RESPONSE TO FDA COMMENTS ON CMC RECEIVED ON 20 OCTOBER 2021

The Sponsor acknowledges FDA comments on CMC topics (in **Bold)**

Manufacturing

Our review of your August 24, 2021 submission (STN 125752/2) is ongoing. We have the following request for additional information:

ITEM 1:

In section 3.2.S.2.3.2.2, Plasmid Manufacturing, (b) (4)) and Aldevron, Fargo, ND (Aldevron), were listed as manufacturers for the linearized plasmid DNA (pDNA), however, in section 3.2.S.2.1, Manufacturer(s) {CX-024414}, Aldevron was listed as the only manufacturer for the linearized pDNA template.

a. Please clarify if (b) (4) is involved with the manufacture of the linearized pDNA template for SPIKEVAX, including but not limited to release testing, stability testing and storage unit operations.

Sponsor Response

(b) (4) performs internal release of pDNA (also released by Aldevron), storage and stability testing for linearized pDNA. (b) (4) is also responsible for the manufacturing of plasmid master and working cell bank, cell bank storage and testing.

ITEM 2:

Please describe the primary container closure system used in storing and shipping the linear DNA template to (b) (4) for further processing.

Sponsor Response

Plasmid is stored and shipped in sterile (b) (4) (b) (4) . The containers are compliant with USP Class VI, non-cytotoxic, USP <661>, non-pyrogenic, and FDA 21CFR 177.1315, and are suitable for use in storage conditions of -100° to +100°C.

ITEM 3:

Please provide the maximum hold time for each manufacturing step of the linear DNA template and provide the at scale (b) (4) (b) (4)

Sponsor Response

Linear DNA template is a critical starting material. (b) (4) (b) (4)

Due to the controls in place, (b) (4) considers hold steps with plasmid DNA to have low risk and such hold studies have not been completed.

ITEM 4:

Please provide the shipping validation summary for shipments of linear DNA template from Aldevron to (b) (4). Also, please clarify if all shipments of linear DNA template will be temperature-monitored.

Sponsor Response

(b) (4) has accessed shipping against ICH 7D guidelines namely that "APIs and intermediates should be transported in a manner that does not adversely affect their quality." Based on the nature of DNA, Shipping validation was not required for linearized plasmid DNA.

However, to ensure the control of shipping conditions, linearized plasmid DNA is shipped via (b) (4) (b) (4) with temperature monitoring. These materials are packed and received through established procedures.

In addition, plasmid DNA is considered to be a low risk material because DNA is generally stable (Nguyen et.al. Polymers, 2018.10,28) and (b) (4) has data stability currently up to (b) (4) (b) (4). Freeze thaw stability assessment was also performed and demonstrated that DNA plasmid can be frozen and thawed up to (b) (4) times with no significant impact to mRNA yield or product purity in the IVT reaction (PD-MEM-0449).

With the controls already in place coupled with the stability of plasmid DNA in general, this approach is consistent with ICH 7D for ensuring product quality.