



FILING AND FIRST COMMITTEE MEETING SUMMARY

To:	The File
Date and Time:	November 24, 2015, 1:00 p.m. – 2:30 p.m.
STN #:	125597/0
Submission Type:	Biological Licensure Application (BLA), Original Submission (OS)
Applicant:	Pax Vax Bermuda Limited
Product:	Vaxchora®, Cholera Vaccine, Live, Oral
Meeting Chair:	Goutam Sen, Ph.D.
Meeting Recorder:	LCDR Kelsy Hoffman, Ph.D./ Christina Houck, B.S.
Signature:	

CDER/FDA Attendees

Goutam Sen, Ph.D., Chair, DVRPA/OVRR
LCDR Kelsy Hoffman, Ph.D., Regulatory Project Manager, DVRPA/OVRR
Christina Houck, B.S., Regulatory Project Manager, DVRPA/OVRR
Tina Mongeau, M.D., Medical Officer, DVRPA/OVRR
Sang Ahnn, Ph.D., Biostatistics Reviewer, DB/OBE
Marie Anderson, Ph.D., M.S., Quality Control Reviewer (LRP, Testing), DBSQC/OCBQ
Noel Baichoo, Ph.D., Quality Control Reviewer (Immunology), DBSQC/OCBQ
Alfred Del-Grosso, Ph.D., Quality Control Reviewer (Chemistry), DBSQC/OCBQ
Deepa Arya, M.D., M.P.H., M.B.A., Epidemiology Reviewer, DE/OBE
Scott Norris, B.S., Regulatory Coordinator, DBPAP/OVRR
Christine Drabick, M.S., BiMo Reviewer, DIS/OCBQ
Oluchi Elekwachi, Pharm.D., M.P.H., Labeling Reviewer, DCM/OCBQ
Christine Harman, Ph.D., CMC/Facility Reviewer, DMPQ/OCBQ
Roger Plaut, Ph.D., CMC Reviewer, DBPAP/OVRR
Manuel Osorio, Ph.D., Serology Assay Reviewer, DBPAP/OVRR
Freyja Williams, B.S., Consultant Serology Assay Reviewer, DBPAP/OVRR
Rana Chattopadhyay, Ph.D., Acting Team Leader, DVRPA/OVRR
CAPTJon Daugherty, Ph.D., Branch Chief, DVRPA/OVRR
Lihan Yan, Ph.D., Team Leader, DB/OBE
Carolyn Renshaw, Ph.D., Chief, DMPQ/OCBQ
Roshan Ramanathan, M.D., M.P.H., DVRPA/OVRR
Jeff Roberts, M.D., Branch Chief, DVRPA/OVRR
Scott Stibitz, Ph.D., Laboratory Chief, DBPAP/OVRR
Lisa Stockbridge, Ph.D., Branch Chief, DCM/OCBQ
Loris McVittie, Ph.D., Deputy Division Director, DVRPA/OVRR
Wellington Sun, M.D., Division Director, DVRPA/OVRR
Drusilla Burns, Ph.D., Deputy Division Director, DBPAP/OVRR
Jay Slater, M.D., Division Director, DBPAP/OVRR
Erik Henchal, Ph.D., Associate Director for Management and Scientific Affairs, OVRR
Richard Heath Coats, M.S., Biologist, DMPQ/OCBQ
Christopher Jankosky, MD, MPH, Acting Division Director, DE/OBE

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1.0 BACKGROUND AND PURPOSE

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 meeting is to discuss the milestones, roles and responsibilities of each member of the review team, the completeness of the BLA submission, and to ensure it is acceptable to file.

2.0 REVIEW PROJECT MANAGEMENT PLAN

2.1 Review Committee

The review committee are as follows:

Name, Certifications/Degree	Review Role	Module Assignment
Reviewer: Goutam Sen, Ph.D. BC: Rakesh Pandey, Ph.D.	Chair	All Modules
Reviewer: Christina Houck, B.S. BC: Jon Daugherty, Ph.D.	Co-Regulatory Project Manager	All Modules
Reviewer: LCDR Kelsy Hoffman, Ph.D. BC: CAPT 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., MPH	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 & 3
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
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

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Name, Certifications/Degree	Review Role	Module Assignment
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

Explanation of Roles and Responsibilities (See CBER SOPP 8401 for more detail)

- Chair – Manages the administrative processing of reviews and ensures the regulatory and scientific content of submissions and their reviews are appropriate. The CDTL, as referred to in the Program of PDUFA V is the same as the Chair within CBER. The Chair is responsible for preparing the Summary Basis of Regulatory Action.
- Director and/or Deputy Director – the Signatory Authority who signs action letters and is responsible for content of reviews.
- Regulatory Project Manager (RPM) – Manages the review of submissions, including reviewing assigned portions, performing quality control checks, capturing review committee communications, and ensures the review and review file is administratively complete. The RPM(s) works in tandem with the Chair to ensure that amendments are disseminated to the appropriate reviewers and that a meaningful short summary is entered into RMS/BLA. Throughout the review cycle, the RPM ensures all FDA documents are uploaded into the EDR as they are generated and the documentation review memo is maintained in real-time. The RPM is also responsible for updating progress in MS Project on a monthly basis.
- Review Committee – Perform review of all assigned areas of submissions, participate in review meetings, and perform and document a review of the submission that is scientifically sound and follows Good Review Management Principles. Documentation of a discipline review may be in the form of a primary review, discipline review letter, and a review addendum. It is imperative that the review committee endeavor to follow the review timetable and finish reviews in a timely manner to allow for adequate supervisory review. **It is critical that the review committee keep management, including senior management, abreast of any significant review issues.**
- Supervisors – Ensures the overall content of reviews are appropriate, all administrative processing steps are being completed, including database data entry, and all deadlines are met. Reviews and approves employees review memorandums and other submission documents per CBER policies and procedures. Supervisory review is considered the Secondary Review.

2.2 Review Timetable –milestones are in blue

Review Milestone	Target Due Date
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:	December 29, 2015
Monthly Team Meetings:	TBD ASAP
Mid-Cycle Meeting:	January 30, 2016 (January 29, 2016)
Mid-Cycle Communication*:	February 13, 2016 (February 12, 2016)

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VRBPAC Determination/Meeting:	NA
PeRC Determination/Meeting:	January 30, 2016
PMC/PMR/SWG Determination:	January 30, 2016
Primary Draft Reviews & Reviewer Reports Due:	January 26, 2016
Primary Final Reviews Due:	March 14, 2016
Final Review Addendum Due*:	May 16, 2016
Complete Inspections:	April 16, 2016
Labeling Meetings:	TBD
Labeling Comments to Applicant:	May 16, 2016
Late-Cycle Briefing Package*:	March 19, 2016 (March 18, 2016)
Late-Cycle Meeting*:	March 31, 2016
Finalize Lot Release Protocol*:	May 16, 2016
Initiate Compliance Check:	May 18, 2016
Finalize Approval Package:	June 15, 2016
Action Due Date (ADD):	June 15, 2016
After Action Meeting*:	July 15, 2016

*required for an original BLA only

Explanation of Milestones:

Committee Assignment:	Date by which reviewers must be assigned to the file. This information must be entered into RMS-BLA and the assignment emails must be captured in the EDR. The committee assignment milestone should be left BLANK in RMS-BLA.
First Committee Meeting:	Committee must meet by this date to discuss the review of the BLA/BLS.
Filing Meeting:	Meeting at which the review committee determines whether or not the BLA can be filed. Reviewers must determine whether the information included in the BLA is sufficient to allow the reviewer to conduct an adequate review. The purpose is not to determine the acceptability of the data but rather to determine whether the appropriate information was submitted to allow the reviewer to conduct a meaningful review.
Filing Action:	Date by which a filing letter (either accepting or refusing to file the BLA) must be issued. The Priority Review request will also be addressed in this letter by communicating the review timeline and action due date.
Deficiencies Identified:	Date by which a letter must be issued in which review issues identified to date are conveyed to the applicant.
Mid-cycle Meeting:	Meeting at which each reviewer is expected to document their review progress and discuss the relevant content of the submission and present an overview. A draft review memorandum identifying key issues should be complete by the time of the meeting. First line supervisors for each review discipline as well as the Director and Deputy Director for DVRPA and OVRR, or their representative, should be in attendance at the meeting. (See CBER T910.06 for the list of minimum required attendees.)
Mid-Cycle Communication**:	Formal telecon with the applicant, no later than two weeks after the mid-cycle meeting, to provide an update on the status of the

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review of the submission including the following, as applicable: any significant issues identified; any IR's; information regarding major safety concerns; proposed dates or updates for the late-cycle meeting and any planned advisory committee meeting. The mid-cycle communication will include the Chair, RPM(s), DVRPA Division Director, ADRM and Eastern Research Group Contractors.

- Late-Cycle Briefing Pkg**: Background package sent to the applicant prior to the late cycle meeting. The briefing package shall contain any discipline review letters issued to date, a current assessment of the need for REMS or other risk management actions and a brief memorandum from the review committee outlining any substantive submission issues.
- Late-Cycle Meeting**: Meeting with applicant to discuss the status of the review. Topics of the meeting should include the information contained in the late-cycle briefing/background package, additional data or analyses the applicant wishes to submit, and outstanding information requests. **[CBER signatory authority, review committee, and team leaders or supervisors from disciplines with substantive issues must be present. The late-cycle meeting must be rescheduled if the signatory authority cannot attend.]**
- Action Due Date: Date by which final action regarding the BLA must be conveyed to the applicant (issue Approval or Complete Response letter, depending on review decision). All review memos, regardless of the Action being taken, must be signed and uploaded to the EDR prior to the date of Action.

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2.3 Documentation of Review

Each discipline reviewer is expected to prepare a written review documenting their review of the file. Timely submissions are imperative to allow time for adequate management review. The following is recommended:

- Identify all materials assigned for review and include an executive summary in each final or complete review memo.
- Summarize all material reviewed. The summary should identify each amendment reviewed and include a list of the submission dates, sections and page numbers etc. as applicable.
- A list of questions communicated to the applicant, in letter ready format, along with the responses received and reviewed should be clearly identified.
- A recommendation for action, approval or CR, based upon the review summary should be clearly stated.
- Draft primary reviews and Reviewer Reports should be prepared and discussed with the reviewer's supervisor and Reviewer Reports are due to the Chair and RPM at least 4 days prior to the internal Mid-cycle meeting. Draft reviews and Reviewer Reports should not be uploaded to the EDR.
- Reviewer's and supervisor's approval stamps should be placed on the final PDF version of the review. A Word version should be attached and the PDF should be certified to prevent modification. The review should be entered into RMS/BLA using **the date of the Reviewer's approval stamp as the date of the memo** and the certified PDF should be uploaded into the EDR.

Note: The final draft clinical review, vetted by the Team Lead or Branch Chief, is due to the Chair 4 weeks before action due. The final draft is due to the Division Director 2 weeks before action due. The final signed clinical review will be uploaded to the EDR no later than the action due date.

- If the file is CR'd, a complete written review is expected and should reflect any amendments that have not been reviewed through the date of the CR decision. The final signed and certified PDF version of the review should be uploaded by the date of the CR action.

3.0 COMMUNICATION PLAN

We can communicate with the applicant via several methods such as telecon, Secure e-mail, fax, and letter. The following is recommended:

- All communication in regard to requests for information or advice for the applicant will be coordinated by the RPM(s) and communicated either via telecon or Secure email. Please contact the Chair and/or RPM(s) if you need to communicate with the applicant (i.e., telecon, send a Secure e-mail, send a letter etc.).
- Although every effort should be made to include the RPM(s) and/or Chair when communicating with the applicant, it may be appropriate to communicate some requests for information (e.g., something that is relatively simple) to the applicant via a telecon. Please ensure that all such communication is formally documented (i.e., write up a telecon memo and send it to the RPM(s) to include in the file).
- Formal telecons with the applicant can be scheduled to address issues for which a direct discussion is helpful. The RPM(s) will coordinate this if/when it is needed.
- Letters can also be used to communicate review issues to the applicant. Although both Secure e-mail and letters provide the necessary documentation for the file, letters are a more formal process than Secure e-mail (letters must go through more levels of supervisory review and concurrence) so typically letters are reserved for communication of policy or serious review issues.

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- Faxes can also be used, if necessary. A copy of the fax (with documentation that transmission was successful) should be given to the RPM(s).
- Please “cc” the Chair on significant e-mail communication and meetings (internal and external). It is helpful for the Chair to have a general overview of the review status and review issues in the various disciplines (allows for more effective communication with internal upper level management and the applicant when necessary). Supervisory concurrence will be sought, when appropriate, prior to sending communications to the applicant (e.g., memos with request for information, providing advice, etc.).

4.0 DISCUSSION

4.1 Filing Review by Discipline

- 4.1.1 **Clinical**/Tina Mongeau-The BLA is acceptable to file. An information request for safety surveillance data or any post-marketing data for Orachol in other countries will be drafted.
- 4.1.2 **Statistical**/Sang Ahnn-The BLA is acceptable to file. Sang will also review the serological assays.
- 4.1.3 **Epidemiology**/Deepa Arya-The BLA is acceptable to file. The applicant proposed a pregnancy registry to monitor outcomes in women exposed to VaxChora but no protocol is submitted at this time.
- 4.1.4 **BiMo**/Christine Drabick-The BLA is acceptable to file. Four investigators/clinical sites from the three pivotal studies (PXVX-VC-200-003, -004, and -005) will be inspected.
- 4.1.5 **Labeling**/Oluchi Elekwachi-The BLA is acceptable to file. The trade name is acceptable. The label should be submitted in SPL format.
- 4.1.6 **Product/CMC**
 - 4.1.6.1 **CMC**/Roger Plaut -The BLA is acceptable to file. There will be an IR drafted regarding leachables/extractables.
 - 4.1.6.2 **Serology Assay** /Manuel Osorio-The BLA is acceptable to file. Freyja Williams indicated that the statistical reviewer reviewed the serology assay during the IND stage and found it to be acceptable.
- 4.1.7 **CMC/Lot Release**
 - 4.1.7.1 **CMC/Lot Release**/Marie Anderson-The BLA is acceptable to file.
 - 4.1.7.2 **CMC/Lot Release**/Alfred Del-Grosso-The BLA is acceptable to file.
 - 4.1.7.3 **CMC/Lot Release**/Simleen Kaur-The BLA is acceptable to file.
 - 4.1.7.4 **CMC/Lot Release**/Noel Baichoo-The BLA is acceptable to file.

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4.1.8 CMC/Facility

4.1.8.1 CMC/Facility/Inspector/Christine Harman-The BLA is acceptable to file. An Information Request will be drafted regarding equipment qualifications and cleaning validation for the (b) (4) facility. The Drug Substance manufacturer, (b) (4), and the Drug Product manufacturer, Pax Vax, Inc. (b) (4), will be inspected. The inspection of product release testing sites, (b) (4) will be waived due to good compliance history. Inspection waiver memos will be prepared. The (b) (4) facility was previously inspected as a drug substance facility in regards to an NDA in CDER, was issued a 483 with inspection outcome classified as OAI, and an Untitled Letter was issued. The firm was not re-inspected due to withdrawal of the NDA; therefore, the inspection issue was not closed and status remains as OAI. This could hinder inspection, and DMPQ is working to resolve the issue. CBER contacted Pax Vax, Inc. regarding production schedules and the firm indicated that they will not be performing commercial manufacturing until approval of the BLA because they do not have approved artwork (carton and container labels). The firm offered to perform a demonstration run of the blending and filling activities after January 20, 2016. The (b) (4) facility will be shut down from (b) (4) therefore, the soonest possible commercial production is scheduled for (b) (4).

4.1.8.2 Inspector/Deborah Trout-Not in attendance.

4.2 Administrative Details

- 4.2.1 The review team was notified that it is not necessary to hold a Vaccines and Related Biological Products Advisory Committee (VRBPAC) meeting to discuss this application, as essentially the same product and indication (for travelers using challenge studies) were previously discussed during the 1993 and 1998 advisory committee meetings.
- 4.2.2 The review team was reminded to be aware of milestones, and that they will receive an email requesting updates on review progress throughout the review process from C. Houck and K. Hoffman.
- 4.2.3 The review team was reminded that every review must be 508 compliant.
- 4.2.4 The review team was asked to send notifications for documents uploaded to the EDR to K. Hoffman and C. Houck.
- 4.2.5 The review team was reminded to keep their outlook calendars up-to-date.

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5.0 CONCLUSION

During the Filing Meeting the committee agreed that the application could be filed.

6.0 SUMMARY OF ACTION ITEMS

- 6.1** Discipline reviewers that would like to request additional information should provide comments to K. Hoffman and C. Houck.
- 6.2** The filing letter will be drafted by K. Hoffman and C. Houck for circulation and sign-off for issuance before or on December 15, 2015. At this point no deficiencies have been identified; therefore there are no plans for issuing a deficiencies identified (DI) letter.
- 6.3** The monthly meetings and mid-cycle meeting will be scheduled as soon as possible.