

We have the following requests and instructions regarding test methods, the lot release process, and the lot release protocol template:

- A. Regarding the RNA integrity assay by CGE: Please explain how the (b) (4) If available, provide the work instructions for CGE (b) (4) or commit to generating these instructions.
- B. Regarding lot release of the 7 EUA lots:
1. Please send samples (20 vials) of each lot to the address noted below as soon as possible. We can receive them any day and prefer that they be received NO LATER THAN Wednesday 18 August 2021. Please contact Mr. Quander at Joseph.Quander@fda.hhs.gov for specific shipping instructions and to notify him of shipments.
- Shipments should be sent to:
- Food and Drug Administration
Center for Biologics Evaluation and Research
Sample Custodian
10903 New Hampshire Avenue
WO75-G707
Silver Spring, MD 20993-0002
2. Please confirm your intent to accept all our instructions for the Lot Release Protocol template in the section below. Please request a telecon for clarification if needed. Please note that because we have expedited the review process, we may request changes to the protocol in the future.
 3. Although we cannot commit to a 48-hour turnaround time for lot release as you have requested, we are committed to completing the required review and testing expeditiously.

C. Comments on lot release protocol (LRP) template submitted to BLA 125742/0.40

NOTE: Page numbers referenced below are from Adobe page numbering (not the page numbers on the footer).

It has been determined that lot release protocols will be submitted electronically. Due to that the following is requested regarding pages 1 and 2.

Throughout document

Renumber the entire document with the Electronic Protocol Signature Page as Page 1

Page 2 of 12

Please remove the reason for submission as that is now on page 1 of 12.

Please replace the Fill Information with the table of Fill Information form Page 3 of 12.

Page 3 of 12

Please remove the Reason for Submission.

Please remove the following:

All lot release tests conducted on this lot, as per the product license are reported and pass specifications as required.

Prepared By:

Approved By:

Page 6 of 12:

RNA encapsulation and content test

Sponsor question: What is required for R2 for standard A and B?

CBER Response: Regarding your RNA encapsulation and content test: The test described in TM#100010402 requires the coefficient of determination (R^2) for (b) (4) to be (b) (4). Please provide the R^2 values for standards A (standard in (b) (4)) and B (standard in (b) (4)) for each test performed. We note that you have not incorporated all requested information for this test in the LRP. Please include Encapsulated RNA and Total RNA results in mg/mL units, as requested previously.

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In Vitro Expression Assay

Sponsor Question: What is required for Average Number of Cells Counted for sample and % cell viability?

CBER Response: Regarding your in vitro expression assay: The SOPs for this assay (SOP#113198 and TM# 100010380) include assay acceptance criteria for number of cells counted (b) (4) cells) and cell viability (b) (4) . Please provide the % cell viability and the average number of cells counted for the test sample (the average number of (b) (4) as described in the Data Analysis section of the test method).

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Please replace the Limulus Amebocyte Lysate Test template with the template in Attachment 1 of this information request.

CBER Questions

We have the following questions to your response (dated 08/11/21) to our IR (dated 08/06/21), regarding submission of diagrams (b) (4) with the Lot Release Protocols (LRP):

Regarding the Lipids assay (TM100010322): Your assay requires visual inspection of (b) (4) (SOP # TM100010322 section 15.2, which states "For identity testing the (b) (4)

(b) (4) Hence, please attach the (b) (4) as requested. These can be attached as a separate page at the end of your LRP if the (b) (4) cannot be inserted into the template itself. In addition, please provide the following information in Table format: Retention times (RT) for each lipid component of the standard and the sample and the (b) (4) Please include a statement at the top or bottom of the table to indicate the assay has a (b) (4) limit as acceptance criterion and indicate if the assay results meet the criterion.

Regarding the RNA integrity assay (TM100010392):

The SOP does not provide instructions on how the (b) (4) In addition, the (b) (4) provided suggest the (b) (4) could be subjective. Hence, please provide the (b) (4) in your LRPs as requested in our previous information request. These can be submitted as PDFs that are attached at the end of your LRP if they cannot be incorporated into the report automatically.

ATTACHMENT 1

Limulus Amebocyte Lysate (LAL) Test

Method Used:

(b) (4)

A horizontal grey bar redacting the text following the 'Method Used:' label.

(b) (4)

A large grey rectangular block redacting the majority of the page's content.