	Technical Summary	Date: 18DEC2020
1 Moderna Way Norwood, MA 02062 www.modernatx.com	Project: mRNA-1273 Drug Product UDP Lot: 6008620003 (Catalent Lot 027L20) LDP Lot: 7006520016 (Catalent Lot 027L20A) Event: REC 284379	Page 1 of 3

1. Triggering Event Summary

- 1.1. **Problem Statement:** During filling start-up activities for Lot 027L20 at Catalent, Bloomington, IN, the fill/finish facility for mRNA-1273 Drug Product, the operators noticed that product had begun to leak from the (b) (4).
(b) (4) An operator was observed that the connection had not been fully seated before removing the connector sealing tabs. When the leak was observed, the connection was seated. No product had been filled at the time of detection. As the leak was (b) (4).
(b) (4) the sterile boundary had been breached. The product was stored in 2-8°C for ~9 hours. A second redundant sterile filtration pathway was setup and the batch was re-filtered following process steps outlined in the batch record. Additional pages from the formulation section of the MBR were issued for Lot 027L20 to document the re-filtration.


2. Root Cause:

- 2.1. The most probable root cause of the leak was determined as gap in method A-PBA-21-01-040-A (Performance based assessment for installation and usage of disposable sterile connectors in parental manufacturing). The procedure did not limit the assessment to low risk connections (for example demonstration in classroom setting). For lot 027L20, the associate in training conducted the connection for the first time at this critical aseptic connection step and failed to make the connection correctly.

3. CAPAs:

3.1. Immediate Actions

- 3.1.1. Re-filtration performed: Leaks are addressed per A-SOP-21-01-066, Drug Product Formulation and Filling Product Leaks Program, a leak (b) (4).
(b) (4) is an overall medium risk to product SIS PQ (minimal risk to bioburden due to (b) (4) environment and gowning).
- 3.1.2. The operators immediately clamped the tubing to stop the leak. The product was stored in 2-8°C for ~9 hours.
- 3.1.3. Manufacturing Technology Specialist reviewed the (b) (4).
The (b) (4) appeared to be fully engaged when they performed a visual review of the connection.
- 3.1.4. A second filtration pathway was setup. Bioburden and (b) (4) were resampled, and the batch was re-filtered (only (b) (4) of the batch was able to be filtered during the subsequent filtration).

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3.2. Long Term Actions

- Update A-PBA-21-01-040-A (Performance based assessment for installation and usage of disposable sterile connectors in parental manufacturing). The PBA will be updated to ensure that initial (b) (4) training is performed on lower risk connections (such as in a classroom setting)
- Conduct awareness communication of this issue per existing action 291349 and Deviation Reporting to remind operators to handle (b) (4) with care and to inspect for damaged (b) (4) prior to making the Aseptic connection.

4. Product Impact

4.1. In-process and release testing passed all specifications:


- The leak potentially impacted sterility of product as a result the leak. The product underwent re-filtration on 30NOV20. Additional bioburden and (b) (4) (b) (4) samples were collected from the re-filtration.
- Pre-filtration bioburden results from both the initial and re-filtration were within specification with counts of (b) (4)
- Final Product Sterility Testing, as well as supplemental B/M/E PPQ sterility testing, was found within specification.
- (b) (4) results pre- and post- the initiation sterile filtration were within specification (b) (4)
- All release testing is within specification (see attached CoA)

4.2. Impact of Refiltration:

Development study data is available for mRNA 1273 diluted Drug product for undergoing multiple filtrations. Moderna document PD-MEM-0432 summarizes work performed to evaluate diluted bulk mRNA-1273 Drug Product sterile filtered for a total of (b) (4). Samples were collected after each of the (b) (4) filtrations and analyzed for particle diameter, encapsulation efficiency, polydispersity, subvisible particulate, RNA content and lipid content. The biophysical and content characteristics of the drug product from this study remained within acceptance criteria for all the materials generated from re-processing.

4.3. Leachables Assessment:

Moderna Document PD-MEM-0433 summarizes that re-filtration of Lot 027L20 through (b) (4) sterilizing grade filters does not pose any additional safety risk due to leachables from these extra filters.

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5. Disposition

5.1. Moderna release of this batch will be put on hold pending response from FDA.

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Document Approvals
Approved Date: 18 Dec 2020

Task: Approval Task Verdict: Approve	(b) (6) [REDACTED] (b) (6) [REDACTED]@modernatx.com) MS&T Approval 18-Dec-2020 17:28:38 GMT+0000
Task: Approval Task Verdict: Approve	Paul Dawidczyk, (b) (6) [REDACTED]@modernatx.com) Regulatory Approval 18-Dec-2020 17:42:20 GMT+0000
Task: QA Approval Task Verdict: Approve	Jennifer White, (b) (6) [REDACTED]@modernatx.com) Quality Assurance Approval 18-Dec-2020 17:51:28 GMT+0000

CERTIFICATE OF ANALYSIS

Product Description:	mRNA-1273	Moderna Part #:	60086
Manufacturer Name:	Catalent	Container/Closure:	10R Valor Glass Vial, 20 mm Stopper, 20 mm Cap
Manufacturer Lot:	027L20		
Moderna Lot Number:	6008620003	Specification:	SPC-1128
Date of Manufacture:	01Dec2020	Expiry Date:	01Jul2021

Product Attribute	Method	Parameter	Specification	Result
Appearance	SOP-0278	Appearance - Color	White to off-white dispersion.	White to off-white dispersion
		Appearance - Particulates	May contain visible, white or translucent product-related particles	Essentially Free of Particulates
Concentration	SOP-0999	RNA Content	(b) (4) (Target: 0.20 mg/mL)	
Identity	SOP-1032	Identity	(b) (4)	
Purity	SOP-0996	Purity		
		% IG1		
		% IG2		
		% IG3		
% RNA Encapsulation	SOP-1000	% Encapsulation		
In vitro Translation	SOP-0937	Result		
pH	SOP-0288	pH		
Osmolality	SOP-0279	Osmolality		
Dynamic Light Scattering	SOP-0998	Particle Size		
		Polydispersity		
Lipid Identification	SOP-1001	SM102		
		Cholesterol		

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CERTIFICATE OF ANALYSIS

Product Description:	mRNA-1273	Moderna Part #:	60086
Manufacturer Name:	Catalent	Container/Closure:	10R Valor Glass Vial, 20 mm Stopper, 20 mm Cap
Manufacturer Lot:	027L20		
Moderna Lot Number:	6008620003	Specification:	SPC-1128
Date of Manufacture:	01Dec2020	Expiry Date:	01Jul2021

Product Attribute	Method	Parameter	Specification	Result
Lipid Content		DSPC	(b) (4)	
		PEG-DMG		
		SM102		
		Cholesterol		
		DSPC		
Lipid Impurities		PEG-DMG		
		% Area 1		
		% Area 2		
		% Area 3		
		% Area 4		
		% Area 5		
		RRT 1		
		RRT 2		
		RRT 3		
		RRT 4		
		RRT 5		
		% Total Impurities		
Particulate Matter	SOP-0509	10 µm particles per container		

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CERTIFICATE OF ANALYSIS

Product Description:	mRNA-1273	Moderna Part #:	60086
Manufacturer Name:	Catalent	Container/Closure:	10R Valor Glass Vial, 20 mm Stopper, 20 mm Cap
Manufacturer Lot:	027L20		
Moderna Lot Number:	6008620003	Specification:	SPC-1128
Date of Manufacture:	01Dec2020	Expiry Date:	01Jul2021

Product Attribute	Method	Parameter	Specification	Result
		25 µm particles per container	(b) (4)	
Container Content	SOP-0950	Container Content	>= 5.0 mL (>=10 doses of 0.5 mL from one vial)	(b) (4)
Bacterial Endotoxins	USP <85>	Bacterial Endotoxins	(b) (4)	
Sterility	USP <71>	Sterility		

This material meets specification: Yes

Revision History:

1.0 - Original

Unlabeled Drug Product Lot 6008620003

Drug Substance Manufacturer: Moderna, Norwood, MA

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Document Approvals
Approved Date: 18 Dec 2020

Approval Verdict: Approved	Steven Anderson, (b) (6) @modernatx.com) Quality Control Approval 17-Dec-2020 18:36:52 GMT+0000
QA Approval Verdict: Approved	(b) (6) (b) (6) @modernatx.com) Quality Assurance Approval 18-Dec-2020 16:12:00 GMT+0000

Site	State	Date Current State	Date Closed	Parent Record #
Bloomington, US	Closed - Done	18-Dec-2020	18-Dec-2020	N/A

General Information

Originator: (b) (6) **Date Opened:** 30-Nov-2020

Short Description: Leak at Sterile Connection / Validated Isolator Hold Time Exceeded MBR 256-100-308P-100, LOT 027L20, WO# 4360573

Assigned To: (b) (6) **Date Due:** 30-Dec-2020

Description:

Project code: 256-100-308
Master Batch Record (MBR) Number: 256-100-308P-100
Item Number: 701902
Room/Location: (b) (4)
Date/time observation: 30NOV20/1645
Date/time occurrence: 30NOV20/1645
Batch Record (BR) step / SOP step: 15.26/ A-SOP-21-01-066 Step 2.1

Before the filling of MBR 256-100-308P-100 Lot 027L20, a sterile (b) (4) was made to the fill line and clamps on product were opened. Connection was performed by Manufacturing Operator (b) (6), who was overseen by Room Lead (b) (6), and verified by Manufacturing Operator (b) (6). Product began to leak at the connection and (b) (6) observed that the connection had not been fully seated before removing the papers. When the leak was observed, the connection was seated. Approximately (b) (4) of product was lost. Value Stream Supervisor (b) (6) and QA Representative (b) (6) were notified. Quality informed Senior Supervisor Manufacturing Technology (b) (6) of the development.

Per A-SOP-21-01-066 step 2.1, a record was opened, and a rapid response was held to determine a path forward. It was decided that the product would be re-filtered. Product was scanned into (b) (4) at 1846, a new pathway was ordered, and B-pages were printed for the re-filtration.

Due to this issue, the validated isolator sterile hold time was exceeded. Segregation was performed, and (b) (4) were segregated and placed on hold per A-SOP-21-01-036.

Attached Files: Attachment 1 Segregation Status Tag REC 284379.pdf

Classification

Classification: Major

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Report template: (Redacted) Deviation Single Report with Family Summary v1.0

Report run by: (b) (6) on 18-Dec-2020 at 6:35 (Central Standard Time)

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Deviation Information

Date of Occurrence:	30-Nov-2020	Date of Detection:	30-Nov-2020
Type:	Contamination	Sub-Type:	Other
Local Deviation Type:	N/A	Process:	Filling
Department:	Drug Product - Filling	Location/Area:	(b) (4)
Customer(s) Affected?	Yes	Is Equipment Involved?:	No
Product(s) Affected?:	Yes	Material(s) Affected?:	No

Immediate Actions

Immediate Actions:

Leak was stopped, Value Stream Supervisor (b) (6) and QA Representative (b) (6) were contacted.

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Impact Analysis**Impact Analysis:**

Reference Attached RPN

Risk Analysis:

Reference Attached RPN

Recurring Deviation?: No**Impact & Risk Attachments:** Attachment 2 to Rec 284379, RPN.pdf**Notification****Notification Required?:** Yes**Notification Requirement:** Customer

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Investigation & Root Cause

Root Cause Analysis:

>>Man (Personnel):

- Room Lead (b) (6) and Manufacturing Associate (b) (6) is current on A-SOP-21-01-040, Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing and Performance Based Assessment (PBA) A-PBA-21-01-040-A, PBA for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing.
- Manufacturing Associate (b) (6) is current on A-SOP-21-01-040. However, they had not yet completed A-PBA-21-01-040-A. Interviews with the associates involved confirmed that (b) (6) was in-process of training/performing A-PBA-21-01-040-A. Room Lead (b) (6) was acting as trainer during this process. The connection (b) (6) performed for this lot was their first attempt as part of on-the-job training.

Human error was a contributing factor to this deviation.

>>Method (Process):

- A-SOP-21-01-040, Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing was reviewed. The procedure provides instructions on how to properly perform connections involving (b) (4)
- A-PBA-21-01-040-A, Performance Based Assessment for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing includes performing a connection utilizing (b) (4). The PBA does not limit how/when the assessment should be conducted. Specifically, training can occur in a classroom or during a production runs for connections that could be at any risk level. This lack of limit and/or guidance allowed for a newly in-training associate to make a critical aseptic connection. An opportunity for improvement was identified to limit the training for connections like the (b) (4) to reduce potential impact.

Method/Process was a root cause for this deviation.

>>Measurement:

- There are no incorrect units of measure, calculations, or standards that impacted this event.

Measurement was not a contributing factor to this deviation.

>>Machine (Equipment/System):

- The equipment/system did not cause the damage to the (b) (4) as there is no specific Catalent equipment is used to create or alter the connection. Within the executed batch record, there was nothing indicating Catalent equipment would cause the (b) (4) to become unengaged.

Equipment/System was not a contributing factor to this deviation.

>>Materials:

- Based on review of the batch record, interviews, and review of the connectors, the (b) (4) most likely would have operated as intended if fully engaged.
- NOTE: During review of materials, it was noted that Deviation 283121 was opened previously due to a leak that occurred at an (b) (4). The events and cause of Deviation 283121 differs from this deviation. The

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investigation of 283121 identified the probable cause of the leak was related to Material. Quality Assurance Supply Chain opened SCR 291442 and 291445 initiated to have the vendors further evaluate the (b) (4) involved in Deviation 283121.

Material was not a contributing factor to this deviation.

>>Mother Nature (Environment):

- There was nothing unusual noted that occurred during the time of use of the (b) (4) that would impact the connection.

Environment was not a contributing factor to this deviation.

Investigation Detail & Summary:

Event Details:

- Project code: 256-100-308P
- Master Batch Record (MBR) Number: 256-100-308P-100
- Room/Location: (b) (4)
- Date/time observation: 30NOV20/1645
- Date/time occurrence: 30NOV20/1645

After completion of sterile filtration and during filling start-up activities of MBR 256-100-308P-100 Lot 027L20, a sterile (b) (4) was made to the fill line and clamps on product were opened. The connection was performed by Manufacturing Operator (b) (6), who was overseen by Room Lead (b) (6), and verified by Manufacturing Operator (b) (6). Product began to leak at the connection and (b) (6) observed that the connection had not been fully seated before removing the papers. When the leak was observed, the connection was seated. Approximately (b) (4) of product was lost. No product had been filled at the time of detection.

Additionally, due to this issue, the validated isolator sterile hold time was exceeded. Segregation was performed, and (b) (4) (b) (4) were segregated and placed on hold per A-SOP-21-01-036, Product Segregation Procedures for Parenteral Manufacturing.

Immediate Actions:

Room Lead (b) (6) immediately clamped off the tubing to stop the leak. Leak was stopped, Value Stream Supervisor (b) (6) and QA Representative (b) (6) were contacted, and the issue was escalated. Quality informed Senior Supervisor Manufacturing Technology (b) (6) of the development. Per A-SOP-21-01-066 Drug Product Formulation and Filling Product Leaks Program step 2.1, a record was opened, and a rapid response was held to determine a path forward. It was decided that the product would be re-filtered.

Product was held in 2 – 8 °C storage in (b) (4). Product was placed in (b) (4) at 1846 on 30NOV20. A new pathway was ordered, and B-pages were printed to document the re-filtration. Product was removed at (b) (4) on 01DEC20. Product was in 2 – 8 °C storage for 8 hours and 47 minutes.

Re-filtration was performed following process steps outlined in MBR 256-100-308P-100. Additional pages (B pages) from the

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formulation section of the MBR were issued for Lot 027L20 to document the re-filtration. Bioburden and Client Characterization samples were re-pulled. Re-filtration was performed starting at (b) (4). The initial sterile filtration resulted in (b) (4) Sterile Filtrate Weight. The second sterile filtration resulted in (b) (4) Sterile Filtrate Weight.

The (b) (4) was retained for investigation.

Background:

Master Batch Record (MBR) 256-100-308P-101 utilizes (b) (4). The filling process uses a disposable sterile assembly integrated with disposable pathways to transfer sterile product into the final container. Per step (b) (4) of MBR, prior to use, all tubing is to be inspected per A-SOP-21-01-059, Inspect Pre-Sterilized Single Use Items. The packaging is also reviewed for damage per the procedure. Damage could indicate a potential lack of integrity of the tubing assembly.

Additionally, per A-SOP-21-01-059 a gross visual inspection is conducted with ambient light and no magnification for approximately 5 minutes. A gross visual inspection is a brief, overall inspection of a single use assembly with intent to identify major issues that are clearly visible, including but not limited to large particles (>1 mm), holes, and incorrectly assembled components. The procedure also states that during installation of tubing into the peristaltic pumps, all tubing hose barb connections are to be examined to ensure they are secure.

(b) (4)

per A-SOP-21-01-040, Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing. (b) (4)

Associates who perform the connection must be trained to procedure A-SOP-21-01-040, Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing. They must also complete a Performance Based Assessment (PBA) A-PBA-21-01-040-A, PBA for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing.

During filling, any leaks discovered are to be addressed per A-SOP-21-01-066, Drug Product Formulation and Filling Product Leaks Program. Per the SOP, leaks are defined as an unintentional and negligible loss of product during processing from a closed system or from a single use assembly due to a loose connection, defect, or other source of damage to equipment that is identified and resolved in a timely manner. Per A-SOP-21-01-066, a leak (b) (4)

(b) (4) environment is an overall medium risk to product SISPG. The procedures required a deviation to be initiated within (b) (4)

The risk level of medium was determined in RA-17-07-001, Risk Assessment for Product Leaks during Formulation and Filling for Vial, Syringe, and Flexible Filling Lines. The severity of the leak at this connection is leveled as Critical however there are existing mitigations in place to prevent and detect this failure. There are existing mitigations such as (b) (4) gowning and environment and aseptic procedures that provide a level of bioburden control to reduce potential impact to product SISPG.

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Evaluation of Leak

Manufacturing Technology Specialist (MT) (b) (6) reviewed the (b) (4) appear to be fully engaged when they had received the components. The connectors showed no abnormal appearance nor any other indication that the connectors would not operate as expected.

Investigation

Per step (b) (4) in MBR 256-100-308P-101, associates are to connect the (b) (4) (b) (4) following the instructions in A-SOP-21-01-040 Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing. Manufacturing Associate (b) (6) performed the connection. (b) (6) signed the executed batch record as a Trainee. Room Lead (b) (6) was acting as the Trainer for (b) (6). Manufacturing Associate (b) (6) performed the verification for this step.

Review of the event log from the executed batch record shows there were no events impacting the connection with the exception of the leak that was observed. There was nothing unusual noted during the inspection of the (b) (4) (b) (4) that would impact the connection.

Per A-SOP-21-01-040, there should be a click from each side of the coupled connectors. Additionally, the procedure instructs to visually ensure that the connectors are secured by confirming the tabs are in the correct position. The auditory and visual inspection ensures that the connection was made per manufacturer instructions.

(b) (6) were each interviewed. They all recall (b) (6) having some difficulty making the connection as it was his first attempt. The trainer, (b) (6), did state they did not perform a visual inspection of the connectors inadvertently. (b) (6), (b) (6) believe they heard the two clicks as an indication that the connection was properly made. The tabs were pulled, and the paper strips/seals were removed. The associates also confirmed that there no issues noted with the paper strips/seals when removed. The associates also noted there were no other distractions or extraordinary situations that occurred while performing the connection.

The associates stated that once the connectors were thought to be fully engaged/coupled, the clamp on the tubing from the product container was removed by (b) (6). Product started to progress in the direction of the connection. Once product reached the connection point, product leaked out. Approximately (b) (4) of product was lost. When the product leak was observed, (b) (6) immediately replaced the clamp on the tubing. (b) (6) also grabbed the connectors and squeezed them together. The connectors clicked and the leak appeared to have stopped. Based on the associates hearing an additional click and stoppage of the leak, it was determined the (b) (4) was not fully engaged as initially assumed.

The investigation team obtained (b) (4) attached to short pieces of tubing to attempt to recreate the failure observed by the operators wherein two clicks were heard but connectors were not fully engaged. The process was reviewed, and the connectors were assembled by the Deviation Writer (b) (6) and Manufacturing Technology Specialist (b) (6). The team assembled and reviewed the connections by inspecting engagement points between the connectors while also listening for clicks or other noises. The team was not able to recreate the event as described.

Employee Training Records were reviewed for (b) (6) who performed and verified activities per step (b) (4)

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Training for the (b) (6) is current on A-SOP-21-01-040, Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing and Performance Based Assessment (PBA) A-PBA-21-01-040-A, PBA for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing.

Review of the Employee Training Records confirmed that (b) (6) was current on A-SOP-21-01-040. However, they had not yet completed A-PBA-21-01-040-A. Interviews with the associates involved confirmed that (b) (6) was in-process of training/performing A-PBA-21-01-040-A. The connection (b) (6) performed for this lot was their first attempt as part of on-the-job training.

Review of A-PBA-21-01-040-A was conducted. The PBA does require the successful completion of performing a connection using the (b) (4). The PBA does not limit how/when the assessment should be conducted. Specifically, training can occur in a classroom or during a production runs for connections that could be at any risk level. This lack of limit and or guidance allowed for a newly in-training associate to make a critical aseptic connection. An opportunity for improvement was identified to limit the training for connections like the (b) (4) to reduce potential impact.

Isolator Sterile Hold Time Exceeded:

Per the MBR, filling batches should not exceed Total Allowable Hold Time as indicated in A-SOP-21-01-042 Aseptic Interventions in the Vial and Syringe Isolators and A-WI-21-01-042-01 Primary Manufacturing Processing Hold Time Matrix. Per A-WI-21-01-042-01, the Total Allowable Time for Isolator Use Time (Isolator Decontamination Expiration) is (b) (4) for the Vial Filler (System 2304). The Isolator Use Time is defined as the time from End of VHP cycle of isolator to end of capping / closure of Lyophilizer subdoor.

Due to the leak on 30NOV20, product was re-filtered. Once the product was re-filtered, the filling was started. Filling started at (b) (4). The Isolator Use Time ended at 2024 01DEC20 while filling was still in process. Filling /capping completed (b) (4). The once the final unit finished capping, the Isolator Use Time exceeded the (b) (4).
(b) (4)

The (b) (4) Total Allowable Time is based on data summarized in A-VAL-01-01-4404, Vial Aseptic Processing Interventions and Hold Time Matrix. Review of the validation documentation identified that the Isolator Use Time was successfully challenged up to (b) (4) as summarized in A-VPPQ-00072, "Requalification Campaign (January 2016) Media Fill Validation Summary Report for a Liquid Fill on the Vial Filler (System 2304) with 2 mL/ 13mm Vial Utilizing Portable Peristaltic Filling (PPF)." The Isolator Use time for Lot 027L20 was less than the longest challenge time captured within the validation. Additionally, the Final Product Sterility Testing was found to meet specification. Refer to Sample description (b) (4) assigned LIMS ID 1723679 and Sample description (b) (4) assigned LIMS IDs 1723685, 1723686, & 1723687.

All the product filled after 2024 01DEC20 was segregated and placed on hold per A-SOP-21-01-036; (b) (4) were segregated. Based on the validation data and sterility testing, the segregated material is recommended to be released.

Root Cause Analysis:

Refer to Root Cause Analysis field.

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Report template: (Redacted) Deviation Single Report with Family Summary v1.0

Report run by: (b) (6) on 18-Dec-2020 at 6:35 (Central Standard Time)

Page 8 of 11

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FDA-CBER-2022-1614-4805444

Trending:

Refer to Recurring Deviation Comments field.

SISPQ Impact:

The leak potentially impacted sterility of product as a result the leak. The product underwent re-filtration 30NOV20. Finish Product samples were collected when filling was resumed after refiltration.

- Post initial In-Process Bioburden Testing was found within specification for Sample description (b) (4) assigned LIMS (Laboratory Inventory Management System) ID 1723677. The sample had a bioburden count of (b) (4).
- Post re-filtration In-Process Bioburden Testing was found within specification for Sample description (b) (4) assigned LIMS (Laboratory Inventory Management System) ID 1732684. The sample had a bioburden count of (b) (4).
- Final Product Sterility Testing was found to meet specification for Sample description (b) (4) assigned LIMS ID 1723679 and Sample description (b) (4) assigned LIMS IDs 1723685, 1723686, & 1723687. The sample IDs are for the Beginning, Middle, and End of filling respectively.
- Initial Product (b) (4) Testing was found within specification for Sample description (b) (4) LIMS ID 1723675. The result from the testing was reported as (b) (4).

Based on product testing, there is no SISQP impact from after completion of re-filtration for lot 027L20. The lot is recommended for release.

(b) (6) provided a memo (PD-MEM-0432) documenting no expected impact to the mRNA-1273 drug product due to the refiltration. Reference Attachment 4 of the record. Additionally, (b) (6) provided a memo (PD-MEM-0433) stating low risk of additional leachable impact due to the refiltration. Reference Attachment 5 of the record. All (b) (6) release testing results were within specification.

Additionally, exceeding the isolator hold time potential impacted product sterility. All the product filled after 2024 01DEC20 (b) (4) was segregated and placed on hold.

- Based on data collected in A-VAL-01-01-4404, Vial Aseptic Processing Interventions and Hold Time Matrix, the Isolator Use Time has been successful challenged up to (b) (4). The Isolator Use time for Lot 027L20 was less than the longest challenge time captured within the validation.
- Additionally, the Final Product Sterility Testing was found to meet specification. Refer to Sample description (b) (4) assigned LIMS ID 1723679 and Sample description (b) (4) assigned LIMS IDs 1723685, 1723686, & 1723687. The sample IDs are for the Beginning, Middle, and End of filling respectively.

Based on the validation data and sterility testing, the segregated material from lot 027L20 is recommended to be release.

Based on product testing, there is no SISQP impact from after completion of re-filtration for lot 027L20.

The lot is recommended for release.

Conclusion

The root cause of the deviation is Method. A-PBA-21-01-040-A, "Performance Based Assessment for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing" does not limit how/when the assessment should be conducted. Specifically, of limit and/or guidance allowed for a newly in-training associate to make a critical aseptic connection. The contributing cause is Man. Associate in training failed to make the connection correctly and the Trainer failed to visually confirm the connection prior to further processing.

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Report template: (Redacted) Deviation Single Report with Family Summary v1.0

Report run by: (b) (6) on 18-Dec-2020 at 6:35 (Central Standard Time)

Page 9 of 11

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FDA-CBER-2022-1614-4805445

Actions

- Update A-PBA-21-01-040-A, "Performance Based Assessment for Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing" to limit and/or add guidance to perform training on lower risk (b) (4) (b) (4) (such as in a classroom setting) to reduce potential impact. Completion of the PBA consist of oral questions and behavioral tasks an employee must perform in front of a Designated Trainer. The PBA allows the employee to demonstrate competency in the performing the connection prior to making an Aseptic connection.
- There is an open action 291349 to conduct awareness communication to remind operators to handle (b) (4) (b) (4) with care and to inspect for damaged (b) (4) prior to making the Aseptic connection. Communication will also remind associates of best practices when using (b) (4) Operations Supervision is the owner of the communication.

Root Cause Attachment 5 to REC 284379 - Client Memo Leachable.pdf
Attachment(s): Attachment 4 to REC 284379 - Client Memo Reprocessing.pdf

Root Cause Grid

Row #	Cause Type	Cause Category	Cause Sub-Category
1	Root Cause	Method (Procedure or Document)	Inadequate - Incorrect Detail / Gap / Unclear / Contradicting
2	Contributing Cause	Man (Personnel) - Inadvertent	Confirmed Human Failure

Action Information

Action Required?: Yes

Effectiveness Check

Effectiveness Check Required?: Yes

Effectiveness Check Date Due: 31-Dec-2021

Effectiveness Check Plan:

Eliminate deviations for Aseptiquik leaks due to operators in-training.

Customer Approval

Customer Approval Required?: Yes
Customer Approval Received?: Yes

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

Report template: (Redacted) Deviation Single Report with Family Summary v1.0

Report run by: (b) (6) on 18-Dec-2020 at 6:35 (Central Standard Time)

Page 10 of 11

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FDA-CBER-2022-1614-4805446

Record Signatures

Supervisor Approval By: (b) (6)

Supervisor Approval On: 17-Dec-2020 6:39 pm

Quality Approval By: (b) (6)

Quality Approval On: 17-Dec-2020 7:39 pm

Optional Approver 1 Function: Operations

Optional Approval 1 By: (b) (6)

Optional Approval 1 On: 17-Dec-2020 7:22 pm

Child Hierarchy:

This section will report dependent children and any descendants for the selected record.

<u>REC ID</u>	<u>Project</u>	<u>Date Due</u>	<u>Date Completed</u>	<u>PR State</u>	<u>Short Description</u>
284379	Deviation	30-Dec-20	18-Dec-20	Closed - Done	Leak at Sterile Connection / Validated Isolator Hold Time Exceeded MBR 256-100-308P-100, LOT 027L20, WO# 4360573
292150	Action	26-Feb-21		Work in Progress	Update A-PBA-21-01-040-A to limit and/or add guidance to perform training

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

Report template: (Redacted) Deviation Single Report with Family Summary v1.0


Report run by: (b) (6) on 18-Dec-2020 at 6:35 (Central Standard Time)

Page 11 of 11

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FDA-CBER-2022-1614-4805447

REC 284379
Attachment 1

	Document Number:	A-FRM-21-01-013	Page 1 of 1
Title: Segregation Status Tag			

Lot Number: 027L20

Printed By/Date (b) (6) 21NOV20

31

(b) (4), (b) (6)

REC 284379
Attachment 2

Catalent BIOLOGICS	Document Number:	N/A	Page 1 of 3
Title: Impact Analysis and Risk Priority Number (RPN) Calculation Template			

Reference A-SOP-03-01-008, Deviation Report

Record Information			
Record #	Impacted Lot(s)	Scribe Initials/Date	
284379	027L20	(b) (6) 01DEC20	
RPN Attendees			
<ul style="list-style-type: none"> • Include Initial Sets/Department of all individuals present. • At minimum QA, a Supervisor or Manager from the affected department. 			
(b) (6)	(MFG)	(b) (6)	(QA)
	(MFG)		(VAL)
	(QA)		(MFG)
	(QC)		(QC)
	(MFG)		(MFG)
			(TS)
			(QA)
			(QA)
			(VAL)
			N/A

Impact Analysis Questions	
What is the potential impact to SISPQ?	TBD through the investigation.
Are multiple lots impacted by this event?	No
Are the impacted products under Catalent control?	Yes
If equipment and/or product on hold, what is the justification for moving forward with processing? (N/A if no items are on hold due to this event)	N/A
Additional Information (As Applicable)	N/A

Attachment #:	1 2	Record #:	284379	Initials/Date:	(b) (6) 01DEC20
(b) (6)					

Catalent BIOLOGICS	Document Number:	N/A	Page 3 of 3
Title: Impact Analysis and Risk Priority Number (RPN) Calculation Template			

Risk Assessment (RPN) Calculation Tool

(b) (4)



Attachment #:	12 0	Record #:	284379	Initials/Date:	(b) (6)	01DEC20
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(b) (6)

08 Dec 20

Catalent BIOLOGICS	Document Number:	N/A	Page 1 of 1
Title: Impact Analysis and Risk Priority Number (RPN) Calculation Template			

Changes and Justifications:		
1.	Change:	Removed (, and someone who can speak to the incident are required to be present.) from RPN Attendees box.
	Justification:	To align with SOP-03-01-008.
2.	Change:	Removed (What mitigations are in place?)
	Justification:	Not necessary to level deviation.
3.	Change:	Removed Impact Analysis Question (Is there any potential impact to patient safety?)
	Justification:	This information is covered in the 1 st question.

Attachment #:	12	Record #:	284379	Initials/Date:	(b) (6) 01DEC20
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(b) (6)

08 Dec 20

REC 284379

Attachment 3



1300 S Patterson Drive
Bloomington, IN 47403 USA
catalent.com

812-340-9698

Initial Notification of Major Deviation

Deviation Report Number: REC 284379

Batch Record: 256-100-308P-100

Lot Number: 027L20

Date of Recognition: 30Nov20

Description of Deviation:

Leak at Sterile Connection/Validated Isolator Hold Time Exceeded; Lot 027L20, MBR 256-100-308P-100, (b) (4)

Deviation Details:

Before the filling of MBR 256-100-308P-100 Lot 027L20, a sterile (b) (4) was made to the fill line and clamps on product were opened. Connection was performed by Manufacturing Operator (b) (6), who was overseen by Room Lead (b) (6), and verified by Manufacturing Operator (b) (6). Product began to leak at the connection and (b) (6) observed that the connection had not been fully seated before removing the papers. When the leak was observed, the connection was seated. Approximately (b) (4) of product was lost. Value Stream Supervisor (b) (6) and QA Representative (b) (6) were notified. Quality informed Senior Supervisor Manufacturing Technology (b) (6) of the development.

Due to this issue, the validated isolator sterile hold time was exceeded. Segregation was performed, and (b) (4) were segregated and placed on hold per A-SOP-21-01-036, *Product Segregation Procedures for Parenteral Manufacturing*.

This deviation was initiated on 30Nov20, escalated to a Major on 08Dec20 as re-filtration equates to re-processing.

Immediate Actions Taken:

Per A-SOP-21-01-066 step 2.1, a record was opened, and a rapid response was held to determine a path forward. It was decided that the product would be re-filtered. Product was scanned into (b) (4) at 1846, a new pathway was ordered, and B-pages were printed for the re-filtration.

(b) (6)
QA Supervisor

REC 284379
Attachment 4



Technical Development Memorandum

Document #: PD-MEM-0432

To: mRNA-1273 Drug Product External Quality Assurance Team

Subject: Assessment of Impact of Sterile Filtration Reprocessing Due to Leak in (b) (4)
During Initial Sterile Filtration Process of Catalent Lot 027L20, REC 284379

Author(s): (b) (6)

Date: 17-Dec-2020

Product: mRNA-1273 DP (LDP 70065)

Executive Summary

This memorandum summarizes the assessment of mRNA-1273 Drug Product (PN 70065; Lot 027L20) that underwent sterile filtration reprocessing and determines that it is considered suitable for human use.

Background

The diluted bulk mRNA-1273 Drug Product intermediate manufactured at the fill/finish site (Catalent) is sterile filtered through (b) (4) prior to being filled into the final container closure system. This sterile filtration activity occurs at controlled room temperature.

After completion sterile filtration and during filling start-up, product was identified to be leaking from the (b) (4) (see Catalent REC 284379, for a detailed description of the event). Operators immediately clamped the tubing to stop the leak and the issue was escalated to the rapid response team.

It was determined to collect new Bioburden and (b) (4) samples from the filtered bulk prior to reprocessing the material through an additional sterile filtration assembly.

Assessment

Reprocessing of sterile filtered mRNA-1273 drug product could potentially cause changes to biophysical characteristics of lipid nanoparticles, specifically particle diameter, polydispersity, and/or mRNA encapsulation. In addition, loss of either mRNA or lipid may occur due to filter absorption.

To understand this sensitivity, a study was conducted (documented in PD-REP-0378) diluted bulk mRNA-1273 Drug Product that were passively thawed to room temperature, and sterile filtered for a total of (b) (4). Samples were collected after each of the (b) (4) filtrations and analyzed for particle diameter, encapsulation efficiency, polydispersity, subvisible particulate, RNA content and lipid content. The biophysical and content characteristics of the drug product from this study remained within acceptance criteria for all the materials generated from re-processing.



For the above-stated reasons, there is no expected impact of this event on the mRNA-1273 drug product (PN 70065; Lot 027L20), and material can be considered suitable for human use.

References

- PD-REP-0378: mRNA-1273 DP Reprocessing Sterile Filtration Product Impact Report
- Catalent REC # 284379

Revision History

Revision #	Change Details	Author	Effective Date
1.0	Introduction of a New Document	(b) (6)	Date of Approval in (b) (4)

Approvals

Function	Name
Drug Product Development	(b) (6)
External Quality Assurance	
Drug Product Development, Data Verifier	
CMC Development Quality	

Document Approvals
Approved Date: 17 Dec 2020

Task: Approve Verdict: Approve content	(b) (6) [REDACTED] (b) (6) @modernatx.com) Task complete 17-Dec-2020 16:05:14 GMT+0000
Task: Approve Verdict: Approve content	(b) (6) [REDACTED] (b) (6) @modernatx.com) Task complete 17-Dec-2020 16:29:22 GMT+0000
Task: Assess Outcome Verdict: Approve document	(b) (6) [REDACTED] (b) (6) @modernatx.com) Task Complete 17-Dec-2020 16:57:04 GMT+0000
Task: Data Verification Verdict: Data Verified	(b) (6) [REDACTED] (b) (6) @modernatx.com) Task Complete 17-Dec-2020 17:03:50 GMT+0000
Task: Final Approval Verdict: Approved	(b) (6) [REDACTED] (b) (6) @modernatx.com) Task completed 17-Dec-2020 17:05:33 GMT+0000

REC 284379
Attachment 5



Technical Development Memorandum

Document #: PD-MEM-0433
To: mRNA-1273 Drug Product Tech Transfer Team
Subject: Assessment of Leachables due to Repeat Sterile Filtration of mRNA-1273 Drug Product Catalent Batch 027L20 (Catalent Rec 284379)
Author(s): (b) (6)
Date: 17-Dec-2020
Product: mRNA-1273 DP (LDP 70065)

Summary

mRNA-1273 drug product lot 027L20 (Catalent Scale B) was re-filtered through (b) (4) (b) (4) due to a leak being observed after sterile filtration just prior to start of filling (Catalent Rec 284379). The potential impact of additional leachables arising from the added filters is assessed here with reference to the toxicology assessment of filter leachables summarized in PD-MEM-0322 (for Catalent Scale A). A new estimate has been made of the leachables per dose for Scale B (worst-case standard process), and for lot 027L20 after re-filtration. It is concluded that re-filtration of lot 027L20 through (b) (4) does not pose any additional safety risk due to leachables from these extra filters.

Introduction

The diluted bulk mRNA-1273 Drug Product intermediate manufactured at the fill/finish site (Catalent, Bloomington, IN) is sterile filtered through (b) (4) prior to being filled into the final container closure system. This sterile filtration activity occurs at controlled room temperature.

During sterile filtration of lot 027L20, product solution was identified to be leaking from the (b) (4) (b) (4) (see Catalent REC 284379, for a detailed description of the event). The bulk solution was subsequently re-sterile filtered with a new single-use sterile filtration assembly prior to being filled into vials. A total bulk solution of (b) (4) (reference Attachment 3) was obtained after reprocessing although the original bulk obtained was (b) (4) Attachment 2). Re-filtration was performed through an (b) (4) (b) (4) (b) (4)

This memo summarizes the impact of this re-filtration on the leachables profile of the final vialled mRNA-1273 drug product lot 027L20.

Background

A toxicology assessment of leachables from (b) (4) used in mRNA-1273 drug product manufacture has been completed (PD-MEM-0322). The assessment concluded that "the presence of



leachables associated with the (b) (4) pose negligible safety risk to humans at the levels currently assessed in the toxicological risk assessment for the mRNA-1273 drug product.”

The assessment in PD-MEM-0322 uses Estimated Amount (of leachables) per Dose as calculated in PD-MEM-0308 (b) (4). However, the estimate in PD-MEM-0308 was performed on Catalent Scale A process. Therefore, a new worst-case estimate for Scale B (standard process) is calculated in Appendix 1. The Estimated Amount (of Leachables) per Dose for Scale B (b) (4) which is lower than the amount estimated in PD-MEM-0308 and assessed in PD-MEM-0322 (b) (4). (b) (4). Thus, the Toxicology assessment in PD-MEM-0322 applies in the worst-case assessment of Catalent Scale B also.

The re-filtration for Lot 027L20 adds (b) (4). An Estimated Amount (of Leachables) per Dose for the 027L20 process (using original bulk obtained (b) (4) and reprocessing bulk obtained (b) (4) results in a dose of (b) (4) (see Appendix 2).

In addition, pre-use filter integrity testing is performed with water for injection (WFI) on (b) (4) (b) (4) that are used in the sterile filtration assembly followed by a filter flushing procedure with product prior to collecting filtered bulk mRNA-1273 drug product, which has the ability to flush additional leachables from the filter.

Since the process includes filter flushing steps, as described above, and the Estimated Amount (of Leachables) per Dose for the 027L20 re-filtered lot is (b) (4) assessed and found safe in PD-MEM-0322, it can be concluded that the re-filtration of Lot 027L20 does not pose any additional safety risk due to leachables from the (b) (4).

Conclusion

Re-filtration of Lot 027L20 through (b) (4) (Catalent Rec 284379) does not pose any additional safety risk due to leachables from these extra filters.



Revision History

Revision #	Change Details	Author	Effective Date
1.0	Introduction of a New Document	(b) (6)	Date of Approval in (b) (4)

Approvals

Function	Name
Data Verifier, Drug Product Development	(b) (6)
Drug Product Development	
CMC Quality Assurance	
Manager, External Quality Assurance and GMP Manufacturing Quality	

(b) (4)





(b) (4)

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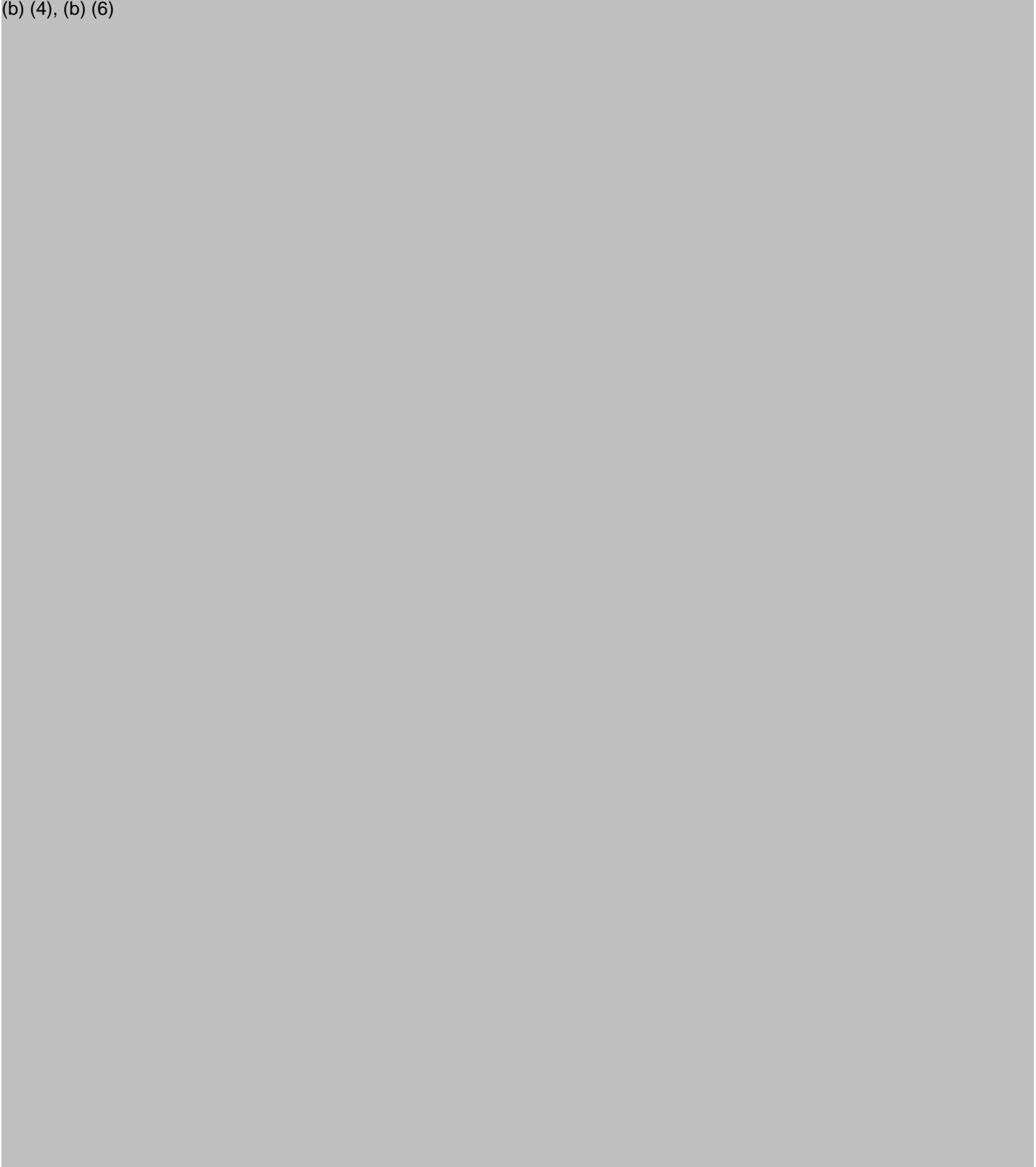


(b) (4)

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(b) (4), (b) (6)

A large, solid grey rectangular box covers the majority of the page, indicating that the content has been redacted under FOIA exemptions (b)(4) and (b)(6).

Document Approvals
Approved Date: 17 Dec 2020

Task: Approve Verdict: Approve content	(b) (6) (b) (6) @modernatx.com) Task complete 17-Dec-2020 16:04:17 GMT+0000
Task: Approve Verdict: Approve content	(b) (6) (b) (6) @modernatx.com) Task complete 17-Dec-2020 17:00:23 GMT+0000
Task: Assess Outcome Verdict: Approve document	(b) (6) (b) (6) @modernatx.com) Task Complete 17-Dec-2020 17:07:29 GMT+0000
Task: Data Verification Verdict: Data Verified	(b) (6) (b) (6) @modernatx.com) Task Complete 17-Dec-2020 17:14:28 GMT+0000
Task: Final Approval Verdict: Approved	(b) (6) (b) (6) @modernatx.com) Task completed 17-Dec-2020 17:21:37 GMT+0000