TABLE OF CONTENTS

QUERY 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) (b) (4) Please explain how you obtained the (b) (4) (b) (4) values in attachment 8.

RESPONSE 1

(b) (4)

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

QUERY 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) (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.

RESPONSE 2

This DLS method (b) (4) (b) (4). However, if significant (b) (4) (b) (4), DLS would be able to (b) (4). DLS method (b) (4)

(b) (4)

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

QUERY 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. 1 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.

RESPONSE 3

a. The density of DP was determined using a representative DP sample at (b) (4) and measuring the (b) (4)

(b) (4)

b. PGS-KZO confirms method TM9106A will be used for DP Container Content release testing. It is also confirmed that the Container Content specification of Not less than (b) (4) mL is the same regardless of test site/method.

   EUA DP specifications initially included USP 697 Container Content for Injections which was later replaced by Vial Content (volume). Since both the Container Content for Injections and Subvisible Particulate Matter were compendial, a combined protocol was executed and documented under Verification report [USP 697 (EP 2.9.17) and USP 788 (EP 2.9. 1 9)-PF-07302048-CMVR-001]. This verification report supports method verification of USP 787 [Subvisible Particulate Matter] under BLA for PGS-KZO.

   USP 697 [Container Content for Injection] was replaced with PGS-KZO method TM9106A [Vial Content (volume)], which no longer includes measuring the total volume after 1.8 mL of sterile 0.9% sodium chloride solution addition. Method verification of TM9106A is documented in Method Equivalency Report: Method Equivalency and Verification of TM9106A, Container Content for PF-07302048 Multi-Dose Vials and USP 697.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None

QUERY 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) (b) (4) results at (b) (4) (b) (4) for the DP and DS. Please calculate the accuracy at each of the (b) (4) (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.

RESPONSE 4

(b) (4)

(b) (4)

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

VAL100136603, RNA Integrity of mRNA Dug Substance and LNP-mRNA Drug Product Samples by Fragment Analyzer (CGE)

QUERY 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.

RESPONSE 5

The applicant understands the general procedures for use of Lot Release Protocols (LRPs) and submitting samples to the Product Release Branch, and Pfizer has experience with this system for other products. We anticipate that there will be a need to continue to expedite release following BLA approval, with a cycle time similar to that achieved under the EUA for as long as pandemic conditions prevail.

At the present time we have not produced launch lots.

Literature References

None

SUPPORTING DOCUMENTATION

New or Replaced Supporting Documentation

None

Previously submitted supporting documentation

None