



**From:** Alfred Del Grosso, OCBQ/DBSQC  
**To:** File: STN 125597/0  
**Through:** Lokesh Bhattacharyya, OCBQ/DBSQC/ Chief LACBRP  
William McCormick, OCBQ/ Director DBSQC  
**Company:** PaxVax Bermuda Ltd. (PaxVax)  
**Product:** Cholera Vaccine, Live, Oral CVD 103-HgR  
**Subject:** Review of Chemistry Related Procedures  
**Recommendation:** Approval

---

### Summary and Conclusion

This document constitutes the Review Memo for the analytical test methods and their validations for the following quality control lot-release tests:

PXVX0200 (b) (4) Drug Product

Appearance  
Moisture Content

Buffer, Effervescent Granule

Appearance  
Visual Control  
Identity of Carbonates and Bicarbonates  
Identity of Lactose

(b) (4)

Reconstitution Time  
Assay for Ascorbic Acid

(b) (4)

**Overall Conclusion of Review:** The proposed assay methods are appropriate for intended usage, adequately described and validated. The reviewer's recommendation is that they be approved for intended use as described.

## Background of Submission

This BLA for Cholera vaccine, live oral (Vaxchora®) was submitted in October, 2015. The drug product consists of a co-package of single doses of two foil packets that separately contain vaccine powder for reconstitution (PXVX0200 CVD-HgR) and a buffer powder (Buffer Effervescent Granule). In clinical use, the buffer is reconstituted in 100 mL bottled water followed by addition of vaccine powder and mixing. Vaccine is administered orally after reconstitution. The buffer component consists of a mixture of sodium bicarbonate (b) (4), ascorbic acid and lactose. The Drug Product Vaccine Powder for reconstitution contains lactose as a stabilizer and bulking agent (major component) and smaller amounts of sucrose as a cryoprotectant, sodium chloride as a stabilizer and ascorbic acid as a stabilizer and anti-oxidant.

## Review Narrative

Information submitted and reviewed included:

- 3.2.S.4.1 Specifications PXVX0200, Bulk Drug Substance
- 3.2.S.4.2 Analytical Procedures
  - Appearance SOP Q108.04
  - Moisture Content SOP Q193.04
- 3.2.S.4.3 Validation of Analytical Procedures
  - Report for Verification of Moisture Content Analysis of PXVX0200 CVD-HgR by (b) (4), VPR-101
- 3.2.P.5.1 Specifications PXVX0200, Powder for Oral Suspension, Drug Product
- 3.2.P.5.2 Analytical Procedures, PXVX0200
  - Appearance SOP Q108
  - Moisture Content SOP Q193.04
- 3.2.P.5.3 Validation of Analytical Procedures
  - Report for Verification of Moisture Content Analysis of PXV0200 CVD-HgR Drug Product and Dried Lactose VPR-135
  - Verification Protocol for Moisture Content Analysis of PXV0200 CVD-HgR Drug Product and Dried Lactose By (b) (4) C30 VP-135
- 3.2.P.5.1 Specifications, Buffer, Effervescent Granule
- 3.2.P.5.2 Analytical Procedures, Buffer, Effervescent Granule
  - Appearance SOP Q108
  - Identity of Carbonates and Bicarbonate (b) (4)
  - Identity of Lactose by (b) (4) Method 5.3
  - (b) (4) SOP Q102
  - Reconstitution Time SOP Q212
  - Average Filling Mass SOP Q215
  - Assay for Ascorbic Acid (b) (4) Method 5.1
  - (b) (4) Method 5.2

**Moisture Content by** (b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Conclusion: Method verification is acceptable. The (b) (4) method for moisture determination in the vaccine product is satisfactory for the intended purpose.

#### Moisture Content of Buffer - Effervescent Granule

PaxVax did not propose a moisture specification for the Buffer-Effervescent Granule Drug Product. A specification of (b) (4) is in place for Lactose raw material used in the formulation of the Buffer.

An information request was submitted on February 17, 2016 in which release and stability tests were requested for the Buffer Drug Product.

CBER: “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) in the buffer.

PaxVax responded in Amendment 13, received on March 01, 2016. It was stated that “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 sponsor explained that ascorbic acid in the buffer causes a side reaction with (b) (4) reagent which prevents the use of a (b) (4). The use of an (b) (4) procedure, as described in the method for PXVX0200 Drug Product would result in a (b) (4) with (b) (4) bias for quantitation.

A reference was made in the response by PaxVax to a (b) (4) “Determining the water content in Ascorbic Acid” that acknowledged that ascorbic acid, as a strong reducing agent, causes a fast side reaction with (b) (4). Determined water content is caused largely by the (b) (4), precluding an accurate determination of water. Similarly (b) (4) was shown to result in a blank value higher than the water content.

PaxVax stated that “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, (b) (4) at release and over the course of buffer stability).

Conclusion regarding IR: The sponsor's claim that determination of moisture in the Buffer Drug Product by (b) (4) is impractical is adequately supported. A criterion for moisture in the buffer is not recommended.

### **Appearance SOP Q108**

SOP Q108.04 describes the test of appearance for liquid, solid and drug product samples including PXVX0200 Powder (b) (4) DP and Effervescent Granule Buffer DP.

The procedure includes detailed descriptions of the inspection of container closures and labels.

Reference is made to SOP Q213 for sample preparation of PXVX0200 CVD 103-HgR.

Drug product samples in sachets are transferred to a clear container and observations made and recorded against black and white backgrounds for color, appearance and foreign debris.

Specification for appearance of effervescent buffer drug product is "White to off-white powder, visually free of foreign particles". Specification of PXVX0200 Drug Product is "White to beige powder, no visible foreign particulates".

Conclusion: Acceptable for use.

### **Identity of Carbonates and Bicarbonate** (b) (4)

Identity of Carbonates and Bicarbonates is performed by a contract laboratory, (b) (4)

(b) (4) – Carbonates and Bicarbonates - (b) (4)

Amendment 12: The original submission included (b) (4) identity test for evaluation of the raw material. However, Amendment 12, submitted on February 26, 2016 removed the (b) (4) identity test from the (b) (4). This was considered inappropriate since the test article contains both sodium bicarbonate and sodium carbonate, and the presence of sodium carbonate can interfere with the test.

(b) (4) Identification Tests - General specifies for Bicarbonate – "See Carbonate".

(b) (4)

Conclusion: The described test by (b) (4) is appropriate as an identity test for Carbonates and Bicarbonates in raw materials and buffer drug product. The deletion of the (b) (4) test as a raw material identity test is satisfactory.

**Identity of Lactose by** (b) (4)

The (b) (4) procedure describes the use of (b) (4)

(b) (4)

Conclusion: Satisfactory for identity testing of lactose in raw materials and buffer drug product.

(b) (4)

(b) (4)

**Reconstitution Time** SOP Q212

Buffer Drug Product sachets are opened after equilibration to room temperature. The entire contents are transferred to a beaker containing 100 mL bottled water and a (b) (4)

(b) (4) The solution is evaluated at time intervals of (b) (4).

Acceptance criteria is complete reconstitution at (b) (4).

Conclusion: Acceptable for use.

**Average Filling** (b) (4) SOP Q215

The SOP referred to both (b) (4)

(b) (4)

Conclusion: Appropriate for use.

**Assay for Ascorbic Acid** (b) (4)

Method 5.1

Ascorbic acid content is determined by a (b) (4)

(b) (4)

Conclusion: Appropriate for use

(b) (4)

(b) (4)

Conclusion: Acceptable for use.