Michael J. Smith -S4
Digitally signed by Michael J. Smith -S4
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=0014080934, cn=Michael J. Smith -S4
Date: 2021.08.12 09:51:36 -04'00'

From: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>
Sent: Monday, August 9, 2021 9:03 AM
To: Rohlfing, Paul <Paul.Rohlfing@pfizer.com>; Smith, Michael (CBER) <Michael.Smith2@fda.hhs.gov>; Harkins Tull, Elisa <Elisa.HarkinsTull@pfizer.com>; Aghajani Memar, Neda <Neda.AghajaniMemar@pfizer.com>; Devlin, Carmel M <Carmel.Devlin@pfizer.com>
Cc: Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>
Subject: RE: STN 125742.0: Questions regarding validation of assay methods and lot release

Dear Mr. Rohlfing,

Please see FDA's clarification response below.

Please confirm receipt of this email and let us know if you have any questions or need additional information.
Regards,
Ram

From: Rohlfing, Paul <Paul.Rohlfing@pfizer.com>
Sent: Tuesday, August 3, 2021 5:49 PM
To: Smith, Michael (CBER) <Michael.Smith2@fda.hhs.gov>; Harkins Tull, Elisa <Elisa.HarkinsTull@pfizer.com>; Aghajani Memar, Neda <Neda.AghajaniMemar@pfizer.com>; Devlin, Carmel M <Carmel.Devlin@pfizer.com>
Cc: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>; Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>
Subject: [EXTERNAL] RE: STN 125742.0: Questions regarding validation of assay methods and lot release

Dear Mike,

So that we can provide a more clear and accurate response to item number 5, could you provide some clarification and context regarding some of the details of that item?

Pfizer is clear about the general requirements for \amples and Lot Release Protocols (LRPs) for vaccines, however we are also aware that since March 20, 2020 CBER has suspended the receipt of lot release samples. It was confirmed in early June for another program that CBER was still operating under this alternate COVID pandemic process and we are not aware that this suspension has been lifted.

By CBER's statement "We recommend submitting LRPs and 20 vials of final DP for launch lots as soon as possible", should we interpret that:

- CBER intends to resume receipt of lot release samples imminently for all vaccines?
- CBER intends to resume receipt of lot release samples for COVID-19 vaccines only?

- Or is this an inadvertent request based on the normal procedure, but which would not be applicable until such time as CBER resumes routine receipt of lot release samples?

  CBER's response:
  While CBER suspended receipt of samples for most products, we continue to receive samples for vaccines considered essential for public health during the pandemic. This includes influenza vaccines and the COVID-19 vaccines once they are approved. A notification will be sent to manufacturers when we resume normal business operations and are ready to receive samples for other products.

Additionally, for a period of time immediately after the BLA is approved, Pfizer will have been manufacturing lots with the EUA labelling, and in some instances under conditions which are authorized by the EUA, but which will not be in full compliance with the BLA (for example vials filled at Pfizer McPherson) until we are able to file a catch-up supplement and it is approved (we will provide an outline of how we propose to amend the BLA for these items in the next several days). For these recently produced, EUA-labelled lots, we plan to continue to provide a CofA (and not a Lot Release Protocol or lot release samples) for lots intended for US and WHO distribution, as we have been doing, until such time as we are ready to release lots with BLA labelling and in compliance with the provisions of the BLA? Is CBER aligned with this approach?

CBER's response:
We are discussing internally and plan to provide our clarification in a separate communication as soon as possible.

Please confirm receipt of this message and let me know if you need further information about these points for clarification.

Regards,

Paul Rohlfing
Executive Director GCMC Vaccines
Pfizer

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From: Smith, Michael (CBER) <Michael.Smith2@fda.hhs.gov>
Sent: Monday, August 2, 2021 7:05 PM
To: Harkins Tull, Elisa <Elisa.HarkinsTull@pfizer.com>; Aghajani Memar, Neda <Neda.AghajaniMemar@pfizer.com>; Devlin, Carmel M <Carmel.Devlin@pfizer.com>; Rohlfing, Paul <Paul.Rohlfing@pfizer.com>
Cc: Naik, Ramachandra <Ramachandra.Naik@fda.hhs.gov>; Gottschalk, Laura <Laura.Gottschalk@fda.hhs.gov>
Subject: [EXTERNAL] 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). Please explain how you obtained the (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 the (b) (4) was determined.
   b. In the verification report [USP 697 (EP 2.9.17) and USP 788 (EP 2.9. I 9)-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. a. Your response includes the (b) (4) integrity results at (b) (4) for the DP and DS. Please calculate the accuracy at each of the (b) (4) accordingly ((b) (4) integrity

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.

Mike Smith, Ph.D.
Captain, USPHS

Senior Regulatory Review Officer
Food and Drug Administration
Center for Biologics Evaluation & Research
Office of Vaccines Research & Review
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