

# RECORD OF TELEPHONE CONVERSATION

## Submission Information

<b>Application Type</b>	BLA
<b>STN</b>	125597/0.0
<b>Review Office</b>	OVRR
<b>Applicant</b>	Pax Vax Bermuda Ltd. / Lic. # 2041
<b>Product</b>	Cholera Vaccine Live Oral
<b>Trans-BLA Group:</b>	No

## Telecon Details

<b>Telecon Date/Time</b>	02-FEB-2016 03:40 PM
<b>Author</b>	HOFFMAN, KELSY
<b>EDR</b>	No
<b>Post to Web</b>	Yes
<b>Outside Phone Number</b>	
<b>FDA Originated?</b>	No
<b>Communication Categories</b>	IR - Information Request
<b>Related STNs</b>	None
<b>Related PMCs</b>	None
<b>Telecon Summary</b>	Information Request regarding numerous CMC and assay issues/information
<b>FDA Participants</b>	Kelsy Hoffman, Christina Houck
<b>Applicant Participants</b>	Kevin Smyth

## Telecon Body:

**From:** Kevin Smyth [mailto:KSmyth@paxvax.com]

**Sent:** Tuesday, February 02, 2016 3:40 PM

**To:** Hoffman, Kelsy

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**Cc:** Houck, Christina M

**Subject:** RE: BLA 125597/0 Information Request

Dear Ms. Hoffman,

Thank you for your below information request, which I confirm I have received.

Regards, Kevin

**Kevin Smyth**

Vice President

Regulatory Affairs and Pharmacovigilance

**PaxVax**

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**From:** Hoffman, Kelsy [<mailto:Kelsy.Hoffman@fda.hhs.gov>]

**Sent:** Tuesday, February 02, 2016 12:36

**To:** Kevin Smyth

**Cc:** Houck, Christina M

**Subject:** BLA 125597/0 Information Request

Mr. Smyth,

We have the following comments regarding your BLA 125597/0, "Cholera Vaccine, Live, Oral:"

1. In Section 2.3.S.2.1, you indicate that (b) (4) no longer manufactures the Master Seed Lot (MSL) or Working Seed Lot (WSL) for PXVX0200. Please provide the following information regarding MSL and WSL from (b) (4):
  - a. Please provide an estimate of the number of doses of final drug product (DP) that can be made using the (b) (4) remaining (b) (4) WSL vials.
  - b. Please provide an estimate of when the remaining vials of MSL will be exhausted.

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2. In section 2.3.S.2.1, you indicate that since January 2015, (b) (4) is the (b) (4) manufacturer of your WSL. The data you provided in support of (b) (4) as a contract manufacturer for your new WSL are insufficient for approval of WSL manufactured by (b) (4). Therefore, we recommend that after approval of your BLA, you submit a Prior Approval Supplement (PAS) for use of (b) (4) as your WSL manufacturer. Your supplement should address the following:
- Please provide data regarding the (b) (4) of the (b) (4) WSL.
  - Please provide a general diagram of the (b) (4) facility and identify the suites, rooms, or areas where your WSL is manufactured and where major equipment (such as the lyophilizer) is located.
  - Please provide a description of the (b) (4) facilities where the manufacture of the WSL will be performed. Specifically, please indicate whether your WSL is manufactured on a campaign basis in a manufacturing suite with other materials including investigational products, approved drug or biologic products, other MSL or WSL, or cultured organisms. Please include the specific identity or general type of these materials. In addition, please indicate whether equipment used to manufacture your WSL is dedicated or shared.
  - If the manufacturing areas or equipment are shared, please indicate whether cleaning verification or cleaning validation studies were performed. You indicate that the lyophilizer used at (b) (4) is different from the one used at (b) (4). In addition, you describe several changes related to the lyophilizer such as (b) (4). Please indicate whether the lyophilization cycle was validated using these changes.
  - Please provide all manufacturing information and testing data from three lots of final DP manufactured using the (b) (4) WSL. In addition, please provide stability data in support of the intermediate bulk drug substance (IBDS), bulk drug substance (BDS) and DP manufactured with the new WSL.
3. The information you provided for the transfer and storage of the MSL and the WSL is unclear. Please address the following:

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- a. Please describe the method of transfer of MSL Lot (b) (4) and WSL Lot (b) (4) to (b) (4) for storage.
  - b. Please describe the conditions and procedures for storage of MSL and WSL at (b) (4).
  - c. Please describe the method of transfer of MSL and WSL as needed to and from (b) (4).
  - d. Please describe the procedures and conditions for storage of MSL and WSL at (b) (4) prior to use.
  - e. Please describe the method of transfer of WSL to (b) (4) for use in manufacturing IBDS and the WSL storage procedures and conditions at (b) (4) prior to use in manufacturing.
4. In Section 3.2.P.2.3.1, BDS (b) (4) Hold Step, you describe a proposed change to the manufacturing process, in which the BDS is held at (b) (4) for (b) (4) rather than (b) (4). Because your clinical studies were conducted using material manufactured using the (b) (4) BDS hold time, and the effect of the proposed manufacturing change on the vaccine is not clear, we do not agree with the proposed change. Please submit a written statement to your pending BLA removing your request to change the BDS hold time. If you intend to change the BDS hold time, we recommend that after approval of your BLA, you submit a Prior Approval Supplement, that includes the following:
  - a. Please provide results of a study of the recovery time of DP made using each of the two processes in which DP is reconstituted in buffer and transferred to broth, and the time of each DP sample to achieve a benchmark concentration is compared.
  - b. Although you have provided some stability data for the conformance and development lots using the (b) (4) BDS hold time, these data did not include evaluation of appearance or (b) (4). Please provide real-time stability data for three lots of DP manufactured using the (b) (4) BDS hold time. These data should include results of all four stability tests (appearance, viable cell count, moisture content, and (b) (4)).
5. Please be advised that on July 2, 2015, the Agency amended the biologics regulations by removing the general safety test (GST) requirement for biological products. Please see <https://www.federalregister.gov/articles/2015/07/02/2015-16366/revocation->

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[of-general-safety-test-regulations-that-are-duplicative-of-requirements-in-biologics](#). You may elect to remove the GST from your application.

6. Please provide information regarding results of tests for leachables and extractables for (b) (4)
7. Please provide the reference “Gurwith M. 2015,” cited in Section 1.2, Request for Priority Review Voucher.
8. In Section 3.2.P.2.2.3, Table 4, and in Section 3.2.P.2.4.4, Table 5, Data Summary of PXVX0200 Vaccine Freeze-Thaw Stability Study, footnotes refer to laboratory investigations QCI-15-29 and QCI-15-30. Please provide QCI-15-29 and QCI-15-30.
9. In TRPDP-0042, Section 6.2, you refer to Stability Program Q120. Please provide a copy of Stability Program Q120 for our review. In Table 6-1, you refer to Stability studies STBR-52-12 and STB-127-15. Please provide these studies for our review.
10. Information provided regarding in-process testing and release testing is unclear. Please provide a complete list of all in-process and release test assays, where they are performed, and their respective validation.
11. Regarding the (b) (4) test used as an identity test for (b) (4) drug product, you provided a Technical Specification for Assay Performance but not the standard operating procedure (SOP). Please provide the SOP for this test.
12. Regarding the (b) (4) assay (b) (4) used as an identity test (b) (4) drug product, you provided a Technical Specification for Assay Performance but not the SOP. Please provide the SOP for this test.
13. Three SOPs were submitted regarding the viable cell count: Viable Cell Count in CVD 103-HgR, (b) (4), AIM-PFT-6001, effective date December 13, 2013; Viable Cell Count in PXVX0200 CVD 103-HgR using the (b) (4), PaxVax, Q208.03, effective date September 29, 2015; and Viable Cell Count of PXVX0200 CVD 103-HgR DP Reconstituted with Aqueous Buffer DP, PaxVax, Q217.00, effective date September 11, 2015.
  - a. None of the SOPs includes a positive control. Please describe how accuracy of the cell counts is verified in each assay run.

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- b. The scope of SOP Q208.03 includes testing of the DP. However, the scope of the SOP Q217.00 states that it applies to release and stability testing of DP. Please clarify which SOP is used for DP release and stability testing.
14. You provided the “Analytical Method Validation Report for Determining the (b) (4) via the (b) (4) in CVD 103-HgR (b) (4) Samples,” Document number RAP-PLT-6001.QC, Version 1. Please provide the raw data (b) (4) generated in that validation and used to calculate the results.
15. We find that the (b) (4) has not been adequately validated for use as an identity test. However, we believe the (b) (4) assay to be adequately sensitive and specific to serve as a stand-alone identity test for (b) (4) drug product. If you decide to pursue the (b) (4) as an identity test, we have the following comments that would need to be addressed regarding “Validation Report for the Quantitation of *Vibrio cholerae* Vaccine Strain CVD103-HgR by (b) (4)” Document number VPPO0255.R00.
- a. Please verify that the (b) (4) performed at (b) (4) is used for (b) (4) drug product testing.
  - b. The method described in this report does not appear to have quality control samples included to evaluate assay performance. Please describe how the assay system suitability criteria adequately monitor and identify assay performance issues.
  - c. The validation was conducted using samples prepared from the reference standard. These samples do not adequately reflect the samples that will be run during routine testing. Please provide accuracy and precision data relevant to the use of this assay as an identification test using (b) (4) drug product culture supernatants generated according to the SOP.
  - d. The validation report does not include analyses of the limit of detection or the lower limit of quantitation. No information was provided regarding the definition of a positive sample sufficient to confirm the identity of the (b) (4) drug product. Please provide data that support the ability of the assay to distinguish between positive and negative samples and thus reliably detect cholera toxin B subunit in the culture supernatants. Please also indicate the level of cholera toxin B subunit determined to be a positive result in the context of the identity test of the (b) (4) drug product.

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- e. Please provide data demonstrating the specificity of the (b) (4), including the level of cross-reactivity to (b) (4)

16. In the “Report for Validation of Q217 Viable Cell Count in CVD 103-HgR DP Reconstituted with Aqueous Buffer DP,” Document number VPR-179, Revision 00, the raw data include comments that indicate that “false” colonies were removed and colonies were added. This comment occurs frequently throughout the data. Please describe what is meant by removing and adding colonies. Please describe how the apparent manual manipulation of the data is objectively controlled to prevent bias or falsification of results.

Please let me know if you have any questions.

Thank you,

Kelsy F. Hoffman, Ph.D.  
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FDA/CBER/OVRR/DVRPA  
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