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3.2.P.3.5 PROCESS VALIDATION AND/OR EVALUATION

mRNA-1273 Drug Product produced at Scale A (nominal [redacted] vial scale) and Scale B (nominal [redacted] vial scale) are intended for Emergency Use Authorization supply.

3.2.P.3.5.1 Scale B Process Performance Qualification

A process performance qualification (PPQ) of the mRNA-1273 Drug Product [redacted] vial (Scale B) manufacturing process is being conducted per the protocol provided as an attachment (Scale B PPQ Protocol). Scale B mRNA-1273 Drug Product PPQs will be conducted on the same flexible filling line as the Scale A mRNA-1273 Drug Product PPQs described in Section 3.2.P.3.5.2.

3.2.P.3.5.2 Scale A Process Performance Qualification

The PPQ of the mRNA-1273 Drug Product [redacted] vial (Scale A) manufacturing process has been completed. A total of three batches ([057G20, (6007320001), 062G20, (6007320002), and 001H20 (6007320003)] were successfully completed per the protocol and the batch record requirements from formulation through completion of inspection. Subsequent to the execution of the Scale A PPQ, it was noted that the specification for mRNA content contained in the protocol was incorrect [redacted]. A change control was initiated and the Scale A PPQ report was revised to describe and correct the discrepancy. The batches met all prospective acceptance criteria listed within the protocol (including the corrected mRNA content specification), as documented in the PPQ report. The Scale A PPQ Protocol and revised Scale A PPQ Report are provided as attachments (Scale A PPQ Protocol, Scale A PPQ Report).

The following product hold times were successfully qualified during PPQ execution.

- 48 hours at room temperature from the end of thawing to the start temperature conditioning
- 240 hours at 2 - 8°C from the end of thawing to the start temperature conditioning

Samples were taken throughout the fill from all PPQ batches and analyzed for concentration homogeneity and tested for appearance, bioburden, pH, osmolality, container content, particulate matter, particle size, polydispersity, mRNA content, identity, purity, product-related impurities, %mRNA encapsulation, lipid ID, lipid content, lipid impurities, sterility, endotoxin, and potency. All concentration homogeneity characterization of beginning, middle, and end of the fill shows consistent product quality and met prospective acceptance criteria.

The maximum batch size of [redacted] was executed during PPQ. The validated batch size, or any other validated range, can be changed only after a risk assessment and if necessary, successful revalidation followed by the routine change control process.

The final diluted batch sizes were between [redacted] during PPQ. The final batch size is determined by the volume of mRNA-1273 Lipid Nanoparticle (LNP) received and its concentration measured in the process. The mRNA-1273 LNP is subsequently diluted to the final target concentration. Given the variability in the above steps, a batch size range of approximately ± 10% is expected.

3.2.P.3.5.2.1 Drug Product Background

The commercial manufacture of this product occurred within classified areas inside drug product manufacturing suites at Catalent in Bloomington, Indiana, United States. Drug product manufacturing suites, located [redacted], and are identified as primary and secondary areas. Primary manufacturing contains dispensing, formulation, and filling activities. Secondary manufacturing encompasses inspection, assembly, and packaging activities. Raw materials and components are received, QC sampled, and warehoused in the [redacted] The series of proposed commercial manufacturing activities at Catalent includes raw material receipt, storage, quality control testing (which can include testing and release), as well as formulation including thawing, pooling, mixing, clarification filtration, buffer formulation, dilution, sterile filtration, vial filling, inspection, temperature conditioning and storage.

3.2.P.3.5.2.1.1 Material Receipt and Storage

Materials and components are received by Catalent in Bloomington, IN. Materials are ordered and tested in accordance with approved Material Specification Sheets (MSS) from approved suppliers. Non-critical process parameters were evaluated through routine manufacturing operations and batch records.

3.2.P.3.5.2.1.2 LNP Thaw

The mRNA-1273 Lipid Nanoparticles (LNP) was provided and shipped frozen in [redacted] The mRNA-1273 LNP is thawed prior to pooling.

mRNA-1273 LNP was shipped to Catalent in [redacted] at a nominal target concentration of [redacted]

The LNP product was thawed at controlled room temperature (CRT) for a minimum of 24 hours. After 24 hours ±1 hour, the shells were slowly lifted to approximately a 45° angle and lowered on each side to gently mix the drug substance. After opening the shells, the exterior bag

temperature was measured with a temperature of [redacted] indicating completion of thaw. If the temperature was still less than 10°C, thaw checks were performed every [redacted] thereafter for a maximum total of [redacted] If the temperature was greater than [redacted] the shells were stored at [redacted] until needed for forward processing.

Multiple manufactured lots of mRNA-1273 LNP were thawed and combined during the pooling stage to support batch sizes.

Non-critical process parameters were evaluated through routine manufacturing operations and batch record instructions.

Table 1 displays the surface bag temperatures and duration for each lot of thawed mRNA-1273 LNP.

Table 1: Bag Surface Temperatures

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
Passive Bulk LNP Thawing	Post Thaw Bag Temperature	NCIPC	[redacted]	Bag 1 [redacted]	Bag 1 [redacted]	Bag 1 [redacted]
				Bag 2	Bag 2	Bag 2
				Bag 3	Bag 3	Bag 3
				Bag 4	Bag 4	Bag 4
				Bag 5	Bag 5	Bag 5
				Bag 6		Bag 6
						Bag 7
	Met NOR?			Yes	Yes	Yes
	Duration	NCPP	[redacted]			
	Met NOR?			Yes	Yes	Yes

3.2.P.3.5.2.1.3 Pooling and Mixing

Drug Product Manufacturing and QA performed [redacted] on assigned rooms per the master batch record. Materials were staged in [redacted] or moved directly into a [redacted] Upon completion of Lipid Nanoparticle (mRNA-1273 LNP) thawing, the solution contained in the shells were transferred via a tubing manifold into the mixing bag. The product was pooled into a [redacted] bag. The mixer speed was set to maintain a gentle vortex of the solution with no visible foaming at [redacted] During the mixing study at the speed of [redacted] a vortex was not observed. A [redacted] with a target of [redacted] was the intended goal of the mixing study; however, during qualifications, a higher mixing speed was challenged. Refer to PER01 for additional details. The solution was mixed between [redacted] After completion of pooling, the LNP underwent Clarification Filtration. Table 2 summarizes the formulation process parameters.

Table 2: Formulation Process Parameters

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
				6007320001	6007320002	6007320003
Post Pooling Mix	Mixing Speed	NCPP	[redacted]			
	Met NOR?			No [a]	No [a]	No [a]
	Mixing Duration	NCPP	[redacted]			
	Met NOR?			Yes	Yes	Yes

a) The goal of the mixing study was to obtain a gentle vortex of the solution with no visible foaming. A vortex was never observed but clear mixing was observed at [redacted] refer to PER 01 for additional details.
b) Samples were collected at timepoints of [redacted] with a total mixing time of [redacted]

Three (3) confirmatory mixing studies per process step were performed during PPQ execution. Mixing speeds were developed to avoid excess mixing and splashing. Mixing study initial timepoint samples were not required to meet acceptance criteria as long as subsequent timepoint samples meets acceptance criteria.

3.2.P.3.5.2.1.4 Clarification Filtration

The LNP was clarification filtered via a filtration assembly consisting of a [redacted] filter and transferred into a pre-sterilized disposable [redacted] Bag. The filter was pre sterilized by gamma irradiation and post-use integrity tested. Samples were collected for an IPC mRNA concentration test before continuing to dilution

Table 3 summarizes the clarification filtration critical in-process controls (CIPC). These parameters and controls were assessed through batch record and protocol execution. Non-critical process parameters were evaluated through routine manufacturing operations and batch records

Table 3: Clarification Filtration Critical In-Process Controls

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
				6007320001	6007320002	6007320003
Clarification Filtration	mRNA Concentration	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes
Post-use Clarification Filter Integrity Testing	Bubble Point (70% IPA/ 30% WFI)	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes

3.2.P.3.5.2.1.5 Buffer Formulation

Water for Injection (WFI) was added to [redacted] to a [redacted] bag in a [redacted] unit. The mixer speed was set to maintain a gentle vortex of the solution at [redacted] Tris Base, Tris HCl, and Sucrose were added to the [redacted] bag, followed by a [redacted] WFI rinse of the dispensing containers. QS with WFI was performed to the final target volume ([redacted]). The solution was mixed for [redacted]

A sample was removed via a sample port to measure the pH with an expected target of [redacted]). Samples were collected for pH and Osmolality testing before continuing to buffer filtration.

The buffer was filtered via a filtration assembly consisting of a [redacted] and transferred into a pre-sterilized disposable [redacted] single use bag. The filter was gamma sterilized and post-use integrity tested.

Table 4 summarizes the buffer critical in-process controls (IPC). These parameters and controls were assessed through batch record and protocol execution. Non-critical process parameters were evaluated through routine manufacturing operations and batch records.

Table 4: Buffer Critical In-Process Controls (CIPCs)

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
				6007320001	6007320002	6007320003
Buffer Formulation	pH	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes
	Osmolality	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes
Post-use Buffer Filter Integrity Testing	Bubble Point (WFI)	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes

3.2.P.3.5.2.1.6 Dilution

A defined amount of buffer was added to the pooled clarified mRNA-1273 LNP in the [redacted] mixing bag to dilute to the target concentration of [redacted] as calculated based on the IPC concentration result. The mixer speed was set to maintain a gentle vortex of the solution with no visible foaming at [redacted]. The solution was mixed for [redacted]. Upon completion of the mixing, the final bulk diluted mRNA-1273 was held at [redacted] until needed for sterile filtration.

Table 5 summarizes the dilution critical process parameters and mixing study parameters. These parameters and controls were assessed through batch record and protocol execution. Non-critical process parameters were evaluated through routine manufacturing operations and batch records.

Table 5: Dilution Critical and Mixing Study Process Parameters

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
				6007320001	6007320002	6007320003
Dilution and Mixing	Dispensed Dilution Buffer Weight	CPP	[redacted]			
	Met NOR?			Yes	Yes	Yes
Post Dilution	Mixing Speed	NCPP	[redacted]			
	Met NOR?			Yes	Yes	Yes
	Mixing Duration	NCPP	[redacted]			
	Met NOR?			Yes	Yes	Yes

Three (3) confirmatory mixing studies per process step was performed during PPQ execution. Mixing speeds are developed to avoid excess mixing and splashing. Mixing study initial timepoint samples are not required to meet acceptance criteria as long as subsequent timepoint samples meets acceptance criteria.

3.2.P.3.5.2.1.7 Sterile Filtration

The product was sterile filtered via a redundant sterilizing filtration assembly consisting of two [redacted] filters and transferred into a pre-sterilized disposable [redacted] Bag. Both sterilizing filters were received pre-sterilized by gamma irradiation. The filters were pre-use integrity tested followed by a [redacted] filter blow down with air. The downstream filter was post-use integrity tested and passed in all cases. The filtered product was then either immediately transferred to the fill room for filling or held in specified storage condition until transport to the fill room.

Table 6 summarizes the sterile filtration critical process parameters and critical in-process controls (CIPC). These parameters and controls were assessed through batch record and protocol execution. Non-critical process parameters were evaluated through routine manufacturing operations and batch records.

Table 6: Sterile Filtration Process Parameters

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20 6007320001	PPQ Batch 2 062G20 6007320002	PPQ Batch 3 001H20 6007320003
Prior to Sterile Filtration	Bioburden	CIPC	[redacted]			
	Met NOR?			**Yes**	**Yes**	**Yes**
Sterile Filtration	Membrane Loading	CPP	[redacted]			
	Met NOR?			**Yes**	**Yes**	**Yes**
	Filtration Pressure	CIPC	[redacted]	Yes	Yes	Yes
	Met NOR?			**Yes**	**Yes**	**Yes**
	Flush Volume (Product)	CPP	[redacted]			
	Met NOR?			**Yes**	**Yes**	**Yes**
Post-use Filter Integrity Testing (Downstream)	Bubble Point (70%IPA/ 30%WFI)	CIPC	[redacted]			
	Met NOR?			**Yes**	**Yes**	**Yes**

Formulation and filtration were successfully executed according to the manufacturing batch record and PPQ protocol, as demonstrated by meeting the pre-defined process parameters and in-process control criteria.

3.2.P.3.5.2.1.8 Filling Equipment Preparation

The filling batch parts were transported to the [redacted] and inspected for visual damage and washed either manually or via the automated parts washers, [redacted]. After washing, the batch parts were assembled under a down flow booth and wrapped to be autoclaved sterilized and/or sanitized [redacted] in the [redacted] After sterilization, the assembled batch parts were unloaded in the [redacted] under laminar flow conditions and stored until setup activities began for the Flexible Filler ([redacted].

Filling equipment preparation was successfully executed according to the manufacturing batch records and protocol.

3.2.P.3.5.2.1.9 Component Preparation

Vials were staged and transported to the Grade C Materials in [redacted] Then, the Ready-To-Use (RTU) vials were staged and transported to the [redacted]

Stoppers and seals were supplied sterile and Ready-To-Use (RTU) by the supplier in [redacted] bags with [redacted]. The stoppers and seals were staged and transported to [redacted] for further processing on the flexible filler line.

Component preparation was successfully executed according to the manufacturing batch records and protocol.

3.2.P.3.5.2.1.10 Isolator Preparation

Manufacturing and QA released the [redacted] for use by manufacturing. Prior to setup, the isolator gloves were visually inspected as well as integrity tested for the Flexible Filler and Automated Loader / Unloader [redacted] sections of the Isolation system [redacted]. Additionally, the Restricted Access Barrier System (RABS) gloves were visually inspected for the Debagger [redacted] and Capper / Trayloader [redacted]. All washed, autoclaved, and assembled equipment parts were transferred via carts and installed / set up on for the Flexible Filler [redacted]. All washed and assembled equipment parts were transferred via carts and installed / set up on the Capper / Trayloader [redacted] The setup took place under laminar airflow with the isolator and RABS doors open to the Grade C environment. All equipment was set up per approved procedures.

Prior to the start of filling line set up, a pre-Steam-In-Place (SIP) leak test on the Flexible Filler ([redacted] product pathway was performed. The Flexible Filler Filling Line Isolator [redacted]) doors were then closed and sealed. Additionally, the RABS for the Debagger [redacted]) and Capper / Trayloader [redacted] was set up and prepared for use. The interior of the isolator, including exterior of the recently installed equipment, were then decontaminated via [redacted] using a validated decontamination cycle. Upon completion of the decontamination cycle, the product pathway was sterilized via the Steam-In-Place (SIP) process.

Isolator preparation was successfully executed according to the manufacturing batch records and protocol.

3.2.P.3.5.2.1.11 Filling

The pre-sterilized intermediate vessel [redacted] Bag / single-use disposable vessel) containing the sterile filtered product was aseptically connected to a pre-sterilized single use tubing assembly via aseptiquik connectors. The single use tubing assembly was positioned within the peristaltic pumps of the Portable Peristaltic Filler located outside the isolator within a Grade C environment. The tubing assembly was then fed into the isolator via a Rapid Transfer Port (RTP) and the sterile filling needles are located within the Grade A barrier isolator environment.

The RTU vials were filled with sterile filtered product. The product was filled at the specified fill volume range into vials via the peristaltic pumps of the Portable Peristaltic Filler (PPF). In-process weight checks were performed on one hundred percent (100%) of all processed vials. All vials were fully stoppered and transported to the vial capper for seal placement and crimping.

All vial filling, weight checking, and stoppering activities were performed within an enclosed/isolator system classified as Grade A. During filling, for each batch, continuous viable (settle plates) and total particulate air environmental monitoring was performed.

Active viable air plates were also performed during filling with viable surface monitoring performed at the end of filling. All environmental monitoring results satisfactorily met established acceptance criteria. Viable surface was performed at the end of filling activities.

All viable and total particulate air monitoring results satisfactorily meet established acceptance criteria.

Table 7 summarizes the filling critical process parameters. These parameters were assessed through batch record and protocol execution. Non-critical process parameters were evaluated through routine manufacturing operations and batch records.

Table 7: Filling, Stoppering Process Parameters and In-Process Controls

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20 6007320001	PPQ Batch 2 062G20 6007320002	PPQ Batch 3 001H20 6007320003
Filling	Fill weight	CIPC	[redacted]			
	Met NOR?			Yes	Yes	Yes

a) Value represents the mean fill weight. Data analysis is provided in VPQQ-256-100-00002-S, Table 13.3.

Vial filling was successfully executed according to the manufacturing batch records and protocol.

3.2.P.3.5.2.1.12 Capping and Tray Loading

Capping activities occurred within the isolator under a Grade A environment. During the capping process, continuous viable and total particulate air environmental monitoring was performed within the isolator. Viable surface environmental monitoring was performed at the end of filling activities.

Vials were processed through the capper [redacted] to place an aluminum seal crimped around the vial neck. After the capper, crimped vials left the isolation system and are transitioned into the tray loader. Vials are then loaded into trays.

Table 8 summarizes the critical process parameters. These parameters were assessed through batch record and protocol execution.

Table 8: Capping Process Parameters

Catalent Process Description	Process Parameter	Parameter Classification	Normal Operating Range (NOR)	Results		
				PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
				6007320001	6007320002	6007320003
Capping	Crimp Pressure	CPP	[redacted]			
	Met NOR?			Yes	Yes	Yes

a) 2.0 was set as the nominal crimp pressure with a range of [redacted] (NOR).

Capping and tray loading was successfully executed according to the manufacturing batch records and protocol.

3.2.P.3.5.2.1.13 Process Hold Times

Table 9 summarizes the process hold times for mRNA-1273 as challenged during process validation activities at Catalent. Hold times are not assigned to each specific unit operation and instead a Total process duration is defined. The hold times were challenged during the PPQ batches as defined in the table. For process hold times intended to be challenged, a processing duration of no less than the expected challenge limit was targeted during PPQ batch manufacturing.

Table 9: Process Hold Times

Hold Time Description	Defined Hold Time Duration and Definition (Start to End)	Hold Time	Results		
			PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
			6007320001	6007320002	6007320003
Total Bulk Drug Processing Time (TOR)	[redacted] End of Thaw / Start of Temperature Conditioning	Hold Time Start	[redacted]		
		Hold Time End			
		Actual Hold Time Duration			
Total Bulk Drug Processing Time (2-8°C)	[redacted] End of Thaw / Start of Temperature Conditioning	Hold Time Start			
		Hold Time End			
		Actual Hold Time Duration			

a) Extended hold time was due to a site wide power outage. Additional details are provided in Catalent REC 229529.

For process hold times intended to be challenged, a processing duration of no less than the expected challenge limit was targeted during PPQ batch manufacturing. Vials were pulled at the end of inspection to challenge hold times and were representative of the batch. Samples 30-35PPQ were collected to perform testing consisting of both a full testing panel and a reduced testing panel of stability indicating tests. Process durations were tracked from the end of

mRNA-1273 LNP thaw until the transfer of material to -40°C conditioning freeze, thus including pooling, clarification, dilution, filtration, filling, visual inspection, and packaging activities. Process hold times were tracked according to the manufacturing batch records and protocol, as demonstrated by meeting the pre-defined process parameters and in-process controls criteria.

The hold times for commercial process are listed in Table 10.

Table 10: Commercial Process Hold Times and Process Duration Time Limits

Description	Defined Hold/Process Duration and Definition (Start to End)	Hold/Process Limit
Total Bulk Drug Processing Time (TOR)	[redacted] End of Thaw / Start of Temperature Conditioning	[redacted]
Total Bulk Drug Processing Time (2 - 8°C)	[redacted] End of Thaw / Start of Temperature Conditioning	[redacted]

3.2.P.3.5.2.1.14 Visual Inspection

Each batch underwent 100% manual inspection by qualified inspectors for container defects, closure defects, and product defects per A-SOP-22-05-001, *Manual Inspection of Vials and Syringes Using a Lighted Inspection Booth.* Samples were taken from the inspected units for statistical visual inspection, also known as an Acceptance Quality Limit (AQL) inspection, per A-SOP-03-04-001, *Performance of AQL for Parenteral Manual Inspection*. Defect limits and definitions are defined in A-WI-03-04-001-002, *Parenteral Inspection Defect Criteria List.*

Table 11 summarizes the visual inspection data for each PPQ batch.

Table 11: Visual Inspection Results

Inspection Information			Results		
			PPQ Batch 1 057G20	PPQ Batch 2 062G20	PPQ Batch 3 001H20
			6007320001	6007320002	6007320003
Quantity Inspected			[redacted]		
Defect Categories and Types	Critical	Container Defects			
		Closure Defects			
		Product Defects			
	Major A	Product Defects			
	Major B	Container Defects			
		Closure Defects			
		Product Defects			
	Minor	Container Defects			
		Closure Defects			
		Other			
Total Quantity of Rejects					
Total Overall Reject Rate (%): Current Control Limit: [redacted]					
AQL Pass/Fail			Pass	Pass	Pass

Visual inspection was successfully executed according to the manufacturing batch records and protocol, as demonstrated by meeting the pre-defined process parameters and in-process controls criteria.

3.2.P.3.5.2.1.15 Events, Deviations, Laboratory and Microbiology Investigation Reports

There were a total of 8 events and deviations generated during execution of the PPQ batches. A summary of Protocol Exception Reports (PERs) is provided in Table 12. A summary of all events and deviations for the PPQ batches [applicable events and minor, major, and critical unplanned deviations, Laboratory Investigation Reports (LIRs), and/or Microbiology Investigation Reports (MIRs) that occurred during the run(s)] is provided in the PPQ Report Section 15.0.

All events and deviations described were satisfactorily documented, investigated, completed, and approved by the corresponding departments. No event/deviation had an impact on product SISPQ that could question the ability to demonstrate that the manufacturing process is under control and consistently produces product that meets all predetermined quality attributes and in-process controls.

Table 12: Protocol Exception Reports

PER #	Description	Date Closed
01	[redacted]	20AUG20
02		18AUG20
03		21SEP20
04		21SEP20
05		22SEP20

3.2.P.3.5.2.1.16 Conclusion

Supplemental studies (i.e. Mixing Hold, CCOQ, CCIT, filter validation, etc.) were determined to be required in VMP-256-100-00001, *mRNA-1273 (Project Code 256-100-300) Drug Product Process Validation Master Plan for Primary Manufacturing*, prior to PPQ execution. The studies were verified as being completed and are summarized in the following reports.

- A-VOQ-000019-S-VL-073MAR17, Flexible Filling Line Component Compatibility Operational Qualification (CCOQ) Summary Report [redacted] Vial (Item 403215), 20mm Vial Stopper (Item 407330) and [redacted] Vial Seal (Item 407312) – Validation Project Number: VL-073MAR17.
- EXT-0820, mRNA-1273 Bacterial Challenge Filter Validation Report

As documented in VPPQ-256-100-00002-S, *mRNA-1273 (Project Code 256-100-300) Drug Product Primary Process Performance Qualification Final Summary Report (2020),* the performance process qualification (PPQ) has been successfully executed following the requirements of the corresponding PPQ protocol.

The data presented in the summary report demonstrates that the manufacturing process is under control and consistently meets all predetermined quality attributes and in-process controls. With the approval of this summary report, the manufacturing process performance for primary manufacturing of mRNA-1273 is considered validated.

3.2.P.3.5.3 Aseptic Manufacturing – Multi-Use Flexible Filler ([redacted]) Validation

The Multi-Use Flexible Filler ([redacted]) is located in a [redacted] room and is fully contained within the Flexible Filling Line Isolator ([redacted]), which provides a [redacted] environment for the aseptic filling and stoppering of vials. The filling operation takes place in a [redacted] configuration with [redacted] of components occurring where necessary to meet the basic requirements of component handling, throughput, and dose accuracy needs. The Multi-Use Filler consists of three machines: Debagger [redacted] and Flexible Filler [redacted]

The [redacted] permits the manual placement of individually sealed polypropylene bagged trays of ready-to-use vials onto the infeed conveyor. A conveyor guides the tray to the cutting station where a knife (mounted on a slide) rises to cut the bag and remove the end. The cut-off section is disposed of through a discharge in the machine table and into a collection bin. After the cutting process, the transfer pusher pushes the opened bag with the packaging container to the debagging station. Bag grippers then hold the top and bottom of the un-open end, securing the bag and allowing exit of the tray from the bag into the isolator, via an automated pass-through door. The tray is automatically placed onto the discharge conveyor and delivered to the [redacted]

The [redacted] is contained within the Flexible Filling Line Isolator. Sterile, Clean, and Ready-to-Fill (SCF) trays are automatically discharged from the [redacted] to the [redacted]. The trays are controlled and delivered to the [redacted] removal position. The trays are centred and held firmly in place. The [redacted] identifies a corner of the [redacted] lid, grabs the corner and pulls off the lid in a diagonal movement in such a way that the lid is removed in one piece, and discarded. The robot then removes the single inlay sheet which is in place within the tray over the vials. The [redacted] then discards the removed inlay sheet to the discharge bin. The discharge chute between the isolator and the bin is protected by a vertical unidirectional airflow curtain.

The Multi-Use Flexible Filler provides accurate, low-loss dosing, and the ability to utilize both time/pressure and peristaltic pump filling technologies. The mRNA-1273 filling process utilizes peristaltic pump filling technologies. In-process (IPC) 100% weight checks are performed for vial filling. Design allows for quick maintenance, repair or changeover without compromising the status of the filling and closing zone.

Detailed information regarding the Multi-Use Flexible Filler validation activities is provided in the Catalent Indiana, LLC Type V Drug Master File #024888 (Letter of Authorization, Module 1.4.2), 3.2.A.1.10, Equipment Validation – Flexible Filling Line.

3.2.P.3.5.3.1 Steam-in-Place (SIP) Cycle Performance Qualification (PQ)

Performance Qualification was executed according to [redacted] ([redacted] Vial Configuration Steam-in-Place Performance Qualification Protocol for the Steam in Place cycle for the vial filling configuration of [redacted], Flexible Filler.

3.2.P.3.5.3.1.1 SIP Cycle PQ

SIP programs for the Vial Configuration of the Flexible Filler include the following recipes:

- Vial Recipe 5 - Validation Vial SIP 4 Head

Table 13 summarizes cycle parameter settings that are utilized during validation and production runs. Validation cycles use reduced parameters to represent worst-case conditions.

Table 13: Worst Case PQ Parameters for Vial Configuration SIP

Parameter	Validation Settings	Production Settings
Recipe Name	Validation Vial SIP	SIP Production Cycle
Dynamic Steam Pressure	[redacted]	
Minimum Sterilization Temperature		
Sterilization Time (Exposure)		

Biological Indicators (BIs) and Thermocouples (TCs) were distributed throughout the Multi-Use Flexible Filler to demonstrate that the SIP cycle could achieve a minimum 6-log spore reduction and result in complete inactivation of the BI used, while also meeting minimum temperature and lethality criteria.

3.2.P.3.5.3.1.2 SIP Cycle PQ Acceptance Criteria

The vial configuration SIP cycle was required to meet the following acceptance criteria during [redacted] consecutive PQ runs in order the successfully qualify the cycle:

- No BIs exhibit growth after the seven-day incubation period. An unexposed control (positive control) BI for each run shall exhibit growth.
- The temperatures as recorded by the calibrated validation sensors should be [redacted] validation setpoint of [redacted] during the exposure period after achieving steady state.
- The minimum F_0 value calculated by the data logger at the end of the cycle should be [redacted]
- The temperatures as recorded by the Filler temperature detectors should be [redacted] during the exposure period after achieving steady state.
- The minimum F_0 value calculated by the Filler at the end of the cycle should be [redacted]
- Thermocouple post-use calibration verification is [redacted] of the reference temperature at each temperature set point, if applicable.
- Actual results meet expected results.
- All test steps pass.

3.2.P.3.5.3.1.3 SIP Cycle PQ Results

The temperature and BI results obtained from the three consecutive PQ runs are summarized in Table 14.

Table 14: Vial Configuration SIP PQ Temperature and BI Results

Summary Report Number		A-VPQ-00067-S-VL-043FEB17	
BI Name	**Lot No.**	**D-Value**	**Expiration Date**
Geobacillus stearothermophilus	GST-454	1.6	21SEP17
	Run 2 [a]	**Run 3**	**Run 4**
Date	26FEB17	26FEB17	01MAR17
Exposed BIs with growth	[redacted]		
Positive Control BI			
Demonstrated Log Reduction			
Min Temp (°C) / Location			
Max Temp (°C) / Location			
Minimum F_0 (min)			
Pass/Fail	Pass	Pass	Pass

a) Run 1 cycle was aborted.

All acceptance criteria for the PQ exercises were met, and the vial configuration SIP cycle recipe is qualified and deemed acceptable for production use.

3.2.P.3.5.3.2 SIP Ongoing Assessment of Qualification

3.2.P.3.5.3.2.1 SIP Cycle Annual Requalification

The vial configuration SIP cycle was successfully qualified for production use and is requalified annually per approved protocol. The SIP cycle parameters for annual requalification and production settings are summarized in Table 15.

Table 15: SIP Cycle Parameters for Annual Requalification and Production

Parameter	Validation Setting	Production Setting
Recipe Name	Recipe 5	Recipe 1
Recipe Type	VALIDATION Vial SIP	TP SIP for solution product 4 pos'
Minimum Temperature	[redacted]	
Pressure Control Setpoint		
Sterilization Time (exposure)		

Biological Indicators (BIs) and Thermocouples (TCs) are distributed throughout the Multi-Use Flexible Filler to demonstrate that the SIP cycle achieves a [redacted] spore reduction and results in complete inactivation of the BI used, while also meeting minimum lethality criteria.

3.2.P.3.5.3.2.2 SIP Cycle Annual Requalification Acceptance Criteria

Annual requalification for the vial configuration SIP cycle must meet the following acceptance criteria:

- [redacted]

3.2.P.3.5.3.2.3 SIP Cycle Annual Requalification Results

Recent requalification studies for the vial configuration SIP cycle are summarized in Table 16.

Table 16: Annual Requalification Results

Summary Report Number		A-VPQ-00067-S-VL-020JAN20	
BI Name	**Lot No.**	**D-Value (min)**	**Expiration Date**
Geobacillus stearothermophilus	GST-493	[redacted]	29JAN21
Attribute		**Result**	
Date		20JAN20	
Exposed BIs with growth		[redacted]	
Positive Control BI			
Demonstrated Log Reduction			
Minimum F_0 (min) Filler			
Minimum F_0 (min) Data Logger			
Pass/Fail		Pass	

3.2.P.3.5.4 Row-by-Row Automated Loader/Unloader ([redacted]) Validation

The Row-by-Row Automated Loader/Unloader [redacted] is fully contained within the Flexible Filling Line Isolator and transfers vials form the Flexible Filler to the Capper/Trayloader ([redacted]).

The [redacted] was qualified for use as part of the Flexible Filling Line Isolator PQ and does not require separate PQ.

3.2.P.3.5.5 Capper/Trayloader ([redacted]) Validation

The Capper/Trayloader efficiently interfaces with the Multi-Use Flexible Filling Line [redacted] to cap and load vials onto trays. The Capper/Trayloader is installed within a restricted access barrier system (RABS) system supplied with [redacted] quality HEPA-filtered air and classified as [redacted]. Stoppered vials are delivered from the upstream system [redacted] to the Capper/Trayloader within the RABS for capping. The capping process takes place within an active RABS, where stoppered vials receive a seal and are crimped by the Capper. The seals are fed into a hopper during processing. Passing vials are then fed to the trayloader section and loaded into trays in a bulk arrangement (i.e., not nested). Each tray receives the same number of vials. Full trays are manually removed from the tray loading unit. The equipment and RABS are installed within a [redacted] room.

The Capper/Trayloader was qualified for use as part of the Multi-Use Flexible Filling Line PQ and does not require separate PQ.

3.2.P.3.5.6 Flexible Filler Isolator ([redacted]) Validation

The Flexible Filling Line Isolator ([redacted]) is designed to create a [redacted] environment for aseptic filling operations. The isolator is decontaminated with [redacted] which is provided by an integrated [redacted] Generator. The Flexible Filling Line Isolator is comprised of the following major components: Manipulation Unit, Recirculation Unit, Air Handling Unit, Environmental Monitoring System (EMS), Decontamination Loop, and [redacted] decontamination system. The [redacted] decontamination system provides dehumidification (to reduce the initial humidity in the isolator), decontamination, and aeration of the isolator. The Flexible Filling Line Isolator also has an incorporated Material Transfer Chamber (MTC), which can be decontaminated with [redacted] separately from the rest of the isolator. This allows the rapid decontamination of supplies or tools which may be required during normal operation of the filling line.

3.2.P.3.5.6.1 [redacted] Cycle

The [redacted] decontamination cycle of the Flexible Filling Line Isolator has been qualified to ensure the system is able to consistently meet acceptance criteria. Requalification occurs annually, utilizing BIs loaded with *Geobacillus stearothermophilus* spores. The initial qualification of the biodecontamination cycle was performed based on cycle development data and a maximum worst-case load. BI locations were originally determined from an air flow visualization study and modified based on biodecontamination and aeration process improvement studies that were performed after aeration units were installed on the Filling Isolator under change control.

Performance Qualification testing of the [redacted] Cycle for the Flexible Filling Line Isolator was performed according to an approved protocol utilizing maximum loads for the vial configuration to demonstrate thorough [redacted] distribution throughout the chamber, which was tested using BIs distributed throughout the isolator. [redacted] runs of the [redacted] cycle for the Filler Isolator, including the [redacted] section of the isolator, were required for the study.

3.2.P.3.5.6.1.1 [redacted] Cycle PQ

[redacted] Cycle PQ for the Flexible Filling Line Isolator Vial Configuration utilized the Vials in Tray configuration. As recommended from executed cycle development studies, the most challenging configuration for vial filling used the "Vials in Tray" format parts, as the Worst-Case Location Study showed these to be more challenging to decontaminate than the larger Nested Vial format parts. [redacted] decontamination for the Flexible Filling Line Isolator and MTC were conducted concurrently during PQ with the MTC door open to the isolator, which allowed for the decontamination of the MTC door seals.

The [redacted] cycle parameters were determined via development studies and are qualified for achieving a [redacted] spore reduction. Key parameters identified for the [redacted] cycle are detailed in Table 17 and Table 18. Cycle parameters used for PQ differed from those used for production by reduced injection time for [redacted], representing a worst-case condition.

Table 17: Isolator Parameters for Vial Cycle PQ and Production

Isolator Preparation Mode	Isolator Decontamination
P09022 SP Differential Pressure Filler (Pa)	P09022 SP Differential Pressure Filler (Pa)
T09001 SP Temperature Filler (°C)	T09001 SP Warm-up temperature transition (°C)
N04201SP Supply Air Filler (%)	SP Watchdog time warm-up (min)
P09024 SP Differential pressure [redacted] (Pa)	M09001 SP Dehumidification humidity transition (% RH)
T09002 SP Temperature [redacted] (°C)	SP Watchdog time dehumidification (min)
N04301 SP Supply air [redacted] (%)	N08001Filler [redacted] Supply Damper (% open)
	N08101 MTC [redacted] Supply Damper (% open)
	N08002 [redacted] Supply Damper (% open)
	N04101 SP MTC supply blower Aeration (%)
	S09001-2 SP LAF Fixed Output Aeration (%)
	SP Aeration 1 time 1 (min)
	SP Aeration 2 time 2 (min)

Table 18: [redacted] Parameters for Vial Cycle PQ and Production

Format Parameter – [redacted] Isolator Decontamination	Service – [redacted] Machine Parameters
S20001 SP Supply air general (m³/h)	T20004 SP Temperature pre-heater (°C)
S20002 AHH Supply air general (m³/h)	T20008 AHH Temperature pre-heater (°C)
S20002 ALL Supply air general (m³/h)	T20008 ALL Temperature pre-heater (°C)
SP Dehumidification time (min)	T20007 SP Temperature vaporizer (°C)
SP Aeration time (min)	T20009 AHH Temperature vaporizer (°C)
S20001 SP air flow aeration (m³/h)	T20009 ALL Temperature vaporizer (°C)
T20004 SP Aeration pre-heating (°C)	M20001 AHH Humidity [redacted] supply (% RH)
SP Injection 1 time (min)	[redacted] Hosing capacity (g)
W20001 SP Injection 1 injection rate (g/min)	W20001 [redacted] Reservoir upper limit (g)
SP Injection 2 time (min)	W20001 [redacted] Reservoir lower limit (g)
W20001 SP Injection 2 injection rate (g/min)	Allowable Injection rate deviation (%)
[redacted] Supply Piping Heating Cable	S20001 C-factor
Thermostat setting SP J20003 (°C)	S20002 C-factor
Key Parameters for the Validation Cycle ([redacted] spore reduction)	**Key Parameters for the Production Cycle**
SP Injection 3 time (min)	SP Injection 3 time (min)
W20001 SP Injection 3 injection rate	W20001 SP Injection 3 injection rate

3.2.P.3.5.6.1.2 [redacted] Cycle PQ Acceptance Criteria

The [redacted] Cycle PQ for the vial configuration was required to meet the following acceptance criteria during [redacted] PQ runs in order to successfully qualify the cycle:

- [redacted] of the total quantity of BIs may exhibit growth following incubation
- [redacted] per location may exhibit growth.
- All test steps pass.

3.2.P.3.5.6.1.3 [redacted] Cycle PQ Results

A total of four (4) [redacted] cycles were performed during PQ activities. The cycle for [redacted] aborted before completing injection and BIs from this run were not processed. All cycle parameters were met for [redacted] and all BIs and controls processed from these runs yielded acceptable results.

All PQ acceptance criteria were met and the Flexible Filling Line Isolator [redacted] Cycle for the vial configuration was deemed qualified and acceptable for use. Results of the PQ are summarized in Table 19.

Table 19: BI Results of [redacted] Cycle PQ – Vial Configuration

Summary Report Number		**A-VPQ-00063-S-VL-003JAN17**	
BI Name	**Lot No.**	**D-value (min)**	**Expiration Date**
Geobacillus stearothermophilus	H1196	[redacted]	31JAN17
Attribute	**Run 1[a]**	**Run 3**	**Run 4**
Date	09JAN17	11JAN17	12JAN17
Exposed BIs with growth	[redacted]		
Positive Control BI			
Negative Control BI			
Demonstrated Log Reduction			
Pass/Fail	Pass	Pass	Pass

a) [redacted] was aborted.

3.2.P.3.5.6.2 [redacted] Cycle PQ – MTC

The Material Transfer Chamber (MTC) is a chamber integrated into the Flexible Filling Line Isolator which can be bio-decontaminated with [redacted] separately from the rest of the isolator. This allows the rapid decontamination and introduction of supplies or tools which may be required during normal operation of the filling line. When the MTC is decontaminated at the same time as the isolator, the MTC door is open to the isolator, which allows for the decontamination of the chamber and door seals concurrently with the isolator.

During the initial qualification, [redacted] different load patterns were identified for challenge. During cycle development it was determined that a [redacted] exposure using [redacted] injection was sufficient to obtain a [redacted] spore reduction. Although complete kill of BIs was obtained using a [redacted] exposure, an [redacted] exposure was recommended for consistency with parameters previously qualified for the MTCs of the two other filling lines in the facility. The key qualification and production [redacted] cycle parameters for a [redacted] spore reduction are summarized in Table 20 and Table 21.

Table 20: MTC Format Parameters for PQ and Production

MTC Controller Measurement		MTC Transfer	
P09121 SP Differential pressure MTC (Pa)	[redacted]	M09101 SP Dehumidification humidity transition (% RH)	[redacted]
T09101 AHH Temperature MTC (°C)		N04101SP Supply air MTC aeration (%)	
T09101 ALL Temperature MTC (°C)		Aeration time SP (min)	
N04101SP Supply air MTC (%)			

Table 21: [redacted] Parameters for PQ and Production

Format Parameter - [redacted] Isolator Decontamination		Service - [redacted] Machine Parameter	
S20001 SP Supply air general (m³/h)	[redacted]	T20004 SP Temperature pre-heater (°C)	[redacted]
S20002 AHH Supply air general (m³/h)		T20008 AHH Temperature pre-heater (°C)	
S20002 ALL Supply air general (m³/h)		T20008 ALL Temperature pre-heater (°C)	
SP Dehumidification time (min)		T20007 SP Temperature vaporizer (°C)	
SP Injection 1 time (min)		T20009 AHH Temperature vaporizer (°C)	
W20001 SP Injection 1 injection rate (g/min)		T20009 ALL Temperature vaporizer (°C)	
SP Injection 3 time (min)		M20001 AHH Humidity [redacted] supply (% RH)	
W20001 SP Injection 3 injection rate (g/min)		[redacted] Hosing capacity (g)	
SP Aeration time (min)		W20001 [redacted] Reservoir upper limit (g)	
S20001 SP air flow aeration (m³/h)		W20001 [redacted] Reservoir lower limit (g)	
T20004 SP Aeration pre-heating (°C)		Allowable Injection rate deviation (%)	
[redacted] **Supply Piping Heating Cable**		S20001 C-factor	
Thermostat setting SP J20003 (°C)	[redacted]	S20002 C-factor	
Key Parameters for 6-log Spore Reduction Cycle		**Key Parameters for Production Cycle**	
SP Injection 2 time (min)	[redacted]	SP Injection 2 time (min)	[redacted]
W20001 SP Injection 2 injection rate (g/min)		W20001 SP Injection 2 injection rate (g/min)	

3.2.P.3.5.6.2.1 [redacted] Cycle PQ Acceptance Criteria

The [redacted] loads described above were challenged with [redacted] runs each, for a total of [redacted] decontamination cycles. All cycle parameters were met and all BIs and controls processed from these runs yielded acceptable results.

All acceptance criteria for the Flexible Filling Line Isolator MTC [redacted] Cycle PQ have been met and the cycle was deemed qualified and acceptable for use.

3.2.P.3.5.6.2.2 [redacted] Cycle Annual Requalification

[redacted] Cycle requalification acceptance criteria is defined as:

- [redacted] of the total quantity of Bis may exhibit growth following incubation
- [redacted] per location may exhibit growth
- All test steps pass

3.2.P.3.5.6.2.3 [redacted] Cycle Annual Requalification Results

Table 22: Routine Requalification – Vial Configuration

Summary Report Number		**A-VPQ-00063-S-VL-034NOV19**	
BI Name	**Lot No.**	**D-value (min)**	**Expiration Date**
Geobacillus stearothermophilus	AH-044	[redacted]	30JUN20
Attribute	**Result**	**Pass/Fail**	
Date	20NOV19	Pass	
Exposed BIs with growth	[redacted]		
Positive Control BI			
Negative Control BI			
Demonstrated Log Reduction			

3.2.P.3.5.7 Overview of Media Fills

The following sections provide a brief description of the current media fill program implemented at Catalent to assess and qualify aseptic manufacturing processes. Detailed information regarding the Flexible Filling Line media fill validation activities is provided in the Catalent Indiana, LLC Type V Drug Master File #024888 (Letter of Authorization, Module 1.4.2), 3.2.A.1.16, Media Fill Validation – Flexible Filling Line.

3.2.P.3.5.7.1 Media Fill Bracketing Approach

Catalent utilizes a bracketing approach to validate aseptic filling operations. The smallest units are challenged to simulate higher operator intervention to the line and units with the largest openings are challenged to simulate maximum exposure at least once annually as a part of routine media fills. A component configuration will be accepted into the qualified media fill bracket for aseptic processing upon successful completion of CCOQ and CCIT. Only clear units will be used for media fills.

In the event that a process required to complete a project does not fit within the qualified media fill bracket and is not intended to be added as worst case, a product specific media fill is required.

Each new process will undergo a minimum of three (3) media fills to validate the aseptic process. Any new process similar to an existing validated process will be evaluated with a risk assessment to determine if additional media fills are required and the number of media fills to perform.

A component that is not within the validated bracket will be assessed to determine the number of media fills required to validate the process. Components that are significantly different dimensionally from the bracket or require increased handling will undergo a minimum of three (3) media fills to validate the process and could result in a change to the validated bracket. New components falling within the bracket will not require a media fill.

Introduction of equipment that is not within the validated bracket will be assessed to determine the number of media fills required to validate the process. Equipment that is significantly different dimensionally from the bracket or which requires increased handling will undergo a minimum of three (3) media fills to validate the process and could result in a change to the validated bracket. New equipment falling within the bracket (identical to parts already used) will not require a media fill.

3.2.P.3.5.7.2 Frequency of Media Fills - Flexible Filling Line

A minimum of four (4) media fills are planned each calendar year. Two media fills will be performed utilizing time pressure filling and two will be performed utilizing peristaltic pump filling.

Both ends of the vial filling flexible filling line bracket [redacted] vial openings) will be challenged every calendar year. Both tub and tray configuration for vials will be challenged every calendar year.

3.2.P.3.5.7.3 Acceptance Criteria

- [redacted] microbial contaminated filled containers discovered in final inspection.
- Media will promote growth of challenge organisms at an inoculum of [redacted]
- Fill and incubate the specified minimum quantity of containers.

3.2.P.3.5.7.4 Batch Size

A [redacted] units are filled and incubated for each media fill batch.

3.2.P.3.5.7.5 Volume of Medium Used in Each Container

A standard fill volume is used for all media fills varying based on the container size. Containers are filled to [redacted] of the nominal volume. This fill volume ensures that media will contact all internal surfaces of the container-closure system when inverted, there is sufficient volume to visually see growth, and that there is adequate headspace to support growth.

3.2.P.3.5.7.6 Type of Medium Used

[redacted] is used for media fills. If a higher viscosity media is needed, additional excipients may be added to increase the viscosity.

Each media fill batch undergoes growth promotion testing and must demonstrate the ability to support microbial growth. Media filled units are inoculated with fungal and bacterial isolates (including a facility isolate as determined by historical EM data). Units inoculated with fungal isolates (*Candida albicans* ATCC 10231, *Aspergillus brasiliensis* ATCC 16404) are incubated at [redacted] units inoculated with bacterial isolates (facility isolate, *Staphylococcus aureus* ATCC 6538, *Pseudomonas aeruginosa* ATCC 9027 and *Bacillus subtilis* ATCC 6633) are incubated at [redacted] After incubation, inoculated units are visually inspected and must demonstrate growth and yield passing morphology verification. Pour plates for each fungal and bacterial isolate must also demonstrate growth and have a plate count between [redacted]

3.2.P.3.5.7.7 Line Speed

Line speeds during a media fill batch are representative of routine batch manufacturing. A range will be challenged from a slow speed to the fastest speed applicable to the container size and configuration on the line.

3.2.P.3.5.7.8 Environmental Monitoring

Environmental Monitoring (EM) is performed during each media fill batch in accordance with the current policy and requirements implemented for routine manufacturing.

3.2.P.3.5.8 Flexible Filling Line Media Fills

For vial filling on the flexible filling line, the bracket consists of components with the smallest and largest vial openings based on the configuration (nested/tub or tray) processed on the equipment, regardless of filling mechanism (peristaltic pump or time pressure). For the nested/tub and tray configuration, the smallest vial opening is [redacted] and comprises the lower end of the bracket, challenging higher operator intervention to the line. The largest container in the nested/tub and tray configuration is a vial with a [redacted] opening and comprises the upper end of the bracket, challenging the largest container opening exposure to the environment.

The filling capabilities that have been validated on the Flexible Filling Line are summarized in Table 23.

Table 23: Vial Qualified Operations and High Risk Interventions

Filling Mechanism	Peristaltic Pump	
Filtration Process	Batch	
Filling Process	Liquid / Lyophilized	
Vial Size / Opening (Bracket)	[redacted]	
Tub/ Tray	Tub /Tray	Tray
Campaign	Yes	
	High Risk Interventions	
Stopper Gassing Equipment Installation	X	X
Filling Needle Replacement	N/A	N/A
Aseptic Connect and Disconnect	N/A	N/A
Wiping of the Stopper Bowl Interior	X	X

3.2.P.3.5.8.1 Routine Media Fill Qualifications

Results from recent routine media fills performed on the Flexible Filling Line are summarized in Table 24.

Table 24: Routine Media Fills – Vial -2020

Summary Report	**A-VPPQ-00203**			
Size	[redacted] Tray	[redacted] Tray	[redacted] Tray	[redacted] Tray
Liquid / Lyo	[redacted]			
Filling Mechanism	[redacted]			
Filtration Process	Batch	Batch	Batch	Batch
Batch Type	Campaign			Single
Lot	032C20	034C20	052C20	020D20
Fill Dates	30MAR20-31MAR20	01APR20-02APR20	02APR20-03APR20	24APR20-27APR20
Total Number of Units Filled	[redacted]			
Total Number of Integral Units and Into Incubation	[redacted]			
Total Number of Rejects	[redacted]			
Acceptable Media Fill	Pass	Pass	Pass	Pass
Total Fill Processing Time	[redacted]			

3.2.P.3.5.9 Environmental Monitoring Program

Environmental monitoring is conducted within Catalent per A-SOP-09-04-001, Environmental Monitoring Program and process qualification data. Results are recorded in the Laboratory Information Management System (LIMS).

The environmental monitoring program is designed to ensure that routine facility sanitization, standard manufacturing operations and gowning procedures are successful in maintaining facility environmental quality. Monitoring is conducted to ensure compliance of the manufacturing environment with established standards for viable surface, viable air and total particulate levels.

Routine sample locations are chosen based upon review of the performance qualification results of the area, high contact/traffic areas, air flow visualization studies and consideration of critical areas and/or operations. This is completed by performing Environmental Monitoring Performance Qualifications (EMPQ) of classified areas.

Defined control levels have been established for the classified areas. Exceeded levels are investigated according to procedure.

In addition to the annual review of common facility microorganisms, quarterly trending of environmental monitoring data is conducted.

3.2.P.3.5.9.1 Routine Environmental Monitoring

Routine monitoring is conducted to ensure compliance of the manufacturing environment with established standards for viable surface, viable air and total particulate levels. Routine testing of the manufacturing environment is performed in the *In Operation* (Dynamic) state and during *At Rest* (Static) conditions.

Microbial identification of each colony morphology present is performed for all environmental monitoring samples collected (EMPQ and batch related) which result in an alert or an action level excursion.

3.2.P.3.5.9.2 Frequency

All routine testing is performed when areas are in the dynamic state according to a defined schedule. Static conditions are monitored at least once annually. Monitoring frequency of the classified areas is summarized in Table 25.

Table 25: Monitoring Frequency

Classification	Environmental Monitoring Required
Grade A During Critical Operations	Total Particulate (continuous from start of setup to end of fill)
	Settling Plates (continuous from start of setup to end of fill)
	Viable Air (at least every 4 hours during setup and fill)
	Contact Plating of Critical Surfaces and Gloves Within the Isolator (at end of fill)
Grade C	Monitored at least Weekly for Viable Air, Surface Viable and Total Particulate
Grade D	Monitored at least Monthly for Viable Air, Surface Viable, and Total Particulate

3.2.P.3.5.9.3 Sampling Category and Technique

The methods and materials used for sample collection during environmental monitoring are summarized in Table 26.

Table 26: Sampling Category and Corresponding Test Technique

Category	Method
Surface Viable Monitoring	[redacted]
Viable Air Monitoring	
Settling Plate Monitoring	
Total Particulate Monitoring	

3.2.P.3.5.9.4 Environmental Monitoring Action Levels

Action levels for the various environmental monitoring methods are summarized in the following tables.

Table 27: Surface Viable Monitoring Action Levels (at rest and in operation)

Classification	Non-Floor Sites (CFU/Plate)	Floor Sites (CFU/Plate)
Grade	**Action Level**	**Action Level**
A	[redacted]	N/A
C		[redacted]
D		

Table 28: Viable Air and Settling Plate Action Levels

Classification	Viable Air Monitoring (CFU/m3)	Settling Plate Monitoring (CFU/Plate)
Grade	**Action Level**	**Action Level**
A[(a)]	[redacted]	[redacted]
C		N/A
D		N/A

a) Grade A Viable Air and Total Particulate Monitoring sites are monitored using the Particle Monitoring System

Table 29: Total Particulate Action Levels

Total Particulate Monitoring AT REST Levels		
[redacted] and [redacted] Sample Volume	[redacted] (particles/m^3)	[redacted] (particles/m^3)
Grade	**Action Level**	**Action Level**
A	[redacted]	
C		
D		
Total Particulate Monitoring IN OPERATION Levels		
[redacted] and [redacted] Sample Volume	[redacted] (particles/m^3)	[redacted] (particles/m^3)
Grade	**Action Level**	**Action Level**
A	[redacted]	
C		
D		

3.2.P.3.5.9.5 Mycological Monitoring

Surface and air mycological monitoring of all classified areas is performed at least monthly. Plates are incubated for [redacted]