

From: Sen, Goutam

Sent: Friday, May 27, 2016 3:30 PM

To: 'Kevin Smyth'

Subject: Revised Vaxchora USPI and justification, STN: 125597

Dear Kevin,

Please find the attached word document containing revised Vaxchora PI, based on your May 17, 2016 revised submission and May 25, 2016 rationale submission by email. Yellow highlighted sections are today's modification. But please look closely for any other changes compared to our May 23, 2016 document sent. I am also attaching a PDF containing our justification to the five changes, containing rationale in your May 25, 2016 email. Please let me know if you have any question.

Thank you,

Goutam

Issues 1 and 2 Section 1 Indications and Usage (including Limitations of Use):

We reviewed the response attached to your May 25th email. We agree that for the Indication statement, the term “traveler” is adequate without the addition of the phrase “with no known previous risk of exposure”. However, that approach is acceptable with the condition that the underlying concern about the lack of data supporting effectiveness in a non-naïve population be addressed. Therefore, under the “Limitations of Use” heading, we have recommended revised language that conveys the uncertainty about efficacy in exposed populations.

Issue 3: Use of Bottled Water for Reconstitution

In your May 25, 2016, communication regarding the package insert, you proposed revising the Dosage and Administration section to state that “bottled water” should be used for reconstitution rather than “purified bottled water.” We do not agree to this proposal for the following reasons:

- 1) According to 21 CFR 165.110, bottled water includes artesian water, mineral water, purified water, spring water, sparkling bottled water, and sterile water. Other beverages that are available in the U.S. could be mistaken for bottled water, because they are similarly packaged and include the word “water” in their names. These beverages may be called “flavored water,” “tonic water,” “nutrient enhanced water beverage,” “flavored sparkling water,” “flavored water beverage,” “flavored purified water beverage,” “purified water with electrolytes,” etc. These beverages are not subject to the same regulations as bottled water and contain a variety of additional ingredients, including vitamins, minerals, preservatives, and natural and artificial sweeteners. The possible effects of these ingredients on the potency of Vaxchora are unknown.
- 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 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. In the bridging studies, several types of water were used for reconstitution, including sterile water for irrigation, purified water, and spring water (Table 1, Section 1.11.4, Amendment 34). However, in no case was artesian water, mineral water, or sparkling water used; therefore, no data are available regarding efficacy of vaccine reconstituted in these water types.

In summary, the data in the BLA do not provide confidence that the potency of Vaxchora would be maintained regardless of the type of bottled water used for reconstitution. Additionally, the term “bottled water” could easily be misinterpreted to include beverages that include other ingredients.

According to the limited *in vitro* data that are available, when purified bottled water was used for reconstitution, vaccine potency remained within the acceptance criteria. Purified bottled water must be treated according to methods specified by USP and would be expected to be of more consistent quality than artesian water, mineral water, spring water, or sparkling bottled water. In particular, mineral water is not subject to the same restrictions as other bottled waters regarding allowable levels of certain chemical substances (21 CFR 165.110) and therefore may contain high levels of zinc, which is known to possess antimicrobial activity. Therefore, CBER requests that the package insert for Vaxchora specify that purified bottled water be used for reconstitution.

Issue 4: Sachet Hold Time at Room Temperature Prior to Reconstitution

In your May 25, 2016, communication regarding thaw time prior to reconstitution of Vaxchora, you state that the data submitted in your BLA support a thaw duration of up to 30 minutes. We do not agree, for the following reasons:

- 1) The Pharmacy Manual for the Phase 3 clinical trials required reconstitution of the vaccine within 30 minutes of removal of the sachets from cold storage. In the challenge study, the mean hold duration was 14.4 minutes, and the median hold duration was 9 minutes (Amendment 39, p. 4). No data are available regarding efficacy of vaccine reconstituted following sachet hold durations closer to the higher end of the 0–30 minute range.
- 2) In addition, in the *in vitro* study referenced above, in which different types of bottled water were used for reconstitution (Figure 1, Section 3.2.P.2.6 Compatibility and Document Number TRDEV-0016), the buffer sachets were held at room temperature for lengths of time ranging from 0 to 28 minutes, and the mean hold time was 16.5 minutes (Table 3, Amendment 34). When the potency of vaccine reconstituted after various hold durations was tested (Figure 5, Section 3.2.P.2.6 Compatibility and Document Number TRDEV-0016), the only type of water used was the type that yielded the highest potency results (Amendment 34, p. 5). You have not provided data regarding a potential worst-case scenario, in which the type of bottled water that yielded the lowest potency result was used to reconstitute sachets that had been held at room temperature for 30 minutes. Moreover, as described above, the drug product used was not manufactured under the process described in the BLA, and there is reason to believe that the drug product that was used for the laboratory study is more stable than the drug product that was used in the clinical trials (Section 3.2.P.2.3.1, STN 125597 original submission).

In summary, the data in the BLA do not provide confidence that the potency of Vaxchora would be maintained if the sachets were held at room temperature for 15–30 minutes prior to reconstitution. Therefore, CBER requests that the package insert for Vaxchora specify that sachets be out of frozen storage for no more than 15 minutes prior to reconstitution.

Issue 5: Section 12.1 Mechanism of Action:

PaxVax, Inc. proposes including references and edits to state that vibriocidal antibodies are a marker of protection against infection in people who live in areas where cholera is endemic. We do not agree with the inclusion of the proposed references and edits because these are implied claims which suggest that Vaxchora can be used in endemic populations and is not permissible according to 21 CFR 201.56. Furthermore, data to support the efficacy of Vaxchora in endemic populations were not submitted to your BLA.