

RESPONSE TO CBER COMMUNICATION REGARDING CMC QUESTIONS RECEIVED ON DECEMBER 11, 2020 (INFORMATION REQUEST # 16)

The Sponsor acknowledges CBER's communication regarding CMC questions which were sent by FDA via email to Carla Vinals on December 11, 2020 (EUA 27073 IR #16) This document provides the Sponsor's responses to CBER's requests (in **Bold**).

Item 1:

Please provide results of quality release tests for the pDNA template lot manufactured at Aldevron.

Sponsor Response:

Certificates of Analysis for the following lots of linearized pDNA template manufactured at Aldevron are provided in this submission.

- 127060A
- 127061A
- 127062A
- 127063A
- 127065A

Item 2:

Regarding the information for DP lot 6007920001 filled in (b) (4) in SIOPlas (RTU) vials at Catalent, we have the following comments:

- a. Please provide Catalent deviation report REC 27079, concerning the particles observed on the nest table and subsequently in unfilled and filled vials and in unopened containers of vials.**
- b. Please provide details about the filling of subplot 6007920002; including, the handling of the formulated bulk, change of filling lines and completion of filling operations.**
- c. Upon visual inspection [per US <790> (destructive visual inspection)] no particles were observed in lot 6007920001. If particles were observed in unfilled and filled vials during filling of this lot, please clarify why particles were not detected by the visual inspection.**

Sponsor Response:

- a) Catalent deviation report [REC 270793](#) is provided in this submission.
- b) Sublot 6007920001 started sterile filtration on 25Oct20 at 1555, and then subsequently started filling on 025Oct20 (2121). Filling ended on 27Oct at 2330 after particles were observed on the nest plate (complete bulk hold duration for first subplot was 34 hours and 35 minutes). REC 270793 was initiated and decision to subplot was made. The product pathway was aseptically disconnected from the flexible filling isolator using aseptic technique per A-SOP-21-01-019, Aseptic Technique for Parenteral Operations. As qualified, the full filling pathway was double clamped and secured, removed by use of Rapid Transfer Port (RTP), and stored with the sterile product. The Sterile bulk product was transferred to a 2 - 8°C cooler in preparation for the next subplot.

In preparation for filling of subplot 6007920002, the flexible filling isolator was inspected and cleaned to remove visible particulate. All rails and format parts were wiped with (b) (4)

The isolator was continuously monitored and remained under positive pressure during the cleaning process. A new aseptic connection as made with an additional available aseptic connection on the bag. The fill was started for subplot 6007920002 on 28Oct2020 at 0322 and ended at 29Oct2020 at 0925.

Both fills were executed within qualified VHP hold of (b) (4) (25Oct20 0040 start). Total sterile bulk hold for subplot 6007920002 was 89 hours 30 minutes (within qualified limit of 220 hours).

- c) The available visual inspection data and visual defect classifications for Scale B lots 6007920001 (Catalent lot 025J20) and 6007920002 (Catalent lot 025J20-2) produced at Catalent are provided in the following tables.

Table 1: Visual Inspection Data and Visual Defect Classifications

Catalent Lot Number (Moderna lot)	# Filled Vials	# Rejected Vials ^{a)}	Reject Categories				
			Critical	Major A	Major B	Minor	Other
025J20 (6007920001)	(b) (4)	(b) (4)	(b) (4)				
025J20-2 (6007920002)							

a) No. of Rejected Vials includes rejects during production and AQL inspection.

(b) (4)

a) Container – Burn defect is not applicable to glass vials.

a) Container – Check defect is not applicable to plastic vials.
b) Container – Short Shot defect is not applicable to glass vials.
c) Closure – Product on Stopper defect is not applicable to plastic vials.
d) Product – Gated Vestige defect is not applicable to glass vials.

a) Container – Airline defect is not applicable to plastic vials.
b) Container – Streak/Flow Marks is not applicable to glass vials.
c) Container – Metal Mark defect is not applicable to plastic vials.
d) Container – String defect is not applicable to glass vials.
e) Container – Parting Line Mismatch defect is not applicable to glass vials
f) Container – Void defect is not applicable to glass vials.
g) Container – Container Discoloration defect is not applicable to glass vials.
h) Closure – Minor Imprint defect is not applicable to plastic vials.

100% visual inspection was conducted for Lot 6007920001 (Catalent lot 025J20) and Lot 6007920002 (Catalent lot 025J20-2). As provided in the previous tables, (b) (4) of Lot 6007920001 (Catalent lot 025J20) and (b) (4) of Lot 6007920002 (Catalent lot 025J20-2) were rejected during visual inspection (Major Defect: Fibers or Intrinsic Particulate Matter). Similarly, (b) (4) of Lot 6007920001 (Catalent lot 025J20) and (b) (4) of Lot 6007920002 (Catalent lot 025J20-2) were rejected during visual inspection (Minor Defect: Foreign Matter (External)). Vials which passed 100% visual inspection were then subjected to a Normal Level II AQL using (b) (4) of each lot. The results of the AQL results are provided in the following table. Based on the Normal Level II AQL, both lots passed the AQL criteria.

Table 2: AQL Criteria and Results

AQL Criteria							
Batch Number	6007920001	6007920002					
Inspection Type	Normal Level II AQL						
Batch Size (vials)	(b) (4)						
Maximum Allowable Defects							
Critical: 1	(b) (4)						
Batch	Total Inspected	Quantity of Rejects				Total AQL Rejects	AQL Assessment
		Critical	Major A	Major B	Minor		
6007920001	(b) (4)						PASS
6007920002							PASS

USP<790> destructive visual inspection was carried out as an AQL test, after the 100% visual inspection described above. Consequently, no particles were observed in this destructive test.

Item 3:

Please specify which container-closure systems will be used for EUA lots and which stoppers (b) (4) or West 4432-50 Grey Chlorobutyl) and vial combinations will be used for each lot.

Sponsor Response:

As described in Section 3.2.P.7, the bulk mRNA-1273 drug product is dispensed into Ompi® 10R clear Type 1 borosilicate glass vials, SIOPlas™ 10-mL (b) (4) Valor® 10R clear Type 1 (b) (4) and closed with a 20 mm 4432-50 Gray B240 S10-F451 Westar stopper and 20 mm flip-off red matte aluminum seal in an isolator. The mRNA-1273 Drug Product container closure systems at Catalent are provided in Table 3.

Table 3: Primary Container/Closure Components/Manufacturer

Presentation	Fill Line	Container Closure Component	Material of Construction ^(a)
mRNA-1273 Drug Product PN 60073	(b) (4)	Vial, Ompi® 10R, sterile, for human use	Type 1 borosilicate glass, clear
		Stopper, West, 4432/50, 20 mm, Ready-to-Use	4432/50 Gray B240 S10-F451 Westar
		Seal, West, 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 Drug Product PN 60079		Vial, SIOPlas™ 10-mL, sterile, for human use	(b) (4)
		Stopper, West, 4432/50, 20 mm, Ready-to-Use	4432/50 Gray B240 S10-F451* Westar
		Seal, West, 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 Drug Product PN 60086		Vial, Corning Valor® 10R, Bulk	(b) (4)
		Stopper, West, 4432/50, 20 mm, Ready-to-Use	4432/50 Gray B240 S10-F451 Westar
		Seal, West, 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red
mRNA-1273 Drug Product PN 60085		Vial, Ompi® 10R, Bulk	Type 1 borosilicate glass, clear
		Stopper, West, 4432/50, 20 mm, Ready-to-Use	4432/50 Gray B240 S10-F451 Westar
		Seal, West, 20 mm, Red Matte flip-off	Aluminum seal with flip-off plastic cap; color Red

a = The "F" designation indicates the presence of a FluroTec coating

The (b) (4) will not be used at Catalent. The (b) (4) (b) (4) is part of the container closure system used with the (b) (4) (b) (4) at ModernaTX, Inc. in Norwood, MA and is used for the filling of clinical trial material only.

Item 4:

We are updating our previous recommendations on the submission of certificates of analysis (CoAs) for vaccine lots to be distributed after approval of the EUA. Based on the absence of complete PPQ data on drug substance manufacture at all sites, please submit the CoAs for drug product lots at least 48 hours before lots are released for distribution by Moderna. The DS and DP manufacturing sites should be included in the COAs.

Sponsor Response:

The Sponsor acknowledges the Agency request and will submit the mRNA-1273 Drug Product CofAs to the EUA at least 48 hours before lots are released for distribution. The DS and DP manufacturing sites will also be provided on the COAs.

Item 5:

We are updating our previous recommendations on the submission of Quarterly Reports. Please submit these reports to your EUA in sections 3.2.S and 3.2 P rather than to your IND.

Sponsor Response:

The Sponsor acknowledges the Agency request and will submit quarterly manufacturing reports for mRNA-1273 LNP final DS and DP lots released in the US to the EUA.

Site	State	Date Current State	Date Closed	Parent Record #
Bloomington, US	Closed - Done	12-Dec-2020	12-Dec-2020	N/A

General Information

Originator: (b) (6) **Date Opened:** 27-Oct-2020

Short Description: Particulates found on nest plate while filling / batch sublot MBR 256-100-311P Lot:025J20 WO: 4277460

Assigned To: (b) (6) **Date Due:** 26-Dec-2020

Description:

Project Code: 256-100-311P
MBR: 256-100-311P-100
Lot: 025J20
WO: 4277460
Room(s): (b) (4)
Date of Observance/Occurrence: 27OCT20
SOP: A-SOP-21-09-005 "FFL (System 2328) Setup and Operation"

At approximately 0330 27OCT20 in (b) (4) during an in process check, A-FRM-21-01-026, Value Stream Supervisor (b) (6) noticed particles on the nest transport table. Value Stream Supervisor (b) (6) wiped the table, particles were removed. QA Representative (b) (6) was present at the time of intervention. Particles were placed in sample bottle per A-SOP-21-01-034 "Response to Unplanned Events During Batch Execution". (b) (6) contacted Quality Manager (b) (6) inspected five more tubs and it was noticed that there were particles inside the vials. (b) (6) was contacted again. Decision was made to hold a rapid response, call for path forward. The forceps and gloves were inspected, and forceps were laid to the deck. The nest transport was cleaned, trays (b) (4) were inspected. 14 vials were rejected for having free floating black particulates. Pathway was removed and product was transferred to cooler. The client, (b) (4), was consulted. (b) (4) made the decision to initiate an unplanned sub-lot with a lot of vials that will need to pass QC inspection. Sub-lot will be identified as 025J20-2.

Classification

Classification: Major

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

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

Report run by: (b) (6) on 12-Dec-2020 at 8:52 (Central Standard Time)

Page 1 of 4

Disclaimer: This is a redacted report - every effort has been made to remove fields containing confidential information from this report. Please check all written content to ensure confidential information is not included.

FDA-CBER-2022-1614-4992436

Deviation Information

Date of Occurrence:	27-Oct-2020	Date of Detection:	27-Oct-2020
Type:	Contamination	Sub-Type:	Foreign Material / Object - in Product or Intermediate
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:

Value Stream Supervisor (b) (6) halted production. Upon further investigation particles were found on incoming tubs inside and outside of vials. QA Representative (b) (6) was contacted per A-SOP-21-01-034 "Response to Unplanned Events During Batch Execution". The decision to have a rapid response was made by QA manager (b) (6). Pathway was removed and product was transferred to cooler. The client, (b) (4) was consulted. (b) (4) made the decision to initiate an unplanned sub-lot with lot of vials that will need to pass QC inspection. Sub-lot will be identified as 025J20-2.

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

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

Report run by: (b) (6) on 12-Dec-2020 at 8:52 (Central Standard Time)

Page 2 of 4

Disclaimer: This is a redacted report - every effort has been made to remove fields containing confidential information from this report. Please check all written content to ensure confidential information is not included.

FDA-CBER-2022-1614-4992437

Impact Analysis

Impact Analysis:

Reference Attached RPN

Risk Analysis:

Reference Attached RPN

Recurring Deviation?: No

Impact & Risk
Attachments: [Attachment 1](#) to REC 270793 RPN .pdf

Notification

Notification
Required?: YesNotification
Requirement: Customer

Investigation & Root Cause

Root Cause Analysis:

Reference [Attachment 3](#) to REC 270793.

Investigation Detail & Summary:

Reference [Attachment 3](#) to REC 270793.Root Cause
Attachment(s): [Attachment 6](#) to REC 270793.pdf
[Attachment 7](#) to REC 270793.pdf
[Attachment 11](#) to REC 270793.pdf
[Attachment 12](#) to REC 270793.pdf
[Attachment 3](#) to REC 270793.pdf
[Attachment 10](#) to REC270793.pdf
[Attachment 8](#) to REC 270793.pdf
[Attachment 4](#) to REC 270793.pdf
[Attachment 9](#) to REC 270793.pdf
[Attachment 5](#) to REC 270793.pdf

Root Cause Grid

Row #	Cause Type	Cause Category	Cause Sub-Category
1	Root Cause	Method (Procedure or Document)	Other

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

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

Report run by: (b) (6) on 12-Dec-2020 at 8:52 (Central Standard Time)

Page 3 of 4

Disclaimer: This is a redacted report - every effort has been made to remove fields containing confidential information from this report. Please check all written content to ensure confidential information is not included.

FDA-CBER-2022-1614-4992438

Action Information

Action Required?: Yes

Effectiveness Check

Effectiveness Check
Required?: No

No EC Justification:

The Actions are specific, discreet tasks (updates to documentation). Therefore, no EC is required.

Customer Approval

Customer Approval
Required?: YesCustomer Approval
Received?: Yes

Record Signatures

Supervisor Approval By: (b) (6)

Supervisor Approval On: 11-Dec-2020 12:50 pm

Quality Approval By:

Quality Approval On: 11-Dec-2020 2:36 pm

Optional Approver 1 Function: Technical

Optional Approval 1 By: (b) (6)

Optional Approval 1 On: 11-Dec-2020 10:24 am

Optional Approver 2 Function: Operations

Optional Approval 2 By: (b) (6)

Optional Approval 2 On: 11-Dec-2020 12:18 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>
270793	Deviation	26-Dec-20	12-Dec-20	Closed - Done	Particulates found on nest plate while filling / batch sublot MBR 256-100-311P Lot:025J20 WO: 4277460
288932	Action	11-Jan-21		Work in Progress	Update MBR MBR 256-100-311P-100
288935	Action	11-Jan-21		Work in Progress	Training

CATALENT CONFIDENTIAL AND PROPRIETARY INFORMATION

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


Report run by: (b) (6) on 12-Dec-2020 at 8:52 (Central Standard Time)

Page 4 of 4

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FDA-CBER-2022-1614-4992439

REC 270793
Attachment 1


	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
270793	025J20	(b) (6) 28OCT20
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) (MT)	(b) (6) (VAL)	(b) (6) (QC)
(b) (6) (MFG)	(b) (6) (MFG)	(b) (6) (MFG)
(b) (6) (ENG)	(b) (6) (QA)	(b) (6) (MFG)
N/A	N/A	N/A

Impact Analysis Questions	
What is the potential impact to SISPQ?	Particles within product.
Are multiple lots impacted by this event?	Yes
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)	Placed on hold.
Additional Information (As Applicable)	N/A

Attachment #:	1	Record #:	270793	Initials/Date:	(b) (6) 28Oct20
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	Document Number:	N/A	Page 2 of 3
Title: Impact Analysis and Risk Priority Number (RPN) Calculation Template			


Risk Assessment Questions	
1 – Is this deviation a variation from a defined critical process or standard that could or does result in product that does not meet its regulatory filed specification and/or required quality standards in each case when that product is no longer within Catalent's control? (Note: Product shipped under quarantine is still considered within Catalent control for the purposes of this question.)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
2 – Is this deviation a quality incident that could result in a failure to supply product which could impact patient treatment? (e.g., media fill failure or sterility test failure)	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
3 – Is this deviation a significant quality system failure that could go undetected and a significant purposeful withholding of information that may constitute fraud or falsification of products or data or give rise to the potential to harm the end user?	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

Recurrence Check		
Legacy TW Search Parameters	Occurrence Dates	N/A
	Keywords/phrases	N/A
Global TW Search Parameters	Occurrence Dates	Date of occurrence is on or after 27OCT19
	Keywords/phrases	Record text with all these words: particulates nest plate
Total # of Potentially Related Records Identified:		1

RPN Calculation and Leveling

(b) (4)

Attachment #:	1	Record #:	270793	Initials/Date:	(b) (6) 28Oct20
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	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 #:	1	Record #:	270793	Initials/Date:	(b) (6) 28Oct20
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	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 #:	1	Record #:	270793	Initials/Date:	(b) (6) 28Oct20
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REC 270793
Attachment 2



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

812-355-6746 x2065

Initial Notification of Major Deviation

Deviation Report Number: 270793

Batch Record: 256-100-311P

Lot Number: Lot 025J20

Date of Recognition: 10/27/2020

Description of Deviation:

Particles observed in vials during the filling of Lot 025J20

Deviation Details:

At approximately 0330 on 27OCT20 in (b) (4) during an in process check, Value Stream Supervisor (b) (6) noticed particles on the nest transport table. Value Stream Supervisor (b) (6) wiped the table with non particulating wipes to remove the particles. During this intervention, QA Representative (b) (6) was present. Particles were placed in sample bottle per A-SOP-21-01-034 "Response to Unplanned Events During Batch Execution". (b) (6) contacted Quality Manager (b) (6) (b) (6) inspected five more tubs and it was noticed that there were particles inside the vials. (b) (6) was contacted again. The decision was made to hold a rapid response call to determine a path forward. Post rapid response call, trays (b) (4) were inspected. 14 vials were rejected for having free floating black particulates. The filling pathway was removed and product was transferred to cooler. The client team was consulted and the decision was made to initiate an unplanned sub-lot with a lot of vials that will need to pass QC inspection. Sub-lot will be identified as 025J20-2.

(b) (6)

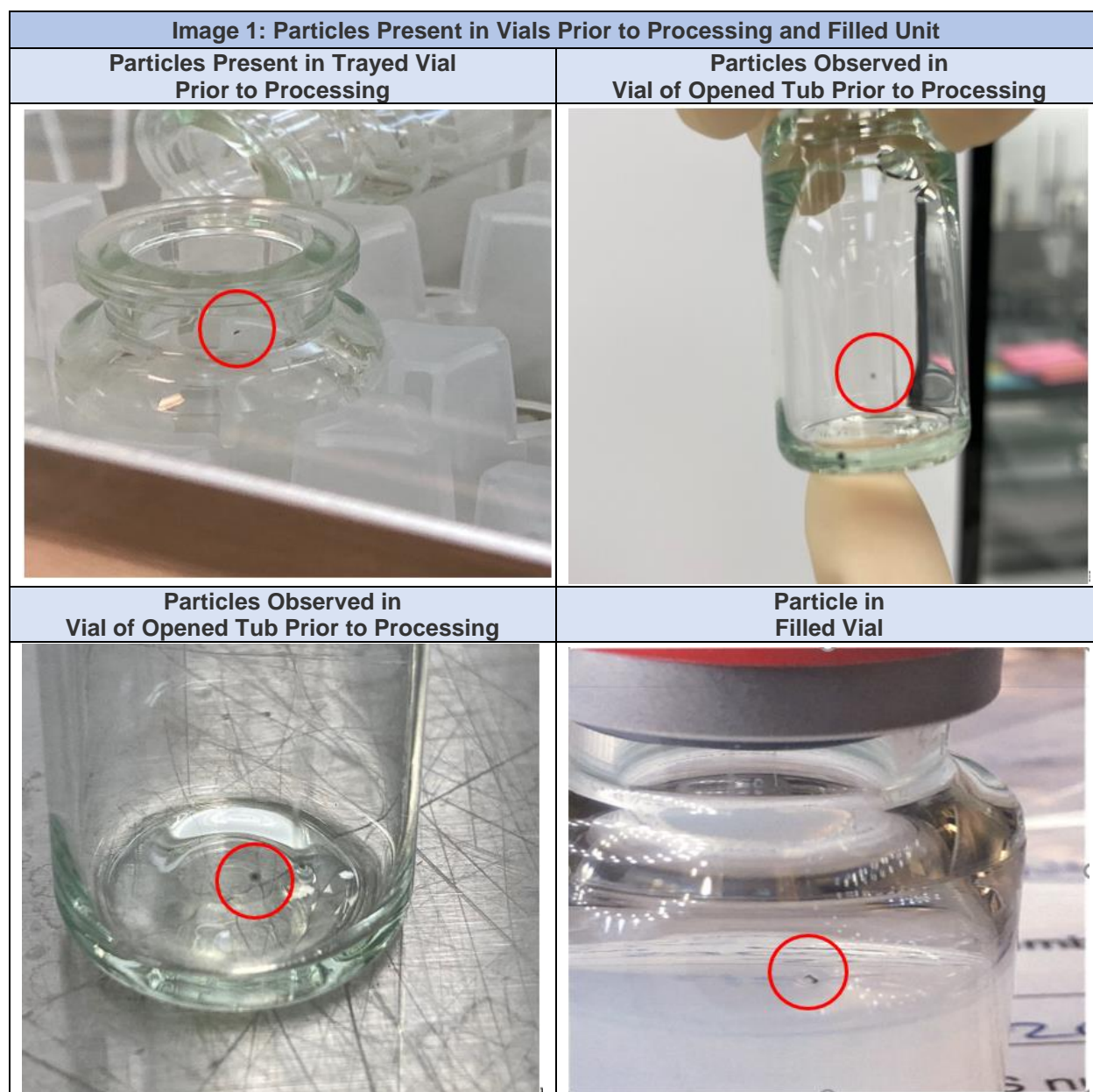
Senior QA Representative

REC 270793
Attachment 3

Background:

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

During filling of Lot 025J20, using Catalent vial lot (b) (4), Master Batch Record (MBR) 256-100-311P-100, at approximately 0330 27OCT20 in (b) (4) during an in-process check, per A-FRM-21-01-026, *In-Process Checks*, Value Stream Supervisor MNR1 noticed particles on the nest transport table. Value Stream Supervisor (b) (6) wiped the table, and the particles were removed. Quality Assurance (QA) Representative (b) (6) was present at the time of intervention. The particles were placed in a sample bottle per A-SOP-21-01-034, *Response to Unplanned Events During Batch Execution*. (b) (6) contacted Quality Manager (b) (6) inspected five (5) more tubs and it was noticed that there were particles inside the filled vials and inside un-opened tubs of vials.



The nest transport was cleaned, (b) (4) were inspected. Fourteen (14) vials were rejected for having free floating black particulates. The product pathway was aseptically disconnected using aseptic technique per A-SOP-21-01-019, *Aseptic Technique for Parenteral Operations*, removed, and the sterile product was transferred to a 2-8°C cooler. After consultation with (b) (4), the decision was made to initiate an unplanned sub-lot. The sub-lot is identified as 025J20-2. The sterile product was reconnected to a new filling pathway per A-SOP-21-01-040, *Installation and Usage of Disposable Sterile Connectors in Parenteral Manufacturing*, 025J20-2 was filled using Catalent vial lot (b) (4). Rec 270293 was initiated on 27OCT20 to document the event.

The investigation into the particles found on the nest plate and within the vials included:

- 1) FFL System Description/Environmental Monitoring/EMS System Description
- 2) Component Flow and Preparation
- 3) Incoming Material Review
- 4) Documentation Review
- 5) Operator Interviews
- 6) Vial Component Manufacturing Process at SiO2
- 7) Particle Analysis Review
- 8) Lot Environmental Data (Particle Monitoring and Viable Air) Review
- 9) Inspection Results Review
- 10) Associate Training
- 11) Root Cause Analysis
- 12) Recurrence Analysis

1) FFL System Description/Environmental Monitoring/EMS System Description

(b) (4)



(b) (4)



2) Component Flow and Preparation

(b) (4)



3) Incoming Material Review

(b) (4)



Incoming Inspection¹

Per A-SOP-09-01-020, *Quality Control Inspection of Incoming Materials*, the initial incoming inspection process verified:

- Catalent Item Number
- Catalent Lot Number
- Manufacturer or Vendor/Supplier Item Number (if applicable)
- Manufacturer or Vendor/Supplier Lot Number
- Total Cases
- Expiration Date
- Expiration Source

(b) (4)



(b) (4)



(b) (4)



(b) (4)




4) Documentation Review

A-SOP-21-01-006, Sanitization of Equipment, Materials, and Supplies for Primary Manufacturing Area

A-SOP-21-01-006 provides instructions for the sanitization and wipe-down of equipment, materials and supplies when entering Primary Manufacturing, and crossing management lines within the area. The SOP applies to components which are defined as consumable items used during filling operations. The procedure clearly defines approved sanitizing solutions, and instructions for when and how components are to be sanitized including:

- Before entering any controlled classified area, all Equipment, Materials and Supplies must be sanitized.
- Sanitization is performed on the entry side of external airlocks before items are moved across the management line.
- Operators are to sanitize all equipment, materials and supplies immediately upon reaching management line in any area and are not to leave materials at the management line awaiting sanitization.
- Equipment, materials and supplies (including the transport cart) are wiped with a non-particulating dry wipe, saturated with sanitizing solution in a uni-directional, overlapping motion, from top to bottom, or from the management line toward the entry side of airlock.

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



A-SOP-21-01-025, Area Clearance Procedure within Parenteral Primary Manufacturing

This document provides general instruction for performing an Area Clearance in Drug Product Primary Manufacturing. A Manufacturing Clearance of (b) (4) was performed on 24OCT20 and 27OCT20², by (b) (6) these clearances ensured that (not limited to):

- The manufacturing areas were sanitized per A-SOP-21-01-004, *Sanitization of Classified and Controlled Areas within Primary Manufacturing Area*.

(b) (4)

- Review of (b) (4) for room temperatures and pressures for the previous 24 hours to ensure that no alarms were identified; if there were any alarms or issues ensure that they have been resolved prior to clearance approval by Manufacturing.

Executed MBR 256-100-311P-100

(b) (4)

(b) (4)

(b) (4)

5) Operator Interviews

Value Stream Supervisor (b) (6) was interviewed as part of this investigation. Per (b) (6) the particles were first noticed on the nest table which is above the filling level. Prior to proceeding with the fill, the format parts were cleaned with (b) (4), finding particles along the (b) (4). (b) (4) Some particulates were also found on some of the (b) (4) but were minimal in comparison to the (b) (4). A visual inspection was performed on the (b) (4) with no findings of particulation. Particles were found along the (b) (4) throughout the filling sections, however the (b) (4) passed a visual inspection with no finding of particulates. The particles were difficult to remove with (b) (4) and very difficult to remove with dry wipes. They didn't appear to float freely throughout the (b) (4) but were more rubbing off the vials onto (b) (4). (b) (6) estimates that with monitoring throughout the fill and checking for these particulates within the isolator during our hourly In-process checks, that it's likely that filling would have to stop every (b) (4) to clean the affected areas.

Senior Production Technician, (b) (6) was interviewed as part of this investigation. (b) (6) indicated that particles were found under the nest plate after setup. (b) (6) directed the team to unbolt and remove the nest plate for cleaning prior to initiating filling. A large number of particles were found under the nest plate.

6) Vial Component Manufacturing Process at SiO2

SiO2 provided the image below which depicts the vial manufacturing Process.

(b) (4)



7) Particle Analysis Review

(b) (4)



(b) (4)



(b) (4)



(b) (4)



8) Lot Environmental Data (Particle Monitoring and Viable Air) Review

(b) (4)



9) Inspection Results Review

(b) (4)



(b) (4)



(b) (4)

(b) (4)



USP 790 Testing

Twenty (20) finished product vials from each lot underwent particulate testing per USP 790 and yielded 0 particles with passing results for both sublots.

10) Associate Training

Incoming Visual Inspection and dimensional Analysis of Components

Senior Lab Technicians (b) (6) and Lab Technicians (b) (6) performed visual inspection and dimensional analysis of the vial lots utilized for manufacturing lots 025J20 and 025J20-2 and were found to be current to A-SOP-09-08-071, *Incoming Inspection of Vials*, via (b) (4)

Sanitization of Components

All Filling participants were found to be current for training to A-SOP-21-01-006 via (b) (4)

Manufacturing and QA Clearance of (b) (4)

(b) (6) performed the required clearances and were found to be current for training to A-SOP-21-01-025 via (b) (4).

(b) (4)

(b) (6) completed the setup check list and were found to be current for training to A-SOP-21-09-010, *Flexible Filling Line (System 2324) Format Change and Setup* via ComplianceWire.

Inspection

All Inspection participants were found to be current for training to A-SOP-22-05-001, A-SOP-22-05-009, *Semi-Automatic Vial Inspection System (System CL145) Setup, Verification, Operation, and Cleaning*, A-WI-03-04-001, *Parenteral Inspection Defect Criteria List for Plastic Vials*, and A-PBA-22-05-009 (C), *Performance Based Assessment for Semi-Automated Inspection of Vials Containing an Emulsion (CL145)* via (b) (4)

11) Root Cause Analysis

Equipment/System

(b) (4)

Equipment/System is not a contributing factor.

Environment

(b) (4)

Environment is not a contributing factor.

Method/Process

(b) (4)



Method/Process (release specifications (Vendor and Catalent)/vial coating process) is the root cause.

Human/Personnel

All associated involved with the processes investigated were found to be compliant to the required training.

Human/Personnel is not a contributing factor.

Materials

(b) (4)



Materials are not a contributing factor.

Measurement

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

Measurement is not a contributing factor to this event.

12) Recurrence Analysis

(b) (4)



There is currently no trend of particles discovered due to method/process concerns.


Conclusion/SISPQ Impact

(b) (4)



Vial Lots 1734451 and 1750749 met vendor and Catalent incoming release requirements. All components were properly sanitized prior to use. The isolator was properly cleared, cleaned, and sterilized prior to initiating production. During production there were no particle alarms that did not have a documented root cause. Lots 025J20 and 025J20-2 passed overall visual inspection and the subsequent QA AQL inspection. Though this product was determined to be difficult to inspect, USP 790 testing was implemented to support that the final product inspection was robust. All USP 790 testing passed all criteria. Additionally, all environmental monitoring performed for the lot passed all acceptance criteria. All personnel who performed relevant tasks were found to be current to training for the given task.

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



(b) (6) conducted a medical assessment of/for the particulates and determined that the nature of the particles, their size, the limited potential exposure, and the route of administration (intramuscular) all serve to mitigate the potential patient safety implications. Per the medical assessment, the rare presence of particulate matter of this nature in mRNA-1273 does not impose an undue risk to patient safety nor adversely affect the benefit/risk profile of the product (Attachment 12).

Future particle excursions identified during the inspection process at Catalent will adhere to the particle identification process as outlined in A-POL-22-01-002, *Drug Product Particle Identification Policy* which specifies (b) (4) successive levels of identification including:

(b) (4)



Lots 025J20 and 025J20-2 are recommended for release.

Completed Actions

- Catalent Initiation of no-conforming material report (NCMR) 20-10-003.
- Customer supplier corrective action request (SCAR) initiated to address SiO₂ particulate observation (refer to QE-002904)


In Process Actions

- Revise the Current MSS for Item (b) (4) to reflect the changes to the Vendor specification per (b) (4) (b) (4)
- Re-Inspect the in-house Vial lots using the revised MSS Specifications.

Proposed Actions

- Eliminate the accumulation of particulates during filling by supplementing MBR 256-100-311P-100 to include inspection for particulates and wipe-down of all areas from (b) (4) (b) (4) between campaign Lots.
- Revise the MBR 256-100-311P-100 to include instructions for documentation of observed particles during filling and include steps to take when particles are observed.
- Provide additional training to applicable personnel regarding the characteristics specific to the 256 project.

REC 270793
Attachment 4

	mRNA-1273 Injection Drug Product, (b) (4) (b) (4)	Page 152 of 256
Master Batch Record Number: 256-100-311P-100		Project: 256-100-311P


Lot Number: 025J20 Work Order #: 4350460/4350369 Issued By/ Date: (b) (6) 19OCT20

Filling Event Log	
A-SOP-21-01-034	When did the Event occur? Who was involved? How was the Event resolved? Include the following information in the Event log: <ul style="list-style-type: none">• Activity occurring at the time of alarm• Isolator Areas Cleared• Segregation, if performed• Root Cause, if known

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

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	mRNA-1273 Injection Drug Product, (b) (4) (b) (4)	Page 153 of 256
Master Batch Record Number: 256-100-311P-100		Project: 256-100-311P

Lot Number: 025J20 Work Order #: 4350460/4350369 Issued By/ Date: (b) (6) 19OCT20

Filling Event Log	
A-SOP-21-01-034	When did the Event occur? Who was involved? How was the Event resolved? Include the following information in the Event log: <ul style="list-style-type: none">• Activity occurring at the time of alarm• Segregation, if performed• Isolator Areas Cleared• Root Cause, if known

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

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REC 270793
Attachment 5

Catalent enologics	mRNA-1273 Injection Drug Product, (b) (4) (b) (4)	Page 151 of 256
Master Batch Record Number: 256-100-311P-100		Project: 256-100-311P

Lot Number: 025J20-2 Work Order #: 4350460/4362271 Issued By/ Date: (b) (6) 27OCT20

Filling Event Log	
A-SOP-21-01-034	<p>When did the Event occur? Who was involved? How was the Event resolved?</p> <p>Include the following information in the Event log:</p> <ul style="list-style-type: none"> • Activity occurring at the time of alarm • Isolator Areas Cleared • Segregation, if performed • Root Cause, if known

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

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REC 270793
Attachment 6



(b) (4)

EMS Report by Date (Version 1.1)

EMS Start Time: 10/25/2020 17:27:00 EDT

EMS End Time: 10/27/2020 15:11:00 EDT

Batches in Time Frame:

Project Code	Lot Number	Batch Start	Batch Start Operator	Batch End	Batch End Operator	Format
256-100-311P	025J20	10/25/2020 7:23:17 PM	(b) (6)	10/27/2020 3:15:25 PM	(b) (6)	256-100-311

(b) (4)


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



(b) (4)

EMS Report by Date (Version 1.1)

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

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Report Executed by: (b) (6)
at 11/3/2020 8:59:09 AM EST

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Attachment 7



(b) (4)

EMS Report by Date (Version 1.1)

EMS Start Time: 10/28/2020 01:52:00 EDT EMS End Time: 10/29/2020 09:44:00 EDT

Batches in Time Frame:

Project Code	Lot Number	Batch Start	Batch Start Operator	Batch End	Batch End Operator	Format
256-100-311P	025J20-2	10/28/2020 2:15:38 AM	(b) (6)	10/29/2020 9:49:24 AM	(b) (6)	256-100-311

(b) (4)


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



(b) (4)

EMS Report by Date (Version 1.1)

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

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Page 2 of 2

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Attachment 8

DOCUMENT APPROVAL INFORMATION

Document Number: LS-20-2914
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Approvals

Note: All dates are in UTC.

(b) (6)



REC 270793
Attachment 9

REC 270793
Attachment 10

REC 270793
Attachment 11



200 Tech Square • Cambridge, MA 02139
phone 617-714-6500 • fax 617-583-1998

Notification for Catalent Indiana, LLC

24Nov2020

Dear Sir / Madam,

This memo is to inform Catalent Indiana, LLC. that it is Moderna's recommendation to continue into mRNA-1273 Drug Product production with the SiO₂ Vials (VIAL SIOPLAS 10ML COATED, (b) (4)) (b) (4)

The major deviation against batch 025J20 and 025J20-2 (REC 270793) currently underway has determined through chemical analysis that the observed particulate matter is derived from intrinsic particulates that are a known aspect of the SiO₂ Vial manufacturing process. The particles are comprised of organosilica flakes that are generated during the coating process, which are equivalent in composition to the vial coating. The particles are routinely observed as dark/colored in nature during vial manufacturing activities.

As part of the ongoing investigation (REC 270793), a significant gap has been identified with respect to incoming quality inspection. The incoming material specification sheet (MSS) will require an update to appropriately capture total quality attributes of the vials in inspection (refer to **Table 1**). The primary difference is that previously (b) (4) were allowed per vial, whereas the change implemented will de-specify the specific quantity of particles allowed, defer to AQL table based on inspection lot size, and evaluate the total number of vials per sample size (total vials inspected). All released SiO₂ vials will be re-inspected to this new criteria below.

Table 1: Current and Future State MSS (b) (4)

Current State	Future State
(b) (4)	

In preparation of future batch manufacture, the following controls have been identified and reviewed for detection and process capability in order to mitigate particle contamination in vials available for disposition and release for potential emergency use authorization. Refer to **Table 2** for a list of controls currently in place.

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Table 2: Production Particulate Controls for mRNA-1273 Drug Product Manufacture

(b) (4)



moderna

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(b) (4)



Catalent and Moderna will conduct all aforementioned controls listed above and follow site procedures. A medical impact assessment is being concurrently generated in preparation for the unlikely event that a particle is observed prior to or after administration to patient. This assessment will be generated and evaluated with Catalent prior to batch disposition of 025J20 (and subplot 025J20-2) in addition to any lots further impacted by particle deviations similar in nature.

In summary, based on the control strategy and risk mitigation strategies in place prior to batch disposition, further production should occur with the use of SiO₂ Vials. Please let us know immediately if you have any questions regarding the contents of this memo.

Regards.

(b) (6)



REC 270793
Attachment 12



Memorandum

Re: Medical Assessment for Particulates

To: Moderna Material Review Board

From: Allison August, MD, VP, Clinical Development, Infectious Disease

(b) (6)

David Martin, MD, MPH, Head, Pharmacovigilance

Jacqueline Miller, MD, SVP and Therapeutic Area Head, Infectious Disease Development

Background:

Particulates were observed during post-fill semi-automated visual inspection at (b) (4) on 27Oct20. These units were rejected. The total number of vials involved is not described. A Medical Assessment has been requested as visual inspection may not be 100% effective to identify vials containing particulate matter. To date, there has been no human exposure to mRNA 1273 packaged in SiO₂ vials. A Particulate Analysis of seven samples conducted by (b) (4) is the source of composition information. Particulates ranged from (b) (4) in size range, sharing an iridescent appearance, and were brittle in consistency. Per manufacturer descriptive materials, "SiO₂ containers are considered a like for like replacement for glass containers." The vials are made from (b) (4)

(b) (4)

(b) (4)

SiO₂ reports that particulate content typically meets or exceeds US Pharmacopeia standards.

(b) (4)

Materials Reviewed:

(b) (4) Particulate Analysis Final Report, 11/5/20

SiO₂ Primary Packaging Containers – Container-Equivalency, Risk Assessment, & Drug Compatibility, PowerPoint presentation, May 2020

SiO₂ Regulatory Summary (SiOPlas Vials), June 3, 2020

SiO₂ Summary Report: Extractable Study & Elemental Impurities in SiOPlas Vials

Catalent DP Lot 025J20 Particulate Investigation Update, November 10, 2020

Visible Particle Analysis Performed by SiO₂ Materials Science on 10 mL Vials Returned by Catalent, November 24, 2020

Factors Considered:

Patient factors: Exposure is planned for the general adult and ultimately pediatric populations

Route of administration: Intramuscular, low volume, not administered in a closed anatomic space

Volume of administration: 0.5mL per dose for two doses separated by approximately one month

Size: visible and presumed subvisible particles

Particle type: *Intrinsic* -> Silicon-rich material in six samples. *Extrinsic* -> Polypropylene with calcium-containing inclusions and a lead-containing inclusion in a single sample

Characterization: Sterile due to the introduction of particulates by equipment during a sterile manufacturing process

Hypothesized fate in body: Likely remains at site of administration in the interstitial space of muscle or subcutaneous tissue (depending on injection technique); Particles may be phagocytosed by macrophages; May potentially enter capillaries; Likely low probability of accessing the central circulatory system

Studies involving IM vaccine administration with similar particulates:

Preclinical toxicology studies: None provided

Human studies or case reports: None provided


Conclusion:

The mRNA-1273 vaccine will serve as a critical component in the on-going global health effort to stem the spread of the highly contagious SARS-CoV-2 virus and its related morbidities.

The clinical implications of visible particulate matter in injectables have been reviewed in a number of recent publications (Langille, S. Particulate Matter in Injectable Drug Products. J. Pharm. Sci. Technol. 2013, 67, 186-200. Bukofzer S. et al, Industry Perspectives on the Medical Risk of Visible Particles in Injectable Drug Products. J. Pharm. Sci. Technol. 2015, 69, 123-139). The presence of particulate matter in parenteral products is accepted as an inherent consequence of parenteral product manufacturing, and multiple compendial sources delineate the number of particles considered objectionable (USP <1> and <788>). In assessing risk of such contamination, particulate source, particulate attributes and characteristics of the patient population were considered. An IM injection consisting of a low volume which is not administered to a closed anatomic space is a lower risk route of administration with fewer hypothesized human health effects relative to other exposure scenarios. Furthermore, the particles are reported to be sterile per the Catalent DP Lot 025J20 Particulate Investigation Update date November 10, 2020. Six of the seven particles characterized were composed of silicon oxide, consistent with debris produced during vial manufacture. Silicon, silica and silicon dioxide are all biologically inert and generally considered non-toxic except in large dose-exposure. The seventh particle was composed primarily of polypropylene; polypropylene is physiologically inert, nontoxic and often used in food contact environments; and is also considered non-toxic. This particle contained an inclusion containing lead; lead exposure to humans occurs primarily through inhalation, ingestion or dermal exposure. While the effects of chronic lead exposure as well as high-level acute exposure are known, low-level effects are generally less well understood, including acute intramuscular administration. ICH Q3D "Guideline for Elemental Impurities" places lead as a 'Class 1' human toxicant with "limited or no use in the manufacture of pharmaceuticals" and a parenteral Permitted Daily Exposure (PDE) of 5µg/day. A target blood level of 1-2 µg/dL was adopted to establish the PDE. The potential intramuscular exposure from a particle containing 6 µg of lead, assuming 100% bioavailability, would likely marginally exceed the established PDE for parenteral administration. As the intended clinical dosing schedule is 2 doses administered 4 weeks apart, the potential risk to the patient is attenuated by the limited exposure and would likely not surpass the presumptive target blood level of 1-2 µg/dL.

Overall, the nature of the particles, their size (less than 1 mm), the limited potential exposure (2 dose vaccine regimen) and the route of administration (intramuscular) all serve to mitigate the possible patient safety implications. The rare presence of particulate matter of this nature in mRNA-1273 does not impose an undue risk to patient safety nor adversely affect the benefit/risk profile of the product. Additionally, this batch is suitable for use subject to meeting established acceptance criteria, specifications or other conditions adopted for release.

Signatures:

Approver (PRINT)	Signature	Title	Date
Allison August		VP, Clinical Development, ID	09 DEC 2020

Signatures:

Approver (PRINT)	Signature	Title	Date
JACQUELINE MILLER	<i>Jacqueline Miller</i>	SVP, Therapeutic Area Head	12/8/2020

ID

Document Approvals
Approved Date: 10 Dec 2020

Task: Approval Task Verdict: Approve	(b) (6) (b) (6) @modernatx.com) Subject Matter Expert Approval 10-Dec-2020 02:02:52 GMT+0000
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Task: QA Approval Task Verdict: Approve	r White, (b) (6) @modernatx.com) Quality Assurance Approval 10-Dec-2020 13:24:51 GMT+0000