

From: Smith, Michael (CBER)

Sent: Monday, August 2, 2021 7:05 PM

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Cc: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>; Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>

Subject: STN 125742.0: Questions regarding validation of assay methods and lot release

Elisa,

The review team has the below questions for you regarding validation of assay methods and lot release.

Our review of the information provided in your BLA STN 125742/0 for COMIRNATY (COVID-19 Vaccine, mRNA), for active immunization to prevent COVID-19 caused by SARS-CoV-2 in individuals 16 years of age and older, is ongoing. We have the following comments and requests for additional information.

1. In your validation report for the 5'-cap assay for drug substance (VAL100136648), the accuracy study report includes a calculation of (b) (4) (b) (4) Please explain how you obtained the (b) (4) (b) (4) values in attachment 8.
2. Regarding the dynamic light scattering (DLS) method to determine lipid size and polydispersity of drug product (DP): please state whether this DLS method can (b) (4) LNPs. Please provide data to support your claim and, if the method does not (b) (4) LNP (b) (4) provide information describing resolution of (b) (4) and explain how the (b) (4) is evaluated.
3. For container content of DP:
 - a. You calculate volume of each vial based on vial (b) (4) and DP (b) (4). Please describe how (b) (4) was determined.
 - b. In the verification report [USP 697 (EP 2.9.17) and USP 788 (EP 2.9.19)-PF-07302048-CMVR-001] from PSG-KZO lab, DP container content was determined by measuring the total volume after 1.8 mL of sterile 0.9% sodium chloride solution was added. Please confirm that this method will be used for lot release testing by the PSG-KZO laboratory and that the container volume specification "Not less than (b) (4) mL" is the same regardless of test site/method.
4. Regarding your response (in STN 125742/0.16 dated July 23, 2021) to our IR dated July 9, 2021, about the validation of the CGE Integrity method:
 - a. Your response includes the (b) (4) results at (b) (4) (b) (4) for the DP and DS. Please calculate the accuracy at each of the (b) (4) accordingly (b) (4) (b) (4)

values). It appears that you did not include predetermined acceptance criteria for assay accuracy in your validation protocol; therefore, we assume the accuracy established in this validation study will be used to support assay transfer or revalidation studies. Please confirm by stating the accuracy acceptance criteria for integrity measurements of both the DP and DS in the integrity assay.

- b. In your response to query 2, it appears that the validation results for the DS RNA integrity range evaluation could not meet the pre-specified acceptance criterion at the higher end ((b) (4) of product specification corresponding to a (b) (4) RNA integrity). Please re-evaluate the DS RNA integrity range using available batches that are able to achieve the RNA integrity level of (b) (4). Alternatively, please adjust your validation acceptance criterion based on the available qualification/validation results should a re-validation and/or assay transfer be performed.

5. Under 21 CFR 610.2(a), manufacturers may be required to submit samples from all lots of a licensed biological product together with the protocols showing results of applicable tests when deemed necessary for the safety, purity, or potency of the product. Lots shall not be distributed until released by the Director, CBER. A brief description of the process follows: samples and Lot Release Protocols (LRPs) must be submitted to the Product Release Branch (PRB), Office of Compliance and Biologics Quality (OCBQ) via an electronic portal that is different from that used for electronic submissions to the product office. If you need instructions on accessing the gateway or where to submit samples, please contact Mr. Joseph Quander, Chief, Product Release Branch, DMPQ, OCBQ at Joseph.Quander@fda.hhs.gov. CBER grants approval to release lots by issuing a letter from the Center Director or his/her representative, that is sent to the firm's representative by email.

If you plan to release lots at the time of approval (launch lots), the LRPs need to be reviewed well before the PDUFA action due date. We recommend submitting LRPs and 20 vials of final DP for launch lots as soon as possible. You will need to use the LRP template that is currently under review; we anticipate providing a description of changes that need to be made to this template within the next two weeks.

Please state how many launch lots you plan to submit and let us know if you need additional information to submit the samples and LRPs.

Please provide your response in an Amendment to STN 125742/0 by Tuesday, August 9, 2021. If you have any questions about this communication, please feel free to contact us.

Regards,

Mike

- Please confirm receipt of this e-mail.

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