



Food and Drug Administration  
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**To:** Administrative File: STN 125597/0  
  
Goutam Sen, Committee Chair, CBER/OVRR/DVRPA  
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**CC:** Review Committee Members

**From:** Christine Harman, Chemist, CMC/Facility Reviewer/Inspector, CBER/OCBQ/DMPQ/BI

**Through:** Carolyn Renshaw, Branch Chief, CBER/OCBQ/DMPQ/BI

**Through:** John Eltermann, Division Director, CBER/OCBQ/DMPQ

**Applicant:** PaxVax, Bermuda Ltd.

**Product:** Cholera Vaccine, Live Oral (Powder for suspension)  
Tradename: Vaxchora®

**Indication:** For active immunization of adults against disease caused by *V. cholera* serogroup O1

**Subject:** Addendum Review: Review of additional information provided in amendments and inspectional follow up not included in the primary review for BLA STN125597/0 covering review of DMPQ aspects

**Due Date:** June 15, 2015

#### **RECOMMENDATION**

Based on the review of the information provided in the original submission, amendments, and the FDA Form 483 response from (b) (4), approval is recommended with an inspectional consideration at the next biennial inspection. The inspectional consideration is part of the standard scope of inspection; please note that DMPQ is not requesting documentation to be submitted to CBER as evidence of completion. Request for consideration is indicated as follows:

- (b) (4), (b) (5), (b) (7)(E)

#### **EXECUTIVE SUMMARY**

This BLA from PaxVax was received by the Agency on October 16, 2015 as an electronic submission in eCTD format (0000). This BLA was granted priority review status; therefore, is reviewed under the 6 month review timeframe. This review is an addendum to the primary review and covers the firm's

responses to the three DMPQ information requests issued during the review, in addition to, the resolution of the inspectional follow ups noted in the primary review.

## **REVIEW NARRATIVE**

During the BLA review, three information requests were issued to the firm. The IRs issued and the firm's responses are indicated as follows:

**IR#1 sent 1/13/16-** Firm's response was received 2/16/16 as amendment 6 (eCTD 0006)

- 1. For the equipment used in the upstream manufacturing operations at (b) (4), please provide a listing of all major product contact equipment used in the manufacturing of the intermediate bulk drug substance and indicate if the equipment is shared or dedicated and how this equipment is cleaned (i.e. (b) (4))**

Firm's response: The firm provided the requested information including a comprehensive listing of equipment used in the manufacturing of IBDS at (b) (4) indicating if equipment is shared and/or dedicated, how the equipment is used, how equipment is cleaned/sterilized, and a reference to the IQ/OQ and PQ (refer to Table 1 in the APPENDIX for details). The only product contact shared piece of equipment includes the (b) (4) fermenter. All other shared equipment including the (b) (4), Biosafety Cabinet, and freeze dryer are indicated to have no product contact. The firm noted that the freeze dryer is listed (b) (4)

(Refer to Figure 1 in APPENDIX). The fermenter and the freeze dryer are cleaned (b) (4) while all other listed equipment are either indicated as single use such as the (b) (4) or are manually cleaned that includes the (b) (4) and the BioSafety Cabinet.

*Reviewer Comments:* For lyophilization step, the firm uses (b) (4)

the firm's claim of the freeze dryer being non-product contact in this specific process for used for Vaxchora<sup>®</sup> is adequately justified. The firm has adequately responded to this IR item and no further action is required. The table provided (Table 1 in APPENDIX) listing the equipment and reference to the corresponding qualification reports, indicates that a qualification was not performed for the (b) (4), which is a (b) (4). This (b) (4) was observed in operation on inspection and is used with (b) (4)

An official IOQ was not performed for the disposable unit; however, a qualification of the (b) (4) that is used with the (b) (4), was performed for verification of the (b) (4). Additionally, the (b) (4) with a certificate of analysis, and no cleaning validation is performed as this (b) (4) are (b) (4). Please refer to section "Facilities and Equipment" section of EIR for additional details.

- 2. Please provide the summaries of the qualifications (OQ and PQ) for the HVAC system, in addition to major equipment (fermenters, freeze dryer, and BSCs) used in the manufacturing of intermediate bulk drug substance at (b) (4).**

Firm's Response: The firm provided summaries of the validation reports (IOQs) for the fermentor, the (b) (4) used to clean fermentor, (b) (4), BioSafety Cabinet, freeze dryer, and validation reports for the HVAC system. Additionally, the firm indicated that (b) (4) performs a Periodic Validation Review (PVR), if applicable, to assess the validated

status incorporating any changes to the area, system or piece of equipment as well as deviations, calibration records, preventive and corrective maintenance records and historical validation data. The reports provided are summarized as follows:

**IOQ Freeze Dryer: RAP-XLP-4500.MF Ver. 001**

This report summarizes the results of the IQ/OQ of the (b) (4) freeze dryer (#MF-LP-4500). Testing for IQ and OQ were performed with results reported as either “Pass” (test passed, without deviations), “Fail” (test did NOT pass) and “Accepted”(test passed, with minor deviations (described and justified in the report)

The IQ testing included the following testing: (b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

[Redacted]

(b) (4)

*Reviewer Comments:* These reports were also reviewed on the inspection performed at (b) (4) and no objectionable observations were noted. Please refer to section "Facilities and Equipment" (specifically under description of equipment qualification) of the EIR for additional details of the the discussion of the OQ and re-qualification of the freeze dryer.

**IOQ Fermenter: RAP-XFR-4920.MF Ver.001**

This report provides the results of an installation and operational qualification performed on the (b) (4) Fermenter. (b) (4)

(b) (4)

All tests were indicated as "Pass" or "Accepted". No failures were indicated. During the IOQ there were four deviations noted and all were indicated as minor and were appropriately resolved.

Additionally to this report the firm provided, PVR-XFR-4920.MF Ver 001, which is a Periodic Validation Review to support the validation status of the (b) (4) fermenter. This report documents a review (completed 01 OCT 2013) of a minimum of five years of historical data and includes a listing and description of the following: changes to the fermenter since 2006, occurrence of deviations since 2008, maintenance history (including preventative maintenance) since 2006, calibration history since 2006, history of use since 2007 and summary of all validation activities since initial validation performed in Jan 2007. The PVR reported and discussed fourteen deviations of which are associated with functionality or design and/or mechanical breakdown, due to wear and tear incidents. No issues were noted in regards preventative maintenance, corrective maintenance, or calibration. The report concludes that fermenter remains in validated state and is fit for use. The performance qualification of the fermenter is covered under the process validation runs previously reviewed in the primary review memo.

**IOQ HVAC:** The following reports were provided to support the qualification of the HVAC system:

RAP-XHV-4025.TS/01, "Validation Report (IQ) for the HVAC AHU- (b) (4) (TS-HV-4025)- Completed 07 APR 2006

RAP-XHV-4025.TS/02, "Validation Report (OQ) for the HVAC AHU- (b) (4) (TS-HV-4025)- Completed

PVR-XHV-0001.TS, "Periodic Validation Review Report for the HVAC Systems for the (b) (4) Floor Facility

PVR-XHV-0001.TS, "Periodic Validation Review Report for the HVAC Systems for the (b) (4) Floor Facility

The reports RAP-XHV-4025.TS/01 and RAP-XHV-4025.TS/02 document the results of the installation and operational qualification performed in April and May of 2006 for the HVAC AHU (b) (4) (ID# TS-HV-4025) installed in room (b) (4) area.

Testing performed for the IQ included verification of the following: (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

The firm also included the result of the Periodic Validation Review reports for the HVAC systems on the (b) (4), performed 26SEP2013 to 03NOV2013. These reports include a review and discussion of the deviations that occurred during the initial IQ and OQ, in addition to documenting and reviewing changes to the system, calibration, preventative maintenance, and work/repairs to the system.

The IOQ reports for the Shaker (RAP-XIN-4042.MF) and for the BioSafety Cabinet (RAP-XBC-(b) (4).MF/01(IQ) and RAP-XBC-(b) (4).MF/01 (OQ). Please see *Reviewer Comments* in regards to the review of these documents.

**IOQ BioSafety Cabinet (BSC):** The IOQ reports for BSCs (b) (4) were provided and included RAP-XBC-(b) (4).MF/01 and RAP-XBC-(b) (4).MF/01. These reports summarize the results of installation and operational qualifications that was performed for the BSCs.

(b) (4)

(b) (4)

(b) (4)

*Reviewer Comments:* As with the Freeze dryer, the IOQ of the fermenter, (b) (4), in addition to the IOQ for HVAC were reviewed on inspection. Additionally, the certifications and environmental monitoring data for the Biosafety Cabinets were reviewed inspection. No objectionable observations were noted. Please refer to section “Facilities and Equipment System” of the EIR for additional details.

**3. Please provide the cleaning validations for major product contact equipment (fermenters, freeze dryer etc.) used at (b) (4) for the manufacturing of intermediate bulk drug substance.**

Firm’s Response: The firm indicated that the only two major pieces of equipment that come into contact during the IBDS manufacturing are the (b) (4) and the fermenter. The (b) (4) is single use and is discarded after manufacturing, thus there is no cleaning involved. The firm indicated that the fermenter is (b) (4) and provided the cleaning validation reports RAP-XFR-4920.MF/12 (b) (4) and RAP-XFR-4920.MF/16 (b) (4). These reports are summarized as follows:

(b) (4)

(b) (4)

(b) (4)

All other

acceptance criteria were met.

*Reviewer Comments:* These reports were also reviewed and discussed with the firm on inspection at (b) (4) and no objectionable observations were noted. Please refer to section "Facilities and Equipment System" in the EIR for the (b) (4) inspection, specifically under subsection "Equipment Cleaning Validation" for additional information. Firm has adequately addressed this item; no further action needed.

**IR#2 sent 3/1/16-** Firm's response was received 3/8/16 as Amendment 18 (eCTD 0018).

- 1. Please provide a summary report of "deviation 01" noted in footnote of Tables 5 (pg.15) and 9 (pg.25) provided in VPR-154, "Interim Report for the cleaning validation for PaxVax Building Process Equipment". This summary should include details for the exclusion of the (b) (4) from the cleaning load during the process validation.**

Firm's Response: The firm indicated that during the blending of the vaccine conformance lots, (b) (4) were used instead of the (b) (4) which were originally planned to be used per validation. Since the (b) (4) are disposable, no cleaning was required. The (b) (4) were only used during process validation and will not be used during commercial manufacturing. In regards to the (b) (4) and the (b) (4) the firm indicated that the (b) (4) is not utilized or required; however, the (b) (4) is used and the components consist of the (b) (4). Since there was no blending process performed as part of the buffer manufacturing process, the (b) (4) was not utilized. Based on the buffer process validation, there was no requirement for (b) (4) out of the (b) (4) and therefore, the (b) (4) were not required. Since the (b) (4) were not utilized, no cleaning of those components were required.

*Reviewer Comments:* The firm adequately responded to this IR item; no further action required.

**IR#3 sent 3/11/16-** Firm's response was received 3/23/16 as Amendment 27 (eCTD 0027).

- 1. In regards to the acceptance criteria for the cleaning validation of the equipment used for manufacturing of the Bulk Drug Substance (BDS) and Drug Product (DP) (indicated in Table 1 of VPR-154), the (b) (4) acceptance criteria (b) (4) (criteria for the (b) (4) to (b) (4) for (b) (4) Intermediate Bulk Container (IBC) and filler removable parts (equipment at later steps in process). The (b) (4) acceptance criteria should be (b) (4) as the process proceeds from the (b) (4) to the Filling steps. Please indicate why the (b) (4) acceptance criteria for equipment cleaning (b) (4) with the progression of the manufacturing steps.**

Firm's Response: The firm provided a description of the calculations that are used to derive the (b) (4) acceptance criteria for the equipment cleaning, and indicated that the calculation is based on the following: 1) (b) (4)

. Based on the

assumptions documented in the response and that are described in the VP-154 protocol (provided with this response), a residual limit for each equipment group in units (b) (4) was determined. The following table was provided to demonstrate how the (b) (4) acceptance criteria for the (b) (4) and the (b) (4) was derived:

(b) (4)

*Reviewer Comments:* The firm's detailed approach and basis for determining the (b) (4) acceptance criteria is reasonable and acceptable, thus firm has adequately addressed this IR item; no further action required.

The complete listing of the inspectional follow-up issues noted in the primary review for PaxVax and for (b) (4), in addition to the resolution of these items are indicated as follows:

(b) (4) (Inspection performed (b) (4), FDA Form 483 issued)

1. **Perform an extensive review of the Cleaning Policy, Site Cleaning Validation Master Plan, the Product Change Over Procedure(s) and cleaning SOP during the inspection. Also, determine if disinfectant studies were performed for the cleaning agents used in the facility and for the equipment.**

*Reviewer Comments:* During inspection, the cleaning policy, site cleaning validation master plan and product change over procedures including facility cleaning SOPs were reviewed and no objectionable observations were noted. Please refer to sections "Facilities and Equipment System" of EIR specifically under sub-sections "Equipment Cleaning Validation" and "Facility Cleaning" for details of the review.

2. **Review the individual IQ/OQ/PQ and requalification documentation of critical pieces of equipment used in the manufacturing process at (b) (4). In addition, review the cleaning of equipment that is product contact.**

*Reviewer Comments:* During the inspection, the IQ/OQ/PQ were reviewed in detail for the fermenter and the (b) (4) freeze dryer.

3. **Review the cleaning validations for major equipment in addition, review all cleaning and maintenance logs for major pieces of equipment.**



*Reviewer Comments:* During the inspection, the cleaning validations of the fermenter and freeze dryer were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section “Facilities and Equipment System” of the EIR, specifically in subsection “Equipment Cleaning Validation” for details.

**4. Review documentation in relation to the qualification of the HVAC system as this information was not included in the BLA submission.**

*Reviewer Comments:* During the inspection, the qualification of the HVAC system and environmental monitoring data was reviewed. No objectionable observations were noted. Please refer to section “Facilities and Equipment System” of the EIR for details of the review.

**5. Review the Qualification documentation for the water systems as this information was not provided in the submission.**

*Reviewer Comments:* During the inspection, the IOQ and monitoring of the water system, in addition to results of water testing was reviewed. No objectionable observations were noted. Please refer to section “Facilities and Equipment System” of the EIR for details of the review.

**6. Review the procedures and acceptance criteria included in the Environmental Monitoring Program as this information was not provided in the BLA.**

*Reviewer Comments:* During the inspection, the Environmental Monitoring Program was reviewed. No objectionable observations were noted. Please refer to section “Facilities and Equipment System” of the EIR for details of the review.

**7. Check the decontamination procedures and use of the (b) (4) system to (b) (4). Ask the firm, if the (b) (4) system is disposable and/or product dedicated and if dedicated how its cleaned for reuse.**

*Reviewer Comments:* During the inspection, the use of the (b) (4) system was observed and the firm confirmed that the system which includes the (b) (4). A brief description of the use of this system is noted in the EIR from the (b) (4) inspection, (b) (4). Please refer to the “Production System” section of the EIR, specifically under subsection “Process Operations Observed”.

**8. Have the firm provide further clarifications in regards to the (b) (4) test which is designed to identify the presence of organisms other than *Vibrio cholera*. Additionally, follow up on all deviations occurring during lyophilization step.**

*Reviewer Comments:* As the inspection time was limited, this item was not covered on the inspection. Additionally, this item can be covered as review issue as it related to an assay used for determining product purity, therefore, this item was deferred to product office and not covered on inspection.

**9. Review the shipping validation protocols and reports for the storage of IBDS at (b) (4) shipment of IBDS from (b) (4) to PaxVax, and the storage of IBDS at PaxVax. In addition, review the qualification reports for the equipment and (b) (4) used in the shipping validation as this documentation was not provided in the BLA submission.**

*Reviewer Comments:* During the inspection, the shipping validation of the transport of IBDS to PaxVax for further manufacturing to drug product was discussed with the firm. The firm noted that according to the Quality Agreement, PaxVax is responsible for performing the shipping validation and (b) (4) packages the IBDS and ships the IBDS as defined by PaxVax. No objectable observations noted. Please refer to section “Materials System” of the EIR, specifically under subsection “Shipping Validation” for details.

1. **Inspectional Follow-Up for Pax Vax:** Check on inspection, the gowning locations (i.e. is there gowning in the airlock Room (b) (4)) for entering into the MBU area and determine how many entries there are into this area as the firm indicated there was only one; however schematics provided indicate there are two. Also, follow up with the exiting to the air shower and how this area (room (b) (4)) is segregated from the gowning area (room (b) (4)).

*Reviewer Comments:* During the inspection, the personnel flow in the MBU was reviewed and discussed with the firm during the walk through of the facility. No objectionable observations were noted. Please refer to section "Manufacturing/Facilities Overview" in the PaxVax EIR, specifically subsection describing the walk thru and description of (b) (4).

2. **Inspectional Follow-Up for Pax Vax:** Check to determine if there is appropriate segregation of the goods stored in storage room (b) (4), in particular, separation of incoming goods to be tested, released goods and buffer filled sachets.

*Reviewer Comments:* During the inspection, the storage of materials including raw materials and finished goods was reviewed and discussed with the firm during the walk through of the facility. There is appropriate segregation of goods, using distinct labeling and separate shelving used in room (b) (4), which is only used for storage of raw materials, labeled as released or quarantined, with exception of the buffer drug product sachets. The buffer drug product sachets, which are stored at (b) (4) are stored in clearly marked (b) (4) within storage room (b) (4). The vaccine drug product sachets are stored in a separate storage room, that is maintained at - (b) (4). No objectionable observations were noted in regards to the storage of raw materials and/or finished goods. Please refer to section "Manufacturing/Facilities Overview" in the PaxVax EIR, specifically subsection describing the walk thru and description of Storage room (b) (4) and (b) (4).

3. **Inspectional Follow-Up for Pax Vax:** Check on the waste flows from the production area as the firm indicated only one path from the production area via Room (b) (4); however, waste flow schematic shows that waste is also removed via air shower through gowning room. The firm should indicate the type of waste that follows these (b) (4) paths from the production area.

*Reviewer Comments:* During the inspection, the waste flows and materials flows were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Manufacturing and Facilities Overview" of PaxVax EIR for details, specifically, subsection describing the walk thru and description of (b) (4).

4. **Inspectional Follow-Up for Pax Vax:** Check and review the IQ/OQ/PQ documentation of all major equipment used in the manufacturing operations at Pax Vax, Inc. facility as this information was not provided in the BLA.

*Reviewer Comments:* During the inspection, the IQ/OQ/PQ for the (b) (4) Integrity Tester were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Facilities and Equipment" of PaxVax EIR for details.

5. **Review all validation protocols and results for cleaning and clean hold validation for all equipment, specifically, the (b) (4) removable parts as the cleaning validation for these pieces of equipment have not yet been completed.**

*Reviewer Comments:* During the inspection, the cleaning validation for equipment with focus on the (b) (4) was reviewed and discussed with the firm. No objectionable observations were noted. Deviations relating to the cleaning validation/verification were discussed with the firm in detail. Please refer to section "Facilities and Equipment System" of PaxVax EIR, specifically subsection "Equipment Cleaning Validation" for details.

6. **Have firm confirm the procedures for the location of (b) (4) testing of the DI water system.**

*Reviewer Comments:* During the inspection, the procedures for DI water testing was reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Facilities and Equipment System" in the PaxVax EIR, specifically subsection "Water Systems" for details.

7. **Discuss the corrective action of the (b) (4) before sampling of water in response to the deviation of (b) (4) samples not meeting acceptance criteria for water sampling (monitoring). In addition, have the firm clarify the root cause of this deviation and corrective actions noted on inspection.**

*Reviewer Comments:* During the inspection, the deviations in the PQ of the water system and SOPs in regards to water sampling was reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Facilities and Equipment System" in the PaxVax EIR, specifically subsection "Water Systems" for details.

8. **Review SOP Q197 and go over with the firm deviations that occurred in (b) (4) of the PQ of the DI water system. In addition, have the firm clarify the root cause of the (b) (4) deviations and corrective actions noted on inspection. Additionally, the firm should clarify where and when routine (b) (4) testing of the DI water system will be conducted i.e. in-house or off-site vendor.**

*During the inspection, the SOPs in regards to water sampling was reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Facilities and Equipment System" in the PaxVax EIR, specifically subsection "Water Systems" for details.*

9. **Check the number of air handling units that service the classified manufacturing areas (MBU and surrounding (b) (4) areas) and check the IQ/OQ documentation. Additionally, have the firm clarify the discrepancy noted in the BLA submission in relation to the number of AHUs that service the MBU.**

*Reviewer Comments:* During the inspection, the IO/OQ documentation was reviewed and discussed with the firm. No objectionable observations were noted. Please refer to "Facilities and Equipment System" section of PaxVax EIR for details, specifically, subsection HVAC.

10. **Review the computer systems that are used for ancillary GMP production purposes.**

*Reviewer Comments:* During the inspection, the firm provided a listing of the computer systems used. These systems were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Facilities and Equipment System" subsection Computer Systems for details.

11. **Review the secondary packaging activities and Quality Agreement with (b) (4) in regards to the secondary packaging.**

*Reviewer Comments:* During the inspection, the Quality agreement with (b) (4) was reviewed, additionally, the secondary packaging activities performed by (b) (4) was discussed with the firm. No objectionable observations were noted. Please refer to section "Quality System" subsection Quality Agreements, in addition to section "Materials System" subsection "Shipping" for details.

12. **Check how the lyophilized (b) (4) of IBDS are packaged and shipped to Pax Vax and if package integrity is checked. Additionally, review the information in relation to the storage of BDS in the intermediate containers including length of storage and if integrity is checked.**

*Reviewer Comments:* During the inspection, the process for the receipt of the IBDs (b) (4) at PaxVax, in addition to the storage of the BDS, was reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Materials System" under subsection "Raw Materials" for details.

- 13. Review all deviations associated with the blending and filling of BDS process validation lots (b) (4) to ensure preventative action were implemented and process is under control.**

*Reviewer Comments:* During the inspection, deviations occurring during the BDS process validation lots were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Quality System" under subsection "Deviation Management/Investigations/CAPA" for details.

- 14. Review the OQ/PQ of the (b) (4) instrument used for the CCIT of the foil sachets.**

*Reviewer Comments:* During the inspection the details of the OQ/PQ for the (b) (4) instrument was reviewed and discussed with the firm. No objectionable observations were noted. However, during the inspection, the (b) (4) system was being replaced with a new system that had not undergone qualification activities and thus was not available for review. Please refer to section "Facilities and Equipment System" under subsection "Equipment" for details. Additionally, please refer to "Recommendations" section of memo as an inspectional consideration was noted in regards to the checking the qualification of the new (b) (4) system.

- 15. Review the deviations associated the process validation covering the filling the buffer drug product conformance lots (b) (4).**

During the inspection, deviations occurring during the filling of buffer drug product conformation lots were reviewed and discussed with the firm. No objectionable observations were noted. Please refer to section "Quality System" under subsection "Deviation Management/Investigations/CAPA" in addition to Section "Production System" under subsection "Process Validation" for details.

2 pages have been determined to be not releasable: (b)(4)

(b) (4)