

Mid-cycle Meeting Summary
PaxVax STN#125597/0

Application type and number: Biological Licensure Application (BLA), Original Submission (OS), STN 125597

Product name: Vaxchora®, Cholera Vaccine, Live, Oral

Proposed Indication: Active immunization against disease caused by V. cholera serogroup O1 in adults 18 years of age and older

Applicant: Pax Vax Bermuda Limited

Meeting date & time: January 25, 2016 11:00AM-12:30PM

Committee Chair: Goutam Sen, Ph.D.

Co-RPMs: Christina Houck /LCDR Kelsy Hoffman, Ph.D.

CBER/FDA Attendees:

Sang Ahnn, Ph.D., Biostatistics Reviewer, DB/OBE

Marie Anderson, Ph.D., M.S., Quality Control Reviewer (LRP, Testing), DBSQC/OCBQ

Deepa Arya, M.D., M.P.H., M.B.A., Epidemiology Reviewer, DE/OBE

Lokesh Bhattacharyya, Ph.D., Chief, LACBRP/DBSQC

Jennifer Bridgewater, M.P.H., Associate Director for Regulatory Policy, DBPAP/OVRR

Drusilla Burns, Ph.D., Deputy Division Director, DBPAP/OVRR

CAPT Jon Daugherty, Ph.D., Regulatory Review Branch I Chief, DVRPA/OVRR

Alfred Del Grosso, Ph.D., Product/CMC Reviewer, DBSQC/OCBQ

Nicolette deVore, PhD, Senior Scientist and Project Manager for Counterterrorism and Emerging Threats Preparedness, IOD/CBER

Christine Drabick, M.S., BiMo Reviewer, DIS/OCBQ

Oluchi Elekwachi, Pharm.D., M.P.H., Advertising and Promotional Labeling Reviewer, DCM/OCBQ

John Eltermann, Jr., R.Ph., M.S., Director, DMPQ/OCBQ

Karen Farizo, M.D., Associate Director for Medical Policy and Vaccine Safety, OVRR

Theresa Finn, Ph.D., Associate Director for Regulatory Policy, OVRR

Marion Gruber, Ph.D., Director, OVRR

Christine Harman, Ph.D., CMC/Facility Reviewer, DMPQ/OCBQ

Erik Henchal, Ph.D., Associate Director for Management and Scientific Affairs, OVRR

LCDR Kelsy Hoffman, Ph.D., Regulatory Project Manager, DVRPA/OVRR

Dale Horne, Ph.D., Vaccine Evaluation Branch Chief, DB/OBE

Christina Houck, Regulatory Project Manager, DVRPA/OVRR

Simleen Kaur, M.S., Quality Control Reviewer (Microbiology), DBSQC/OCBQ

CAPT Craig Zinderman, M.D., M.P.H., Associate Director for Product Safety, DE/OBE

Loris McVittie, Ph.D., Deputy Director, DVRPA/OVRR

Tina Mongeau, M.D., Medical Officer, DVRPA/OVRR

Scott Norris, B.S., Regulatory Coordinator, DBPAP/OVRR

Laurie P. Norwood, Ph.D., Deputy Director, DMPQ/OCBQ

Manuel Osorio, Ph.D., Serology Assay Reviewer, DBPAP/OVRR

Roger Plaut, Ph.D., CMC Reviewer, DBPAP/OVRR

Carolyn Renshaw, Manufacturing Review Branch I Chief, DMPQ/OCBQ

Jeff Roberts, M.D., Clinical Branch Chief, DVRPA/OVRR

David Rouse, MS, Senior Scientist for Counterterrorism and Emerging Threats Preparedness, IOD/CBER

Goutam Sen, Ph.D., Chair, DVRPA/OVRR

Jay Slater, M.D., Director, DBPAP/OVRR

LCDR Matthew Steele, Ph.D., Regulatory Review Branch I Acting Team Leader, DVRPA/OVRR

Scott Stibitz, Ph.D., Laboratory Chief, DBPAP/OVRR

Wellington Sun, M.D., Director, DVRPA/OVRR

Deborah Trout, Manufacturing Team Leader, DMPQ/OCBQ

Freyja Williams, B.S., Consultant Serology Assay Reviewer, DBPAP/OVRR

Lihan Yan, Ph.D., Statistical Team Leader, DB/OBE

Review Committee

Name, Certifications/Degree	Review Role	Module Assignment
Reviewer: Goutam Sen, Ph.D. BC: Rakesh Pandey, Ph.D.	Chair	All Modules
Reviewer: Christina Houck BC: Jon Daugherty, Ph.D.	Co-Regulatory Project Manager	All Modules
Reviewer: LCDR Kelsy Hoffman, Ph.D. BC: Jon Daugherty, Ph.D.	Co-Regulatory Project Manager	All Modules
Reviewer: Jennifer Bridgewater, M.P.H. DD: Jay Slater, M.D.	Regulatory Coordinator	All Modules
Reviewer: Scott Norris, B.S. DD: Jay Slater, M.D.	Regulatory Coordinator	All Modules
Reviewer: Tina Mongeau, M.D. BC: Jeff Roberts, M.D.	Clinical	Modules 1, 2 & 5
Reviewer: Sang Ahnn, Ph.D. BC: Dale Horne, Ph.D.	Biostatistics	Modules 1, 2 & 5
Reviewer: Deepa Arya, M.D., M.P.H., M.B.A. Acting DD: Christopher Jankosky, M.D., M.P.H.	Pharmacovigilance/ Epidemiology	Modules 1 & 2
Reviewer: Roger Plaut, Ph.D. LC: Scott Stibitz, Ph.D.	CMC/Product	Modules 2 & 3
Reviewer: Manuel Osorio, Ph.D. LC: Scott Stibitz, Ph.D.	Serology Assay	Modules 2 & 5
Reviewer, Freyja Williams, B.S. DD: Jay Slater	Serology Assay (Consult)	Modules 2 & 3
Reviewer: Christine Harman, Ph.D. BC: Carolyn Renshaw	CMC/Facility Inspector	Modules 2 & 3
Reviewer: Deborah Trout, B.S. BC: Carolyn Renshaw	Inspector	Modules 2 & 3
Reviewer: Marie Anderson, Ph.D., M.S. DD: William McCormick, Ph.D.	CMC/Lot Release	Modules 2 & 3
Reviewer: Alfred Del-Grosso, Ph.D. DD: William McCormick, Ph.D.	CMC/Lot Release (Chemistry)	Modules 2 & 3

Name, Certifications/Degree	Review Role	Module Assignment
Reviewer: Simleen Kaur, M.S. DD: William McCormick, Ph.D.	CMC/Lot Release (Microbiology)	Modules 2 & 3
Reviewer: Noel Baichoo, Ph.D. DD: William McCormick, Ph.D.	CMC/Lot Release (Immunology)	Modules 2 & 3
Reviewer: Christine Drabick, M.S. BC: Patricia Holobaugh, M.S.	Bioresearch Monitoring	Modules 2 & 5
Reviewer: Oluchi Elekwachi, Pharm.D., M.P.H. BC: Lisa Stockbridge, Ph.D.	APLB/Promotional Labeling	Modules 1 & 2

Background

BLA STN#125597/0 was submitted by Pax Vax Bermuda Limited on October 16, 2015, and received by CBER on October 16, 2015. The proposed BLA indication is active immunization against disease caused by *V. cholerae* serogroup O1 in adults 18 years of age and older. The purpose of this Mid-Cycle meeting is to discuss the review progress, identify and resolve any substantive issues and obtain supervisory feedback.

Report and Discuss:

1. Reviewer Reports

1.1 **Clinical/** Tina Mongeau- The clinical review is currently ongoing and no substantive issues that would impact approval or the review timeline have been identified. Issues that affect labeling have been identified:

- 1.1.1 lack of an upper age limit without data in adults ≥ 65 years of age
- 1.1.2 an intended population of travelers visiting cholera-endemic or epidemic areas while efficacy was only demonstrated in a population from a non-endemic region with no history of exposure to cholera
- 1.1.3 the review team should discuss and gain concurrence on whether data from Orochol should be requested and used in the PI
- 1.1.4 the clinical and/or review team should discuss and gain concurrence on the acceptability of including a claim of cross protection against cholera due to non-homologous *V. cholerae* biotypes and serotypes
- 1.1.5 the clinical and/or review team should discuss and gain concurrence on the clinical significance of lower peak GMTs in 46-64 year old Vaxchora recipients in study -005 and if these data should be added to the PI

1.2 **Statistical/** Sang Ahnn- The statistical review is currently ongoing and no substantive issues have been identified.

1.3 **Epidemiology/** Deepa Arya- The Pharmacovigilance Plan (PVP) review is currently ongoing and no substantive issues that would impact approval or the review timeline have been identified. Issues that affect labeling have been identified:

1.3.1 Same issue as notated in 1.1.1

1.3.2 Agree with sponsor's plan to establish a pregnancy registry, as safety in pregnant women has not been established

1.4 **BiMo/ Christine Drabick-** The BiMo review is currently ongoing and no substantive issues have been identified. The inspections at Site # 15 (Protocols PXVX-VC-200-004 and PXVX-VC-200-005) and at Site # 4 (Protocol PXVX-VC-200-005) are pending. The BIMO inspections at Site # 3 and Site # 13 are complete and no Form FDA 483 was issued at either site. A Form FDA 483 was issued at Site #4 regarding Protocol PXVX-VC-200-003 and a response addressing the inspectional findings was received. The inspection for Protocol PXVX-VC-200-005 at Site #4 is pending. The findings will be reviewed and communicated to the committee upon completion of all inspections and after final review.

1.5 **Labeling/Oluchi Elekwachi-** The label review is currently ongoing and no substantive issues have been identified.

1.6 **Product/CMC**

1.6.1 **CMC/Roger Plaut-** The CMC review is currently ongoing. An IR will be sent to the Applicant regarding:

1.6.1.1 the change in manufacturer of the Working Seed Lot (WSL)

1.6.1.2 the change in the manufacturing process such that the BDS will be held at (b) (4) for (b) (4) rather than (b) (4)

1.6.1.3 information regarding the transfer and storage of the Master Seed Lot (MSL) and WSL

1.6.1.4 Other minor issues

1.6.2 **Serology Assay /Manuel Osorio-** The clinical serology assays, serum vibriocidal antibody assay for *V. cholerae* and cholera toxin IgG (b) (4) review is complete and no substantive issues were identified.

1.7 **CMC Lot Release**

1.7.1 **CMC/Lot Release/Marie Anderson-** The primary review of the Lot Release Protocol (LRP) templates for the DP and buffer are complete. The LRP templates were sent to the CMC and PRB reviewers for comments with a requested response date of February 2, 2016. Subsequently, an IR will be sent for samples and LRP template comments.

1.7.2 **CMC/Lot Release/Alfred Del-Grosso-** The quality control (chemistry) review is complete and no substantive issues were identified.

1.7.3 **CMC/Lot Release/Simleen Kaur**- The quality control (microbiology) review is currently ongoing and no substantive issues have been identified. An IR was sent to the applicant on January 19, 2016 regarding re-evaluation of bioburden test specification for (b) (4) drug product and buffer. In addition, clarification was requested for (b) (4) testing (b) (4) performed on (b) (4) drug product.

1.7.4 **CMC/Lot Release/Noel Baichoo**-Not present.

1.8 CMC/Facility

1.8.1 **CMC/Facility/Inspector/Christine Harman**- The review is currently ongoing and no substantive issues have been identified. An IR was sent to the applicant on January 13, 2015, regarding submission of qualifications and cleaning validations of major (product contact) equipment used in manufacturing of intermediate bulk drug substance at (b) (4). Environmental Assessment will be reviewed by Product/CMC reviewer.

1.8.2 **Inspector/Deborah Trout**-Not present.

2. Will Discipline Review Letters be issued? *Information requests will be sent to the sponsor as needed.*
3. If the application will be discussed at an Advisory Committee, potential issues for presentation. *This application will not be presented to the VRBPAC.*
4. Determine whether Postmarketing Commitments (PMCs), Postmarketing Requirements (PMRs) or a Risk Evaluation Mitigation Strategy (REMS) are needed. *As previously noted, at this time, no CMC related PMC is anticipated. The review team does not anticipate the need for any REMS at this time. The only PMR will be the agreed pediatric study in children 2 to 17 years of age for which PaxVax requested deferral in the BLA submission.*
5. National Drug Code (NDC) assignments to product/packaging. *The NDC has been provided on the product packaging.*
6. Proper naming convention. *The currently proposed proper name is: Cholera Vaccine Live Oral.*
7. Status of inspections (GMP, BiMo, GLP) including issues identified that could prevent approval. *The review is currently ongoing, however, at this time, no issues have been identified that could prevent approval.*

Confirm

8. Components Information Table was obtained and notification to the Data Abstraction Team (DAT) if discrepancies were found per *SOPP 8401.5: Processing Animal, Biological, Chemical Component Information Submitted in Marketing Applications and Supplements*. If not complete, indicate date it will be completed. ***The process for obtaining the components information table and identifying potential deficiencies has been initiated.***
9. New facility information is included in the application, requiring implementation of regulatory job aid *JA 910.01: Facility Data Entry*. If not complete, indicate date it will be completed. ***Facility information is up-to-date in RMS-BLA.***
10. Status of decisions regarding lot release requirements, such as submitting samples and test protocols and the lot release testing plan. ***As previously noted, the review of the lot release protocol and lot testing plan is currently ongoing.***
11. Unique ingredient identifier (UNII) code process has been initiated. See regulatory job aid *JA 900.01: Unique Ingredient Identifier (UNII) Code* for additional information. ***The process for acquiring UNII codes will be initiated shortly after the mid-cycle meeting.***
12. PeRC presentation date is set, and the clinical reviewer has addressed waiver/deferral/assessment of the PREA decision. ***PeRC has been scheduled for April 6, 2016. PeRC forms will be submitted two weeks in advance of scheduled PeRC meeting.***
13. Reach agreement on information to be included in the Mid-cycle communication with the applicant (see section below). The Mid-cycle communication is only for applications that qualify under the PDUFA V Program. ***The Mid-cycle communication with the sponsor has been scheduled for February 3, 2016. Information to be included in the Mid-cycle communication was agreed upon by the review committee members and management present at the meeting.***

Review

14. Major target and mile stone dates from RMS/BLA for this review cycle.

Submitted: October 16, 2015

Received: October 16, 2015

Committee Assignment: October 30, 2015

First Committee Meeting: November 24, 2015

Filing Meeting: November 24, 2015

Filing Action: December 15, 2015

Deficiencies Identified: N/A

VRPAC Determination: N/A

PeRC Determination: January 13, 2016

SWG Determination: January 30, 2016

Mid-cycle Communication: February 3, 2016

Late Cycle Briefing Package: March 19, 2016 (March 18, 2016)

First Draft Reviews Due: March 14, 2016
Final Reviews Due: May 14, 2016
Final Review Addendum due: May 16, 2016
Action Due: June 15, 2016
Action Packing for Posting Due: June 15, 2016

MEETINGS

First Committee Meeting: November 24, 2015
Filing Meeting: November 24, 2015
Monthly Team Meetings: 2nd Wednesday of each month
Mid-Cycle Review Meeting: January 25, 2016
Mid-cycle Communication with Sponsor: February 3, 2016
Late Cycle Meeting: TBD March 31, 2016
PeRC: April 6, 2016
VRBPAC: N/A
Labeling Meetings: TBD

15. The status of the review for each discipline, inspection, EIR. If any primary reviews have not met the target date, provide the date the review will be completed. Include any consult disciplines. *Discussed above (#1 in the Report and Discuss section).*
16. Discuss pending dates of targets and milestones (e.g. PeRC, labeling discussion). *Discussed above (#14 in the Review section).*
17. Establish a labeling review plan and agree on future labeling meeting activities. *The labeling meeting will be scheduled shortly after Mid-Cycle.*

Action items:

- 1. Requests for additional information will be drafted and sent to the sponsor.**
- 2. The Mid-cycle Communication will be drafted and sent to the sponsor two days prior to the communication, which is scheduled on February 3, 2016.**
- 3. Labeling meetings will be scheduled to be start no later than March 16, 2016.**
- 4. The process for acquiring UNII codes will be initiated.**