RESPONSE TO FDA COMMENTS ON RESPONSE TO INFORMATION REQUEST#26 DATED DECEMBER 01, 2021

The Sponsor acknowledges FDA Comments on RESPONSE TO INFOMRATION REQUEST#26 dated 01 DECEMBER 2021 for BLA 125752 in (**BOLD**)

Product: COVID-19 Vaccine, mRNA (SPIKEVAX)

Subject: Analytical method procedure and validation

In reviewing BLA (STN 125752/0), we have the following information request (IR) regarding the measurement of endotoxin in the Drug Product (DP) using the (b) (4) **LAL procedure.**

ITEM 1:

Your procedure for measuring endotoxin in DP includes a sample "preparation" step. While you provide data demonstrating the sample (b) (4) (b) (4) **you have not provided data to evaluate the potential endotoxin-like activity of the lipid components of your product** (b) (4) (b) (4) **. Please provide data to address potential endotoxin-like activity of each of the lipid components.**

Endotoxin is comprised predominantly of lipopolysaccharide (LPS). It consists of a polar saccharide chain, polysaccharide core, and is attached to a lipid component know as lipid A. The composition of endotoxin is more soluble in water than in nonpolar solvents. Lipid-based drug substances / products are known to present complications for bacterial endotoxin testing. Lipopolysaccharides are amphipathic in nature. (b) (4)

(b) (4)

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During method development, the Sponsor worked with Associates of Cape Cod, Inc. (ACC) to (b) (4)

The Sponsor understands the Agency's reference to "endotoxin like activity" of the individual lipids to mean potential interference of the individual lipids with the conduct of the assay. The (b) (4)

(b) (4)

ITEM 2:

A dilution series is the usual approach to overcome DP interfering factors. Please provide data from a dilution study of (b) (4) **samples that includes the percent positive product control (PPC %) recovery at each dilution of DP, up to the Maximum Valid Dilution (MVD).**

(b) (4)

DP Lot Number	ACC Report Number	Maximum Valid Dilution (MVD)	PPC Recovery of Drug Product	PPC Recover of Challenge Sample
6007520001	0620-003TESCVR	(b) (4)		
6007520003	0620-033TESVR			
6007520002	0620-038TESVR			
6007520005	0720-010TESC			
6007520006	0720-036TESC			
6007320001	0820-039TESVR			
6007320002	0820-074TESVR			
6007320004	0920-076TESVR			
6007320005	1020-111TESVR			

During Method Execution the challenge sample (Drug Product sample spiked with endotoxin standard) and an unspiked Drug Product sample (test article) are analyzed, and a PPC value is generated for each. The PPC Recovery of the Drug Product column contains results for the PPC recovery for the unspiked Drug Product sample. The PPC Recovery of Challenge Sample column contains results for the spike recovery of endotoxin standard and the PPC recovery of the challenge sample.

ITEM 3:

From the data generated in the preceding request, we ask that you identify a dilution for testing DP within the range of 50-200% recovery of endotoxin, (b) (4) step. Please use this information to establish the endotoxin limit and commit to establishing specifications for DP endotoxin activity levels for samples that are (b) (4). Please comment and provide a date by which this can be implemented for release of DP lots.

Sponsor Response:

Out of an abundance of caution, the Sponsor believes that (b) (4)
(b) (4)
(b) (4). The method is fit for purpose and there is no negative consequence to executing the sample preparation step. This step does not inhibit or enhance the detection of potential endotoxin present in mRNA-1273 DP samples, by virtue of controls in the methods.

(b) (4)