BNT162b2 (PF-07302048) Comparability Report for PPQ Drug Product Lots

INX100451158

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INTRODUCTION

BioNTech and Pfizer are developing an investigational vaccine intended to prevent Coronavirus Disease 2019 (COVID-19) caused by the virus, SARS-CoV-2. The goal of the development program is to rapidly develop and apply for a Marketing Authorization for a vaccine for use in adults ≥ 16 years of age, followed by a pediatric indication. 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 mRNA Vaccine (BioNTech code number BNT162b2; Pfizer code PF-07302048).

In this section, drug product quality is demonstrated to be comparable for bulk drug product (LNP) manufactured at mibe (Dermapharm), Polymun, Puurs, and Kalamazoo, with fill and finish operations occurring at Puurs (lines WSL5, FC2, and VC2) and Kalamazoo (lines 8 and 18). Product quality comparability establishes the capability of the commercial process to produce a consistent drug product across the proposed commercial manufacturing facilities.

The drug product manufacturing process has evolved from clinical supply to emergency supply and finally to commercial supply, undergoing transfer to different manufacturing sites and process scale-up.

Clinical supply was initially produced at Polymun, Austria ("classical" process). In order to improve the mass throughput of the LNP process and increase the batch size, the process was scaled up at Polymun ("upscale" process) followed by transport of the bulk drug product (fully formulated LNPs prior to sterile filtration) to Pfizer Puurs, Belgium for fill/finish operations (for the manufacture of "emergency supply" and commercial supply).

This process has also been set-up at mibe (Dermapharm), Germany for manufacture of emergency supply material. Within this scope, the fill/finish operations at Puurs were initially conducted on the S2F2 line (for clinical supply) with transition to the WSL5 line for larger batch volumes (emergency use supply, and subsequently for commercial supply). For routine commercial production, the LNP production process has been fully transferred to Pfizer, Puurs, Belgium with fill/finish operations on filling lines WSL5, FC2 and VC2 and to Pfizer, Kalamazoo, US with fill/finish operations on filling lines L8 and L18 (for the manufacture of "commercial supply").

The process validation approach for all supply nodes included within the emergency supply and commercial supply network as described above is composed of two phases. The process validation plan for Phase I covers the validation of the overall network, by performing one (1) validation run of each supply node (also known as Network PPQ), whereas the Phase II validation covers the full validation of each of the supply nodes (with separate protocols at each site).

The study described herein focuses on an assessment of BNT162b2 drug product throughout the emergency supply and commercial supply manufacturing network, including the Phase I

and Phase II PPQ lots ("upscale" process) and bridging to the previous comparability study by including a representative clinical lot ("classical" process) and initial emergency use lot ("upscale" process).

1. SCOPE AND APPROACH FOR COMPARABILITY

[redacted]

Table 1. BNT162b2 DP Lots Included in the Comparability Assessment

DP Lot Number	DP Site of Manufacture	Date of DP manufacture	Drug substance Batch	DS Process and Site of Manufacture	Purpose of Material
EE3813 / BCV40820-P[a]	LNP: Polymun F&F: Puurs S2F2	29 Jul 2020	R445-P020.2-DS	Process 1: BNT IMFS, Germany	Clinical Inventory, Stability
EE8493[a]	LNP: Polymun (scale-up) F&F: Puurs WSL5	05 Aug 2020	20Y513C101	Process 2: Andover, USA	Clinical Inventory, Emergency Supply, Stability
EL1491[b]	LNP: Puurs F&F: Puurs FC2	18 Nov 2020	1071539	Process 2: BNT/ Rentschler, Germany	PV Phase I, Stability
EL8723		11 Dec 2020	20Y513C801	Process 2: Andover, USA	PV Phase II, Stability

EP2166		23 Dec 2020	20Y513C1301	Process 2: Andover, USA	PV Phase II, Stability
EM6950	LNP: Puurs F&F: Puurs VC2	11 Dec 2020	20Y513C501	Process 2: Andover, USA	PV Phase II, Stability
EL8713		23 Dec 2020	1071542	Process 2: BNT/ Rentschler, Germany	PV Phase II, Stability
EP2163		23 Dec 2020	20Y513C1101 20Y513C1401	Process 2: Andover, USA	PV Phase II, Stability
EP6775		04 Jan 2021	20Y513C1201	Process 2: Andover, USA	PV Phase II, Stability
EK4242[b]	LNP: mibe (Dermapharm) F&F: Puurs WSL5	17 Nov 2020	1071548	Process 2: BNT/ Rentschler, Germany	PV Phase I, Stability
EN1195		08 Jan 2021	1071552	Process 2: BNT/ Rentschler, Germany	PV Phase II, Stability
EN1196		18 Jan 2021	1071558	Process 2: BNT/ Rentschler, Germany	PV Phase II, Stability
EL7834[b]	LNP: Polymun (scale-up) F&F: Puurs WSL5/FC2[c]	17 Nov 2020	1071546	Process 2: BNT/ Rentschler, Germany	PV Phase I, Stability
EM4965		20 Jan 2021	1071559 1071560	Process 2: BNT/ Rentschler, Germany	PV Phase II, Stability
ET0384		28 Jan 2021	20Y513C1601	Process 2: Andover, USA	PV Phase II, Stability
EL3248[b]	LNP: Kalamazoo F&F: Kalamazoo L8	25 Nov 2020	20Y513C501	Process 2: Andover, USA	PV Phase I, Stability
EL9267		29 Dec 2020	20Y513C601	Process 2: Andover, USA	PV Phase II, Stability
EN6198		13 Jan 2021	20Y513C701 20Y513C801	Process 2: Andover, USA	PV Phase II, Stability
EN6200		05 Jan 2021	20Y513C1501	Process 2: Andover, USA	PV Phase II, Stability
EL3249[b]	LNP: Kalamazoo F&F: Kalamazoo L18	02 Dec 2020	20Y513C601	Process 2: Andover, USA	PV Phase I, Stability
EL9266		21 Dec 2020	20Y513C1301	Process 2: Andover, USA	PV Phase II, Stability
EN6199		19 Jan 2021	20Y513C1501 20Y513C1601	Process 2: Andover, USA	PV Phase II, Stability

a. Lot also included in previous side-by-side comparability assessment (Section 3.2.P.2.3 Development History)
b. PV Phase I ("Network PPQ") lot
c. F&F for lot ET0384 was performed at Puurs line FC2.

Abbreviations: BNT – BioNTech; F&F – Fill & Finish; PV – Process Validation

1.2. Analytical Comparability Testing Strategy

The panel of tests, both release and heightened characterization, performed to evaluate drug product comparability are shown in Table 2. Additional heightened characterization methods were performed to evaluate selected drug product LNP and purity attributes.

Table 2. BNT162b2 Drug Product Comparability Testing Panel

Quality Attribute	Analytical Procedure	Release / Characterization
Composition and Strength		
Appearance	Appearance (Visual)	Release
Appearance (Visible Particulates)	Appearance (Particles)[a]	Release
Subvisible Particles	Subvisible Particulate Matter[a, b]	Release
pH	Potentiometry[a]	Release
Osmolality	Osmometry [a, c]	Release
LNP Size	Dynamic Light Scattering (DLS)	Release
LNP Polydispersity	Dynamic Light Scattering (DLS)	Release
RNA Encapsulation	Fluorescence assay	Release
RNA content	Fluorescence assay	Release
ALC-0315 content	HPLC-CAD	Release
ALC-0159 content	HPLC-CAD	Release
DSPC content	HPLC-CAD	Release
Cholesterol content	HPLC-CAD	Release
Surface Charge	[redacted]	Characterization
Size Distribution and Shape		Characterization
Surface PEG Characterization		Characterization
Identity		
Lipid identities	HPLC-CAD	Release
Identity of encoded RNA sequence	RT-PCR	Release
Potency		
In Vitro Expression	Cell-based Flow Cytometry	Release
Purity		
RNA Integrity	Capillary Gel Electrophoresis	Release
5'- Cap	RP-HPLC[d]	Characterization
Poly(A) Tail	ddPCR	Characterization
Poly(A) Tail: Length and Distribution	RP-HPLC [d]	Characterization

a. Compendial
b. USP<787> (obscuration method), and aligned with upcoming (Jan 2021) revision of Ph. Eur. 2.9.19
c. USP<785>; also in accordance with Ph Eur. 2.2.35, with minor difference in instrument calibration
d. Tested side-by-side

Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; [redacted] ddPCR = droplet digital PCR; qPCR = quantitative PCR

2. COMPARABILITY RESULTS AND DISCUSSION

2.1. Discussion of Release and Characterization Data to Support BNT162b2 Product Quality Comparability

Comparability result ranges are tabulated in Table 3 by supply node for the PPQ DP lots specified in Table 1. Historical data ranges, taken from clinical and emergency supply lots, are included for comparison. The comparability results are additionally shown graphically in Figure 1 through Figure 17, with acceptance criteria at the time of testing indicated by red dashed lines for release methods (Figure 3 through Figure 13). Historical data are included in the graphs for non-compendial release test results (and where available for characterization results). Supportive profiles and data from selected side-by-side heightened characterization tests are provided in Section 2.2 below.

All quality attributes evaluated during drug product release testing (as noted in Table 2) met the specification acceptance criteria at the time of testing and are consistent with historical ranges from clinical and emergency supply lots.

Subvisible particles ≥10 µm and ≥25 µm showed slight variability across lots but remain well below compendial limits. To maintain an appropriate scale, acceptance criteria are not shown for subvisible particles in Figure 1 and Figure 2.

[redacted]

Table 3. Comparability Data Ranges for BNT162b2 Drug Product Lots[a]

Quality Attribute	Analytical Procedure	Bulk DP Site:		Puurs	Puurs	mibe	Polymun	Kalamazoo	Kalamazoo
		F&F Line:		Puurs FC2	Puurs VC2	Puurs WSL5	Puurs WSL5 Puurs FC2[g]	Kalamazoo L8	Kalamazoo L18
		Historical Range: Clinical Lots[b]	Historical Range: Emergency Supply[d]	EL1491 EL8723 EP2166	EM6950 EL8713 EP2163 EP6775	EK4242 EN1195 EN1196	EL7834 EM4965 ET0384	EL3248 EL9267 EN6198 EN6200	EL3249 EL9266 EN6199
Appearance	Appearance (Visual)	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	White to off-white suspension
Appearance (visible particulates)	Appearance (Particles)	Free from observable particles	Essentially free from visible particulates	Essentially free from visible particulates / Meets test[f]	Essentially free from visible particulates / Meets test[f]	Essentially free from visible particulates	Essentially free from visible particulates	Essentially free from visible particulates	Essentially free from visible particulates
Subvisible particles	Subvisible particulate matter	[redacted]							
pH	Potentiometry	[redacted]							
Osmolality	Osmometry								
LNP size (nm)	Dynamic light scattering (DLS)								
LNP polydispersity	Dynamic light scattering (DLS)								
RNA encapsulation (%)	Fluorescence assay								
RNA content (mg/mL)	Fluorescence assay								
ALC-0315 content (mg/mL)	HPLC-CAD								

Table 3. Comparability Data Ranges for BNT162b2 Drug Product Lots[a]

Quality Attribute	Analytical Procedure	Bulk DP Site:		Puurs	Puurs	mibe	Polymun	Kalamazoo	Kalamazoo
		F&F Line:		Puurs FC2	Puurs VC2	Puurs WSL5	Puurs WSL5 Puurs FC2[g]	Kalamazoo L8	Kalamazoo L18
		Historical Range: Clinical Lots[b]	Historical Range: Emergency Supply[d]	EL1491 EL8723 EP2166	EM6950 EL8713 EP2163 EP6775	EK4242 EN1195 EN1196	EL7834 EM4965 ET0384	EL3248 EL9267 EN6198 EN6200	EL3249 EL9266 EN6199
ALC-0159 content (mg/mL)	HPLC-CAD	[redacted]							
DSPC content (mg/mL)	HPLC-CAD								
Cholesterol content (mg/mL)	HPLC-CAD								
Lipid identities	HPLC-CAD	Conforms to reference	Retention times consistent with references	Retention times consistent with references	Retention times consistent with references	Retention times consistent with references	Retention times consistent with references	Retention times consistent with references	Retention times consistent with references
Identity of encoded RNA sequence	RT-PCR	N/A	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed	Confirmed
In vitro expression (% cells positive)	Cell-based flow cytometry	[redacted]							
RNA integrity	Capillary gel electrophoresis								
5' – Cap (%)[c]	RP-HPLC								
Capped-Intact RNA (%) [e]	Capillary gel electrophoresis and RP-HPLC								
Poly (A) Tail	ddPCR								
Poly A Tail: Length and distribution (%)[c]	RP-HPLC								

Table 3. Comparability Data Ranges for BNT162b2 Drug Product Lots[a]

Quality Attribute	Analytical Procedure	Bulk DP Site:		Puurs	Puurs	mibe	Polymun	Kalamazoo	Kalamazoo
		F&F Line:		Puurs FC2	Puurs VC2	Puurs WSL5	Puurs WSL5 Puurs FC2[g]	Kalamazoo L8	Kalamazoo L18
		Historical Range: Clinical Lots[b]	Historical Range: Emergency Supply[d]	EL1491 EL8723 EP2166	EM6950 EL8713 EP2163 EP6775	EK4242 EN1195 EN1196	EL7834 EM4965 ET0384	EL3248 EL9267 EN6198 EN6200	EL3249 EL9266 EN6199

a. For data ranges showing of a single value, all lots had the same test result
b. Clinical lots BCV40420-A, BCV40620-A, BCV40620-B, BCV40620-C, BCV40620-D, BCV40720-A, BCV40720-B, BCV40720-C, BCV40720-P and BCV40820-P
c. Tested side-by-side
d. [redacted] supply lots from Puurs/Puurs FC2 (EL0725, EL0739, EL1484, EJ6795, EJ6796, EJ6797), mibe/Puurs WSL5 (EK4175, EL0140, EL0142, EK4237, EK4243, EK4244, EK4245, EJ1688), Polymun/Puurs WSL5 (EE8492, EE8493, EJ0553, EJ1685, EJ1686, EK4176, EK1768, EL0141, EK4241), Kalamazoo/Kalamazoo L8 (EH9899, EK5730, EL3246), Kalamazoo/Kalamazoo L18 (EJ0724, EK9231, EL1283, EL1284)
e. [redacted]
f. Differences in reporting the appearance result for lots EP2163 and EP2166 (“Meets test”) occurred due to changes in testing location.
g. F&F for lot ET0384 was performed at Puurs line FC2.

Abbreviations: LNP = Lipid nanoparticles; CAD = charged aerosol detector; RT-PCR = reverse transcription polymerase chain reaction; ddPCR = droplet digital PCR; qPCR = quantitative PCR; RP-HPLC = reversed-phase high performance liquid chromatography; GC = gas chromatography

Figure 1. BNT162b2 Drug Product Comparability Release Results – Subvisible Particles ≥ 10 µm

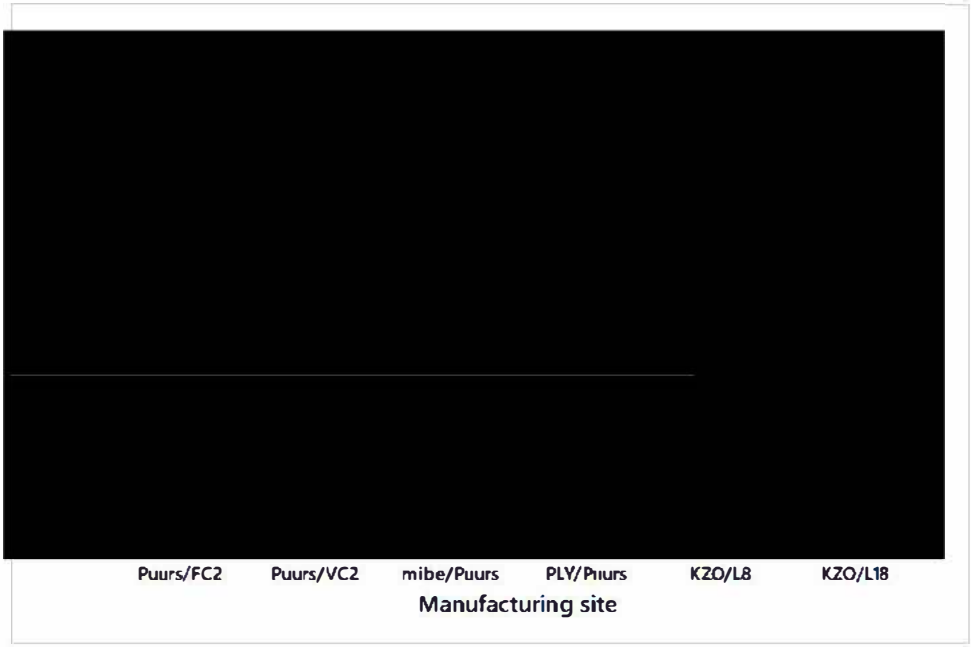

Figure 2. BNT162b2 Drug Product Comparability Release Results – Subvisible Particles ≥ 25 µm

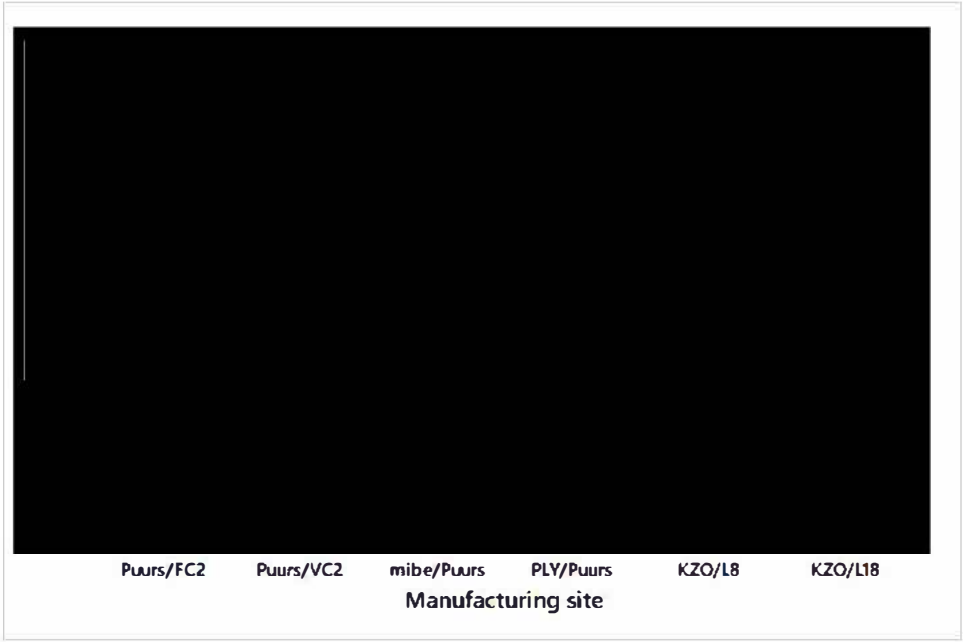

Figure 3. BNT162b2 Drug Product Comparability Release Results – pH

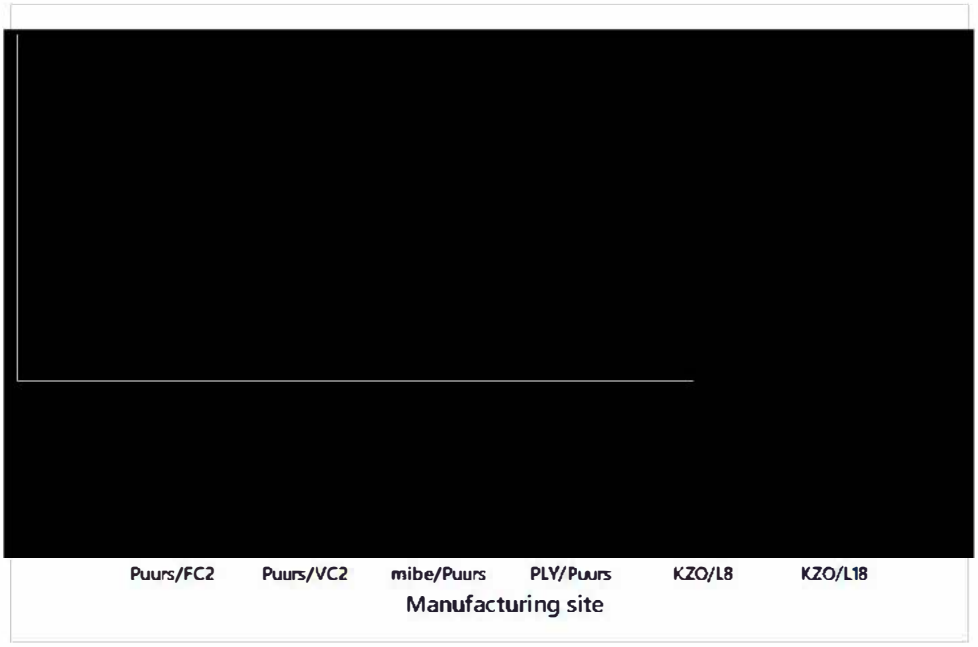

Figure 4. BNT162b2 Drug Product Comparability Release Results – Osmolality

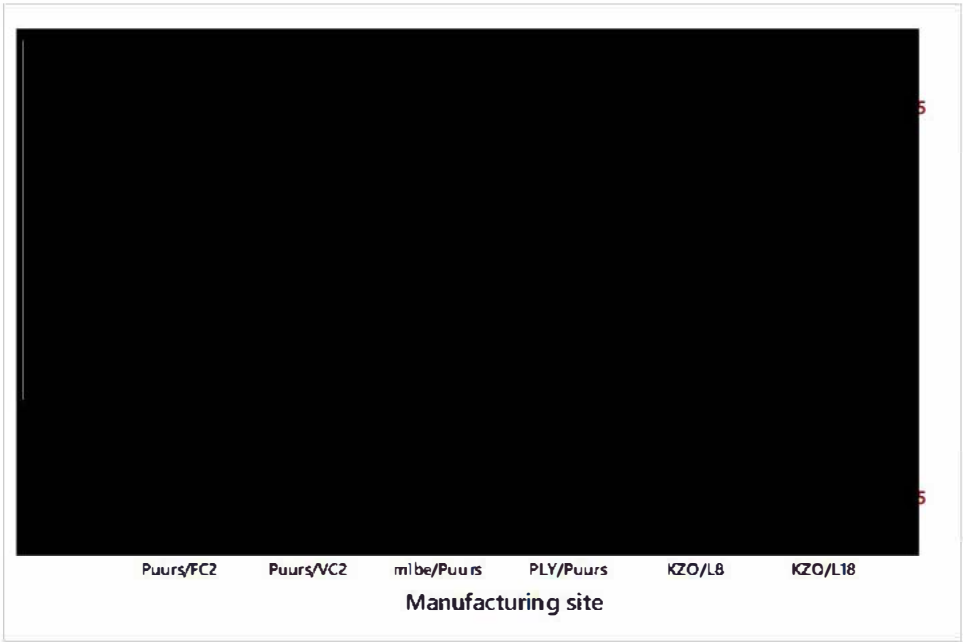

Figure 5. BNT162b2 Drug Product Comparability Release Results – LNP Size

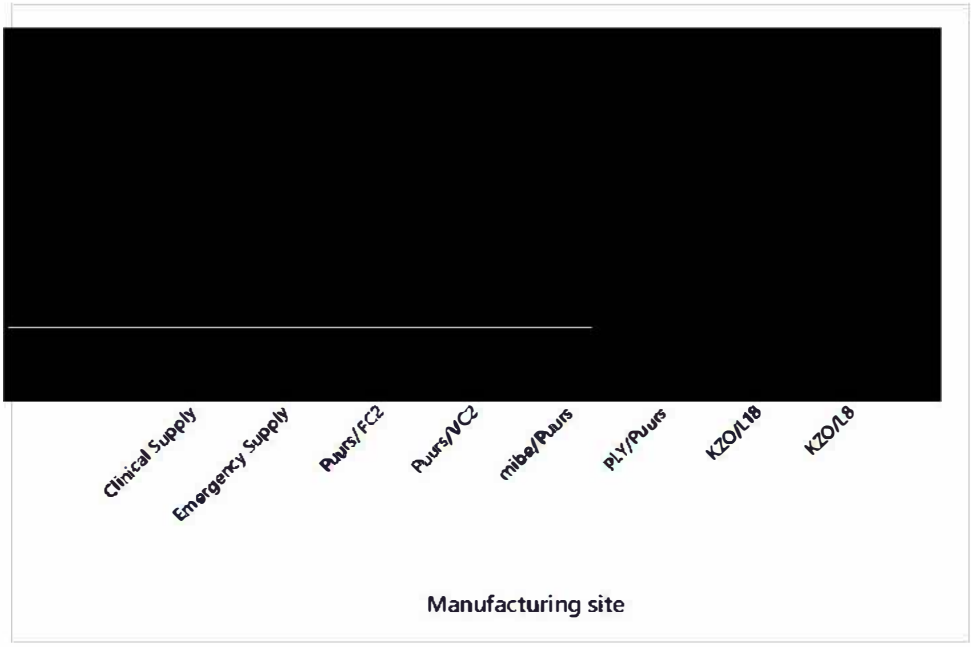

Figure 6. BNT162b2 Drug Product Comparability Release Results – LNP Polydispersity

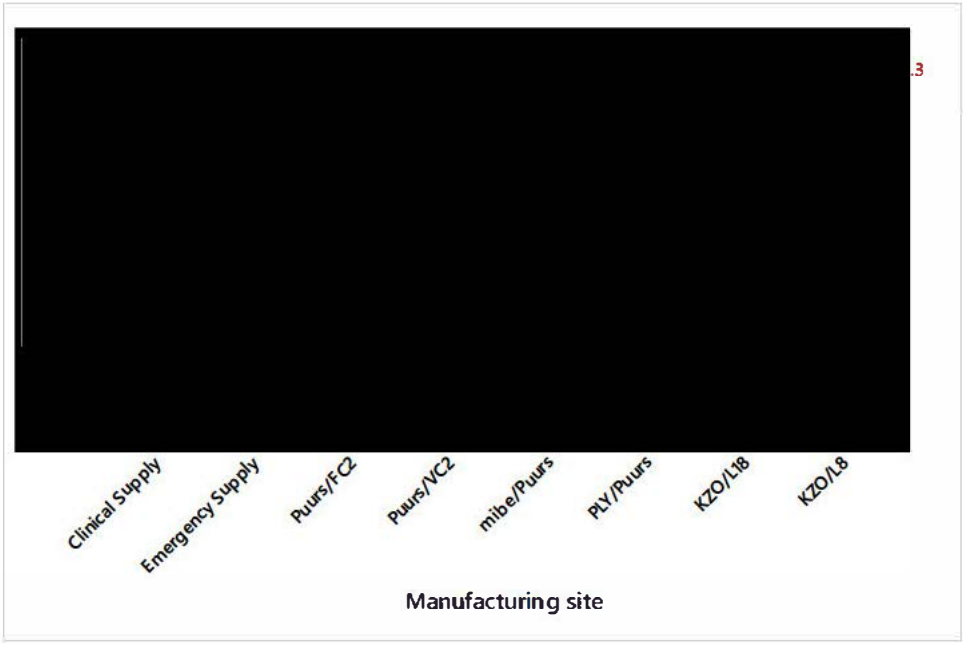

Figure 7. BNT162b2 Drug Product Comparability Release Results – RNA Encapsulation

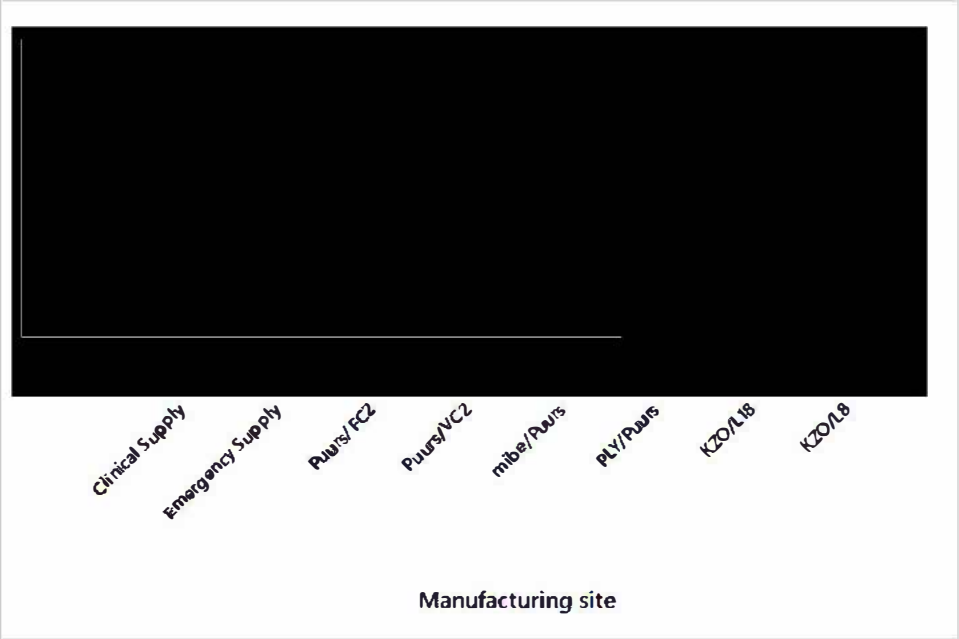

Figure 8. BNT162b2 Drug Product Comparability Release Results – RNA Content

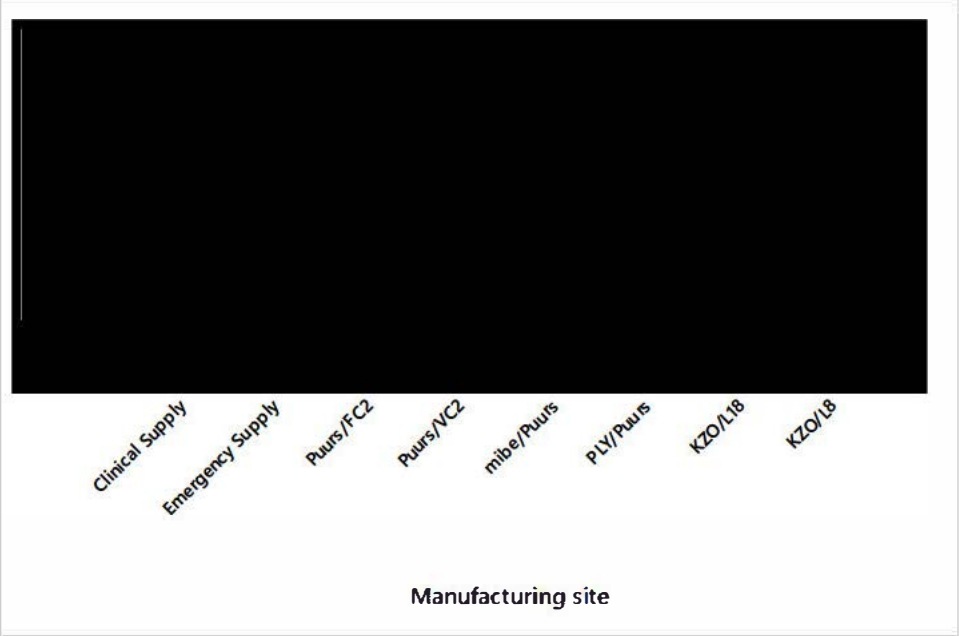

Figure 9. BNT162b2 Drug Product Comparability Release Results – ALC-0315 Content

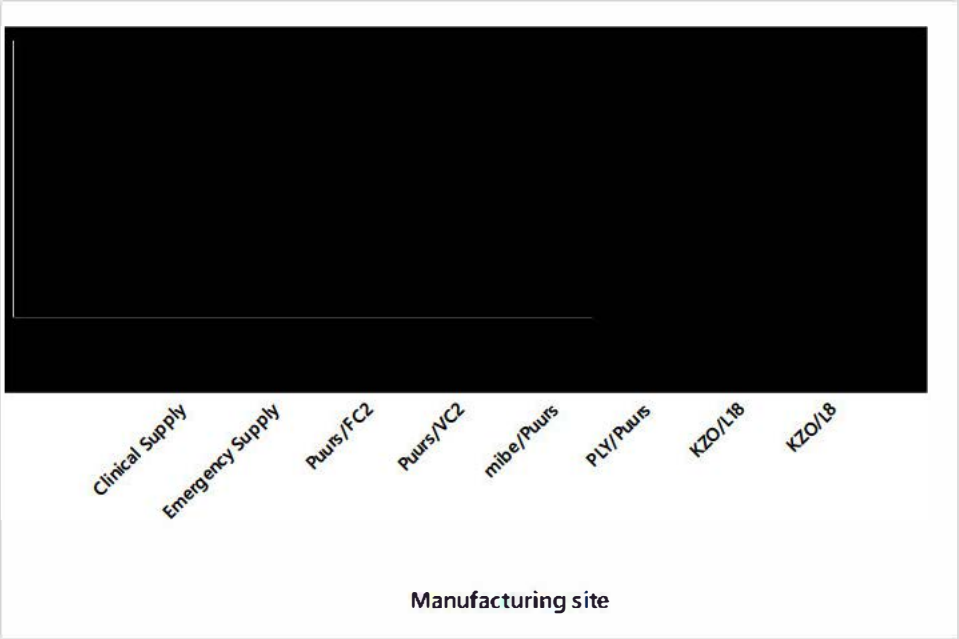

Figure 10. BNT162b2 Drug Product Comparability Release Results – ALC-0159 Content

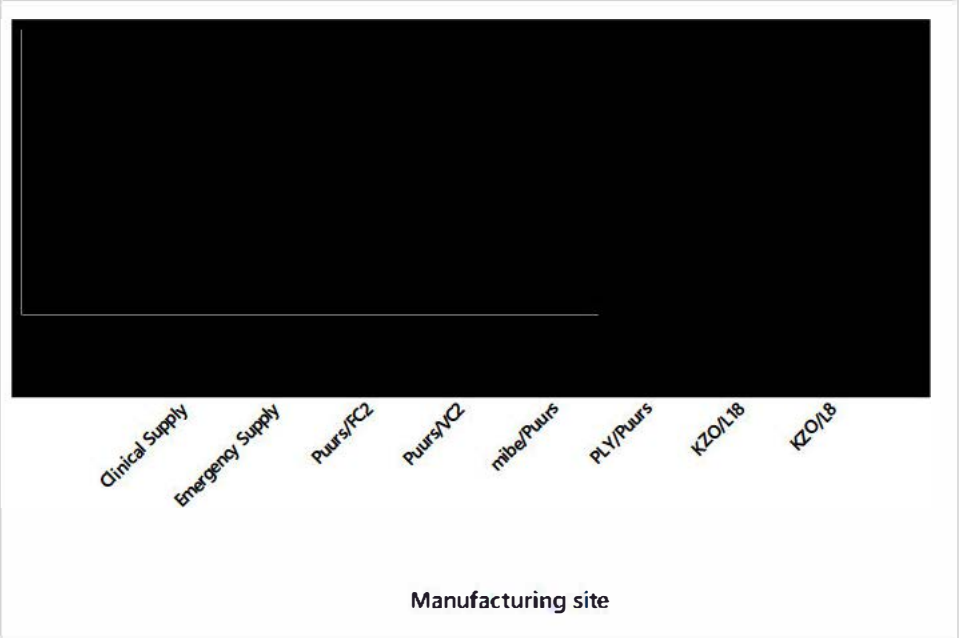

Figure 11. BNT162b2 Drug Product Comparability Release Results – DSPC Content

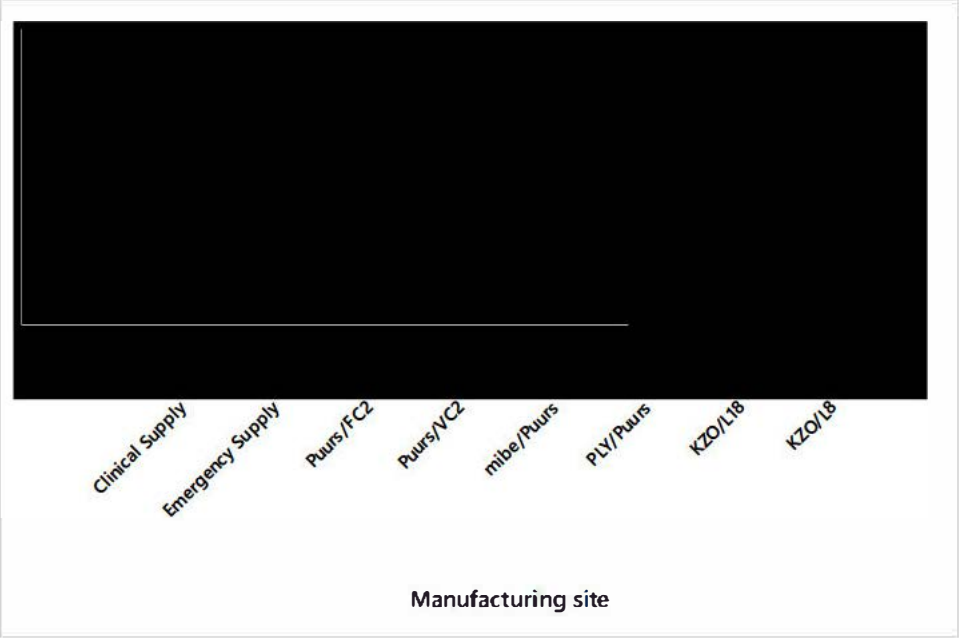

Figure 12. BNT162b2 Drug Product Comparability Release Results – Cholesterol Content

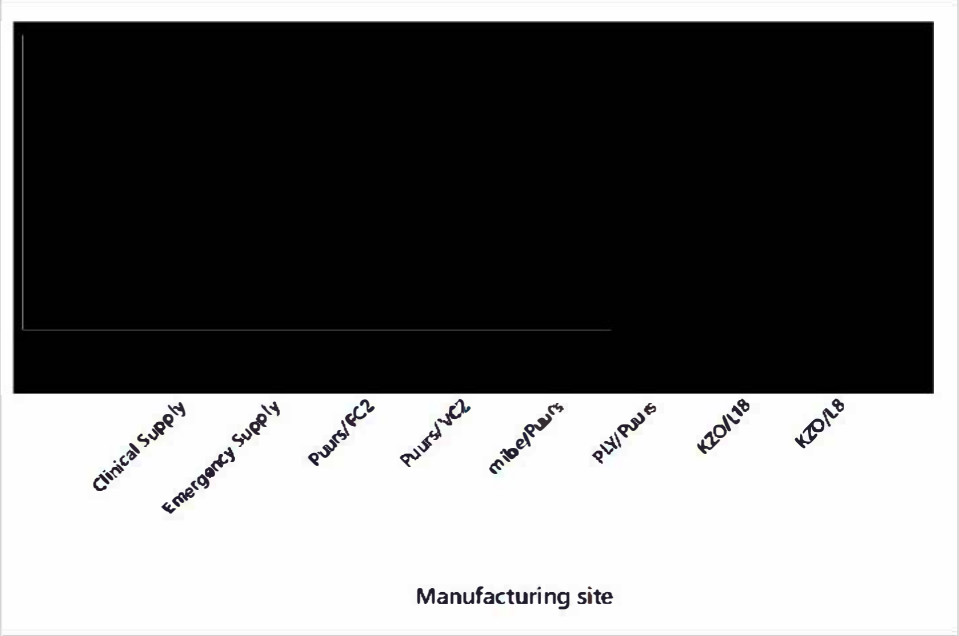

Figure 13. BNT162b2 Drug Product Comparability Release Results – In Vitro Expression

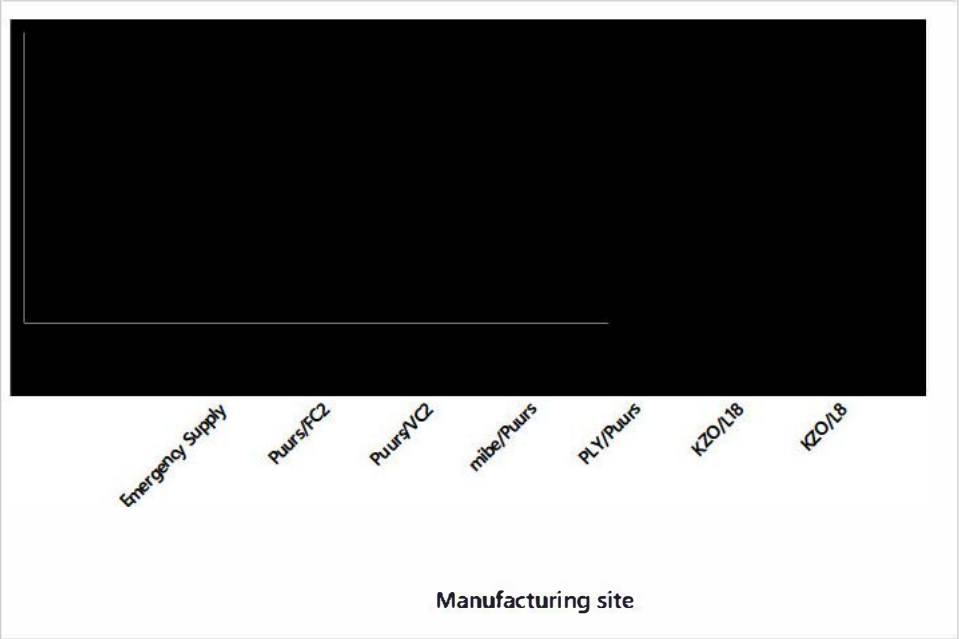

Figure 14. BNT162b2 Drug Product Comparability Release Results – RNA Integrity

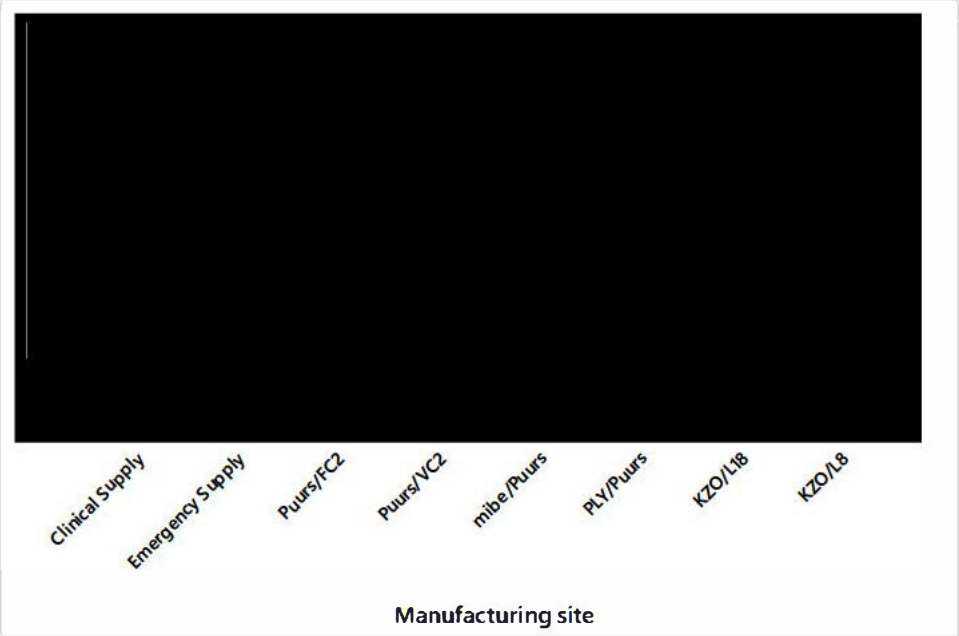

Figure 15. BNT162b2 Drug Product Comparability Release Results – 5'-Cap

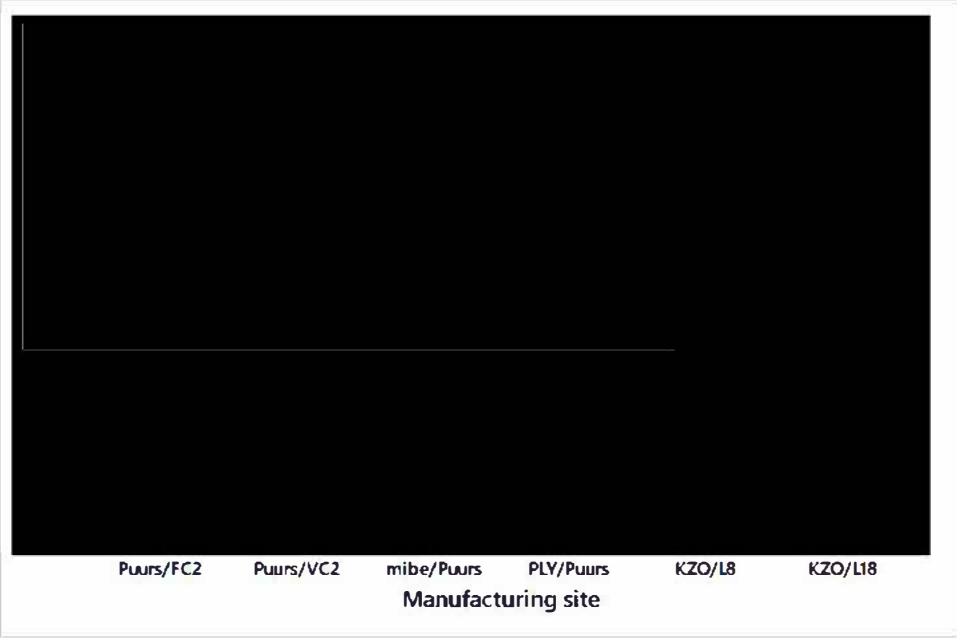

Figure 16. BNT162b2 Drug Product Comparability Release Results – Poly(A) Tail

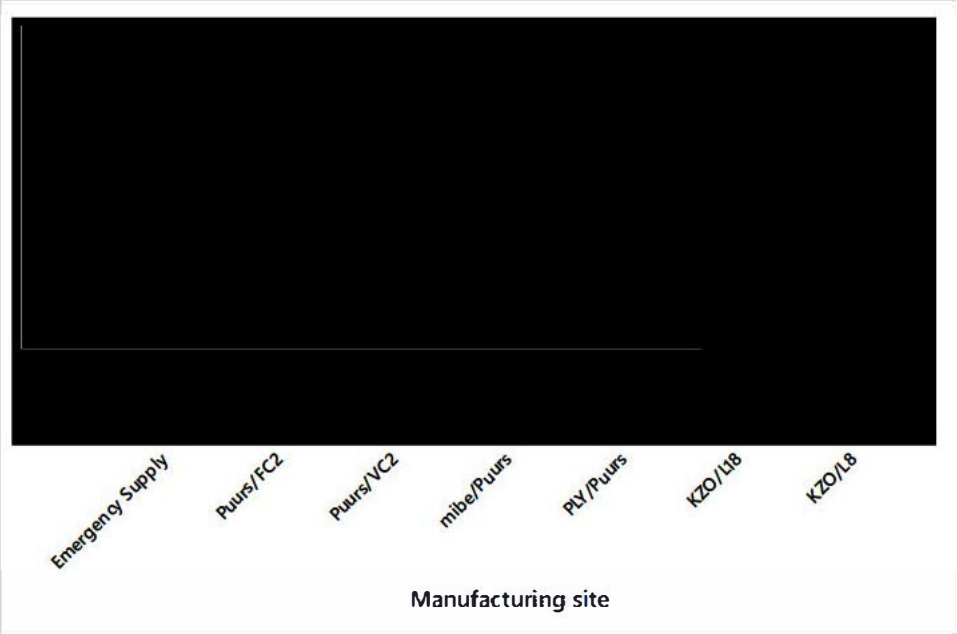

Figure 17. BNT162b2 Drug Product Comparability Release Results – Poly(A) Tail Length and Distribution

2.2. Additional [redacted] and Profiles to Support BNT162b2 Product Quality Comparability

[redacted]

Table 4. BNT162b2 DP Side-by-Side PPQ Comparability Assessment Strategy

DP Batch Number	DP Site of Manufacture	Sample Set 1	Sample Set 2	Sample Set 3	Sample Set 4	Sample Set 5
EE3813 / BCV40820-P[a]	Bulk DP: Polymun F&F: Puurs S2F2	X	X	X	X	X
EE8493[a]	Bulk DP: Polymun F&F: Puurs WSL5	X	X[b]	X	X	X
EL1491	Bulk DP: Puurs F&F: Puurs FC2	X				
EL8723			X			
EP2166				X		
EM6950	Bulk DP: Puurs F&F: Puurs VC2		X			
EL8713			X			
EP2163				X		
EP6775				X		
EK4242	Bulk DP: mibe F&F: Puurs WSL5	X				
EN1195					X	
EN1196					X	
EL7834	Bulk DP: Polymun F&F: Puurs WSL5	X				
EM4965					X	
ET0384						X
EL3248	Bulk DP: Kalamazoo F&F: Kalamazoo L8	X				
EL9267			X			
EN6198				X		
EN6200				X		
EL3249	Bulk DP: Kalamazoo F&F: Kalamazoo L18	X				
EL9266			X			
EN6199				X		

a. Comparator lots; also included in previous side-by-side comparability assessment
b. Lot EE8493 was omitted from 5'-cap and poly(A) tail length and distribution side-by-side testing

2.2.1. BNT162b2 Drug Product Surface [redacted]

[redacted] and any small differences within each sample set are within the variability of the method.

2.2.2. BNT162b2 Drug Product Size Distribution and Shape by [redacted]

[redacted]

Table 5. BNT162b2 DP Lot Surface Charge by [redacted]

Sample Set 1	Sample Set 2	Sample Set 3	Sample Set 4	Sample Set 5
Lot [redacted]	Lot [redacted]	Lot [redacted]	Lot [redacted]	Lot [redacted]
EE3813	EE3813	EE3813	EE3813	EE3813
EE8493	EE8493	EE8493	EE8493	EE8493
EL1491	EE8723	EP2166	EN1195	ET0384
EK4242	EM6950	EP2163	EN1196	
EL7834	EL8713	EP6775	EM4965	
EL3248	EL9267	EN6198		
EL3249	EL9266	EN6200		
		EN6199		

Table 6. BNT162b2 DP Lot Size Distribution and Shape by [redacted]

Sample Set 1	Sample Set 2	Sample Set 3	Sample Set 4	Sample Set 5
Lot [redacted]	Lot [redacted]	Lot [redacted]	Lot [redacted]	Lot [redacted]
EE3813	EE3813	EE3813	EE3813	EE3813
EE8493	EE8493	EE8493	EE8493	EE8493
EL1491	EE8723	EP2166	EN1195	ET0384
EK4242	EM6950	EP2163	EN1196	
EL7834	EL8713	EP6775	EM4965	
EL3248	EL9267	EN6198		
EL3249	EL9266	EN6200		
		EN6199		

2.2.3. BNT162b2 Drug Product Surface PEG Characterization by [redacted]

The drug product lots were subjected to 1D proton NMR analysis in 1x PBS pH 7.4, 10% D_2O. The spectra are shown in Figure 18 through Figure 22, and all the lots have visually superimposable spectra. Major peaks are labeled for assigned protons.

Figure 18. [redacted] Spectra for BNT162b2 Drug Product Lots – Sample Set 1

Figure 19. [redacted] Spectra for BNT162b2 Drug Product Lots – Sample Set 2

Figure 20. [redacted] Spectra for BNT162b2 Drug Product Lots – Sample Set 3

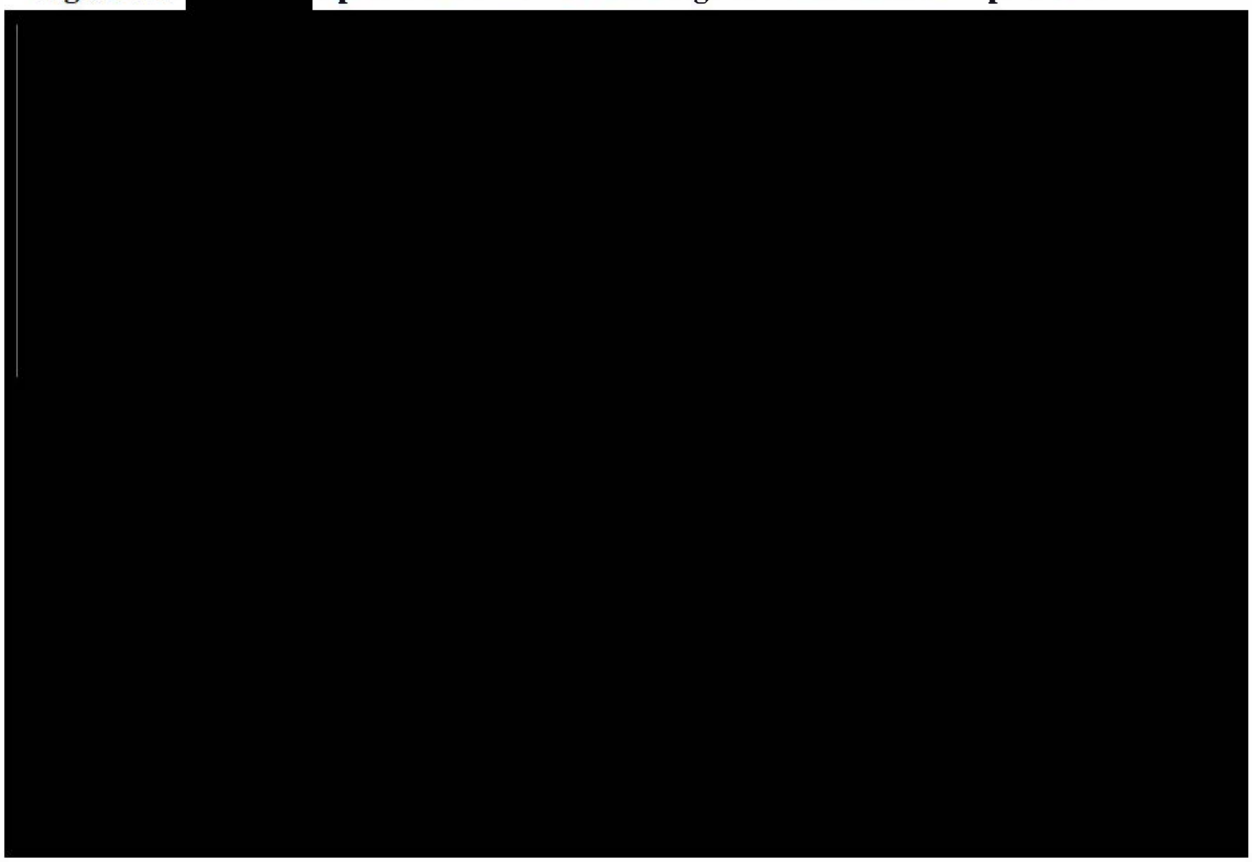

Figure 21. [redacted] Spectra for BNT162b2 Drug Product Lots – Sample Set 4

Figure 22. [redacted] Spectra for BNT162b2 Drug Product Lots – Sample Set 5

2.2.4. Comparative Analysis of BNT162b2 Drug Product 5'-Cap by RP-HPLC

Figure 23. 5'-Cap RP-HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 1

Figure 24. 5' Cap RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 2

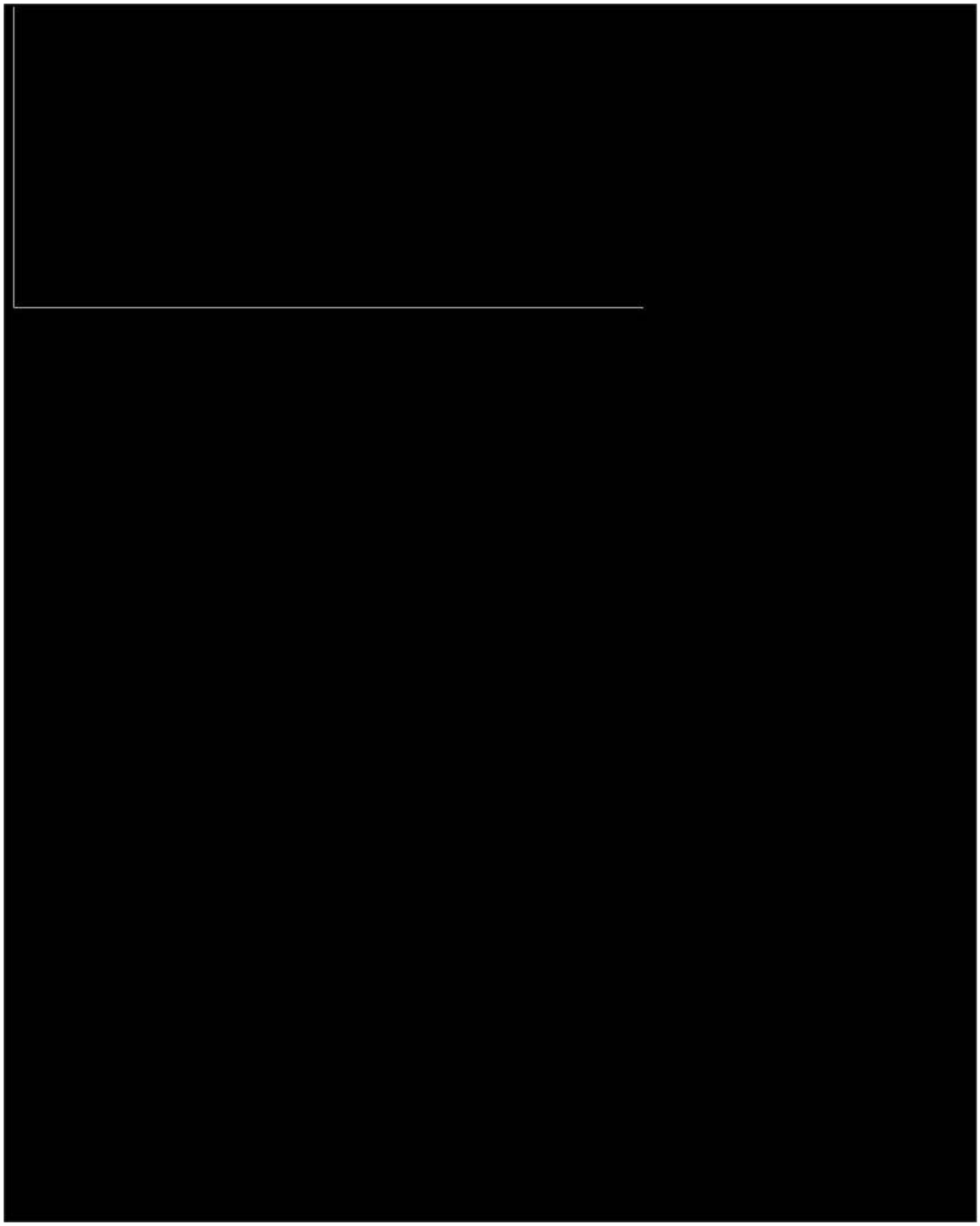

Figure 25. 5' Cap RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 3

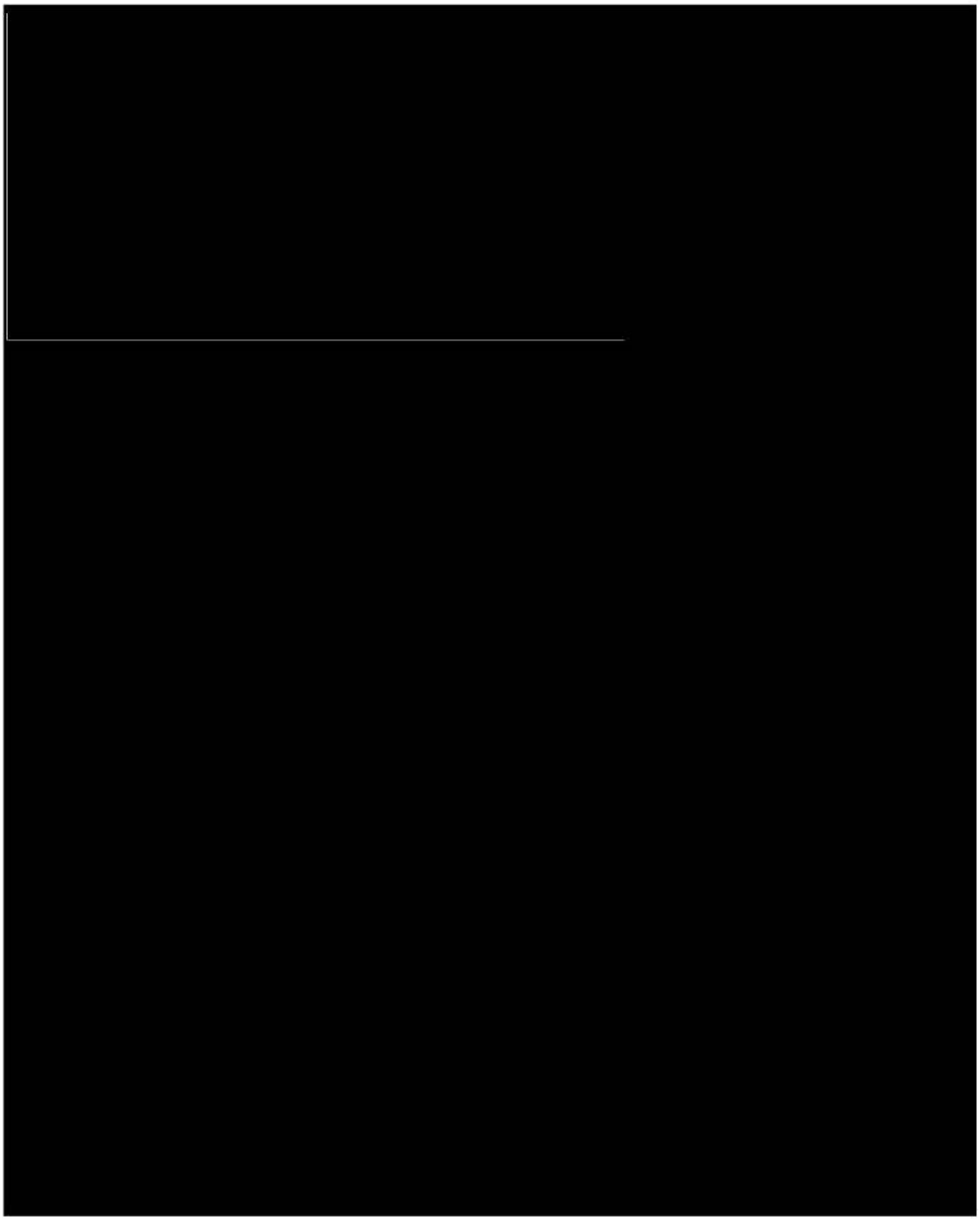

Figure 26. 5' Cap RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 4

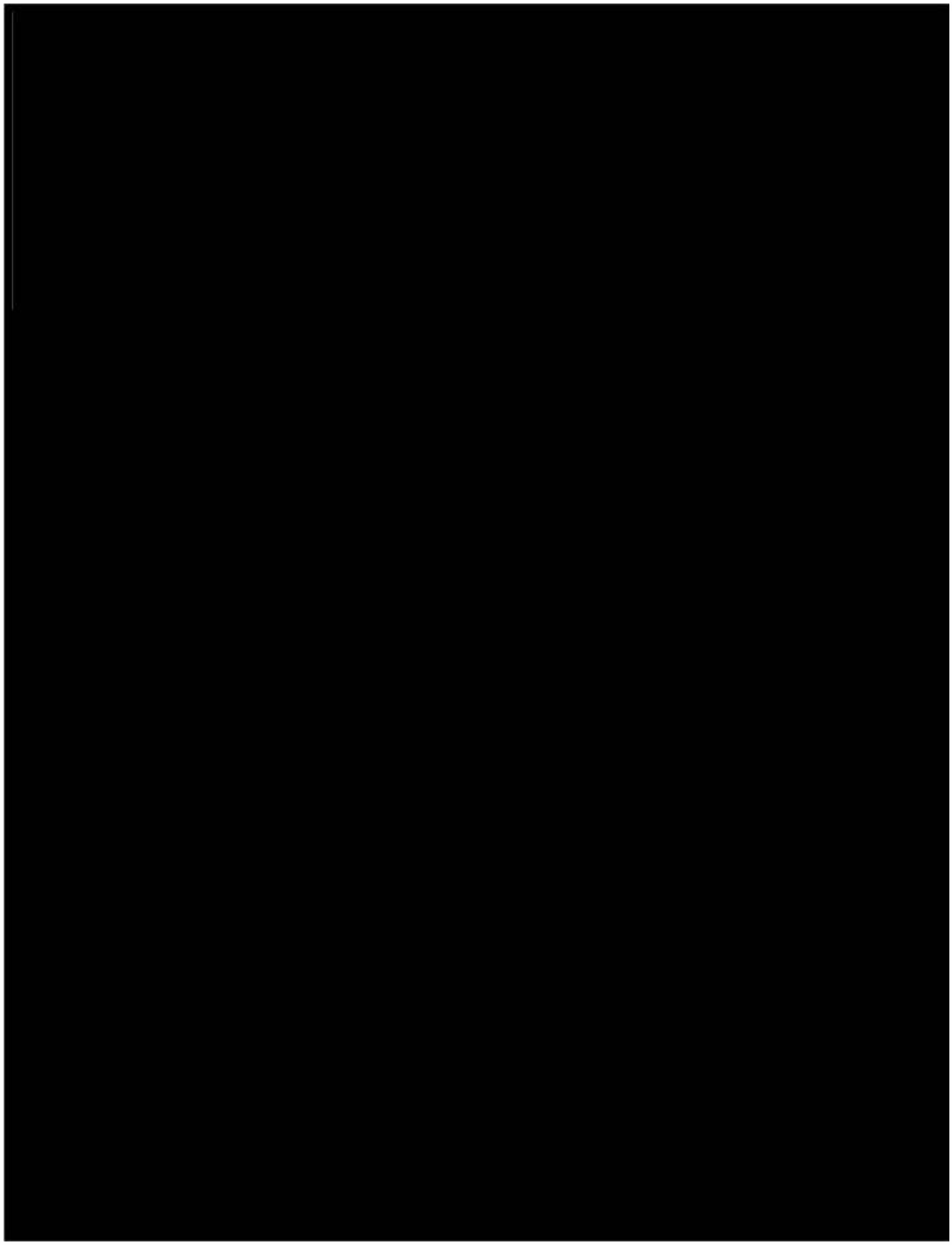

Figure 27. 5' Cap RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 5

2.2.5. Poly(A) Tail Length and Distribution by RP-HPLC

Figure 28. Poly(A) Tail RP-HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 1

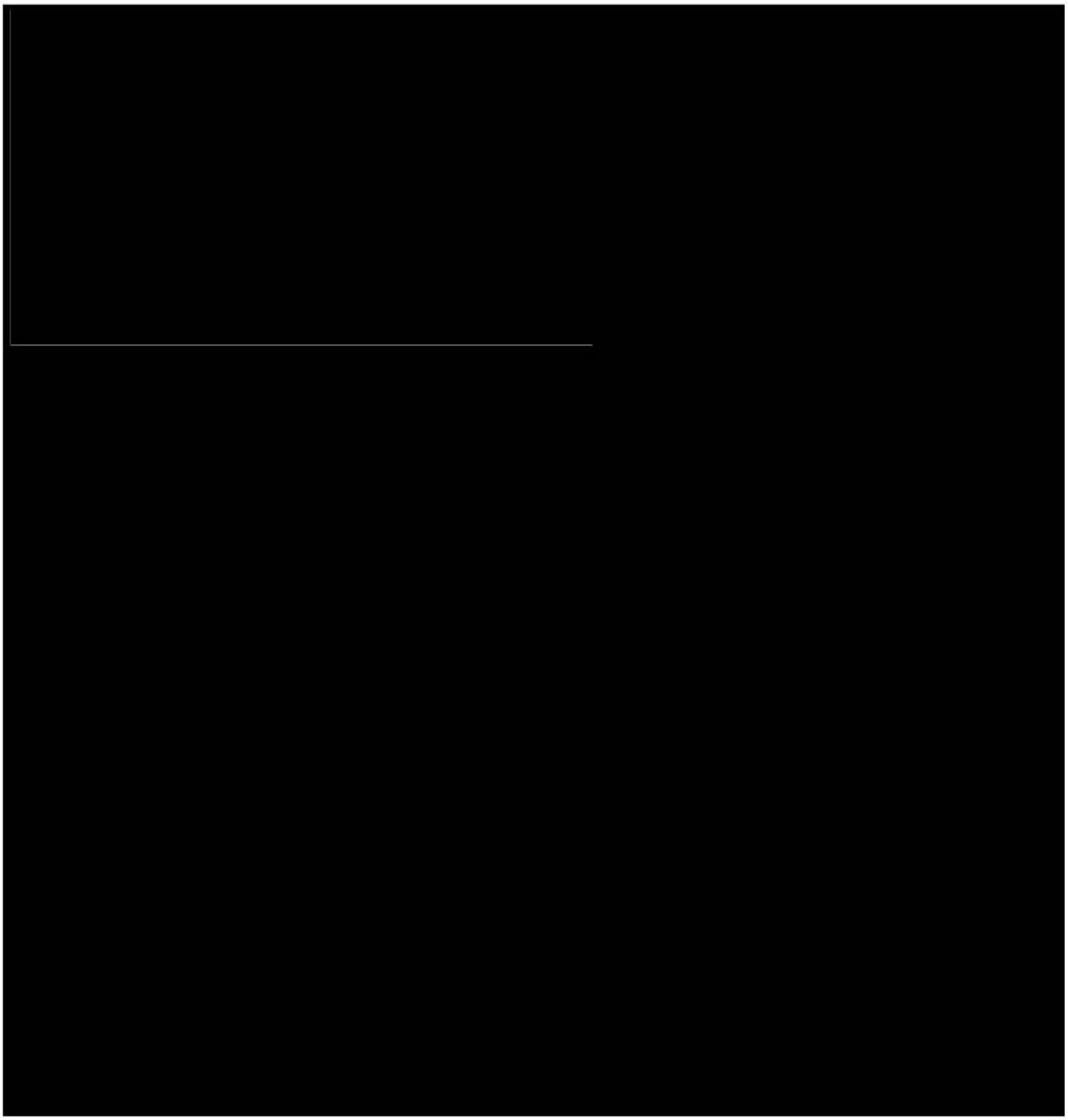

Figure 29. Poly(A) Tail RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 2

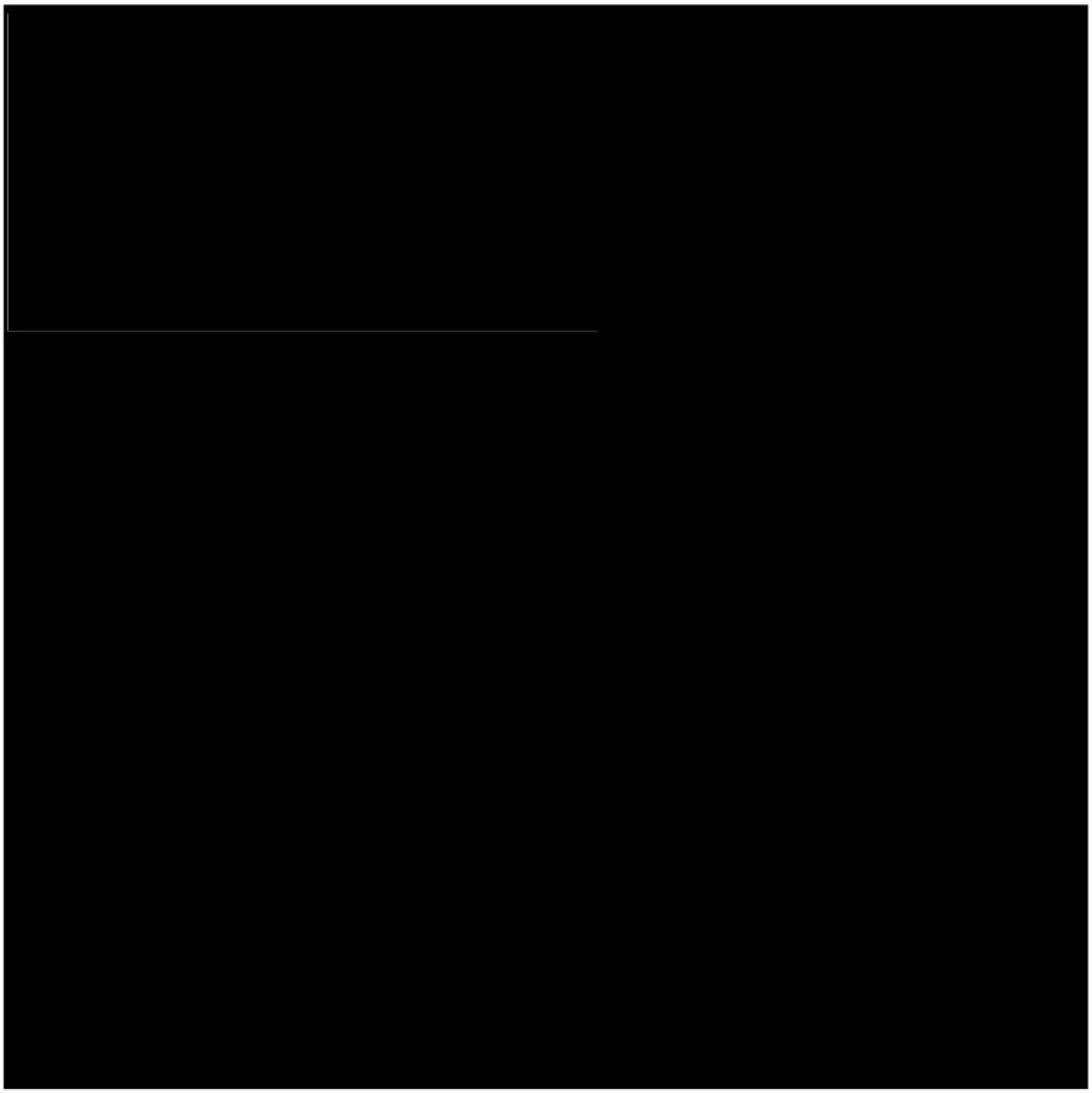

Figure 30. Poly(A) Tail RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 3

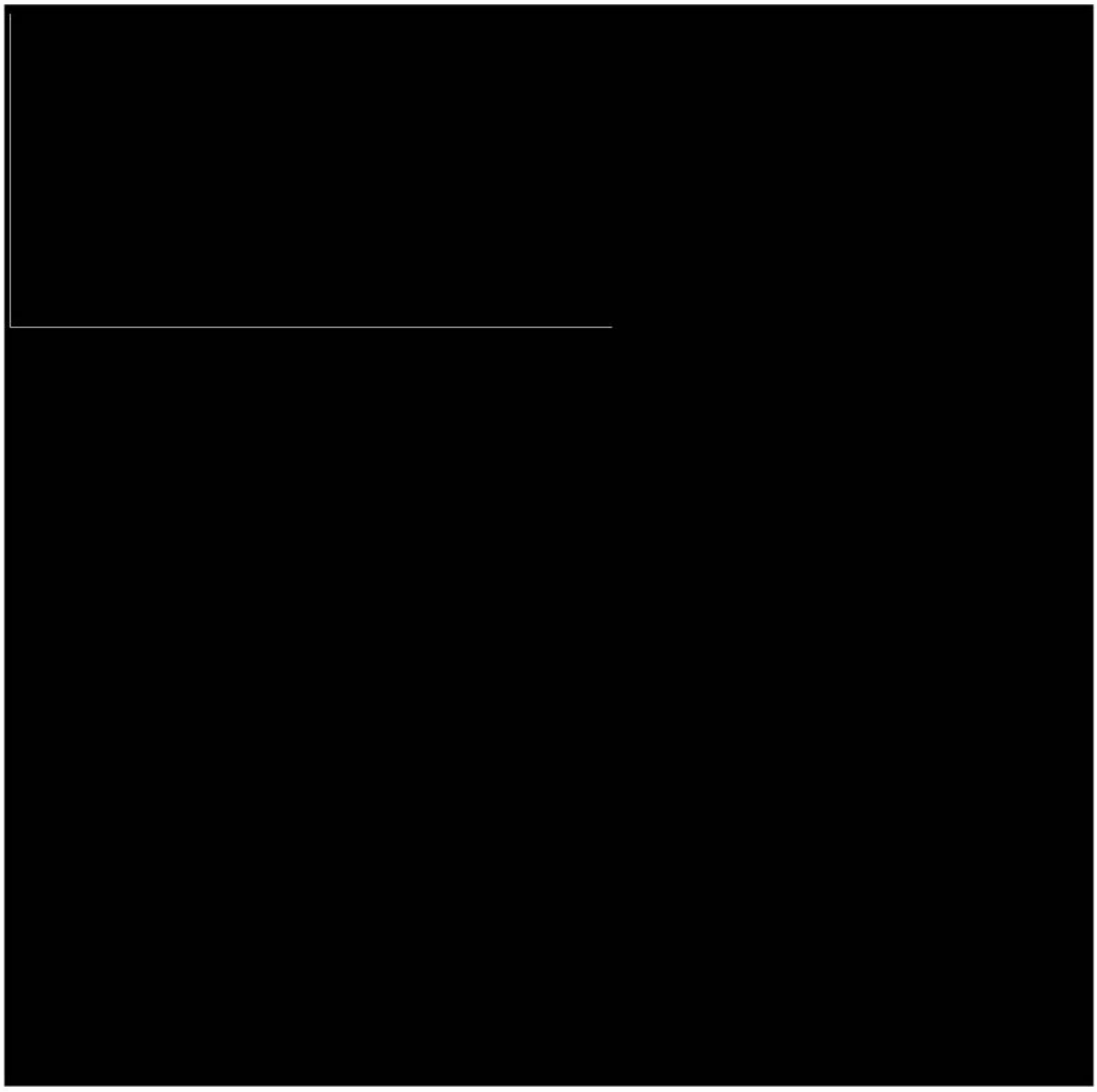

Figure 31. Poly(A) Tail RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 4

Figure 32. Poly(A) Tail RP HPLC Chromatograms for BNT162b2 Drug Product Lots – Sample Set 5

2.3. Overall Conclusions for Comparability

The comparability assessment presented here focused on an evaluation of the product quality in the Phase I and Phase II PPQ drug product lots, compared with clinical and emergency supply lots. Comparability of the "classical" and "upscale" LNP processes is additionally supported in the previous comparability assessment (MAA Section 3.2.P.2.3 Development History).

The BNT162b2 drug product analytical comparability evaluation employed release testing [redacted] methods to evaluate product quality in drug product lots factured using the commercial DP supply nodes (Bulk DP manufactured at Puurs, mibe, Polymun and Kalamazoo followed by fill and finish at Puurs and Kalamazoo). Release data and [redacted] demonstrate that the drug product lots evaluated in the current study are comparable, with only small differences that are not expected to impact product safety or efficacy. Further, the comparisons to clinical and emergency supply lot data demonstrate comparable product quality from clinical through commercial supply of BNT162b2. Taken together, the comparability demonstrated here

establishes the capability of the commercial manufacturing process to produce a consistent drug product across the proposed commercial manufacturing facilities.

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