SOP-009 was revised to specify that), whereas non-time sensitive samples (e.g., histology and sterility) may be carried out with personnel at the same time as the waste. Sample segregation from waste is achieved via closing samples in ISO (b) (4) and bagging them in ISO (b) (4) The outer bag remains in place until the samples are prepared for QC analysis.

Reviewer Comment: The response is acceptable.

Entry and exit of non-biological materials and supplies (including expired) and small equipment is via cart pass through (CNC) between non-controlled area and Receiving/Supply (ISO (b) (4) and then via Gown In (ISO (b) (4), together with personnel. Large equipment is transferred into Receiving/Supply (ISO (b) (4) through Changing room (CNC). As personnel is no longer permitted to return to Access Corridor 1 (ISO (b) (4) to retrieve additional materials from Clean Storage (ISO (b) (4), the toolboxes were modified to include extra supplies. If additional supplies are needed, they will be brought in by another operator, who would gown into the facility. Any unused supplies remaining after

completion of processing are taken out of the (b) (4) facility and can only be used for research purposes or discarded. The reusable toolbox containers are cleaned (inside and outside) after emptying, upon transfer into the facility through cart pass through and before loading.

On days when either multiple cellular-based materials are expected to be transferred into the facility or multiple samples are expected to be passed out of the facility, hall monitors might remain in the entry or exit hallway to transfer materials from active pass through to passive passthroughs into manufacturing rooms or samples from passive pass throughs to active passthrough out of the facility.

Waste flow. Manufacturing waste exits the facility together with personnel, (b) (4). Packaging waste produced in Receiving /Supply while unpacking supply and packing toolboxes can exit via cart pass through to non-classified space.
Procedural modifications

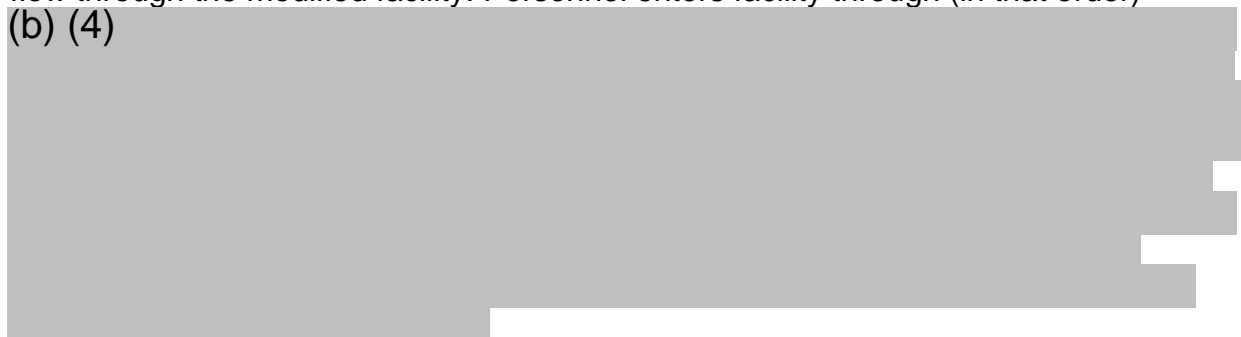
Reviewer Comment: Per the flow diagram, cart pass through is not used for waste. Instead, the waste from Receiving/Supply (and Gown In) exits facility via Changing room.

On 9/13/2021 in the amendment STN 125685/0.70 (response to Q.24) the firm clarified that the waste flow diagram reflects the current procedures, i.e., waste from Receiving/Supply (discarded packaging, wipes, etc.) is carried out via the Changing room primarily by the cleaning staff during weekly cleaning.

Reviewer Comment: The response is acceptable.


Additionally, the firm provided a flow diagram showing cleaning personnel and process flow through the modified facility. Personnel enters facility through (in that order)

(b) (4)



Reviewer Comment: There are no arrows showing cleaning personnel flow out of the facility (i.e., flow from Gown In to (b) (4) and no flow from Access (b) (4) to Gown Out is shown).

On 9/13/2021 in the amendment STN 125685/0.70 (response to Q.25) the firm clarified that after cleaning of ISO (b) (4) areas, cleaning personnel leaves facility (b) (4)



(b) (4)

A revised diagram and (b) (4)-SOP-006 were provided.

Reviewer Comment: The response is acceptable.

Updated room classification and pressure differential diagram was also provided.

(b) (4)

(b) (4)


In support of facility layout changes as well as in response to other deficiencies, the firm performed facility recertification, APV (described above; see Deficiency 7; most recent performed in 01-02/2021 was not provided), EMPQ (described above, see Deficiency 1, Observation 3), and PPQ.

Facility certification was not provided. The firm stated that it included (b) (4) monitoring of active cart pass throughs added to the facility during the remodel. (b) (4)

(b) (4) levels in the smaller HEPA passthroughs between the access corridors and office hallways were not evaluated during certification or the EMPQ due to their size and lack of a port for placement of a sampling horn within the passthrough with the door closed. However, (b) (4) were subsequently checked using a (b) (4) and met ISO (b) (4) standards. More recently, (b) (4) were measured with (b) (4) ISO (b) (4) standards under (b) (4) conditions. Under both conditions, the HEPA passthrough remained within ISO (b) (4) acceptance criteria. The firm stated that given that the pass throughs met ISO (b) (4) requirements even with the door open, no delay was implemented for pass through door interlock.

Reviewer Comment: Facility recertification and any additional data supporting pass through classification as well as the most recent APV should be provided for review. Additionally, if any modifications were made to HVAC system beyond rebalancing, such modifications should be described.

On 9/13/2021 in the amendment STN 125685/0.70 (response to Q.26 and Q.27) the firm provided (b) (4)-2021-020.1-E (b) (4) Assessment for HEPA-equipped Pass-Throughs report dated 04/02/2021. The report covers (b) (4)




Reviewer Comment: The response is acceptable. Though the limited number of measurements were performed for each pass through, obtained results were over a log lower than acceptable limits.

The firm confirmed that no modifications to HVAC system were made beyond rebalancing during 2020 remodeling. Recertification following facility modifications included measuring differential pressures, air changes, particle counts sampling at all EM sites, measuring airflow from each HEPA (b) (4) testing of all HEPA filters.

Reviewer Comment: Recertification report was not provided for assessment and was re-requested on 9/16/2021.


On 9/21/2021 in the amendment STN 125685/0.75 (response to Q.4) the firm provided (b) (4) clean room recertification summary report dated 05/20/2020. The following tests were performed:

(b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers approximately 10 lines of text.

Reviewer Comment: All acceptance criteria were met. The response is acceptable.

January 2021 APV report approved on 05/15/2021 was provided in the amendment STN 125685/0.70 (response to Q.29). The firm committed to provide June 2021 report by 09/23/2021. (b) (4)

A large rectangular area of the document is redacted with a solid grey fill. The redaction covers approximately 20 lines of text.

June 2021 APV report approved on 09/23/2021 was provided in the amendment STN 125685/0.77. Media simulation was performed similarly to the one described above, except (b) (4) was manufactured over ^{(b) (4)} days. One excursion was noted (Day (b) (4) Sterility and growth promotion acceptance criteria were met.

Reviewer Comment: The response is acceptable. I reviewed deviations and concluded that they had no impact on validity or outcomes of the media simulations.

The further additional details were provided in the updated 3.2.A.1 section:

- Active pass throughs are multi-product use.

Reviewer Comment: Per (b) (4) -SOP-009 active pass throughs between Access Corridors and outside of the facility are cleaned as part of (b) (4) line clearance if they were used during manufacture.

- (b) (4)

Reviewer Comment: 2019 OQ, PQ, and cleaning validation data was reviewed during the initial review cycle. The firm should clarify whether (b) (4) is no longer used for Rethymic as it was omitted from the summary report as well as equipment list in 3.2.A.1.

On 9/13/2021 the firm explained in the amendment STN 125685/0.70 (response to Q.11 and Q.28) that (b) (4) has been taken out of service and is no longer in use for RETHYMIC.

Reviewer Comment: The response is acceptable. Deficiency #12 is resolved.

Most sections of the BLA were updated with information either described above or within OTAT/DBSQC purview, some sections were revised to avoid duplication, for clarity, or to move information to more relevant sections. The main change is additional in-process testing (per OTAT request):

- (b) (4)

Process Validation. Since the original PPQ lots were manufactured, there were changes in DP primary (b) (4) culture dish) and (b) (4) container, in-process testing and sampling timepoints, cleaning and EM sampling procedures, facility design and personnel flow. As such, process validation was repeated. The following study components were included:

- Source material quality evaluation after transport to (b) (4) (maximum hold times)
- (b) (4) lots of (b) (4) received and processed to produce (b) (4) PPQ lots
- DP quality evaluation after transport to Duke hospital

Each qualifying thymus was received and held (b) (4)

Additional characterization sampling and testing was included in these PPQ batches, including additional histology testing, (b) (4) Day (b) (4) filter coverage analysis, assessment of slice thickness, and yield calculations.

The following in-process and release testing within DMPQ purview was performed:

- (b) (4)

(b) (4)

(b) (4)

- (b) (4)

As incubator parameters show skewed distributions due to temperature and (b) (4) when door is opened (b) (4), the spread of the data was defined by the interquartile range (b) (4)

Environmental Monitoring. PPQ batches were manufactured immediately after EMPQ, hence interim EM locations and frequency were used. It included (b) (4)

(b) (4)

The testing is performed for information only until sufficient amount of data is accumulated to establish acceptance criteria.

Notable deviations during PPQ lot manufacture (in addition to those described above) were related to

- (b) (4)

(b) (4)

[REDACTED]

Reviewer Comment: PPQ design was improved over the initial. All acceptance criteria within DMPQ purview and in-process parameters were within their specifications. Isolated EM excursions did not have an impact on the product quality, (b) (4) excursions on air sampler and eyewash bowl required additional remediation post-PPQ (see EMPQ above) and were successfully resolved. Deviations have no impact on validity of PPQ or its outcomes. I recommend inspectional follow-up for software validation/data integrity to include (b) (4) software, for which multiple deviations were noted during PPQ.