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3.2.P.3.3 DESCRIPTION OF MANUFACTURING PROCESS AND PROCESS CONTROLS

3.2.P.3.3.1 Batch Description mRNA-1273 Drug Product

The nominal manufacturing batch size for mRNA-1273 Drug Product is 150,000 multiple dose vials. Batch size is maintained through the execution of approved, controlled batch records. Batch or lot numbers are unique identifiers for materials, received or produced, in the SAP. Batch numbers for commercial products will be generated utilizing the part number and the following logic: 60073YYXXX, where "60073" represents the five-digit Item Number, YY represents the year, and XXX represents a sequential number.

The SAP computer system is discussed in Section 3.2.A.1 {ModernaTX, Inc.} and Catalent batch numbering is described in Section 3.2.A.1 {Catalent}.

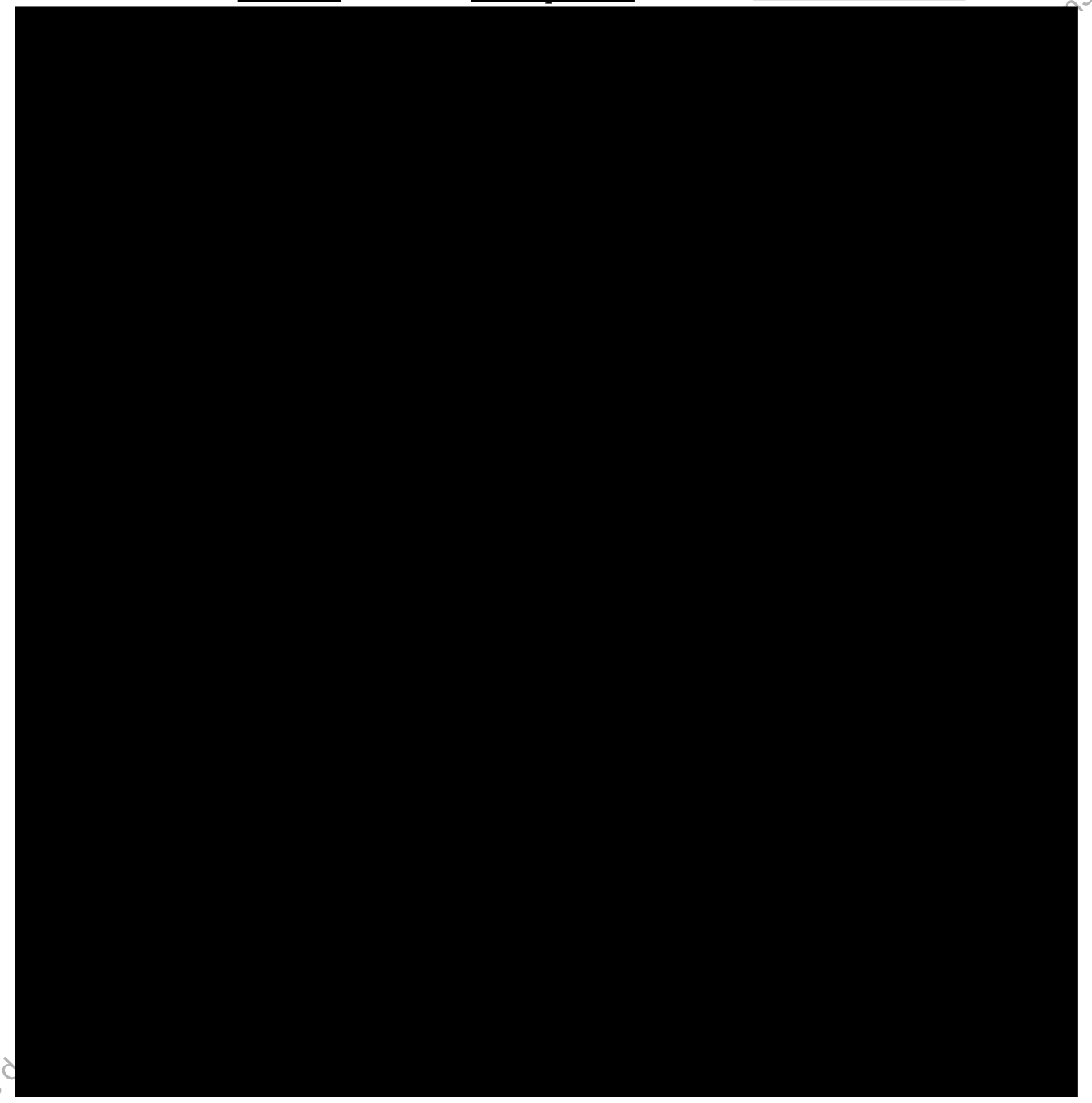
3.2.P.3.3.2 Overview of the mRNA-1273 Drug Product Manufacturing Process

mRNA-1273 Drug Product is a sterile, preservative-free, multiple-dose product comprising 0.20 mg/mL mRNA-1273 Lipid Nanoparticle (LNP) solution in a buffer containing 20 mM Tris, 87 g/L sucrose, and 4.3 mM acetate, pH 7.5. mRNA-1273 Drug Product is manufactured by a conventional aseptic process. Prior knowledge and experience from other sterile aseptically manufactured mRNA LNP-based drug products were leveraged in the development of the mRNA-1273 Drug Product process.

A detailed mRNA-1273 Drug Product manufacturing process flow diagram is provided in Figure 1 and the parameters are described in the tables associated with detailed descriptions of each unit operation in subsections of Section 3.2.P.3.3.3. The process parameters listed in each table include parameters for the mRNA-1273 Drug Product, 0.20 mg/mL manufacturing process specific to the Catalent Indiana, LLC (Catalent) facility.

At the Catalent facility, all assemblies and storage bags used in the manufacturing of mRNA-1273 Drug Product process are single use. In addition, all product contact components used in the filling process are single use; therefore, cleaning validation and component hold times are not applicable. General controls for consumables are summarized in Section 3.2.A.1.6 and a list of consumables used in the mRNA-1273 Drug Product manufacturing process is provided in Section 3.2.P.3.3.6.

Figure 1: Process Flow Diagram for mRNA-1273 Drug Product Manufacturing with In-process Controls



Abbreviations: FIT = filter integrity testing; LNP = lipid nanoparticle

Table 1: In-Process Controls

In-process Control	Process Step	Sample Pool	Acceptance Criteria
pH	Dilution Buffer Prep	Dilution Buffer	[redacted]
Osmolality	Dilution Buffer Prep	Dilution Buffer	
Post-filtration Integrity Testing	Dilution Buffer Prep	N/A	
Post-filtration Bioburden	Dilution Buffer Prep	Dilution Buffer	
Post-filtration Endotoxin	Dilution Buffer Prep	Dilution Buffer	
Filtration Pressure	Clarifying Filtration	N/A	
Post-clarification mRNA concentration	Clarifying Filtration	Pooled Clarified mRNA-1273 Bulk LNP	
Post-filtration Integrity Testing	Clarifying Filtration	N/A	
Filtration Pressure	Sterilizing Filtration	N/A	
Pre-filtration Integrity Test Value	Sterilizing Filtration	N/A	
Pre-sterilizing Filtration Bioburden	Sterilizing Filtration	Diluted mRNA-1273 Bulk Drug Product	
Post-filtration Integrity Testing	Sterilizing Filtration	N/A	
Fill Weight	Filling	In-line [b]	
USP <790> Destructive Visual Inspection	Visual Inspection	Vialed mRNA-1273 Drug Product	

Abbreviations: WFI = water for injection; IPA = isopropyl alcohol; CFU = colony-forming unit(s); FIT = filter integrity testing; NMT = not more than; TAMC = total aerobic microbial count; TYMC = total yeasts and mold count; EU = endotoxin unit; LNP = lipid nanoparticle;
a) [redacted] is the LNP specification and the IPC should not exceed those boundaries
b) Fill weight is performed 100% during the filling process.

3.2.P.3.3.3 Narrative Description of the Manufacturing Process

3.2.P.3.3.3.1 mRNA-1273 LNP Receipt and Storage

The frozen bulk mRNA-1273 LNP is received and stored between [redacted] at the drug product manufacturing site.

3.2.P.3.3.3.2 Dilution Buffer Preparation

The mRNA-1273 Drug Product dilution buffer (20 mM Tris, 87 g/L sucrose, pH 7.5) is used to dilute the mRNA-1273 LNP to the target product concentration of 0.20 mg/mL. The preparation of the dilution buffer consists of the addition of Tris, Tris-HCl, and sucrose to water for injection. An appropriate amount of buffer is prepared to allow the mRNA-1273 LNP to be diluted. The buffer is filtered for reduction of bioburden risk prior to use and transferred into a second pre-sterilized disposable sing-use bag. The filter is integrity tested after use and the Dilution buffer is held at room temperature until use. The dilution buffer composition is summarized in Table 2.

Table 2: Dilution Buffer Composition Material

Material	Target/Range
Tris	[redacted]
Tris-HCl	
Sucrose	
WFI	

Abbreviations: HCl = hydrogen chloride; QS = quantum sufficit; WFI = water for injection

3.2.P.3.3.3.3 mRNA-1273 LNP Thawing

The purpose of this step is to thaw the frozen mRNA-1273 LNP (in bags) in an active manner. Up to [redacted] bags containing mRNA-1273 LNP housed within the Robust Shipping and Storage (RoSS) shells are placed in the large-scale plate freeze- thaw unit (pFTU). The bags are thawed using a pre-defined thawing recipe with a [redacted] duration. After the [redacted] the pFTU switches to a setpoint of [redacted] to initiate a hold at [redacted] When the product is removed from the pFTU, the mRNA-1273 LNP solution is transferred to a [redacted] controlled temperature unit (CTU) in the event continuous processing does not occur. The thawed mRNA-1273 LNP is held in the CTU until pooling and clarification. Thawing process controls are provided in Table 3.

Table 3: mRNA-1273 LNP Thawing Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted]Scale
[redacted]	[redacted]	N/A	pFTU Recipe	[redacted]
		[redacted]	Thaw Duration	
			pFTU Temperature	
			CTU Temperature	

Abbreviations: CTU = controlled-temperature unit

3.2.P.3.3.3.4 Pooling

Post thawing, multiple bags of mRNA-1273 LNP are pooled into a pre-sterilized, single-use bag via a tubing manifold and mixed using a single use mixer. Process controls and parameters for pooling are summarized Table 4.

Table 4: mRNA-1273 Pooling Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted]Scale
[redacted]	[redacted]	[redacted]	Controlled Room Temperature	[redacted]
			Maximum transfer rate	
			Mixing rate for pooling	
			Mixing duration for pooling	

a) The mixing speed target for Scale B (Catalent) pooling is [redacted] The mixing rate may be changed to achieve a [redacted] during manufacturing. Mix rates are dependent on equipment used for mixing. When determining mix rates, high and low volumes should be evaluated to determine appropriate rates to achieve a [redacted]

3.2.P.3.3.3.5 Clarification

The pooled material is then clarified with a [redacted] filters [redacted] membrane) filtration assembly and collected in a new pre-sterilized single-use storage bag. Post clarification, samples are collected for in-process concentration (mRNA content) measurement as listed in Table 5, Section 3.2.P.3.4. Process parameters for clarification are summarized in Table 5.

Table 5: Clarification Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted] Scale
[redacted]	[redacted]	N/A	[redacted]	[redacted]

a Assumes [redacted] scale using [redacted] filter with [redacted] area. Filter size will be selected based on batch size to achieve as close as possible to a target loading of [redacted] The [redacted] filter loading may be exceeded during processing as long as the measured pressure is controlled below [redacted]

3.2.P.3.3.3.6 Dilution

The amount of dilution buffer required to dilute the mRNA-1273 LNP to the desired drug product concentration (0.20 mg/mL) is based on the mRNA content measured in the previous step. The bag containing the diluted mRNA-1273 bulk drug product solution is mixed using a single use mixer to obtain a homogeneous solution. Process controls for the final dilution step are summarized in Table 6. Once mixed, the diluted mRNA-1273 bulk Drug Product solution is transferred to the sterile filtration operation or refrigerated until needed for forward processing.

Table 6: Dilution Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted] Scale
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
				Calculated [a]
				[redacted]

a Target weight of dispensed dilution buffer = density of dilution buffer* [(volume of clarified mRNA-1273 LNP × mRNA concentration of clarified mRNA-1273 LNP/DP final dilution target concentration) - volume of clarified mRNA-1273 LNP]

b The mixing speed target for Scale B (Catalent) pooling is [redacted]. The mixing rate may be changed to achieve a [redacted] during manufacturing. Mix rates are dependent on equipment used for mixing. When determining mix rates, high and low volumes should be evaluated to determine appropriate rates to achieve a [redacted]

3.2.P.3.3.3.7 Sterile Filtration

Sterile filtration is performed on the diluted mRNA-1273 bulk drug product using a [redacted] filters [redacted] membrane) redundant filtration assembly. Prior to use, pre-use post sterilization integrity testing (PUPSIT) is performed on the filters. The filters are wetted using WFI, tested, and blown down for drying. Prior to sterile filtration, a product flush of the filters is performed [redacted] per filter). The sterile filtered drug product is collected in a sterile single use collection bag. Prior to sterile filtration, a pre-filtration bioburden sample is collected (as listed in Table 5, Section 3.2.P.3.4,) from the bag containing the mRNA-1273 Drug Product. A post-use filter integrity test is performed on the sterilizing filter.

Process parameters for sterile filtration are summarized in Table 7.

Table 7: Sterile Filtration Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted] Scale
[redacted]		[redacted]		
		N/A		

a The total filter flush volume is [redacted] for two filters
b The Catalent Controlled Room Temperature (CRT) normal operating range (NOR) is [redacted] and PAR is from [redacted] If the room temperature is increased above [redacted] the room HVAC system will control the temperature and any excursions beyond [redacted] would be short such that the product temperature is not impacted. The sterile filters bacterial challenge validation was completed up to [redacted]
c Assumes [redacted] scale using [redacted] filter with [redacted] area. Filter size will be selected based on batch size to a target loading of [redacted] The filter loading may be exceeded during processing as long as the measured pressure is controlled below [redacted]

3.2.P.3.3.3.8 Filling, Stoppering and Capping

Manufacturing and QA release the Flexible Filling Room for use. Prior to setup, the isolator gloves are visually inspected as well as integrity tested for the Filler and [redacted] sections of the Isolation system [redacted]. Additionally, the restricted access barrier system (RABS) gloves are visually inspected for the Debagger [redacted] and Capper / Trayloader [redacted]. All washed, autoclaved and assembled equipment parts are transferred via carts, installed and set up on the Flexible Filler [redacted] and Capper / Trayloader [redacted]. The setup takes place under laminar airflow with the isolator doors open to the Grade C environment. All equipment is set up per approved procedures.

Vial components used at the Catalent facility are received sterile ready-for-use trays and [redacted] lids. The vials are sterilized via a validated [redacted] sterilization cycle by the supplier (see Letter of Authorization for [redacted]). The [redacted] gray [redacted] stoppers are received ready-to-use [redacted] Letter of Authorization (LoA) [redacted] and LoA [redacted]. The stoppers are sterilized via steam sterilization by the supplier [redacted] LoA [redacted] A technical report describing the [redacted] Ready-to-Use Steam Sterilization Process Validation Summary is provided in Catalent [redacted] The flip off red matte seals are received ready-to-use. The seals are sterilized via gamma irradiation by the suppliers [redacted]

Pre-ETO sterilized bagged trays of vials are staged and transported to the Grade C Materials in Staging Room. The Ready-To-Use (RTU) vials are staged, wiped down and transported to the Grade C Flexible Filling Room.

Stoppers and seals are suppled sterile and Ready-To-Use (RTU) by the supplier in beta bags with Rapid Transfer Port (RTP) fittings. The stoppers and seals are staged and transported to the Grade C Flexible Filling Room.

The Flexible Filling Line Isolator [redacted] doors are then closed and sealed. The interior of the isolator, including exterior of the recently installed equipment, are decontaminated via [redacted] using a validated decontaminated cycle.

At the Catalent GMP facility, the sterile filtered drug product is filled with peristaltic pumps as part of the automated Filling Isolator with 100% weight checks. The mRNA-1273 Drug Product is filled into [redacted] vial (RTU trays). Table 8 summarizes the process parameters for filling, stoppering, and capping. Environmental monitoring performed throughout the filling process.

Table 8: Filling, Stoppering, and Capping Process Parameters

Process Variable	Process Condition	Range	Process Material or Equipment Parameter	Requirement at [redacted] Scale [a]
[redacted]				

[a] Based on product density of [redacted]

The single-use receiving bag containing the sterile filtered bulk product is connected to a pre-sterilized single use tubing assembly via sterile connectors. The single use tubing assembly is positioned within the peristaltic pumps located outside the isolator within a Grade C environment. The tubing assembly is then fed into the isolator via a Rapid Transfer Port and the sterile filling needles are located within the Grade A barrier isolator environment.

Trays of nested vials in sealed bags are loaded into the Debagger ([redacted] in the Grade C Flexible Filling Room. Under an integrated RABS with unidirectional Grade A air within a Grade C environment, the Debagger cuts and removes the bag while transporting the tray into the decontaminated Flexible Filling Line Isolator ([redacted]. The tray is transported to the [redacted], where the robotic arm removes the [redacted] lid and the [redacted] inner liner from the tray, exposing the vials to an Isolator Grade A environment. The tray is then transported to the Flexible Filler [redacted].

The Flexible Filler [redacted] robot picks up rows of vials from each tray and places it on the infeed transport belt to the filler. Empty trays are transported out of the isolator through the tray discharge.

Vials are filled with sterile filtered product. In-process weight checks are performed on one hundred percent (100%) of all filled vials. All vials are fully stoppered and transported to the Capper / Trayloader for seal placement and crimping.

Capping activities occur within an integrated RABS with unidirectional Grade A air within a Grace C environment. Filled stoppers vials are sent to the Capper / Trayloader from the flexible filler via conveyor. Vials are processed through a raised stopper vision detection system to ensure stoppers are fully seated prior to being capped. Vials are processed through the Capper / Trayloader ([redacted] to place an aluminium seal crimped around the vial neck. After capping, crimped vials leave the RABS system and are transitioned into the Trayloader. Vials are loaded into trays for transition to the inspection process.

3.2.P.3.3.3.9 Visual Inspection

At the Catalent facility, all vials undergo 100% visual inspection by qualified operators for container defects, closure defects and product defects. Vials that failed visual inspection are segregated from the batch as clearly labeled visual inspection rejects. An acceptance quality limit visual inspection is also performed by the Quality Unit according to USP <790> and USP <1790>.

3.2.P.3.3.3.10 Packaging and Labelling Procedure

Inspected vials are labeled and then packaged 10 per carton with an insert. The carton label is printed in-line with: Global Trade Identification Number (GTIN), Lot, Manufacture Date and 2D code. The vials are labeled in the Vial labeling room using an automated vial labeler. Product pallets actively being labeled and packaged are removed from [redacted] while the remaining vials are stored at [redacted] until ready for labeling. Inspection, labeling and packaging activities must occur with the validated [redacted] at room temperature. A tamper evident seal is applied to the carton and 12 cartons are placed into the case. The cases are then prepared for storage as described in Section 3.2.P.3.3.3.11.

3.2.P.3.3.3.11 Vial Storage

The mRNA-1273 Drug Product vials are transferred to [redacted] and held for [redacted] After the freeze hold, the vials are transferred to [redacted] as the final storage condition.

3.2.P.3.3.4 Process Durations

The mRNA-1273 Drug Product processing duration parameters are monitored as summarized in Table 9. These two durations are cumulative over the course of the mRNA-1273 Drug Product process.

Table 9: mRNA-1273 Drug Product Process Duration Parameters

Process Variable	Parameter Name	Maximum Duration
Cumulative Process Duration	Cumulative process duration at [redacted]	[redacted]
	Cumulative process time out of refrigeration [redacted]	

3.2.P.3.3.5 Reprocessing

Reprocessing is not performed during the production of mRNA-1273 Drug Product, 0.20 mg/mL.

3.2.P.3.3.6 mRNA-1273 Drug Product Single-Use Consumables

All single-use consumables used to manufacture mRNA-1273 Drug Product, materials of construction, and the related process steps are listed in Table 10. Per procedures, all manufacturing consumables are sourced to meet sterility (where required), USP VI biocompatibility, and BSE/TSE requirements, at a minimum. No consumables used in the mRNA-1273 Drug Product manufacturing process are sampled or tested in-house. All consumables used to manufacture mRNA-1273 Drug Product are certified for biocompatibility conformance against USP VI and all consumables are received from the vendor as gamma-irradiated. Some consumables, such as processing bags and transfer containers, are evaluated against additional criteria such as endotoxins/pyrogenicity, particulates, physical dimensions, and/or functionality testing by the supplier. All consumables are dispositioned by QC and QA prior to release in JDE (Enterprise resource planning software system). Pre-use filter integrity testing is performed by the vendor on the final sterilizing filter.

The mRNA-1273 Drug Product container closure system is described in Section 3.2.P.7.

Table 10: mRNA-1273 Drug Product Consumables

Consumable	Batch Size	Fluid Path Primary Materials of Construction	Process Step
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation Filtration
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation Filtration
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Buffer Formulation
[redacted]	[redacted]	[redacted]	Formulation
[redacted]	[redacted]	[redacted]	Formulation

Consumable	Batch Size	Fluid Path Primary Materials of Construction	Process Step
[redacted]			Formulation
			Formulation
			Formulation Filtration
			Formulation
			Filtration
			Formulation
			Formulation
			Formulation
			Formulation
			Filling

Abbreviations: AQ = Aseptiquik connector; AQG = Aseptiquik G connector; HDPE = high-density polyethylene; ID = inner diameter; PES = polyethersulfone; PETG = polyethylene terephthalate glycol; PP = polypropylene; ULDPE = ultra-low density polyethylene; PVDF = Polyvinylidene fluoride