Process Validation Report
For
Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size

AUTHOR:

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Product/Process:
Introduction of Covid-19 Vaccine in FC2/VC2 for 139 L batch size (Phase II)

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1 Introduction

1.1 Purpose

This document is a process validation report for process validation activities for Phase II for Covid-19 Vaccine (PF-07302048, BNT-162) drug product manufacturing processes in Vaccine Cell 2 (formulation), Focus Cell 2 and Vaccine Cell 2 (filling) and Logistics 2 (freezing) for 139 L batch size as described in the referenced Process Validation Plan (Ref. 10) and Validation Project Plan (Ref. 3).

The initial Phase I process validation of the Covid-19 Vaccine (PF-07302048, BNT-162) drug product formulation and fill/finish processes is covered by referenced Phase I Network Process Validation Plan (Ref. 1*).* The Phase I process validation plan includes one PV batch for all drug product (DP) supply nodes to support the 'Emergency Use Authorization' (EUA) application and conditional approval. The Phase I validation plan covered 2 site specific protocols, for Puurs this protocol is documented in 20043-COVID-PRP0-A1 (Ref. 2) and report in 20043-COVID-PRRC-A1 (Ref. 24).

The process validation plan (20043-10000-PVP0-A2) described the Phase II of the validation process of the manufacturing process of the Covid-19 Vaccine with filling in Focus Cell 2 and Vaccine Cell 2. Two different protocols were written. The first protocol covers the validation activities of the 139 L batch size (20043-10000-PRP1-A3, Ref. 15), the second protocol covers the validation activities of the 278 L batch size (20043-10000-PRP2-A1, Ref. 11).

In the conclusion of this report it is determined whether or not the process validation activities and all other studies per referenced protocol (Ref. 15) for process validation of Covid-19 Vaccine (PF-07302048, BNT-162) drug product manufacturing processes in Vaccine Cell 2 (formulation), Focus Cell 2 and Vaccine Cell 2 (filling) and Logistics 2 (freezing) for 139 L batch size are successful.

1.2 General description

The scope of the validation is defined in detail in the referenced Validation Project Plan (Ref. 3). An overview of the manufacturing process is shown in Figure 1. In Figure 2, the tanks used during formulation are shown.

The BNT162b2 drug product is prepared as a preservative-free, sterile, multi-dose concentrate of RNA-containing lipid nanoparticles (LNP) formulated in phosphate-buffered saline and 300 mM sucrose at pH 7.4 to be diluted for intramuscular administration. The drug product is filled at 0.45 mL/vial (0.5 mg/mL) into 2 mL glass vials which are stoppered and capped to provide total of 225 µg of the RNA in a multi-dose vial. At the administration site, the vaccine drug product is diluted with 0.9% sodium chloride and is intended to supply 5 to 6 doses per vial at 30 µg/dose.

The manufacturing process in scope of this validation protocol consists of following steps:

- Thawing of drug substance in the freeze-thaw area
- Weighing of raw materials in the Vaccine Cell 1 area
- Formulation in Vaccine Cell 2 – formulation booths 3 and 4 / Aseptic 1 – formulation booths
- Transport to the fill line

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- Filling of the product in Focus Cell 2 / Vaccine Cell 2
- Inspection of the product in Focus Cell 2 / Vaccine Cell 2
- Labeling and Packaging in Focus Cell 1 / Vaccine Cell 2
- Transport prior to freezing
- Freezing at Logistics 2
- Storage in freezers in Logistics 2

Step	Process Inputs	Process Step
1	[redacted]	
2		
3		
4		
5		
6		
7		
8		

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Step	Process Inputs	Process Step
9	[redacted]	
10		
11		

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Figure 2: Formulation flow.

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2 References

This process validation report is aligned with SOP-51080 and the therein-referenced quality standards.

The project is covered by the following change request gQTS PR#4953874 and PR#5409849 (Ref. 5 and 6) and Process Validation Plan (Ref. 10) and Validation Project Plan (Ref. 3).

Table 1. References

Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 1	VAL100130986	Process Validation Plan for Covid-19 Vaccine (PF-07302048, BNT-162) Drug Product – Phase I	19/11/2020	[redacted]	QA Archive	NA
Ref. 2	20043-COVID-PRP0-A1	Process Validation Protocol For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)	20/11/2020	[redacted]	QA Archive	NA
Ref. 3	20043-00000-VPP0-A1	Validation Project Plan for Introduction of COVID-19 Vaccine PF-07302048	14/08/2020	[redacted]	QA Archive	NA
Ref. 4	20043-00000-VPRB-A1	Validation Project Report for Introduction of COVID-19 Vaccine PF-07302048	11/12/2020	[redacted]	QA Archive	NA
Ref. 5	CRF PR4953874	Introduction of COVID-19 Vaccine PF-07302048	14/08/2020	[redacted]	gQTS	NA
Ref. 6	CRF PR5409849	Introduction of 278 L batch size of COVID-19 Vaccine PF-07302048	05/03/2021	[redacted]	gQTS	NA
Ref. 7	INX100426829	Process Definition Document for PF-07302048 BNT162b2 Vaccine (SARS-CoV-2 full spike protein S-P1 variant)	08/09/2020	[redacted]	GDMS	NA
Ref. 8	20043-12000-RRPA-A2	Process Review and Risk Assessment Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) into Vaccine cell and Focus Cell	11/12/2020	[redacted]	QA Archive	NA
Ref. 9	20043-COVAL-RAT0-A2	Rational for Concurrent Validation Approach for Covid-19 Vaccine	19/11/2020	[redacted]	QA archive	NA

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Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 10	20043-100000-PVP0A2	Process Validation Plan For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2	23/12/2020	[redacted]	QA Archive	NA
Ref. 11	20043-10000-PRP2-A1	Process Validation Protocol For Introduction of Covid-19 vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size	23/12/2020	[redacted]	QA archive	NA
Ref. 12	CRF PR#5415644	CRF Implementation of additional lipid suppliers for Covid vx bulk	08/12/2020	[redacted]	QTS	NA
Ref. 13	PR#5506629	VC2 – vials with incorrectly rolled caps found after inspection of batch EM6950	Opened on 23/12/2020	[redacted]	QTS	NA
Ref. 14	INX100438928	PF-07302048 Suspension for Injection Drug Product Cumulative Temperature Cycling Study: interim report for study #2 (eLN 00710368-0131)	05/01/2021	[redacted]	GDMS	NA
Ref. 15	20043-10000-PRP1-A3	Process Validation Protocol For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size	06/01/2021	[redacted]	QA Archive	NA
Ref. 16	20043-10000-PRR1-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size	20/01/2021	[redacted]	QA Archive	NA
Ref. 17	20043-10000-PRR2-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size – EM6950/ER0641	25/01/2021	[redacted]	QA Archive	NA

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Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 18	20043-10000-PRR3-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size – EN9090/EL8713	29/01/2021	[redacted]	QA Archive	NA
Ref. 19	FORM-26075 EL8723 (Gnosis object ID 0901201b87a0dbba)	FORM-26075 EL8723	21/01/2021	[redacted]	Gnosis	NA
Ref. 20	FORM-26075 EM6950 (Gnosis: (object ID 0901201b87933486)	FORM-26075 EM6950	27/01/2021	[redacted]	Gnosis	NA
Ref. 21	FORM-26075 EL8713 (Gnosis object ID 0901201b87a0e421)	FORM-26075 EL8713	29/01/2021	[redacted]	Gnosis	NA
Ref. 22	INX100436631	Memo: COVID-19 Vaccine Proposed Initial Network PPQ Drug Product Stability Protocol Plan	07/12/2020	[redacted]	GDMS	NA
Ref. 23	20043-10000-MPL0-A1	Continued Process Verification Plan For Introduction of Covid-19 Vaccine (PF-07302048) in FC2/VC2	12/01/2021	[redacted]	QA Archive	NA
Ref. 24	20043-COVID-PRRC-A2	Process Validation Report For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)	TBD	[redacted]	QA Archive	1
Ref. 25	PF-07302048:1-023	Stability protocol: PF-07302048:1-023	20/01/2021	[redacted]	LIMS ARD	NA
Ref. 26	PF-07302048:1-024	Stability protocol: PF-07302048:1-024	20/01/2021	[redacted]	LIMS ARD	NA
Ref. 27	PF-07302048:1-025	Stability protocol: PF-07302048:1-025	25/01/2021	[redacted]	LIMSARD	NA

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Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 28	20043-10000-PRRB-A2	Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size	TBD	[redacted]	QA Archive	1
Ref. 29	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*	15/01/2021	[redacted]	QA Archive	N/A

1. These documents will be approved together with this document.

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3 Results of the Process Validation activities

The following section reports the process validation activities that were required in alignment with the process validation approach and as defined in the Process Validation Protocol (*Ref. 15*).

3.1 Prerequisites check

3.1.1 Documents

The prerequisites to start Process Validation are covered in the referenced Validation Project Report (VPR) (*Ref. 4*). The document prerequisites listed in Table 2 below were ongoing and not closed yet when protocol was written.

Table 2. Prerequisites

Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
Equipment Verification/qualification	Y	Y	20043-51001-PQRA-A1: Performance Qualification Report phase 1 - Visual inspection machine Innoscan VC2	17/12/2020	[redacted]	QA Archive	NA
	Y	Y	20043-51002-PQP0-A1: Performance Qualification Protocol phase 2 - Visual inspection machine Innoscan and Vacuum based leak tester VC2	17/12/2020	[redacted]	QA Archive	NA
Filtration validation	Y	Y	5344432-FILCV-PQRA-A1: Filter validation report A (Sartorius)	23/12/2020	[redacted]	Gnosis	NA

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Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
Raw material qualifications	Y	Y	20027-30600-VPRB-A1: Process Materials Project Report	25/01/2021	[redacted]	Gnosis	NA
Extractables/leachables assessment of product contact materials (components)	Y	Y	20043-COVID-QRM-A2: QRM E&L assessment for product contact materials	15/01/2021		Gnosis	NA
Master batch records	Y	Y	F000051208 & F000048567 (CL200626): EBR for filling/inspection/packaging/freezing VC2	18/12/2020		EBR	Packaging VC2 was not in scope yet
Other	Y	Y	SOP-113055/FORM-105821: New batch record review FORM/SOP VC2 – Addition VC2 packaging	20/11/2020		PDOCS	NA
	Y	Y	Update of LAL-20-018 v5.0	08/01/2021		LMIC	NA

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3.1.2 Training

Operators are trained for general production Standard Operating Procedures (SOP). Additional testing and sampling activities was performed as instructed in the batch record attachments which were trained to the involved operators by the responsible department. This training was signed off in the batch record attachments as 'read and understood'. A product support representative was present to support qualified personnel with sampling and testing instructions during the production process of the process validation batches.

3.1.3 Release status of the materials

The table below provides an overview of the raw materials and components that were used for these process validation batches and their release status.

Table 3. Raw material and component overview

Raw materials			
Description	**Material number**	**Specification number**	**Status**
LIPID ALC-0315	R000011933	SPEC-43234 v2.0	Released / waived for production[1]
LIPID ALC-0315 G	R000012511	NA[2]	Released / waived for production[1]
LIPID ALC-0159	R000011760	SPEC-43237 v2.0	Released / waived for production[1]
LIPID DSPC	R000011932	SPEC-43236 v2.0	Released / waived for production[1]
LIPID CHOLESTEROL	R000011931 R000012184[3]	SPEC-43235 v1.0 SPEC-44155 v2.0	Released / waived for production[1]
PF-07305885 Drug Substance BNT	H0●●●22798	SPEC-43238 v1.0	Released / waived for production[1]
PF-07305885 Drug Substance	H0●●●22908	CLM#271597 v4.0[4]	Released / waived for production[1]
CITRIC ACID MONOHYDRATE	R000007711	SPEC-28814 v5.0	Released
SODIUM CITRATE GRANULAR	R00000●595	SPEC-8686 v7.0	Released
SODIUM CHLORIDE	R00000●594 or R00000●590	SPEC-8685 v5.0	Released
Potassium Chloride	R000011784	SPEC-43217 v1.0	Released / waived for production[1]
Disodium hydrogen phosphate dihydrate	R000006513	SPEC-27162 v1.0	Released
Potassium phosphate monobasic	R000006514	SPEC-27163 v3.0	Released
Sucrose (low in endotoxin), excipient grade	R000006469	SPEC-27310 v1.0	Released

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Sodium Hydroxide	R000000596 or R000000597	SPEC-8687 v6.0	Released
Sodium Hydroxide	R000011790	SPEC-43212 v1.0	Released
Hydrochloric acid[5]	R000000520	SPEC-8668 v4.0	Released
Ethanol	R000011789	SPEC-43233 v1.0	Released / waived for production[1]
Components			
Description	**Material number**	**Specification number**	**Status**
GC-VIAL 2ML BLOW BACK SCHOTT	PAA147946 (FC2)	SPEC-18047 v13.0	Released
GC-VIAL 2ML BLOW BACK SCHOTT MATCHBOX	PAA148986 (VC2)	SPEC-19936 v4.0	Released
RUB-STOP 13MM BB FM457/0 GREY	PPUSF0474	SPEC-8816 v11.0	Released
RUB-STOP 13MM BB FM457/0 GREY NEW	PAA159467	SPEC-8816 v11.0	Released
CAP-13MM PURPLE	PAA074463	SPEC-8812 v9.0	Released

[1] New raw materials: method verification is ongoing. Raw materials will be approved for use for DP production at risk while still performing release testing, and will be dispositioned before DP disposition. (PTC PR#5235501)
[2] For Groton lipid, no SPEC-document is required, since specifications are covered in the quality agreement between Pfizer Puurs, Pfizer Kalamazoo and Pfizer Groton for ALC-0315, which is approved and effective, see Ref. 8.
[3] PTC PR#5410905: supplier qualification is ongoing. Actions covered in CRF PR#5415644.
[4]According to SOP-51014, no SPEC-document required for other Pfizer-sites since specifications are covered in quality agreement (QAA-20-0068 Version 01)).
[5]HCl is only used optionally for adjustment of pH in citrate buffer.

3.1.4 Blocking mechanism for validation batches

Proof for blocking of the validation batches and item numbers can be found in Gnosis (Ref. 19-21). Blocking of the item numbers was not required as a concurrent validation approach is used as justified in Ref. 9.

3.2 Process Validation Approach

3.2.1 CQAs, CPPs, IPCs and operating ranges

A list of relevant Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), In process controls (IPCs) and their operating ranges as determined in the referenced Review Report and Risk Assessment Report (Ref. 8) can be found in Attachment 2. (Protocol deviation N°01)

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3.2.2 Process Validation bracket and strategy

Process validation was performed using a concurrent validation approach (Ref. 9). This section provides a general overview of the Phase II validation filling on FC2 and VC2. Details on all testing activities can be found in sections 3.3 and 3.4 below.
In Table 4, the bracketing strategy to support the Phase II validation filling on FC2 and VC2 as described in the validation plan (Ref. 10) is shown. PV-batch 1 was included in Phase I validation (Ref. 2). PV-batches 2 to 4 are covered in this report. In Table 5, an overview of the validation batches 2-4 is shown.

Table 4: PV strategy justification to support EU and US submissions

PV batch	PV1[1]	PV 2	PV 3	PV 4	PV 5	PV 6	PV 7	Remarks/ justification
[redacted]								

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PV batch	PV1[1]	PV 2	PV 3	PV 4	PV 5	PV 6	PV 7	Remarks/ justification
[redacted]								

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PV batch	PV1[1]	PV 2	PV 3	PV 4	PV 5	PV 6	PV 7	Remarks/ justification
[redacted]								

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PV batch	PV1[1]	PV 2	PV 3	PV 4	PV 5	PV 6	PV 7	Remarks/ justification
[redacted]								

[1]PV 1 was performed in Phase I validation (Ref. 1, 2 and 24).

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Table 5. Overview of PV batches.

PV Batch	Material code	Description	Batch number	Bulk / F	Lot size (theoretical)	Formulation booth / Filling line	Inspection line	Freezing
[redacted]								

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[1] Due to deviation PR#5506629 (VC2 – vials with incorrectly rolled caps found after inspection of batch EM6950) part of the batch was split off for reinspection. This reinspected part will be released as batch ER0641.
[2] Inspection was performed on FC2 instead of VC2 as described in Protocol deviation N°02 and Batch deviation N°10. In PR#5700247 was described that incorrect inspection line was described in interim reports.
[3] PTC PR#5500216 was started to use a Sartorius sterile filter instead of a Pall sterile filter to follow the validation plan (Ref. 10). In PR#5700247 was described that incorrect filter was described in interim reports.

3.2.3 Stability studies

Stability samples were taken for all PV batches at end of filling (19 tray boxes). The stability strategy is written in a memo (Ref. 22 and 25-27)

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3.3 Process testing results

Each validation lot was manufactured according to the approved master batch record (MBR), which is a combination of the approved electronic batch record (EBR) and BRAs. The batch record contains all operating parameters and instructions for sampling and testing.

3.3.1 Formulation

3.3.1.1 Microbial load during formulation

Testing activity	An overview of the microbial hold times that were challenged/targeted is given in Table 6.
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance / evaluation criteria detailed in Table 7.
Conclusion	*PASS*

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Table 6: Overview of microbial hold times:

Hold time	*Process Step*	*Hold time*	*PV2 (hh:mm)*	*PV3 (Challenge)[1] (hh:mm)*	*PV4 (hh:mm)*	*Comments*
[redacted]						

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[redacted]

1 During the challenge, the hold times were exceeded to validate the targeted hold times.

[2] In PR#5571170, small temperature excursions are described. The temperature of the product was evaluated for monitoring purposes only in addition to the controlled room temperature. There was concluded that there is no impact on the quality of the product.

[3] In PR#5588244, small temperature excursions are described. The temperature of the product was evaluated for monitoring purposes only in addition to the controlled room temperature. There was concluded that there is no impact on the quality of the product.

[4] In interim reports, incorrect hold times were documented. This is described in PR#5700247.

Discussion of results:

Bioburden

Results of bioburden for beginning and end were compared to their draft monitoring limits and listed in Table 8. All results were within specifications.

Appropriate sampling location for bioburden samples was evaluated according to SOP-86254 v2.0 in Attachment 1 of the Continued Verification Plan (CPV) (Ref. 23). In this document was defined that bioburden samples will be taken at begin position, except for T10 (sucrose) and T8. This will further be evaluated during CPV. Furthermore, the internal limits for bioburden samples will be determined during CPV.

Hold times

Challenges were performed during PV3, as described in Table 6. [redacted]

During phase I and phase II validation, challenge of hold times were performed. In Table 7, an overview of the challenged times is shown. [redacted]

Table 7: Overview of challenged validation batches.

Hold time	PV1 (Phase I (Ref. 24)) (hh:mm)[2]	PV3 (Phase II, 139 L) (hh:mm)	PV6 (Phase II, 278L (Ref. 28)) (hh:mm)	Proposed hold time
[redacted]				

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[1] A temperature adjustment to 2-25°C will be proposed since the DS is hold at 2-8 °C after thawing and during dilution, the temperature will not always be increased to 15 °C (PR#5719477).
[2] During Phase I, not all microbial hold times were challenged and different hold time was challenged for sucrose solution.
[3] In interim reports, incorrect hold times were documented. This is described in PR#5700247.

Endotoxins
Results of endotoxins are listed in Table 8 and were all within specifications.

Conclusion
Bioburden and endotoxin results were within the limits mentioned in protocol. Evaluation of the sample location and draft limits will be performed during CPV.

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Table 8: Summary of microbial load testing and results of the formulation process

Process step	Sampling location	Sample qty	Lab method	UOM	Acceptance / Evaluation criteria	Limit type	PV2	PV3	PV4	Conclusion (PASS/FAIL)
Drug substance after hold (PV2 and PV3)	Drug substance bag after hold	10 mL	Bioburden – 200528-0099-001	CFU/10 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Drug substance bag after hold	0.5 mL	Endotoxins – TM-072-030	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
Citrate buffer T2	Vessel – Start hold time	2 x 100 mL	Bioburden - LAB 11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Vessel – Start hold time	10 mL	Endotoxins – LAB37351	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
Citrate buffer T3	Vessel – Start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Outlet – after	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS

	complete hold time									
	Vessel – start hold time	10 mL	Endotoxins – LAB37351	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
PBS Buffer T6	Vessel – start hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Outlet – after complete hold time (PBS bag)	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Vessel – start hold time	10 mL	Endotoxins – LAB37353	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
Sucrose solution in T10	Vessel – start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS

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	Vessel – start hold time	10 mL	Endotoxins – LAB37354	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
Bulk in T7	Vessel – end TFF	2 x 20 mL	Bioburden - LAB12943	CFU/20 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Vessel – after complete hold time	2 x 20 mL	Bioburden - LAB12943	CFU/20 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Vessel – end TFF	10 mL	Endotoxins – LAB37451[3]	EU/mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
Bulk in T8 prior to sterile filtration	Vessel – end of BBR filtration (before dilution)	2 x 20 mL	Bioburden - LAB12943	CFU/100 mL	[redacted]	Monitoring limit[1]	[redacted]	[redacted]	[redacted]	PASS
	Vessel - end of total hold (end of sterile filtration)	2 x 100 mL	Bioburden - LAB12943	CFU/100 mL	[redacted]	Acceptance criterion	[redacted]	[redacted]	[redacted]	PASS
	Vessel – end of BBR filtration	10 mL	Endotoxins – LAB37451[3]	EU/mL	[redacted]	Acceptance criterion	[redacted]	[redacted]	[redacted]	PASS

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	(before dilution)									
	Vessel – end of BBR filtration (after dilution)	2 x 5 mL	Endotoxins – LAB36816	EU/mL	[redacted]	Acceptance criterion	[redacted]	[redacted]	[redacted]	PASS

[1] Draft limits are used during PV-batches. During Continued Process Verification (CPV, Ref. 23), limits will be determined using historical data according to SOP-86254 v2.0.

[2] Based on experience of the process, a draft monitoring limit of [redacted] is used. During CPV (Ref. 23), limits will be determined using historical data.

[3] See Protocol deviation N°04: different methods were used as described in protocol

[4] In interim report, the results were not separated in TYMC and TAMC results (PR#5700247).

[5] In interim report, incorrect result was documented (PR#5700247).

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3.3.1.2 DS thawing

Testing activity	Thawing time of the drug substance (BioNTech/ACMF – Controlled room temperature thaw) [redacted] the drug substance.
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:
Controlled room temperature thaw of drug substance (DS) was performed. Visual check was assessed after 24 hours and every 4 hours. In Table 9, an overview of thawing time for PV3 and 4 is shown. After these thawing times, all DS bags were thawed. The target thaw is currently set at [redacted] This will be further assessed during CPV (Ref. 23). Downstream testing and sampling is evaluation in Section 3.3.1.9 and 3.3.2.5. All results are within specifications.

Table 9: Thawing time of DS

Batch	*DS*	*Start of thawing*	*Complete thawing*	*Thawing time (hh:min)*
PV3	*ACMF*	[redacted]		[1]
PV4	*BNT*			

[1] In PR#5700247 was described that incorrect thawing time was calculated in BRA.

Conclusion:
The DS was completely thawed prior to start hold time of the thawed DS.

3.3.1.3 Confirmation mixing parameters T2 and T3 (citrate buffer) and T6 (PBS buffer)

Testing activity: Confirm that the mixing of the citrate and PBS buffer comply with the specific mixing speed and time (dependent on which vessel is used) after dilution with WFI.

Tank	*Mixing Speed*	*Mixing Time*
T2	[redacted]	[redacted]
T3		
T6		

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Data collection & evaluation method	[redacted] *Evaluation:* - Results for osmolality and pH measurement were compared towards the acceptance criteria. - The results for the different batches were tabulated in the final report and inter batch consistency was evaluated.
Acceptance/evaluation criteria	All test results meet the acceptance criteria detailed in Table 10.
Conclusion	*PASS*

Discussion of results:

The results of osmolality and pH are shown in Table 10. All results are within specifications. Therefore, the mixing parameters as described above are confirmed. Furthermore, inter batch consistency was evaluated. This was performed by visual evaluation based on Figure 3. No practical differences were observed.

Table 10: pH and osmolality results.

	Limit	PV2	PV3	PV4
T2 citrate buffer				
Osmolality	[redacted]	[redacted]	[redacted]	[redacted]
pH	[redacted]	[redacted]	[redacted]	[redacted]
T3 citrate buffer				
Osmolality	[redacted]	[redacted]	[redacted]	[redacted]
pH	[redacted]	[redacted]	[redacted]	[redacted]
PBS buffer				
Osmolality	[redacted]	[redacted]	[redacted]	[redacted]
pH	[redacted]	[redacted]	[redacted]	[redacted]

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Figure 3: Time series plots of pH and osmolality after mixing.

Conclusion:
The mixing parameters for citrate buffer (T2/T3), PBS buffer (T6) and sucrose solution (T10) were confirmed.

3.3.1.4 Confirmation DS dilution (T4)

Testing activity	
Data collection & evaluation method	Evaluation: - Results were compared towards the acceptance criteria.
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 11.
Conclusion	*PASS*

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Discussion of results:
The results of osmolality and pH are shown in Table 11. All results are within specifications. Therefore, the mixing parameters as described above are confirmed.

Table 11: [redacted] result in T4.

[redacted]	Limit	PV2	PV3	PV4
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conclusion:
The mixing parameters for DS dilution in T4 were confirmed.

3.3.1.5 Evaluation of LNP formation

Testing activity	[redacted]
Data collection & evaluation method	[redacted] Evaluation: The impacted CQAs should be conform to their specifications (Table 11).
Acceptance/evaluation criteria	The final results for the impacted CQAs should meet the acceptance criteria detailed in Table 12.
Conclusion	*PASS*

Discussion of results:
The LNP formation is evaluated based on downstream results of impacted CQAs described above. The final bulk and release results of the impacted CQAs are listed in Table 12. All results are within specification. Therefore, LNP formation can be considered successful.

Table 12: Impacted CQAs by LNP.

		PV2		PV3		PV4	
	Limit	Bulk	Release	Bulk	Release	Bulk	Release
LNP size (nm)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LNP polydispersity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RNA encapsulation (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RNA content (mg/ml)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALC-0315 content (mg/ml)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ALC-0159 content (mg/ml)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

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DSPC content (mg/ml)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cholesterol content (mg/ml)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
RNA-Integrity (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
In vitro expression (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Conclusion:
All results of impacted CQAs by LNP process are within specification. Therefore, LNP formation can be considered as successful.

3.3.1.6 Confirmation of TFF parameters

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	The results should meet the acceptance criteria detailed in Table 14.
Conclusion	*PASS*

Discussion of results:
Results of the samples from the [redacted] at different time points during [redacted] ep for pH are listed in Table 13.Results of the samples from the [redacted] at different timepoints during the [redacted] step for pH are listed in Table 13.

Table 13: Overview of [redacted] pH during TFF.

	PV2	PV3	PV4
[redacted]	[redacted]	[redacted]	[redacted]

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[redacted]

[redacted] All results were within specification.

Table 14: Ribogreen final bulk.

	Limit	PV2	PV3	PV4
RNA encapsulation (%)	[redacted]			
RNA content (mg/ml)				

Conclusion:
All Ribogreen results are within specification. Therefore, the TFF process can be considered as successful.

3.3.1.7 In process testing prior to final dilution

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 15.
Conclusion	*PASS*

Discussion of results:

[redacted]

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[redacted] Therefore, the dilution based on the [redacted] can be considered as successful and will be used in future manufacturing of batches.

Table 15: Results for [redacted]

	Limit	PV2	PV3	PV4
[redacted]				

[redacted]

Conclusion:
Dilution of bulk in [redacted] calculation was successfully validated.

3.3.1.8 Confirmation mixing parameters T10 (sucrose)

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 16.
Conclusion	*PASS*

Discussion of results:

[redacted]

Figure 4. No practical differences were observed.

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Table 16: Osmolality results in T10.

	Limit	PV2	PV3	PV4
Osmolality	[redacted]			

[redacted]

Figure 4: [redacted]

Conclusion:
All osmolality results are within specification. Therefore, the mixing parameters of T10 as described above are confirmed.

3.3.1.9 Confirmation mixing parameters in T8

Testing activity	[redacted]

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Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 17.
Conclusion	*PASS*

Discussion of results:

Results of DLS, Ribogreen and lipid content of final bulk were within specification. All results are shown in Table 17. Mixing parameters described above were therefore conform. Furthermore, pH and osmolality data were collected to enhance process knowledge. Also there results were within specification. Furthermore, inter-batch consistency was evaluated visually based on Figure 5 and 6. [redacted]

Table 17: Overview of impacted CQAs of T8.

	Limit	PV2	PV3	PV4
LNP size (nm)	[redacted]			
LNP polydispersity				
LNP size (nm) (ARD)				
LNP polydispersity (ARD)				
RNA content (mg/ml)				
% encapsulation				
pH				

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Osmolality (mOsmol/kg)	[redacted]
ALC-0315 content (mg/ml)	
ALC-0159 content (mg/ml)	
DSPC content (mg/ml)	
Cholesterol content (mg/ml)	
RNA-integrity (%)	

Conclusion:
The mixing parameters of final bulk (T8) were confirmed.

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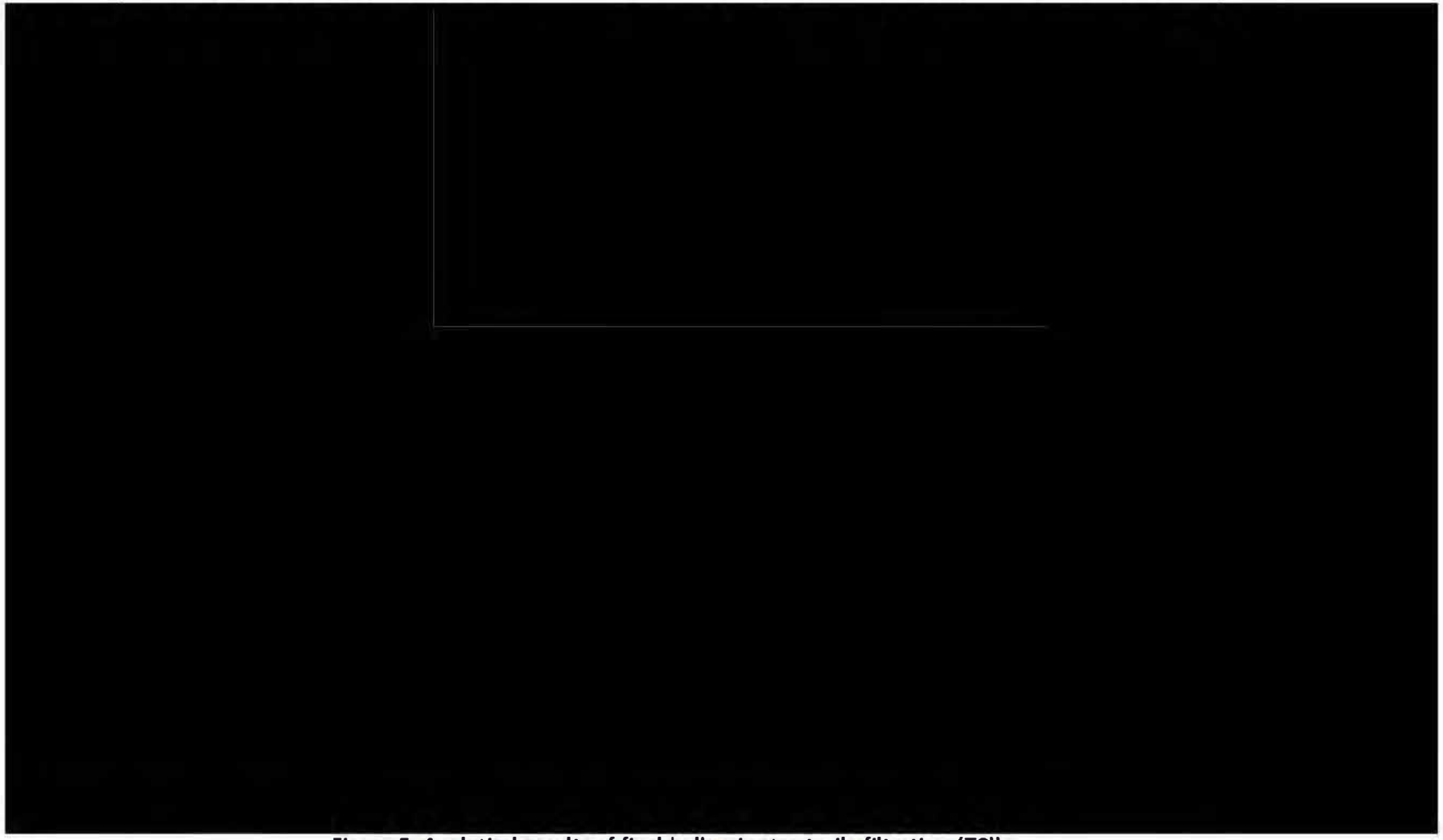

Figure 5: Analytical results of final bulk prior to sterile filtration (T8)).

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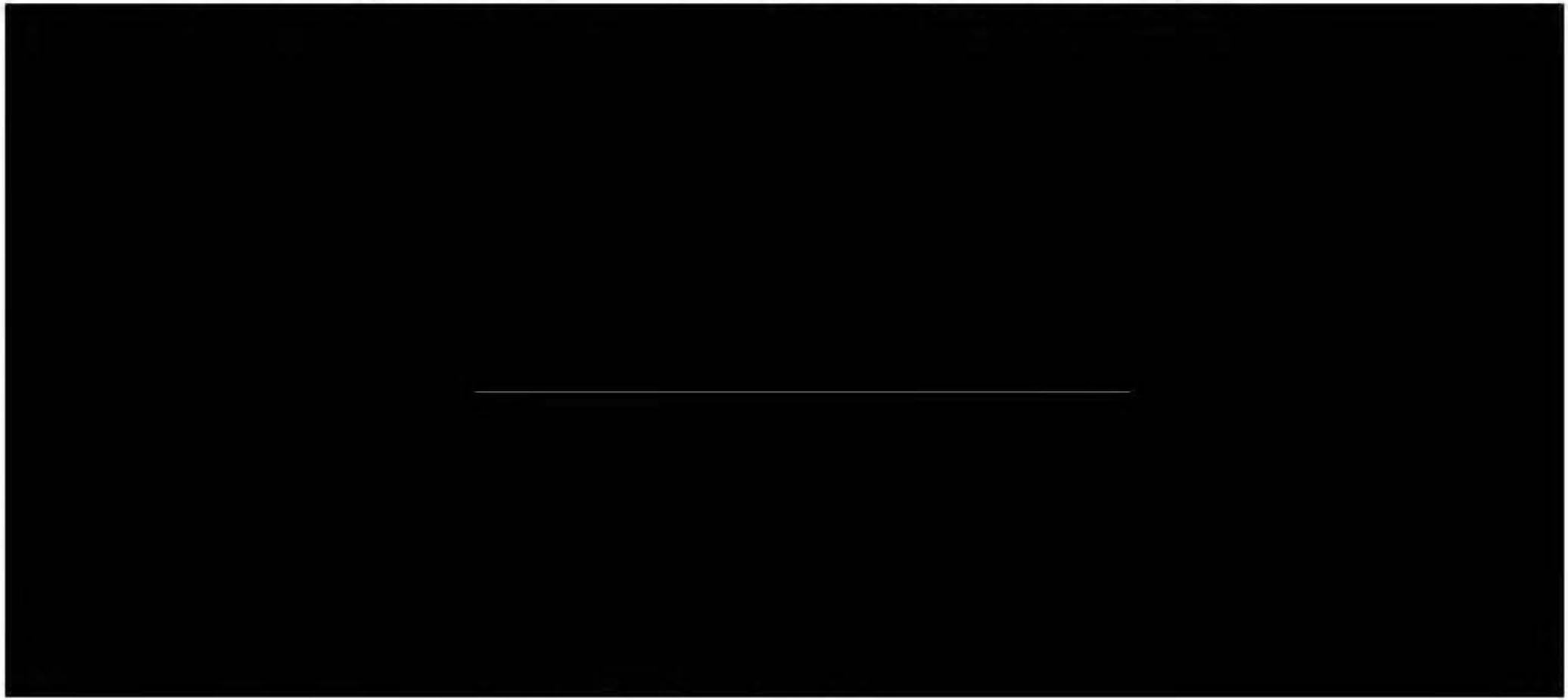

Figure 6: Results final bulk.

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3.3.1.10 Hold time challenge during formulation

Testing activity	[redacted]
Data collection & evaluation method	[redacted] ***Overview of product hold times during formulation:*** [redacted] Evaluation: Release data will be evaluated by comparing towards the acceptance criteria.
Acceptance/evaluation criteria	Release data should meet the acceptance criteria of the release lot plan.
Conclusion	*NA*

Discussion of results:
The product hold times described in the test above will not be performed for batch size 139 L. For PV2-4, the product hold times were within the targeted hold times (Table 18).

[redacted]

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Table 18: Overview of (challenged) validation batches.

Hold time	PV2 (hh:mm)	PV3 (hh:mm)	PV4 (hh:mm)	PV6 (Phase II, 278L (Ref. 28)) (hh:mm)	PV7 (Phase II, 278L (Ref. 28)) (hh:mm)	Proposed hold time
[redacted]						

3.3.2 Filling activities

3.3.2.1 Standstill Validation during filling

Testing activity	[redacted]
Data collection & evaluation method	[redacted] Evaluation: - Results are compared towards the acceptance criteria. - Consistency within batch is evaluated.
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 20.
Conclusion	*PASS*

Table 19: Stand still strategy

Standstill time	*Action FC2*	*Action VC2*
[redacted]		

[2] This is the amount in vials needed to flush the FC2 product path.
[3] This is the amount in vials needed to flush the VC2 product path.

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Discussion of results:

A standstill could have an impact on the drug product because of long contact with the product path [redacted] All results were within specifications. There are no additional actions necessary than mentioned in Table 19 after a [redacted].

Table 20: Overview of impacted CQAs after [redacted]

	Limit	PV1	PV3
LNP size (nm)	[redacted]		
LNP polydispersity			
RNA content (mg/ml)			
% encapsulation			

Conclusion:

A [redacted] is successfully validated for VC2 filling line.

3.3.2.2 Intra and inter batch homogeneity

Testing activity	[redacted]
Data collection & evaluation method	[redacted]

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[redacted]	
Acceptance/evaluation criteria	- All test results should meet the acceptance criteria detailed in Table 21. [redacted]
Conclusion	*PASS*

Discussion of results:

In table 21, all CQA results for the impacted CQAs are shown. Samples were analysed in duplicate. All results were within specifications. Inter and intra batch variability was performed based on interval plots (Figures 8 and 9) (protocol deviation N°06).Table 21: Overview of impacted CQAs of T8.

	Limit	PV2			PV3			PV4		
		Begin	Middle	End	Begin	Middle	End	Begin	Middle	End
LNP size (nm)	[redacted]									
LNP polydispersity										
RNA content (mg/ml)										
% encapsulation										
ALC-0315 content (mg/ml)										
ALC-0159 content (mg/ml)										
DSPC content (mg/ml)										
Cholesterol content (mg/ml)										

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[redacted]

In Figure 8, the interval plots for all CQAs are shown where the 6 results per batch were pooled. For LNP

[redacted]

[redacted] will be further evaluated during CPV (20043-10000-MPL0-A1).

[redacted]

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Product/Process:
Introduction of Covid-19 Vaccine in FC2/VC2 for 139 L batch size (Phase II)

Document ID:
20043-10000-PRRA-A2

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3.3.2.3 Minimum and maximum loading in freezer

Testing activity	[redacted]
Data collection & evaluation method	[redacted]

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[redacted]

Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 22.
Conclusion	*PASS*

Discussion of results:

[redacted]

Results are shown in Table 22 and were all within specifications.

Table 22: Overview of impacted CQAs of minimum and maximum freeze load.

	Limit	PV2 (maximum load)	PV4 (minimum load)
LNP size (nm)	[redacted]		

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LNP polydispersity	[redacted]
In Vitro Expression (%)	
RNA integrity (%)	

[redacted] Furthermore, all results were well within specification. Therefore, there can be concluded that no difference between the freeze locations can be observed.

[redacted]

Conclusion:
Minimum and maximum freeze load were successfully validated. Furthermore, no practical relevant differences between the position of the freezers were observed.

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3.3.2.4 Cumulative hold time target/challenges

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

[redacted]

times.

Table 23: Overview of cumulative hold time and RNA-integrity of worst case TIR/TOR sample.

	Limit	PV2	PV3[1]	PV4
RNA integrity (%)	[redacted]			
TIR/TOR				
TOR				

[1] PV3

[2] In PR#S700247 was described that incorrect TOR time was documented in the interim report.

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[redacted]

Table 24: Overview of challenged validation batches.

Hold time	PV3 (Phase II, 139L) (hh:mm)	PV6 (Phase II, 278L (Ref. 28)) (hh:mm)	Proposed hold time
Cumulative TIR/TOR	[redacted]		

Conclusion:
Cumulative hold time of [redacted] is validated successfully.

3.3.2.5 Routine testing at release

Routine sampling was performed at end of filling. In Table 25, the release results of the PV-batches are shown. All results were within specification. Comparability study is performed by ARD.

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Table 25: Routine testing at release.

Method	Procedure ARD	Procedure	Limits on LIMS test plan	PV2	PV3	PV4
Appearance	Appearance (Visual)	TM100010539	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)	TM100010539	May contain white to off white opaque amorphous particles	Meets test	Meets test	Meets test
Subvisible particles	[redacted]	USP<787> TM100010541	[redacted]	187 particles/container 7 particles/container	30 particles/container 0 particles/container	37 particles/container 0 particles/container
pH	[redacted]	TM100010538	[redacted]	[redacted]	[redacted]	[redacted]
Osmolality	[redacted]	TM100010540	[redacted]	[redacted]	[redacted]	[redacted]
LNP size	[redacted]	TM100010649	40 to 120 nm	[redacted]	[redacted]	[redacted]
LNP polydispersity	[redacted]	TM100010649	[redacted]	[redacted]	[redacted]	[redacted]
RNA encapsulation	[redacted]	TM100010402	[redacted]	[redacted]	[redacted]	[redacted]
RNA content	[redacted]	TM100010402	[redacted]	[redacted]	[redacted]	[redacted]

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Method	Procedure ARD	Procedure	Limits on LIMS test plan	PV2	PV3	PV4
ALC-0315 content	[redacted]	TM100010322	[redacted]	[redacted]	[redacted]	[redacted]
ALC-0159 content		TM100010322	[redacted]	[redacted]	[redacted]	[redacted]
DSPC content		TM100010322	[redacted]	[redacted]	[redacted]	[redacted]
Cholesterol content		TM100010322		[redacted]	[redacted]	[redacted]
Lipids Identity		TM100010322	[redacted]	[redacted]	[redacted]	[redacted]
Container Content for injections		TM100010614		[redacted]	[redacted]	[redacted]
Identity of encoded RNA sequence		TM100010407	Identity confirmed	Confirmed	Confirmed	Confirmed
In Vitro Expression		TM100010380	[redacted]	[redacted]	[redacted]	[redacted]
RNA integrity		TM100010392	[redacted]	[redacted]	[redacted]	[redacted]
Bacterial Endotoxin		LAB-36816	[redacted]	[redacted]	[redacted]	[redacted]
Sterility		LAB-37166	No growth detected	Meets test	Meets test	Meets test

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Method	Procedure ARD	Procedure	Limits on LIMS test plan	PV2	PV3	PV4
Container Closure Integrity[1]	Dye incursion	USP697 TM100010635	Pass	NA	NA	NA

[1] Tested for stability batches only at release.

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3.3.3 Freezing activities

3.3.3.1 Freeze thaw cycle

Testing activity	[redacted]
Data collection & evaluation method	[redacted] Evaluation: Results were compared towards the acceptance criteria.
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 12.
Conclusion	*PASS*

Discussion of results:

[redacted]

Table 26: TIR and TOR time during freeze thaw cycle.

	Time out	Residence time at room temperature	Residence time in refrigerator
Time out freezer	[redacted]		
Time in refrigerator			
Time out of refrigerator			
Time in freezer			

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Table 27: Results Freeze Thaw test.

	Limit	Result
LNP size	[redacted]	
LNP polydispersity		
RNA integrity		

Conclusion:
A freeze thaw cycle [redacted] was successfully validated.

3.4 Process performance results

Yield and inspection results are considered to be good indicators of overall process performance.

3.4.1 Formulation

3.4.1.1 Yield after formulation

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

[redacted]

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Table 28: Yield after formulation.

	PV2	PV3	PV4
Samples	[redacted]	[redacted]	[redacted]
Preproduction of LNP process	[redacted]	[redacted]	[redacted]
Yield	[redacted]	[redacted]	[redacted]
Comments	NA	NA	[redacted]

3.4.2 Filling

3.4.2.1 Yield after filling

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:
The calculated yield as shown in Table 29, is above the adapted minimum limit of [redacted], so conform the acceptance criterion. The yield limits will be re-evaluated during CPV.

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Table 29: Yield after filling.

	PV2	PV3	PV4
Samples	[redacted]	[redacted]	[redacted]
Yield	[redacted]	[redacted]	[redacted]

3.4.3 Inspection

3.4.3.1 Automated inspection

Testing activity	The PV batches will be inspected through AI.
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

The calculated yield as shown in Table 30. [redacted]

Table 30: Yield after inspection.

	PV2 (EL8723)	PV3 (EM6950)	PV3 rework (ER0641)	PV4 (EL8713)
Samples	[redacted]			
Yield				

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[redacted]

AQL sampling results are shown in Table 28. AQL sampling results were within limits.

Table 31: AQL sampling results.

Type of defects	AQL limit	PV2 (EL8723)		PV3 (EM6950) (pallet 4-5)		PV3 (EM6950) (Pallet 6-9)		PV3 rework (ER0641)		PV4 (EL8713)	
		Number of defects	%	Number of defects	%	Number of defects	%	Number of defects	%	Number of defects	%
Critical	[redacted]										
Major											
Minor											

3.4.4 Packaging

3.4.4.1 Yield after packaging

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:
The calculated yield as shown in Table 29, is above the adapted minimum limit of [redacted] so conform the acceptance criterion.

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Table 32: Yield after inspection.

	PV2 (EL8723)	PV3 (EM6950)	PV3 rework (ER0641)	PV4 (EL8713)
Samples	[redacted]			
Yield				

4 Data verification

Data was not changed in A2 version. Therefore, the data verification table of the A1 version is still in place. In *Attachment 3 of A1 version*, a data verification table is given. The table gives an overview of the different data sources used together with the name, signature and date of signature of the verifier.

5 Deviation discussion for process validation activities

5.1 Protocol deviations

This section lists and discusses all deviations that occurred versus the referenced protocol. These deviations are assessed upon impact on validation and lot release.

Deviation:	***Deviation n° 01*** ***List of CQAs in Attachment 1***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 02*** ***Inspection performed on FC2 for PV3 and PV4***
Deviation description:	*Due to deviation PR#5506629 (Batch deviation N°10), PV3 and PV4 were (re)inspected on FC2 line instead of the VC2 line as described in the protocol.*

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Evaluation:	*No impact towards product quality of the batches and validation since the batch was inspected by a qualified line (FC2) and inspection on VC2 line is covered by a qualification.*
Correction / corrective action:	*PV3 and PV4 were (re)inspected on FC2 line.*
Status:	*Closed*

Deviation:	***Deviation n° 03*** ***No challenge of 48 hours for drug substance post thaw at 2-8°C***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 04*** ***Different LAB method was used for bioburden and endotoxin testing***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*NA, test were performed as expected and the results were conform.*
Status:	*Closed*

Deviation:	***Deviation n° 05*** ***Internal limit LNP size***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 06*** ***Inter and intra batch variability evaluated based on interval plots***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*Interval plots were used to evaluate inter and intra batch variability.*
Status:	*Closed*

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Deviation:	***Deviation n° 07*** ***Inter batch variability of IPC RNA content***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*NA*
Status:	*Closed*

Deviation:	***Deviation n° 08*** ***Formulation product hold time***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*NA*
Status:	*Closed*

Deviation:	***Deviation n° 09*** ***Crimping pressure operating range***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

5.2 Batch deviations

5.2.1 Overview batch deviations

In *Attachment 5*, all deviations (including unplanned interventions) that occurred during the manufacturing process under scope are listed with an evaluation of the impact of the lot deviation on the validity of the process validation and lot release.

Deviation:	***Deviation n° 10*** ***PR#5506629 – EM6950***
Deviation description:	[redacted]

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Evaluation:

Correction / corrective action:

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[redacted]

Status:	*Closed, open actions were described above.*
Deviation:	***Deviation n° 11*** ***PR#5531553 – EM6950***
Deviation description:	[redacted]
Evaluation:	

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Correction / corrective action:	[redacted]
Status:	*Closed, open actions are described above.*

5.2.2 Cumulative assessment

All deviations reported for the PV batches are special cause events and non-recurring deviations without impact on the validation activities for process validation of the 139L lot size Covid 19 vaccine per referenced protocol (Ref. 15).
Based on the above, it can be concluded that there is no cumulative impact on process validation or process robustness.

6 Recommended Changes

Following actions will be performed:

[redacted]

7 Conclusion for Process Validation activities

In this report the following three requirements were met:

1) *All analytical results are within the acceptance criteria (see section 1.1)*
2) *The overall process performance results are within the acceptance criteria (see section 3.4)*
3) [redacted]
4) *Deviations (unplanned interventions included) are discussed and a cumulative deviation assessment is carried out. There is no link between the deviations and the validation activities (see section 5)*
5) Data assessment demonstrates that the batches are comparable.

Consequently, the process validation activities as per referenced Process Validation Protocol of Covid-19 Vaccine are successful. An overview of the validated CPPs and operating ranges is given in attachment 4.

The remarks left, if any, have no impact on the quality of the product and GMP requirements.

General conclusion: ***PASS***

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The lots are subject of a stability as detailed in Ref. 25-27.

8 Control Strategy and Continued Process Verification Plan

8.1 Control strategy

The current process is maintained in a validated state using the process parameter settings, ranges, process restrictions, work instructions, in-process controls, release tests, etc. which are secured in batch records, PLC, forms, procedures, … No new control strategies have to be implemented as a consequence of this validation.

Validated challenged hold times will be adjusted in the filing (PR#5719477).

8.2 Continued Process Verification plan

The continued process verification plan is already available in document 20043-10000-MPL0-A1.

9 Glossary

Abbreviation	Explanation
AI	Automatic Inspection
AOA	Analyse op Aanvraag (Analysis on request)
BBR	Bioburden Reducing
BP	Bulk Product
BRA	Batch Record Attachment
CPP	Critical process parameter
CPV	Continued Process Verification
CQA	Critical quality attribute
DLS	Dynamic Light Scattering
DS	Drug Substance
EBR	Electronic Batch Record
F	Finished
FB	Formulation Booth
FC	Focus Cell
IPC	In process control
IL	Inspection Line
LNP	Lipid Nano Particles
MBR	Master Batch Record
RMS	Recipe Management System
SOP	Standard Operating Procedure
TBD	To Be Determined

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TFF	Tangential Flow Filtration
TIR	Time In Refrigerator
TOR	Time Out Refrigerator
VC	Vaccine Cell
WSL	Washing and Sterilizing line

10 Attachments

1. Process Validation Protocol (0901201b87799f6a)
2. Overview of CPPs and IPCs
3. Data verification table (see Attachment 3 of 20043-10000-PRRA-A1, gnosis ID: 0901201b87ab0d8b)
4. Validated critical process parameters and operating ranges
5. Batch deviations
6. Signed Approval Page

11 Document History

Version:	Author:	Last edited on:
A2	[redacted]	*18/03/2021*
In Table 6 and Attachment 2, clarification about the temperature deviations were added.		
A1	[redacted]	*05/03/2021*
First Version		

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[redacted] 19 Mar 2021 09:21:003-0400

REASON: I approve this document.

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1. **CPPs**

[redacted]

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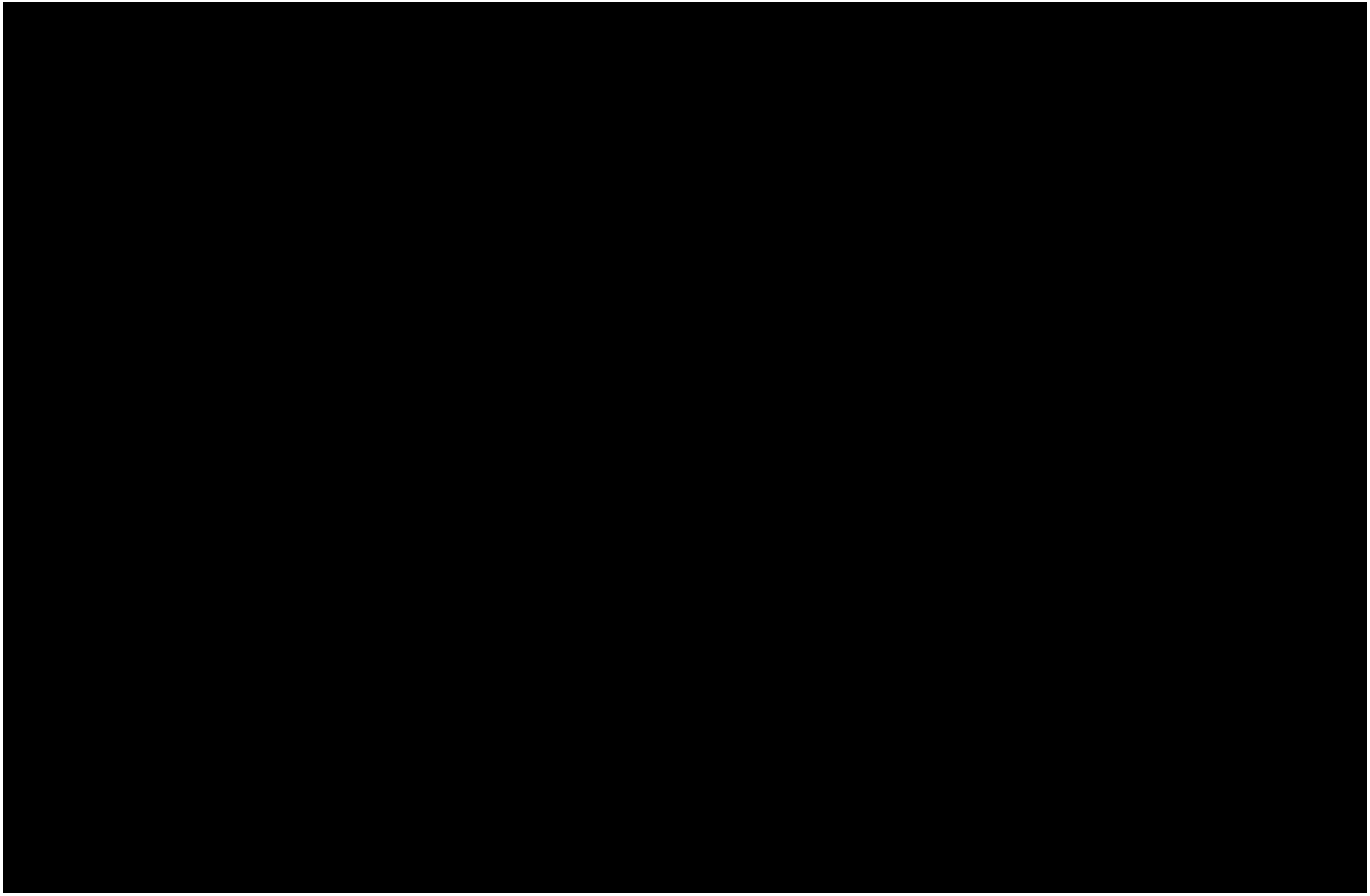

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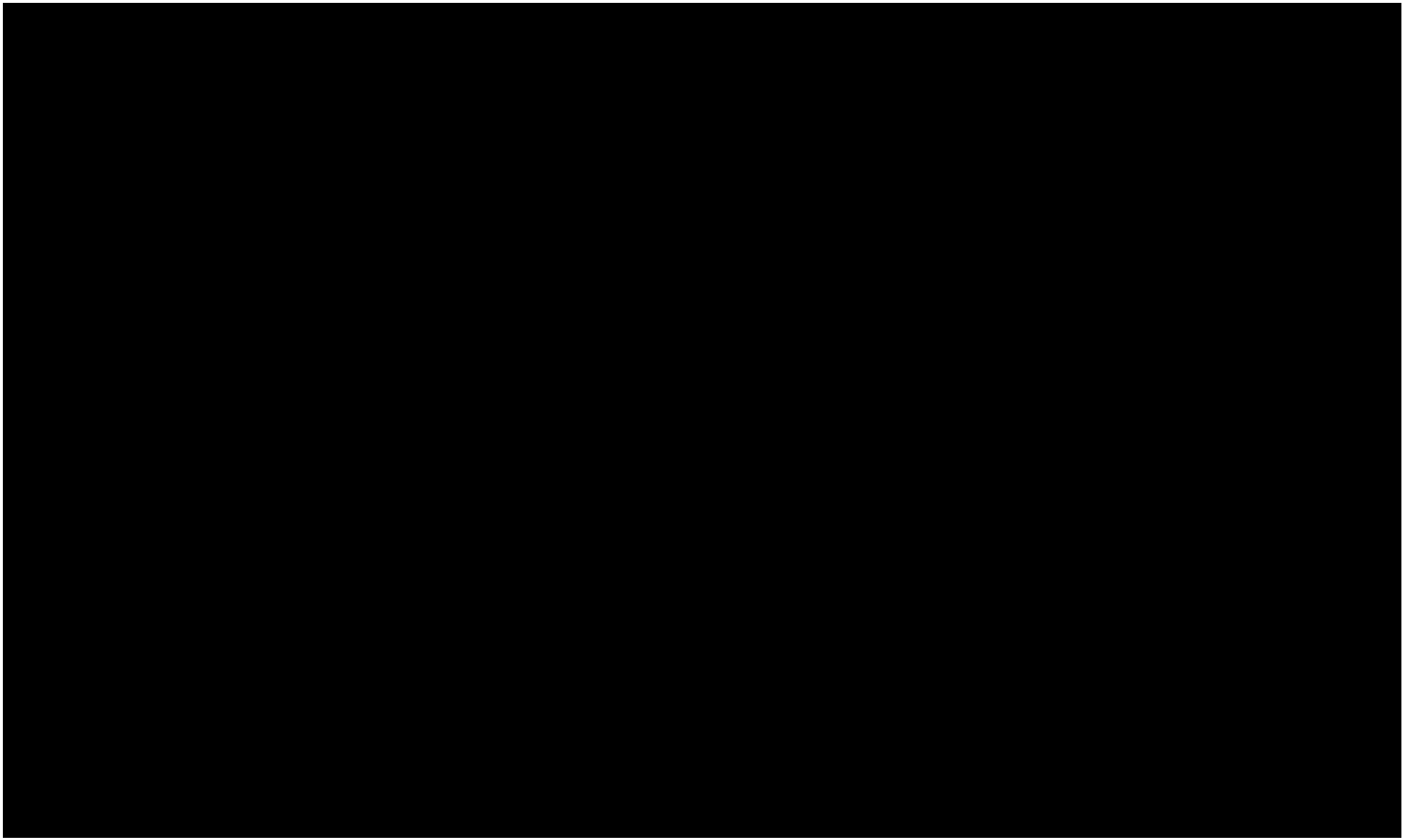

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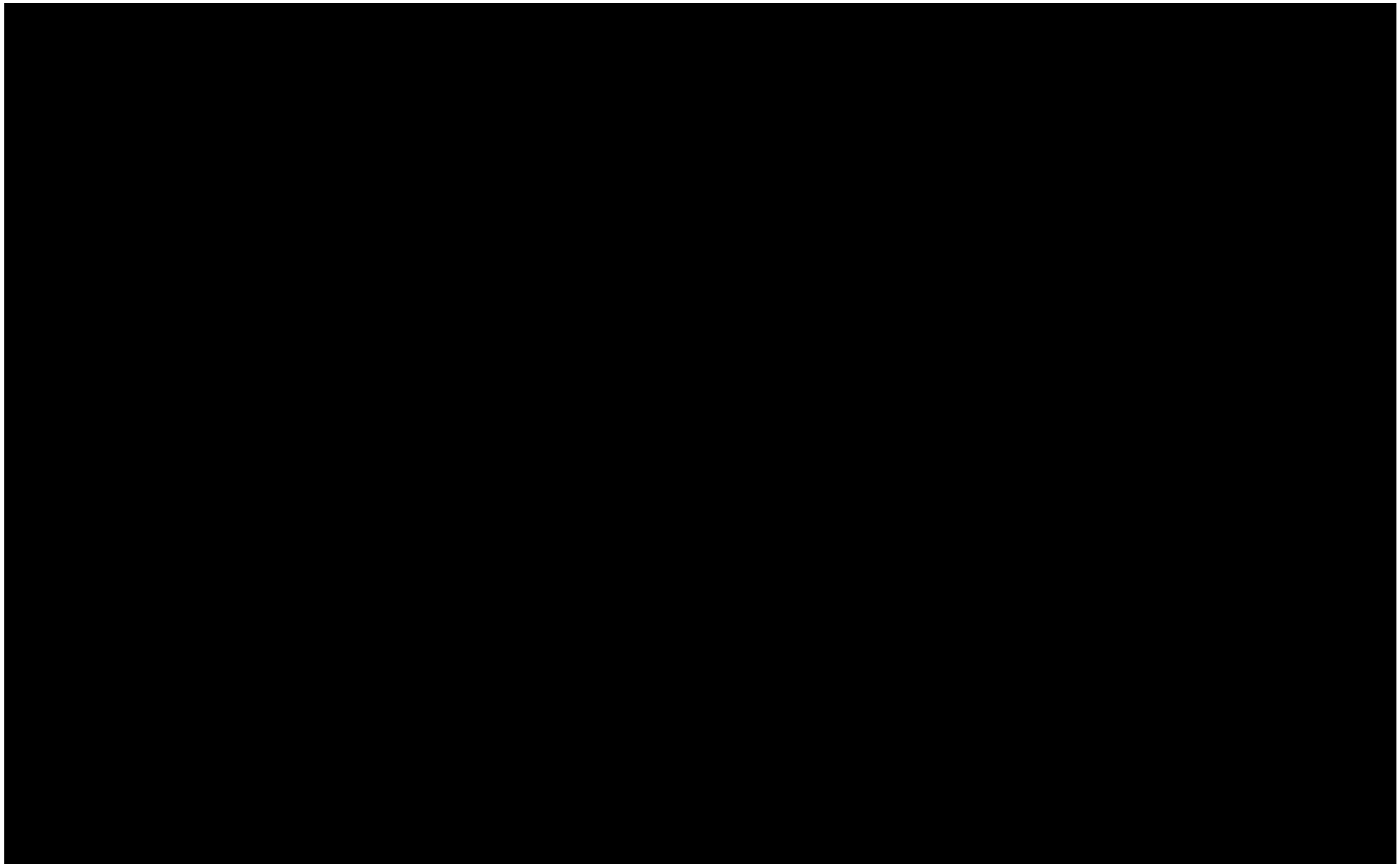

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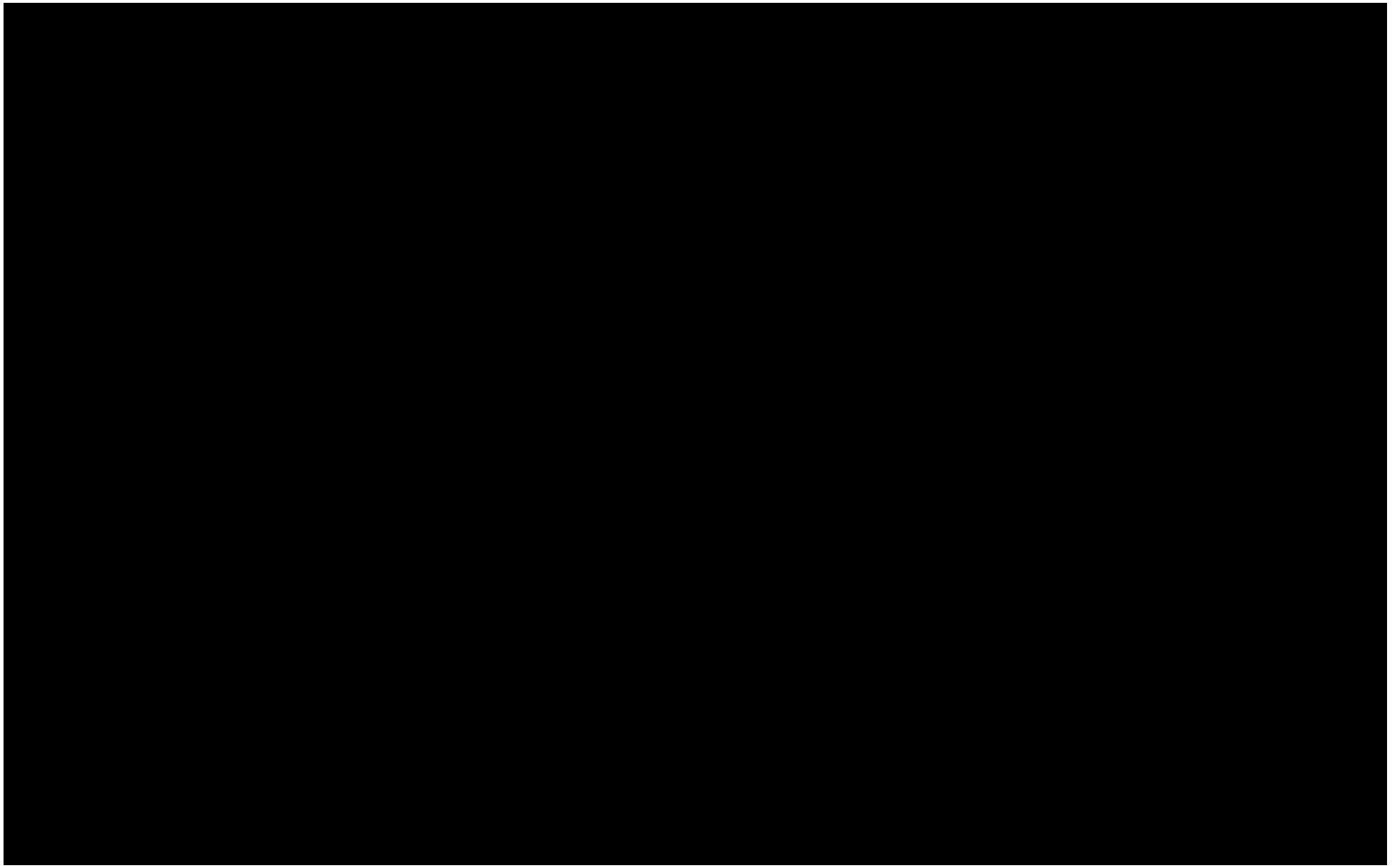

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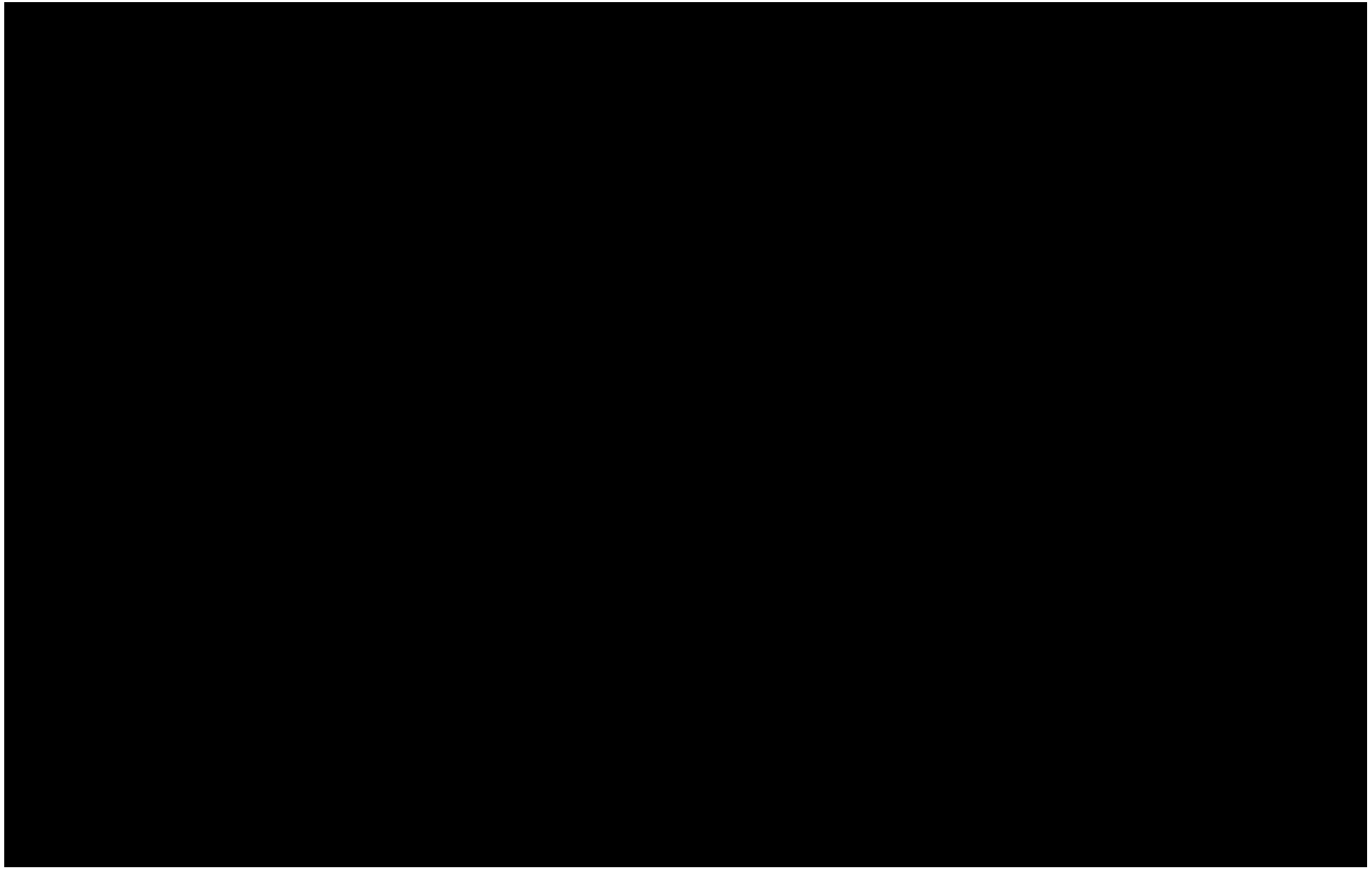

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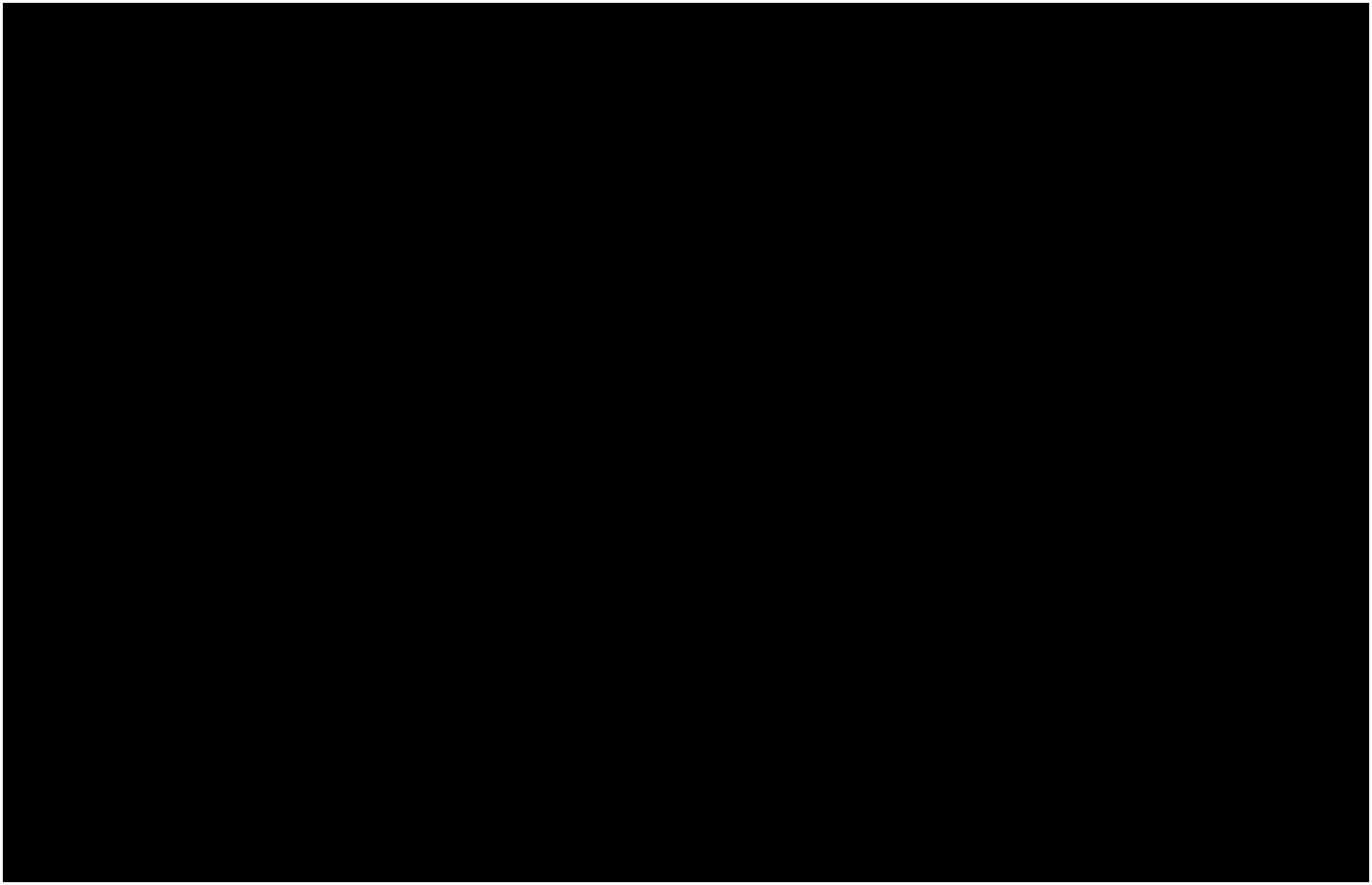

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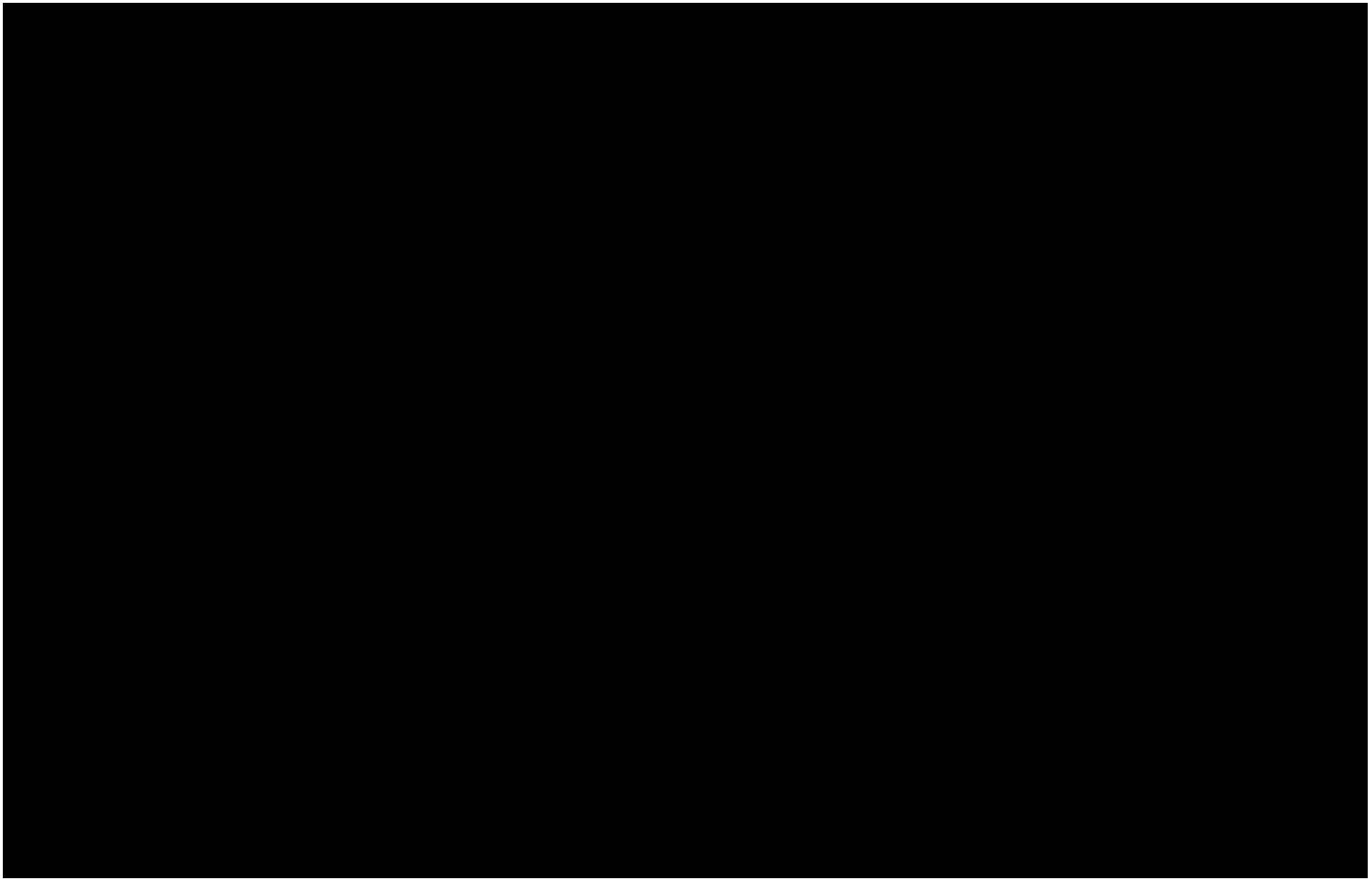

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Attachment 4 to 20043-10000-PRRA-A2

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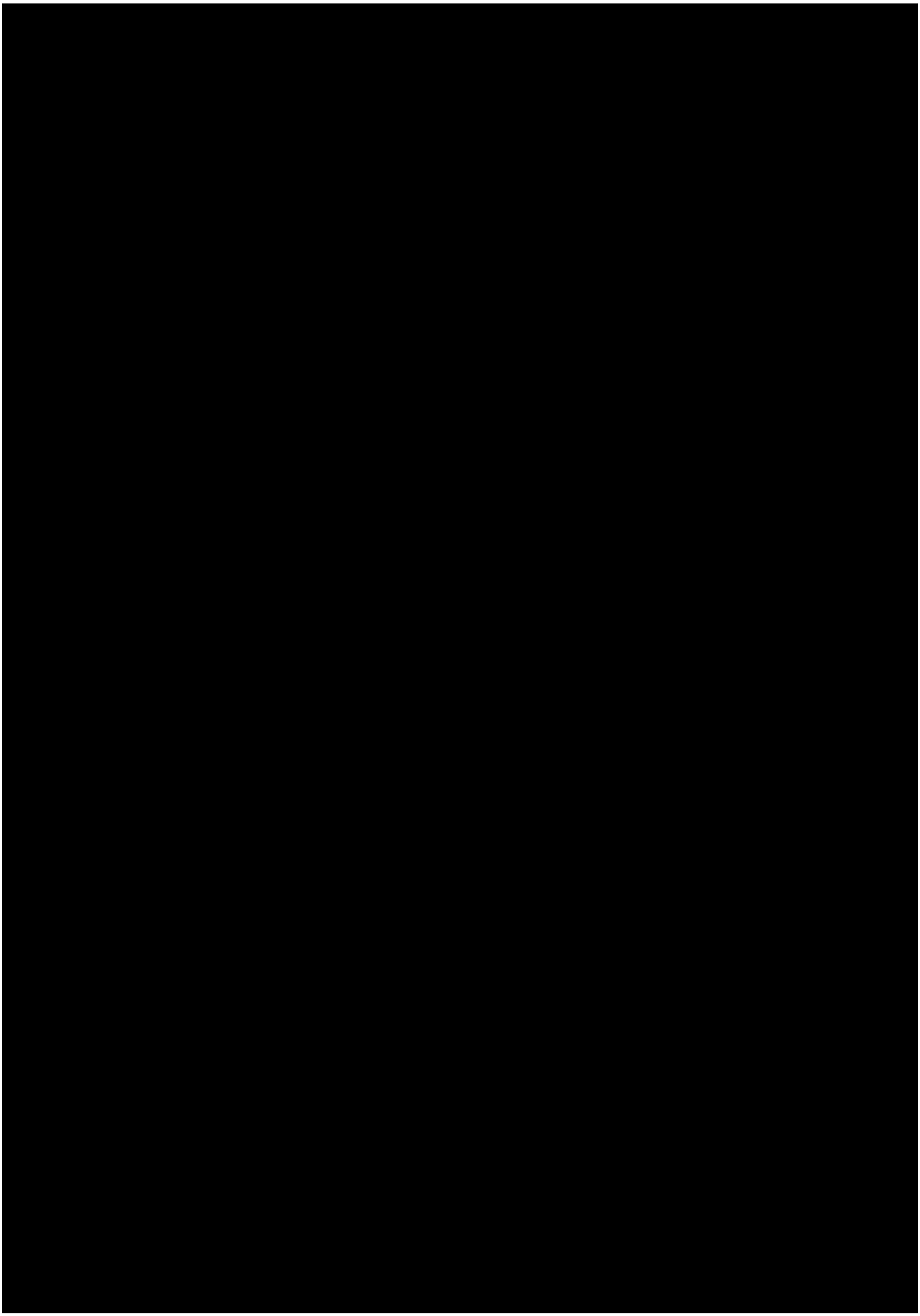

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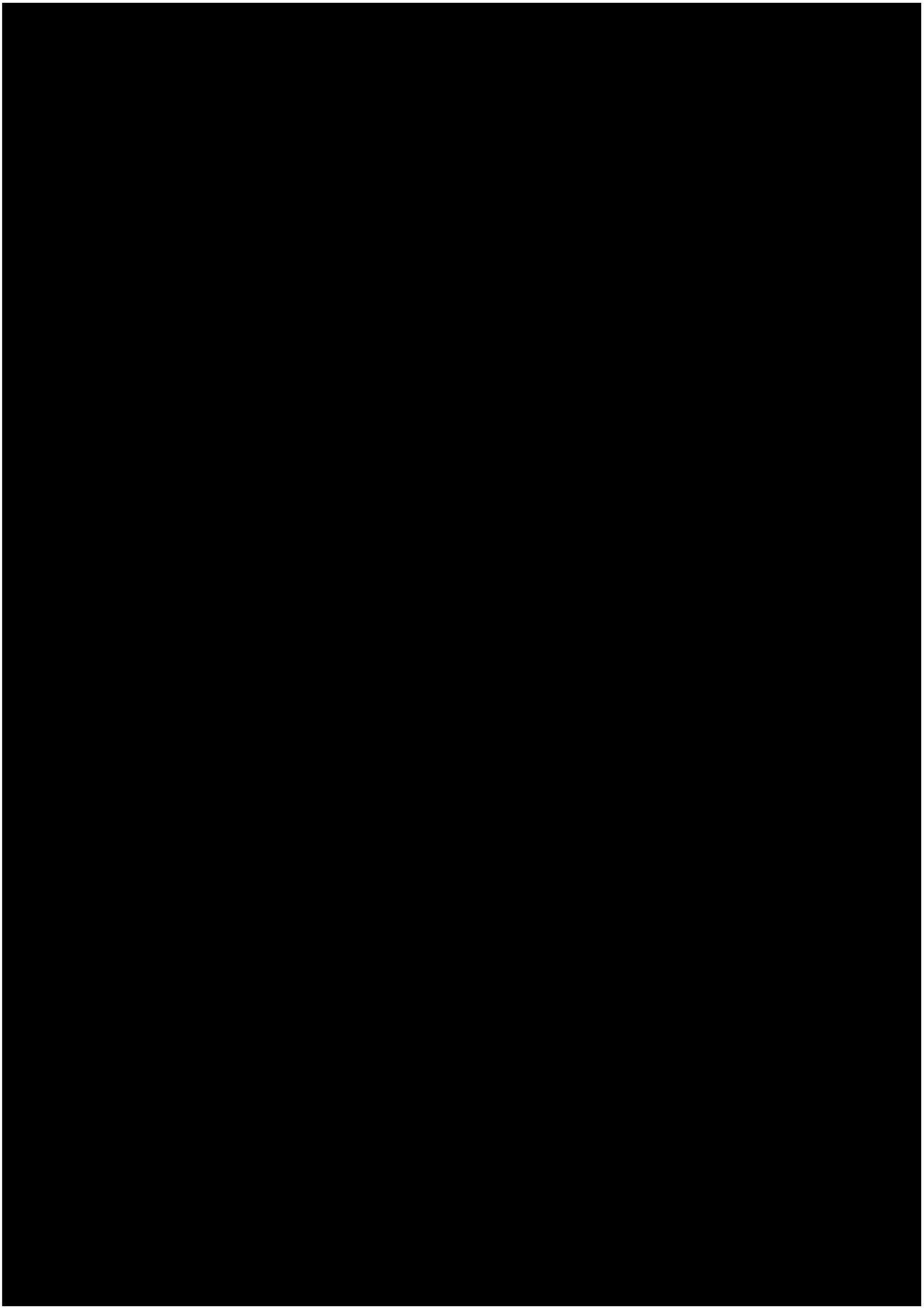

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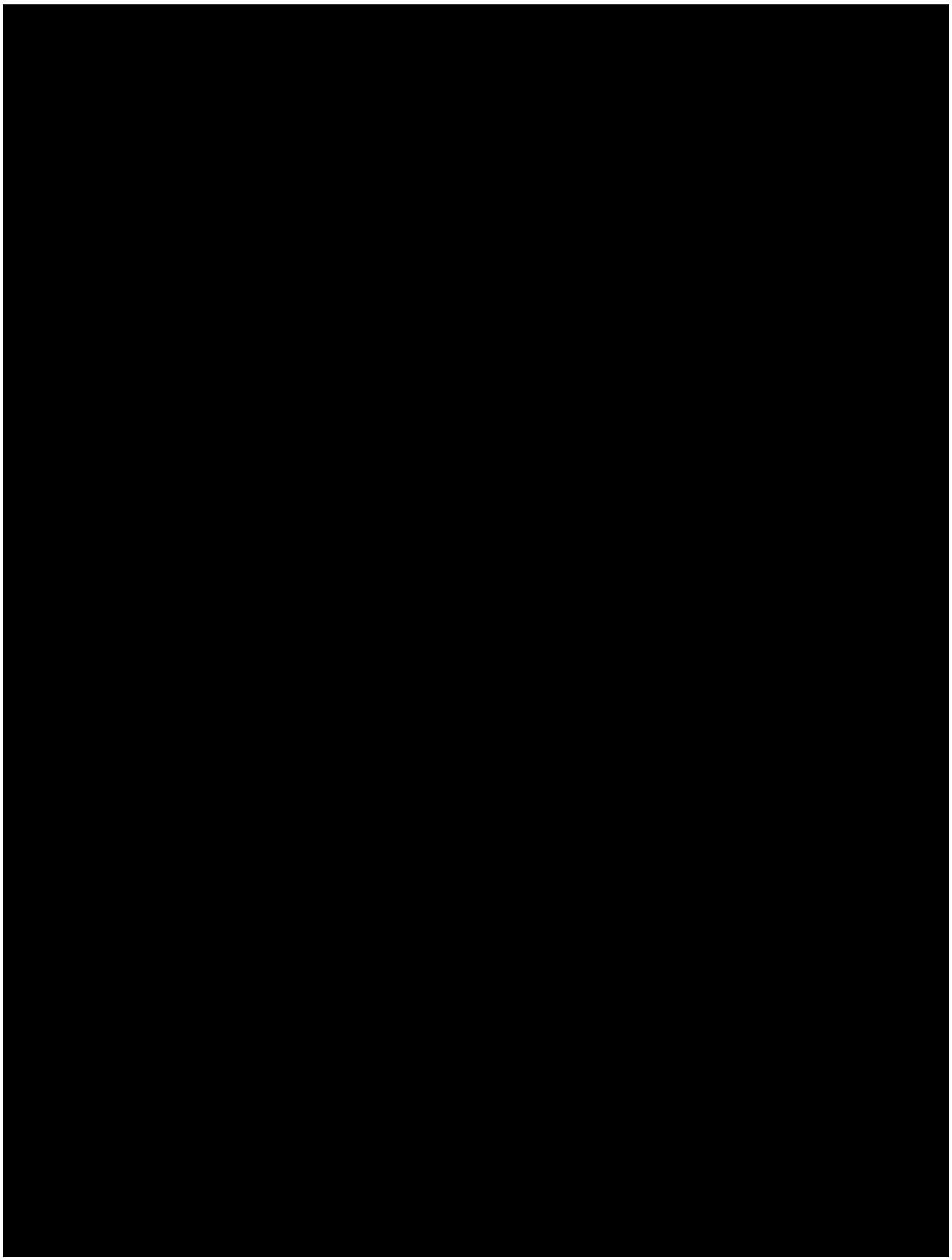

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DocUUID : 64e561f5-19a1-4e94-acb1-c0e4b2cfd8b5

DeskTop View

Report Executed By: [redacted] **Report Executed On:** 25-February-2021

PR #	Site	Record Type	Title / Short Description	Responsible Person	Date Opened	Due Date	Status	Batch #
5506629	Puurs	Manufacturing Investigations / Quality Assurance Report (QAR)	VC2 - vials with incorrectly rolled caps found after inspection of Covid Vx batch EM6950	[redacted]	23-Dec-20	29-Jan-21	Approved	ER0641 EM6950
5531553	Puurs	Manufacturing Investigations / Quality Assurance Report (QAR)	ECO - VACC2 - Missing SM G02 - LAF vial Filling isolator - EM6950 (PF07302048 195 x 0,45ml GVL PUU - ACMF EUA)	[redacted]	6-Jan-21	05-Feb-21	Closed	EM6950

[redacted] 19 Mar 2021 09:21:003-0400

REASON: I approve this document.

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DocU UID : 81e561f5-19a14a94-acb1-c0e4b2cd8b5

Scope Used To Run Report: Puurs / Manufacturing Investigations / Quality Assurance Report (QAR)

Query Description: CLOSED PRs included; Batch #: EM7321, EL8723, EN4765, EM6950, ER0641, EN9090, EL8713

-End of Report-

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DocUUID : 64e561f5-19a1-4e94-acb1-c0e4b2cfd8b5

Status	Effective	Effective Date	-	Version	1.0	Doc Name	FORM-105489
Title	FORM: Process Validation Report (Drug Product)						
Doc Alias	F(2)-19-002-PV Report	Site Code / Department	Puu / Validation Master Plan				

EXTERNAL COMPANY AUTHORITY:

BIONTECH	[redacted] ASSOCIATE DIRECTOR GLOBAL, CMC	[redacted] Digitally signed by [redacted] Date: 2021.03.18 20:13:51 +01'00'
NAME OF EXTERNAL COMPANY	NAME & JOB TITLE EXTERNAL COMPANY REPRESENTATIVE	SIGNATURE & DATE

The signature of the External Company Representative indicates that the information in the document comply with the requirements and is correct from a technical standpoint.

VERIFICATION OF EXTERNAL APPROVAL:

SITE QUALITY AUTHORITY:

[redacted]	QUALITY PROJECTS ASSOCIATE	
NAME	JOB TITLE	SIGNATURE & DATE

The signature of the Site Quality Authority indicates that this document has been reviewed by the External Company Authority and the External Company approval is attached to this document.

This document is valid as from the date of the last signature.

[redacted] 19 Mar 2021 09:21:003-0400

REASON: I approve this document.

f453dc71f5d7-4477-b488-53652414f722

090177e196a2968c\Approved\Approved On: 26-Mar-2021 16:13 (GMT)

Product/Process:
Introduction of Covid-19 Vaccine in FC2/VC2 for 139 L batch size (Phase II)

Document ID:
20043-10000-PRRA-A2

DocUUID : 64e661f5-19a1-4e84-acb1-c0e4b2cfd8b5

Process Validation Report
For
Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size

AUTHOR:

ISSUED BY:

NAME	JOB TITLE	SIGNATURE & DATE
[redacted]	Project Engineer Launch Excellence	[redacted] 19 Mar 2021 09:27:009-0400 REASON: I approve this document. 453dc71-5d7-4477-b488-53652414722

The signature of the Author indicates that the information gathered in this document is complete and accurate, that all validation activities and requirements have been identified and the document is written following site validation SOP's.

APPROVALS:

SITE VALIDATION AUTHORITY:

NAME	JOB TITLE	SIGNATURE & DATE
[redacted]	DIRECTOR LAUNCH EXCELLENCE	[redacted] 19 Mar 2021 0:10:014-0400 REASON: I approve this document. 824b1985-ec754 de-a b6-b591c67508e9

The signature of the Site Validation Authority indicates that the information in the document has been gathered, is complete and accurate, is correct from a technical standpoint and the document is written following site validation SOPs.

SITE PRODUCTION AUTHORITY/SYSTEM OWNER:

[redacted]	SYSTEM OWNER VC	[redacted] 9 Mar 2021 0:42:015-0400 REASON: I approve this document. 378 0b0a-2 8-46da-8 22-b2b9269c1a35
[redacted]	SYSTEM OWNER FC2	[redacted] 21 Mar 2021 5:36:02 80400 REASON: I approve this document. 3cda23 3-9034-4406-8 3a-ed715 bd89 69

Product/Process:
Introduction of Covid-19 Vaccine in FC2/VC2 for 278 L batch size (Phase II)

Document ID:
20043-10000-PRRB-A2

090177e196a2968c\Approved\Approved On: 26-Mar-2021 16:13 (GMT)

DocUUID : 5b9a9b8c-f9f2-421e-80ec-2d1ca5a54458

[redacted]	SYSTEM OWNER L2	[redacted] 19 Mar 2021 09:38:015-0400 REASON: I approve this document. 1ed9d96bd415-4d 6-b447-65 a9290 27d
NAME	JOB TITLE	SIGNATURE & DATE

The signature of the System Owner indicates that the information in this document has been reviewed and that it will prove that the process will operate consistently and meet the user's needs.

SITE QUALITY AUTHORITY:

[redacted]	QUALITY PROJECT ASSOCIATE	[redacted] 22Mar 2021 0 :07:056-0400 REASON: I approve this document. a795930-17a4-44e1-9e64-6ec84dde1d46
NAME	JOB TITLE	SIGNATURE & DATE

The signature of the Site Quality Authority indicates that this document has been reviewed for Regulatory Compliance Practices and meets Good Documentation Practices and site validation SOP's.

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DocUUID : 5b9a9b8c-f9f2-421e-80ec-2d1ca5a54458

EXTERNAL COMPANY AUTHORITY:

NAME OF EXTERNAL COMPANY	NAME & JOB TITLE EXTERNAL COMPANY REPRESENTATIVE	SIGNATURE & DATE
BIONTECH	[redacted] ASSOCIATE DIRECTOR GLOBAL, CMC	

The signature of the External Company Representative indicates that the information in the document comply with the requirements and is correct from a technical standpoint.

VERIFICATION OF EXTERNAL APPROVAL:

SITE QUALITY AUTHORITY:

NAME	JOB TITLE	SIGNATURE & DATE
[redacted]	QUALITY PROJECTS ASSOCIATE	[redacted] 22 Mar 2021 03:07:056-0400 REASON: I approve this document. a795930-17a4-44e1-9e64-6ec84dde1d46

The signature of the Site Quality Authority indicates that this document has been reviewed by the External Company Authority and the External Company approval is attached to this document.

This document is valid as from the date of the last signature.

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1 Introduction

1.1 Purpose

This document is a process validation report for process validation activities for Phase II for Covid-19 Vaccine (PF-07302048, BNT-162) drug product manufacturing processes in Vaccine Cell 2 (formulation), Focus Cell 2 and Vaccine Cell 2 (filling) and Logistics 2 (freezing) for 278 L batch size as described in the referenced Process Validation Plan (Ref. 10) and Validation Project Plan (Ref. 3).

The initial Phase I process validation of the Covid-19 Vaccine (PF-07302048, BNT-162) drug product formulation and fill/finish processes is covered by referenced Phase I Network Process Validation Plan (Ref. 1*).* The Phase I process validation plan includes one PV batch for all drug product (DP) supply nodes to support the 'Emergency Use Authorization' (EUA) application and conditional approval. The Phase I validation plan covered 2 site specific protocols, for Puurs this protocol is documented in 20043-COVID-PRP0-A1 (Ref. 2) and report in 20043-COVID-PRRC-A1 (Ref. 24).

The process validation plan (20043-10000-PVP0-A2) described the Phase II of the validation process of the manufacturing process of the Covid-19 Vaccine with filling in Focus Cell 2 and Vaccine Cell 2. Two different protocols were written. The first protocol covers the validation activities of the 139 L batch size (20043-10000-PRP1-A3, Ref. 15), the second protocol covers the validation activities of the 278 L batch size (20043-10000-PRP2-A1, Ref. 11).

In the conclusion of this report it is determined whether or not the process validation activities and all other studies per referenced protocol (Ref. 15) for process validation of Covid-19 Vaccine (PF-07302048, BNT-162) drug product manufacturing processes in Vaccine Cell 2 (formulation), Focus Cell 2 and Vaccine Cell 2 (filling) and Logistics 2 (freezing) for 278 L batch size are successful.

1.2 General description

The scope of the validation is defined in detail in the referenced Validation Project Plan (Ref. 3). An overview of the manufacturing process is shown in Figure 1. In Figure 2, the tanks used during formulation are shown.The parallel set-up of 2 membranes in series (2x2 membranes set-up) for 278 L batch size is shown in Figure 3.

The BNT162b2 drug product is prepared as a preservative-free, sterile, multi-dose concentrate of RNA-containing lipid nanoparticles (LNP) formulated in phosphate-buffered saline and 300 mM sucrose at pH 7.4 to be diluted for intramuscular administration. The drug product is filled at 0.45 mL/vial (0.5 mg/mL) into 2 mL glass vials which are stoppered and capped to provide total of 225 µg of the RNA in a multi-dose vial. At the administration site, the vaccine drug product is diluted with 0.9% sodium chloride and is intended to supply 5 to 6 doses per vial at 30 µg/dose.

The manufacturing process in scope of this validation protocol consists of following steps:

- Thawing of drug substance in the freeze-thaw area
- Weighing of raw materials in the Vaccine Cell 1 area
- Formulation in Vaccine Cell 2 – formulation booths 3 and 4 / Aseptic 1 – formulation booths

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- Transport to the fill line
- Filling of the product in Focus Cell 2 / Vaccine Cell 2
- Inspection of the product in Focus Cell 2 / Vaccine Cell 2
- Labeling and Packaging in Focus Cell 1 / Vaccine Cell 2
- Transport prior to freezing
- Freezing at Logistics 2
- Storage in freezers in Logistics 2

Step	[redacted]
1	
2	
3	
4	
5	
6	
7	
8	

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Step	
9	[redacted]
10	
11	

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2 References

This process validation report is aligned with SOP-51080 and the therein-referenced quality standards.

The project is covered by the following change request gQTS PR#4953874 and PR#5409849 (Ref. 5 and 6) and Process Validation Plan (Ref. 10) and Validation Project Plan (Ref. 3).

Table 1. References

Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 1	VAL100130986	Process Validation Plan for Covid-19 Vaccine (PF-07302048, BNT-162) Drug Product – Phase I	19/11/2020	[redacted]	QA Archive	NA
Ref. 2	20043-COVID-PRP0-A1	Process Validation Protocol For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)	20/11/2020	[redacted]	QAArchive	NA
Ref. 3	20043-00000-VPP0-A1	Validation Project Plan for Introduction of COVID-19 Vaccine PF-07302048	14/08/2020	[redacted]	QAArchive	NA
Ref. 4	20043-00000-VPRB-A1	Validation Project Report for Introduction of COVID-19 Vaccine PF-07302048	11/12/2020	[redacted]	QAArchive	NA
Ref. 5	CRF PR4953874	Introduction of COVID-19 Vaccine PF-07302048	14/08/2020	[redacted]	gQTS	NA
Ref. 6	CRF PR5409849	Introduction of 278 L batch size of COVID-19 Vaccine PF-07302048	05/03/2021	[redacted]	gQTS	NA
Ref. 7	INX100426829	**Process Definition Document for PF-07302048 BNT162b2 Vaccine (SARS-CoV-2 full spike protein S-P1 variant)**	08/09/2020	[redacted]	GDMS	NA
Ref. 8	20043-12000-RRPA-A2	Process Review and Risk Assessment Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) into Vaccine cell and Focus Cell	11/12/2020	[redacted]	QAArchive	NA
Ref. 9	20043-COVAL-RAT0-A2	Rational for Concurrent Validation Approach for Covid-19 Vaccine	19/11/2020	[redacted]	QAarchive	NA

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Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 10	20043-100000-PVP0-A2	Process Validation Plan For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2	23/12/2020	[redacted]	QA Archive	NA
Ref. 11	20043-10000-PRP2-A1	Process Validation Protocol For Introduction of Covid-19 vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size	23/12/2020		QA Archive	NA
Ref. 12	CRF PR#5415644	CRF Implementation of additional lipid suppliers for Covid vx bulk	08/12/2020		QTS	NA
Ref. 13	PR#5506629	VC2 – vials with incorrectly rolled caps found after inspection of batch EM6950	Opened on 23/12/2020		QTS	NA
Ref. 14	INX100438928	PF-07302048 Suspension for Injection Drug Product Cumulative Temperature Cycling Study: interim report for study #2 (eLN 00710368-0131)	05/01/2021		GDMS	NA
Ref. 15	20043-10000-PRP1-A3	Process Validation Protocol For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size	06/01/2021		QA Archive	NA
Ref. 16	20043-10000-PRR4-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size EM5261/EP2163	05/02/2021		QA Archive	NA
Ref. 17	20043-10000-PRR5-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size EM5260/EP2166	10/02/2021		QA Archive	NA
Ref. 18	20043-10000-PRR6-A1	Interim Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 278 L batch size EP4357/EP6775	11/02/2021		QA Archive	NA

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Ref N°	Document ID	Document	Approval date	Author	Location	Remarks
Ref. 19	FORM-26075 EP2163 (Gnosis: object ID: 0901201b879b80df)	FORM-26075 EP2163	05/02/2021	[redacted]	Gnosis	NA
Ref. 20	FORM-26075 EP2166 (Gnosis: object ID: 0901201b87a07778)	FORM-26075 EP2166	10/02/2021		Gnosis	NA
Ref. 21	FORM-26075 EP6775 (Gnosis: object ID: 0901201b87a0e42d)	FORM-26075 EP6775	11/02/2021		Gnosis	NA
Ref. 22	INX100436631	Memo: COVID-19 Vaccine Proposed Initial Network PPQ Drug Product Stability Protocol Plan	07/12/2020		GDMS	NA
Ref. 23	20043-10000-MPL0-A1	Continued Process Verification Plan For Introduction of Covid-19 Vaccine (PF-07302048) in FC2/VC2	12/01/2021		QA Archive	NA
Ref. 24	20043-COVID-PRRC-A2	Process Validation Report For the Covid-19 Vaccine (PF-07302048, BNT-162) in Pfizer Puurs (Phase I)	TBD		QA Archive	1
Ref. 25	PF-07302048:1-026	Stability protocol: PF-07302048:1-026	25/01/2021		LIMS ARD	NA
Ref. 26	PF-07302048:1-027	Stability protocol: PF-07302048:1-027	25/01/2021		LIMS ARD	NA
Ref. 27	PF-07302048:1-039	Stability protocol: PF-07302048:1-039	19/02/2021		LIMS ARD	NA
Ref. 28	20043-10000-PRRA-A2	Process Validation Report For Introduction of Covid-19 Vaccine (PF-07302048, BNT-162) (Phase II) in FC2/VC2 for 139 L batch size	TBD		QA Archive	1
Ref. 29	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	15/01/2021		QA Archive	N/A

1. The reports will be approved together with this document.

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3 Results of the Process Validation activities

The following section reports the process validation activities that were required in alignment with the process validation approach and as defined in the Process Validation Protocol (*Ref. 15*).

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3.1 Prerequisites check

3.1.1 Documents

The prerequisites to start Process Validation are covered in the referenced Validation Project Report (VPR) (*Ref. 4*). The document prerequisites listed in Table 2 below were ongoing and not closed yet when protocol was written.

Table 2. Prerequisites

Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
Equipment Verification/qualification	Y	Y	20043-51001-PQRA-A1: Performance Qualification Report phase 1 - Visual inspection machine Innoscan VC2	17/12/2020	[redacted]	QA Archive	NA
	Y	Y	20043-51002-PQP0-A1 : Performance Qualification Protocol phase 2 - Visual inspection machine Innoscan and Vacuum based leak tester VC2	17/12/2020		QA Archive	NA
	Y	Y	5382340-00000-VTRA-A1: Verification Test Report for Tangential Flow filtration (TFF) skid (8903075)	22/12/2020		Gnosis	NA
	Y	Y	5382340-00000-SRRA-A1: System Acceptance and Release Report For Tangential Flow Filtration (TFF) skid (8903075)	22/12/2020		Gnosis	NA

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Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
Equipment Verification/qualification	Y	Y	5409849-10000-PQRA-A1: Performance Qualification Report For Dryness Validation of bioburden reduction for Covid19 disposable material with Serpentine et-up of TFF in Fedegari 12 (89010022) and 13 (89010114)	26/02/2021	[redacted]	Gnosis	Test script 5409849-10001-TSC0-A1 execution 1 was approved with docID 5409849-10001A-TSC0-A1 on 22/12/2020
Filtration validation	Y	Y	5344432-FILCV-PQRA-A1: Filter validation report A (Sartorius)	23/12/2020		Gnosis	NA
Raw material qualifications	Y	Y	20027-30600-VPRB-A1: Process Materials Project Report	25/01/2021		Gnosis	NA
Extractables/leachables assessment of product contact materials (components)	Y	Y	20043-COVID-QRM-A2: QRM E&L assessment for product contact materials	15/01/2021		Gnosis	NA
Master batch records	Y	Y	F000051208 & F000048567 (CL200626): EBR for filling/inspection/packaging/freezing VC2	18/12/2020		EBR	Packaging VC2 was not in scope yet

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Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
Other	Y	Y	SOP-113055/FORM-105821: WI: Nazicht van batch records van Filling in Vaccines Cell 2 (VACC2)	09/11/2020	[redacted]	PDOCS	NA
	Y	Y	ASMT-54546: Final Technical Assessment for tubing from ESI used in Formulation of COVID-19 Vaccine (PF-07302048, BNT162) in Vaccine Cell 2	22/01/2021		PDOCS	NA
	Y	Y	SOP-113531: Assemblage van assemblies voor covid (VAC2)	22/01/2021		PDOCS	Training of these procedures is covered in the BRA's and actions described in these procedures are performed under supervision of a SME
Other	Y	Y	SOP-113656: WI: Opstelling van TFF skid maken in formulatiebooth 4C voor Covid grote lotsize (VAC2)	29/01/2021		PDOCS	Training of these procedures is covered in the BRA's and actions described in these procedures are performed under supervision of a SME

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Pfizer Internal Use

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Description	Impacted by validation? (Y/N)	Qualified/ Executed? (Y/N)	Documentation	Approval date	Author	Location	Remarks
	Y	Y	SOP-113657: WI: Tangential Flow Filtration in formulatiebooth 4C voor Covid grote lotsize (VAC2)	29/01/2021	[redacted]	PDOCS	Training of these procedures is covered in the BRA's and actions described in these procedures are performed under supervision of a SME

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3.1.2 Training

Operators are trained for general production Standard Operating Procedures (SOP). Additional testing and sampling activities were performed as instructed in the batch record attachments which were trained to the involved operators by the responsible department. This training was signed off in the batch record attachments as 'read and understood'. A product support representative was present to support qualified personnel with sampling and testing instructions during the production process of the process validation batches.

3.1.3 Release status of the materials

The table below provides an overview of the raw materials and components that were used for these process validation batches and their release status.

Table 3. Raw material and component overview

Raw materials			
Description	**Material number**	**Specification number**	**Status**
LIPID ALC-0315	R000011933	SPEC-43234 v2.0	Released / waived for production[1]
LIPID ALC-0315 G	R000012511	NA[2]	Released / waived for production[1]
LIPID ALC-0159	R000011760	SPEC-43237 v2.0	Released / waived for production[1]
LIPID DSPC	R000011932	SPEC-43236 v2.0	Released / waived for production[1]
LIPID CHOLESTEROL	R000011931 R000012184[3]	SPEC-43235 v1.0 SPEC-44155 v1.0	Released / waived for production[1]
PF-07305885 Drug Substance BNT	H000022798	SPEC-43238 v1.0	Released / waived for production[1]
PF-07305885 Drug Substance	H000022908	CLM#271597 v4.0[4]	Released / waived for production[1]
CITRIC ACID MONOHYDRATE	R000007711	SPEC-28814 v5.0	Released
SODIUM CITRATE GRANULAR	R000000595	SPEC-8686 v7.0	Released
SODIUM CHLORIDE	R000000594 or R000000590	SPEC-8685 v5.0	Released
Potassium Chloride	R000011784	SPEC-43217 v1.0	Released / waived for production[1]
Disodium hydrogen phosphate dihydrate	R000006513	SPEC-27162 v1.0	Released
Potassium phosphate monobasic	R000006514	SPEC-27163 v3.0	Released

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Sucrose (low in endotoxin), excipient grade	R000006469	SPEC-27310 v1.0	Released
Sodium Hydroxide	R000000596 or R000000597	SPEC-8687 v6.0	Released
Sodium Hydroxide Avantor	R000011790	SPEC-43212 v1.0	Released
Hydrochloric acid[5]	R000000520	SPEC-8668 v4.0	Released
Ethanol 99.5%	R000011789	SPEC-43233 v1.0	Released / waived for production[1]
Components			
Description	**Material number**	**Specification number**	**Status**
GC-VIAL 2ML BLOW BACK SCHOTT	PAA147946 (FC2)	SPEC-18047 v13.0	Released
GC-VIAL 2ML BLOW BACK SCHOTT MATCHBOX	PAA148986 (VC2)	SPEC-19936 v4.0	Released
RUB-STOP 13MM BB FM457/0 GREY	PPUSF0474	SPEC-8816 v11.0	Released
RUB-STOP 13MM BB FM457/0 GREY NEW	PAA159467	SPEC-8816 v11.0	Released
CAP-13MM PURPLE MAT	PAA074463	SPEC-8812 v9.0	Released

[1] New raw materials: method verification is ongoing. Raw materials will be approved for use for DP production at risk while still performing release testing, and will be dispositioned before DP disposition. (PTC PR#5235501)
[2] For Groton lipid, no SPEC-document is required, since specifications are covered in the quality agreement between Pfizer Puurs, Pfizer Kalamazoo and Pfizer Groton for ALC-0315, which is approved and effective, see Ref. 8.
[3] PTC PR#5410905: supplier qualification is ongoing. Actions covered in CRF PR#5415644.
[4]According to SOP-51014, no SPEC-document required for other Pfizer-sites since specifications are covered in quality agreement (QAA-20-0068 Version 01)).
[5]HCl is only used optionally for adjustment of pH in citrate buffer.

3.1.4 Blocking mechanism for validation batches

Proof for blocking of the validation batches and item numbers can be found in Gnosis (Ref. 19-21). Blocking of the item numbers was not required as a concurrent validation approach is used as justified in Ref. 9.

3.2 Process Validation Approach

3.2.1 CQAs, CPPs, IPCs and operating ranges

A list of relevant Critical Quality Attributes (CQAs), Critical Process Parameters (CPPs), In process controls (IPCs) and their operating ranges as determined in the referenced Review Report and Risk Assessment Report (Ref. 8) can be found in Attachment 2. (Protocol deviation N°01)

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3.2.2 Process Validation bracket and strategy

Process validation was performed using a concurrent validation approach (Ref. 9). This section provides a general overview of the Phase II validation filling on FC2 and VC2. Details on all testing activities can be found in sections 3.3 and 3.4 below.
In Table 4, the bracketing strategy to support the Phase II validation filling on FC2 and VC2 as described in the validation plan (Ref. 10) is shown. PV-batch 1 was included in Phase I validation (Ref. 2). PV-batches 5 to 8 are covered in this report. In Table 5, an overview of the validation batches 5-8 is shown.

Table 4: PV strategy justification to support EU and US submissions

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Product/Process:
Introduction of Covid-19 Vaccine in FC2/VC2 for 278 L batch size (Phase II)

Document ID:
20043-10000-PRRB-A2

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[redacted]

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Product/Process:	Document ID:
Introduction of Covid-19 Vaccine in FC2/VC2 for 278 L batch size (Phase II)	20043-10000-PRRB-A2

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[1]PV 1 was performed in Phase I validation (Ref. 1, 2 and 24).

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Table 5. Overview of PV batches.

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[1] Inspection was performed on FC2 instead of VC2 as described in Protocol deviation N°02.
[2] Incorrect lot size at finished level as described in protocol deviation N°03.
[3] Different item numbers were used as described in protocol and interim report (protocol deviation N°13)

3.2.3 Stability studies

Stability samples were taken for all PV batches at end of filling (19 tray boxes). The stability strategy is written in a memo (Ref. 22 and 25-27).

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3.3 Process testing results

Each validation lot was manufactured according to the approved master batch record (MBR), which is a combination of the approved electronic batch record (EBR) and BRAs. The batch record contains all operating parameters and instructions for sampling and testing.

3.3.1 Formulation

3.3.1.1 Microbial load during formulation

Testing activity	An overview of the microbial hold times that were challenged/targeted is given in Table 6. [redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance / evaluation criteria detailed in Table 7.
Conclusion	*PASS*

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Table 6: Overview of microbial hold times.

Hold time	*Process Step*	*Hold time*	*PV5 (hh:mm)*	*PV6 (Challenge)[1] (hh:mm)*	*PV7 (hh:mm)*	*Comments*
[redacted]						

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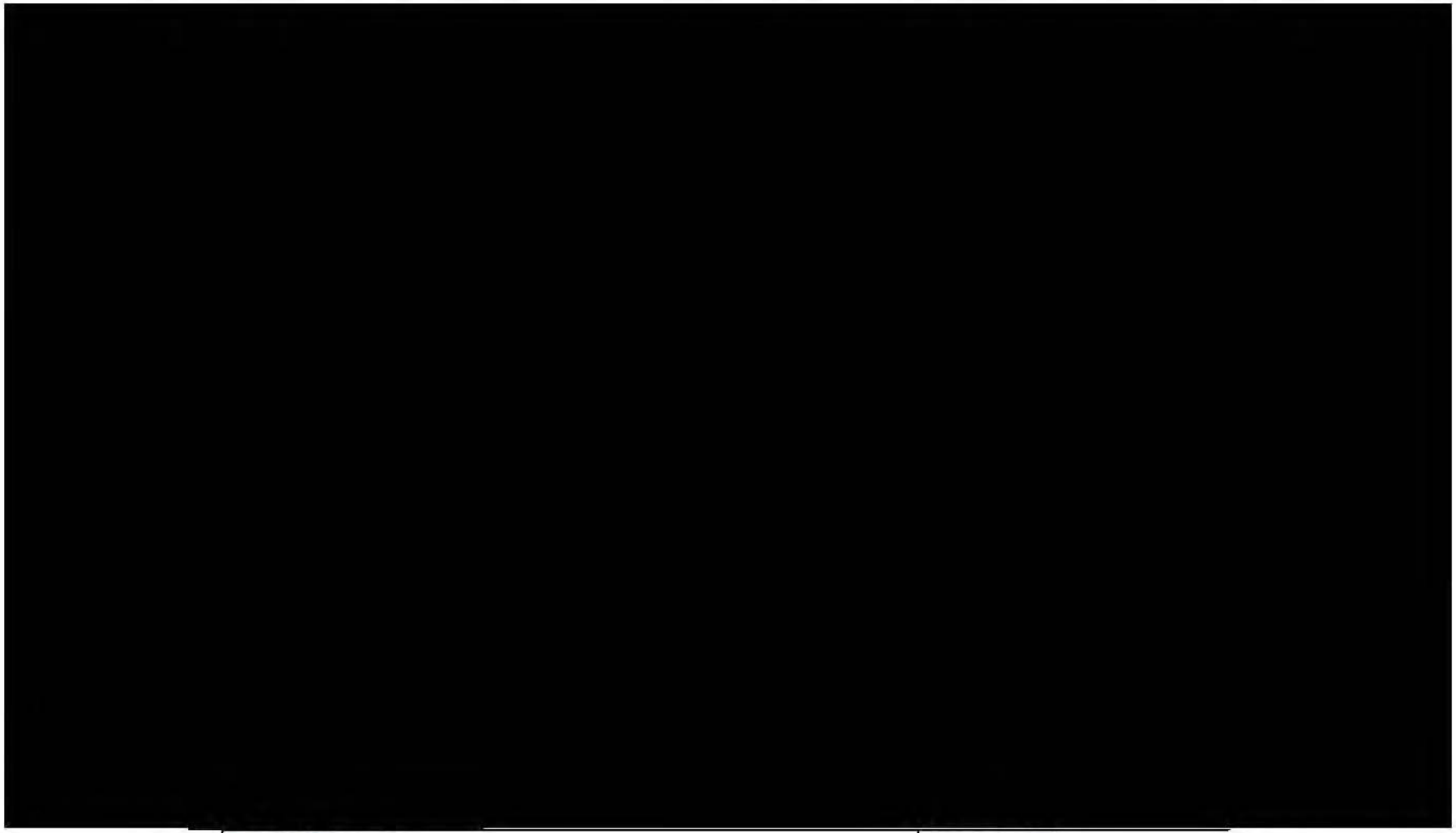

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[redacted]

[1] During the challenge, the hold times were exceeded to validate the targeted hold times.
[2] In PR#5624806, small temperature excursions are described for this hold time. The temperature of the product was evaluated for monitoring purposes only in addition to the controlled room temperature.There was concluded that there is no impact on the quality of the product.
[3] In PR#5643186, small temperature excursions are described for this hold time. The temperature of the product was evaluated for monitoring purposes only in addition to the controlled room temperature.There was concluded that there is no impact on the quality of the product.
[4] In interim reports, incorrect hold times were documented. This is described in PR#S700247.

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Discussion of results:

Bioburden

Results of bioburden for beginning and end were compared to their draft monitoring limits and listed in Table 8. All results were within specifications.

Appropriate sampling location for bioburden samples was evaluated according to SOP-86254 v2.0 in Attachment 1 of the Continued Verification Plan (CPV) (Ref. 23). In this document was defined that bioburden samples will be taken at begin position, except for T10 (sucrose) and T8. This will further be evaluated during CPV. Furthermore, the internal limits for bioburden samples will be determined during CPV.

Hold times

Challenges were performed during PV6, as described in Table 6. [redacted]

During phase I and phase II validation, challenge of hold times were performed. In Table 7, an overview of the challenged times is shown. [redacted]

Table 7: Overview of challenged validation batches.

Hold time	PV1 (Phase I (Ref. 24)) (hh:mm)[2]	PV3 (Phase II, 139 L (Ref. 28)) (hh:mm)	PV6 (Phase II, 278L) (hh:mm)	Proposed hold time
[redacted]				

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[redacted]

[1] A temperature adjustment to 2-25°C will be proposed since the DS is hold at 2-8 °C after thawing and during dilution, the temperature will not always be increased to 15 °C. (PR#S719477)
[2] During Phase I, not all microbial hold times were challenged and different hold time was challenged for sucrose solution.
[3] In interim reports, incorrect hold times were documented. This is described in PR#5700247.

Endotoxins
Results of endotoxins are listed in Table 8 and were all within specifications.

Conclusion
Bioburden and endotoxin results were within limits mentioned in protocol. Evaluation of the sample location and draft limits will be performed during CPV.
New microbial hold times will be proposed in the filing based on the challenged hold times.

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Table 8: Summary of microbial load testing and results of the formulation process

Process step	Sampling location	Sample qty	Lab method	UOM	Acceptance / Evaluation criteria	Limit type	PV5	PV6	PV7	Conclusion (PASS/FAIL)
Drug substance after hold (PV7 (Protocol deviation N°09)[6]	Drug substance bag after hold	10 mL	Bioburden – 200528-0099-001	CFU/10 mL	[redacted]	Monitoring limit[1]	NA	NA	[redacted]	PASS
	Drug substance bag after hold	0.5 mL	Endotoxins – TM-072-030	EU/mL	[redacted]	Monitoring limit[1]	NA	NA	[redacted]	PASS
Citrate buffer T2	Vessel – Start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit[1]*	[redacted]	[redacted]	[redacted]	*PASS*
	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit[1]*	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – Start hold time	10 mL	Endotoxins – LAB37351	EU/mL	[redacted]	*Monitoring limit[1]*	[redacted]	[redacted]	[redacted]	*PASS*
Citrate buffer T3	Vessel – Start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit[1]*	[redacted]	[redacted]	[redacted]	*PASS*
	Outlet – after	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit[1]*	[redacted]	[redacted]	[redacted]	*PASS*

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	complete hold time									
	Vessel – start hold time	10 mL	Endotoxins – LAB37351	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
Citrate buffer T3'	Vessel – Start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – start hold time	10 mL	Endotoxins – LAB37351	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
Citrate buffer T3 mixed	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – start hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
PBS Buffer T6	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Outlet – after complete hold time (PBS bag)	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*

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PBS Buffer T6'	Vessel – start hold time	10 mL	Endotoxins – LAB37353	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – start hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – start hold time	10 mL	Endotoxins – LAB37353	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
PBS buffer T6 mixed	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11464	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
Sucrose solution in T10	Vessel – start hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Outlet – after complete hold time	2 x 100 mL	Bioburden - LAB11465	CFU/100 mL	[redacted][2]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
Bulk in T7	Vessel – start hold time	10 mL	Endotoxins – LAB37354	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – end TFF	2 x 20 mL	Bioburden - LAB12943	CFU/20 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – after	2 x 20 mL	Bioburden - LAB12943	CFU/20 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*

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	complete hold time									
	Vessel – end TFF	10 mL	Endotoxins – LAB37451[3]	EU/mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
Bulk in T8 prior to sterile filtration	Vessel – end of BBR filtration (before dilution)	2 x 20 mL	Bioburden - LAB12943	CFU/100 mL	[redacted]	*Monitoring limit*[1]	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel - end of total hold (end of sterile filtration)	2 x 100 mL	Bioburden - LAB12943	CFU/100 mL	[redacted]	*Acceptance criterion*	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – end of BBR filtration (before dilution)	10 mL	Endotoxins – LAB37451[3]	EU/mL	[redacted]	*Acceptance criterion*	[redacted]	[redacted]	[redacted]	*PASS*
	Vessel – end of BBR filtration (after dilution)	2 x 5 mL	Endotoxins – LAB36816	EU/mL	[redacted]	*Acceptance criterion*	[redacted]	[redacted]	[redacted]	*PASS*

[1]Draft limits are used during PV-batches. During Continued Process Verification (CPV), limits will be determined using historical data according to SOP-86254 v2.0.

[2]Based on experience of the process, a draft monitoring limit of NMT 100 is used. During CPV, limits will be determined using historical data.

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[3]See Protocol deviation N°04: different methods were used as described in protocol.

[4] Sample was not taken, due to low volume in the tank. However, a bioburden sample was taken at start position (initial WFI). Furthermore, a bioburden sample was taken at the end of the formulation process (T8) which was within acceptance criteria.

[5] Result of a 10 ml sample, instead of 20 ml sample, due to small volume of sample. PR#5547010 (gQTS)

[6] Results are missing in interim report . This was described in PR#5700247.

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3.3.1.2 DS thawing

Testing activity	Thawing time of the drug substance (ACMF – Controlled room temperature thaw)
Data collection & evaluation method	
Acceptance/evaluation criteria	
Conclusion	*PASS*

Discussion of results:
Controlled room temperature thaw of drug substance (DS) was performed. Visual check was assessed after 24 hours and every 4 hours. In Table 9, overview of thawing time for PV7 is shown. After these thawing times, all DS bags were thawed. The target thaw is currently set at . This will be further assessed during CPV (Ref. 23). Downstream testing and sampling is evaluation in Section 3.3.1.9 and 3.3.2.5. All results are within specifications.

Table 9: Thawing time of DS

Batch	*DS*	*Start of thawing*	*Complete thawing*	*Thawing time (h:min)*
PV7	*ACMF*			

[1] In PR#5700247 was described that incorrect thawing time was calculated in BRA.

Conclusion:
The DS was completely thawed prior to start hold time of the thawed DS.

3.3.1.3 Confirmation mixing parameters T2, T3 and T3' (citrate buffer) and T6 and T6' (PBS buffer)

Testing activity	Mixing parameters confirmation for Citrate buffer in T2 , T3 and T3' and for PBS buffer in T6 and T6'. Confirm that the mixing of the citrate and PBS buffer comply with the specific mixing speed and time (dependent on which vessel is used) after dilution with WFI.

Tank	*Mixing Speed*	*Mixing Time*
T2		
T3		

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	T3' [redacted] T6 T6'
Data collection & evaluation method	[redacted] *Evaluation:* – Results for osmolality and pH measurement were compared towards the acceptance criteria. – The results for the different batches were tabulated in the final report and inter batch consistency was evaluated.
Acceptance/evaluation criteria	All test results meet the acceptance criteria detailed in Table 10.
Conclusion	*PASS*

Discussion of results:

The results of osmolality and pH are shown in Table 10. All results are within specifications. Therefore, the mixing parameters as described above are confirmed. Furthermore, inter batch consistency was evaluated. This was performed by visual evaluation based on Figure 3. [redacted]. No practical differences were observed.

Table 10: pH and osmolality results.

	Limit	PV5	PV6	PV7
T2 citrate buffer				
Osmolality	[redacted]			
pH				
T3 citrate buffer				
Osmolality	[redacted]			
pH				
T3' citrate buffer				
Osmolality	[redacted]			
pH				
T6 PBS buffer				
Osmolality	[redacted]			
pH				
T6' PBS buffer				
Osmolality	[redacted]			
pH				

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[redacted]

Conclusion:
The mixing parameters for citrate buffer (T2/T3/T3') and PBS buffer (T6/T6') were confirmed.

3.3.1.4 Confirmation DS dilution + DS pooling (T4)

Testing activity	[redacted]
Data collection & evaluation method	[redacted]

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Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 11.
Conclusion	*PASS*

Discussion of results:
The results of osmolality and pH are shown in Table 9. All results are within specifications. Therefore, the mixing parameters as described above are confirmed.

[redacted]

Table 11: [redacted] result in T4.

	Limit	PV5	PV6	PV7
[redacted]				

Conclusion:
The mixing parameters used during validation for diluted DS in T4 confirms that UV results are within specifications and complete mixing was performed.
DS pooling was validated successfully.

3.3.1.5 Evaluation of LNP formation

Testing activity	[redacted]).
Data collection & evaluation method	[redacted] *Evaluation:* The impacted CQAs should be conform to their specifications (Table 11).
Acceptance/evaluation criteria	The final results for the impacted CQAs should meet the acceptance criteria detailed in Table 12.
Conclusion	*PASS*

Discussion of results:
The LNP formation is evaluated based on downstream results of impacted CQAs described above. The final bulk and release results of the impacted CQAs are listed in Table 12. All results are within specification. Therefore, LNP formation can be considered successful.

Table 12: Impacted CQAs by LNP.

		PV5		PV6		PV7	
	Limit	Bulk	Release	Bulk	Release	Bulk	Release
LNP size (nm)	[redacted]						

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LNP polydispersity	[redacted]
RNA encapsulation (%)	
RNA content (mg/ml)	
ALC-0315 content (mg/ml)	
ALC-0159 content (mg/ml)	
DSPC content (mg/ml)	
Cholesterol content (mg/ml)	
RNA-Integrity (%)	
In vitro expression (%)	

Conclusion:
All results of impacted CQAs by LNP process are within specification. Therefore, LNP formation can be considered as successful.

3.3.1.6 Confirmation of TFF parameters

Testing activity	[redacted]
Data collection & evaluation method	
Acceptance/evaluation criteria	The results should meet the acceptance criteria detailed in Table 14.
Conclusion	*PASS*

Discussion of results:

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Results of the samples from the [redacted] at different time points during [redacted] step for pH are listed in Table 13.

Table 13: Overview of [redacted]

	PV5	PV6	PV7
[redacted]			

[redacted]

[redacted] ll results were within specification.

Table 14: [redacted] final bulk.

	Limit	PV5	PV6	PV7
RNA encapsulation (%)	[redacted]			
RNA content (mg/ml)				

Conclusion:
All [redacted] results are within specification. Therefore, the TFF process can be considered as successful.

3.3.1.1 [redacted]

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]

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[redacted]

Conclusion:
The flow assures a smooth filtration of the product and show no blockages of the bioburden reducing and sterile filtration during the process.

3.3.1.2 In process testing prior to final dilution

Testing activity	[redacted]
Data collection & evaluation method	[redacted]

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	- The multiple results are used for inter-batch consistency.
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 15.
Conclusion	*PASS*

Discussion of results:

[redacted] Therefore, the dilution based on the theoretical [redacted] can be considered as successful and will be used in future manufacturing of batches.

Table 15: Results for [redacted].

	Limit	PV5	PV6	PV7
[redacted]				

[redacted]

Conclusion:
Dilution of bulk in [redacted] calculation was successfully validated.

3.3.1.3 Confirmation mixing parameters T10 (sucrose)

Testing activity	[redacted]
Data collection & evaluation method	A sample of at least 5 ml of the final sucrose solution in T10 was evaluated for [redacted]
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 16.

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Conclusion	*PASS*

Discussion of results:
The osmolality result is shown in Table 16. The results were within specification. [redacted] o practical differences were observed.

Table 16: Osmolality results in T10.

	Limit	PV5	PV6	PV7
Osmolality	[redacted]			

Conclusion:
All osmolality results are within specification. Therefore, the mixing parameters of T10 as described above are confirmed.

3.3.1.4 Confirmation mixing parameters in T8

Testing activity	[redacted]

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Data collection & evaluation method	[redacted] The results for the different batches will be tabulated in the final report and inter-batch consistency will be evaluated.
Acceptance/evaluation criteria	All test results should meet the acceptance criteria detailed in Table 17.
Conclusion	*PASS*

Discussion of results:

Results of [redacted]. All results are shown in Table 17. Mixing parameters described above were therefore conform. Furthermore, pH and osmolality data were collected to enhance process knowledge. Also these results were within specification. Furthermore, inter-batch consistency was evaluated visually based on Figure 7. No practical differences were observed.

[redacted] (see Table 22).

Table 17: Overview of impacted CQAs of T8.

	Limit	PV5	PV6	PV7
LNP size (nm)	[redacted]			
LNP polydispersity				
LNP size (nm) (ARD)				

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	[redacted]
LNP polydispersity (ARD)	
RNA content (mg/ml)	
% encapsulation	
pH	
Osmolality (mOsmol/kg)	
ALC-0315 content (mg/ml)	
ALC-0159 content (mg/ml)	
DSPC content (mg/ml)	
Cholesterol content (mg/ml)	
RNA-integrity (%)	

Conclusion:
The mixing parameters of final bulk (T8) were confirmed.

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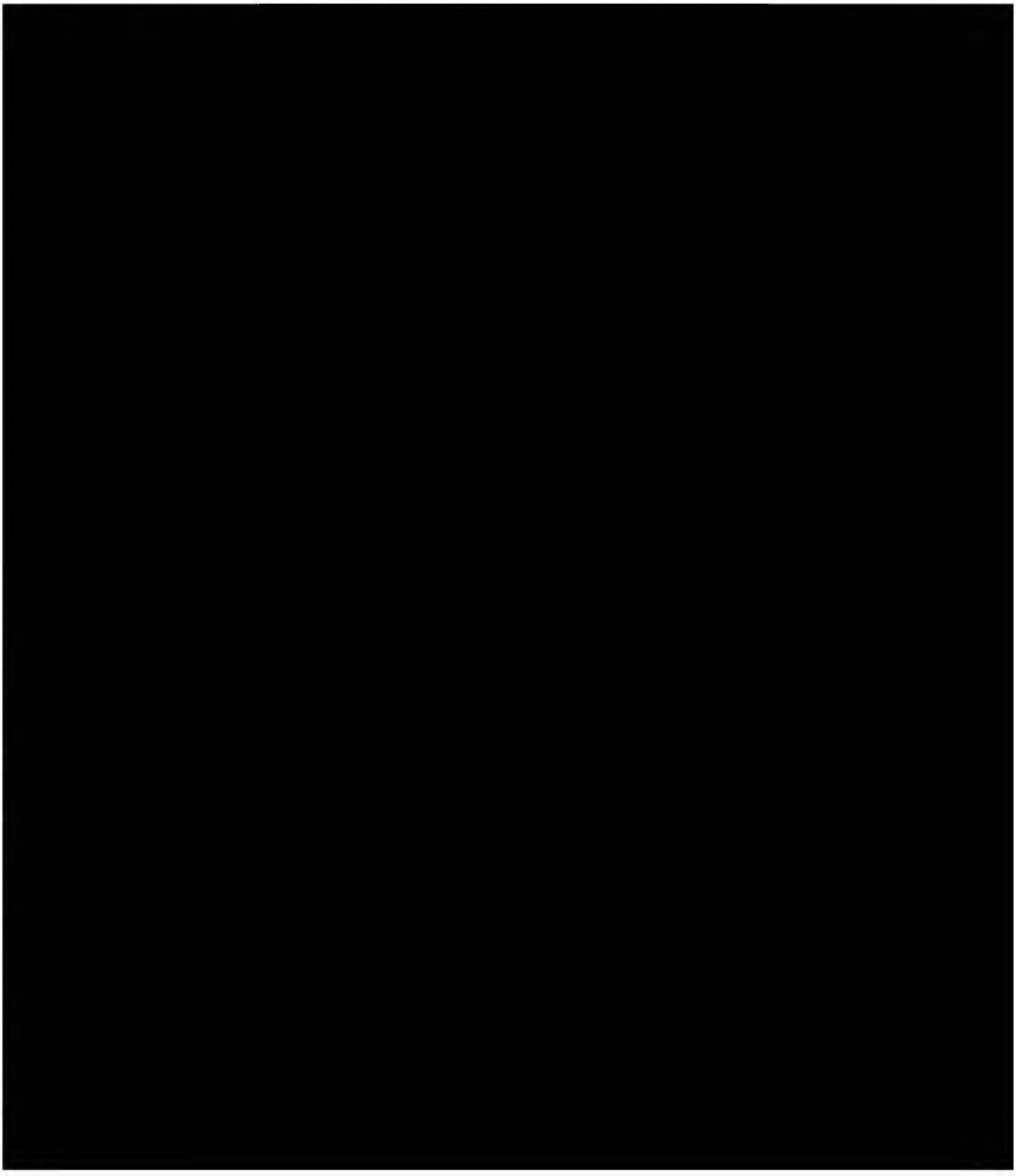

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3.3.1.5 Hold time challenge during formulation

Testing activity	[redacted]
Data collection & evaluation method	[redacted] ***Overview of hold times and challenges:*** [redacted] Evaluation: Release data were evaluated by comparing towards the acceptance criteria.
Acceptance/evaluation criteria	Release data should meet the acceptance criteria of the release lot plan.
Conclusion	*NA*

Discussion of results:
The product hold time challenges described in the test above were performed during PV6 and PV7. The [redacted]

Table 18: Hold time challenges during formulation.

Hold time	*Process Step*	*PV5*	*PV6*	*PV7*	*Currently filed and proposed*
[redacted]					

[1] During the challenge, the hold times were exceeded to validate the targeted hold times.

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Conclusion:
The product hold times during formulation were confirmed.

3.3.2 Filling activities

3.3.2.1 Intra and inter batch homogeneity

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	– All test results should meet the acceptance criteria detailed in Table 10. – [redacted]

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	– [redacted]
Conclusion	*PASS*

Discussion of results:

In Table 19, all CQA results for the impacted CQAs are shown. Samples were analysed in duplicate. All results were within specifications. Inter and intra batch variability was performed based on interval plots (Figures 8 and 9) (protocol deviation N°06).

Table 19: Overview of impacted CQAs of T8.

	Limit	PV5			PV6			PV7		
		Begin	Middle	~~End~~	Begin	Middle	End	Begin	Middle	End
LNP size (nm)	[redacted]									
LNP polydispersity										
RNA content (mg/ml)										
% encapsulation										
ALC-0315 content (mg/ml)										
ALC-0159 content (mg/ml)										
DSPC content (mg/ml)										
Cholesterol content (mg/ml)										

[redacted]

In Figure 8, the interval plots for all CQAs are shown where the 6 results per batch were pooled. [redacted]

[redacted] will be further evaluated during CPV (20043-10000-MPL0-A1).

[redacted]

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3.3.2.1 Cumulative hold time target

Testing activity	[redacted]
Data collection & evaluation method	For all PV-batches, worst case process times of the batch was sampled for RNA-integrity. [redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

[redacted]

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3.3.2.2 Routine testing at release

Routine sampling was performed at end of filling. In Table 22, the release results of the PV-batches are shown. All results were within specification. Comparability report will be written by ARD.

Table 22: Routine testing at release.

Method	Procedure ARD	Procedure (Protocol deviation N°12)	Limits on LIMS test plan	PV5	PV6	PV7
Appearance	[redacted]					
Appearance (Visible particulates)						
Subvisible particles						
pH						
Osmolality						
LNP size						

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Method	Procedure ARD	Procedure (Protocol deviation N°12)	Limits on LIMS test plan	PV5	PV6	PV7
	[redacted]					
LNP polydispersity						
RNA encapsulation						
RNA content						
ALC-0315 content						
ALC-0159 content						
DSPC content						
Cholesterol content						
Lipids Identity						
Container Content for injections						

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Method	Procedure ARD	Procedure (Protocol deviation	Limits on LIMS test plan	PV5	PV6	PV7
Identity of encoded RNA sequence	[redacted]					
In Vitro Expression						
RNA integrity						
Bacterial Endotoxin						
Sterility						
Container Closure Integrity[1]						

[1] Tested for stability batches only at release.

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3.4 Process performance results

Yield and inspection results are considered to be good indicators of overall process performance.

3.4.1 Formulation

3.4.1.1 Yield after formulation

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

[redacted]

Table 23: Yield after formulation.

	PV5	PV6	PV7
Samples	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Yield	[redacted]	[redacted]	[redacted]

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3.4.2 Filling

3.4.2.1 Yield after filling

Testing activity	[redacted]
Data collection & evaluation method	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

[redacted]

Table 24: Yield after filling.

	PV5	PV6	PV7
Samples	[redacted]	[redacted]	[redacted]
Yield			

3.4.3 Inspection

3.4.3.1 Automated inspection

Testing activity	The PV batches will be inspected through AI.
Data collection & evaluation method	[redacted]

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	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*PASS*

Discussion of results:

The calculated yield as shown in Table 25. [redacted]

Table 25: Yield after inspection.

	PV5	PV6	PV7
Samples	[redacted]		
Yield			

[redacted]

AQL sampling results are shown in Table 26. AQL sampling results were within limits.

Table 26: AQL sampling results.

Type of defects	AQL limit	PV5	PV6	PV7
[redacted]				

3.4.4 Packaging

3.4.4.1 Yield after packaging

Testing activity	[redacted]
Data collection & evaluation method	

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	[redacted]
Acceptance/evaluation criteria	[redacted]
Conclusion	*Provide a short PASS/FAIL conclusion based on the discussion of results below.*

Discussion of results:

[redacted]

Table 27: Yield after packaging.

	PV5	PV6	PV7
Samples	27 tray boxes (stability, retain, reference, comparability, inter batch variability, OMCL, release)	29 tray boxes (stability, retain, reference, comparability, inter batch variability, OMCL, release, TIR/TOR challenge)	26 tray boxes (stability, retain, reference, comparability, inter batch variability, OMCL)
[redacted]			
Yield	[redacted]		

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4 Data verification

Data was not changed in A2 version. Therefore, the data verification table of the A1 version is still in place. In *Attachment 3 of A1 version*, a data verification table is given. The table gives an overview of the different data sources used together with the name, signature and date of signature of the verifier.

5 Deviation discussion for process validation activities

5.1 Protocol deviations

This section lists and discusses all deviations that occurred versus the referenced protocol. These deviations are assessed upon impact on validation and lot release.

Deviation:	***Deviation n° 01*** ***List of CQAs in Attachment 1***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 02*** ***Inspection performed on FC2 for PV5***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 03*** ***Wrong lot size at finished level in protocol***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 04*** ***Different LAB method was used for bioburden and endotoxin testing***

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Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 05*** ***Internal limit LNP size***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 06*** ***Inter and intra batch variability evaluated based on interval plots***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 07*** ***SNL III inspection level performed for PV7***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 08*** ***Inter batch variability of IPC RNA content***
Deviation description:	[redacted]
Evaluation:	

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Correction / corrective action:	*NA*
Status:	*Closed*

Deviation:	***Deviation n° 09*** ***DS BB and endotoxin analysis***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 10*** *Crimping pressure operating range*
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 11*** ***Wrong procedure and test location in Table 9 of protocol***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 12*** ***Compendial release testing performed by Puurs and Grange Castel for PV5 and PV6***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*PV5 and PV6 will not be released to ROW*
Status:	*Closed*

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Deviation:	***Deviation n° 13*** ***Different item numbers were used in PV7***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

Deviation:	***Deviation n° 14*** ***Wrong mixing time in protocol***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	
Status:	*Closed*

5.2 Batch deviations

5.2.1 Overview batch deviations

In *Attachment 5*, all deviations (including unplanned interventions) that occurred during the manufacturing process under scope are listed with an evaluation of the impact of the lot deviation on the validity of the process validation and lot release.

Deviation:	***Deviation n° 15*** ***PR#5674046 – EP2163***
Deviation description:	[redacted]
Evaluation:	
Correction / corrective action:	*TBD*
Status:	*Open, however since this is not related to the validation, this is not followed up.*

Deviation:	***Deviation n° 16*** ***PR#5537169 – EP2163***
Deviation description:	[redacted]

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	[redacted]
Evaluation:	*Not related to product quality and validation strategy.*
Correction / corrective action:	[redacted]
Status:	*Closed*

5.2.2 Cumulative assessment

All deviations reported for the PV batches are special cause events and non-recurring deviations without impact on the validation activities for process validation of the 278L lot size Covid 19 vaccine per referenced protocol (Ref. 11).
Based on the above, it can be concluded that there is no cumulative impact on process validation or process robustness.

6 Recommended Changes

Following actions will be performed:

[redacted]

7 Conclusion for Process Validation activities

In this report the following three requirements were met:

1) ***All analytical results are within the acceptance criteria (see section 3.3)***
2) ***The overall process performance results are within the acceptance criteria (see section 3.4)***
3) **The filling process performance will be evaluated through IPC testing. All IPC results should meet the acceptance criteria stated in this protocol and if required, appropriate actions should be taken as described in the related working instructions.**
4) ***Deviations (unplanned interventions included) are discussed and a cumulative deviation assessment is carried out. There is no link between the deviations and the validation activities (see section 5)***
5) **Data assessment demonstrates that the batches are comparable.**

Consequently, the process validation activities as per referenced Process Validation Protocol of Covid-19 Vaccine are successful. An overview of the validated CPPs and operating ranges is given in attachment 4.

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The remarks left, if any, have no impact on the quality of the product and GMP requirements.

General conclusion: ***PASS***

The lots are subject of a stability as detailed in Ref. 25-27.

8 Control Strategy and Continued Process Verification Plan

8.1 Control strategy

The current process is maintained in a validated state using the process parameter settings, ranges, process restrictions, work instructions, in-process controls, release tests, etc. which are secured in batch records, PLC, forms, procedures, … No new control strategies have to be implemented as a consequence of this validation.

Validated challenged hold times will be adjusted in the filing (PR#5719477).

8.2 Continued Process Verification plan

The continued process verification plan is already available in document 20043-10000-MPL0-A1.

9 Glossary

Abbreviation	Explanation
AI	Automatic Inspection
AOA	Analyse op Aanvraag (Analysis on request)
BBR	Bioburden Reducing
BP	Bulk Product
BRA	Batch Record Attachment
CPP	Critical process parameter
CPV	Continued Process Verification
CQA	Critical quality attribute
DLS	Dynamic Light Scattering
DS	Drug Substance
EBR	Electronic Batch Record
F	Finished
FB	Formulation Booth
FC	Focus Cell
IPC	In process control
IL	Inspection Line
LNP	Lipid Nano Particles

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MBR	Master Batch Record
RMS	Recipe Management System
SOP	Standard Operating Procedure
TBD	To Be Determined
TFF	Tangential Flow Filtration
TIR	Time In Refrigerator
TOR	Time Out Refrigerator
VC	Vaccine Cell
WSL	Washing and Sterilizing line

10 Attachments

1. Process Validation Protocol (20043-10000-PRP2-A1, Gnosis ID: 0901201b876f8aaa)
2. Overview of CPPs and IPCs
3. Data verification table (Attachment 3 of 20043-10000-PRRB-A1, Gnosis ID: 0901201b87ab0d4f)
4. Validated critical process parameters and operating ranges
5. Batch deviations
6. Signed Approval Page

11 Document History

Version:	**Author:**	**Last edited on:**
A2	[redacted]	*18/03/2021*
Following adjustments were performed: – *In Table 6 and Attachment 2, clarification about the temperature deviations were added.* – *Protocol deviations 11-14 were added.*		
A1	[redacted]	*05/03/2021*
First Version		

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1. CPPs

[redacted]

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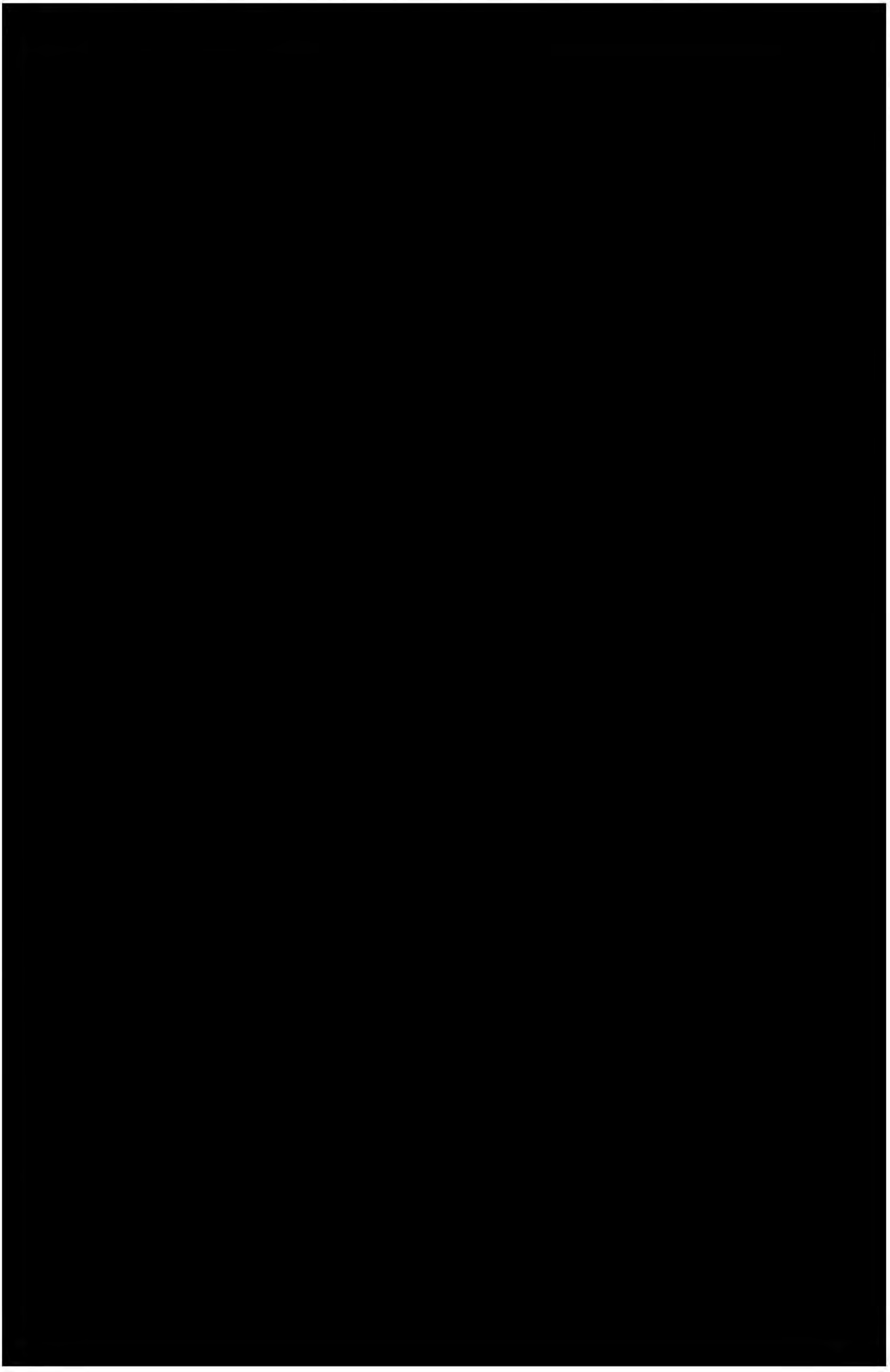

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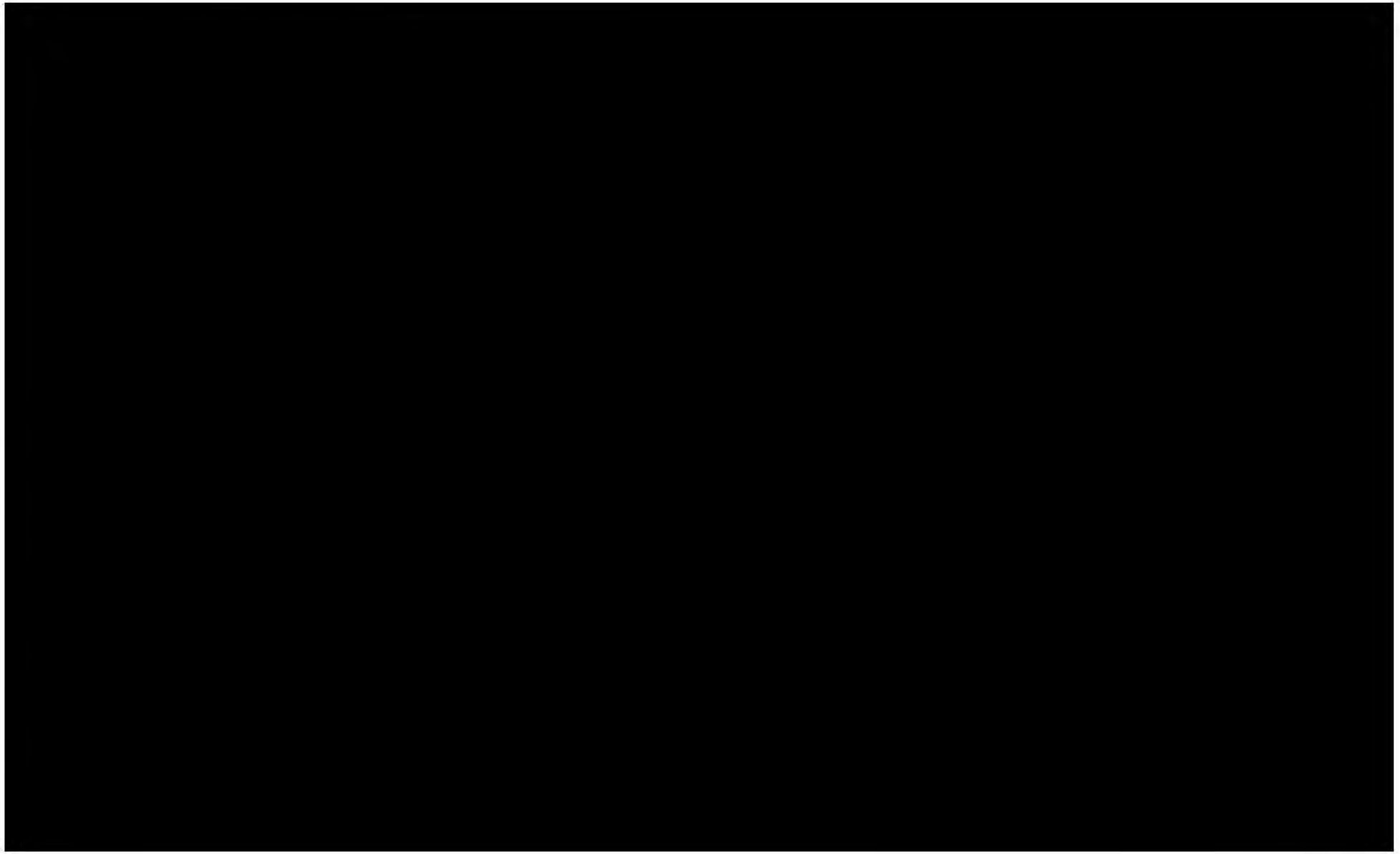

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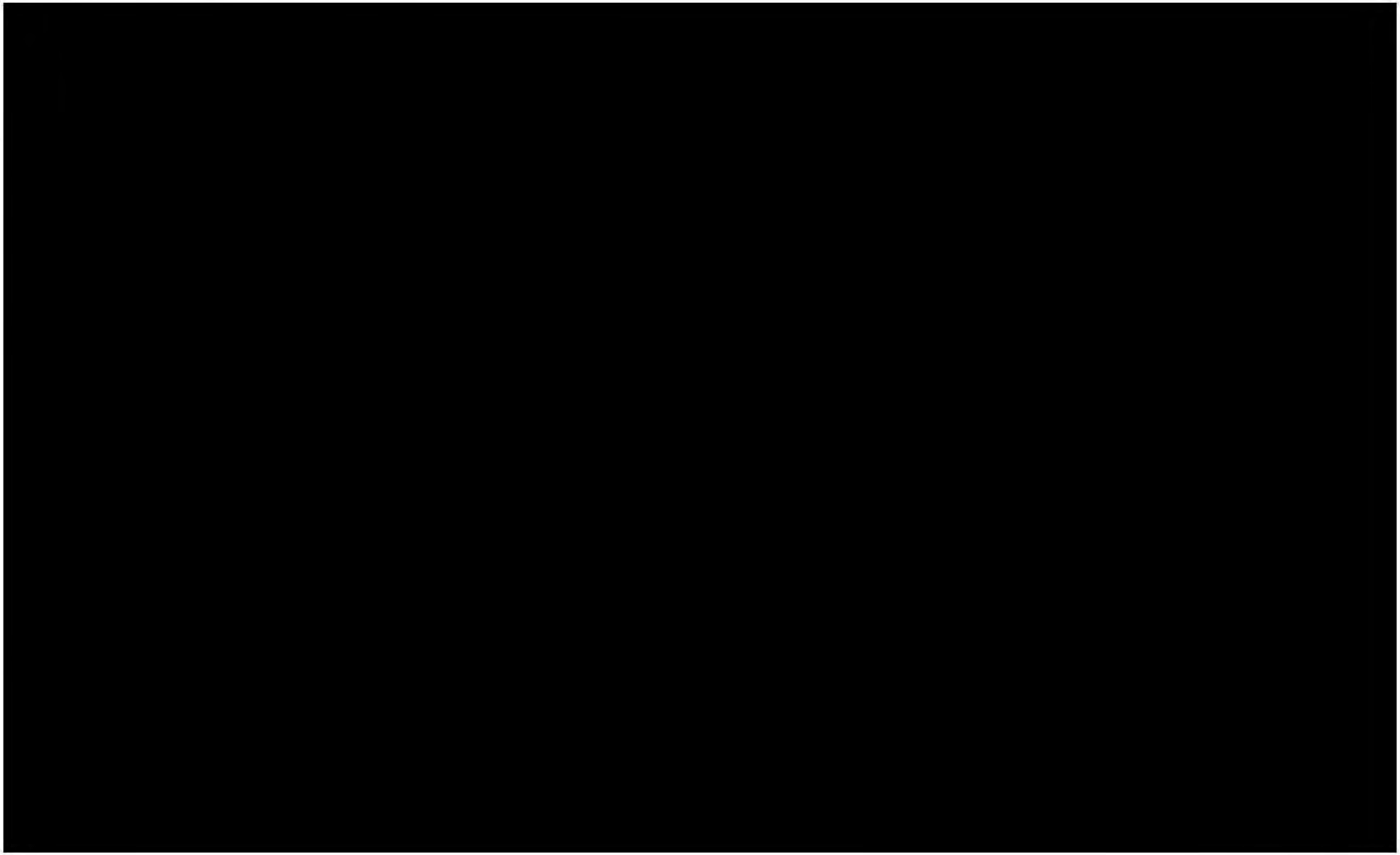

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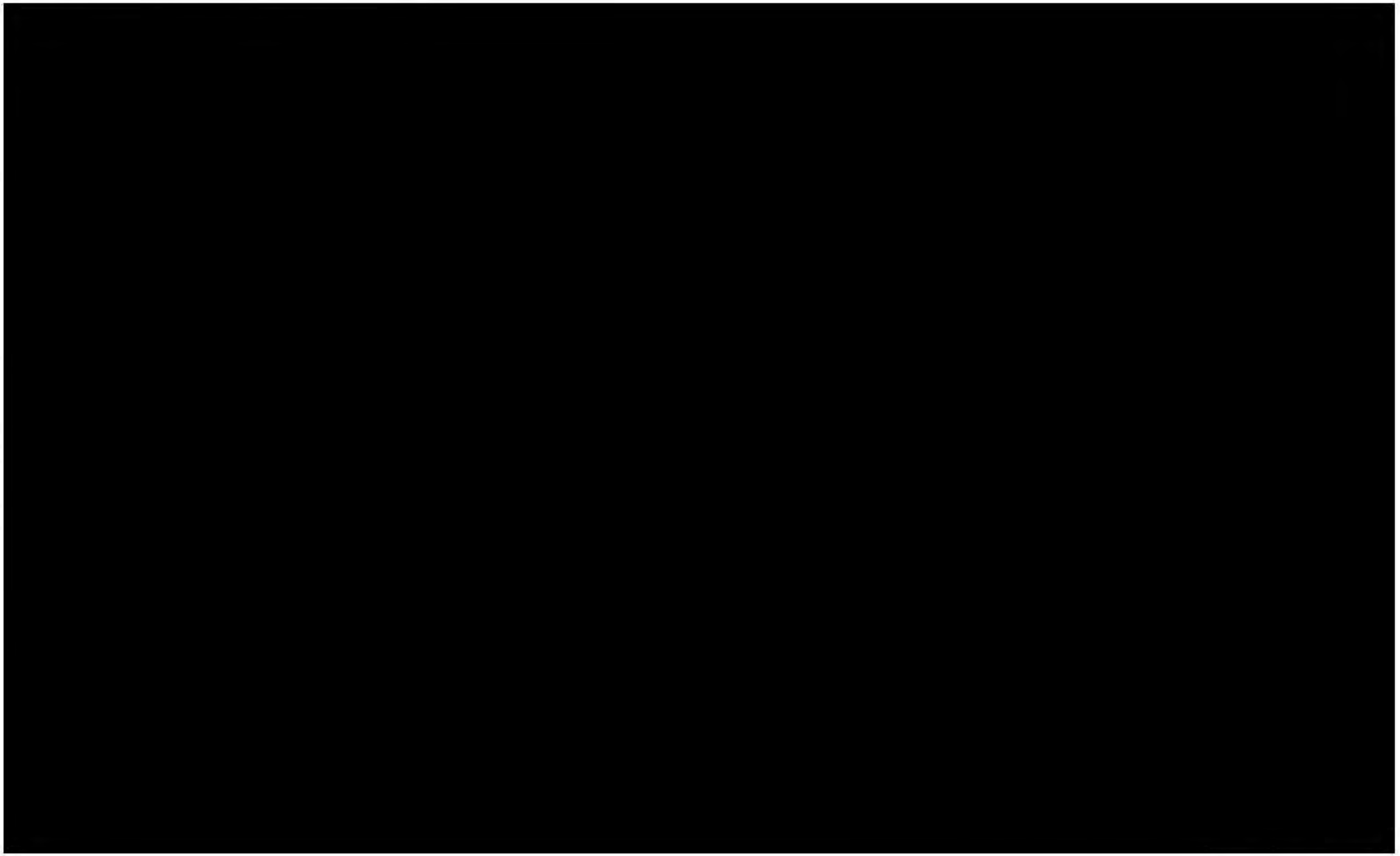

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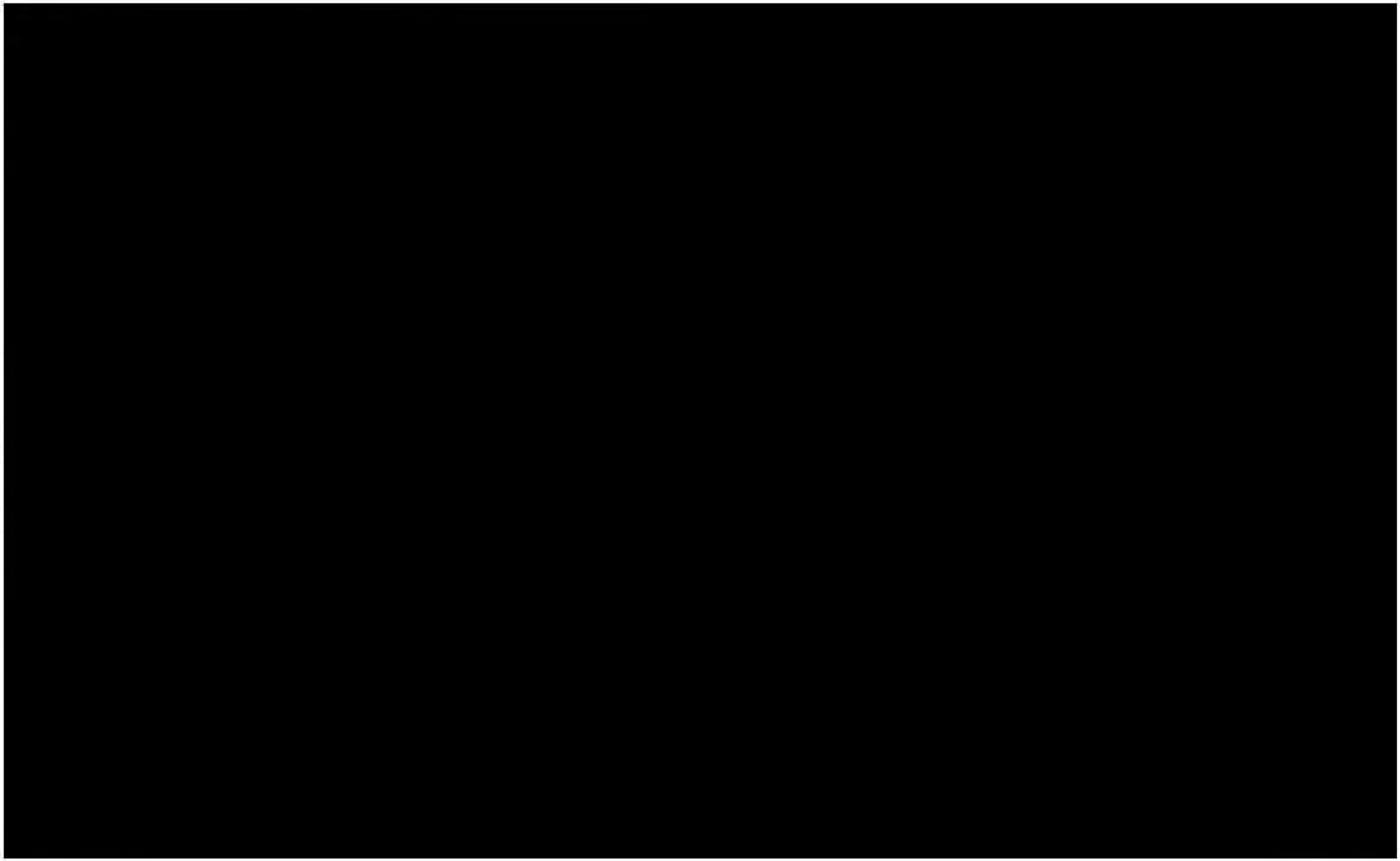

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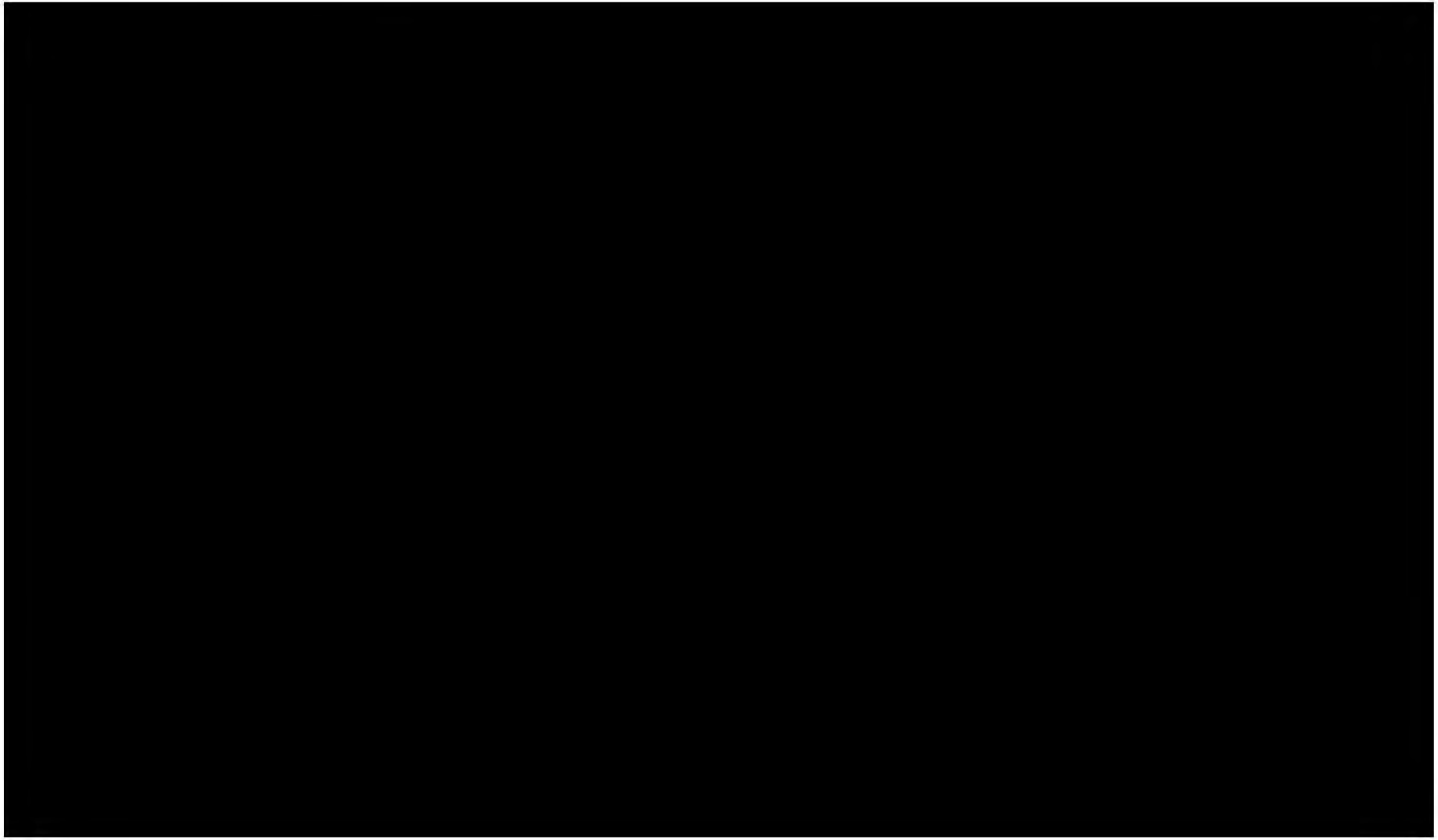

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All tests in italic are IPT-M tests, for monitoring purposes.
[1]Only one of the two filters needs to pass both pre- and post-use filter integrity

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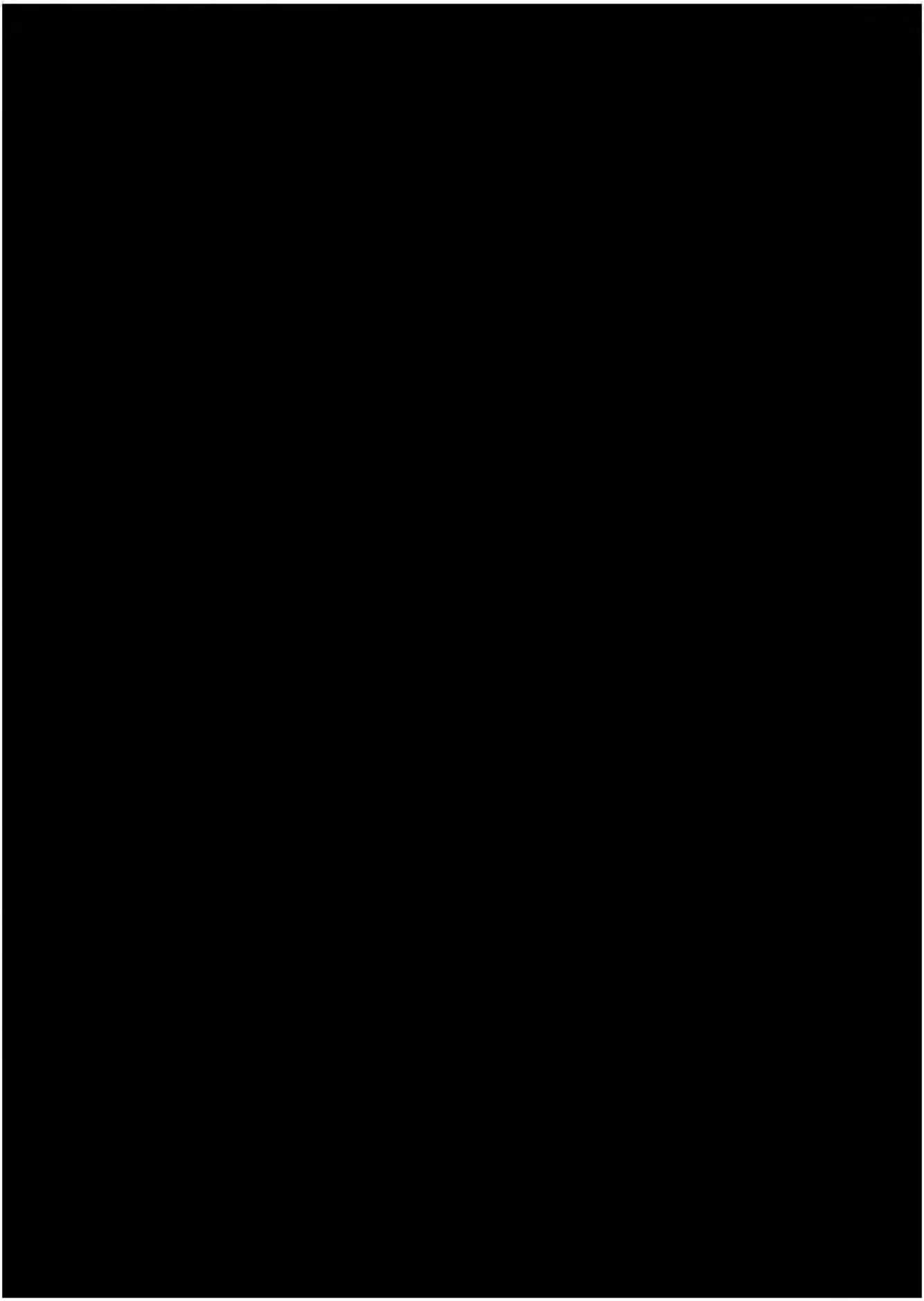

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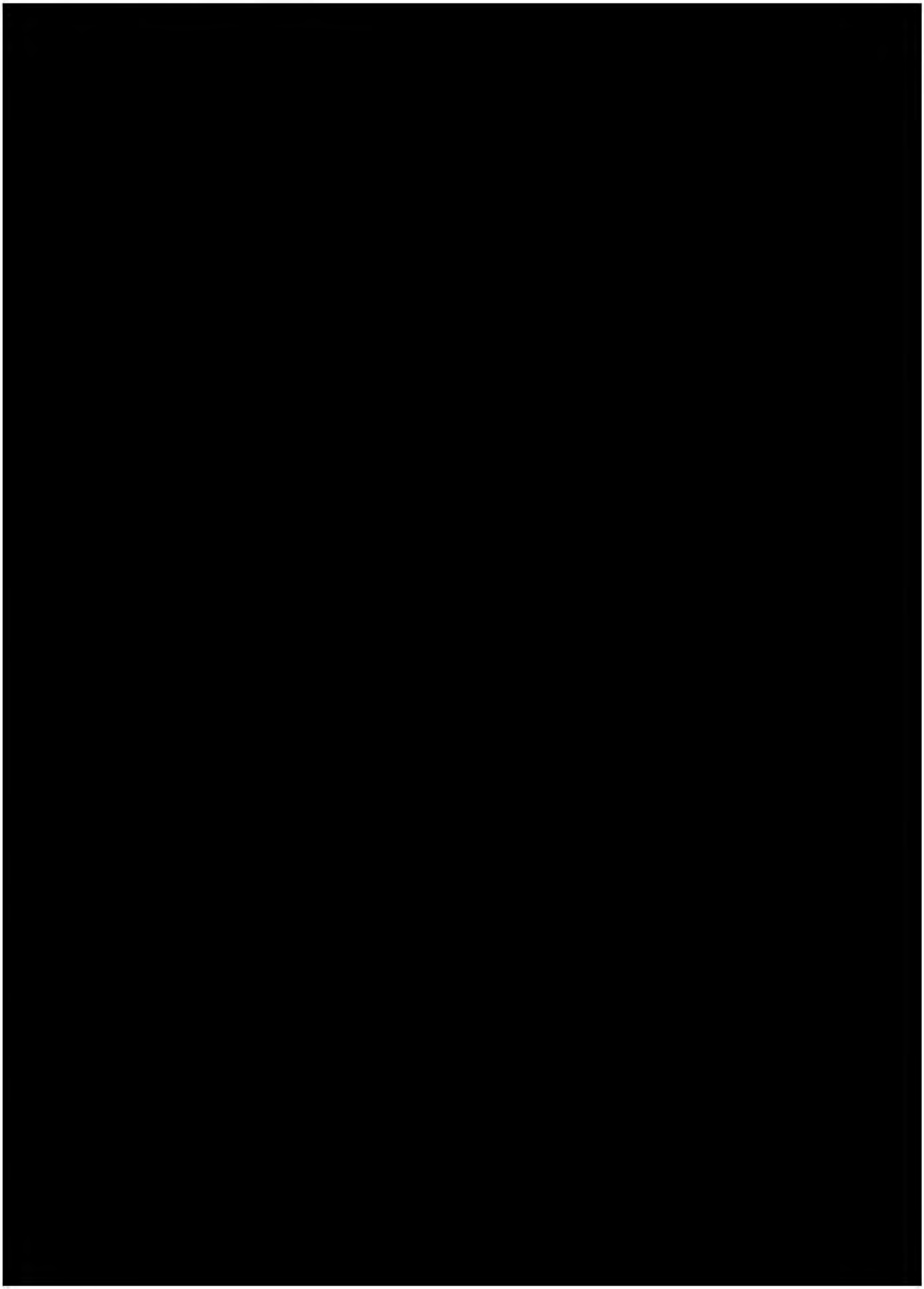

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DeskTop View

Report Executed By: Elien Rosier **Report Executed On:** 25-February-2021

PR #	Site	Record Type	Title / Short Description	Responsible Person	Date Opened	Due Date	Status	Batch #
5537169	Puurs	Manufacturing Investigations / Quality Assurance Report (QAR)	ECO - VACC 2- grade A WACC 2 isolator - missing samples (dropped & damaged) - PAS P1, P2 & AAS A1 - EP2163 - Comirnaty	[redacted]	8-Jan-21	07-Feb-21	Approved	EP2163
5674046	Puurs	Manufacturing Investigations / Quality Assurance Report (QAR)	LG2: verkeerd batchnummer in OBD's voor Zweden	[redacted]	17-Feb-21	18-Mar-21	In Progress	EP9598 EP2163

[redacted] 19 Mar 2021 09:27:009-0400

REASON: I approve this document.

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docUUID : [redacted]

Scope Used To Run Report: Puurs / Manufacturing Investigations / Quality Assurance Report (QAR)

Query Description: CLOSED PRs included; Batch #: EM5261, EP2163, EM5260, EP2166, EP4357, EP6775

-End of Report-

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Status	Effective	Effective Date	-	Version	1.0	Doc Name	FORM-105489
Title	FORM: Process Validation Report (Drug Product)						
Doc Alias	F(2)-19-002-PV Report			Site Code / Department		Puu / Validation Master Plan	

EXTERNAL COMPANY AUTHORITY:

BIONTECH	[redacted] ASSOCIATE DIRECTOR GLOBAL, CMC	[redacted] Digitally signed by [redacted] Date: 2021.03.18 20:19:43 +01'00'
NAME OF EXTERNAL COMPANY	NAME & JOB TITLE EXTERNAL COMPANY REPRESENTATIVE	SIGNATURE & DATE

The signature of the External Company Representative indicates that the information in the document comply with the requirements and is correct from a technical standpoint.

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SITE QUALITY AUTHORITY:

[redacted]	QUALITY PROJECTS ASSOCIATE	
NAME	JOB TITLE	SIGNATURE & DATE

The signature of the Site Quality Authority indicates that this document has been reviewed by the External Company Authority and the External Company approval is attached to this document.

This document is valid as from the date of the last signature.

[redacted] 19 Mar 2021 09:27:009-0400

REASON: I approve this document.

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