

DEPARTMENT OF HEALTH & HUMAN SERVICES
FDA, Center for Biologics Evaluation and Research

MEMORANDUM

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To: File for BLA 125597/0

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Subject: Product Review of BLA 125597/0 (Vaxchora)

Applicant: PaxVax Bermuda Ltd.

Additional submissions reviewed:

Amendment 1, received 19 October 2015 (List of clinical, manufacturing, and testing sites)

Amendment 2, received 28 October 2015 (List of contract manufacturers)

Amendment 4, received 8 January 2016 (Response to 12/17/15 Information Request (IR))

Amendment 5, received 11 January 2016 (Response to 1/6/16 IR)

Amendment 6, received 12 February 2016 (Partial response to 1/13/16 IR)

Amendment 7, received 12 February 2016 (Response to 2/4/16 IR)

Amendment 8, received 17 February 2016 (Partial response to 1/13/16 IR)

Amendment 9, received 19 February 2016 (Partial response to 2/2/16 IR)

Amendment 11, received 26 February 2016 (Partial response to 2/2/16 IR)

Amendment 12, received 26 February 2016 (Removal of identity test for Effer-Soda 12)

Amendment 13, received 1 March 2016 (Response to 2/17/16 IR)

Amendment 14, received 4 March 2016 (Response to 2/24/16 IR)

Amendment 15, received 4 March 2016 (Corrected report on buffer BDP filling)

Amendment 16, received 4 March 2016 (Partial response to 2/2/16 IR)

Amendment 18, received 8 March 2016 (Response to 3/1/16 IR)

Amendment 19, received 8 March 2016 (Partial response to 2/2/16 IR)

Amendment 22, received 15 March 2016 (Updated stability data)

Amendment 23, received 16 March 2016 (Corrected potency data)

Amendment 25, received 21 March 2016 (Response to 3/10/16 IR)

Amendment 27, received 23 March 2016 (Response to 3/11/16 IR)

Amendment 28, received 6 April 2016 (Response to 3/25/16 IR)

Amendment 29, received 6 April 2016 (Response to 4/1/16 IR)

Amendment 31, received 19 April 2016 (Response to 4/18/16 IR)

Amendment 33, received 20 April 2016 (Response to 483 observations following inspection)

Amendment 34, received 22 April 2016 (Response to 4/6/16 IR)

Amendment 36, received 3 May 2016 (Response to 1/19/16 and 2/4/16 IRs)

Amendment 40, received 19 May 2016 (Response to 5/6/16 and 5/10/16 IRs)

Amendment 41, received 23 May 2016 (Response to 1/19/16 and 2/4/16 IRs)

Amendment 43, received 31 May 2016 (Response to 5/23/16 and 5/27/16 IRs)

Amendment 45, received 6 June 2016 (Response to 6/3/16 IR)

Amendment 46, received 7 June 2016 (Response to 6/6/16 IR)

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1. SUMMARY/BACKGROUND

PaxVax previously submitted an IND for PXVX0200 Cholera Vaccine, Live Attenuated, Oral (strain CVD 103-HgR), indicated for the active immunization of individuals at risk for cholera. PaxVax received Fast Track designation on 20 December 2012. In this BLA, PaxVax seeks approval of Vaxchora (Cholera Vaccine, Live, Oral), indicated for active immunization against disease caused by *Vibrio cholerae* serogroup O1 in adults 18 through 64 years of age traveling to cholera-affected areas.

The vaccine consists of a sachet of lyophilized powder (vaccine DP) and a sachet of buffer (buffer DP). The sachets are mixed in 100 mL of purified bottled water for oral administration (first the buffer, then the lyophilized powder), in a single dose. The lyophilized powder sachet contains 4×10^8 to 2×10^9 colony-forming units (CFU) of strain CVD 103-HgR, *V. cholerae* serogroup O1, biotype classical, serotype Inaba. The buffer sachet contains sodium bicarbonate and sodium carbonate. The vaccine and buffer sachets are intended to be stored frozen (-25 to -15°C).

The Drug Substance (DS) is PXVX0200, also known as CVD 103-HgR. The strain was genetically engineered from *V. cholerae* strain 569B. The majority of the catalytic domain of the gene encoding the A subunit of cholera toxin (*ctxA*) was deleted, rendering the strain non-toxicogenic. Additionally, a mercury resistance operon was inserted into the hemolysin gene *hlyA*, in order to enable differentiation of the vaccine strain from wild-type.

The Master Seed Lot (MSL) and the initial Working Seed Lot (WSL) were manufactured by [REDACTED]. All clinical trials in the BLA were conducted using vaccine DP manufactured from WSL made by [REDACTED]. Since January 2015, the WSL has been manufactured by [REDACTED]. The Intermediate Bulk Drug Substance (IBDS) is manufactured by [REDACTED]. Processing of the IBDS to the Bulk Drug Substance (BDS) is performed by PaxVax, Inc., in [REDACTED].

There are two Drug Products (DPs): PXVX0200, Powder for Oral Suspension (vaccine DP); and Buffer, Effervescent Granule (buffer DP). Manufacturing and primary packaging of the vaccine DP is performed by PaxVax, Inc., in [REDACTED]. For the buffer DP, manufacturing is performed by [REDACTED], whereas filling and primary packaging is conducted by PaxVax, Inc., in [REDACTED]. Secondary packaging is performed by [REDACTED].

2. BLA REVIEW OF DRUG SUBSTANCE

The Drug Substance, PXVX0200, was engineered from *V. cholerae* classical Inaba strain 569B. Two genetic modifications were made: 94% of the *ctxA* gene encoding cholera toxin A subunit was deleted; and a mercury resistance operon (*mer*) was inserted into the gene encoding hemolysin (*hlyA*), deleting [REDACTED]. The genotype of the strain is therefore $\Delta ctxA$, $\Delta hlyA::mer$. DNA sequencing confirmed the presence of the modifications.

The strain expresses cholera toxin B subunit, which may be important for the generation of a protective antibody response. The [REDACTED]

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

(b) (4)

2.2. Control of Materials

A description of the control of the materials used for manufacture of the DS is provided, as is the specification for the raw materials used in the manufacture of the IBDS. No additional materials are used during processing of the IBDS to the BDS. Compendial materials are used to the extent possible. Non-compendial materials consist of [REDACTED] and Hy-Case SF. For the non-compendial materials, the manufacturers' certificates of analysis are verified by the IBDS manufacturer. Two of these materials [REDACTED] and Hy-Case SF) are of biological origin; the former is sourced from [REDACTED], and the latter is sourced from either [REDACTED]. BSE/TSE statements for these materials are provided, stating that the materials were manufactured using milk sourced from healthy animals in the same conditions as milk collected for human consumption. Certificates of Analysis are also included, providing adequate information regarding the quality of all raw materials.

Strain CVD 103-HgR was engineered at the Center for Vaccine Development, University of Maryland, Baltimore (CVD UMB). In 1987, vials of the strain were transferred to the Swiss Serum and Vaccine Institute; these vials were used to make the MSL for Orochol[®] (also known as Mutacol[®] Berna). After PaxVax acquired the license for the strain, CVD UMB generated a seed lot from a frozen vial of the original strain and transferred several vials of the new seed lot to PaxVax.

Characterization of the vaccine strain is described. Identity tests include [REDACTED]

[REDACTED] assay.

(b) (4)

PaxVax has provided information regarding the cell banks (MSL and WSL). Starting from CVD 103-HgR Lo (b) (4) from CVD UMB, (b) (4) generated the MSL, leading to the production of (b) (4) vials in March 2010. Subsequently, in September 2010, the same manufacturer used the MSL to produce (b) (4) vials of WSL, designated Lot (b) (4), part of which was used for the Phase 1 clinical trial. In January 2015, (b) (4) s used the same MSL to generate (b) (4) vials of WSL Lot 5267-15-02.

Manufacture of the MSL begins with (b) (4)


The manufacturing procedure for the WSL is nearly identical to that for the MSL. PaxVax compared the WSL manufacturing process conducted at (b) (4) to the process conducted previously at (b) (4), generating Doc. No. TRPDP-0042, Comparability of PXVX0200 Working Seed Lot Manufacturing Process Changes. The report lists the changes in manufacturing and evaluates the impacts of these changes, concluding that WSL produced by (b) (4) meets acceptance criteria and is of acceptable quality. The conclusions regarding comparability of the two manufacturing processes are reasonable; however, the clinical studies described in the BLA were conducted with vaccine DP that was manufactured using the (b) (4) WSL. The data that were provided in support of (b) (4) as a contract manufacturer are insufficient for approval of WSL manufactured by (b) (4). Therefore, in an information request (IR), CBER recommended that the applicant submit a Prior Approval Supplement (PAS) for use of (b) (4) as the WSL manufacturer. The applicant agreed to do so. Details regarding these communications are in Section 14 of this memorandum.

2.3. Control of Critical Steps and Intermediates

For manufacture of the IBDS and BDS, controls of critical steps and intermediates are described. Process parameters are categorized as either critical or non-critical. Document VP-082, PXVX0200 (Platinum) Upstream Process Quality Risk Assessment, identifies the process parameters that are considered critical for manufacture of the IBDS, and Document VP-152, PXVX0200 Cholera Vaccine Downstream Process Quality Risk Assessment, provides the equivalent information regarding manufacture of the BDS. For the critical process parameters, tables listing each parameter, set point, acceptable range, and rationale are included. Additionally,

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

(b) (4)



2.11. Review of Drug Substance: Summary

Overall, the BLA content regarding the vaccine DS is acceptable.

3. BLA REVIEW OF DRUG PRODUCT PXVX0200, POWDER FOR ORAL SUSPENSION

The active portion of the vaccine is DP PXVX0200 (vaccine DP), which consists of a single-dose, multilayer foil sachet containing vaccine powder for reconstitution. In the same package is a separate single-dose, multilayer foil sachet containing buffer powder. For administration, the buffer is dissolved in 100 mL of purified bottled water. The vaccine powder is then dissolved in the buffer solution and mixed, and the mixture is taken orally. The dose is 4×10^8 to 2×10^9 CFU of recombinant live attenuated *V. cholerae* strain CVD 103-HgR.

Table 3.2.P.1-1 lists the composition of PXVX0200.

Table 3.2.P.1-1. Complete Composition of PXVX0200

Ingredient	Function	Manufacturer	Reference to Standard	Quantity (per dose)
Viable CVD 103-HgR	Active Ingredient	(b) (4)	None	4×10^8 to 2×10^9 CFU
Sucrose	Cryoprotectant	(b) (4)	(b) (4)	(b) (4) 165.37 mg
Sodium Chloride	Stabilizer	(b) (4)	(b) (4)	(b) (4) 17.11 mg
Hy-Case SF	Stabilizer (Cryoprotectant)	(b) (4)	Manufacturer	(b) (4) 17.11 mg
Ascorbic acid	Stabilizer (Antioxidant)	(b) (4)	(b) (4)	(b) (4) 8.55 mg
Dried Lactose	Stabilizer (Desiccant) and Bulking Agent	(b) (4)	Manufacturer	(b) (4) 2.09 g
Buffer	Buffer	(b) (4)	None	100 mL

The container closure system is a foil sachet composed of three layers. The interior surface, which contacts the product, is made of low-density polyethylene film. The middle layer is made of aluminum foil, and the outer layer is made of paper.

3.1. Pharmaceutical Development

3.1.1. Components of the Drug Product PXVX0200, Powder for Oral Suspension

The vaccine DP consists of the BDS blended with dried lactose. The BDS consists of the *V. cholerae* O1 classical strain attenuated derivative CVD 103-HgR, along with the excipients sucrose, sodium chloride, Hy-Case SF, and ascorbic acid.

Excipients in the vaccine sachet are listed in Table 3.2.P.2.1.2-1, along with the amounts present and their functions.

Table 3.2.P.2.1.2-1. Excipients Present in the PXVX0200 Cholera Vaccine Sachet

Ingredient	Amounts	Function
Sucrose	(b) (4) 165.37 mg	Cryoprotectant
Sodium chloride	(b) (4) 17.11 mg	Stabilizer
Hy-Case SF	(b) (4) 17.11 mg	Stabilizer (Cryoprotectant)
Ascorbic acid	(b) (4) 8.55 mg	Stabilizer (Antioxidant)
Dried Lactose	(b) (4) 2.09 g	Desiccant (Stabilizer) and Bulking Agent

3.1.2. Drug Product PXVX0200, Powder for Oral Suspension

The formulation for PXVX0200 was based on information from the manufacture of Orochol[®], a previous vaccine based on CVD 103-HgR that was not licensed in the U.S. Differences in composition between Orochol[®] and PXVX0200 used in different studies are listed in Table 3.2.P.2.2.1-1. Aspartame, an artificial sweetener, was part of the formulation of Orochol[®] but is not included in PXVX0200. Sodium chloride is in the (b) (4) and the sucrose stabilizer solution used in the manufacture of PXVX0200 IBDS, in order to provide optimal survival and proliferation of the vaccine strain. Sodium chloride is therefore an excipient of PXVX0200, which was not the case for Orochol[®].

Table 3.2.P.2.2.1-1. PXVX0200 Drug Product Formulations used in Clinical Trials and Orochol[®] Drug Product Formulation

Ingredient	Orochol DP Package Insert	Phase 1 Study PXVX-VC-200-002 PXVX0200 DP Lot No. PR1002-B	Phase 3 Study PXVX-VC-200-003 Challenge Study PXVX0200 DP Lot No. P701.550-8WA02	Phase 3 Study PXVX-VC-200-004 Lot Consistency Study PXVX0200 DP Lot No. P700.550-6BA03 Lot No. P700.550-1CA03 Lot No. P700.550-3CA03	Phase 3 Study PXVX-VC-200-005 Older Adults Study PXVX0200 DP Lot No. P700.550-6BA03	Commercial Formulation PXVX0200 DP
Viable CVD 103-HgR	$2 \times 10^8 - 1 \times 10^9$ CFU	4.43×10^8 CFU ^a	5×10^8 CFU	1×10^9 CFU	1×10^9 CFU	$4 \times 10^8 - 2 \times 10^9$ CFU
Hy-Case SF	0.15–3 mg	4.66 mg	0.33 mg	0.32–0.51 mg	0.32 mg	(b) (4) 17.11 mg
Ascorbic acid	0.06–1 mg	None	0.16 mg	0.16–0.25 mg	0.16 mg	(b) (4) 8.55 mg
Sucrose	1.4–30 mg	46.6 mg	3.25 mg	3.12–4.90 mg	3.12 mg	(b) (4) 165.37 mg
Sodium chloride	None	None	0.33 mg	0.32–0.51 mg	0.32 mg	(b) (4) 17.11 mg
Dried Lactose	1.8–2.1 g	None	1.99 g	1.99 g	1.99 g	(b) (4) 2.09 g
Aspartame	20–30 mg	None	None	None	None	None
Manufacturing Site	(b) (4)	(b) (4)	PaxVax, Inc. (b) (4)			
Container Closure	(b) (4)	(b) (4)	Sachet			
Storage Conditions	(b) (4)	(b) (4)	Frozen –15°C to –25°C			

^a Potency data taken from the 18 month stability time point which was prior to the start of the Phase 1 Study. The original release titer is 6.9×10^8 CFU.

For the Phase 1 trial, vials of WSL were used as the study material. The formulation did not contain sodium chloride or lactose, which were included in the lots of vaccine DP manufactured for use in subsequent clinical studies. An additional difference among the clinical lots was the dose: 4.43×10^8 CFU for the Phase 1 lot; 5×10^8 CFU for the initial Phase 3 challenge study lot;

1 x 10⁹ CFU for the Phase 3 lot consistency study and for the Phase 3 study in older adults; and 4 x 10⁸ to 2 x 10⁹ CFU for the proposed commercial formulation.

No formulation overages are used for the vaccine DP. The potency acceptance criterion is 4 x 10⁸ to 2 x 10⁹ CFU/dose. The target fill is [REDACTED] CFU/dose, because the goal is for vaccine DP potency to remain within the specification criterion until the end of shelf life, and the number of viable bacteria is expected to decrease over time. The acceptance criterion is appropriate; however, the possibility of a decrease in potency raises concern regarding monitoring of potency over the course of the shelf life of the vaccine DP. An IR was sent to the applicant regarding the issue, and the applicant agreed to establish a potency alert limit. For details, see Sections 3.10 and 17 of this memorandum.

A description of the physicochemical and biological properties for the vaccine DP is provided and is summarized below.

Moisture:

For a product that includes lyophilized bacteria, moisture content should be low, but over-drying should also be avoided. The vaccine DP acceptance criterion for moisture is [REDACTED]

[REDACTED]

[REDACTED]

Reconstitution:

Different types of bottled water were tested for reconstitution of the vaccine. The use of purified, spring, mineral, artesian, or sparkling water led to CFU/dose above the lower limit of 4 x 10⁸, although the use of sparkling or artesian water led to potency values that were near the lower limit. In response to an information request, the applicant stated that these *in vitro* tests were conducted using vaccine DP that was manufactured using a BDS hold time of [REDACTED] rather than [REDACTED] (the process that was used to manufacture vaccine DP that was used in the clinical trials; see Sections 3.1.3.1 and 14 of this memorandum). Therefore, the results of these tests may not be applicable to vaccine DP made using the process proposed in the BLA. In the original submission, the applicant proposed that the instructions for preparation of the vaccine state that any type of bottled water could be used for reconstitution. However, the composition of spring, mineral, artesian, or sparkling water may vary depending on the source or brand. Because

purified bottled water must be treated according to methods specified by USP, it would be expected to be of more consistent quality. An IR regarding the package insert was sent to the applicant, in which the instructions for preparation of the vaccine were modified to specify that only purified bottled water be used for reconstitution of the vaccine. The applicant subsequently agreed with this change. For details, see Section 18 of this memorandum.

Chlorine in purified bottled water:

Chlorine can inactivate *V. cholerae*. Ascorbic acid (1.5 to 1.8 g per dose) is therefore included in the buffer, to neutralize chlorine that may be present in purified bottled water. Spiking of buffer solution with chlorine at (b) (4) followed by addition of the lyophilized vaccine led to potency levels within the specification, if the mixture was held for 0 or 15 minutes. However, the addition of chlorine at (b) (4) led to viable cell counts below the lower limit if the mixture was held for 30 minutes. Because 21 CFR 165.110 specifies that purified bottled water may not contain more than 4 ppm (4 mg/l) of chlorine, and because the instructions for preparation of the vaccine state that it must be consumed within 15 minutes of reconstitution, these results do not raise any concern regarding potency of the vaccine as administered. More information regarding this issue is in Section 4.1.1 of this memorandum.

Buffer sachet and vaccine sachet thaw time:

The buffer and vaccine sachets are stored at -20°C. The need for thawing the sachets before reconstitution was tested. Regardless of whether (1) neither sachet was thawed, (2) both sachets were thawed for 30 minutes, or (3) the buffer was reconstituted immediately and the vaccine was thawed for 30 minutes, the potency of the vaccine remained within the specification for 30 minutes after reconstitution. In the original submission, the applicant proposed that the instructions for preparation of the vaccine state that reconstitution should occur within 30 minutes of removal of the sachets from frozen storage. However, the *in vitro* tests described above were conducted using vaccine DP that was manufactured using a BDS hold time of (b) (4) rather than (b) (4), so the relevance of the results is questionable (see “Reconstitution” above). Additionally, in the challenge study, the mean sachet thaw time was 14.4 minutes, and the median thaw time was 9 minutes. No data were provided regarding efficacy of vaccine reconstituted following sachet hold durations closer to the higher end of the 0–30 minute range. Therefore, An IR regarding the package insert was sent to the applicant, in which the instructions for preparation of the vaccine were modified to specify that the vaccine must be reconstituted within 15 minutes after removal of the carton from frozen storage. The applicant subsequently agreed with this change. More information regarding this issue is in Section 16 of this memorandum.

Reconstitution order of vaccine and buffer:

The effect on potency of reconstitution of the sachets in reverse order was evaluated. Reconstitution of the vaccine sachet in bottled water followed by addition of the contents of the buffer sachet led to viable cell counts below the lower limit of 4×10^8 CFU/dose.

Vaccine freeze-thaw:

To test stability following multiple freeze-thaw cycles, vaccine was thawed from the storage temperature of -20°C to 2–8°C three times and was assessed for appearance, potency, and moisture content. No differences were observed versus samples kept at -20°C or 5°C constantly for the same length of time, and all results were within the acceptance criteria.

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

(b) (4)

3.1.3.3. Filling and Packaging of Vaccine Drug Product

In an automated sachet filling machine, augurs are used to direct the blend of BDS and dried lactose into filling hoppers. A reel of (b) (4)

(b) (4)

During Instrument Qualification and Operational Qualification (IQ/OQ), critical process parameters for the filling step were determined as follows: (b) (4)

The filling process was assessed using dried lactose as a surrogate for the vaccine; all parameters for the filling process met the requirements, and all in-process tests met the acceptance criteria.

For manufacture of the Phase 3 CTM, the operational parameters and in-process tests were the same as those used in the dried lactose surrogate test, except that (b) (4) sachets were made per batch rather than (b) (4) sachets. Results of tests for the Phase 3 challenge study lot, in which a batch size of (b) (4) was used, are provided; acceptance criteria were met.

After manufacture of the CTM, additional critical process parameters were added, (b) (4)

The latter change occurred because PaxVax ended its relationship with the previous supplier of the sachet foil (b) (4). Tables 3.2.P.2.3.3-19 and 3.2.P.2.3.3-20 summarize the results for product filling in-process parameters and tests. All parameters met the requirements, and all in-process tests met the acceptance criteria.

1 page has been determined to be not releasable: (b)(4)

(b) (4)

3.1.3.4. Comparability

Changes were made to the production process between manufacture of the Phase 3 CTM and the conformance lots. In a comparability report, TRDEV-0017, the applicant summarized the changes and evaluated their potential impact on product quality and safety. The changes

For each change, the applicant has provided a description, rationale, and evaluation of potential impact, concluding that the change is not expected to reduce quality of the vaccine product. The conclusion is reasonable for each of the changes described, with the exception of the change in BDS hold time. As discussed in Sections 3.1.3.1 and 14 of this memorandum, the applicant withdrew the request to change the BDS hold time and plans to submit a Prior Approval Supplement regarding the change. Product quality will continue to be monitored in ongoing stability studies.

3.1.3.5. Container Closure

Container Closure will be evaluated in full by DMPQ. Vaccine DP sachets are formed from a three-ply foil material manufactured by . The product contact layer is made of low-density polyethylene. The next layer is aluminum foil, and the outer layer is made of bleached kraft paper. Between the layers, polyurethane adhesive is used.

To evaluate integrity of the sachets, sachets were filled with dried lactose. Visual inspection was conducted to confirm sachet integrity. Additionally, a was used to detect weak seals and holes. The machine Out of sachets sampled, all passed the visual control test, and only one sachet failed the integrity test.

Dose reproducibility was studied by removing vaccine DP from sachets of each of lots, assessing the potency and of the contents, and calculating the average potency and %RSD. The average potency ranged from 1×10^9 to 2×10^9 CFU/, with a %RSD of 1–2%, meeting the potency label claim.

3.2. Microbiological Attributes

PXVX0200 is a live bacterial vaccine and is therefore not sterile. However, controls are in place to exclude organisms that would present a risk of infection. Specifically, raw materials are tested for contamination; IBDS in-process tests include , and ; and release and stability tests include a test and a test for the absence of specified organisms.

For the (b) (4) test, in a modified version of (b) (4), the (b) (4) The acceptance criteria are (b) (4) For the test for the absence of specified organisms, (b) (4) is also used, and the ability of the test to detect (b) (4) organism is validated. Recovery of positive control organisms in the presence of the product demonstrated suitability of the method. The acceptance criterion is no growth of any of the (b) (4) listed organisms. The test for absence of specified organisms is conducted on vaccine DP at release, and the (b) (4) test is conducted at release and on stability.

3.3. Manufacture

Manufacturing and primary packaging of the vaccine DP are by PaxVax, Inc., of (b) (4) Secondary packaging is performed by (b) (4). Commercial testing is conducted by three companies: PaxVax (release and stability testing (except identity by (b) (4), absence of specified organisms, and (b) (4) release testing—identity by (b) (4), and (b) (4) release and stability testing—(b) (4) release testing—absence of specified organism).

The batch formula is presented in Table 3.2.P.3.2-1. The batch size is (b) (4)

Table 3.2.P.3.2-1: PXVX0200 Drug Product Batch Formula

Components	Reference to Standards	Amount per Batch*
Viable CVD 103-HgR	None	(b) (4)
Sucrose	(b) (4)	
Sodium Chloride		
Hy-Case SF	Manufacturer	
Ascorbic Acid	(b) (4)	
Dried Lactose	Manufacturer	

*Excipients are inactive ingredients that are food substances. Ranges are based on calculated, not measured values.

Each vaccine BDP lot is designated (b) (4)

Steps in vaccine DP manufacturing include IBDS receipt and storage, milling and mixing to form BDS, blending with dried lactose to form vaccine BDP, and filling and packaging to form vaccine DP. Figure 3.2.P.3.3-1 is a flow chart depicting the vaccine DP manufacturing process. Steps from BDS stabilization hold to vaccine BDP primary packaging are performed in a room classified at (b) (4) air cleanliness level, in which the temperature is maintained between (b) (4) and the relative humidity is maintained (b) (4)

The amount of BDS required for a (b) (4) of vaccine DP is calculated as follows: (b) (4)

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

3.5. Process Validation and/or Evaluation

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3.6. Control of Excipients

The compendial excipients for the vaccine DP are sucrose, sodium chloride, and ascorbic acid. The non-compendial excipients are dried lactose and Hy-Case SF. For the dried lactose, the release specification of the manufacturer [REDACTED] includes [REDACTED]

[REDACTED]. The raw material for dried lactose is [REDACTED], for which the specification includes review of the certificate test results, [REDACTED]

For Hy-Case SF, [REDACTED] specification includes only [REDACTED]; however, the manufacturer's [REDACTED] specification includes [REDACTED]

[REDACTED] Analytical procedures used for the excipients are provided. Validations of these procedures and justifications of the acceptance criteria in the specification are also provided. The validations are adequate, and the acceptance criteria are appropriate.

There are two excipients of animal origin in the vaccine DP: dried lactose and Hy-Case SF. Both are derived from bovine milk and therefore do not require a certificate of suitability. There are no novel excipients in the vaccine DP.

3.7. Control of Drug Product PXVX0200, Powder for Oral Suspension

The vaccine DP specification is provided in Table 3.2.P.5.1-1. Methods and acceptance criteria for the tests are listed.

Table 3.2.P.5.1-1: PXVX0200 Drug Product Specification

Attribute	Method	Acceptance Criteria
Description		
Appearance	PaxVax Q108 ^a	White to beige powder, no visible foreign particulates
Visual Control	PaxVax Q198	Off-white sachet, two visible black (registration) marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides and lot number and date of manufacture expiry printed on the sachets is accurate and legible
Identity		
(b) (4)	(b) (4) 512020GMP	(b) (4)
General		
Moisture Content	PaxVax Q193 ^a (b) (4)	(b) (4)
Sachet Integrity Test	PaxVax Q211	Inspection Level II with AQL of (b) (4) Failures have defect of (b) (4)
Potency		
Viable Cell Count	PaxVax Q217 ^a	4 x 10 ⁸ to 2 x 10 ⁹ CFU/dose
Safety		
(b) (4)	(b) (4) 0493 ^a	(b) (4)
Absence of Specified Organisms: (b) (4) (b) (4)	(b) (4) 0493	(b) (4)

^a Methods used for release and stability

Validations of the analytical procedures are provided; each validation is adequate to provide assurance that the method is appropriate for its intended use and can be performed consistently. See Section 2.7 of this memorandum for a review of validation of the (b) (4) identity test.

For the vaccine DP, the method for potency (viable cell count) is PaxVax Q217. In the method, the buffer DP is used as diluent rather than (b) (4) which was used previously in method Q208. The change was instituted to more closely simulate the conditions of reconstitution of the vaccine DP in a clinical setting. The contents of the DP buffer sachet are dissolved in 100 mL of water, and the vaccine DP is then added and solubilized. The reconstituted vaccine is diluted in (b) (4) and assayed for viable cell count. Parameters evaluated in the validation of the assay were accuracy, repeatability, intermediate precision, reconstituted

vaccine stability, and reconstituted buffer stability. As described in the validation report (Doc. No. VPR-179), acceptance criteria were met for all parameters. For intermediate precision, the overall result for %RSD was 14%, well below the acceptance criterion of (b) (4) RSD. The intermediate precision acceptance criterion was therefore (b) (4) RSD. As discussed in Section 2.7 of this memorandum, no positive control is included in the assay. An IR was sent to the applicant regarding this issue, and the applicant subsequently agreed to develop an appropriate positive control for the assay (see Section 14 of this memorandum).

Full-scale vaccine DP lots are listed in Table 3.2.P.5.4-1.

Table 3.2.P.5.4-1: Description of PXVX0200 Drug Product Lot Information for Batch Analyses

Drug Product Lot No.	P700.550-1CA03	(b) (4)	P700.550-3CA03	(b) (4)	P700.550-6BA03	(b) (4)	P703.9FA03
IBDS Batch No. (b) (4) (PaxVax)	(b) (4)						
PaxVax BDS Batch No.	(b) (4)						
Drug Product Mfg. Site:	PaxVax, Inc.						
Drug Product Mfg. Scale:	(b) (4)						
Drug Product Pkg. Scale:							
Primary Container Closure:	Multi-Layer Foil Sachets						
Drug Product Mfg/Pkg Date:	March 2014	May 2015	March 2014	April 2015	March 2014	April 2015	June 2015
Drug Product Lot Use:	Phase 3 Lot Consistency	Conformance	Phase 3 Lot Consistency	Conformance	Phase 3 Lot Consistency	Conformance	Conformance

Batch analyses for the Phase 3 CTM and conformance lots are provided in Tables 3.2.P.5.4-2 and 3.2.P.5.4-3 respectively.

Table 3.2.P.5.4-2: Batch Analyses for PXVX0200 Phase 3 CTM Drug Product Lots

Attribute	Acceptance Criteria	Drug Product Lot P700.550-6BA03	Drug Product Lot P700.550-1CA03	Drug Product Lot P700.550-3CA03
Appearance	White to beige powder, no visible foreign particulates	White powder, no visible foreign particulates	White powder, no visible foreign particulates	White powder, no visible foreign particulates
Visual Control	Off-white sachet, two visible black marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides	Meets Spec	Meets Spec	Meets Spec
Identification by (b) (4) (b) (4)	Confirm presence of cholera toxin B subunit (CTB)	Meets Spec	Meets Spec	Meets Spec
Viable/Non-viable Cells	Report results	Mean Viable Cell Count = 4.95×10^9 /dose; Mean Non-Viable Cell Count = 4.06×10^8 /dose	Mean Viable Cell Count = 7.13×10^9 /dose; Mean Non-Viable Cell Count = 6.28×10^8 /dose	Mean Viable Cell Count = 3.05×10^9 /dose; Mean Non-Viable Cell Count = 1.59×10^8 /dose
Moisture Content	(b) (4)	2%	2%	2%
Potency by Viable Cell Count	(b) (4)	1×10^9 CFU/dose	1×10^9 CFU/dose	1×10^9 CFU/dose
General Safety Test	Meets 21CFR610.11	Meets 21CFR610.11	Meets 21CFR610.11	Meets 21CFR610.11
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Absence of Specified Organisms: (b) (4) (b) (4)	No growth for (b) (4) (b) (4)	Meets Spec	Meets Spec	Meets Spec

Table 3.2.P.5.4-3: Batch Analyses for PXVX0200 Conformance Drug Product Lots

Attribute	Acceptance Criteria	Drug Product (b) (4)	Drug Product (b) (4)	Drug Product (b) (4)	Drug Product (b) (4)
Appearance	White to beige powder, no visible foreign particulates	Beige powder, no visible foreign particulates	Beige powder, no visible foreign particulates	White powder, no visible foreign particulates	Beige powder, no visible foreign particulates
Visual Control	Off-white sachet, two visible black (registration) marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides and lot number and date of manufacture printed on the sachets is accurate and legible	Meets Spec	Meets Spec	Meets Spec	Meets Spec
Identification by (b) (4)	Confirm presence of cholera toxin B subunit (CTB)	Presence of cholera toxin B subunit (CTB) Confirmed	Presence of cholera toxin B subunit (CTB) Confirmed	Presence of cholera toxin B subunit (CTB) Confirmed	Presence of cholera toxin B subunit (CTB) Confirmed
Identification by (b) (4)	(b) (4)	Meets Spec	Meets Spec	Meets Spec	Meets Spec
Moisture Content	(b) (4)	2%	2%	2%	2%
Sachet Integrity	Inspection Level II with AQL of (b) (4) Failures have defect of (b) (4)	Number of allowable failures for (b) (4) samples: 3 Number of failures found: 0	Number of allowable failures for (b) (4) samples: 3 Number of failures found: 0	Number of allowable failures for (b) (4) samples: 3 Number of failures found: 0	Number of allowable failures for (b) (4) samples: 3 Number of failures found: 0
Potency by Viable Cell Count	(b) (4)	1×10^8 CFU/dose	2×10^8 CFU/dose	1×10^8 CFU/dose	1×10^8 CFU/dose
General Safety Test	Meets 21CFR610.11	Meets Spec	Meets Spec	Meets Spec	Meets Spec
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Attribute	Acceptance Criteria	Drug Product (b) (4)	Drug Product (b) (4)	Drug Product (b) (4)	Drug Product (b) (4)
Absence of Specified Organisms: (b) (4)	No growth for (b) (4)	Meets Spec	Meets Spec	Meets Spec	Meets Spec
(b) (4)	(b) (4)				

Justification of the specification is provided and is summarized below for each test:

- **Appearance:**
The appearance criterion of a white to beige powder with no visible foreign particles is based on the appearance of the BDS and of the dried lactose. It is also based on the appearance observed during development at release and during stability testing.
- **Visual control:**
For the sachet, the visual control criterion is off-white, with two visible black registration marks on each side, continuous seals on all four sides, with no less than (b) (4) from the inner weld line to the outer edge, and with legible and accurate lot number and date of manufacturing expiry. The seal width criterion was based on a study of (b) (4) sachets, in which seal integrity was maintained if the seal was a minimum of (b) (4) wide.
- **Moisture content:**
The criterion of (b) (4) moisture was based on release and stability data, taking into consideration the (b) (4) and the dried lactose upper acceptance criterion of (b) (4). Data from the conformance lots met the release criterion.
- **Sachet integrity:**
The acceptance criterion of no more than three failures in (b) (4) sachet samples is based on ANSI-ASQ-Z1.4.2008. Conformance lots have met the criterion.

- Potency by viable cell count:
The acceptance criterion of 4×10^8 to 2×10^9 CFU/dose is based on the potency of CTM for Phase 1 and Phase 3, which ranged from 4.5×10^8 to 1.3×10^9 CFU/dose. The method used in the challenge trial was Q202, and the method used for the lot consistency trial was Q208. For commercial lots, the method is proposed to be Q217, which uses buffer DP for reconstitution to more closely mimic the reconstitution procedure that is proposed in a clinical setting. Validation of the method is discussed above in this section of the memorandum.
- (b) (4)
[REDACTED]
- Absence of specified organisms:
The acceptance criterion of no growth of the (b) (4) specified organisms is based on data obtained during development and release. Conformance lots met the criterion.

For each attribute, the test method that was used and the acceptance criteria that were set were appropriate and adequate.

A discussion of impurities in the vaccine DP is included. Impurities in the DS may be present in the vaccine DP, including residual medium components present in the Precultures and the Main Culture; however, these components are (b) (4). There are no additional process-related impurities. Dried lactose, the only excipient added to the DS, is derived from bovine milk. A BSE/TSE statement stating that the product is sourced from healthy animals in the same conditions as milk collected for human consumption is provided.

The primary container closure system includes (b) (4)
[REDACTED]

Contamination of the vaccine DP is monitored by testing for (b) (4) at release and on stability, and by testing for the absence of specified microorganisms at release. In the original submission, the General Safety Test (GST) was included as a release test. Because this test is no longer required by the Agency for biological products, CBER informed the applicant that the GST could be removed from the BLA, and the applicant elected to do so. Details regarding these communications are in Section 14 of this memorandum.

The certificate of analysis provided by the manufacturer of the (b) (4) lactose states that the product complies with the ICH guideline on residual solvents. The sachet foil contains no Class 1 or Class 2 solvents. The applicant states that residual levels of solvents do not exceed Class III solvent limits. The sachet foil complies with levels recommended for the heavy metals lead, mercury, cadmium, and chromium (VI).

3.8. Reference Standards and Materials

There are no reference standards for this vaccine. Reference materials used as controls are: *V. cholerae* strains 569B and CVD 103-HgR (research bank) for identity by (b) (4); and *V. cholerae* strains O1 Inaba, O1 Ogawa, and O139 for the (b) (4) assay. (b) (4) is used as a control in the identity test for dried lactose by (b) (4).

3.9. Container Closure System

Container closure will be reviewed by DMPQ. The primary container closure system for the vaccine is a 60mm x 90 mm three-ply foil sachet, which is heat-sealed on all four sides. A single dose (b) (4) is in each sachet. The sachet consists of: low density polyethylene, which contacts the vaccine DP; polyurethane adhesive; aluminum foil, which excludes light, oxygen, and moisture; another layer of polyurethane adhesive; and bleached kraft paper, on which graphics, text, lot codes, and expiry dates are printed. The applicant has submitted a letter authorizing cross-reference to the drug master file (DMF (b) (4)) of the manufacturer, (b) (4). The applicant states that the film layer that contacts vaccine DP complies with the relevant sections of 21 CFR. The specification for the sachet foil includes review of the manufacturer's certificate of analysis, (b) (4).

For secondary packaging at (b) (4), one vaccine sachet and one buffer sachet are placed in a carton, which protects the sachets from cosmetic damage and reduces the potential for dispensing errors. The applicant states an intention to conduct a validation on the secondary packaging process of the first commercial lot.

3.10. Stability

Samples of several lots of vaccine DP have been placed in a stability program: (b) (4) conformance lots, four lots used in Phase 3 trials, and (b) (4) development lots. The (b) (4) conformance lots were manufactured using the (b) (4) BDS hold time, the use of which has been withdrawn from the BLA by the applicant (see Sections 3.1.3.1 and 14 of this memorandum). For the (b) (4) Phase 3 CTM lots, which were manufactured using the (b) (4) BDS hold time, (b) (4) of the planned (b) (4) of storage at -20°C have been completed, and studies of stability at storage at other temperatures are at various stages of completion. For the (b) (4) development lots, (b) (4) of the planned (b) (4) of storage at -20°C have been completed. (b) (4) of these development lots were manufactured using the (b) (4) BDS stabilization hold time. In addition to storage at -20°C, stability studies are underway in which vaccine DP is stored at (b) (4) relative humidity (RH), and (b) (4) RH. Because the vaccine is packaged in a foil sachet that is impermeable to light, no photostability study was conducted.

Tests performed on vaccine DP on stability are appearance, viable cell count, moisture, and (b) (4). Appearance is a qualitative assessment of product quality. Viable cell count is quantitative and stability-indicating; the method has evolved during product development, and validations of each method have been provided. Moisture is a quantitative assessment of vaccine DP quality (b) (4) supports safety of the vaccine DP. In a modified (b) (4) test, the (b) (4)

(b) (4). Validation reports for the two methods used have been provided and are acceptable.

Results of stability tests are provided. For three of the four Phase 3 CTM lots, a decrease in viable cell count was observed through 18 months of storage at -20°C, from 1×10^9 CFU/dose at the start of the study to as low as 4×10^8 CFU/dose at the 18-month time point; this potency result still met the acceptance criterion. For the (b) (4) CTM lot ((b) (4)), potency results met the acceptance criterion for all time points except for 12-month time point, at which time the result was above the acceptance criterion. An investigation was conducted, but no assignable cause for the increase in potency was found. At subsequent time points (18 and (b) (4)), potency results for this lot met the acceptance criterion.

The data that the applicant provided regarding stability of vaccine DP at the proposed long-term storage temperature of -20°C did not address long-term stability of vaccine DP with initial potency toward the lower end of the range of the acceptance criteria (4×10^8 CFU/dose). An information request regarding the issue was sent to the applicant. The applicant agreed to set a potency alert limit; any lot(s) with potency results below the alert limit will be placed on stability. Details regarding these communications are in Section 17 of this memorandum.

Storage of three of the CTM lots at (b) (4) led to a decrease in viable cell count, with CFU/dose falling below the acceptance criterion at the 3-month time point. Storage at higher temperature led to potency below the acceptance criterion after periods as short as two weeks (b) (4) or 5–10 days (b) (4).

In a freeze-thaw stability study, sachets from vaccine DP conformance lot (b) (4) were subjected to three freeze-thaw cycles of storage at -20°C and thawing at 5°C over a period of (b) (4). Control sachets were held at -20°C or 5°C for (b) (4). Appearance, viable cell count, and moisture content criteria were all met following the freeze-thaw cycles, and no differences were observed between experimental and control samples.

Based on 18 months of real-time data for the CTM lots, the applicant proposes a commercial shelf life of 18 months when the vaccine DP is stored at $-20 \pm 5^\circ\text{C}$. This proposal is reasonable. Post-approval, one vaccine DP commercial lot per year will be entered into a (b) (4) stability program at $-20 \pm 5^\circ\text{C}$.

3.11. Review of Drug Product PXVX0200, Powder for Oral Suspension: Summary

Overall, the BLA content regarding the vaccine DP is acceptable.

4. BLA REVIEW OF DRUG PRODUCT BUFFER, EFFERVESCENT GRANULE

A single-dose foil sachet of buffer is co-packaged with the vaccine DP sachet. In the reconstitution procedure, the contents of the buffer sachet are dissolved in 100 mL of purified bottled water. The contents of the vaccine sachet are then added, the solution is mixed, and the vaccine is taken orally. The composition of the buffer is listed in Table 3.2.P.1-1.

Table 3.2.P.1-1: Quantitative Composition of Buffer

Ingredient	Function	Manufacturer	Reference to Standard	Quantity (per dose)
Sodium Bicarbonate and Sodium Carbonate ^a	Buffer	(b) (4)	Manufacturer	2.4–2.9 g
Ascorbic Acid	Buffer; Water Chlorine Neutralizer	(b) (4)	(b) (4)	1.5–1.8 g
Dried Lactose	Mfg Flowability	(b) (4)	Manufacturer	0.18–0.22 g

(b) (4)

4.1. Pharmaceutical Development

4.1.1. Components of the Drug Product Buffer, Effervescent Granule

Bicarbonate is effective at neutralizing gastric acid. (b) (4) is a mixture of (b) (4) surface modified sodium carbonate and sodium bicarbonate powder. The moisture sensitivity of sodium bicarbonate can cause premature effervescence during manufacture and storage. In the manufacture of (b) (4)

reducing the likelihood of premature effervescence.


Ascorbic acid is included with bicarbonate because when the two substances are combined in water, carbon dioxide is produced, stabilizing the vaccine after administration. Additionally, ascorbic acid can inactivate chlorine, which may be present in water. Exposure of the bacterial strain to chlorine can lead to loss of viability. U.S. EPA and WHO limits for chlorine in water are 4–5 mg/L. In the 100 mL of purified bottled water used for reconstitution of the vaccine, up to 0.5 mg of chlorine may be present. At a molar ratio of 2.5 to 1, ascorbic acid can inactivate chlorine. Therefore, 1.25 mg of ascorbic acid would be required to neutralize the chlorine that could be present in the water. In the DP buffer, (b) (4) of ascorbic acid is present per sachet, which is in excess of the amount needed.

Lactose, derived from bovine milk, is a disaccharide of glucose and galactose. (b) (4)

In this anhydrous form, the dried lactose is useful as a flow-aid during blending of the buffer.

4.1.2. Drug Product Buffer, Effervescent Granule

The functions of the buffer are to provide the (b) (4) for the vaccine DP during reconstitution and to stabilize the vaccine DP after administration by neutralizing stomach acid. (b) (4)




There are no overages in the formulation of the buffer DP.

A description of the physicochemical and biological properties of the buffer DP is included and is summarized below.

(b) (4)



(b) (4)



Reconstitution:

For convenience, the buffer is designed to be completely dissolved in (b) (4) or less. Once the buffer powder is dissolved, the solution is clear and colorless.

4.1.3. Developmental History

4.1.3.1. Buffer Bulk Drug Product Blending Process



(b) (4)

The manufacturer of buffer BDP for the clinical trials was (b) (4). For manufacture of the bulk commercial buffer, (b) (4) was contracted, and PaxVax assumed responsibility for filling buffer BDP into sachets. A study was conducted to compare bulk buffer blend from the two manufacturers. Results of (b) (4) comparisons indicated that the (b) (4) material was comparable to the (b) (4) material.

4.1.3.2. Filling Process

The automated sachet filler used for the vaccine DP is also used for the bulk buffer DP. A summary of the filling process parameters is provided in Table 3.2.P.2.3.2-8, and in-process tests for the buffer DP filling process are listed in Table 3.2.P.2.3.2-9. For a batch size of (b) (4) sachets, not more than five failures are allowed, and all (b) (4) sachets that were tested passed the (b) (4) in-process tests.

(b) (4)

(b) (4)

To evaluate the effects of environmental conditions during the filling process on the appearance of the buffer BDP, a stability study was conducted in which the temperature and exposure of samples to (b) (4) were varied. (b) (4)

(b) (4)

(b) (4)

(b) (4)

4.1.3.3. Comparability Study of Buffer Clinical Phase 3 to Buffer Conformance Lots

The impact of the change in manufacturer of the buffer BDP from (b) (4) to (b) (4)/PaxVax was evaluated in a comparability study. Three lots made by each of the manufacturers were compared. Changes included (b) (4)

(b) (4)

. Thirteen critical process parameters and eight critical quality attributes were affected by these changes. Samples were taken and tested, and all acceptance criteria were met for each of the attributes, which included (b) (4)

The applicant concluded that the (b) (4) manufacturing processes were comparable, which is a reasonable conclusion. The impact of the changes will be monitored under the stability program.

4.1.4. Container Closure System

The sachets for the buffer DP are made of the same materials as the sachets for the vaccine DP (reviewed in Section 3.1.3.5 of this memorandum). Sachet integrity and visual control were assessed, and all (b) (4) sachets tested met the acceptance criteria. Reproducibility of the dose was assessed by measuring the amount of powder removed from the sachets. The acceptance criterion of (b) (4) was met for (b) (4) sachets tested from each of the three lots.

4.1.5. Microbiological Attributes

The buffer DP is non-sterile. Specifications for raw materials include acceptance criteria for (b) (4) for (b) (4) and for (b) (4) and absence of specified organisms for dried lactose. Release and stability programs also include these two tests to assess the microbiological attributes of the buffer (b) (4) and DP.

4.2. Manufacture

Manufacturing of the buffer BDP is performed by (b) (4). Filling and primary packaging is performed by PaxVax (b) (4) and secondary packaging is performed by (b) (4). Commercial testing of the buffer BDP is conducted by three companies: (b) (4) and PaxVax. Commercial testing of the packaged buffer DP is conducted by (b) (4), and PaxVax.

The batch formula for the buffer BDP is presented in Table 3.2.P.3.2-1.

Table 3.2.P.3.2-1: Buffer Bulk Drug Product Batch Formula

Component	Reference to Standards	Amount per Batch
Sodium Bicarbonate and Sodium Carbonate ^a	Manufacturer	(b) (4)
Ascorbic Acid	(b) (4)	
Dried Lactose	Manufacturer	

(b) (4)

The manufacturing process includes the following steps: (b) (4)

final blending; packaging, storage, and shipping of buffer BDP to PaxVax; and receipt, storage, and filling of buffer into sachets.

1 page has been determined to be not releasable: (b)(4)

[REDACTED]

[REDACTED]

The filling process is depicted in Figure 3.2.P.3.3.4-2. Filling is conducted in a room classified at [REDACTED] air cleanliness level, maintained at [REDACTED]. Buffer BDP received at PaxVax is stored at [REDACTED] for no longer than [REDACTED]. For filling, a batch of [REDACTED] maximum is used to fill approximately [REDACTED] sachets.

[REDACTED]

The filling process for the buffer BDP is the same as that for the vaccine BDP, which is reviewed in Section 3.3 of this memorandum.

Critical process parameters are: [REDACTED]

[REDACTED]. Operating parameters are [REDACTED]. In-process tests during primary packaging are [REDACTED]. The overall process duration from opening of the first buffer BDP [REDACTED] to filling of the last sachet is [REDACTED].

Buffer final DP is stored at [REDACTED] prior to shipment to a secondary packager, where each sachet is placed into a carton along with a vaccine DP sachet. Long-term storage is at -20°C.

(b) (4)

4.3. Controls of Critical Steps and Intermediates

For manufacture of the buffer DP, Table 3.2.P.3.4.2-1 lists the critical process parameters, along with the process set point, process range, and rationale for each parameter. Criticality was assigned after a risk assessment was conducted to determine which parameters could impact product quality or safety. Table 3.2.P.3.4.3-3 lists the controlled and monitored process parameters for manufacture of the buffer DP. In-process tests are [REDACTED]

[REDACTED] The buffer BDP blending and filling processes were evaluated in validation project plans.

Table 3.2.P.3.4.4.1-5 outlines the release specification for the buffer BDP. The critical quality attributes are [REDACTED].

The PaxVax release specification includes review of the tests listed on the certificate of analysis, [REDACTED].

The stability specification for the buffer BDP includes assessment of [REDACTED]

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

(b) (4)

(b) (4)

4.4. Process Validation and/or Evaluation

Validation protocols were generated for the manufacturing processes for buffer bulk DP and final DP. To evaluate consistency of the processes, three commercial-scale lots of buffer BDP were manufactured by (b) (4), and three commercial-scale lots of buffer DP were manufactured by PaxVax.

Manufacture of the three (b) (4) buffer BDP lots was consistent during the blend process, with parameters maintained within the acceptable ranges. Uniformity of the blend was studied by (b) (4). Information has been provided regarding deviations that occurred; appropriate corrective actions were taken. Acceptance criteria were met for all three (b) (4) buffer BDP lots, demonstrating uniformity of the buffer BDP blend.

Table 3.2.P.3.5.2.3-9 lists the (b) (4) buffer BDP lot numbers, PaxVax buffer BDP lot numbers, and resulting buffer DP lot numbers, along with the dates of manufacture of the Buffer DP lots.

Table 3.2.P.3.5.2.3- 9: Buffer DP Commercial-Scale Validation Lots

(b) (4) (b) (4) Buffer BDP Lot	Resulting PaxVax Buffer BDP Lot	Resulting Buffer DP Lot ^a	Buffer DP Date of Manufacture
(b) (4)	(b) (4)	(b) (4)	01Jul2015
(b) (4)	(b) (4)	(b) (4)	08Jul2015
(b) (4)	(b) (4)	(b) (4)	13Aug2015

^aNote that lot Buffer filling lot (b) (4) was cancelled due to a mechanical issue with the filler (refer to DEV-0001), and lot (b) (4) was cancelled prior to production of the lot.

The manufacture of the three PaxVax buffer DP validation lots is described in Validation Report VPR-177. Details are provided regarding validation of each step in the processing of buffer BDP into buffer final DP, including receipt and storage of the buffer BDP, filling into sachets, and release testing. Buffer BDP storage temperature and duration were within acceptable ranges for all three lots. For the filling process, criteria were met for each controlled or monitored parameter. In-process tests during the filling process were (b) (4). Acceptance criteria were met, with no failures out of the (b) (4) sachets tested from each lot. Additionally, in an Acceptable Quality Level evaluation, (b) (4) sachets from each lot were assessed for (b) (4); all acceptance criteria were met. Information has been provided regarding deviations that occurred. Deviations were related to exposure of the buffer DP samples to excessive moisture prior to testing. Appropriate corrective actions were taken.

In the original submission, as part of the validation of the filling process, the applicant included an assessment of content uniformity of the final buffer DP according to (b) (4). In a subsequent amendment, the applicant stated that such an assessment is not appropriate, as the buffer is not itself a drug substance and does not contain any drug substance. This conclusion is reasonable. In the validation, acceptance criteria were met for buffer capacity and ascorbic acid content for the sachets that were tested. During commercial manufacture, release testing serves to demonstrate consistency of the buffer DP.

4.5. Control of Excipients

The only compendial excipient in the buffer DP is ascorbic acid. Non-compendial excipients are dried lactose and sodium bicarbonate/sodium carbonate (b) (4). The specification for the dried lactose is described in Section 3.6 of this memorandum. For (b) (4), attributes tested by (b) (4) are (b) (4), and assessment of the

manufacturer's certificate of analysis. For each attribute, the method used and acceptance criteria are provided.

Dried lactose is the only excipient of animal origin in the buffer DP. As it is derived from bovine milk, it does not require a certificate of suitability. There are no novel excipients in the buffer DP.

4.6. Control of Drug Product Buffer, Effervescent Granule

The buffer DP specification is provided in Table 3.2.P.5.1-1. Methods and acceptance criteria for the tests are listed.

Table 3.2.P.5.1-1: Buffer Drug Product Specification

Attribute	Method	Acceptance Criteria
Description		
Appearance	PaxVax [®] Q108	White to off-white powder, visually free of foreign particles
Visual Control	PaxVax Q198	Off-white sachet, two visible black registration marks on each side of the sachet, seals are continuous on all 4 sides, and weld lines are NLT (b) (4) from the inner weld line to the outer edge of the sachet on all 4 sides and lot number and date of manufacturer expiry are printed on the sachets are accurate and legible
Identity		
Identity of Carbonates and Bicarbonates	(b) (4)	Conforms
Identity of Lactose (b) (4)	(b) (4)	Conforms
General		
(b) (4)	PaxVax Q102 (b) (4)	(b) (4)
Sachet Integrity Test	PaxVax Q211	Inspection Level II with AQL of (b) (4). Failures have defect of (b) (4)
Reconstitution Time	PaxVax Q212	(b) (4)
Content		
(b) (4)	PaxVax Q215 EP 2.9.5	(b) (4)
(b) (4)	PaxVax Q215 EP 2.9.5	(b) (4)
Assay for Ascorbic Acid	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)
Safety		

(b) (4)	(b) (4)	(b) (4)
Absence of Specified Organisms (b) (4)	(b) (4) ^{er}	No growth for (b) (4) (b) (4)

(b) (4)

^c Methods used for release and stability

Validations of the analytical procedures are provided; each validation is adequate to provide assurance that the method is appropriate for its intended use and can be performed consistently. Non-compendial methods for the buffer DP are sachet integrity test, reconstitution time, and ascorbic acid assay. Compendial methods are identity of carbonates and bicarbonates, identity of lactose by [REDACTED] and absence of specified organisms. Justification of the specification is provided and is summarized below for each test.

- Appearance:
The acceptance criterion is based on components of the buffer DP. All conformance lots met the criterion.
- Visual control:
The acceptance criterion is the same as for the vaccine DP sachet, described in Section 3.7 of this memorandum.
- Identity of carbonates and bicarbonates:
This test is described in Section 4.3 of this memorandum. All buffer DP lots have met the criterion.
- Identity of dried lactose
This test is described in Section 4.3 of this memorandum. All buffer DP conformance lots have met the criterion.
- [REDACTED]
- Sachet integrity test
The acceptance criterion is the same as for the vaccine DP sachet, described in Section 3.7 of this memorandum. All buffer DP conformance lots have met the criterion.
- Reconstitution time
This test is described in Section 4.3 of this memorandum. All buffer DP conformance lots have met the criterion.

- [REDACTED]
- [REDACTED]
- Assay for ascorbic acid
This test is described in Section 4.3 of this memorandum. The acceptance criterion is based on manufacturing data, assay verification, and historical experience. All buffer DP conformance lots have met the criterion.
- [REDACTED]
- [REDACTED]
- Absence of specified organisms
The acceptance criterion of no growth of the [REDACTED] specified organisms per [REDACTED] is based on data obtained during development and release. Buffer DP process conformance lots met the criterion.

For each attribute, the test method that was used and the acceptance criteria that were set were appropriate and adequate.

The applicant did not include a test for moisture content in the specification for the buffer DP. CBER requested that the applicant include moisture content in release tests and stability tests (first and last time points) for the buffer DP. The applicant responded, stating that the methods available for assessing moisture content of the buffer DP were found to be inconsistent, because the presence of ascorbic acid in the product caused interference. The DMPQ reviewer stated that the existence of such interference was reasonable. The applicant's position on this issue is acceptable. Details regarding these communications are in Section 15 of this memorandum.

Buffer DP lots are listed in Tables 3.2.P.5.4-1 and 3.2.P.5.4-2.



[REDACTED]

Batch analyses are provided. Acceptance criteria were met for all [REDACTED] lots of buffer DP.

4.7. Reference Standards and Materials

During testing of the buffer DP, the only reference material used is [REDACTED] lactose [REDACTED]. It is used as a control for the identity test for dried lactose by [REDACTED].

4.8. Container Closure System

Sachets used as the container closure system for the buffer DP are the same as for the vaccine DP, which is reviewed in Section 3.9 of this memorandum. The applicant states that a process validation protocol will be executed during packaging of the first commercial lot of buffer DP.

4.9. Stability

Three commercial-scale conformance lots of buffer DP have been entered into a stability program. Stability data have been provided for storage of these lots at -20°C for up to six months. Additionally, a stability study for a pilot-scale lot of buffer DP is underway; this lot was used as CTM in three Phase 3 trials. Stability results have been provided for storage of this lot at [REDACTED] for up to [REDACTED] and at [REDACTED] for up to [REDACTED].

Stability tests for the buffer DP conformance lots are appearance, reconstitution time, [REDACTED] ascorbic acid assay, [REDACTED]. For the buffer DP CTM lot, stability tests are appearance, average [REDACTED] percent loss on drying, disintegration (reconstitution) time, [REDACTED], ascorbic acid assay, and microbial purity. Validation reports for the test methods are provided and are acceptable.

Appearance is a qualitative assessment of product quality. Ascorbic acid content and [REDACTED] are quantitative assessments and stability-indicating parameters. [REDACTED] is an assessment of buffer DP safety. Although loss on drying was included as a stability test by [REDACTED] (the manufacturer of the CTM lot), it is no longer used, as the applicant states that moisture content is not appropriate for any of the excipients in the buffer DP.

For the buffer DP conformance lots, acceptance criteria were met for all three lots for storage at the long-term storage conditions of -20°C and of (b) (4) through the six-month time point, and at the accelerated condition of (b) (4) through (b) (4). For the Phase 3 CTM lot, acceptance criteria were met for storage at (b) (4) through the (b) (4) time point and at the accelerated condition of (b) (4) through the (b) (4) time point.

A freeze-thaw study was conducted in which buffer DP was subjected to three cycles of freezing at -20°C and thawing at 5°C over the course of (b) (4). No differences in appearance, reconstitution time, (b) (4), ascorbic acid content, or buffer capacity were observed for these samples compared to control samples that were stored at -20°C or 5°C for the length of the (b) (4).

Based on the long-term stability results for three conformance lots and the results for the pilot lot stored at the long-term and accelerated conditions, the applicant proposes a shelf life for the buffer DP of 24 months at -20°C. This proposal is reasonable.

The applicant states that post-approval, one commercial lot of buffer DP per year will be placed on stability at -20°C ± 5°C for (b) (4).

4.10. Review of Drug Product Buffer, Effervescent Granule: Summary

Overall, the BLA content regarding the buffer DP is acceptable.

5. BLA REVIEW OF ADVENTITIOUS AGENTS

Vaxchora is a live bacterial product. Ingredients of animal origin are used in the preparation of both the vaccine component and the buffer component. The main theoretical risk associated with these ingredients is contamination of the product by agents of Bovine Spongiform Encephalopathy (BSE) or other Transmissible Spongiform Encephalopathies (TSE).

Animal-derived materials for the vaccine DP are (b) (4), Hy-Case SF, and dried lactose. The only animal-derived material for the buffer DP is dried lactose. BSE/TSE statements for the raw materials are provided. The milk derivatives used in the manufacture of the raw materials were sourced from healthy animals in the same conditions as milk collected for human consumption and deemed fit for human consumption.

Materials of construction of equipment (stoppers, filters, manifold, and/or containers) that come into contact with drug substance and drug product during their manufacture as well as a packaging component used in the final packaging process (b) (4) may contain trace levels of animal tallow derivatives. As tallow is processed under rigorous conditions, it is considered compliant with the TSE guidelines.

6. BLA REVIEW OF EXCIPIENTS

Excipients in the vaccine DP and the buffer DP are reviewed in Sections 3.6 and 4.5 of this memorandum respectively. There are no novel excipients in either DP.

7. BLA REVIEW OF LOT RELEASE PROTOCOL

I reviewed the Lot Release Protocols for the vaccine DP and the buffer DP and found them to be acceptable.

8. BLA REVIEW OF BATCH PRODUCTION RECORDS

Master batch record documents (templates for batch production records) were provided. For the vaccine DP, representative executed batch records were provided and were reviewed. These batches and lots are:

(b) (4) vaccine IBDS Batch (b) (4)
PaxVax vaccine BDS Batch (b) (4)
PaxVax vaccine BDP Lot (b) (4) 3
PaxVax vaccine DP Lot (b) (4)
PaxVax vaccine DP Phase 3 CTM Lot (b) (4)

For the buffer DP, representative executed batch records were provided and were reviewed. These lots are:

(b) (4) buffer BDP Lot (b) (4)
(b) (4) buffer BDP Lot (b) (4)
(b) (4) buffer BDP Lot (b) (4)
PaxVax buffer DP Lot (b) (4)
PaxVax buffer DP Lot (b) (4) and Lot (b) (4)

For the MSL and WSL, representative executed batch records were provided and were reviewed. These lots are:

(b) (4)

All batch records were acceptable.

9. BLA REVIEW OF LABELING

I reviewed and provided comments on the proposed labeling (container, carton, and package insert). I recommended that the instructions for administration of the vaccine emphasize the importance of resuspension of the buffer DP and vaccine DP in purified bottled water in the proper order. The instructions should state that if resuspension occurs in an improper order, the vaccine must be discarded. Additionally, the label should state that the purified bottled water must be in the temperature range of 5–22°C. These instructions are intended to ensure that the potency of the vaccine remains within the specification.

10. ENVIRONMENTAL ASSESSMENT

The applicant submitted an environmental assessment (EA) in accordance with 21 CFR 25 and CBER's Guidance for Industry ("Environmental Assessment of Human Drug and Biologics Applications" and "Determining the Need for and Content of Environmental Assessments for Gene Therapies, Vectored Vaccines, and Related Recombinant Viral or Microbial Products").

The EA consists of a description of the proposed product, an evaluation of potential environmental issues, identification of characteristics that may cause adverse effects, an evaluation of the potential consequences of each adverse effect, an evaluation of the likelihood of occurrence of each adverse effect, an estimation of the risk posed by each characteristic of the product, a description of management strategies for risks from deliberate release or marketing of the product, a determination of the overall risk of the product, and planned mitigation measures.

The applicant has addressed the risk of shedding of the vaccine strain by vaccinees. In previous human trials with CVD 103-HgR, shedding at low levels was detected in approximately 30% of recipients, resulting in maximal shedding of 4×10^4 total CFU per person. Considering that the infectious dose for wild-type *V. cholerae* is approximately 10^6 CFU when stomach acid has been neutralized, household transmission of the attenuated vaccine strain is unlikely. In the PaxVax Phase 1 study, the product strain was shed in the stools of 11.3% of vaccine recipients on any day through 7 days post-vaccination, and no transmission or increase in antibody titer was detected among 24 household contacts.

The vaccine strain would not be expected to survive sewage treatment processes. Even if survival did occur, persistence of the strain in the environment is considered unlikely, as a study examining survival in estuarine water showed a decrease from an inoculum of 10^5 CFU/mL to non-detectable levels within 14 days. Considering the infectious dose, transmission of the vaccine strain via the environment is unlikely; even if it were to occur, the consequences would be minor, given the safety profile of the strain.

The applicant has addressed the risk of reversion of the vaccine strain to toxicity. Because the genetic modifications consist of deletion of DNA sequences, reversion to toxicity would require re-acquisition of these sequences. The likelihood of re-acquisition from virulent cholera is considered low, as mating experiments have not been able to detect such transfer. Even if it were to occur, the resulting strain would need to compete with the environmental cholera from which the sequence was transferred. The likelihood of gene transfer via bacteriophage is also considered low, as studies have shown that infection of *V. cholerae* classical strains with the cholera toxin bacteriophage from El Tor strains has not led to stable lysogeny, perhaps because of the lack of the required integration sequence.

After estimating each of the risks, the applicant states that the overall risk of the vaccine is negligible. Mitigation measures include a statement in the package insert instructing physicians to advise vaccinees to wash their hands thoroughly after using the bathroom and before preparing or handling food to reduce the likelihood of transmission of the vaccine strain to household contacts. The package insert also states that all vaccine materials must be disposed of as medical waste. Any spilled vaccine must be inactivated with 70% isopropyl alcohol or 10% bleach solution, and any non-disposable equipment used in the preparation of Vaxchora must be cleaned in the same way.

The potential environmental exposure and environmental stability of the vaccine are expected to be minimal. No significant environmental impacts were identified, and a finding of no significant impact has been prepared.

11. UNII CODE DESIGNATIONS

I reviewed the UNII code designations and found them to be acceptable.

12. COMPONENTS INFORMATION TABLE

I reviewed the components information table (Appendix A). Three components of animal origin are used in the manufacturing process: (b) (4), Hy-Case SF, and lactose. Also listed in the components information table are four substances used in the manufacturing process that contain one or more of the three animal-derived components: (b) (4). No discrepancies were identified. All components have been investigated for the origin of animal material and have been determined to comply with the relevant guidance. Therefore, the components are acceptable for use. This is documented throughout my review.

13. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION, DATED 6 JANUARY 2016

After complete examination of the submission, information was needed to complete the review. An IR was sent to the applicant on 6 January 2016. The applicant submitted a response on 11 January 2016 (Amendment 5). Below is the IR comment (in bold), followed by the applicant's response.

1. We note that you have changed the manufacturer of the working seed lots going forward. We also note that you currently have (b) (4) vials of the working seed lot manufactured by the previous manufacturer and that vials from that lot were used to manufacture the vaccine used in the clinical trials submitted in your license application. Please specify how many seed lot vials will be used per batch and per year. Please also provide a timeline of use of remaining vials (i.e., date remaining vials will be exhausted).

The (b) (4) vials of working seed lot (WSL) in the description of Lot (b) (4) manufactured by the previous manufacturer (b) (4) referred to the batch size and does not reflect the current inventory. Most of this batch has been used for process development, stability, and for the Phase 1 clinical trial. There are only (b) (4) vials remaining in the current manufacturing inventory. (b) (4) WSL vials are used per batch. It is planned that (b) (4) batches will be manufactured in 2016 and this will therefore exhaust the (b) (4) WSL supply. Hence, the WSL manufactured by (b) (4), the previous manufacturer, will no longer be available in the near term and all subsequent production will use the WSL from the new manufacturer, (b) (4).

Review: The response is adequate.

14. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION AND AMENDMENT 5, DATED 2 FEBRUARY 2016

An IR was sent to the applicant on 2 February 2016. The applicant submitted a partial response on 19 February 2016 (Amendment 9) and additional responses on 26 February 2016 (Amendment 11), 4 March 2016 (Amendment 16), and 8 March 2016 (Amendment 19). Listed below are the IR comments (in bold), followed by the applicant's response to each comment.

- 1. In Section 2.3.S.2.1, you indicate that [REDACTED] 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 [REDACTED]**

- a. Please provide an estimate of the number of doses of final drug product (DP) that can be made using the [REDACTED] remaining [REDACTED] WSL vials.**

The remaining [REDACTED] vials of [REDACTED] WSL are sufficient to manufacture [REDACTED] IBDS batches, which will result in approximately [REDACTED] doses of Vaxchora drug product.

Review: The response is adequate.

- b. Please provide an estimate of when the remaining vials of MSL will be exhausted.**

The remaining MSL vials may be exhausted by [REDACTED]

Review: The response is adequate.

- 2. In section 2.3.S.2.1, you indicate that since January 2015, [REDACTED] the sole manufacturer of your WSL. The data you provided in support of [REDACTED] as a contract manufacturer for your new WSL are insufficient for approval of WSL manufactured by [REDACTED]. Therefore, we recommend that after approval of your BLA, you submit a Prior Approval Supplement (PAS) for use of [REDACTED] as your WSL manufacturer. Your supplement should address the following:**

- a. Please provide data regarding the [REDACTED] WSL.**
- b. Please provide a general diagram of the [REDACTED] facility and identify the suites, rooms, or areas where your WSL is manufactured and where major equipment (such as the lyophilizer) is located.**
- c. Please provide a description of the [REDACTED] 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.

- d. 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 [REDACTED] is different from the one used at [REDACTED]. In addition, you describe several changes related to the lyophilizer such as [REDACTED]. Please indicate whether the lyophilization cycle was validated using these changes.
- e. Please provide all manufacturing information and testing data from three lots of final DP manufactured using the [REDACTED] 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.

PaxVax agrees to submit a Prior Approval Supplement (PAS) for the [REDACTED] WSL. The PAS will contain the data and information requested above (items 2a-e). PaxVax plans to manufacture the three lots of vaccine DP from [REDACTED] batches of bulk drug substance (BDS). These BDS batches would be manufactured from [REDACTED] batches of IBDS produced using the current [REDACTED] WSL lot. At least [REDACTED] of stability data from the proposed IBDS, BDS, and vaccine DP lots will be provided at the time of submission to support the new [REDACTED] WSL lot. Does the Agency agree that a minimum of three months of stability data for DP may be sufficient at the time of submission?

Review: The response is adequate. In response to the applicant's question, an IR was sent to the applicant on 10 March 2016, as follows:

When you submit your Prior Approval Supplement (PAS) for the [REDACTED] Working Seed (WS), please include a minimum of [REDACTED] of stability data for three lots each of vaccine intermediate bulk drug substance, bulk drug substance and final drug product produced using the [REDACTED] WS.

The applicant responded on 25 March 2016 (Amendment 25) as follows:

PaxVax agrees to submit as a PAS, [REDACTED] of stability data for three lots each of vaccine intermediate bulk drug substance, drug

substance, and final drug product, all being manufactured using the [REDACTED] working seed lot.

Review: The response is adequate.

3. The information you provided for the transfer and storage of the MSL and the WSL is unclear. Please address the following:

a. Please describe the method of transfer of MSL Lot [REDACTED] and WSL Lot [REDACTED] for storage.

Vials were removed from the [REDACTED] and packed in temperature controlled containers with [REDACTED] and temperature loggers. Containers were shipped from [REDACTED]. Upon receipt, the shipment and contents were inspected, inventoried, and data from the temperature data logger(s) downloaded. The downloaded data was reviewed, found to be acceptable and archived. The vials were then stored at [REDACTED] for long term storage at [REDACTED] in qualified and calibrated [REDACTED].

Review: The response is adequate.

b. Please describe the conditions and procedures for storage of MSL and WSL at [REDACTED]

The inventory of the MSL and WSL vials are divided between [REDACTED] qualified and calibrated [REDACTED] as part of a risk management procedure. The vials are stored at [REDACTED] for long term storage. The [REDACTED] are on a 24 hour temperature monitoring system [REDACTED] that alerts staff when any temperature excursion occurs. The temperatures are checked [REDACTED] by a qualified staff and the data from the data loggers are printed and reviewed by Biorepository Specialist [REDACTED]. The [REDACTED] are locked for limited access. [REDACTED] keeps an inventory for all incoming and outgoing vials to ensure an accurate accountability.

Review: The response is adequate.

c. Please describe the method of transfer of MSL and WSL as needed to and from [REDACTED]

Vials are removed from the [REDACTED] and packed into single-use qualified shipping container(s) (e.g. [REDACTED]), along with temperature data loggers. The containers are then [REDACTED], sealed, and shipped to [REDACTED]. [REDACTED] updates their inventory system to ensure accurate accountability. Upon receipt, the shipment and contents are inspected and inventoried. Data from the temperature data logger(s) are downloaded, reviewed for acceptability, and archived. The vials are stored at [REDACTED] in a qualified (i.e. temperature mapped) and calibrated [REDACTED] and logged into the [REDACTED] inventory. The [REDACTED] are on a temperature monitoring system that alerts staff when preset limits are exceeded. The temperatures are checked

by a qualified staff and the data from the data loggers are printed and reviewed by QA . The are locked for limited access. For shipment, PaxVax notifies to ship the WSL to or deputy then removes the vials from their and the vials are logged out per the log book. The vials are then placed into a qualified shipping container, , along with a temperature data logger, sealed, and shipped to .

Review: The response is adequate.

d. Please describe the procedures and conditions for storage of MSL and WSL at prior to use.

The vials were stored at in a qualified (i.e. temperature mapped) and calibrated . The are on a temperature monitoring system that alerts staff to any temperature excursion. The temperatures are checked by a qualified staff and the data from the data loggers are printed and reviewed by QA . The are locked for limited access.

Review: The response is adequate.

e. Please describe the method of transfer of WSL to for use in manufacturing IBDS and the WSL storage procedures and conditions at prior to use in manufacturing.

At , the vials are removed from their and then placed into a single-use qualified shipping container (e.g. , along with a temperature data logger, sealed, and shipped to . updates their inventory system to ensure accurate accountability.

Review: The response is adequate.

4. In Section 3.2.P.2.3.1, BDS Hold Step, you describe a proposed change to the manufacturing process, in which the BDS is held at for rather than . Because your clinical studies were conducted using material manufactured using the 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 , 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 [REDACTED] BDS hold time, these data did not include evaluation of appearance or [REDACTED]. Please provide real-time stability data for three lots of DP manufactured using the [REDACTED] BDS hold time. These data should include results of all four stability tests (appearance, viable cell count, moisture content, and [REDACTED])

PaxVax hereby withdraws from the BLA the request for a BDS hold-step duration of 6 [REDACTED] of drug product manufacturing). PaxVax agrees to licensure with the [REDACTED] hold time, and confirms that any request to change from the [REDACTED] to the [REDACTED] hold-step will be submitted post-licensure and as a Pre-Approval Supplement (PAS). Such a PAS would contain a minimum of 12 months real time stability data for three lots of Drug Product made from BDS using the [REDACTED] hold-step.

Review: The response is adequate. However, the applicant did not provide updates to the relevant section of the BLA. An IR was sent to the applicant on 25 March 2016, as follows:

In your amendment #19, received on March 8, 2016, you agreed to the [REDACTED] hold time for BDS and withdrew from the BLA the request for the BDS hold-step duration of [REDACTED] of drug product manufacturing). We note that there are several sections in your BLA (Sections 3.2.P.3.3 (Description of Manufacturing Process and Process Controls), 3.2.P.3.4 (Controls of Critical Steps and Intermediates) and Section 3.2.P.3.5, (Process Validation and/or Evaluation) that describe the hold time as [REDACTED]. Please amend these sections and any other relevant sections to remove reference to the BDS hold step of [REDACTED]

The applicant submitted a response on 6 April 2016 (Amendment 28). The amendment included updated sections of Modules 2 and 3, removing reference to a BDS hold step of [REDACTED] from the BLA. The response is adequate. The updated content is reviewed in the relevant sections of this memorandum.

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-of-general-safety-test-regulations-that-are-duplicative-of-requirements-in-biologics>. You may elect to remove the GST from your application.

PaxVax has elected to remove the GST from the vaccine and buffer specifications (Section 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.6 [PXVX0200, Powder for Oral Suspension] and 3.2.P.5.1, 3.2.P.5.2, 3.2.P.5.3, 3.2.P.5.6 [Buffer, Effervescent Granule]) in accordance with the July 2, 2015 amended biological regulations (Federal Register “Revocation of General Safety Test Regulations That Are Duplicative of Requirements in Biologics License Applications”).

Review: The response is adequate.

6. Please provide information regarding results of tests for leachables and extractables for [REDACTED] Ready to process [REDACTED].

[REDACTED], the manufacturer of the [REDACTED], has performed extractable studies based on representative classes of components according to their materials of construction since they manufacture hundreds of individual and combined components for their bioprocess assembly products. The extractable data are provided in Chapter 7 of their [REDACTED] and a copy of the Certificate of Quality for the [REDACTED] has also been provided.

Review: The response is adequate.

7. Please provide the reference “Gurwith M. 2015,” cited in Section 1.2, Request for Priority Review Voucher.

A copy of the presentation “Gurwith M. (2015) Development of a “Second Generation” Oral Cholera Vaccine for Epidemic Response and Endemic Country Use” cited in Section 1.2 is provided. This was presented at the Vaccines for Enteric Diseases conference held in Edinburgh, Scotland on July 9, 2015.

Review: The response is adequate.

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.

Investigations QCI-15-29 and QCI-15-30 have been provided.

Review: The response is adequate.

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.

PaxVax Stability Program SOP Q120 and stability studies STB-52-12 and STB-127-15 have been provided.

Review: The response is adequate.

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.

Table 1 through Table 4 list the critical and non-critical in-process tests and release tests for IBDS, BDS, Vaccine, Bulk Buffer, and Buffer products.

(b) (4)



For IBDS and BDS, the [REDACTED] was removed per our response to Question 15.
For BDS, there are no critical or non-critical in-process tests.

Table 3: PXVX0200 Vaccine List of In-Process and Release Assays

Test Name	Method No.	Test Type	Validation Status	Testing Performed At
(b) (4)	(b) (4)	(b) (4)	(b) (4)	(b) (4)
Sachet Integrity Test	Q211	(b) (4)	Validated	PaxVax
		PaxVax PXVX0200 Release		
Appearance	Q108	PaxVax PXVX0200 Release	n/a	PaxVax
(Sachet) Visual Control	Q198	PaxVax PXVX0200 Release	n/a	PaxVax
(b) (4)	512020GMP	PaxVax PXVX0200 Release	Validated	(b) (4)
Moisture Content	Q193	PaxVax PXVX0200 Release	Qualified	PaxVax
Viable Cell Count	Q217	PaxVax PXVX0200 Release	Validated	PaxVax
(b) (4)	0493	PaxVax PXVX0200 Release	Validated	PaxVax
Absence of Specified Organisms	0493	PaxVax PXVX0200 Release	Validated	PaxVax

Table 4: Bulk Buffer and Buffer List of In-Process and Release Assays

Test Name	Method No.	Test Type	Validation Status	Testing Performed At
(b) (4)				
Appearance	Q108	PaxVax In-Coming Bulk Buffer Release	n/a	PaxVax
		PaxVax Buffer Release		
(Sachet) Visual Control	Q198	PaxVax Buffer Release	n/a	PaxVax
Identity of Carbonates and Bicarbonates	(b) (4)	PaxVax Buffer Release	n/a	(b) (4)
Identity of Lactose (TLC)	M680004	PaxVax Buffer Release	n/a	
Sachet Integrity Test	Q211	PaxVax Buffer Release	Validated	PaxVax
(b) (4)	Q102	PaxVax Buffer Release	Qualified	PaxVax
Reconstitution	Q212	PaxVax Buffer Release	Validated	PaxVax
(b) (4)	Q215	PaxVax Buffer Release	Qualified	PaxVax
	Q215	PaxVax Buffer Release	Qualified	PaxVax
Assay for Ascorbic Acid	M680004	PaxVax Buffer Release	Qualified	(b) (4)
(b) (4)	M680004	PaxVax Buffer Release	Qualified	
(b) (4)	0493	PaxVax Buffer Release	Validated	
Absence of Specified Organisms	0493	PaxVax Buffer Release	Validated	

The General Safety Test has been deleted from the vaccine and buffer release specifications per our response to Question 5.

Review: The response is adequate.

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.

(b) (4) Assay SOP PROC-(b) (4)-US-OP-034992 has been provided and included in Section 3.2.S.2.4, Section 3.2.S.4.2, and Section 3.2.P.5.2 [PXVX0200, Powder for Oral Suspension].

Review: The response is adequate.

- 12. Regarding the (b) (4) [REDACTED] used as an identity test for (b) (4) [REDACTED] drug product, you provided a Technical Specification for Assay Performance but not the SOP. Please provide the SOP for this test.**

The (b) (4) [REDACTED] method has been discontinued as described in the response to Question 15 below, therefore the SOP is not provided here.

Review: The response is adequate.

- 13. Three SOPs were submitted regarding the viable cell count: Viable Cell Count in CVD 103-HgR, (b) (4) [REDACTED], AIM-PFT-6001, effective date December 13, 2013; Viable Cell Count in PXVX0200 CVD 103-HgR using the (b) (4) [REDACTED] 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.**

Microbiological methods have a degree of variability and are inherently different from analytical ones (Sandle 2015). All three methods employed during manufacture of PXVX0200 are (b) (4) [REDACTED] methods relying on (b) (4) [REDACTED] Colony Forming Units (CFU) (b) (4) [REDACTED] are only estimates of cells present. They are estimates of cells that can grow under the conditions of the test. Each colony could arise from a single cell or several thousand. Since the true cell count of a traditional analytical reference or positive control is not possible to quantify, a reference or control is generally not included in (b) (4) [REDACTED] methods. Instead, to ensure accuracy of the method of counting, the range of countable colonies that is dependent on how the organism grows under the test conditions has to be established. The common acceptance for countable colonies (b) (4) [REDACTED]. Error of estimates increases below the lower limit while competition for space and nutrients occur at the higher limit resulting in underestimation (Sutton 2012). For the (b) (4) [REDACTED] methods, Q208 and Q217, the equivalent of the range of countable colonies (b) (4) [REDACTED] which are calculated as CFU/mL. In addition, it is common to ensure that the test method, dilution and (b) (4) [REDACTED] do not inhibit or enhance growth by a spike and recovery study. These two approaches were established during validation of the Q208 and Q217 methods to ensure the accuracy of the methods.

PaxVax is currently assessing the feasibility and merits of establishing a system check reference to detect any unusual event, such as, a media lot that could cause an out-of-trend result. This is not to be confused with the typical reference or positive control used in more precise analytical methods.

Review: The response is not adequate. An IR was sent to the applicant on 25 March 2016. The applicant submitted a response on 6 April 2016 (Amendment 28). Below is the IR comment (in bold), followed by the applicant's response.

In your response to question 13a in amendment #11, received on February 26, 2016, regarding Viable Cell Count Methods, you state that “the true cell count of a positive control for the viable cell count is not possible to quantify.” This would imply that the test sample also cannot be quantified, which would negate the utility of the test. However, the viable cell count method is in fact a quantitative test. The method needs to be adequately controlled such that the viable cell counts in the final vaccine are within the range shown to be safe and effective. Both underestimation and overestimation of viable counts could adversely affect the product. Please develop an appropriate positive control to allow monitoring of the assay accuracy over time. Please indicate when you will be able to implement this control into your testing.

PaxVax will be developing and qualifying an appropriate positive control for monitoring the assay accuracy over time for the (b) (4) vaccine potency methods (Q208 and Q217, respectively). The positive control will be implemented prior to the release testing of the commercial vaccine product. The positive control qualification report and revised methods will be submitted as a CBE-30 BLA supplement.

Review: The response is adequate.

- 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.**

The vaccine process conformance lots were released using Method Q208. Subsequently, we developed and validated Q217 which requires reconstitution of the vaccine in the buffer prior to analysis. The stability program for the conformance lots was then modified to include methods Q208 and Q217 to collect titer values from both methods in order to collect data to establish a more refined potency acceptance criterion. The stability data from both methods will be reported to the FDA and the official stability results will be based on data from Q217. Method Q217 will be used for the commercial release and stability of the vaccine.

Review: The response is adequate.

- 14. You provided the “Analytical Method Validation Report for Determining the (b) (4) via the (b) (4) Method 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.**

Table 5 lists the raw data file for the plate counts used to calculate the validation results for the Method Validation Report RAP-PLT-6001.QC. The Method

Validation Protocols XAM-PLT-6001.QC and RAP-PLT-6001.QC have also been provided.

Table 3: Potency Method Validation Data to Support Report RAP-PLT-6001

Validation Parameter	Raw Data Reference
Intermediate Precision	(b) (4)
Repeatability	
Range	

Review: The response is adequate.

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.
- Please verify that the (b) (4) performed at (b) (4) is used for (b) (4) drug product testing.
 - 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.
 - 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.
 - 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.

- e. Please provide data demonstrating the specificity of the [REDACTED], including the level of cross-reactivity to [REDACTED].

PaxVax has removed the Identity test using the [REDACTED] for the [REDACTED] Vaccine release specifications as shown in updated Section 3.2.S.2.4, 3.2.S.4.1, 3.2.S.4.2, 3.2.S.4.3, 3.2.S.4.5 and 3.2.P.5.1 , 3.2.P.5.2 , 3.2.P.5.3 , 3.2.P.5.6 [PXVX0200, Powder for Oral Suspension].

Review: The response is adequate.

- 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.**

The [REDACTED] used in the viable cell count methods (Q208 and Q217) come with an [REDACTED] To mitigate the false colony counts, Method Q217 provides instruction for the use of [REDACTED]

[REDACTED] These “false” colonies can be clearly identified by the trained analyst and can be [REDACTED] without any visible colony so that only the actual colonies (circled in red in Figure 4 for clarity) are left to be counted. All analysts are qualified for removing the false colonies and adding the enumerated colonies to appropriately reflect an accurate colony count. The final results are reviewed by the QC Manager and then QA to ensure no bias and/or falsification of the results.

1 page has been determined to be not releasable: (b)(4)



Review: The response is adequate.

15. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION, DATED 17 FEBRUARY 2016

An IR was sent to the applicant on 17 February 2016. The applicant submitted a response on 1 March 2016 (Amendment 13). Below is the IR comment (in bold), followed by the applicant's response.

In Sections 3.2.P.5.6 Justification of Specifications [Buffer] and 3.2.P.8 Stability [Buffer] of your BLA, we note that you do not include a test for Moisture Content. Please include Moisture Content in your release tests and stability tests (first and last time points) for the buffer.

Moisture content analysis is not currently performed for release and stability of buffer as it was found to be impractical to perform and not an appropriate indicator of product quality. The buffer is comprised of three excipients (b) (4) ascorbic acid and dried lactose), of varying concentrations (Table 1). The ascorbic acid in the buffer causes a side reaction with (b) (4) which prevents the use of a (b) (4). The combined excipients also form a reactive mixture that decomposes and generates water when exposed to a sufficiently high temperature, precluding the meaningful use of (b) (4) and (b) (4) methods.

In spite of these limitations, the buffer used for clinical programs was evaluated for moisture content (per (b) (4)) on stability and, at that time, data were collected for informational purposes only. As expected, the moisture results for buffer Lot (b) (4) at the storage conditions of (b) (4) showed that the product moisture content was very low (b) (4) through (b) (4) (Table 2). PaxVax subsequently performed development experiments to evaluate (b) (4) methods using (b) (4) temperatures sufficiently (b) (4) such that (b) (4). Ultimately, the (b) (4) methods could not reproducibly determine the buffer moisture content, due in large part to the very low moisture content of the buffer (Table 2).

(b) (4) is the major excipient in the manufacture of buffer blend (b) (4) and is a highly stable mixture of surface modified sodium carbonate (b) (4) composition) and sodium bicarbonate powder (Section 3.2.P.2.1). (b) (4) is dried and desiccated to increase its stability, making it a more stable form of sodium bicarbonate. It is manufactured by (b) (4)

Sodium carbonate in the presence of moisture forms a hydrate salt (sodium sesquicarbonate), which is stable up to (b) (4), thereby reducing moisture sensitivity of the formulation. Since water is consumed by this reaction, moisture content does not provide a meaningful stability-indicating measure as the water content will remain low until there is no longer sodium carbonate to react.

Based on the buffer low moisture content causing poor assay reproducibility and assay interferences, PaxVax's assessment is that moisture content analysis would not be an appropriate test for the buffer for release and stability.

In addition, any increase in moisture over time would be apparent from other attributes tested for the buffer (i.e. appearance, (b) (4), assay for ascorbic acid, buffer capacity) at release and over the course of the buffer stability. Development studies have demonstrated that the appearance of buffer changes substantially after brief exposure to ambient moisture, resulting in agglomeration of the buffer after (b) (4) and discoloration in as little as one day (Section 3.2.P.2.3). Therefore, any change in moisture would be readily observed by a corresponding change in the results of the appearance test results performed at release and stability. Furthermore, the appearance, (b) (4), assay for ascorbic acid, and (b) (4) assays were included on the release and stability specifications as they were deemed critical in ensuring the quality of the buffer. These factors indicate that the buffer moisture content does not impact the established quality attributes and thus is not expected to adversely impact product quality.

Table 1: Buffer Composition

Buffer Composition	(b) (4)	Ascorbic Acid	Dried Lactose
% w/w	(b) (4)		

(b) (4)

(b) (4)

16. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION, DATED 6 APRIL 2016

An IR was sent to the applicant on 6 April 2016. The applicant submitted a response on 22 April 2016 (Amendment 34). Listed below are the IR comments (in bold), followed by the applicant's response to each comment.

The following comments pertain to our review of the following documents submitted to STN 125597_0: the instructions for reconstitution of Vaxchora in section 2.2 of the proposed package insert; Figures 1 and 5 of the Compatibility document in module 3.2.P.2.6; and the clinical study reports in section 5.3.5.1.

- 1) Please clarify the following information regarding the administration of Vaxchora to study participants in the three phase 3 clinical studies (PXVX-VC-200-003, PXVX-VC-200-004 and PXVX-VC-200-005):**
 - a. Please clarify the type(s) of bottled water used by each of the clinical sites for reconstitution of Vaxchora (i.e., purified water, spring water, artesian water, etc.). If known, please also specify the brand name/manufacturer of the water that was used.**

The applicant responded that Sterile Water for Irrigation was used during the challenge study, and Sterile Water for Irrigation and bottled water (purified or spring) were used for the bridging studies.

Review: The response is adequate. However, based on this information and other concerns with the use of bottled water for reconstitution of the vaccine, the

product insert was modified to state that only purified bottled water be used. The applicant agreed to this change. See Section 3.1.2 of this memorandum for more information.

- b. Please clarify whether clinical sites documented (1) the time frame between removal of Vaxchora (vaccine and buffer sachets) from the freezer and reconstitution and (2) the time frame between reconstitution of Vaxchora and administration.**

The applicant responded that these data were recorded. In a subsequent response (Amendment 39), the applicant provided information regarding the sachet thaw time during the challenge study, stating that the range in time between removal of the sachets from refrigeration to reconstitution was 3 to 29 minutes, with a mean of 14.4 minutes (standard deviation of 9.57 minutes and a median duration of 9 minutes).

Review: The response is adequate. However, see the response to question 2d below for a discussion of this issue.

- c. We note that the Investigator's Brochure does not instruct clinical sites to thaw the vaccine and buffer sachets prior to reconstitution. Please confirm whether the vaccine and buffer sachets were (or were to be) reconstituted immediately after removal from the freezer (i.e., no thaw).**

The instruction in the Pharmacy Manual provided to sites was as follows: "The PXVX0200 vaccine and buffer sachets must be reconstituted within less than 30 minutes after removing from the freezer/refrigerators." It was therefore not required that the vaccine sachet be reconstituted while still frozen.

Review: The response is adequate.

- d. We note that the Investigator's Brochure instructs clinical sites to administer the vaccine immediately after reconstitution and mixing. Please confirm how quickly Vaxchora was (or was to be) administered following reconstitution.**

The instruction in the Pharmacy Manual provided to sites was as follows: "Once vaccine is reconstituted in the buffer solution, it must be stored at room temperature and must be administered no more than 30 minutes after reconstitution." It was therefore specified that Vaxchora be administered within 30 minutes of reconstitution.

Review: The response is adequate. However, in a subsequent communication (Amendment 39), the applicant stated that during the challenge study, the range in time between reconstitution to administration was 1 to 45 minutes, with a mean of 9.2 minutes (standard deviation of 9.37 minutes and a median duration of 5 minutes). Based on this information and other concerns, the package insert was changed to specify that the vaccine be consumed within 15 minutes of reconstitution; the applicant agreed to the change.

- 2) The comments below pertain to our review of the Compatibility document in module 3.2.P.2.6 of STN 125597_0. We note that Figure 1 in the Compatibility document shows the impact of different sources of bottled water on drug product potency. We have the following questions and information requests regarding the data presented in this figure:

- a. Please clarify whether the same lot of Vaxchora was used in the evaluation of each type of bottled water.

The same vaccine lot was used in the evaluation of each type of bottled water. Vaccine conformance lot (b) (4) was used in conjunction with Buffer development lot (b) (4) to evaluate each type of bottled water tested (TRDEV-0005 Report Section 9).

Review: The response is adequate.

- b. Please specify the potency of the lot(s) used in the evaluations that support Figure 1.

The potency of lot (b) (4) was 9×10^8 CFU/dose. This potency value is based on the result of the one month stability time point (Section 3.2.P.8.3, PXVX0200), which represents the potency at the nearest stability time point prior to the evaluations that support Figure 1.

Review: The response is adequate.

- c. Please discuss the variability of the potency of the product at time zero depending on the source of water used for reconstitution.

The variability of the potency at time zero was 19% RSD across all sources of bottled water (TRDEV-0005 Report Table 5), which is within the variability of the potency assay of (b) (4) RSD (PaxVax method Q208). This report provides the detailed data behind Figure 1 in Section 3.2.P.2.6 of the BLA.

Review: The response is adequate.

- d. Please clarify whether the vaccine and buffer sachets were thawed for 30 minutes prior to reconstitution (time zero). If not, please evaluate and provide a summary of the impact of different sources of bottled water on drug product potency when the vaccine and buffer sachets are thawed for 30 minutes prior to reconstitution. Please use lots at the lower end of the potency specification for these evaluations.

The vaccine and buffer sachets used in the evaluations that support Figure 1 were thawed for between 15 and 30 minutes prior to reconstitution, with the exception of a single buffer sachet that was removed from storage and immediately reconstituted, as shown in Table 3 below (from TRDEV-0005 Report Table 3).

(b) (4)

Based on the data for the various types of bottled water (Figure 1), the vaccine could be reconstituted with any of the different sources of bottled water and still remain within the acceptable potency range (4×10^8 to 2×10^9 CFU/dose) for 30 minutes after reconstitution. Therefore, the impact of thaw duration was evaluated using only one type of bottled water source, i.e. purified water (b) (4).

The thaw duration study described in Section 3.2.P.2.6.4 was performed with buffer Lot (b) (4) that was reconstituted with purified water (b) (4) and with the same vaccine Lot (b) (4). The vaccine potency was 9×10^8 CFU/dose, which represents the lower end of the acceptable potency range. This study included the vaccine and buffer thawed for 30 minutes and then reconstituted (Section 3.2.P.2.6.4 Table 2). The variability of the potency across each of the time points (0, 15, and 30 minutes) was within the assay acceptance criterion of (b) (4) RSD. As a result, the reconstituted vaccine potency remained within the specification for 30 minutes, whether the vaccine and buffer sachets were reconstituted immediately after removal from storage (no thaw) or allowed to thaw for 30 minutes (Figure 5).

PaxVax considers that these data indicate that there is no likely impact of different sources of bottled water on drug product potency when the vaccine and buffer sachets are thawed for 30 minutes prior to reconstitution, which supports the instructions given in the Phase 3 Pharmacy Manual and proposed package insert reconstitution instructions for Vaxchora.

Review: The response is adequate. However, based on this information and other concerns regarding thaw time of the sachets, the product insert was modified to state that the vaccine must be reconstituted within 15 minutes after removal of the carton from frozen storage. The applicant subsequently agreed with this change. See Section 3.1.2 of this memorandum for more information.

- e. **Please clarify the manufacturing process used for the lot(s) used in Figure 1. Specifically, please indicate whether the bulk drug substance hold time was (b) (4).**

Lot (b) (4) was manufactured using bulk drug substance stabilized with a (b) (4) hold time.

Review: The response is adequate. However, based on this information and other concerns, the package insert was modified to specify that only purified bottled water be used, that the vaccine be reconstituted within 15 minutes of removal of the carton from frozen storage, and that the vaccine be consumed within 15 minutes of reconstitution. See Section 3.1.2 of this memorandum for more information.

17. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION, DATED 6 MAY 2016

An IR was sent to the applicant on 6 May 2016. The applicant submitted a response on 19 May 2016 (Amendment 40). Below is the IR comment (in bold), followed by the applicant's response.

We note that your proposed potency acceptance criteria are 4×10^8 to 2×10^9 CFU/dose, with a target sachet fill of [REDACTED] CFU/dose. In addition, in your stability data, we note that the potency of lots with initial potency of 1×10^9 CFU/dose decreased to a range of $4\text{--}6 \times 10^8$ CFU/dose after 18 months of storage at $-20 \pm 5^\circ\text{C}$. Please comment on how you will ensure and/or monitor whether the potency of the drug product remains within the acceptance criteria through the end of the proposed 18-month dating period, considering that some lots may have initial potency toward the lower end of the range of the acceptance criteria.

A potency alert limit [REDACTED] criterion will be set for the viable cell count drug product release assay. The potency alert limit will be selected to ensure vaccine drug product remains within the acceptance criteria through the end of the proposed shelf life as demonstrated by current stability data. Drug product lots that are manufactured with release potency results [REDACTED], if released, will be placed on stability.

Review: The response is adequate.

18. INFORMATION REQUEST REGARDING ORIGINAL SUBMISSION, DATED 7 JUNE 2016

An IR was sent to the applicant on 6 June 2016. The applicant submitted a response on 7 June 2016 (Amendment 46). Below is the IR comment (in bold), followed by the applicant's response.

In your May 31, 2016, communication regarding the package insert, you proposed revising the Dosage and Administration section to state that "bottled purified or spring water" should be used for reconstitution rather than "purified bottled water." We do not agree to this proposal for the following reasons:

- 1) In the pivotal human challenge study, sterile water for irrigation was used for reconstitution of the vaccine (Table 1, Section 1.11.4, Amendment 34); this choice of water represents a “best-case” scenario, because sterile water for irrigation must meet USP standards. Purified bottled water also must be processed by methods specified by USP. Bottled spring water is not processed to the same extent as purified bottled water and is therefore less likely to be of consistent quality. No data are available regarding the ability of vaccine reconstituted in bottled spring water to protect individuals from *V. cholerae* infection. In the bridging studies, several types of water were used for reconstitution, including (b) (4) different brands of bottled spring water (Table 1, Section 1.11.4, Amendment 34). In aggregate, serum vibriocidal antibody assay results from the bridging studies were non-inferior to results from the challenge study. However, at only a minority of sites (8 of 26) was bottled spring water used; the majority of investigators used water that was processed using more rigorous standards (water for irrigation, sterile water, distilled water, or purified bottled water).
- 2) You conducted an *in vitro* study in which drug product manufactured using a modified manufacturing process (a (b) (4) bulk drug substance hold time; Response 2e, Amendment 34) was reconstituted in bottled water from various sources, and vaccine potency was assessed at various time points following reconstitution (Figure 1, Section 3.2.P.2.6 Compatibility and Document Number TRDEV-0016). The study was limited in that: the drug product used was not manufactured under the process described in the BLA; only one or two brands of each type of water were used; and sterile water for irrigation was not used. In the future, if you wish to pursue the use of bottled spring water for reconstitution in a Prior Approval Supplement, data that could be supportive of such a change would include results of *in vitro* studies using (1) drug product made using the process that was used to manufacture drug product used in the clinical studies; (2) several brands of purified bottled water, several brands of bottled spring water, and sterile water for irrigation (as a comparator); and (3) multiple replicates of each brand of water, to provide confidence in the statistical significance of the results.

Further to the Agency’s request, the package insert has been revised to specify “purified bottled water” for reconstitution of Vaxchora. The carton and active and buffer packet labels previously submitted in SN0042 have also been revised to specify “purified bottled water” be used for reconstitution. PaxVax thanks the Agency and acknowledges the recommendations regarding a potential future Prior Approval Supplement in the event the use of spring water is to be pursued.

Review: The response is adequate.

19. APPROVAL RECOMMENDATION

After a complete and thorough review of the original BLA submission and all amendments listed on the first page of this memorandum, I recommend approval of Vaxchora. The IBDS will be manufactured by (b) (4). Processing of the IBDS to the BDS and manufacturing and primary packaging of the vaccine DP will be by PaxVax, Inc., in (b) (4). Manufacturing of the buffer DP will be by (b) (4). Filling and primary packaging of the buffer DP will be by PaxVax, Inc., in (b) (4). Secondary packaging of the two DPs will be by (b) (4). The expiry of vaccine DP will be 18 months from the date of initiation of filling when stored at the recommended temperature of -20°C. The expiry of buffer DP will be 24 months from the date of initiation of filling when stored at the recommended temperature of -20°C. The two DP sachets that will be packaged together in the secondary packaging (carton) may have different expiration dates, in which case the date of expiry printed on the carton will be the earlier of the two expiration dates.

1 page has been determined to be not releasable: (b)(4)