

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	06-JUN-2016 07:57 AM
	SEN, GOUTAM
	No
	No
	Yes
	AD - Advice
	None
	None
	Advised on studies required to use spring water for reconstitution of the vaccine
	Goutam Sen
	Kevin Smyth

Telecon Body:

From: Kevin Smyth [mailto:KSmyth@paxvax.com]
Sent: Monday, June 06, 2016 5:42 PM
To: Sen, Goutam
Subject: RE: Spring water issue, STN: 125597

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Dear Goutam,

Thank you so much for the below explanation and guidance on data required to support the use of Spring water.

We accept the Agency's recommendation and justification.

On Tuesday Jun 07 we will publish and transmit to the BLA, a revised USPI and artwork that definitively state "Purified Bottled Water".

Regards, Kevin

Kevin Smyth

Vice President

Regulatory Affairs and Pharmacovigilance

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From: Sen, Goutam [<mailto:Goutam.Sen@fda.hhs.gov>]

Sent: Monday, June 06, 2016 12:27

To: Kevin Smyth <KSmyth@paxvax.com>

Subject: Spring water issue, STN: 125597

Dear Kevin,

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

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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.

Please let me know, if you have any question or want to have a telecon for clarification. If you agree to remove spring water for reconstitution from the Vaxchora PI, please submit a revised PI to your STN as an amendment.

Thank you,

Goutam

Goutam Sen, Ph.D.
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