EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA/CHMP/429590/2021
Human Medicines Division

Type IB variation report

COMIRNATY	EMEA/H/C/005735/IB/0055
INN / Common name	covid-19 mRNA vaccine (nucleoside-modified)
Scope as per guideline	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method
Precise scope	To add Activity test methods to the specifications of the raw materials of 5 enzymes (DNase I, Proteinase K, Pyrophosphatase, RNase inhibitor and T7 polymerase) used in the manufacturing process of the active substance. The specification is set as "report results". The variation addresses REC#3 for Pfizer, Andover, USA and provides information to partially fulfil REC#7.
Approved scope	To add Activity test methods to the specifications of the raw materials of 5 enzymes (DNase I, Proteinase K, Pyrophosphatase, RNase inhibitor and T7 polymerase) used in the manufacturing process of the active substance. The specification is set as "report results". The variation partially addresses REC#3 for Pfizer, Andover, USA and provides information to partially fulfil REC#7.
Annexes affected	None
EU numbers affected	EU/1/20/1528/001
Rapporteur	Filip Josephson
Procedure manager	[redacted]
Contact person (if LoA provided)	n/a
eCTD sequence related to the procedure	0142

Status of the procedure		
	Application received by the EMA on	28 July 2021
	Start of the procedure	29 July 2021
☒	This report is sent to the Rapporteur for assessment by	17 August 2021
☒	Final updated AR	17 August 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		
	Annexes affected are correctly selected.			x
	Declaration of the Applicant: Boxes 1 and 2 are ticked and date of implementation is stated.	1	2	
DOCUMENTATION	Only the relevant documents are included, correctly updated, and presented in appropriate EU-CTD format headings and numbering. 1a, b	x		
	~ffected section(s) of the dossier correctly show the changers) applied for.	x		

		Yes	No	N/A
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	
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, IliA, I1IB 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 QBJL 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.I.b.I.c	-	

1.2. Validation outcome

~ Satisfactory

2. Assessment

2.1. Initial submission

2.1.1. Introduction

This variation addresses Recommendation #3 for Pfizer, Andover, USA: The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites and is classified as follows:

- Type IB (B.I.b.1.c) Change in the specification parameters and/or limits of an active substance, starting material/intermediate/reagent used in the manufacturing process of the active substance, Addition of a new specification parameter to the specification with its corresponding test method (Condition 1 unmet).

2.1.2. Control of Materials - Andover (3.2.5.2.3)

Activity test methods have been developed, validated and implemented for release testing for the five enzymes that are utilized as raw materials in the drug substance manufacturing process (DNase I, Proteinase K, Pyrophosphatase, RNase inhibitor and T7 polymerase). This testing is being performed by or on behalf of the drug substance manufacturer in order to confirm the vendor's certificate of analysis. Section 3.2.S.2.3 Control of Materials - Materials Used in Manufacture [Andover] has been updated to reflect this change.

These analytical activity assays have a different activity unit definition than what is utilized by and reported on the vendor certificate of analysis. Specification for the enzyme activity testing has been set as "report results" until adequate correlation between the activity results reported by the vendor and those obtained by Pfizer can be established. Results on a minimum of 5 different vendor batches of each enzyme will be needed to set an appropriate numerical specification for each enzyme activity assay. This comparison will ensure that appropriate specifications are being established for application of the release testing. As stated above, examination of vendor certificate of analysis, including assessment of the vendor reported activity, will continue to be performed on all incoming lots as a part of the overall release of enzyme raw materials.

The Applicant claims that implementation of the activity testing for the enzymes at Pfizer, Andover, USA fulfills REC #3 (for the site). In addition, the additional information provided also partially fulfills REC #7.

Table 3.2.S.2.3 Acceptance Criteria for Non-compendial Starting Materials and Raw Materials used in Manufacturing has been updated to contain the in-house methods.

Table 3.2.S ..2.3-3. Acceptance Cdtel'ia for ~ **<m-Comlllendial Starting** ~bte"l'ials **and Raw]\iateti;lis l7sed in]\'Ianufadming**

Material	Characteristic	Acceptance Criteria
5'-cap solution[a]	Identity[b]	Identity confirmed
	Purity	[redacted]
	Concentration	
i\..t1l1110ni1l.lm 5ulfa,te	Identity[b]	Meets Requirements
A TP solution~	Identity[b]	Identity confirmed
	Purity	[redacted]
	Concentration	
CTP solutiOIl~	Identity[b]	Identity confirmed
	Purity	[redacted]
	Cotlcenitra tion	
DL-Dithiothreitol	Identity[b]	Meets Requirements; Spectrum exhibits maxima at same wavelengths as that of reference
	Appearance (color)	White
	Appearance (form)	Powder
	Purity	[redacted]
DNase I[c]	Identity[b]	Identity confirmed
	Activity	[redacted]
	Activity[b]	Report Results
	Purity	[redacted]
GTP solution[a]	Identity[b]	Identity confirmed
	Purity	[redacted]
	Concentration	
HEPES	Appearance[b]	White crystals or crystalline powder (Passes test)
	Identity[b]	Passes test
HEPES sodium salt	Appearance[b]	White powder
	Identity[b]	Spectrum is consistent with reference spectrum
Magnesium acetate tetrahydrate	Identity[b]	Meets Requirements

TablE' 3.2.S.2.3-3. AccE''ptance Cdtel'ia foJ:'.'1oo-Compendial Starting ::\latE'riaJ'i and Raw lUatel'ials Used in l\'lanufadllring

Material	Characteristic	Acceptance Criteria
	Appearance (color)	White
	Appearance (form)	Powder to crystalline powder
N1-methylpseudo UTP solution[a]	Identity[b]	Identity confirmed
	Purity	[redacted]
	Concentration	
Proteinase K[c]	Identity[b]	Identity confirmed
	Activity	[redacted]
	Activity[b]	Report Results
Pyrophosphatase[c]	Identity[b]	Identity confirmed
	Activity	[redacted]
	Activity[b]	Report Results
	Purity	[redacted]
RNase inhibitor[c]	Identity[b]	Identity confirmed
	Activity	[redacted]
	Activity[b]	Report Results
	Purity	[redacted]
Spermidine	Identity[b]	Identity confirmed
	Appearance (color)	White/colorless to light yellow
	Appearance (form)	Clear liquid/solid
	Purity	[redacted]
T7 polymerase[c]	Identity[b]	Identity confirmed
	Activity	[redacted]
	Activity[b]	Report Results
	Purity	[redacted]

a. Starting material
b. Test is performed by or on behalf of the drug substance manufacturer to confirm vendor's certificate of analysis
[redacted]

2.1.3. Post Authorisation Measure

Recommendation #7 to provide the results of the studies performed to enhance the robustness of the DNase digestion step has only been partly fulfilled. Further actions are required to fulfil Recommendation #7 including submission of a detailed summary of the results from the studies and inclusion of these data in Module 3.2.5.2.5 of the dossier by the end of second quarter 2021. It also recommended that Recommendations 3 and 7 are grouped.

Response **to** Post Authorisation Measure

Following the increase in residual DNA observed during the ACMF PPQ campaign, small scale experiments were initiated to enhance the robustness of the DNase I digestion step. Studies were conducted to better understand the impact of reaction components, process parameters, and operation parameters on levels of residual DNA template. The small-scale studies are inconclusive and no adjustments to the DNase step are recommended, therefore the data from these studies are not provided.

The root cause analysis is supported by the data previously shown in EMEA/H/C/005735/PAM-ANX REC027. [redacted]

Pfizer has implemented an activity assay for incoming enzymes to monitor and identify outliers that trend with drug substance product quality until acceptance criteria for the new assay can be established. This includes [redacted]

Assessor's comments:

The Applicant states that activity test methods have been developed, validated and implemented for release testing of the five enzymes that are utilized as raw materials in the drug substance manufacturing process (DNase I, Proteinase K, Pyrophosphatase, RNase inhibitor and T7 polymerase). This testing is being performed by or on behalf of the drug substance manufacturer in order to confirm the vendor's certificate of analysis. Table 3.2.5.2.3-3 in Section 3.2.5.2.3 has been updated to reflect this change.

No descriptions of the five tests used to analyse the enzymes are provided. The specification limits are set to "report results" until adequate correlation between the activity results reported by the vendor and those obtained by Pfizer can be established.

From a regulatory point of view, this Type IB variation is found acceptable. However, as regards REC#3, the methods cannot be regarded as fully implemented as long as the correlations to the activity results reported by the vendor have not been established. REC#3 is therefore considered as only partially fulfilled. To complete REC#3, the Applicant should provide short descriptions of the methods applied and present data to demonstrate adequate correlation between the activity results reported by the vendor and the implemented methods. In addition, the specification limits should be defined by numerical values for all five activity methods.

Furthermore, the Applicant has submitted a response to post authorization measure related to REC#7. The Applicant confirms that small scale experiments were initiated to enhance the robustness of the DNase I digestion step. However, the studies were considered inconclusive and no adjustment to the DNase step is recommended. Data from these studies are therefore not provided. This is not found acceptable. Data from the small-scale study should be submitted to support that no change is needed. In addition, the correlation of DNase I activity and levels of Residual DNA template as measured by the in-house methods should be sufficiently evaluated (refer to PAC-PAM REC027). [redacted] This result should also be discussed with respect to the corresponding DNase I activity.

In conclusion, this Type IB variation is found acceptable. However, REC#3 and REC#7 are considered only partly fulfilled.

Active substance master file (ASMF)

Not applicable

Conclusion:

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

2.2. Specific Obligations and Recommendations

No specific obligation is related to this Type IB variation. The related recommendations are described below.

Recommendation	Status
Active substance	
3. The MAH should implement in-house functional activity analytical methods for release testing of enzymes used in the manufacturing process at all relevant manufacturing sites, by Q1 2021.	**Partly fulfilled** eCTD seq 0041: Request to extend the due date from Ql-2021 to Q2-2021. Agreed by email 16.03.2021. REC/027: note link to REC 7. It is recommended that REC3 and REC 7 are grouped in future submission. VAR IB-55: The methods cannot be regarded as fully implemented as long as the correlations to the activity results reported by the vendor have not been established. The Applicant should provide short descriptions of the methods applied and present data to demonstrate adequate correlation between the activity results reported by the vendor and the implemented methods. In addition, the specification limits should be defined by numerical values for all five activity tests.
7. The MAH should provide the results of the studies performed to enhance the robustness of the DNase digestion step in the active substance manufacturing process.	**Partly fulfilled** REC/027 ongoing, CHMP conclusion 20/05/2021: Further actions are required to fulfil Recommendation 7 including submission of a detailed summary of the results from the studies and inclusion of these data in Module 3.2.5.2.5 of the dossier by the end of second quarter 2021. It also recommended that Recommendations 3 and 7 are grouped. VAR IB-55: No results are provided, since the Applicant considers the small-scale study to be inconclusive and no adjustment to the DNase digestion step is recommended. This is not found acceptable, and data should be provided to support that no change is needed. In addition, the correlation of DNase I activity and levels of Residual DNA template as measured by the in-house methods should be sufficiently evaluated.

2.3. Request for supplementary information (RfSI)

List of Issues to be resolved:

N/A

2.4. Responses to RfSI

[redacted]cable
[redacted]
Summary of the MAH responses:

Assessment of the responses:

[redacted]
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:	[redacted] Date: 2021-08-16

☒ The assessor confirms that proprietary information on, or reference to, other products are not made in this assessment and that [redacted] on behalf of the Rapporteur: Filip Josephson endorses this report.