

CBER CMC BLA Review Memorandum

BLA STN 125690

Product Name Ebola Zaire Vaccine, Live.

Richard Lewis, Consumer Safety Officer, CBER/OCBQ/DMPQ

1. BLA#: STN 125690

2. APPLICANT NAME AND LICENSE NUMBER

Merck Sharp and Dohme, License Number 002

3. PRODUCT NAME/PRODUCT TYPE

Ebola Zaire Vaccine, Live

4. GENERAL DESCRIPTION OF THE FINAL PRODUCT

5. MAJOR MILESTONES

6. CMC/QUALITY REVIEW TEAM

Reviewer/Affiliation	Section/Subject Matter
Richard Lewis, OCBQ/DMPQ/MRBII	Facility Inspection, Manufacturing (Facilities, Equipment), Container Closure, and Aseptic Processing
Christian Lynch, OCBQ/DMPQ/MRBII	Facility Inspection
Randa Melhem, OCBQ/DMPQ/MRBII	Facility Inspection, Manufacturing (Facilities, Equipment), Container Closure, and Aseptic Processing
Anthony Lorenzo, OCBQ/DMPQ/MRBII	Facility Inspection, Manufacturing (Facilities, Equipment), Container Closure, and Aseptic Processing

7. INTER-CENTER CONSULTS REQUESTED

8. SUBMISSION(S) REVIEWED

Date Received	Submission	Comments/ Status
10/31/2018	STN 125690/0	Reviewed
12/13/2018	STN 125690/1 (CMC Section)	Reviewed
02/15/2019	STN 125690 /6 (Process Simulation)	Reviewed
03/20/2019	STN 125690 /12 (483 Response)	Reviewed
04/02/2019	STN 125690 /14 (Equipment)	Reviewed
07/15/2019	STN 125690 /21 (CCI)	Reviewed
07/23/2019	STN 125690 /24 (Deviation)	Reviewed
08/27/2019	STN 125690 /27 (DP PPQ)	Reviewed
09/10/2019	STN 125690 /34 (QIP Update #2)	Reviewed
10/03/2019	STN 125690 /38 (PPQ Data)	Reviewed
10/14/2019	STN 125690 /40 (Equipment)	Reviewed
10/24/2019	STN 125690 /44 (Manufacturing)	Reviewed

10/31/2019	STN 125690 /45 (PPQ Report)	Reviewed
11/01/2019	STN 125690 /46 (Manufacturing)	Reviewed

9. Referenced REGULATORY SUBMISSIONS (e.g., IND BLA, 510K, Master File, etc.)

Submission Type & #	Holder	Referenced Item	Letter of Cross-Reference	Comments/Status
DMF (b) (4)	(b) (4)	Elastomer Formulations, Films, and Coatings	yes	Information was reviewed and deferred to the Product Office

10. REVIEWER SUMMARY AND RECOMMENDATION

A. EXECUTIVE SUMMARY

The information provided in this rolling BLA submission was the result of an agreement between FDA and Applicant that was reached prior to the submission of the first module. This agreement outlined the volume and timing of information that would be submitted for consideration by FDA, and an understanding of the readiness of the manufacturing site's physical facility, equipment, and GMPs at the time of both inspection and licensure. It was agreed that (b) (4) successful lots of (b) (4) and (b) (4) successful lot of Drug Product would be submitted to support licensure. The rationale for these agreements is the urgent need for a US licensed Ebola Vaccine to combat the current outbreak on the African Continent. The DMPQ review was conducted in the confines of these agreements.

This agreement does not modify the metric individual reviewers are to use to evaluate if the product under review is suitable for licensure, and therefore to be used by the US population. With that stated, the Applicant has not provided sufficient information at this time to support the claim that they can execute their manufacturing process without critical process deviations that could call into question the potential safety and/or efficacy of the units distributed.

This determination was reached based on a combination of inspectional findings, Aseptic Process Simulation Results, and Drug Product PPQ (b) (4) results.

Inspection

The inspection of the manufacturing facility in (b) (4) yielded a snapshot into the status of the Applicant's Quality System as a work-in-progress where large sweeping changes were in the early stages of implementation. Typically, a Quality System can be used as a risk mitigator for manufacturing as it instills a culture of data integrity checks and detailed documentation. The inspectional findings supported the position that the site's Quality System was not up to a level where it could be relied upon to support GMP

manufacturing. It is possible that once the sweeping changes executed by the staff at the Applicant's manufacturing facility are implemented, this could result in a more effective Quality Systems.

Manufacturing

Each of the (b) (4) Aseptic Process Simulation Runs and (b) (4) lot of Drug Product executed by the Applicant included errors associated with vial accountability.

- The Applicant reported an error in the accountability of the final drug product containers.
- An unknown number of (b) (4) vials may have been allowed to carry-over to the sole production batch that supports this application. The applicant was not able to rule out carry-over of (b) (4) vials as they did not document the number of (b) (4) vials produced. It was also not possible to reconcile the (b) (4) vials inspected by accident and therefore mitigate this potential carry-over issue as there was no documentation for the number of (b) (4) vials produced leading to the aforementioned mix-up. This deviation took place due to a culmination of factors, but in no small part to lack of experience of site staff and inadequate documentation practices.
- Additionally, the Applicant has established an Acceptance Criterion where they allow for (b) (4) of filled vials to remain unaccounted for. Such a criterion was not supported by any meaningful rationale, and presents an avenue for vials to be carried-over between lots.

Neither the inspection team nor the review team for this BLA has been given an opportunity to review any executed batch records for Drug Product as it was not submitted for review. DMPQ was informed by the Product Office that the Applicant committed to supplying the executed batch records for review in October or November 2019. Only a portion of the executed batch record for Drug Substance was available to review during the Pre-License Inspection. The batch records were not submitted in any amendment to this BLA. There has been a number of instances during this review process where the poor quality of the information provided by the applicant in the submission and on inspection, may have been remedied with a supplementary review of the batch record.

The totality of the manufacturing and Quality Systems problems encountered during the review of the limited manufacturing information in this submission indicate that the Applicant does not have control over their manufacturing process.

There is still the potential for additional manufacturing data and further updates regarding the manufacturing site's Quality Systems to be submitted to this BLA prior to the due date. Currently, there are four months between the compilation of this memo and the PDFUA mandated action due date of March 20, 2020. It is possible that additional data could be submitted to support this BLA, therefore it is not appropriate for

a final recommendation to be rendered without giving the Applicant time to respond. Considering the aforementioned concerns regarding the data that is currently part of the BLA, I must therefore defer to my management regarding the approval of this BLA in advance of the action due date.

B. RECOMMENDATION: None

II. SIGNATURE BLOCK

Reviewer/Title/Affiliation	Concurrence	Signature and Date
Richard Lewis/CSO/OCBQ-DMPQ	Concur	
Randa Melhem/CSO/OCBQ-DMPQ	Concur	
CDR Qiao Bobo/RO/OCBQ-DMPQ	Concur	
John Eltermann/Supervisory CSO/OCBQ-DMPQ	Concur	

3.2.S DRUG SUBSTANCE¹

3.2.S.1.1 - 1.3 Nomenclature, Structure and General Properties

3.2.S.2 Manufacture

(b) (4)

3.2.P DRUG PRODUCT²

3.2.P.1 Description and Composition of the Drug Product

DMPQ defers to the Product Office for the review of this section

3.2.P.2 Pharmaceutical Development

3.2.P.2.1 Components of the Drug Product

3.2.P.2.1.1 Drug Substance

DMPQ defers to the Product Office for the review of this section.

3.2.P.2.1.2 Excipients

DMPQ defers to the Product Office for the review of this section.

3.2.P.2.2 Drug Product

3.2.P.2.2.1 Formulation Development

DMPQ defers to the Product Office for the review of this section.

3.2.P.2.2.2 Overages

DMPQ defers to the Product Office for the review of this section.

3.2.P.2.2.3 Physicochemical and Biological Properties

DMPQ defers to the Product Office for the review of this section.

3.2.P.2.3 Manufacturing Process Development

3.2.P.2.4 Container Closure System

Suitability

The Applicant provided the suitability of the container closure system is substantiated by the following studies:

- Container Closure Integrity (3.2.P.7)
- Stability (Not Included in DMPQ Memo)
- (b) (4) (Not Included in DMPQ Memo)
- Vial cartons are opaque and intended to protect from light (Reviewed on Inspection)

Shipping

Shipping qualification consisted of thermal qualification, physical protection of product during distribution, transport qualification and representative shipping for product requiring $\leq -60^{\circ}\text{C}$ temperature maintenance during shipping for a period of at least (b) (4).

Thermal Qualification

The thermal containers for shipment include an electronic temperature recording device in each container. In the event the temperature measured by the electronic monitor during shipment is outside the required temperature range, an alarm is triggered.

The shipping qualification demonstrated that the thermal container can maintain product temperature at $\leq -60^{\circ}\text{C}$ for a maximum of (b) (4) when exposed to hot ambient profiles.

Hot temperature profile includes temperatures ranging between (b) (4) for the duration of the test. Hot profiles only were tested, given that colder ambient temperatures will lengthen duration of temperatures below required limit.

Worst Case Analysis

For the qualification test, (b) (4) is considered the most sensitive location for temperature change. (b) (4). This exposes the top of the product load first.

Results

Test results indicate that all packing configurations maintained the product temperatures $\leq -60^{\circ}\text{C}$ for a maximum of (b) (4) when exposed to ambient profiles that represent worst-case hot temperatures during all seasons.

Simulated Distribution

The packaged Ebola vaccine Drug Product (DP) vials were packed in a (b) (4) (b) (4) and transported from the DP manufacturing site (MSD (b) (4) to the testing facility (MSD (b) (4)). In addition, (b) (4) vials. The (b) (4) containing DP and the (b) (4) vials were subjected to methods to challenge the packaged product against shock and vibration hazards in the distribution environments.

Minimum and maximum load packaging configurations of caseloads and thermal container loads were tested during shipping distribution qualification to protect any product load against damage in transportation. (b) (4) tested a minimum and maximum caseload of real product in a thermal container. (b) (4) tested (b) (4) maximum caseloads of (b) (4) vials in a thermal container.

Results

Table 7 below describes the results of the post distribution testing that was run on the samples that were subjected to simulated distribution.

Table 7 – Results from Simulated Distribution

Test	Specification	Result – Simulated
Sterility	No growth	Pass
Potency	(b) (4)	Pass

Physical Appearance – Color	(b) (4)	Pass
Physical Appearance – Opalescence	(b) (4)	Pass
Physical Appearance – Particulates	No visible particulates	Pass
(b) (4)	(b) (4)	Pass
Container Closure Integrity	(b) (4) Method: no (b) (4) detected	Pass

Representative Shipping

The packaged DP was shipped using packaging, shipping configurations, conditions, shipping lanes and transportation modes representative of the commercial process. The study included shipments by (b) (4)

(b) (4). Ebola vaccine was filled into vials at the manufacturing site (MSD (b) (4)) and sent to MSD (b) (4), then to test laboratories in (b) (4) to evaluate the effect of shock and vibration on product quality attributes.

Results

All testing conducted after executing representative shipping passed the acceptance criteria.

Reviewer Comment

The shipping validation for the product under review was covered during the Pre-License Inspection in (b) (4) and documented in the EIR. No objectional conditions were noted in the shipping validation plan.

3.2.P.2.5 Microbiological Attributes

Please refer to 3.2.A.1 and 3.2.P.3.5 for the information contained within this section.

3.2.P.2.6 Compatibility

DMPQ defers to the Product Office for the review of this section.

3.2.P.3 Manufacture

3.2.P.3.1 Manufacturer(s)

<i>Address of Site</i>	<i>Responsibility</i>
MSD (b) (4)	<ul style="list-style-type: none"> • Drug Product manufacturing • Drug Product (b) (4) In-Process testing during formulation process • Drug Product inspection, labeling and secondary packaging
(b) (4)	<ul style="list-style-type: none"> • Drug Product release testing
(b) (4)	<ul style="list-style-type: none"> • Drug Product release testing
(b) (4) (b) (4)	<ul style="list-style-type: none"> • Drug Product release testing and stability testing
(b) (4)	<ul style="list-style-type: none"> • Drug Product stability testing

3.2.P.3.2 Batch Formula

DMPQ defers to the Product Office for the review of this section.

3.2.P.3.3 Description of Manufacturing Process

Ebola Zaire Vaccine (Ebola Zaire Vaccine, Live.) Drug Product (DP) is manufactured as a sterile, aseptically filled solution into a single-dose ISO standard (b) (4) vial. The DP batch size range is (b) (4) for the Final (b) (4). Each (b) (4) vial is filled to achieve a label claim of 1.0 mL.

The formulation process consists of (b) (4) the Drug Product Stabilizer Solution into a formulation vessel, and adding the BDS to the formulation vessel. The formulation vessel is (b) (4). The aseptic formulation process is performed under Grade (b) (4) environmental conditions using (b) (4).

The (b) (4) is subsequently filled, aseptically, into vials using (b) (4) and the vials are then stoppered. The filling process takes place in a Grade (b) (4) Restricted Access Barrier System (RABS). Stoppered vials are transferred into the capping room using (b) (4) that provide Grade (b) (4) air supply and capped/sealed under Grade (b) (4) air supply. The filled and sealed vials are then inspected, labeled, and packaged prior to freezing and storage at -80°C to -60°C. Figure 6 below is a flow chart for the production of Drug Product.

Figure 6 – Drug Product production flow chart

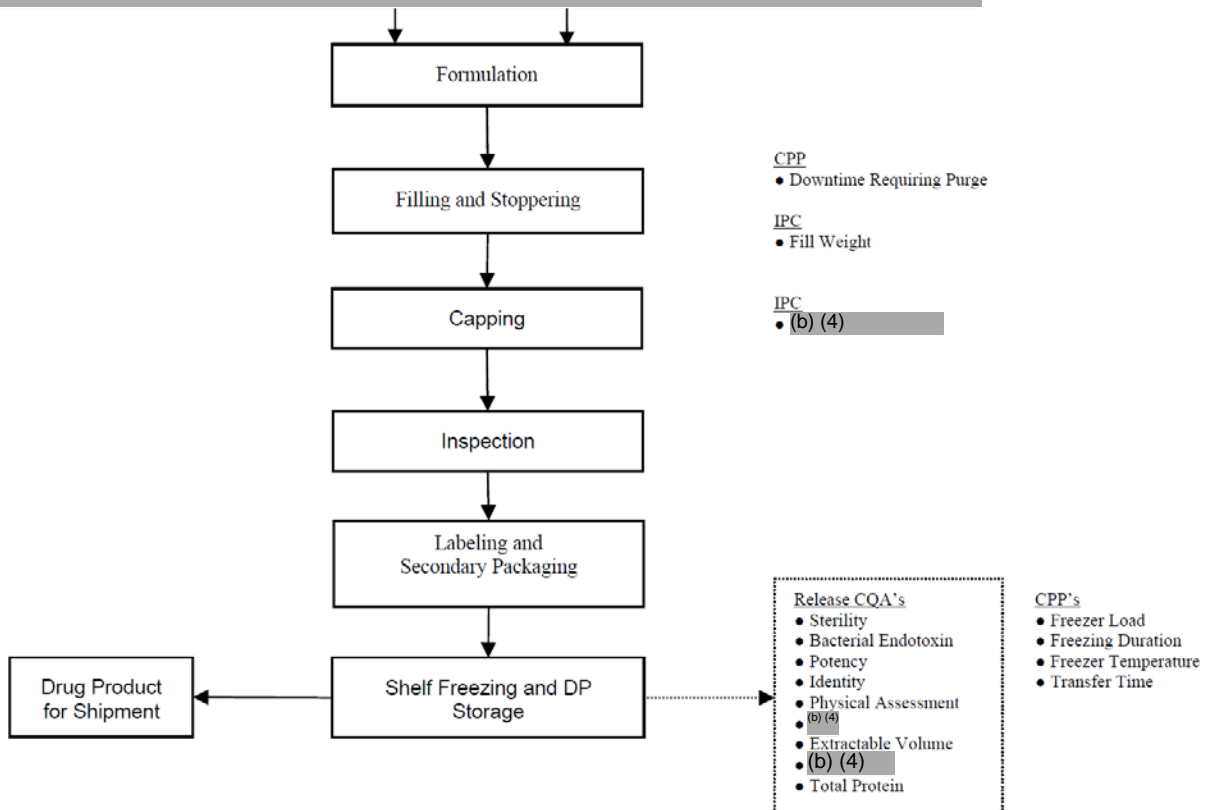
(b) (4)

Hold Times

- (b) (4)

Process Times

- (b) (4)
- Total Processing Time



(b) (4)

(b) (4)

Formulation

Prior to the start of manufacture, the required amounts of DP Stabilizer Solution and BDS are calculated based on the (b) (4) the target potency of the (b) (4) to ensure that the DP potency and (b) (4) will be within specification at release. Formulation is performed in a Grade (b) (4) room using (b) (4). The (b) (4) batch size range is (b) (4), with a target range of (b) (4) based on process development studies.

Filling and Stoppering

The formulation vessel containing the (b) (4) is transferred to the Grade (b) (4) background filling room from either (b) (4) storage for a maximum of (b) (4) or directly from the formulation area. The outlet line from the formulation vessel is connected to a (b) (4) assembly via an aseptic connection. The (b) (4) is filled into single-dose (b) (4) glass vials using (b) (4) and stoppered on a filling line within a Grade (b) (4) Restricted Access Barrier System (RABS).

The (b) (4) glass vials are supplied washed by the vendor and are depyrogenated in-line in the depyrogenation tunnel. Prior to filling, (b) (4). Once dose is set, the vials are filled using (b) (4) with a fill weight of (b) (4). Excess volume is included during filling to ensure recovery of the label claim of 1.0 mL per vial of DP. Studies performed to establish the required overfill Dose is controlled by manual weight checks which are performed periodically throughout the fill for each fill pump ((b) (4)). The fill pumps are adjusted, if necessary, to maintain dose within a specified range around the target. The filling line is purged for a minimum of (b) (4) vials if the allowable downtime limit of (b) (4) is exceeded during the fill, or a minimum of (b) (4) vials are purged if a downtime exceeds (b) (4). A contingency process has been established to aseptically disconnect and reconnect the (b) (4) vessel from the filling line to minimize exposure to (b) (4) in the event of an extended downtime. The end-of-fill process is manual, and it is stopped when air is observed in the filling manifold prior to the fill pumps.

The vials are stoppered with 13 mm chlorobutyl stoppers that are supplied Ready-to-Use (RTU) by the vendor. Filled and stoppered vials are automatically inspected for

missing stoppers prior to being loaded onto (b) (4). The (b) (4) of filled vials are then transferred into (b) (4) that provide Grade (b) (4) air supply and then manually transported to the capping room.

Capping

Capping occurs under Grade (b) (4) air supply in a RABS with a Grade (b) (4) background. Vials are loaded onto the capping machine and automatically inspected for raised or missing stoppers prior to applying the seal. Aluminum seals are applied and then crimped. Seals are supplied (b) (4) by the vendor and supplied Cleaned, Certified, Sterile (CCS). (b) (4) is tested at the beginning and end of the capping process for each capping head with a specification of (b) (4). Capped vials are transferred into (b) (4), and stored at (b) (4) prior to inspection.

Inspection

Trays of vials are taken out of (b) (4) storage and then the vials are subjected to 100% manual visual inspection. The vials are transferred from a (b) (4), inspected, and placed into a new separately labeled (b) (4). After the inspection, the vials are returned to storage at (b) (4).

Labeling and Secondary Packaging

(b) (4) of inspected vials are taken out of (b) (4) storage and then the vials are labeled using an automatic labeling machine, which performs a 100% verification of labeling. The vials are manually packed into 10-vial cartons with package inserts and loaded into shipping cases. Up to (b) (4) cartons are placed into each shipping case. The cases of packaged vials can be stored an undefined amount of time at (b) (4) if not directly transferred to the (b) (4).

Shelf Freezing and Drug Product Storage

The cases of packaged vials are transferred to (b) (4) dedicated to freezing the DP, with a limit of (b) (4) cases per freezer. The end of DP processing time is triggered when the last case of packaged vials is placed in the freezer. The cases of packaged vials are held in the (b) (4) for a minimum of (b) (4) to complete the initial freezing of the DP to -80°C to -60°C. After the minimum initial freeze time, release samples are taken, and the cases of frozen packaged vials are transferred to long term storage at -80°C to -60 °C. When transferring cases of frozen packaged vials, there is a limit of (b) (4) until either the cases of frozen vials are in the storage freezer (b) (4).

Drug Product Shipping

Final container vials are shipped in thermal protective systems qualified to maintain an internal temperature of < -60 °C for the duration of shipment.

Overall Reviewer's Assessment of Section 3.2.P.3.3:

This Section was reviewed for the components that are under DMPQ's purview with an additional comment to the Applicant. The limit for time out of cold storage for inspection and labeling should be sent as an information request to the Applicant.

The other data provided appears to be appropriate.

3.2.P.3.4 Controls of Critical Steps and Intermediates**Table 8 – Critical In-Process Parameters**

Process Step	IPC	Associated CQA	Limits
(b) (4)	(b) (4)	Sterility	(b) (4)
Formulation	(b) (4) Test for (b) (4)	Sterility	Product (b) (4)
Capping	(b) (4)	Sterility	(b) (4)

Overall Reviewer's Assessment of Section 3.2.P.3.4:

This Section was reviewed for the components that are under DMPQ's purview with no additional comment to the Applicant. The data provided appears to be appropriate to support licensure.

3.2.P.3.5 Process Validation and/or Evaluation

The applicant provided an interim report for a single PPQ lot of Drug Product in amendment 125690/0.27 (Received August 27, 2019), which provided a very high-level summary of the results, and the Applicant concluded that all of the CQA tests for the validation batch were within specification.

Overall Qualification Strategy

At the time of this review, the Applicant has only completed a single batch of Drug Product produced from (b) (4) PPQ (b) (4). The production of (b) (4) additional PPQ lots are planned to be completed by the close of this calendar year.

(b) (4) consecutive batches of V920 (b) (4) will be formulated. One of the formulated batches will be (b) (4) to demonstrate the recovery process. As a result of the recovery process challenge, (b) (4) successful batches of V920 (b) (4) will be filled, capped, inspected, labelled, packaged, and frozen to qualify the drug product process.

Requirements are for (b) (4) passing consecutive formulation batches and (b) (4) passing consecutive filling batches.

Table 9 below describes the applicant progress toward the filling multiple batches of drug product.

Table 9 – DP PPQ Batches

PPQ Formulation No.	BDS Batch No.	DP Stabilizer Batch No.	Formulation Batch No.	Formulation Batch Size	Batch Initiation Date
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	TBD	TBD	TBD	TBD	TBD
	TBD	TBD	TBD	TBD	TBD

Sampling Plan

Expanded samples from (b) (4) or (b) (4) approximately spaced intervals across the batch are taken in the form of frozen product vials to demonstrate uniformity of appropriate Critical Quality Attributes. According to the Applicant, additional samples are taken for release testing, stability, general safety testing, container closure integrity and compatibility, particle size characterization, (b) (4) and retains.

Full sample quantity for release testing is collected for each batch, including each filling segment from (b) (4) fills. Stability samples are required to be taken from the end of the batch. In instances of a (b) (4) fill, stability samples will be taken from the (b) (4) fill only.

Expanded Sampling Plan

All PPQ samples are taken as frozen vials. According to the Applicant, mixing was not identified as a Critical Process Parameter as the formulation is a true solution and not known to segregate like a suspension or emulsion. Total Protein is being measured across the fill and show product uniformity across the batch.

The full series of tests in the Expanded Sampling Plan include: Extractable Volume, Total Protein, Physical Assessment, (b) (4), and Potency.

Table 10 below describes the critical quality attributes and release specifications under DMPQ purview

Table 10 – Release Specification

Process Step	Attribute	Classification	Acceptance Criteria
(b) (4)	Sterility	Release CQA	No growth

Reviewer Comment:

The Applicant has indicated that the PPQ run has passed the release sterility testing, however, no information was provided to understand the protocol that was used to make this determination or how many samples were involved in this test.

Batch Size

The drug product batch size is defined as the total volume of (b) (4) manufactured during the formulation process with a target range of (b) (4) and with an acceptable range of (b) (4). To demonstrate the proposed process, (b) (4) process performance qualification batches will be manufactured.

Process Capability Analysis

Long Term Static Process Control Limits (LTSPCL) are limits indicative of long-term process performance. LTSPCLs have not been established for V920 because this is a new process and product. Therefore, Process Control Analysis will not be conducted as part of this PPQ.

Hold Times

The Cumulative (b) (4) will be challenged for (b) (4) of the PPQ batches ((b) (4)). The Total Process Time will be challenged for (b) (4) the PPQ batches ((b) (4)). Each maximum time for these two process times will be confirmed for (b) (4) the remaining PPQ batches.

Deviations

There were fourteen deviations associated with the qualification study. Zero deviations were categorized as protocol deviations, eight deviations were categorized as process deviations, and six deviations were categorized as environmental monitoring deviations.

Overall Reviewer's Assessment of Section 3.2.P.3.5:

The information provided about DP manufacturing was not sufficient for our evaluation of the process and product. Additional information was requested from the Applicant to supplement the review. After reviewing the additional information, it was concluded that additional Drug Product manufacturing lots would be necessary to complete the review.

Information Requests Sent to the Applicant:

All tables in this section are numbered as they were received from the applicant in their response to the information request

Information Request Sent October 23, 2019:

1. In an amendment to this BLA 125690/0.27 (Received August 27, 2019) you provided the interim report for the Drug Product PPQ (b) (3) (b) (4) (3.2.R.7). Please respond to the following:
 - A. In this report you listed the observed deviations for Drug Product PPQ (b) (3) (b) (4). Please provide the full deviation report and all associated CAPAs with supporting documents for DV0005580 (Visual Inspection) as an amendment to this BLA. Please also clarify if the vials that are the subject of this deviation were the same vials processed in the presence of this FDA inspection team.

The Applicant's Response

"The full deviation report with all associated CAPAs for DV0005580 is included herein. The report is in (b) (4) so we have provided an unofficial translation below in Attachment 1. The deviation occurred on (b) (4) which was while the FDA inspection team was on site however the tour of the Visual Inspection room occurred on (b) (4) according to our notes.

During the visual inspection of the (b) (4), the DP Manager provided a waste container for glass waste and labelled it by transferring the label of the (b) (4) to the container. The manager noticed that the inspected vials came from a (b) (4) run and that the boxes were labelled (b) (4) RUN" accordingly. accordingly, the vials of the (b) (4) examined by the operators were not PPQ vials but (b) (4) vials.

The manager immediately stopped the visual inspection and checked the cold stores. The vials filled with were stored in cold room (b) (4), the vials of the PPQ batch were stored in cold room (b) (4).

In addition, the entry to remove the vials from storage in the logbook was made from memory instead of by reading the label of the removed cartons.

In the batch record it is noted in which cold store the vials were stored after capping. However, there is no guarantee that the operators of the visual inspection will use this information to remove the vials from the correct cold store.

The (b) (4) operators who carried out the visual inspection did not check the label of the (b) (4) when they received them. The entries on the worksheet HH-ILP/0021-2-AB were made from memory.

There is no checkpoint in the HH-ILP/0021-2-AB worksheet that requires that the data in the batch record match the data on the label of the (b) (4) and the entries on HH-ILP/0021-2-AB.

(b) (4) vials and product vials are visually indistinguishable (stoppers, caps, color, viscosity, clarity, fill level).

There was no manufacturing instruction for the (b) (4) run on (b) (4). It is not possible to balance the (b) (4) vials."

DMPQ Review of Applicant's Response

The response by the applicant was reviewed and the response adds to FDA's concern regarding this applicant's lack of control over product in their manufacturing process. There were multiple errors that occurred during this single incident: Operators not verifying the label on the (b) (4) they retrieved from cold storage, inscribing lot information into the logbook to remove the vials from storage was made from memory, and no check of labels prior to starting this inspection step. Also, the (b) (4) run was not sufficiently documented.

The applicant has confirmed in this report that: "There was no manufacturing instruction for the (b) (4) run on (b) (4). It is not possible to balance the (b) (4) vials."

The applicant has no way of confirming if (b) (4) vials were left behind in the inspection room as a result of this deviation. Furthermore, per the applicant's own analysis the detectability of (b) (4) vials in the room after a clearance procedure was executed is near zero as (b) (4) vials and product vials are visually

indistinguishable (stoppers, caps, color, viscosity, clarity, fill level).”

The execution of an additional line clearance of the room is the appropriate action to take, but it cannot be considered an adequate risk mitigator given the aggregate deficiencies mentioned above and the fact that this is the first visual inspection for DP at this facility, so the operators are less experienced. This is further substantiated by FDA’s inspection team and documented in the accompanying EIR as the inspection team observed inadequate line clearance execution by the operators during the visual inspection of DP PPQ (b) (4).

The impact summary provided by the applicant was reviewed and determined to be inadequate for the following reasons:

- 1. The applicant is not able to rule out carry-over of (b) (4) vials into the visual inspection to DP PPQ (b) (4). The inspection of product vials occurred immediately after this event.***
- 2. The effectiveness of the multitude of changes (Re-Training, Label Confirmation, Locked Carts, New Worksheets, Color-coded Caps) that is being proposed by the applicant will not be made available during the current review timeframe.***

Question 1B

- B. On page 27 of 35 in this report, you have provided a table that outlines the percent of rejected vials encountered during the final visual inspection. The “Total Rejects” row does not equal the sum of all of the reject types listed in this table. Please explain this discrepancy and provide an accounting for all of the vials that went through this visual inspection step. Furthermore, please state the acceptance criteria for each type of reject for visual inspection.

The Applicant’s Response

The total rejects row is a compilation of all rejects and includes more defect types than the defects in the other Process Control Limit (PCL) categories. An accounting for all of the vials from PPQ (b) (4) that went through the visual inspection step is also shown in Table 2. As indicated in the PPQ report, Process Control Limits were not established prior to DP PPQ (b) (4).

However, post PPQ (b) (4), initial PCLs were established using a statistical analysis of visual inspection data available from drug product batches manufactured at the (b) (4) site (including pre-PPQ batches). Due to insufficient historical visual inspection data, these initial limits will be considered dynamic in nature. These limits will be re-evaluated periodically as additional drug product manufacturing data is collected or if deemed required as a result of an investigation until static limits are established. Initial PCLs are now in place and are being used for PPQ (b) (4). Defects are incorporated into a PCL category that most appropriately aligns with potential failure modes. Consequently, PCL categories can consist of multiple defect types. Additionally, a category for total rejects is incorporated to encompass wholistic process monitoring of all defect types.

Table 1 – PCL for Visual Inspection

Category		Initial PCL (%)
Particles	Particles	(b) (4)
Critical CCI Defects	Loose Cap	(b) (4)
	Notch on Cap	
	Damaged Stopper	
Empty Vials	Empty Vials	(b) (4)
Critical Glass Defect	Crack on Side of Vial	(b) (4)
	Crack on Bottom of Vial	
All Other Critical Defects	Discoloration of Content	(b) (4)
	Wrong Color Flip Top	
	Wrong Color Stopper	
	Dirt on Stopper	
Total Rejects	All defect types	(b) (4)

DMPQ Review of Applicant's Response

The applicant has clarified that the defect limits that are outlined in their response are initial process limits that will be refined as more data is collected from subsequent manufacturing batches. This approach is common and is acceptable in concept. The applicant did not address the first part of the Information Request regarding the discrepancy in the results of Drug Product PPQ (b) (4) inspection. The reason for this discrepancy in the results is that there are non-trivial categories of defects that were not included in the results table for this step.

A full account of the defects observed during visual inspection of DP PPQ (b) (4) was provided in table 2 of this response. This table includes a wide range of possible defects and stratifies the accounting of the observed defects by (b) (4) number.

The Applicant claims the sum of all reject vials to be (b) (4) for DP PPQ (b) (4) visual inspection. When one adds up the numbers provided in this table, a total of (b) (4) vials is obtained. The applicant is potentially missing (b) (4) more vials than they claim.

The response that the Applicant has provided to this information request is not adequate. Additional information is needed. Please see the follow-up information request sent on October 30, 2019 located below, for additional information.

Question 1C

- C. Not found in this report is an accounting for all of the vials produced in the run. Please account for all the vials produced in this PPQ run and submit this information for review.

The Applicant's Response

Vial accountability is summarized below (referenced from batch record HH-DP/0014 (b) (4)

for batch (b) (4).

Table 3 Vial Quantities for Filling through Capping

Filling through Capping	Number of vials
Total vials filled	(b) (4)
Total rejects from filling	(b) (4)
Total rejects from capping	(b) (4)
Total vials for visual inspection after	(b) (4)

Table 4 Vial Quantities for Inspection

Inspection	Number of vials
Sum of good vials after visual inspection	(b) (4)
Sum of vial rejects from visual inspection	(b) (4)
Sum of glass breakage/fallen vials during visual inspection	(b) (4)
Sum of vials for Acceptable Quality Limit	(b) (4)

Total vials inspected (B)	(b) (4)
---------------------------	---------

Table 5 Overall Vial Accountability

Overall Vial Accountability	Number of vials
Total vial count to Inspection (A)	(b) (4)
Total vial count from Inspection (B)	(b) (4)
% Difference [(A-B) / A * 100]	(b) (4)

Per HH-DP/0014 version 1.0, vial accountability criteria is (b) (4) difference between vial count to inspection (A) versus from inspection (B). As such, this criteria has been met for PPQ batch (b) (4), as the actual result was (b) (4). Risk to material control is mitigated through line clearance procedures and documented in the batch records.

DMPQ Review of Applicant's Response

The Applicant's response is not acceptable. The Applicant is not able to account for all of the vials produced in this manufacturing run. In their response to this Information Request, the applicant states that the total number of vials lost is (b) (4). This number should be considered a minimum and can be as high as (b) (4) vials given the discrepancy between the stated number of rejects in visual inspection and the total number of vials provided in accompanying 'Table 2' of this response that was discussed in "b" above.

The applicant claims that they have established a criterion for the visual inspection step that allows for a (b) (4) variation in the vials that begin visual inspection versus end. This level of variation from a 100% manual visual inspection is not supported by any rationale as to why the high degree of variance is appropriate. Furthermore, to codify in the acceptance criteria the ability to have more vials post inspection than what was started with increases the risk of carry-over vials from previous runs of other activities being accepted into a production lot.

It is noted that the applicant does identify a risk mitigator for this criterion, but as stated in the review of part 'b' above, the execution of line clearance by the applicant at this time is not an effective measure to reduce risk.

Furthermore, this error in accountability is not an isolated incident. There were observed vial accountability issues in each of the (b) (4) aseptic process simulation runs for Drug Product. To date, the applicant has yet to execute their established protocol without losing vials.

There is also a concern regarding the volume of 'glass breakage/fallen vials during visual inspection' that was observed in this single lot of drug product. As stated by the Applicant, there were (b) (4) vials in this category. This number is concerning for three reasons:

1. If the vials that are referenced by this number are vials that were found to be damaged upon visual inspection they should be counted as tracked via a defect type with an appropriate process limit. Given the magnitude of this value (b) (4) of the total run) a deviation should have been opened to document and investigate the underlying root cause as this would have failed the critical glass defect acceptance criteria for a commercial production lot (b) (4).
2. If the vials that are referenced by this number are vials that were broken by the operators during the visual inspection step this should be a cause for concern in either the design of the visual inspection room or the training of the operators. Given the magnitude of this value (b) (4) of the total run) a deviation should have been opened to document and investigate the underlying root cause.
3. A deviation list was provided by the applicant for this lot. The applicant did not open a deviation for the high number of broken vials in this lot. While it is not possible to ascertain the cause of the vial breakage from the information provided, the inaction on the part of the Applicant and lack of any deviation opened for this issue cause for serious concern as it is further evidence that the Quality Systems of the manufacturing site is not yet adequate to monitor commercial manufacturing.

The response that the Applicant has provided to this information request is not adequate. Additional information is needed. Please see the follow-up information request sent on October 30, 2019 located below, for additional information.

There is a final noteworthy observation from the data submitted in this response. The data provided in Table 3 indicates that in the filling of over (b) (4) vials there was only a need to reject (b) (4).

vials during the filling step. While there is no direct evidence to doubt the veracity of this number, the cumulative understanding of the operation of the filling lines under aseptic procedures suggests that this number is expected to be (b) (4) for a lot this size.

This concern was raised to the applicant in the information request sent on October 30, 2019 located below.

Information Request Sent October 30, 2019:

We refer to your October 24, 2019 submission to STN 125690 for V920 Ebola Zaire Vaccine (rVSVΔG-ZEBOV-GP, Live, Attenuated) which included your response to the CBER information request dated October 23, 2019. We have the following request for additional information:

1. In your response to Item 1b, you provided a full account of the defects observed during visual inspection of DP PPQ (b) (4) in Table 2. This table contained a wide range of possible defects and stratified the accounting of the observed defects by tray number. This table claims the sum of all reject vials to be (b) (4) vials for DP PPQ (b) (4) visual inspection. When one adds up the numbers provided in this table, a total of (b) (4) vials is obtained. It appears that your vial accountability is potentially missing (b) (4) more vials than claimed in the response (Tables 4 and 5). Please review your accounting of rejected vials during this step and provide a detailed explanation supporting the result's veracity.

The Applicant's Response

On the morning of October 31, 2019, the Applicant provided the following:

I wanted to provide an answer to one of the responses (#1 below) via email due to the fact that we inadvertently only provided half of Table 2 in our response. Please see the full table attached (and we will re-provide in our response document). We will respond to the remaining questions in our amendment to the BLA.

DMPQ Review of the Applicant's Response

The information that was provided by the Applicant clears up the discrepancy concerning the total number of rejects for DP PPQ (b) (4). It appears that the firm is missing (b) (4) vials not (b) (4). The loss of (b) (4) vials is still not appropriate.

A review of the revised Table 2 was conducted and there are additional concerns with the data:

- a. (b) (4) of the (b) (4) needles used for filling was not used due to it failing the performance check prior to filling DP PPQ (b) (4). As a result of this, (b) (4) in (b) (4) vial moving past the filling step will be empty. This would mean in a run of (b) (4) vials, it would be expected that (b) (4) vials we be observed as empty. Additionally, it would be expected that there would be empty vials observed in all (b) (4) collected to varying degrees. In a review of the (b) (4), it appears that the total number of empty vials was found to be (b) (4). Furthermore, only (b) (4) of the (b) (4) were found to have empty vials in them. There are gaps in the (b) (4) that are observed with empty vials which does not track with the expected manifestation of a decommissioned filling needle.

In DV0005992, it was noted that the Applicant decommissioned Needle (b) (4) and claimed to have accounted for “all of the empties during visual inspection”. It is not clear from the information that was provided in this submission when the needle was decommissioned, how the Applicant was able to account for all of the empty vials produced, and if the needle was decommissioned mid-run how the applicant treated the vials between the last passed in-process check and the failed check.

- b. *The table has a section for vials that were observed to have ‘Dirt on Vial’. This table indicates that there is a persistent number of vials in every (b) (4) of DP PPQ (b) (4) that were observed to have dirt on them. This is a concern as the uniformity of this observation suggests that there is some form of contact happening during filling/capping or handling in visual inspection that is leaving a residue on product vials. The total number of vials impacted was (b) (4). It is not clear from the information provided by the Applicant if such a defect is tracked in the Quality System as there is no establishing criterion for this issue.*
- c. *The table has a section for vials that were observed to have ‘Scratch on Vial’. With the new information that was provided by the applicant, it appears that within the first (b) (4) of the run, scratches on the vials were a minor issue; however, in the final (b) (4), there is a large spike in the vials that are observed to be scratched (b) (4) which is a cause for concern. This spike during the manufacturing process should*

be appropriately noted in the batch record and investigated for the cause. It is not clear from the information provided by the applicant if such a defect is tracked in the Quality System as there is no establishing criterion for this issue.

- d. There appears to be a spike in rejects for (b) (4).*
 - e. The FDA has not been made aware of any deviations surrounding vial rejects.*
 - f. There are no criteria for moderate or minor vials defects in this submission. It is not clear how the vast majority of the criteria listed in table 2 are to be monitored as additional production lots are executed.*
- 2. In your response to Item 1c in Table 4, you provided the volume of 'glass breakage/fallen vials for the visual inspection' that was observed in this single lot of drug product. You stated that there were (b) (4) vials in this category. A deviation list was provided in an amendment to the BLA for Drug Product PPQ (b) (4). However, a deviation for the high number of broken vials in this lot during visual inspection was not included in the deviation list. It is not possible to ascertain the cause of the vial breakage from the information provided, as no deviation was opened for this issue. Please respond to items (a) and (b) below, and provide any additional explanation as to why this incident was not documented as a deviation in your Quality System, whether the issue was investigated, and the root cause.*
- a. If the (b) (4) referenced vials are vials that were found to be damaged upon visual inspection, they should be counted as tracked via a defect type with an appropriate process limit. Given that this would have failed the critical glass defect acceptance criteria for a commercial production lot ((b) (4), (b) (4) vials) and the magnitude of the rejected vials ((b) (4) of the total run), a deviation appears to be warranted to document and investigate the underlying root cause.*
 - b. If the (b) (4) referenced vials were broken by the operators during the visual inspection step, this should be a cause for concern regarding the design of the visual inspection process, inadequate training of the operators, or a catastrophic failure. Given the magnitude of this value ((b) (4) of the total run) a deviation appears to be warranted to document and investigate the underlying root cause.*

The Applicant's Response

The (b) (4) vials referenced were not damaged vials found during visual inspection, but rather were removed as floor losses due to dropping the vials. If the vials were found while performing visual inspection of vials, then they would be rejected as one of the critical glass defect categories: crack on side of vial or crack on bottom of vial. (b) (4) of the (b) (4) vials were dropped during visual inspection. Per site procedures, these vials were removed and documented via the visual inspection worksheet as fallen vials. Further, an inspection tray containing (b) (4) vials was dropped while manually transferring the (b) (4) to cold storage. Per site procedures, these vials were removed and documented as fallen vials as well. Because site procedures were followed, no deviation was warranted.

Site procedures were followed for removal of the fallen vials. Fallen vials are not a defect category for the process, and thus are not part of our Process Control Limits and a deviation was not warranted. However, we recognized that a considerable amount of vials were documented as floor losses. As explained, (b) (4) of these vials were from dropping a (b) (4) during transfer of the (b) (4) post-inspection. After PPQ (b) (4), handling of vials before and after visual inspection was revised, and (b) (4) that improve (b) (4) handling have been implemented, reducing the risk of dropping (b) (4).

DMPQ Review of the Applicant's Response

The response by the applicant clarified that the broken vials identified during visual inspection were broken by the site staff during this process. (b) (4) of these vials were broken as a result of a catastrophic failure in the dropping of a full (b) (4).

The lack of a deviation in this instance may be appropriate as the firm has established procedures to mitigate this spill and claims that the batch record is appropriately crafted to allow for the documentation of this event in the inspection step of the record. However, it is not possible to verify this information as neither an unexecuted or executed batch record was submitted for this application.

3. Please provide additional information for the data provided in Table 3 of your response. Specifically, please provide an explanation for rejecting (b) (4) vials that were rejected during Filling and (b) (4) vials that were rejected during Capping.

The Applicant's Response

Rejects from the Filling operation and the Capping operation are counted at the end of the respective process. During Filling, vials can be removed automatically by the filler for missing stopper or down vial, or manually during aseptic interventions according to our procedures. For PPQ^{(b) (4)}, there was an aseptic intervention to correct for a mechanical problem at the filling needle station and starwheel.

During Capping, vials are removed from each batch to perform the (b) (4) test. Additionally, vials can be removed automatically as a down vial or manually according to our procedures (ex. missing stopper or at the end of processing during line clearance). During PPQ^{(b) (4)}, (b) (4) vials were removed for (b) (4) testing. The remaining were rejects from the process per our procedure.

DMPQ Review of the Applicant's Response

The Applicant states that the (b) (4) vials were rejected from the filling step due to an intervention into the filling line to correct a mechanical problem at the filling needle and starwheel. This explanation raises more questions about this process. The additional concerns are as follows:

1. It is not clear from the information provided by the applicant how it was determined that the rejection of only (b) (4) vials from the filling line for this intervention was appropriate. There is no deviation noted in the Summary PPQ Report and there is no mention of rejected vials at all.
2. From the information provided in this response, it appears that the automatic rejection of vials by the filling line would be considered a reject per their procedure. If there was a non-functional filling needle, it would be expected for there to be hundreds of more vials rejected by this process. Without the batch record, it is not possible to discern what is going on.

The Applicant's response to The Agency questions regarding rejects during Filling and Capping is not acceptable. The applicant's response simply stating that they were rejected per procedure does not answer the question of why they were rejected. This is another example of how the limited information in this submission is making a faithful review near impossible.

4. The FDA team was present for the visual inspection of DP PPQ^{(b) (4)} (Vials (b) (4)). Please list the tray number that this corresponds to.

The Applicant's Response

On (b) (4), Final Product Unpackaged (also known by UIN 180504) PPQ (b) (4) trays (b) (4) through (b) (4) were being inspected.

DMPQ Review of the Applicant's Response

The Applicant has satisfactorily clarified where in the process the FDA inspection team observed visual inspection.

DMPQ Assessment of Drug Product PPQ:

All process deviations were investigated and the impact on the validation was assessed. However, the actions the applicant has taken in response to the observed deviations as corrective and preventative actions were not provided for review. Given the status of the manufacturing site's Quality System observe during the Pre-License Inspection and in conjunction with the information that has been provided in this interim report, a determination cannot be made regarding the applicant's ability to manufacture a consistent product to their specifications, adequately identify issues that may impact product quality, or appropriately address issues in real-time.

The information contained within this summary report is very high-level that is not possible to conduct a faithful review. The Applicant had to be asked to provide via a follow-up information request for very basic data (number of vials filled, vial accountability, and visual inspection results)

Furthermore, the Applicant has failed to provide either an unexecuted or executed batch record for DP PPQ (b) (4) for this BLA. This was noted in the filing memo by both DMPQ and DVP with the expectation that this record was going to be submitted at some point in this review cycle. There is a gap in this review where manufacturing issues encountered during the execution of this single PPQ run may be addressed per the site's SOPs and noted in the batch record without requiring the opening of a deviation investigation. Without this batch record, it is not possible to execute a complete review of this submission.

For example, there is no deviation for the deselection of filling needle (b) (4) for the only PPQ run that was provided to support licensure. It may be appropriate for this event to have been documented in the batch record, but we do not have this record for reference.

The FDA inspection team was present for the filling of DP PPQ (b) (4). Under more typical circumstances for BLA reviews the inspection team would have been able to review completed batch records for PPQ runs at this time and any inconsistencies or deficiencies would have been addressed

on inspection. The agreement between FDA and the Applicant did not allow the inspection team the opportunity.

Issues like the deselection of Needle (b) (4), the dropping of an entire tray of vials, and the accidental inspection of (b) (4) vials are just three examples where the applicant could have made the inspection team aware of these issues in real-time as we were on-site when these incidents occurred. The interim report was not going to be submitted for an additional six months. Since we were not able to verify the batch record on inspection, the Applicant is hamstringing our ability to do an in-depth review of the very limited data they have presented to support licensure.

3.2.P.4 Control of Excipients

3.2.P.4.1 Specifications

DMPQ defers to the Product Office for the review of this section.

3.2.P.4.2 and 3.2.P.4.3 Analytical Procedures and Validation of Analytical Procedures

DMPQ defers to the Product Office for the review of this section.

3.2.P.4.4 Justification of Specifications

DMPQ defers to the Product Office for the review of this section.

3.2.P.4.5 Excipients of Human or Animal Origin

DMPQ defers to the Product Office for the review of this section.

3.2.P.4.6 Novel Excipient

DMPQ defers to the Product Office for the review of this section.

3.2.P.5 Control of Drug Product

3.2.P.5.1 and 3.2.P.5.6 Specification(s) and Justification of Specification(s)

DMPQ defers to the Product Office for the review of this section

3.2.P.5.2 and 3.2.P.5.3 Analytical Procedures and Validation of Analytical Procedures

DMPQ defers to the Product Office for the review of this section.

3.2.P.5.4 Batch Analyses

DMPQ defers to the Product Office for the review of this section

3.2.P.5.5 Characterization of Impurities

DMPQ defers to the Product Office for the review of this section.

3.2.P.6 Reference Standards or Materials

DMPQ defers to the Product Office for the review of this section.

3.2.P.7 Container Closure System

The container closure system for the final drug product consists of three separate pieces that are described in table 11 below with supporting Figures 7, 8, and 9.

Table 11 – components of the final container closure

Component	Description
Vial	(b) (4) borosilicate clear tubing glass vial, 13 mm finish
Vial Stopper	13 mm (b) (4) coated (b) (4) elastomer
Cap/Seal	13mm Aluminum seal with dark red plastic flip- off cap

Figure 7 – (b) (4) Glass Product Vial

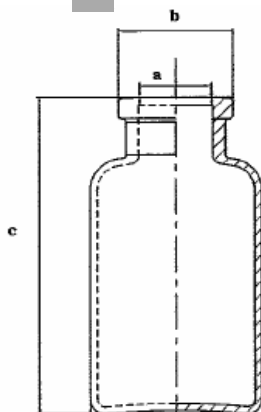
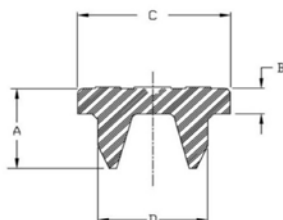
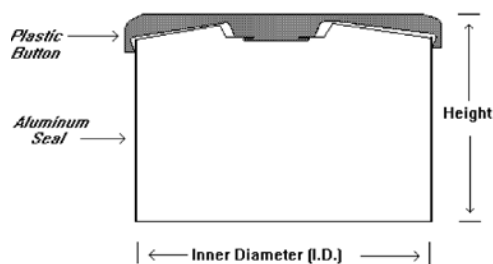


Figure 8 – Vial Stopper



- A. Overall Height
- B. Flange Thickness
- C. Flange Outside Diameter
- D. Plug Outside Diameter

Figure 9 – Vial Cap



Determination of Vial Integrity – (b) (4)

The container closure integrity was verified using the (b) (4) test which is a deterministic test based on (b) (4) measurements.

The test is performed by (b) (4)

Results

In Table 12 below displays the results and acceptance criteria for the CCI testing to support the final drug product container closure.

Table 12 – CCI Testing

Sample Description	Quantity Tested	Acceptance Criteria (b) (4)	Sample (b) (4)	Positive Controls (b) (4)	Negative Controls ((b) (4))	Results
DP (b) (4)	(b) (4)	(b) (4)	(b) (4)	Pass	Pass	Pass
DP (b) (4) Lot				Pass	Pass	Pass
DP (b) (4) Lot				Pass	Pass	Pass
DP PPQ Lot (b) (4)				Pass	Pass	Pass

Reviewer Comment:

The testing plan for the Drug Product CCIT was discussed with the inspection team during the Pre-License Inspection in (b) (4). This testing plan was discussed

with DMPQ management and no issues were noted regarding the plan. The data that the Applicant submitted to the BLA (125690/0.21, Received on July 15, 2019) was obtained from the previously discussed protocol. The data passed the established acceptance criteria and appears to be adequate.

Overall Reviewer's Assessment of Section 3.2.P.7:

The Applicant did run positive controls, but the information submitted did not indicate the sensitivity of test system. It is not clear if this test is able to detect minor, but meaningful defects.

Overall, the testing conducted to establish that the final drug product container is integral was reviewed and determined to be adequate.

3.2.P.8 Stability

3.2.P.8.1 Stability Summary and Conclusion and 3.2.P.8.3 Stability Data

DMPQ defers to the Product Office for the review of this section.

3.2.P.8.2 Post-Approval Stability Protocol and Stability Commitment

DMPQ defers to the Product Office for the review of this section.

3.2.A APPENDICES

3.2.A.1 Facilities and Equipment

Table 13 – Facilities Table

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Manufacturing of the (b) (4)	No	No	Yes	
Merck Sharp Dohme Corp (b) (4)				
FEI: (b) (4)				

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Storage of the (b) (4) [REDACTED]	No	No	Yes	
(b) (4) [REDACTED]				
FEI: (b) (4) Drug Substance and Drug Product Manufacturing MSD (b) (4) [REDACTED]	Yes	Yes	Yes	Inspection Completed
FEI# (b) (4) Release testing of (b) (4) [REDACTED]				
(b) (4) [REDACTED]	No	No	No	Facility is not required to register
Release testing of (b) (4) [REDACTED]				
(b) (4) [REDACTED]	No	No	No	Facility is not required to register
[REDACTED]				

Manufacturing/ Testing activities	Inspection? Waiver? or Not Required?	Compliance Check Required for Approval?	RMS-BLA Entry Required?	Comments
Release testing of (b) (4)	No	No	Yes	
(b) (4)				
FEI: (b) (4)				
Release testing of (b) (4)	No	No	Yes	
(b) (4)				
FEI: (b) (4)				
Release testing of (b) (4)	No	No	Yes	
(b) (4)				
FEI: (b) (4)				
Release testing of (b) (4)	No	No	Yes	
(b) (4)				
FEI: (b) (4)				
Stability testing of (b) (4)	No	No	Yes	
(b) (4)				
FEI: (b) (4)				

The (b) (4) area of this facility is a single product manufacturing area, dedicated to the manufacture of Ebola Zaire vaccine. The Applicant's campus includes (b) (4) Manufacturing Suites. These suites are isolated from one another in (b) (4).

Table 14 below breaks down the processing step with a brief description and identifies the associated rooms in the facility that are used for that activity.

Table 14. Summary of Manufacturing Steps

Processing Step	Description	Rooms
(b) (4)		
DP Formulation	Drug Product is formulated with DP Stabilizer Solution and BDS.	(b) (4)
Filling	DP is filled into single dose vials and stoppered.	
Capping	Aluminum seals are applied and crimped.	
Visual Inspection	Vials are manually inspected.	
Labeling and Packaging	Inspected vials are labeled using an automatic labeling machine and manually packaged into cartons.	

Facility and Flow

The applicant provided flow diagrams and/or narrative statements for the manufacturing for V920 on the following topics:

- Room Classification
- Clean Material Flow
- Personnel Flow
- Product Flow
- Waste Flow

Room Classification

Figure 10 below is the room classification diagram for the manufacturing suite of Ebola Zaire V920. The manufacturing steps where product is open to the surrounding environment is conducted under Grade (b) (4) air with a Grade (b) (4) background. The other manufacturing steps where the process is closed is conducted under Grade (b) (4) air. Rooms where manufacturing is not taking place but lead to manufacturing area and maintained under Grade (b) (4) air. This information was reviewed and determined to be acceptable.



Figure 10 above is the layout of the facility with an overlay depicting the room classifications. It is important to note that all of the open manipulations are carried out in Grade (b) (4) environments with a Grade (b) (4) background environment.

Clean Material Flow

The Applicant provided a general narrative for the movement of Clean Material in the facility. (b) (4)

(b) (4) Material moves through the facility utilizing a (b) (4) path. Materials cannot move across the viral barrier without completion of appropriate (b) (4) procedures. Corridor (b) (4) serves the Material Airlock (b) (4) and Personnel Airlock (b) (4). All other airlocks in the facility are (b) (4) except for (b) (4) and segregation is achieved temporally for clean material, waste, and in process material.

Reviewer Comment:

The Clean material flow diagram was reviewed during the PLI in (b) (4). The flow appears adequate and the implementation of temporal segregation appears to be appropriate to mitigate cross contamination concerns.

Personnel Flow and Gowning

The Applicant has confirmed that the gowning requirements increase as personnel progress into higher classifications of the facility. Personnel are required to wear (b) (4)

and Grade (b) (4) areas. (b) (4) are used in the (b) (4) corridors and between areas. To enter Grade (b) (4) areas, clean (b) (4)

(b) (4) is added over top of the production clothing. Gowning requirements to enter Grade (b) (4) include removing Grade (b) (4)

(b) (4) (over top of the production clothing), (b) (4) of the production shoes and (b) (4). When Employees are working in Grade (b) (4) areas (such as the Bio-Safety cabinets), personnel are required to wear (b) (4)

(b) (4). Personnel are to de-gown in the appropriate areas following the order of removing garments indicated in SOPs.

The Applicant confirmed that personnel are trained and certified in gowning procedures and are required to follow instructions outlined in approved standard operating procedures prior to entering the manufacturing suites. Personnel are responsible for the movement of equipment, products, and solid waste throughout the classified areas utilized.

Reviewer Comment:

The Personnel Flow diagram was reviewed during the PLI in (b) (4). The flow appears adequate and the use of multi-tiered gowning as one progresses into higher classifications appears to be appropriate to mitigate cross contamination concerns in this specific aspect of cross-contamination prevention.

The hands-on training provided by the applicant is appropriate to introduce employees to aseptic gowning.

Product Flow

Product moves from (b) (4) suite prior to proceeding into the (b) (4) area prior to (b) (4) of the Bulk Drug Substance (BDS). The (b) (4) BDS will move from (b) (4) to Drug Product (DP) Formulation, through to filling, capping, inspection, and labeling and packaging.

Reviewer Comment:

The Product Flow diagram was reviewed during the PLI in (b) (4). The product will flow through airlocks that are also used to transport waste and in-process material (DS and DP). The flow appears adequate and the implementation of temporal segregation appears to be appropriate to mitigate cross contamination concerns.

Waste Flow

The Applicant has affirmed that all process waste generated in the production facility is inactivated prior to removal from the facility. All solid waste generated in the processing suites is contained prior to removal from processing suites via (b) (4)

(b) (4) prior to removal from the facility for waste disposal. A (b) (4) was added in a dedicated (b) (4) room. Liquid bio-waste from both virus suites and the purification suite that is potentially contaminated with virus is (b) (4)

In addition, (b) (4)

Reviewer Comment:

The Waste Flow diagram was reviewed during the PLI in (b) (4). The waste will flow through airlocks that are also used to transport personnel, clean material, and product. The flow appears adequate and the implementation of temporal segregation appears to be appropriate to mitigate cross contamination concerns.

HVAC Zones and Pressure Differentials

The applicant provided facility diagrams depicting how the Air Handling Units are zoned and the pressure differentials between rooms of the facility versus ambient pressure.

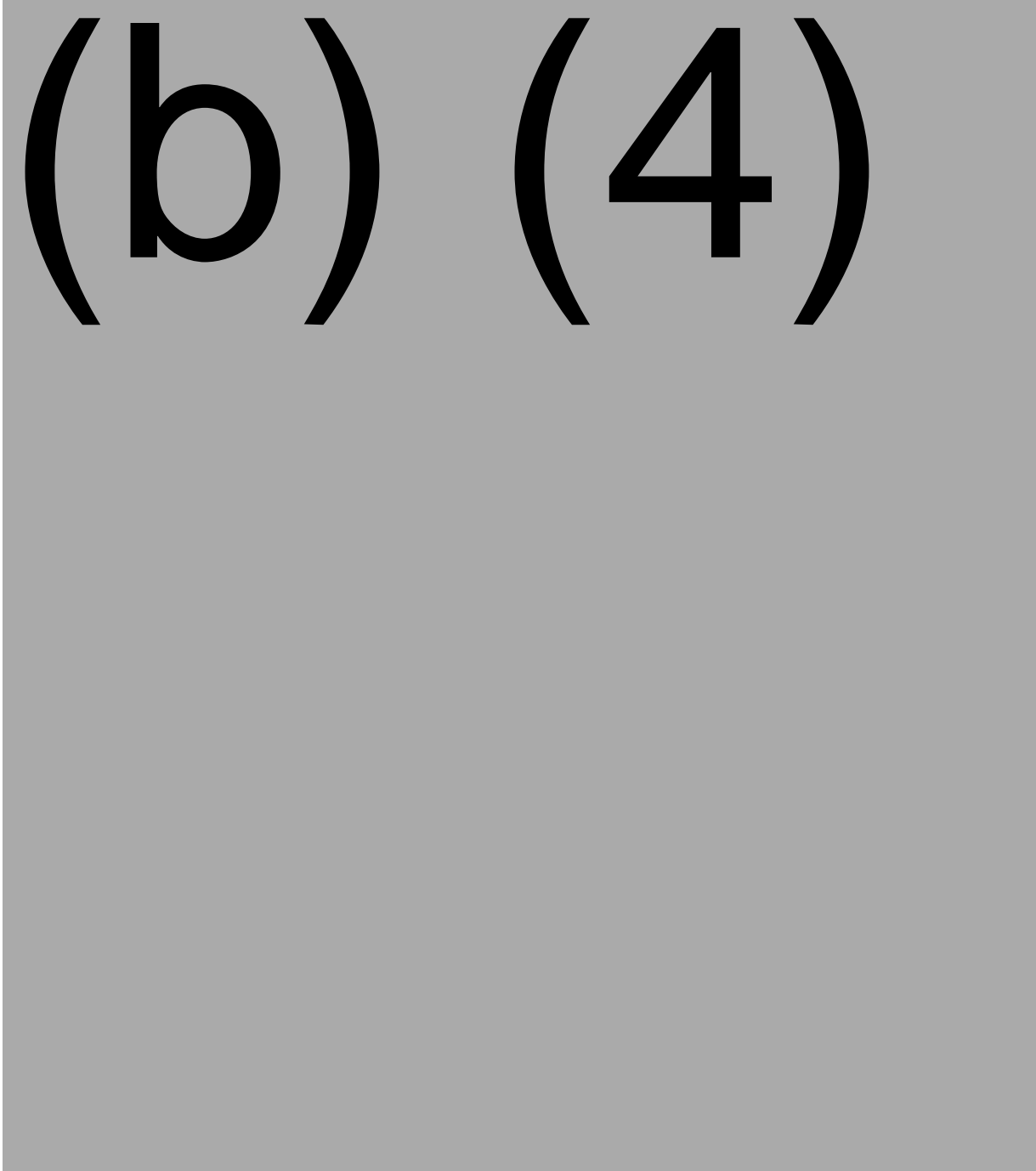


Figure 11 above is the zoning diagram for the HVAC system for the manufacturing facility. The facility's Air Handling Units (AHU) Zones are stratified by the activities conducted within the rooms in question. For example, each (b) (4) is served by

independent AHUs ((b) (4)) and the main corridor for (b) (4) processing is on a separate AHU ((b) (4)) from the main corridor that serves both (b) (4) DP ((b) (4)).

The Airflow Pressure Cascade for this facility utilizes bubbles in the airlocks to maintain containment. As one proceeds to areas of higher classification, the pressure relative to ambient increases.

Equipment and Equipment Flow:

Reviewer Comment:

The Flow of equipment was not submitted in the BLA. The applicant provided minimal information about the product contact and non-product contact equipment used for the production of V920 and is reviewed below.

In discussions with the Applicant prior to the Pre-License Inspection, it was made clear that full reports for all of the equipment at the facility would not be available to the inspection team. Prior to the execution of the inspection, the firm was asked to provide full reports for the following pieces of equipment:

(b) (4) Sterilization Autoclave
(b) (4) Filling and Stoppering
(b) (4) Capper
(b) (4) Depyrogenation Tunnel
(b) (4) Air Handler (b) (4)
(b) (4) Air Handler (b) (4)
(b) (4) Air Handler (b) (4)
(b) (4) Air Handler (b) (4)
(b) (4) Vial Labeler

It is important to note that when the inspection team arrived on site the requested full reports were not present for review. In their place, was found, summary reports for the equipment requested.

The Applicant was asked for full reports for the executed equipment qualifications in an Information Request received on April 2, 2019 and logged in as 125690/0.14. In this response, the firm instead provided summary reports for the requested information.

The reports provided for the equipment in this application lack details for the test method and raw results that would be found in full test reports.

The Preventative Maintenance and Routine Monitoring of critical equipment and utilities was reviewed during the Pre-License Inspection in (b) (4).

Multi-Use Indirect Product Contacting Equipment

All equipment in this facility is dedicated to the production of V920.

Cleaning of the Equipment and the Facility is not validated at this time. Verification of effectiveness of the current cleaning program is conducted after each cleaning.

All product contacting equipment used for manufacturing is single-use except for the following components of the fill line which has been classified by the Applicant to be in-direct product contact:

- Star Wheel
- Stopper Lock
- Needle Holders
- Stopper Bowl
- Stopper Hopper

(b) (4) Filling and Capping Lines

The Applicant provided a Performance Qualification Checklist for the (b) (4) Filling ((b) (4)) and Capping Lines ((b) (4)) used for this product.

Acceptance Criteria

- (b) (4) lot Stabilizer filled and capped (b) (4)
- Filled Volume – Samples taken at (b) (4) and every (b) (4) vials after
- (b) (4) Measurement – Samples Taken at the (b) (4)
- CCI – Samples taken at (b) (4) and every (b) (4) vials
- Effective Line Speed

Results

The checklist provided by the Applicant indicate that all testing passed the acceptance criteria and that the filling lines was qualified for use for batch sizes that range from (b) (4) vials.

Reviewer Comment:

No additional information for the qualification of this filling line was provided by the applicant. The information provided was found to be insufficient for a complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended

Summary reports detailing the validation of Clean Equipment Hold Times were reviewed upon inspection and established to be (b) (4) .

Two deviations were documented during the execution of this Performance Qualification and the assessment that there was no impact to the qualification was reviewed and determined to be appropriate.

Non-Product Contacting Equipment

Tables 15, 16, 17, and 18 below list the manufacturing equipment used in the different stages in the process. The Applicant submitted summaries of select equipment qualifications and are reviewed following the Table where the equipment is listed. All equipment in this facility is dedicated to the production of V920.

(b) (4)

Area	Equipment ID	Equipment
Drug Product	(b) (4)	Sterilization Autoclave
Drug Product		(b) (4) Tester
Drug Product		Depyrogenation Tunnel
Drug Product		2-8°C Cold room (b) (4)
Drug Product		2-8°C Cold room (b) (4)
Drug Product		Mobile UDAF
Drug Product		(b) (4)
Drug Product		(b) (4)
Drug Product		(b) (4)
Drug Product		(b) (4)
Drug Product		(b) (4)
Drug Product		(b) (4)

Sterilization Autoclave (b) (4)

This piece of equipment was reviewed in detail with the Applicant during the Pre-License Inspection. The loads were conducted in (b) (4) with minimum and maximum configurations for each load type. The loads are flexible within the constraints bracketed by the maximum and minimum runs. The thermocouples were placed in worst-case positions. The protocol was executed per (b) (4)

Loads Executed:

- (b) (4) Load
- Paper Load
- (b) (4) Load (b) (4)
- Filling Equipment Load

Results

All tests were verified to have passed the Acceptance Criteria. All bio indicators show no growth after a (b) (4) incubation period.

Reviewer Comment

The verification of the Autoclave Records is documented in the Establishment Inspection Report for this BLA.

(b) (4) Tester - (b) (4)

The applicant provided a summary PQ report for this piece of equipment. To qualify this filter integrity tester the applicant conducted (b) (4) test on the following filter/media combinations in (b) (4) :

(b) (4)

Results

All Filter types and Media combinations passed the Acceptance Criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Depyrogenation Tunnel - (b) (4)

The Depyrogenation Tunnel used for this manufacturing process was made by (b) (4) and was previously used by the (b) (4) group on the Applicant's Campus prior to be repurposed for use with this vaccine. This tunnel was then modified with a new airflow system and reconfigured to accommodate the (b) (4) vials used as the final container closure.

The temperature range of the tunnel is (b) (4). The temperature of the cool zone is monitored to yield vials that are less than (b) (4) upon exit. The cool zone of the tunnel is (b) (4), but it is (b) (4).

The Applicant provided a report for the Performance Qualification of the depyrogenation tunnel used in the facility that is dedicated to this product. It was confirmed that the applicant had successfully completed Installation Qualification and Operational Qualification for this piece of equipment prior to Performance Qualification. Tests performed in this qualification were run in (b) (4) and divided into the following groups of tests: (b) (4).

Acceptance Criteria

General Acceptance Criteria

(b) (4)

(b) (4)

Results

All tests run on the Depyrogeneration Tunnel passed the Acceptance Criteria

Deviations

Four deviations were reported in the execution of this protocol.

Reviewer Comment

A summary report for this piece of equipment was reviewed on inspection where the deviations were reviewed in detail. However, the reports that were provided on inspection were not the same reports included as part of this BLA. The inspection team

was provided with IOQ summary reports while the BLA contains a PQ summary report. Both sets of reports were reviewed for completeness.

The deviations were reviewed in the PQ report submitted to this BLA, and it was determined that there was no impact to the qualification of this piece of equipment.

The Endotoxin Indicator that was used in this qualification was not defined nor were any details provided regarding the Endotoxin recovery studies.

The qualification report indicates that the differential pressures defined in this protocol was to be (b) (4). A justification for the (b) (4) was not described in the report and does not appear to be adequate to prevent cross contamination.

The information provided was found to be insufficient for a complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended

2 to 8°C Cold Rooms (b) (4)

The Applicant provided summary PQ reports for (b) (4). These cold rooms are reviewed collectively below. To qualify each room the applicant conducted (b) (4) tests on each unit, (b) (4).

The cold room (b) (4) was filled with the expected Maximum Liquid Volume of (b) (4).

The cold room (b) (4) was filled with the expected Maximum Liquid Volume of (b) (4) vials.

Acceptance Criteria

(b) (4)

Results

The reports indicate that the results of these tests met the Acceptance criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Mobile UDAF - (b) (4)

The Applicant provided a summary report for the qualification of the Mobile UDAF. To qualify this piece of equipment, a series of (b) (4) tests were run: (b) (4)

Results

All functional IQ and OQ tests for the Mobile UDAF were confirmed to have passed the acceptance criteria.

Deviations

Three minor deviations were reported in the execution of this protocol. The deviations were reviewed, and it was determined that there was no impact to the qualification of this piece of equipment.

Reviewer Comment:

Qualification of this piece of equipment was in progress at the time of the Pre-License Inspection and therefore it was not possible to document the review in the EIR.

The information provided was found to be insufficient for a complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended

(b) (4)

Reports for all the (b) (4) used to Manufacture Drug Product (b) (4) are reviewed collectively below. In the qualification of each (b) (4), the applicant conducted a series of (b) (4) tests:

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria except for Active Air Sampling.

It was reported for each of the (b) (4) tested, the (b) (4) test for (b) (4) Acceptance Criteria was not met.

Deviations

Three deviations were reported in the execution of this protocol. Two of the deviations were documentation errors classified as minor by the applicant. The third deviation as the failure of the (b) (4) which the Applicant designated as minor.

Reviewer Comment

The deviations were reviewed, and it was determined that the failure of the (b) (4) does impact the qualification status of this piece of equipment. The information provided was found to be insufficient for a complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended.

(b) (4)

Reports for all the (b) (4) used to Manufacture Drug Product (b) (4) are reviewed collectively below. In the qualification of each (b) (4), the applicant conducted a series of (b) (4) tests: (b) (4)

Acceptance Criteria

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria

Deviations

Two deviations were reported in the execution of this protocol. The Applicant classified them as minor with no justification.

Reviewer Comment

The deviations were reviewed, and it was determined that the failure of the (b) (4) during the (b) (4) test may impact the qualification of this piece of equipment. The information provided was found to be insufficient for a

complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended.

Table 17 – Labeling and Packaging Equipment

Area	Equipment ID	Equipment
Label & Packaging	(b) (4)	- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer
Label & Packaging		- 70 Freezer

- 70°C Freezers – Labeling and Packaging Equipment

Reports for Freezers (b) (4)

are reviewed collectively below.

The applicant provided a summary PQ report for each of the freezers. All of the freezers are in Room (b) (4) (Freezer Farm) on the facility map. To qualify these freezers the applicant conducted (b) (4) tests on each unit, (b) (4).

The freezers were filled with the expected Maximum Liquid Volume of (b) (4).

Acceptance Criteria

(b) (4)

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Table 18 – Labeling and Packaging Equipment

Area	Equipment ID	Equipment
Label & Packaging	(b) (4)	2-8°C Refrigerator
Label & Packaging		Cell Bank Storage (b) (4)
Label & Packaging		Carton Feeder
Label & Packaging		Checkweigher including labeler
Label & Packaging		Conveyor Installation
Label & Packaging		(b) (4)
Label & Packaging		Literature Feeder
Label & Packaging		Vial Labeler
Label & Packaging		Visual Inspection Booth
Label & Packaging		Visual Inspection Booth
Label & Packaging		Visual Inspection Booth
Label & Packaging		Visual Inspection Booth

2 - 8°C Cold Room – (b) (4) – DP Filled Vial Storage

The applicant provided a summary PQ report for the Cold Room (room (b) (4)) which includes (b) (4) tests on this unit, (b) (4) .

The freezer was filled with the expected Maximum Liquid Volume of (b) (4) of filled DP vials.

Acceptance Criteria

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Cell Bank Storage (b) (4)

The Applicant provided a summary PQ report for this piece of equipment. This Cell Bank Storage System is used to house the (b) (4) manufacturing. To qualify this storage system the applicant conducted (b) (4) tests on this unit: (b) (4)

Acceptance Criteria

(b) (4)

Results

The Applicant stated that all tests passed the acceptance criteria

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

V920 Labeling and Packaging Equipment - (b) (4)

The applicant provided a summary PQ report for the equipment responsible for packaging and labeling of product at the manufacturing facility. The summary report indicates that all qualification activities: IQ, OQ and PQ have been successfully completed and met the established acceptance criteria.

Reviewer Comment

The total amount of information provided for these pieces of equipment was a single summary report that was 13 pages long. The report consisted of high level tables that listed the key elements of the equipment and provided a check mark to indicate that the activity was completed. No information was provided to indicate how any of the tests were conducted and a review of the appropriateness of the qualification tests is not possible. The information provided was found to be insufficient for a complete review of the qualification of the equipment and an additional information request or follow up at the next inspection is recommended.

Visual Inspection Booths - (b) (4)

Reports for Inspection Booths (b) (4)

were provided in a single summary report by the Applicant and they are reviewed collectively below. A single operation test was executed for the booths: 'OQ Tests Register'.

Acceptance Criteria

OQ Tests Register – Confirm the operational functionality of the equipment.

Results

The checklist indicated that the acceptance criteria were met.

Deviations

Two deviations were noted in the execution of the qualification

Reviewer Comment:

The two deviations were reviewed, and it was determined that they do not impact the qualification of this equipment.

Utilities

Tables 19 and 20 below list the critical supporting utilities for this facility stratified by the stage in the process in which it is used. Following each table is a review of the qualification summaries provided by the applicant.

All utilities in this facility is dedicated to the production of V920.

Table 19 – Critical Utilities to support the production of V920

Utilities	(b) (4)	Clean Steam Generator
Utilities	(b) (4)	Clean Steam Distribution
Utilities	(b) (4)	CO ₂ Supply and Distribution
Utilities	(b) (4)	Compressed Clean Air

Clean Steam Generator and Steam Distribution System - (b) (4)

The applicant provided a summary report for the qualification of the Clean Steam Generator and the Clean Steam Distribution System. These two systems are reviewed collectively below. (b) (4) types of testing, (b) (4) testing was conducted at access points for this system in the facility.

Reviewer Comment:

The Clean Steam Generator and Clean Steam Distribution system were reviewed as part of the PLI that was conducted in (b) (4) and documented in the EIR. No objectional conditions were noted in the review of this material on inspection.

(b) (4)

(b) (4)

Acceptance Criteria

Table 20 below outlines the Acceptance Criteria for the tests conducted to support the qualification of the clean steam utility.

Table 20 - Acceptance Criteria for the Clean Steam System

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria.

Deviations

No deviations were noted in the execution of these Performance Qualification tests

Monitoring

(b) (4) are checked (b) (4) with all other parameters checked on an (b) (4) basis

CO₂ Supply and Distribution System - (b) (4)

The applicant provided a summary report for the qualification of the CO₂ Supply and Distribution System. (b) (4) types of testing were conducted to qualify this utility: (b) (4)

(b) (4)

(b) (4)

Acceptance Criteria

Table 21 below lists the acceptance criteria for the (b) (4) Test

Table 21 – CO₂ (b) (4) Tests

(b) (4)

(b) (4)

Results

The reports indicate that the results of these tests met the Acceptance criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Monitoring

(b) (4) will be checked every (b) (4) months with (b) (4) checked on an (b) (4) basis

Compressed Clean Air - (b) (4)

The applicant provided a summary report for the qualification of the Compressed Clean Air Supply and Distribution System. (b) (4) types of testing were conducted to qualify this utility: (b) (4).

(b) (4)

(b) (4)

Results

The reports indicate that the results of these tests met the acceptance criteria.

Deviations

No Deviations were noted in the execution of these Performance Qualification tests

Monitoring

(b) (4) will be checked every (b) (4) with (b) (4) checked on an (b) (4) basis.

Reviewer Comment:

The Preventative Maintenance and Routine Monitoring of critical equipment and utilities was reviewed during the Pre-License Inspection in (b) (4) and documented in the EIR.

HVAC System

Room classifications that required qualification included Grade (b) (4), Grade (b) (4), Grade (b) (4), and Grade (b) (4). The Applicant described a very general overview of how they qualified the classified areas, and the methods used (b) (4). The Applicant stated that they performed both static and dynamic monitoring of the classified areas with the additional details listed in Table 22 below:

(b) (4)

The Applicant stated that for samples with alert or action level (b) (4). The Applicant listed the acceptance criteria for the room performance qualifications in Tables 23 and 24 below:

Table 23 – HVAC Specifications for (b) (4)

(b) (4)

The Applicant presented the environmental monitoring qualification data. The areas were qualified in separate phases with a separate PQ protocol for each area. The PQ results are grouped below according to the air handling unit (AHU) that serves each area. The PQ activities were conducted from (b) (4).

Routine Environmental Monitoring

The number, location, and type of test sites which have been tested routinely were based on the results of the initial qualification as well as established criteria outlined in approved procedures. The routine test sites comprise a subset of the initial qualification test sites. At least (b) (4) are routinely tested in each room.

For Grade (b) (4) and Grade (b) (4) rooms routine testing has been performed at least (b) (4). For Grade (b) (4) and Grade (b) (4) rooms routine testing has been performed (b) (4). For routine monitoring, the alert and action levels have been the same as the alert and action levels presented for the initial qualification.

Process Monitoring

Batch related environmental monitoring is performed as part of the batch documentation and must be evaluated during batch review. Samples reflect the risks with respect to contamination of the product as per approved procedures. Batch related monitoring consists of:

(b) (4)

(b) (4)

Table 25 – HVAC for the Manufacturing Suite

Production Stage	Equipment ID	Responsible Area	Qualification	System Outdoor Air Portion
(b) (4)				
Drug Product	(b) (4)	Air Handler (b) (4), DP Filling & Stoppering (Room (b) (4) and adjacent PALs & MALs)	Pass	Re-Circulation – (b) (4) Fresh Air

Production Stage	Equipment ID	Responsible Area	Qualification	System Outdoor Air Portion
V920	(b) (4)	Air Handler (b) (4) Corridor (Rooms (b) (4))	Pass	Re-Circulation – (b) (4) Fresh Air
Label & Packaging	(b) (4)	Air Handler (b) (4) (Rooms (b) (4))	Pass	Once Through – (b) (4) Fresh Air
V920	(b) (4)	Air Handler (b) (4), Media Preparation (Room (b) (4), and adjacent PAL & MAL)	Pass	Re-Circulation – (b) (4) Fresh Air
Drug Product	(b) (4)	Air Handler (b) (4), Formulation (Room (b) (4), and adjacent PAL & MAL)	Pass	Re-Circulation – (b) (4) Fresh Air

Computer Systems

The computer systems used to support the manufacture of the proposed product are separated into two component systems: Environmental Monitoring (EMS) and Programmable Logic Controller (PLC)/ Human Machine Interface (HMI) on local equipment. Table 26 below breaks down the two groups and lists the equipment controlled by the two systems:

Table 26 – Automation System Summary

Component	Description
Environmental Monitoring System EMS	Monitors the following for the (b) (4), DP, L& P process <ul style="list-style-type: none"> • (b) (4) storage temperature • -70°C freezer temperature • Room differential pressures humidity and temperature • Particle monitoring

Programmable Logic Controller PLC Human Machine Interface HMI on local equipment	Controls the following for the (b) (4), DP, L&P process <ul style="list-style-type: none"> • Autoclave recipes • (b) (4) testing recipes • Tube welder recipes • Depyrogenation tunnel recipes • Filler recipes • Capper recipe • (b) (4) measurement • Labeling and Packaging recipes • (b) (4) recipes
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EMS Validation

Automation development for the EMS was implemented and validated using the system-lifecycle method approach to computer-system validation. The EMS qualification (IQ and OQ) was performed in (b) (4) Stages: (b) (4) systems, Drug Product systems, and Labeling and Packaging systems. Labeling and Packaging systems will be qualified prior to use.

PLC/HMI Validation

The PLC/HMI systems do not have separate automation qualification and any testing for automation features was integrated in to the equipment's associated IQ/OQ testing.

Automation Change Control Process

The Applicant confirmed that automation changes performed after a system is qualified are managed in accordance with approved Standard Operating Procedures.

Cross Contamination

Engineering and Process Controls

The renovated V920 production facility provides dedicated manufacturing capability for Bulk Drug Substance, Drug Product, packaging, and inspection. The V920 facility is independent from other manufacturing areas at the (b) (4) site with full segregation between (b) (4). Cross-flow of personnel and materials between (b) (4) production areas are procedurally controlled to ensure segregation; personnel, and material. This segregation was verified during the Pre-License Inspection.

Gowning

Personnel are trained in gowning procedures and are required to follow instructions outlined in approved standard operating procedures prior to entering the manufacturing suites. Gowning requirements increase as personnel progress into higher classifications of the facility.

required to wear (b) (4) Personnel are to de-

gown in the appropriate areas following the order of removing garments indicated in SOPs.

Cleaning and Disinfection

Facility cleaning/disinfection is carried out systematically from areas of (b) (4) classification (Grade (b) (4)). Within a room, cleaning starts from the (b) (4) and ends with the (b) (4). Sterile cleaning agents and disinfectants are used in Class (b) (4) rooms. Low-particle, disposable cleaning materials are used (mop covers, cloths, etc.). Each production area uses separate cleaning and disinfection utensils.

Clean of the facility is not yet validated, but cleaning verification is conducted to ensure the environment is controlled.

Single Use Equipment

Single use equipment is used for production for all product contacting components.

Waste

All process waste generated in the production facility is inactivated prior to removal from the facility. All solid waste generated in the processing suites is placed into containers prior to removal from processing suites via material airlocks.

Security

The V920 production facility has a separate and secure personnel entrance with controlled badge access. The gowning area and lockers for V920 are located inside the facility and are separate from other areas of the site and secured.

Open Manipulation Steps

Open Manipulation steps are performed in Grade ^(b)₍₄₎ Biological Safety Cabinets.

(b) (4)

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(b) (4)

(b) (4)

Aseptic Process Simulation – Drug Product

The V920 Drug Product (DP) process consists of (b) (4), Formulation, Filling/Capping, Inspection and Packaging prior to the finished DP vials being frozen for distribution. The Formulation and Filling/Capping steps are within the sterile boundary.

Interventions

The protocol defined the quantity and relative risk of each intervention so that the operators schedule would ensure that they performed a high and medium risk intervention to meet the initial qualifications to perform these interventions in future commercial production.

Media

(b) (4) was substituted for routine process media and product in the process simulation

Setup

During Formulation process simulation manufacture, (b) (4) was transferred from sterile (b) (4) into the (b) (4) in the same manner as the commercial process. This included (b) (4) to represent the Formulation Stabilizer and at least (b) (4) to represent the (b) (4). The transferred media was (b) (4) in the (b) (4) to ensure all unique product contact surfaces were contacted and the media was held to represent the target sterile hold time for the commercial process. The (b) (4) was then transferred into the filling room and aseptically connected to the line during setup.

Acceptance Criteria

(b) (4)

Formulation (b) (4)	(b) (4)	(b) (4)	Satisfactory, Valid (No Growth)	Satisfactory, Valid (Growth)
Straight Through Fill (b) (4)	(b) (4)	(b) (4)	Satisfactory, Valid (No Growth)	Satisfactory, Valid (Growth)
Recovery Fill (b) (4)	(b) (4)	(b) (4)	Satisfactory, Valid (No Growth)	Satisfactory, Valid (Growth)
Recovery Fill (b) (4)	(b) (4)	(b) (4)	Satisfactory, Valid (No Growth)	Satisfactory, Valid (Growth)

Filling Duration

The maximum duration demonstrated was shorter than the target duration of (b) (4). Commercial production will be limited to (b) (4) until future process simulations are conducted to extend this duration.

Table 31 – Filling Duration

Batch Number	Target Processing Duration	Actual Processing Duration
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)

Environmental Monitoring

Results from routine sampling and batch specific sampling were reviewed by Quality Assurance and were conforming to expected limits. There were (b) (4) total Microbial Out Of Specification (M-OOS) events that occurred during process simulation processing days. These investigations have been closed and the applicant claims that there is no impact to the validity of the process simulation series.

Reviewer Comment:

The primary review of the deviations observed in the Drug Product process simulation was executed during the Pre-License Inspection in (b) (4). The Applicant was

made aware that there appeared to be a lack of experience in manufacturing and a lack of follow through in the quality oversight of the Drug Product process simulation.

The most critical issues with respect to this process simulation, vial accountability, will be discussed in the Overall Assessment box on the next page.

Other eCTD Modules

Module 1

A. Environmental Assessment or Claim of Categorical Exclusion

The Applicant provided an Environmental Assessment for this BLA.

B. Labeling Review

Full Prescribing Information (PI):