

Food & Drug Administration Silver Spring, MD 20993

DBSQC/OCBQ ANALYTICAL METHOD REVIEW MEMO

To: The file: STN 125742/0

From:

Reviewer	Date finalized	Stamp	Supervisor	Stamp
Emnet Yitbarek (Lead reviewer)	8/20/2021		Kori Francis	
Hsiaoling Wang	8/19/2021		Tao Pan	
Esmeralda Alvarado- Facundo	8/20/2021		Muhammad	
Anil Choudhary	8/20/2021		Shahabuddin	
			James Kenney	
Karla Garcia	8/20/2021		Simleen Kaur	

Through: Maryna Eichelberger, Ph.D., Division Director, CBER/OCBQ/DBSQC

Mary A. Malarkey, Director CBER/OCBQ

Applicant: BioNTech Manufacturing GmbH

Subject: Review of Analytical Methods used for the Lot release of COMIRNATY

Drug Substance (DS) and Drug Product (DP)

Recommendation: Approval

Summary:

The following analytical methods used for lot release of COMIRNATY and the associated method validations or qualifications, were reviewed:

1. RNA (b) (4) DP by (b) (4) (Emnet Yitbarek)

2. Identification and quantification of lipids in DP by (b) (4) (Émnet Yitbarek)

3. (b) (4) (Hsiaoling Wang)

4. (b) (4) (Hsiaoling Wang)

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5. General (b) (4)
                       methods to test (b) (4)
                                                 DP: Appearance, Particulate
   Matter, (b) (4)
                             (Hsiaoling Wang)
6. Identity of (b) (4) DP by (b) (4) Assay (Esmeralda Alvarado-Facundo)
7. (b) (4)
                                                    (Esmeralda Alvarado-Facundo)
8. (b)
       (4)
                                                 (Esmeralda Alvarado-Facundo)
9. (b) (4)
                                           (Anil Choudhary)
10.(b) (4)
                                                              (Anil Choudhary)
11.(b) (4)
                                                (Anil Choudhary).
12.(b) (4)
                   (Karla Garcia)
13. Endotoxin of (b) (4)
                                            DP (Karla Garcia)
14. Sterility of DP (Karla Garcia)
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Conclusion: The analytical methods and their validations and/or qualifications reviewed for the COMIRNATY drug substance and drug product were found to be adequate for their intended use.

Documents Reviewed

Information in sections of the original BLA (STN125742) and IND19736 submissions that describe control of DS and DP (3.2.S.4 and 3.2.P.5, respectively), including descriptions of DS and DP specifications, analytical procedures of DS and DP and validation of these analytical procedures were reviewed. Additional information in amendments specified by each reviewer were also reviewed.

Background

On May 6, 2021, Pfizer/BioNTech (sponsor) submitted an original rolling BLA, STN 125742, for COMIRNATY (BNT162/PF-07302048), a prophylactic vaccine for the prevention of COVID-19 which is caused by SARS-CoV-2 virus. COMIRNATY is a white suspension solution composed of mRNA that encodes for the spike protein of the SARS-CoV-2 virus and is encapsulated in a lipid nanoparticle (LNP). The concentrated suspension is stored at -60 °C and is diluted with a sterile 0.9% Sodium Chloride solution, USP, to administer intramuscularly to individuals ≥16 years of age. The proposed dosage is a 30 µg regimen of two 0.3 mL doses given 3 weeks apart.

DBSQC reviews BLAs and their supplements to ensure analytical methods are appropriately described, validated and suitable for the intended purposes. The following facilities perform the methods reviewed:

- Pfizer Biotherapeutics Pharmaceutical Sciences Analytical Research & Development, Chesterfield, MO (ARD-STL)
- 2. Pfizer Biotherapeutics Pharmaceutical Sciences Analytical Research & Development, Andover, MA (ARD-AND)
- 3. Pfizer Global Supply, Kalamazoo, MI (PGS-KZO)
- 4. Pfizer Global Supply, Andover, MA (PGS-AND)
- 5. Pfizer Global Supply, Puurs, Belgium (PGS-Puurs)
- 6. Pfizer Global Supply, Grange Castle, Ireland (PGS-GC)

7.

The following analytical methods used for DS and DP release were reviewed:

1. RNA (b) (4) DP by (b) (4) Method description (b) (4)



(b) (4)			
Conclusion The (b) (4) method is adequate COMIRNATY DP (b) (4). The (b) (4) . They have a procedure to their IND.	ly validated for the ore firm's test method greed to add the inf	includes limited in	nstructions for
2. Identification and	guantification of li	pids in DP by (b) (4)
Method description			
The identity and quantity of th and ALC-0315, are determine	e four lipids in the D d by (b) (4)	P, ALC-0159, cho . In this method,	olesterol, DSPC (b) (4)
			E

The as	say system suit	ability criteria includ	e:		
(b) (4)					
Assay	and DP sample	acceptance criteria	include:		_
	d Validation:				
(b) (4)				
					_



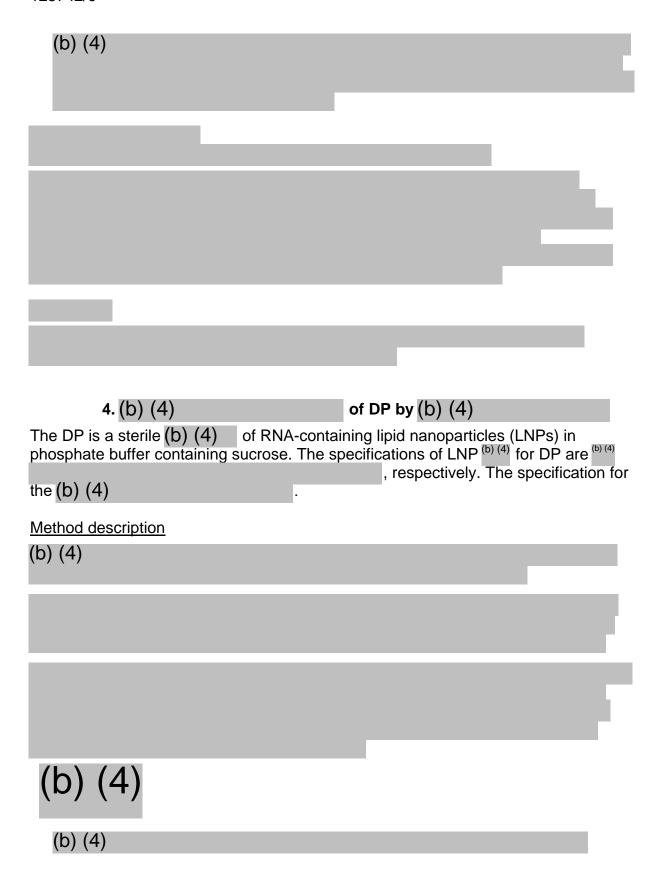
(b) (4)

Conclusion:

The (b) (4) method is adequately described and validated for the identification and quantitation of four lipids (ALC- 0159, cholesterol, DSPC and ALC- 0315) in COMIRNATY DP.

(b) (4)







(b) (4)

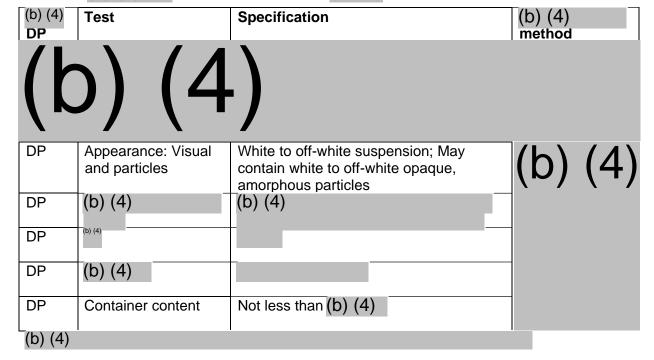
Conclusion

Based on the information provided in the original BLA and the amendment, the method has been validated for its intended purpose.

5. General (b) (4) Methods to test (b) (4) DP

(b) (4) methods used for (b) (4) DP analyses are shown in Table 7 below.

Table 7. (b) (4) methods used to test (b) (4) DP



These methods do not require validation. Suitability of the methods for this (b) (4) DP was verified as described below.

Review of Appearance Methods and Method Verifications:

The appearance of $^{^{(b)}(4)}$ includes the tests for (b) (4) . The appearance tests described in TM100010539 for ARD labs and in LAB- $^{^{(b)}(4)}$ for PGS-AND lab are equivalent.

(b) (4)





(b) (4)	
The container content is calculated to decimal places and every one of the vials should have a volume of no less than (b) (4) to be reported as "No Less Than (b) (4) ".	
(b) (4)	
Information Request and Reviews:	
The following IR was sent to the firm on August 2, 2021: a. You calculate volume of each vial based on (b) (4) . Pleas	е
describe how (b) (4) was determined.	
b. In the verification report (b) (4)] from PGS-KZO lab, DP container content was	
determined by measuring the total volume after 1.8 mL of sterile 0.9% sodium	ì
chloride solution was added. Please confirm that this method will be used for lot release testing by the PGS-KZO laboratory and that the container volume	
specification "Not less than (b) (4) " is the same regardless of test	

Review of the response:

site/method.

The response was received on August 9, 2021 in amendment 35.

a. The firm stated that the was obtained by

b. The firm confirmed that the container content specification of Not less than is the same regardless of test site/method. Container content for was used as a DP specification under EUA, which was replaced by

vial container content in BLA. PGS-KZO will perform DP container content test as other labs described in analytical procedure TM9106A.

The responses are acceptable. Re-verification from PGS-KZO is not necessary because the analytical steps are equivalent.

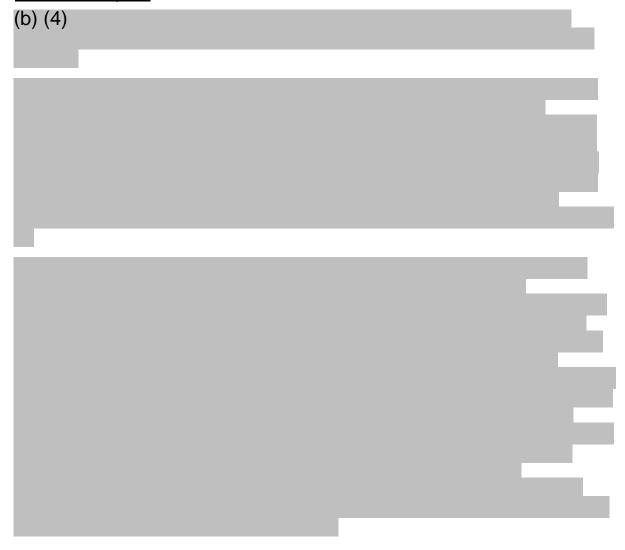
Conclusion

Based on the information provided in the original BLA and the amendment, these methods have been verified for their intended purposes.

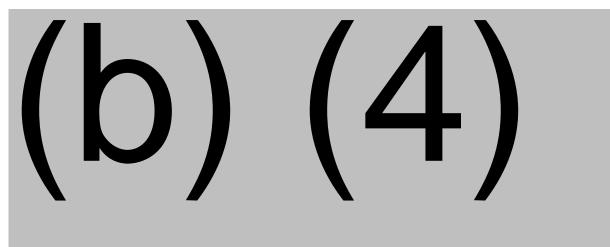
6. Identity of (b) (4) DP by (b) (4) Assay

The (b) (4) assay is a release test to verify the identity of (b) (4) DP by demonstrating the presence of the mRNA target. The test is performed at Pfizer facilities PGS-GC, PGS-AND, ARD and (b) (4). The specification for (b) (4) DP is "Identity confirmed".

Method description



The assay validity criteria are	ə:	
(b) (4)		1
_		
If the assay fails to meet pred must be repeated. If the DP a processed from the beginning	assay acceptance o	
The sample acceptance crite	eria are:	
(b) (4)		
If the assay acceptance crite reported as "Identity Confirm confirmed" for the absence o	ed" for the presence	
Method Validation		
(b) (4)		_
		ı.

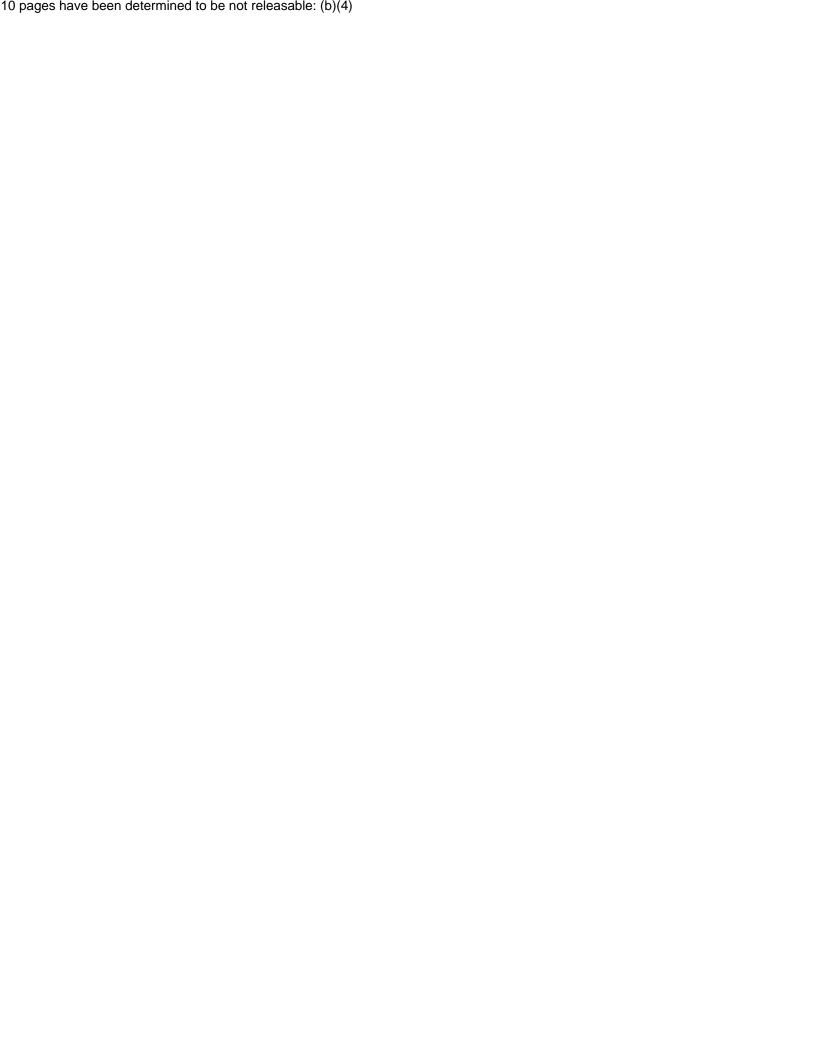


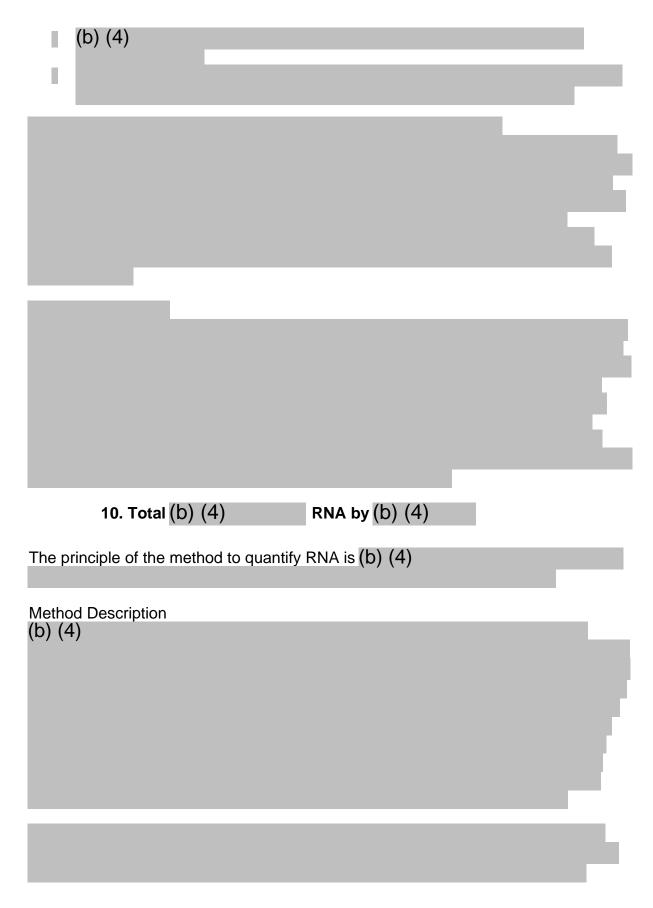


Conclusion:

The (b) (4) method to confirm the identity of (b) (4) DP mRNA was adequately described and the validation data demonstrate the assay is suitable for its intended use.







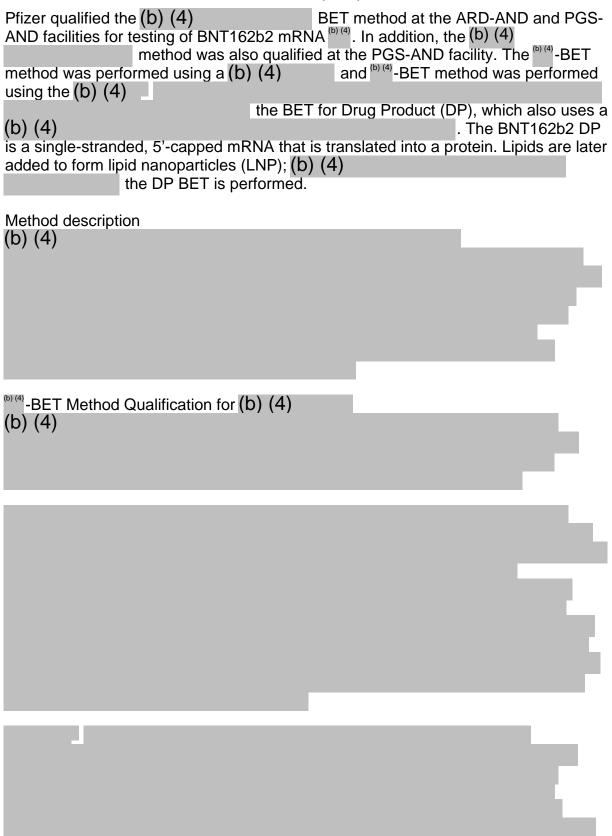
(b) (4)					
Access contains	iitaria ara sa fa	llavva			
Assay acceptance cr (b) (4)	iteria are as fo	llows:			
Sample acceptance	criteria are as f	follow:			
(b) (4)					
Reporting of the Res (b) (4) number. The current	; the (l	b) (4)	RNA is	each test san reported as	nple in a whole
Method Qualification					
(b) (4)					



(b) (4)	
Overall Conclusion The RNA (b) (4) method is adequately described suitable for measuring total RNA and (b) (4) (b) (4)	and demonstrated to be
(C) (1)	



13. Bacterial Endotoxin Test (BET)



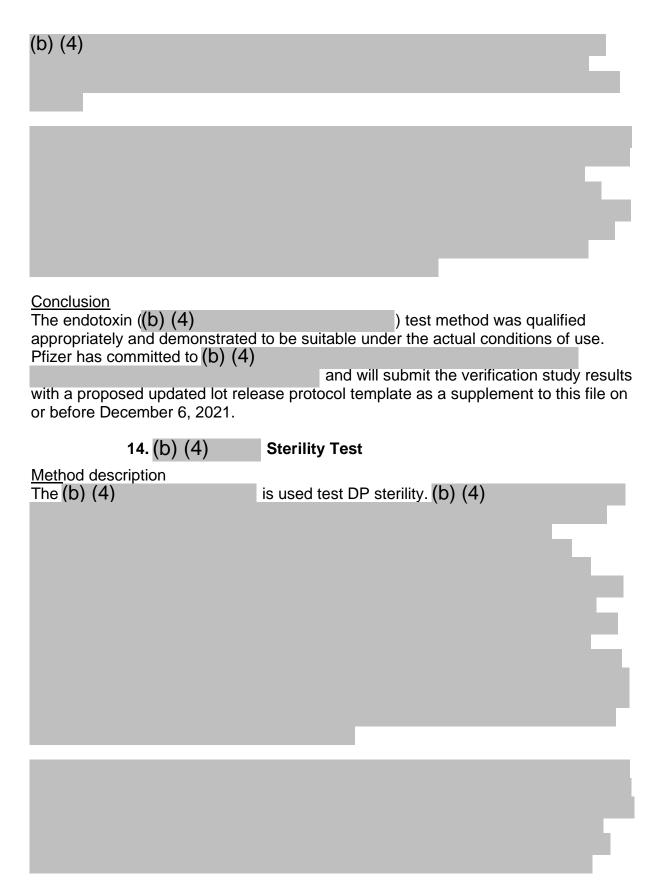
(b) (4)
BET Qualification for Drug Product Pfizer qualified the body -BET method for DP at the Pfizer Global Supply in Puurs, Belgium (PGS-Puurs) and Pfizer Global Supply in Kalamazoo, MI (PGS-KZO) facilities.
The (b) (4) -BET Method Qualification for BNT162b2 mRNA DP: The (b) (4) -BET is performed to detect or quantitate bacterial endotoxins present in test samples. (b) (4)

The original submission did not include qualification data from the PGS-Puurs and PGS-KZO laboratories. CBER sent an information request (IR) to Pfizer on July16, 2021, regarding their test for interfering factors at the PGS-Puurs and PGS-KZO facilities. Response to this IR was received on July 30, 2021 in amendment number 21.

Pfizer submitted supplemental verification reports performed on DP at each requested facility. These verification tests were performed with (b) (4)

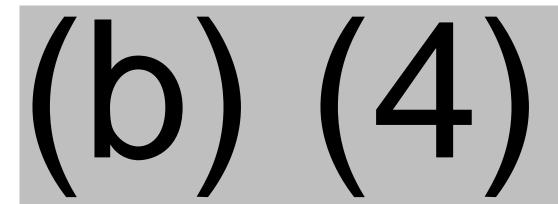
(b) (4)	ь
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	F
The current DP bacterial endotoxin test method involves sample preparati (b) (4) Pfizer performed a bacterial endotoxin (b) (4) demonstrate the (b) (4)	on in which
demonstrate the (b) (4) . This (b) (4) test is described below:	
(b) (4)	Œ







(b) (4)



(b) (4)

Conclusion: The (b) (4)

accordance with (b) (4)

(b) (4)

sterility Test method was validated in and was found to provide detection results equivalent sterility test method. The data provided show that the (b) (4) method is suitable for its intended use.