

From: [Kevin Smyth](#)
To: [Sen. Goutam](#)
Subject: RE: Response to your Question and Information request for DP potency, STN: 125597
Date: Tuesday, May 10, 2016 8:42:49 AM

Dear Goutam,

Thanks for the clarification!

Regards, Kevin

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From: Sen, Goutam [mailto:Goutam.Sen@fda.hhs.gov]
Sent: Tuesday, May 10, 2016 13:16
To: Kevin Smyth
Subject: RE: Response to your Question and Information request for DP potency, STN: 125597

Dear Kevin,

Here is the clarification of our May 6, 2016, information request, item#3 as per your request: "If you currently have data regarding the impact of different sources of bottled water and the impact of different thaw durations on drug product potency, using drug product that was manufactured using the bulk drug substance hold time of (b) (4) , please provide it. However, if you do not, we are not requesting that you obtain such additional data at this time."

Please let me know if you have any question.

Thank you,

Goutam

From: Kevin Smyth [mailto:KSmyth@paxvax.com]
Sent: Friday, May 06, 2016 4:39 PM
To: Sen, Goutam
Subject: RE: Response to your Question and Information request for DP potency, STN: 125597

Dear Goutam,

Regarding Item 3 – The paragraph states that we have not provided data for the hold time of [REDACTED] and then goes on to discuss data required to support post-approval changes. Would you please clarify if you would require that reconstitution data for the hold time of [REDACTED] be submitted prior June 15 (i.e. no manufacturing changes).

Regards, Kevin

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

Sent: Friday, May 06, 2016 11:45

To: Kevin Smyth

Subject: Response to your Question and Information request for DP potency, STN: 125597

Dear Kevin,

Thank you for the telephone conversation of this morning, discussing some of our questions/comment. As we stated during this morning's telecon, I am sending our response to your question as well as information request. Please submit your response as an amendment to your STN: 125597.

- 1) The lower limit of the potency (b) (4) of your DP as stated in 2b of our May 5, 2016 email IR should be stated as: 4×10^8
- 2) We note that your proposed potency acceptance criteria are 4×10^8 to 2×10^9 CFU/dose, with a target sachet fill of (b) (4) CFU/dose. In addition, in your stability data, we note that the potency of lots with initial potency of 1×10^9 CFU/dose decreased to a range of $4-6 \times 10^8$ CFU/dose after 18 months of storage at $-20 \pm 5^\circ\text{C}$. Please comment on how you will ensure and/or monitor whether the potency of the drug product remains within the acceptance criteria through the end of the proposed 18-month dating period, considering that some lots may have initial potency toward the lower end of the range of the acceptance criteria.
- 3) In your correspondence dated April 22, 2016, you stated that the lot used to study the impact of different sources of bottled water and the impact of different thaw durations on drug product potency (Figures 1 and 5 of the compatibility document in module 3.2.P.2.6 of STN 125597_0) was manufactured using bulk drug substance that was stabilized using a (b) (4) hold time, a manufacturing process that you have withdrawn from your BLA. You have not provided corresponding data using drug product manufactured using a bulk drug substance hold time of (b) (4), which is the manufacturing process that you are proposing in your BLA. If you intend to propose a change in the manufacturing process in the future, at that time, please include results of a study of the impact on potency of different sources of bottled water, different lengths of sachet thaw time, and different hold times after reconstitution. Please include Water for Irrigation, USP, as one of the bottled water types assessed. Please conduct the study using drug product manufactured using the process proposed in your BLA and drug product manufactured using the proposed

change, for comparison purposes. In addition, please include tests of a worst-case scenario, in which the type of bottled water that yields the lowest potency result is assessed in studies of sachet thaw time and reconstituted vaccine hold time.

Please let me know if you have any question.

Thank you,

Goutam

From: Kevin Smyth [<mailto:KSmyth@paxvax.com>]
Sent: Friday, May 06, 2016 2:32 AM
To: Sen, Goutam
Subject: RE: CBER comments to Vaxchora Package insert and carton labels, STN: 125597

Dear Goutam,

We have begun our internal meetings to review and align on FDA's recommended label revisions, and I commit to a full response by no later than March 19.

We note that the potency range lower limit has been (b) (4) from 4×10^8 to (b) (4), and have a couple of follow-up requests/clarifications:

- Would you please provide brief justification for the (b) (4), in light of the fact that P3 subjects were administered product at 4.2×10^8 ?
- At this time may I ask you to please reiterate your intent to grant at least 18M of drug product shelf-life for a lower potency limit of (b) (4)
- No request was received to change the drug product release specification from 4×10^8 to (b) (4)...might additional specification-related changes be forthcoming?

Thanks so much for any response you can provide to the above.

Regards, Kevin

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From: Sen, Goutam [<mailto:Goutam.Sen@fda.hhs.gov>]
Sent: Thursday, May 05, 2016 12:43
To: Kevin Smyth
Subject: CBER comments to Vaxchora Package insert and carton labels, STN: 125597

Dear Kevin,

Please find the attached word document containing our edit/comment to your Vaxchora package

insert. Also, please find below our comments to your Buffer and Vaccine sachet carton label. Please submit your response to these comments as an amendment to your STN by May 19, 2016. Please let me know if you have any question.

Thank you,

Goutam Sen, Ph.D.

Scientific Reviewer

Food and Drug Administration

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CBER Comments Regarding Draft Buffer & Vaccine Sachet Mock-up and Draft Carton Mock-up:

1. Please revise the draft Buffer Sachet as follows:
 - a. Please revise the "BUFFER" label of this sachet to read "BUFFER COMPONENT of VAXCHORA (Cholera Vaccine, Live, Oral)."
 - b. Please add language that emphasizes the importance of using the recommended purified bottled water for reconstitution.
2. Please revise the draft Vaccine Sachet as follows :
 - a. Please revise the "VACCINE" label of this sachet to read "BACTERIAL COMPONENT of VAXCHORA (Cholera Vaccine, Live, Oral)."
 - b. Please revise the contents to read as follows: "Contents (Single-Dose): (b) (4) to 2×10^9 CFU of lyophilized *V. cholerae* CVD 103-HgR."
 - c. Please delete "Cholera Vaccine, Live, Oral Vaxchora™," which is located above the contents, as Vaxchora is the final product after reconstitution of both sachets.
2. The following comments apply generally to both sachets, to reduce the risk of either sachet alone being mistaken for the complete vaccine:
 - a. Please consider redesigning the sachets such that they can accommodate larger labels (to reduce label crowding) and increased font size of important text.
 - b. We recommend that you provide on each sachet clear directions for reconstituting the product and warnings to administer the contents of both sachets.
 - c. Please consider labeling each sachet as "Sachet 1 of 2" and "Sachet 2 of 2," or use a similar scheme to distinguish, yet link, the two sachets, the contents of which must be administered together.
3. Please consider conducting usability testing with vaccine users to test labels, packages and preparation processes for safety, clarity and effectiveness.

4. FDA recommends use of 12-point font wherever label size permits.
5. The following comments apply to the Draft Carton Mock-up:
 - a. We recommend revision of the contents to read as follows: "Contents: Single-dose Bacterial Sachet (b) (4) to 2×10^9 CFU of *V. cholerae* CVD 103-HgR) and Single-dose Buffer Sachet."
 - b. We recommend revision of the carton to indicate that the vaccine must be reconstituted prior to use.
 - c. We recommend that clear directions for reconstituting the product and warnings to administer the contents of both sachets be included on the front of the carton.

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