

MEMORANDUM**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Biologics Evaluation and Research**

Date: March 3, 2016

From: CDR Oluchi Elekwachi, PharmD, MPH Regulatory Reviewer
OCBQ/DCM/APLB

Through: Lisa Stockbridge, Ph.D., Branch Chief
OCBQ/DCM/APLB

To: Christina Houck, Regulatory Project Manager, DVRPA/OVRR
Tina Mongeau, M.D., Medical Officer, DVRPA/OVRR

Subject: Labeling Review - Comments on product labeling (prescribing information,
carton insert, and carton/sachet labels)

Product: **VAXCHORA (Cholera Vaccine, Live, Oral)**
BLA STN: **125597/0**
Sponsor: PaxVax, Inc.

The sponsor submitted:

<input checked="" type="checkbox"/>	Original Application
<input type="checkbox"/>	Major Amendment
<input type="checkbox"/>	Prior Approval Supplement (PAS)
<input type="checkbox"/>	Changes Being Effected (CBE) Supplement

Submission contains:

<input checked="" type="checkbox"/>	Prescribing Information (PI) – submitted on October 16, 2015
<input type="checkbox"/>	Patient Package Insert (PPI) –
<input checked="" type="checkbox"/>	Carton/Sachet- labels submitted on October 16, 2015

Pax Vax Bermuda Limited submitted VAXCHORA (Cholera Vaccine, Live, Oral) (BLA STN#125597/0) on October 16, 2015. The proposed indication is active immunization against disease caused by *V. cholerae* serogroup O1 in adults 18 years of age and older.

The action due date for this application is June 15, 2016.

APLB reviewed the prescribing information (PI) and carton/sachet labels received from the sponsor on October 16, 2015.

OVERALL

- Present the proprietary name, VAXCHORA, in upper case letters because it will appear that way in SPL format.
- APLB suggests revision of the dosage form to read “Powder, for Suspension for Oral Administration”. For reference, the following FDA Data Council website lists acceptable dosage forms:

<http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/ucm162038.htm>

- Use active voice when possible.
- Avoid bold text unless required by the regulations (see 21 CFR §201.57(d)(1)). Consider using underlining for subheadings and italics for sub-subheadings. For example,

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

Vaccine-associated maternal and/or embryo/fetal risk

- Avoid trailing zeros in text. For example, use 0.5 instead of 0.50.
- Refrain from using the following terminology: Phase I, II, III, primary endpoint, secondary endpoint. Instead, simply describe the study(ies) that are supported.
- Ensure that the section and subsection headings in the HIGHLIGHTS (HL) and the TABLE OF CONTENTS (TOC) match the section and subsection headings in the FULL PRESCRIBING INFORMATION (FPI).
- Delete the “Rx only” statement that appears at the end of the labeling. This statement is not required for package insert labeling, only container labels and carton labeling. (See *Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements*)

HIGHLIGHTS (HL)

- The information in the HL section is limited in length to one half of an 8 ½ x 11 inch page, when printed in two columns, single spaced, 8 point font, with half inch margins on all sides and between columns. (See 21 CFR §201.57(d)(8))
- For a new BLA, or supplement, the initial approval date is placed on the next line immediately beneath the proper name. Leave the revision date blank for original BLA applications. It will be edited to the month/year of a supplement approval.

- Add a Limitation of Use subsection to the INDICATIONS AND USAGE section. The limitation of use, currently listed under WARNINGS AND PRECAUTIONS, belongs here.
- Place the bold statement, “For oral use only.” directly beneath the header, DOSAGE AND ADMINISTRATION.
- For the CONTRAINDICATIONS section, APLB suggests the following revision for readability:
 - Do not use in patients with history of severe allergic reaction (e.g. anaphylaxis) to any component of the vaccine or buffer, including milk protein, or to a previous dose of any cholera vaccine. (4)
- For readability, APLB suggests the following active voice revision to the warning regarding acute in patients taking antibiotics:

Postpone administration of VAXCHORA in patients receiving systemic antibiotics or suffering from acute gastrointestinal illness or acute febrile illness. (5)
- Ensure that the WARNINGS AND PRECAUTIONS section of the HL is consistent with the FULL PRESCRIBING INFORMATION (FPI).
- In the ADVERSE REACTIONS section, delete the phrase “and greater than placebo.”
- For the USE IN SPECIFIC POPULATIONS section, consider the following:
 - Information about the availability of a pregnancy registry and enrollment information does not belong in this section of the HL. Include this information in the Pregnancy subsection of USE IN SPECIFIC POPULATIONS section in the FPI.
 - When there are no clinically important differences in response or recommendations for use of the drug in specific populations, the USE IN SPECIFIC POPULATIONS heading should be omitted from HL. Ordinarily, the absence of information about the safety and effectiveness of a drug in a specific population (e.g., pregnant women, children) is not included in the HL. Therefore, APLB recommends deleting this section in the HL.

TABLE OF CONTENTS

Ensure that the section and subsection headings in the TOC match the section and subsection headings in the revised FPI.

FULL PRESCRIBING INFORMATION (FPI)

1 INDICATIONS AND USAGE

Include the limitations of use in this section.

2 DOSAGE AND ADMINISTRATION

- Add the bolded statement, “For oral use only.” directly beneath the section header.
- Include the dose information under 2.1 Dosage. For consistency with other products, consider renaming this subsection 2.1 Dose.
- Short bulleted instructions would improve readability.
- Delete the first paragraph under subsection 2.2. The approved product labeling provides the instructions for use. Information regarding common medical practice does not belong in this label.
- Revise the second paragraph to readable instructions with good grammar. For example

Reconstitute the vaccine within 30 minutes after removal of the two component sachets (vaccine and buffer) from the freezer.

- Is it accurate to say that the vaccine must be consumed within one hour after removal from the freezer? If not, then Step 9 requires revision.

4 CONTRAINDICATIONS

APLB suggests the following revision for readability:

Do not use in patients who have history of severe allergic reaction, e.g. anaphylaxis, to any component of the vaccine or buffer, including milk protein, or to a previous dose of any cholera vaccine.

5 WARNINGS AND PRECAUTIONS

For consistency with prescribing information for other live vaccines, APLB recommends addition of the following subheadings, in this order, under this section:

5.1 Hypersensitivity Reactions

5.2 Transmission of Vaccine Bacteria

5.3 Concomitant Illnesses

Follow each subheading with a succinct descriptive paragraph presented in active voice. For example

5.2 Transmission of Vaccine Bacteria

VAXCHORA is a live, attenuated bacterial vaccine that replicates in the intestinal tract. Vaccine bacteria are shed in the stool for at least 7 days following vaccination, creating the potential for transmission of vaccine bacteria to household contacts.

6 ADVERSE REACTIONS

- The common adverse reactions statement, positioned directly beneath the section heading, is the same statement that is used in the HL. It is not useful to state that these adverse reactions were greater than placebo, and this phrase decreases the readability of the sentence. Thus, APLB suggests omitting this phrase.
- Unsolicited adverse reactions are still adverse reactions by regulatory definition. It is not necessary to provide discourse on the determination of an adverse experience as a reaction or an event. These are defined by the regulations and cannot be modified. Only adverse reactions belong in 6.1 Clinical Trials Experience. (See *Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*)
- Reference to the “memory aid” may be promotional in the absence of a description of this tool.

7 DRUG INTERACTIONS

- Revise the wording in this section to active voice.
- For subsection 7.2 Use with Antibiotics
 - Please revise the below statement to specify the antibiotic class(es) and timeframe of use avoidance.

“Concomitant administration of VAXCHORA with sulfonamides or antibiotics should be avoided since these agents may be active against the vaccine strain and prevent a sufficient degree of multiplication to occur in order to induce a protective immune response.”
 - Consider a cross reference to WARNINGS AND PRECAUTIONS

8 USE IN SPECIFIC POPULATIONS

- Under subsection 8.1 Pregnancy, APLB recommends clarifying the Risk Summary subsection to read:

Risk Summary

Vaccine-associated maternal and/or embryo/fetal risk

- To comply with labeling regulations for pediatric language, please revise subsection 8.4 to read:

“Safety and effectiveness of VAXCHORA in pediatric patients under 18 years of age have not been established.”

13 NONCLINICAL TOXICOLOGY

Delete this section when there are no data.

15 REFERENCES

Refrain from citing National Clinical Trials. These citations may be used in promotion of unapproved uses and other information that is inconsistent with the approved product labeling.

16 HOW SUPPLIED/STORAGE AND HANDLING

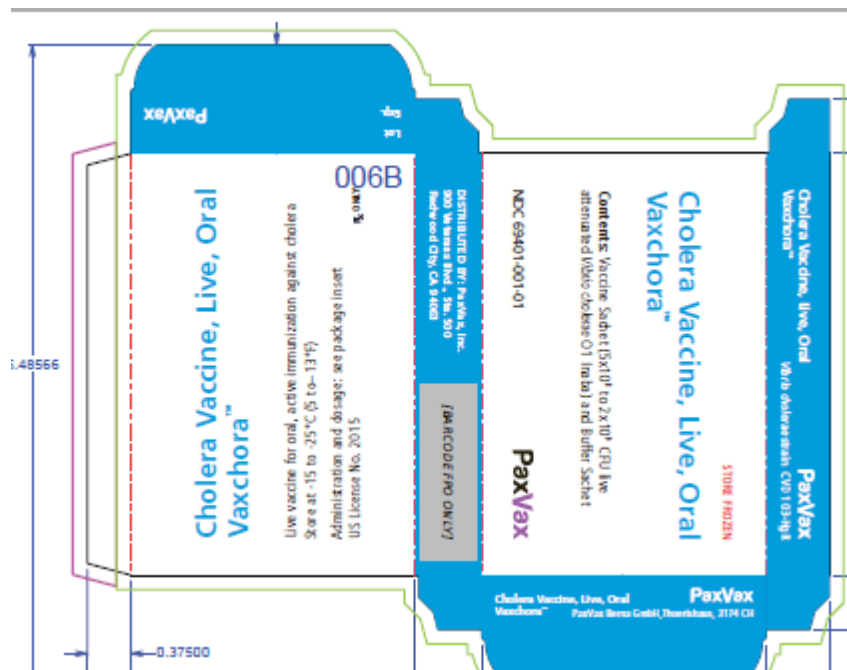
- Information in this section is minimal and readability would benefit from the omission of subsections. Instead, bullet important concepts in short sentences or phrases.
- For clarity, place NDC numbers on the same line as the dose form and packaging that is described. Consider using a table for this information.
- Information about administration belongs in the DOSAGE AND ADMINISTRATION section.

17 PATIENT COUNSELING INFORMATION

Revise the section to conform to the [Guidance for Industry: Patient Counseling Information Section of Labeling for Human Prescription Drug and Biological Products – Content and Format.](#)

CARTON AND SACHET LABELS

- FDA recommends use of 12-point font wherever label size permits
- Include instructions for reconstituting the product and the resultant concentration on the sachet, if space permits
- We recommend revision of the carton to indicate that the vaccine must be reconstituted prior to use.



If you have any questions regarding this review please contact CDR Oluchi Elekwachi, PharmD, MPH Regulatory Review Officer at 240-402-8930

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