EMA/CHMP/466567/2021
Human Medicines Division

Type IB variation report

COMIRNATY	EMEA/H/C/005735/IB/0061
INN / Common name	COVID-19 mRNA vaccine (nucleoside-modified)
Scope as per guideline	B.II.f.1.b.5 – Stability of FP – Extension of the shelf life of the finished product – Biological/immunological medicinal product in accordance with an approved stability protocol
Precise scope	IB, B.II.f.1.b.5 To extend the shelf-life of the biological finished product Comirnaty 0.5mg/ml Concentrate for dispersion for injection in accordance with the approved stability protocol, from 6 months to 9 months when stored at the intended storage conditions of -90 to -60 °C. The MAH is also taking the opportunity to - implement Annex IV according to revised CHMP Opinion dated 22 July 2021 for procedure EMEA/H/C/005735/II/0030 - amend a mistake in section 4 of the PIL as requested in procedure PAM-MEA-002.6 (PRAC Assessment Report dated 05 August 2021) - amend section 4.4 of the SmPC for French and Latvian translations according to the agreed wording with the respective national authorities
Annexes affected	None
EU numbers affected	EU/1/20/1528/001
Rapporteur	Redacted
Procedure manager	Redacted
Contact person (if LoA provided)	
eCTD sequence related to the procedure	0159, 0175 and closing sequence

Status of the procedure		
	Application received by the EMA on	18 August 2021
	Start of the procedure	19 August 2021
☐	This report is sent to the Rapporteur for assessment by	26 August 2021
☐	Request for Supplementary Information (RfSI) (see section 2.2)	26 August 2021
	Responses to RfSI were received on	08 September 2021
	Updated responses to RfSI were received on	09 September 2021
☒	This report is sent to the Rapporteur for assessment by	09 September 2021
☒	Final updated AR	10 September 2021

1. Validation

1.1. Checklist

		Yes	No	N/A
APPLICATION FORM	**Present dated and signed by the authorised contact person (or letter of authorisation is provided).**	X		
	States the correct name and address of the MA Holder and of the contact person.	X		
	EU numbers of all affected presentations are correctly listed in the Application Form, Annex A and Product Information.	X		
	All changes applied for are correctly classified.	X		
	Identical classification scopes are indicated as many times as needed (e.g. new pack size, new sites).			X
	Relevant conditions to be fulfilled and documentation are ticked (if applicable).	X		
	'Precise scope' includes detailed description of change(s). In case of grouping also includes corresponding classification scopes.	X		
	'Present/Proposed table' (or attachment) reflects all changes applied for, dossier section numbers refer to the lowest possible level and include the precise current and proposed wording as in the relevant sections of the dossier and, if applicable, in the Product Information and/or RMP.	x		
	Product Information changes underlined or highlighted in the table or provided as a separate Annex in tracking mode.	x		
	Annexes affected are correctly selected.	x		
	Declaration of the Applicant: Boxes 1 and 2 are ticked	x		

		Yes	No	N/A
	and date of implementation is stated.			
DOCUMENTATION	*Only the relevant documents are included, correctly updated, and presented in appropriate EU-CTD format headings and numbering.*[1a, b]	x		
	Affected section(s) of the dossier correctly show the change(s) applied for.	x		
GMP	**GMP-inspection check is satisfactory**			x
ASMF [2]	**ASMF Holder has submitted the applicant's and/or restricted part.**			x
	EMA or EU ASMF number is included in the 'Present/Proposed' table.			x
	ASMF applicant's part version is in-line with the updated version in 3.2.S.			x
PI	**Correctly reflects the scope of the variation, based on the latest approved version and do not contain other changes than those covered by the scope of the variation.**	x		
	Provided as Word files (with track changes) and clean PDF files [3] in all EEA languages (for procedures not requiring linguistic review)	x		
	Provided as Word files in all EEA languages (with track changes) and clean PDF files EN only [3] (for procedures requiring linguistic review)			x
	If applicable, Annex A provided in all EEA languages (highlighted in word and clean in PDF) and changes in EU numbers correctly reflected (corresponding to EU numbers previously reserved with EMA).			x
New indications of a generic medicinal product	**For new indications falling under an orphan designation, similarity report (and derogation claim, if applicable) is included.**			x

[1a] For variations implementing PI text agreed with Competent Authority: copy of the request or previous assessment is included as attachment to the cover letter or application form.

[1b] For variations implementing PI text of a new indication of an originator product, and if there are orphan authorised medicinal products for a condition related to the proposed new indication, similarity report is included in Module 1.7.1.

[2] See EMA pre-submission guidance Q24 for further information on ASMF submission and EMA/EU ASMF number.

[3] The final product information i.e. Annex I, II, IIIA, IIIB and A, must be submitted electronically as one clean PDF file for each EEA language (see also the User guide on the preparation of PDF versions of the product information). The Annexes should be presented in strict compliance with the QRD Convention.

[4] Mandatory in case of update to the latest RMP template.

Note: For new indication for a generic, please check that the indication of the reference medicinal product is

not under data protection (e.g. see Art. 10(5), Art 74. of Dir 2001/83/EC).

Note on text: **Bold**: blocking validation issue; Italics: information needed for documentation check but not blocking; Normal: Information considered for completeness of submission, not blocking but MAH may be reminded in variation report to address for future submissions.

Issues (related to the checklist) raised during validation:

Classification	Issues identified	Resolved/Comments/For info
B.II.f.1.b.5		

1.2. Validation outcome

☒ Satisfactory

2. Assessment

2.1. Initial submission

2.1.1. Introduction

Pfizer and BioNTech have developed a vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus SARS-CoV-2. The vaccine is based on SARS CoV-2 spike (S) glycoprotein antigens encoded in RNA and formulated in lipid nanoparticles (LNPs), referred to as COVID-19 Vaccine (BioNTech code number BNT162, Pfizer code number PF 07302048).

To enhance global distribution of and broad patient access to the Pfizer/BioNTech COVID-19 vaccine, the shelf-life of the BNT162b2 drug product is being extended to 9 months when stored at the intended storage conditions of -90 to -60 °C.

The Applicant is submitting a variation to support:

- A Type IB variation (B.II.f.1.b.5), Change in the shelf-life of the finished product, in accordance with the approved stability protocol, from 6 months to 9 months when stored at the intended long-term storage condition of -90 to -60 °C.

Assessor´s comments:

The applicant has provided an acceptable background and overview to this Type IB variation to support the change in shelf-life of the finished product, from 6 months to 9 months, when stored at the long-term storage conditions of -90 to -60 °C.

A present and proposed table has been provided in module 1.

It is described that sections 3.2.P.8.1 and 3.2.P.8.3 as well as the product information have been updated.

2.1.2. Stability summary and conclusions (3.2.P.8.1)

The commercial shelf life of the BNT162b2 drug product is being extended to 9 months when stored at the intended storage condition of -90 to -60 °C. The shelf life is based on the currently available data from stability studies utilizing material from process performance qualification lots, emergency supply lots, clinical lots and one non-clinical lot of drug product. The stability data generated to date on the emergency supply and process performance qualification lots also support an additional storage condition at -20 ± 5°C for up to 2 weeks, as well as short term storage at 5 ± 3°C for up to one month (within the 9 month shelf life). Additionally, supportive stability studies are also being presented for two clinical BNT162b1 lots. At this time, process performance lots have been enrolled in formal stability programs and available data is provided.

Drug product stability lots have been enrolled in stability programs and are being monitored in accordance with the approved protocols. All testing to date has been performed using analytical methodology and phase appropriate specifications in place at time of testing. The analytical procedures used in the stability programs were developed to monitor the composition, strength, purity, safety and general quality attributes of the drug product.

Drug Product Shelf Life at Recommended Storage Temperature

The shelf life of the BNT162b2 is 9 months when stored at the long-term storage condition of -90 to -60 °C. The shelf-life claim is based on up to 12 months of available stability data for clinical and non-clinical drug product lots, up to 9 months of available stability data for the emergency supply and/or process performance qualification lots and up to 12 months of available supportive BNT162b1 clinical stability lot data, along with scientific rationale and the understanding of the mRNA platform. All drug product lots enrolled in the stability studies are considered to be predictive of the stability of the commercial materials based on comprehensive comparability assessments performed during development.

Additionally, the stability data generated to date on the emergency supply and process performance qualification lots also support an additional storage condition at -20 ± 5 °C for up to 2 weeks, as well as short term storage at 5 ± 3°C for up to one month (within the 6-month shelf life). This is based on current available stability data for the accelerated conditions of -20 ± 5 °C and 5 ± 3°C on emergency supply and process performance qualification lots.

In-use Period of Drug Product

The initial in-use period for the thawed, undiluted vial is room temperature for not more than 2 hours (Section 3.2.P.2.6 Compatibility). Formal thermal cycling stability studies have been initiated on both emergency use lots and PPQ lots in order to further support the in-use period. Available data from these studies is provided in Section 3.2.P.8.3 Stability Data - Thermal Stress and Cycling. The in-use shelf life of undiluted and diluted vials is defined in Section 3.2.P.2.6 Compatibility.

Stability Batches and Studies

The stability program is designed to follow ICH guidelines for stability of drug product (ICH Guideline Q1A: Stability Testing of New Drug Substances and Products; ICH Guideline Q5C: Quality of Biotechnological Products, Stability Testing of Biotechnological/Biological Products). To date, 8 emergency supply lots, 30 process performance qualification/emergency use lots, 7 clinical lots, 1 non-clinical lot and 2 supportive BNT162b1 clinical lots have been placed on stability and stored under long term, accelerated, and thermal stress conditions. The drug product lots placed on stability, to date, were packaged in glass vials, which are the comparable to the commercial packaging or representative of commercial packaging (for early non-clinical and clinical drug product studies).

Both the clinical and non-clinical drug product lots manufactured by [redacted] using the BNT162b2 construct are considered to be predictive of the stability of the commercial materials based on comprehensive comparability assessments performed during development. The emergency supply lots were manufactured using the commercial process.

As both BNT162b2 and BNT162b1 materials were under clinical development at the same time, it was considered whether available stability data for BNT162b1 could provide additional support for the establishment of shelf life for BNT162b2 drug product. Since the difference between the two constructs is the length of the mRNA (BNT162b2 RNA: 4283 nucleotides; BNT162b1 RNA: 1262 nucleotides) it is reasonable that once encapsulated in the LNPs and processed to DP, quality attributes may be impacted in a similar fashion for both constructs during storage. Therefore, drug product lots manufactured by [redacted] using the BNT162b1 construct are considered predictive of the stability of the commercial materials.

A summary of all drug product lots on stability studies and current available stability data are shown in Table 3.2.P.8.1-1. At this time, stability studies are on-going. Data from these studies will be used to confirm the initial shelf life of the drug product. Further information on confirmation and extension of the drug product shelf life is discussed in Section 3.2.P.8.1.7 Shelf Life and Conclusions.

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	Ongoing
			Accelerated	-20 ± 5 °C	Release	Ongoing
			Accelerated	5 ± 3 °C	Release	Ongoing
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long Term	-90 to -60 °C	Release	To be started
			Accelerated	-20 ± 5 °C	Release	To be started
			Accelerated	5 ± 3 °C	Release	To be started

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
[redacted]	May 2021	Stability, Commercial Supply, Process performance qualification	Long term	-90 to -60 °C	Release/T=0	On-going
[redacted]	April 2021	Stability, Commercial Supply, Process performance qualification	Long term	-90 to -60 °C	Release	On-going
[redacted]	April 2021	Stability, Commercial Supply, Process performance qualification	Long term	-90 to -60 °C	Release	On-going
[redacted]	March 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	Complete
[redacted]	March 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	Complete
[redacted]	April 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	1 month	Complete
[redacted]	March 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
[redacted]	March 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going
[redacted]	March 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going
[redacted]	May 2021	Stability, Commercial supply, Process performance qualification	Long Term	-90 to -60 °C	Release	On-going
			Accelerated	-20 ± 5 °C	Release	On-going
			Accelerated	5 ± 3 °C	Release	On-going
[redacted]	April 2021	Emergency Supply, Stability	Long Term	-90 to -60 °C	Release/T=0	On-going
[redacted]	February 2021	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
[redacted]	December 2020 (January 2021 for Thermal Cycling Study)	Stability, Clinical, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C Upright Vials	6 months	On-going
				-90 to -60 °C Inverted Vials	6 months	On-going
			Accelerated	-20 ± 5 °C Upright Vials	6 months	On-going
				-20 ± 5 °C Inverted Vials	6 months	On-going
			Accelerated	5 ± 3 °C Upright Vials	6 months	On-going
				5 ± 3 °C Inverted Vials	6 months	On-going
			Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C , followed by 2 weeks at -20 ± 5 °C, 4 weeks at 2 to 8°C and 1 week at 25 ± 2 °C/60 ± 5% RH.	8 weeks	Complete
	January 2021		Long Term	-90 to -60 °C	3 months	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
CCI CCI		Stability, Emergency Supply[a], Process performance qualification	Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
CCI	December 2020	Stability, Clinical, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C Upright Vials	6 months	On-going
				-90 to -60 °C Inverted Vials	6 months	On-going
			Accelerated	-20 ± 5 °C Upright Vials	6 months	On-going
				-20 ± 5 °C Inverted Vials	6 months	On-going
			Accelerated	5 ± 3 °C Upright Vials	6 months	On-going
				5 ± 3 °C Inverted Vials	6 months	On-going
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month (complete)	On-going
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month (complete)	On-going
CCI	March 2021	Stability, Emergency Supply[a], Process performance qualification	Photostability	Dark Control and Light Exposed		Complete
CCI	February 2021	Stability, Emergency Supply[a], Process performance qualification	Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	16 weeks	On-going
CCI	February 2021	Stability, Emergency Supply[a], Process performance qualification	Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -90 to -60 °C for 5 months and then a subset of vials moved to 2 to 8°C for 1 month. Samples pulled at 6M for testing at both -90 to -60°C and 2 to 8°C. This is repeated at 11/12M, 17/18M and 23/24M	Release	On-going
CCI	February 2021	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
CCI	December 2020 (January 2021 for Thermal Cycling and Photostability Study)	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C Upright Vials	6 months	On-going
				-90 to -60 °C Inverted Vials	6 months	On-going
			Accelerated	-20 ± 5 °C Upright Vials	6 months	On-going
				-20 ± 5 °C Inverted Vials	6 months	On-going
			Accelerated	5 ± 3 °C Upright Vials	6 months	On-going
				5 ± 3 °C Inverted Vials	6 months	On-going
			Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 4 weeks at 2 to 8°C. and 1 week at 25 ± 2 °C/60 ± 5% RH.	10 weeks	Complete
			Photostability	Dark Control and Light Exposed		Complete
CCI	March 2021 (February 2021 for Thermal Cycling Study)	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Cycling	Thermal Cycling: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	12 weeks	On-going
CCI	December 2020 (January 2021 for Thermal Cycling Study)	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C Upright Vials	6 months	On-going
				-90 to -60 °C Inverted Vials	6 months	On-going
			Accelerated	-20 ± 5 °C Upright Vials	6 months	On-going
				-20 ± 5 °C Inverted Vials	6 months	On-going
			Accelerated	5 ± 3 °C Upright Vials	6 months	On-going
				5 ± 3 °C Inverted Vials	6 months	On-going
			Thermal Cycling	Thermal Cycling: 1 week at -90 to -60°C followed by 4 weeks at 2 to 8°C	5 weeks	Complete
CCI	January 2021	Stability, Emergency	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
		Supply[a], Process performance qualification	Accelerated	5 ± 3 °C	3 months	On-going
[redacted] CCI	January 2021	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
[redacted] CCI	January 2021	Stability, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
[redacted] CCI	January 2021 (February 2021 for Thermal Cycling Study 1 and April 2021 for Thermal Cycling Studies 2 & 3)	Stability, Clinical, Emergency Supply[a], Process performance qualification	Long Term	-90 to -60 °C	3 months	On-going
			Accelerated	-60 to -30 °C	Release	On-going
			Accelerated	-20 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	3 months	On-going
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month (complete)	On-going
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month (complete)	On-going
			Thermal Cycling	Thermal Cycling 1: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks and then moved to 2 to 8°C for 12 weeks. Samples will be pulled for testing every 2 weeks throughout protocol.	16 weeks	On-going
			Thermal Cycling	Thermal Cycling 2: Ultra frozen vials are placed at -20 ± 5 °C for 4 weeks (1 month) and then moved to -90 to -60 °C for the shelf life of the drug product.	1 month	On-going
			Thermal Cycling	Thermal Cycling 3: Ultra frozen vials are placed at 5 ± 3 °C for 4 weeks (1 month) and then moved to -90 to -60 °C for the shelf life of the drug product.	1 month	On-going

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
			Thermal Cycling	Ultrafrozen vials were cycled between 25 ± 2 °C/60 ± 5%RH (for 2 to 7 hours) and -90 to -60 °C (for 24 ± 2 hours) for a total of 10 cycles	10 freeze thaw cycles	Complete
[redacted] CCI	December 2020	Stability, Emergency Supply[a], Clinical, Process performance qualification	Long Term	-90 to -60 °C Upright Vials	6 months	On-going
				-90 to -60 °C Inverted Vials	6 months	On-going
			Accelerated	-20 ± 5 °C Upright Vials	6 months	On-going
				-20 ± 5 °C Inverted Vials	6 months	On-going
			Accelerated	5 ± 3 °C Upright Vials	6 months	On-going
				5 ± 3 °C Inverted Vials	6 months	On-going
[redacted] CCI	November 2020	Stability, Emergency Supply[a]	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	On-going
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
[redacted] CCI	November 2020	Stability, Emergency Supply[a]	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
[redacted] CCI	November 2020 (December 2020 for Thermal Cycling Study)	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Cycling	Thermal Cycling: 2 weeks at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 8 weeks at 2 to 8°C. Samples will be pulled for testing every 2 weeks throughout protocol.	14 weeks	Complete

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
CCI	November2020 (December 2020 for Thermal Cycling Study)	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Cycling	Thermal Cycling: 2 weeks at -90 to -60°C followed by 4 weeks at -20 ± 5 °C and then 8 weeks at 2 to 8°C. Samples will be pulled for testing every 2 weeks throughout protocol.	14 weeks	Complete
CCI	November 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-60 to -30 °C	6 months	Complete
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
CCI	November 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	6 months	On-going
			Accelerated	-60 to -30 °C	6 months	Complete
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
CCI	September 2020	Stability, Emergency Supply[a], Clinical inventory	Long Term	-90 to -60 °C	9 months	On-going
			Accelerated	-60 to -30 °C	6 months	Complete
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
			Thermal Stress	25 ± 2 °C/ 60 ± 5 % RH	1 month	Complete
			Thermal Stress	30 ± 2 °C/ 65 ± 5 % RH	1 month	Complete
CCI	September 2020	Stability, Emergency Supply[a]	Long Term	-90 to -60 °C	9 months	On-going
			Accelerated	-20 ± 5 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
CCI			Accelerated	5 ± 3 °C	3 months	Complete
CCI	August 2020	Stability, Clinical inventory	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
CCI	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
CCI	August 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
CCI	July 2020	Stability, Nonclinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
BCV40620-A CCI	July 2020	Stability, Clinical	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	5 ± 3 °C	3 months	Complete
CCI	May 2020	Stability, Clinical	Long Term	-70 ± 10 °C	12 months	On-going
			Accelerated	-40 ± 5 °C	12 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C	4 months	Complete
CCI	March 2020	Stability, non-clinical toxicology[b]	Long Term	-70 ± 10 °C	6 months	Complete
			Accelerated	-40 ± 5 °C	3 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
Supportive Stability (BNT162b1)						
CCI	April 2020	Supportive Stability, Clinical	Long Term	-70 ± 10 °C	12 months	Complete

Table 3.2.P.8.1-1. Summary of On-going Stability Studies

Lot Number	Stability Study Start	Drug Product Batch Use	Study Type	Storage Condition	Data Available	Study Status
CCI	April 2020	Supportive Stability, Clinical	Long Term	-70 ± 10 °C	12 months	On-going
			Accelerated	-40 ± 5 °C	9 months	On-going
			Accelerated	5 ± 3 °C	6 months	Complete
			Thermal Stress	25 ± 2 °C	3 months	Complete

a. Emergency supply designation applies to US market.
b. -40 °C study started in April 2020.
c. This lot number is equivalent to BCV40820-P
d. This lot number is equivalent to BCV40720-P.
TBD = To be Determined, RH = Relative Humidity

3.2.P.8.3 Stability data

Selected stability data from section 3.2.P.8.3

Table 3.2.P.8.3-16. Stability Data for Drug Product Emergency Supply Lot EE8493 Stored at -70 °C (-90 to -60 °C)

Analytical Procedure/Quality Attribute	Appearance		pH	Subvisible Particles[a]	Dynamic Light Scattering (DLS)		Fluorescence Assay	
	Appearance (Visual)	Visible Particulates			LNP Size	LNP Polydispersity	RNA Encapsulation	RNA Content
Timepoint / Acceptance Criteria	White to off-white suspension	May contain white to off-white opaque, amorphous particles	CCI					
0	WOFS	EFVP						
1M	WOFS	EFVP						
3M	WOFS	Meets (EFVP)						
6M	WOFS	Meets (EFVP)						
9M	WOFS	Meets (EFVP)						
12M	S	S	S	S	S	S	S	S
18M	S	S	S	S	S	S	S	S
24M	S	S	S	S	S	S	S	S

Analytical Procedure/Quality Attribute	HPLC-CAD				Cell-based Flow Cytometry	Capillary Gel Electrophoresis	Endotoxin	Sterility	Dye Incursion
	ALC-0315 Content	ALC-0159 Content	DSPC Content	Cholesterol Content	In Vitro Expression	RNA Integrity			Container Closure Integrity
Timepoint / Acceptance Criteria[a]	CCI							No growth detected	Pass
0								No growth detected	Pass
1M								NS	NS
3M								NS	Pass
6M								NS	Pass
9M								NS	NS
12M	S	S	S	S	S	S	S	S	S
18M	S	S	S	S	S	S	NS	NS	NS
24M	S	S	S	S	S	S	S	S	S

a. Acceptance criteria in place at time of testing.
b. Subvisible particles are reported per container.
W = Week, M = Month, S = To be Scheduled, NS = Not Scheduled at Time Point; WOFS = White to off-white suspension, EFVP = Essentially Free from Visible Particulates; LNP = Lipid Nanoparticle; HPLC-CAD = high performance liquid chromatography-charged aerosol detector, MCR = Meets Compendial Requirements

Table 3.2.P.8.3-17. Stability Data for Drug Product Emergency Supply Lot EE8492 Stored at -70 °C (-90 to -60 °C)

Analytical Procedure/Quality Attribute	Appearance		pH	Subvisible Particles[b]	Dynamic Light Scattering (DLS)		Fluorescence Assay	
	Appearance (Visual)	Visible Particulates			LNP Size	LNP Polydispersity	RNA Encapsulation	RNA Content
Timepoint / Acceptance Criteria[a]	White to off-white suspension	May contain white to off-white opaque, amorphous particles	CCI					
0	WOFS	EFVP						
1W	WOFS	EFVP						
2W	WOFS	EFVP						
1M	WOFS	EFVP						
2M	WOFS	EFVP						
3M	WOFS	Meets (EFVP)						
6M	WOFS	Meets (EFVP)						
9M	WOFS	Meets (EFVP)						
12M	S	S	S	S	S	S	S	S
18M	S	S	S	S	S	S	S	S
24M	S	S	S	S	S	S	S	S

Analytical Procedure/Quality Attribute	HPLC-CAD				Cell-based Flow Cytometry	Capillary Gel Electrophoresis	Endotoxin	Sterility	Dye Incursion
	ALC-0315 Content	ALC-0159 Content	DSPC Content	Cholesterol Content	In Vitro Expression	RNA Integrity			Container Closure Integrity
Timepoint / Acceptance Criteria[a]	CCI							No growth detected	Pass
0								No growth detected	Pass
1W								NS	NS
2W								NS	NS
1M								NS	NS
2M								NS	NS
3M								NS	Pass
6M								NS	Pass
9M								NS	NS
12M	S	S	S	S	S	S	S	S	S
18M	S	S	S	S	S	S	NS	NS	NS
24M	S	S	S	S	S	S	S	S	S

Table 3.2.P.8.3-24. Stability Data for CCI Drug Product BNT162b2 Lot BCV40420-A Stored at -70 ± 10 °C

Analytical Procedure/Quality Attribute	Appearance	pH	Subvisible Particles		LNP Size	LNP Polydispersity	RNA Encapsulation	RNA Content
Timepoint/ Acceptance Criteria[a]	White to off-white suspension/Free from observable particles	CCI						
0	Pass							
1	Pass							
3	Pass							
4	Pass							
6	Pass							
9	Pass							
12	Pass							
18	S	NS	NS	NS	S	S	S	S
24	S	S	S	S	S	S	S	S

Analytical Procedure/Quality Attribute	ALC-0315 Content	ALC-0159 Content	DSPC Content	Cholesterol Content	RNA Integrity	Sterility
Timepoint/ Acceptance Criteria[a]	CCI					Sterile
0						Pass
1						NS
3						NS
4						NS
6						NS
9						NS
12						NS
18	S	S	S	S	S	NS
24	S	S	S	S	S	S

a. Acceptance criteria in place at time of testing.
b. Method integration parameters were changed after the 1 month time point
S = Scheduled, NS = Not Scheduled at Time Point, LNP = Lipid Nanoparticle, RP = Result Pending

Assessor´s comments:

Updated documents have been provided for sections 3.2.P.8.1 and 3.2.P.8.3 and include updated stability data for the DP at long-term storage at -90 to -60 °C as well as for accelerated and stressed storage conditions. The drug product stability data cover clinical lots, emergency supply and PPQ lots. Current stability data at the long-term storage condition at -90 to -60 °C includes up to 12 months data for one clinical trial material lot, up to 9 months data from two emergency supply lots, up to 6 months data for several other emergency supply and PPQ lots and up to 12 months data for a supportive lot.

All stability data generated to date for the DP stored at the long-term storage conditions at -90 to -60 °C complies with the acceptance criteria in the DP specification and show, at large, that there are no significant changes in terms of quality, purity, potency or strength of the drug product.

It can also be noted that all drug product lots enrolled in the stability studies are considered to be predictive of the stability of the commercial materials based on comprehensive comparability assessments performed during development.

Additionally, the stability data generated to date on the emergency supply and process performance qualification lots also support an additional storage condition at -20 ± 5 °C for up to 2 weeks, as well as short term storage at 5 ± 3°C for up to one month (within the 6 month shelf life). This is based on current available stability data for the accelerated conditions of -20 ± 5 °C and 5 ± 3°C on emergency supply and process performance qualification lots.

Consequently, from a scientific point-of-view, the proposed shelf-life extension of undiluted drug product from 6 months to 9 months at the long-term storage condition at -90 to -60 °C is agreed to.

For comments on the proposal for extension of expiry dates of drug product batches already manufactured and released to the market, see the assessor´s comments on the SmPC section 6.3 below.

2.1.3. Product information

The following changes are proposed in the SmPC.

Section 6.3

Unopened vial

Frozen vial

~~6~~ ***9*** months at -90 °C to -60 °C

Within the ~~6~~ ***9*** months shelf-life unopened vials may be stored and transported at -25 °C to -15 °C for a single period of up to 2 weeks and can be returned to -90 °C to -60 °C.

Cartons with an expiry date of August 2021 through January 2022 printed on the label may remain in use for 3 months beyond the printed date as long as approved storage conditions between -90 °C to -60 °C have been maintained. Updated expiry dates are shown below.

Printed Date		***Updated Expiry Date***
August 2021	→	***November 2021***
September 2021	→	***December 2021***
October 2021	→	***January 2022***

November 2021	***→***	***February 2022***
December 2021	***→***	***March 2022***
January 2022	***→***	***April 2022***

Section 5 of the package leaflet is also updated in the same way to reflect the changes proposed in the SmPC.

Assessor´s comments:

It should be noted that the change in shelf life will apply to all batches released after the approval of this Type IB procedure.

As this change is an extension of shelf life without changes in the storage conditions, it is presumed that from a scientific point of view, the new 9 months shelf life might apply to already released batches of the medicinal product provided that the approved storage conditions have been guaranteed throughout the supply chain and an agreement been made with relevant national authorities.

The proposal from the MAH to reflect this extended use of certain released batches in the SmPC and PIL is not acceptable. Specific data on expiry dates should not be included in the product information in line with the QRD template. The MAH is requested to provide an alternative proposal of effectively communicating this information to health care providers (e.g. letter by QP, dissemination of information through product website, dear health care professional communication).

Any proposal should be properly justified. Furthermore, the MAH is requested to provide details of the concerned batches (e.g. batch number, batch size/doses released, member states affected), as well as an estimate of the stock left in each EU/EEA markets, where known.

- The proposal from the MAH to reflect an extended expiry date of certain released batches in the product information is not found acceptable. An updated version of the product information should be provided, excluding the text and tables with updated expiry dates.
- The MAH is requested to provide an alternative proposal for communicating the applicability of an extended expiry date to certain released batches. The proposal should be fully detailed and properly justified.
- The MAH is requested to provide details in relation to the batches that may need extended expiry dates (e.g. batch number, batch size/doses released, MS affected), as well as an estimate of the stock left in each EU/EEA markets, where known.

Active substance master file (ASMF)

Not applicable

Conclusion:

☐ The changes proposed by the MAH are accepted and the variation(s) is/are approvable.

☒ The changes proposed are not accepted and the MAH may amend the application within 30 days in order to address the issues outlined in Section "2.2. Request for Supplementary Information", before the variation(s) can be approved.

2.2. Request for supplementary information (RfSI)

List of Issues to be resolved:

1. The proposal from the MAH to reflect an extended expiry date of certain released batches in the product information is not found acceptable. An updated version of the product information should be provided, excluding the text and tables with updated expiry dates.
2. The MAH is requested to provide an alternative proposal for communicating the applicability of an extended expiry date to certain released batches. The proposal should be fully detailed and properly justified.
3. The MAH is requested to provide details in relation to the batches that may need extended expiry dates (e.g. batch number, batch size/doses released, MS affected), as well as an estimate of the stock left in each EU/EEA markets, where known.

2.3. Responses to RfSI

Question 1

The proposal from the MAH to reflect an extended expiry date of certain released batches in the product information is not found acceptable. An updated version of the product information should be provided, excluding the text and tables with updated expiry dates.

Summary of the MAH responses:

Updated version of product information is provided in Appendix 1. Information on extended expiry dates for released batches has been removed from section 6.3 of the SmPC as requested by the Agency.

The MAH is following EMA's recommendation to align with Member States on the extended use of released batches and agrees to remove this information from section 6.3 of the SmPC.

Assessment of the responses:

As requested, the MAH has provided an updated version of the product information excluding the text and tables with updated expiry dates from section 6.3 of the SmPC.

In the first response provided 08 September 2021 (eCTD sequence 0175) the MAH also proposed to include a general reference to the product website in section 10 of the SmPC. The inclusion of a QR code in the SmPC is not in line with EMA guidelines and cannot be accepted. Therefore, an updated version of the product information was provided via Eudralink 09 September 2021, excluding the QR code from section 10 of the SmPC. The MAH confirms that the updated product information will be submitted in the closing sequence.

The response is found acceptable and the issue is resolved.

Question 2

The MAH is requested to provide an alternative proposal for communicating the applicability of an extended expiry date to certain released batches. The proposal should be fully detailed and properly justified.

Summary of the MAH responses:

MAH plans to provide instructions on use of the extended shelf-life of 9 months to produced and thereby labelled batches via:

• Product website of Comirnaty accessible via QR code

• Dear Healthcare Professional letter will be sent to all recipients.

• Further information is available in local language via MedInfo Hotline

A draft Dear Healthcare Professional letter is provided in Appendix 2. The MAH believes that the communication plan as outlined above, and in particular the issuance of a Dear Healthcare Professional letter, will ensure that accurate information is made available across all Member States in a timely manner following approval of the extended shelf life, and this will allow swift and consistent implementation.

Furthermore, availability of relevant details in local language on the QR code website and via MedInfo will ensure a reliable reference for any immediate queries that may arise at local level.

Assessment of the responses:

The alternative proposal for communicating the applicability of an extended expiry date to certain released batches via Product website and QR code, Dear Healthcare Professional (DHCP) letter and information in local language via MedInfo Hotline seems reasonable. After comments from EMA a revised DHPC implementing EMA´s suggestions were provided via Eudralink on 09 September 2021. The MAH confirms that the updated DHCP letter will be submitted in the closing sequence.

The response is found acceptable and the issue is resolved.

Question 3

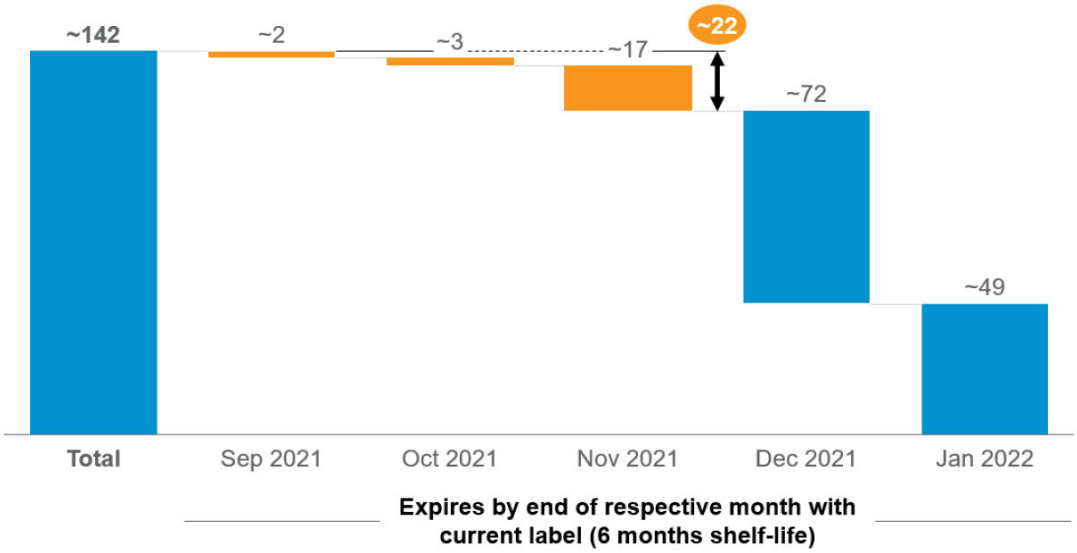
The MAH is requested to provide details in relation to the batches that may need extended expiry dates (e.g. batch number, batch size/doses released, MS affected), as well as an estimate of the stock left in each EU/EEA markets, where known.

Summary of the MAH responses:

In total ~142 million doses usable for EC supply are in stock in the Pfizer/BioNTech network (unreleased and released) that would potentially expire by Jan 2022 (with 6 months shelf-life). Thereof ~22 million doses would potentially expire within next 3 months (by Nov 2021) with a 6 months shelf-life. In August and early September, three new Fill and Finish sites become active in supply of Comirnaty. 10 of 22 million doses have been manufactured for process qualification and subsequently batches. Release of these batches were / are dependent on completed registration of the respective Fill and Finish site, which led to an increased stock.

Information about in-market inventory and consumption after supply to the market are not available to MAH.

Est. inventory by expiration date usable for EC market supply (released and unreleased) at PFE/BNT locations[1], in million doses



[1] Stocks included at PFE Puurs, PFE Karlsruhe DC, BNT Frigo-Trans Storage

Assessment of the responses:
The information presented in relation to the batches that need extended expiry dates do not include any details on batch numbers or MS affected. However, it is clear that a large number of doses are concerned and thus it is agreed there is a need for communication as described in the response to Q2 above. The response is found acceptable and the issue is resolved.

3. Overall conclusion

Based on the review of the data, the change(s) proposed by the MAH

☒ is/are approvable.

☐ is/are not approvable based on the following grounds:

Rapporteur's assessor:	
	Name: Redacted
	Tel: Redacted
	Email: Redacted
	Date: 2021-09-09

☒ The assessor confirms that proprietary information on, or reference to, other products are not made in this assessment and that (Redacted), Head of Biotechnology, on behalf of the Rapporteur: (Redacted) endorses this report.