

RECORD OF TELEPHONE CONVERSATION

Submission Information

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

Telecon Details

Telecon Date/Time	02-FEB-2016 09:24 AM
Author	SEN, GOUTAM
EDR	No
Post to Web	No
Outside Phone Number	
FDA Originated?	Yes
Communication Categories	AD - Advice
Related STNs	None
Related PMCs	None
Telecon Summary	Informed that we will review their WSL and BDS hold time proposal in response to our Feb. 2, 2016 IR
FDA Participants	[Entered by the user, not system generated.]
Applicant Participants	[Entered by the user, not system generated.]

Telecon Body:

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From: Sen, Goutam
Sent: Tuesday, February 02, 2016 11:04 PM
To: 'Kevin Smyth'; Daugherty, Jon
Cc: Houck, Christina M; Hoffman, Kelsy; Harman, Christine; Trout, Deborah
Subject: RE: STN 125597/0: Vaxchora - MidCycle Review Meeting PreRead

Dear Kevin,

Thank you for your response below to our WSL and DS hold time comments sent today. I am informing the review team to look at your response. We need time to review your proposal as well as internal discussion before commenting on your proposal. I will talk to my review team tomorrow morning about it and will let you know during our 11:00 AM scheduled meeting.

Thank you,

Goutam

From: Kevin Smyth [<mailto:KSmyth@paxvax.com>]
Sent: Tuesday, February 02, 2016 10:52 PM
To: Daugherty, Jon; Sen, Goutam
Cc: Houck, Christina M; Hoffman, Kelsy; Harman, Christine; Trout, Deborah
Subject: STN 125597/0: Vaxchora - MidCycle Review Meeting PreRead

Dear Mr. Sen and Mr. Daugherty,

Thank you for the mid-cycle communication that we received on Feb01, and related CMC information request, received on Feb02.
To help promote discussion between the Agency and PaxVax during the Feb03 mid-cycle review meeting, we provide the following responses to Topics 1 and 2.

Topic 1: Change to (b) (4) WSL from (b) (4) WSL

Our intent to change the WSL supplier was described in the preBLA briefing package, and written advice on this topic was received from the Agency in the attached preBLA meeting minutes (Item 20a, b). The requested information was included in the BLA and additionally, a detailed description of the manufacturing process, (b) (4) of the WSL. (b) (4) is a vendor qualified by an on-site audit by PaxVax, and the Site Master File for (b) (4), which provides the facility information requested in the Items 2b, 2c (Feb02 Information Request), is immediately available.

Data will be available post-approval for Items 2a and 2e (Feb02 information request). Specifically, a full genome sequence and stability data for three lots of drug product manufactured with the (b) (4) WSL can be made available post-approval, but not at the current time. Although the preBLA briefing package fully disclosed our intent to change WSL supplier, we acknowledge that the Agency's preBLA meeting minutes do not routinely prescribe the full data requirements for each BLA topic.

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The change in WSL supplier is driven by the need to manufacture sufficient WSL to support commercial operations. We believe that the remaining (b) (4) vials of (b) (4) WSL are sufficient to manufacture no more than (b) (4) lots of IBDS, which will result in approximately (b) (4) doses of Vaxchora drug product. However, a contingency plan is not in-place at the current time.

Topic 2: Change from (b) (4) Interval in (b) (4) Step of Drug Product Manufacture

Our intent to change to the (b) (4) interval in the (b) (4) step of drug product manufacture was described in the preBLA briefing package and written advice on this topic was received from the Agency in the attached preBLA meeting minutes (Items 8, 10, and 20). The (b) (4) interval that was used to manufacture all (b) (4) drug product conformance lots is designed to increase product quality, and this change was implemented only after receiving the encouraging text in the preBLA meeting minutes (Items 8, 10, and 20). Specifically, the change is supported by data in the BLA that includes: a favorable improvement in the stability profile (Item 8 requests stability data to cover the change), four lots of drug product (Item 10 requests three lots), and a comparability study (Item 20 requests a comparability study to cover the changes in Table 24, for which the (b) (4) interval is listed in Row 2).

The Agency's Feb02 request for two additional datasets can be easily satisfied during the BLA review as follows:

- Data to satisfy Item 4a "...a study of the recovery time of DP....to achieve a benchmark concentration..." can be submitted to the BLA by March 15.
- Data to satisfy Item 4b "...real-time stability...should include all four stability tests..." can also be submitted to the BLA and in the previously agreed March stability update.

Preliminary stability data for the three lots of Phase 3 clinical trial material, all manufactured with the (b) (4) interval, show that drug product appears to remain above the lower limit of the proposed potency range ($4 \times 10^8 - 2 \times 10^9$ CFU/dose) for 18 months, with the lowest 18 month value at about 4.5×10^8 CFU/dose. This preliminary stability data will be reviewed by Quality and then submitted in the previously agreed March stability update. The (b) (4) interval has been identified as a risk to our ability to commercialize Vaxchora because 1) the lower limit of potency (4×10^8 CFU/dose) although justified in Section 2.5.3.4 of the BLA, has not been approved and, 2) neither PaxVax Quality nor the Agency has not reviewed the 18M stability data. i.e. a commercial shelf-life assignment of substantially <18 months could be permanently assigned for material manufactured with the (b) (4) interval.

Would the Agency agree to review data that supports Items 4a and 4b in March 2016 to help ensure that an improved drug product stability profile and corresponding shelf-life is achieved as early as possible in the commercial lifecycle?

Regards, Kevin

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Kevin Smyth

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