BioNTech RNA Pharmaceuticals GmbH

Summary Report on Process Performance Qualification for manufacturing of BNT162b2 Bulk DP at mibe and Polymun

Report code: R-21-0148

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1 Introduction

1.1 Purpose and Scope

This document describes the process validation approach for Phase II of Covid-19 Vaccine drug product formulation (Bulk DP) at mibe GmbH Arzneimittel and Polymun Scientific Immunbiologische Forschung GmbH with subsequent filling at Pfizer, Puurs.

The process validation has been a 2-phased approach. The first phase included manufacturing of one (1) batch at each supply node. In a later phase, the full validation of all supply nodes was completed. Phase I results are covered in report VAL100136132.

The overall process validation is covered by the following documents:

Table 1. List of Documents

ID	Document
BCVVP003_01	Process Validation Plan (Phase I Network PPQ) BNT162 LNP Preparation and Bulk DP Filling Manufacturing Process (Polymun)
BCVVR003_02	Process Validation Report (Phase I Network PPQ) BNT162 LNP Preparation and Bulk DP Filling Manufacturing Process (Polymun)
V-PS-118-02	Validation Protocol: Process validation CorVac vaccination (DER-BNT162b2) Phase I (mibe)
V-PS-118-02	Validation Report: Process validation CorVac vaccination (DER-BNT162b2) Phase I (mibe)
VAL100130986	Process Validation Plan For Covid-19 Vaccine (PF-07302048, BNT-162) Drug Product – Phase I
20043-COVID-PRP0-A1	Network Process Validation Protocol For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)
20043-COVID-PRRC-A2	Process Validation Report For For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)
VAL100136132	Process Validation Report For Covid-19 Vaccine (PF-07302048, BNT-162) Drug product – Phase I
BCVVP004_01	Process Validation Plan (Phase II PPQ) BNT162 LNP Preparation and Bulk DP Filling Manufacturing Process (Polymun)
BCVVR004_01	Process Validation Report (Phase II PPQ) BNT162 LNP Preparation and Bulk DP Filling Manufacturing Process (Polymun)
V-PS-118-03	Validation Protocol: Process validation CorVac vaccination (DER-BNT162b2) Phase II (mibe)
V-PS-118-03	Validation Report: Process validation CorVac vaccination (DER-BNT162b2) Phase II (mibe)
5336199-BPW5FC2-PVP0-A1	Process Validation Plan For The Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) with Supplied Covid Vaccine Bulk Product at PGS Puurs
5336199-BPW5FC2-PRPB-A1	Process Validation Protocol For Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) with supplied Covid-19 Vaccine Bulk Product from Polymun at PGS Puurs

5336199-BPFC2-PRRF-A1	Process Validation Report For the Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) with supplied Covid-19 Vaccine Bulk Product from Polymun at PGS Puurs
5336199-BPW5FC2-PRPA-A1	Process Validation Protocol For Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) with supplied Covid-19 Vaccine Bulk Product from Dermapharm (mibe) at PGS Puurs
5336199-BPW5FC2-PRRC-A1	Process Validation Report For the Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) with supplied Covid-19 Vaccine Bulk Product from Dermapharm (mibe) at PGS Puurs

2 Process description

2.1 Description of the Bulk DP Production Process Steps

An overview on the bulk drug product manufacturing process is provided in Figure 1. The differences are shown in italics for those conditions only applicable to Polymun site and underlined for those conditions only applicable to mibe.

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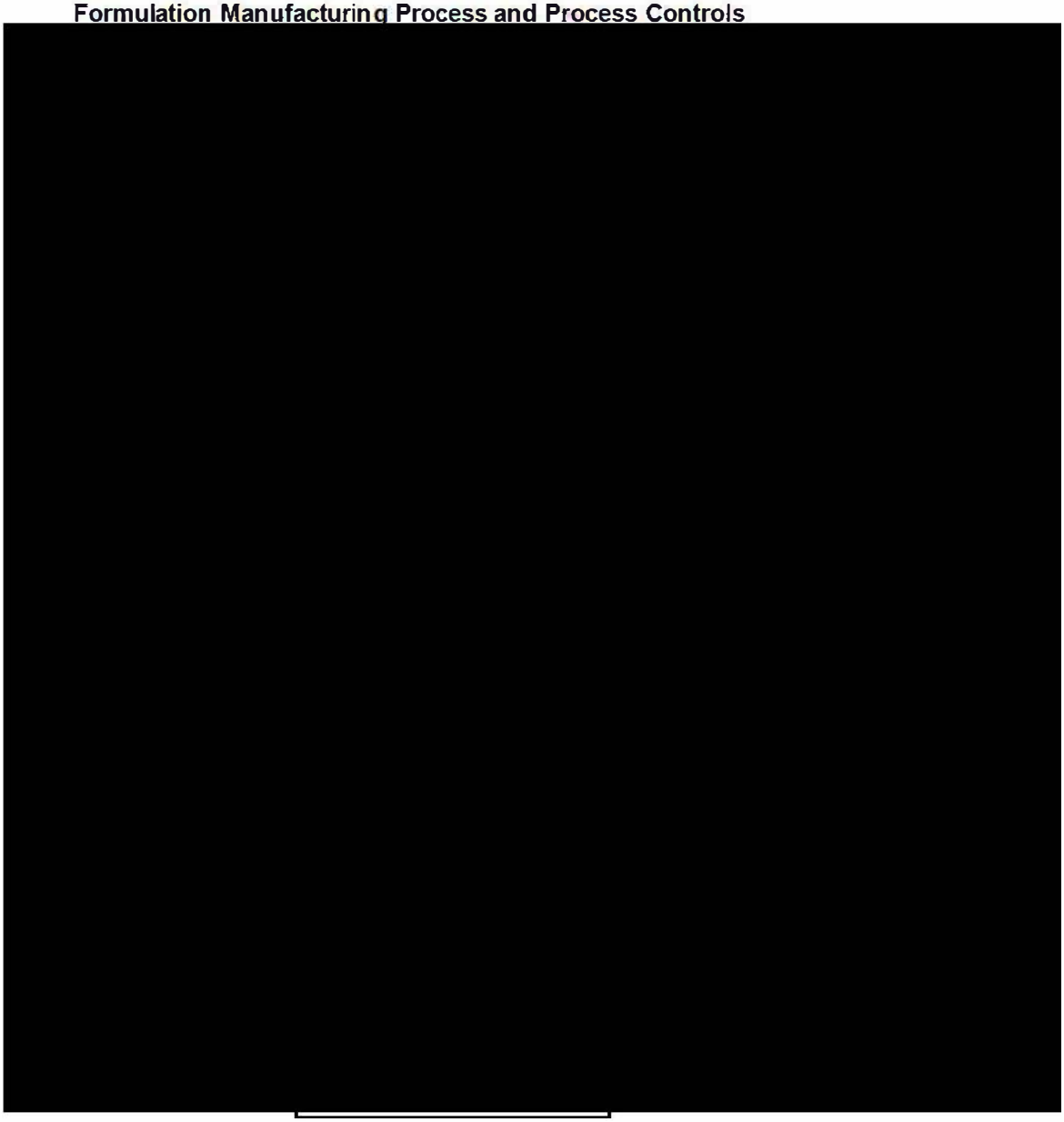
Figure 1: Flow Diagram of the BNT162b2 LNP Fabrication and Bulk Drug Product Formulation Manufacturing Process and Process Controls

Step	Process Inputs	Process Step	Process Controls
1	[redacted]		
2			
3			
4			

Figure 1: Flow Diagram of the BNT162b2 LNP Fabrication and Bulk Drug Product Formulation Manufacturing Process and Process Controls



a. [redacted]
Abbreviations: [redacted] ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine; LNP = lipid nanoparticle; IPT-C = in-process test for control; [redacted]; PBS = phosphate-buffered saline; $Na_2HPO_4 \cdot 2\ H_2O$ = dibasic sodium phosphate, dihydrate; KCl = potassium chloride; KH_2PO_4 = monobasic potassium phosphate; NaCl = sodium chloride

2.2 Process Validation Overview

An overview on the sites involved in the PPQ runs and the step which was part of the validation is provided in Table 2.

Table 2. Sites involved in the PPQ runs

Process part	LNP Bulk Drug Product	Fill and finish (Fill line)	Batch number(s) LNP bulk	Batch number(s) finished product
Company	Polymun Scientific	Pfizer, Puurs (FC2)	BVC4/L21	ET0384
	Polymun Scientific	Pfizer, Puurs (WSL5)	BCV4/L15[a]	EL7834[a]
			BCV4/L19, BCV4/L20	EM4965
	mibe	Pfizer, Puurs (WSL5)	201113[a]	EK4242[a]
			210101	EN1195
			210103	EN1196

a. Batches manufactured within the scope for Phase I Process Validation.

b. Pooling of two bulk DP batches covered in Pfizer, Puurs protocol 5336199-BPW5FC2-PRPB-A1.

3 Results of Validation

The detailed results of the validation runs are presented in the attachments. The overview on the critical and non-critical process performance parameters for the LNP bulk drug product process carried out at Polymun Scientific and mibe is provided in Attachment 1. For all critical process parameters, the values used during the process were within the defined limits. There were no significant differences in the ranges applied at both site, except for those that are different due to site differences in equipment.

The in-process test results for the LNP bulk drug product process are depicted in Attachment 2. All results were within the defined limits. For the majority of critical process tests the variability of the results within is not significant. There is a difference observed for RNA content after TFF between Polymun and mibe but this is caused by the higher load of RNA on the filters at the Polymun site. At the subsequent step concentration is adjusted and both sites have comparable results.

The testing results on the intermediate LNP bulk drug product (Attachment 3) showed all batches fulfill the acceptance criteria for all quality attributes and furthermore, similar results for both sites.

The fill and finish process at Pfizer Puurs with bulk DP supplied by Polymun and mibe (respective PPQ batches) was performed on two different lines (FC2 and WSL5). In addition, two Polymun bulk drug product batches (BCV4/L19 and BCV4/L20) were pooled and filled on line WSL5.

The critical process parameters applied during the fill and finish step (Attachment 4) were within the limits except for the transfer pressure during the sterile filtration for the 3 mibe PPQ batches. The pressure for these batches was measured on the manufacturing tank and found to be outside of the

control limit. However, before sterile filtration the pressure never exceeded the maximum validated pressure of [redacted].

The fill weight tests carried out on the PPQ batches (Attachment 5) was well within the range defined. There was also no difference between the filling lines used.

The results of batch testing (Attachment 6) were all well within the specification. The variability was low for the majority of testing results independently of the source of the LNP bulk drug product used for filling. A slightly higher variability was observed in the lipids contents, but the results were well within the specification. The results for batch ET0384 filled on line FC2 were within the results of the 5 batches filled on line WSL5. Results of batch EM4965 which was filled from two pooled LNP bulk drug product batches was well within the results of the other 5 batches covered by the process validation.

4 Conclusion

The result of 4 PPQ batches manufactured at Polymun Scientific and 3 batches manufactured at mibe demonstrate that the process at both sites is consistent and results in an intermediate drug product with the adequate quality.

The final fill and finish step confirmed that line WSL5 at Pfizer Puurs is adequately validated for this purpose. The exercise also demonstrates that the fill and finish process is not impacted by the source of the LNP bulk drug product used allowing full interchangeability between bulk DP batches from Polymun and mibe. In addition, it was shown that pooling of LNP bulk batches into one fill and finish batch don't have an impact of final product critical quality attributes.

As an overall conclusion, all PPQ batches fulfill all pre-defined acceptance criteria hence; process are considered validated.

Summary Report on Process Performance Qualification for manufacturing of BNT162b2 Bulk DP at mibe and Polymun (R-21-0148)

Attachment 1: Critical Process Parameters – Bulk DP Process

CPPs (italic = nonCPP)	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe		
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]								
						N/A	N/A	N/A
						N/A	N/A	N/A

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CPPs (italic = non CPP)	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe		
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]								

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CPPs (italic = non CPP)	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe		
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]								

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CPPs (italic = nonCPP)	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe		
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]								

Abbreviations: PLY = Polymun Scientific, PPQ = process performance qualification, RT = room temperature, h = hour. M = month, D = day, CPP = critical process parameters

Attachment 2: In Process Tests – Bulk DP Process

Parameter (Italic: non critical)	Acceptance criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
Solutions								
[redacted]								
Organic Phase Preparation								
ALC-0315 content (mg/mL)	[redacted]							
ALC-0159 content (mg/mL)								
DSPC content (mg/mL)								
Cholesterol content (mg/mL)								

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Parameter (Italic: non critical)	Acceptance criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
Aqueous Phase Preparation								
RNA content *(mg/mL)*	[redacted]							
LNP Preparation								
RNA content (mg/mL)	[redacted]							
Particle size (nm)								
Polydispersity index								
TFF								
Appearance	[redacted]							
RNA content *(mg/mL)*								
RNA encapsulation (%)								
ALC-0315 content (mg/mL)								
ALC-0159 content (mg/mL)								
DSPC content (mg/mL)								
Cholesterol content (mg/mL)								

Summary Report on Process Performance Qualification for manufacturing of BNT162b2 Bulk DP at mibe and Polymun (R-21-0148)

Parameter (Italic: non critical)	Acceptance criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
Particle size (nm)	[redacted]							
Polydispersity index								
pH	6.9 – 7.9	7.4	7.4	7.4	7.2	7.4	7.3	7.4
***Osmolality* (mOsmol/kg)**	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	N/A	N/A	N/A
Post-use filter integrity	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

a. The limits for this parameter are given in µg/mL at Polymun Scientific. For matter of data presentation these have been transferred into mg/mL while keeping the number of digits from the specification.

Abbreviations: PLY = Polymun Scientific, PPQ = process performance qualification, N/A = not applicable, RT = room temperature, CFU = colony forming units, h = hour, M = month, DP = day, CPP = critical process parameters, PBS = phosphate buffered saline, ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine

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Attachment 3: LNP Bulk Drug Product - Intermediate Testing Results

Parameter (Italic: non critical)	Acceptance criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
Bulk DP intermediate Product								
Appearance	PLY: White to off-whie suspension, free from observable particles Mibe: White to off-white suspension,	Pass	Pass	Pass	Pass	Pass	Pass	Pass
RNA identification	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	Pass
RNA content (mg/mL)	[redacted]							
RNA integrity (%)								
RNA encapsulation (%)								
ALC-0315 content (mg/mL)								
ALC-0159 content (mg/mL)								
DSPC content (mg/mL)								
Cholesterol content (mg/mL)								

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Parameter (Italic: non critical)	Acceptance criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)			Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		BCV4/L15	BCV4/L19	BCV4/L20	BCV4/L21	201113	210101	210103
Lipids identification	[redacted]	Pass	Pass	Pass	Pass	Pass	Pass	Pass
Particle size (nm)	[redacted]							
Polydispersity index								
pH	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Osmolality (mOsmol/kg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bioburden (CFU)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Endotoxins (EU/mL)	[redacted]	N/A	N/A	N/A	N/A	[redacted]	[redacted]	[redacted]
Post-use filter integrity	Pass	Pass	Pass	Pass	Pass	Pass	Pass	Pass

a. The limits for this parameter are given in µg/mL at Polymun Scientific. For matter of data presentation these have been transferred into mg/mL while keeping the number of digits from the specification.

Abbreviations: PLY = Polymun Scientific, PPQ = process performance qualification, N/A = not applicable, RT = room temperature, CFU = colony forming units, h = hour, M = month, DP = day, CPP = critical process parameters, PBS = phosphate buffered saline, ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine

Attachment 4: Critical Process Parameters – F&F Drug Product Process

CPPs	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)		Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		EL7834	EM4965	ET0384[a]	EK4242	EN1195	EN1196
	Bulk DP batch number:	BCV4/L15	BCV4/L19 BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]							

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CPPs	Operating range	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)		Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		EL7834	EM4965	ET0384 [a]	EK4242	EN1195	EN1196
	Bulk DP batch number:	BCV4/L15	BCV4/L19 BCV4/L20	BCV4/L21	201113	210101	210103
[redacted]		Conforms	Conforms	Conforms	Conforms	Conforms	Conforms
		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

a. This batch was filled on line FC2 whereas all other batches were filled on line WSL5
b. This is the pressure measured in the manufacturing tank which was outside of the control limit. However, before the pressure never exceeded the maximum validated test pressure of [redacted] (maximum validated for bacterial retention).
c. Challenged time

Abbreviations: PPQ = process performance qualification, TOR = time at room temperature, h = hour, m = minutes, CPP = critical process parameters

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Attachment 5: In Process Tests – F&F Drug Product Process

	Acceptance Criteria	Polymun (Phase I PPQ)	Polymun (Phase II PPQs)		Mibe (Phase I PPQ)	Mibe (Phase II PPQs)	
		EL7834	EM4965	ET0384[a]	EK4242	EN1195	EN1196
	Bulk DP batch numb er	BCV4/L15	BCV4/L19 BCV4/L20	BCV4/L21	201113	210101	210103
	Pass	Pass	Pass	Pass	Pass	Pass	Pass
	Pass	Pass	Pass	Pass	Pass	Pass	Pass

[redacted]led on line FC2 whereas all other batches were filled on line WSL5

Abbreviations: PPQ = process performance qualification, DP = drug product

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Attachment 6: Batch Release Results

Parameter	Acceptance Criteria	EL7834	EM4965[a]	ET0384[b]	EK4242	EN1195	EN1196
Appearance	White to off-white suspension	White to off-white suspension	White to off-white suspension	White to off-white suspension	White to off-white suspension	White to off-white suspension	White to off-white suspension
Appearance (Visible particulates)	May contain white to off white opaque amorphous particles	Essentially free from visible particles	Essentially free from visible particles	Essentially free from visible particles	Essentially free from visible particles	Essentially free from visible particles	Essentially free from visible particles
Subvisible particles (particles/container)	Particles ≥10 µm: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	Particles ≥25 µm: [redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
pH	[redacted]						
Osmolality (mOsmol/kg)							
LNP size (nm)							
LNP polydispersity							
RNA encapsulation (%)							
RNA content (mg/mL)							
ALC-0315 content mg/mL							
ALC-0159 content mg/mL							
DSPC content mg/mL							
Cholesterol content mg/mL							

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Parameter	Acceptance Criteria	EL7834	EM4965[a]	ET0384[b]	EK4242	EN1195	EN1196
Lipids Identity	[redacted]						
Container Content for injections	Not less than the sum of the nominal volumes of 5 doses	Not less than the sum of the nominal values of 5 doses	Not less than the sum of the nominal values of 5 doses	Not less than the sum of the nominal values of 5 doses	Not less than the sum of the nominal values of 5 doses	Not less than the sum of the nominal values of 5 doses	Not less than the sum of the nominal values of 5 doses
Identity of encoded RNA sequence	Identity confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed
In Vitro Expression (% cells positive)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RNA integrity(% intact RNA)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bacterial Endotoxin (EU/mL)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sterility	No growth detected	No growth detected	No growth detected	No growth detected	No growth detected	No growth detected	No growth detected

a. This batch combined two LNP bulk drug product batches of Polymun Scientific

b. This batch was filled on line FC2 whereas all other batches were filled on line WSL5

Abbreviations: LNP = lipid nanoparticle, EU = endotoxin units, ALC-0315 = ((4-hydroxybutyl)azanediyl)bis(hexane-6,1-diyl)bis(2-hexyldecanoate); ALC-0159 = 2-[(polyethylene glycol)-2000]-N,N-ditetradecylacetamide; DSPC = 1,2-distearoyl-sn-glycero-3-phosphocholine