Refine TECHNOLOGY

CleanLine™

CleanLine™ 1.5” Single Use Connector

Product Validation Report

Revision Date: January 25, 2017

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Validation Report Overview

The CleanLine™ 1.5” Single Use Connector is a true 1.5” single use aseptic connector for high volume transfers at low differential pressures. It has an open design that facilitates connections to standard 1.5” TC ports that are commonly available on stainless steel or disposable aseptic processing systems, including large scale fermenters, filtration, media, purification, weight and dispense vessels and other fluid handling applications. The CleanLine™ 1.5” Single Use Connector assembles easily in a simple 1, 2, 3 step process that is audible and provides a robust secure connection. The connector’s transparency assures visibility of processing streams, and its sturdy construction is perfectly suited for high pressure and vacuum applications.

This report documents the mechanical and microbial testing that has been conducted on the CleanLine™ 1.5” Single Use Connector and the testing that has been completed for the process fluid contact materials of construction.

The data supports the following parts:

CleanLine™ 1.5” Single Use Connector – Part # CLC-1.5

Hose Barb to T.C. Adapter – Part # CLCOP:QP-BR

Summary of Testing

Microbial Ingress Test on Assembled Connector **– Bioburden Testing**

Gamma Irradiated and Steam Sterilized CleanLine™1.5" Single Use Connector parts were subjected to assembly in a variety of environments to confirm that the device's method of assembly in controlled and uncontrolled environments will not compromise the aseptic environment that is created in the interior of the device after it is effectively sterilized. Devices were either pre-sterilized with gamma irradiation to a dose level of 50 kGy or steam sterilized at 124°C for 60 minutes with a post vacuum dry cycle that is typical for a porous or wet load type of autoclave cycle. The sterilized connectors were then assembled, injected with Phosphate Buffered Saline, agitated, plated, and disc filtered. The filters were incubated on growth promotion tested Tryptic Soy and Sabauraud Dextrose Agar at 30-35°C for 2-3 days and at 20-25°C for 5-7 days. The plated filter specimens were then assessed for aerobic and anaerobic growth colony morphology.

Results: No growth was observed on any of the devices accepted for testing.

Endotoxin Level Test **– Interior Surfaces**

To demonstrate that the CleanLine™ 1.5" Single Use Connector contains low levels of Endotoxin Units (EU) per device the product contact surfaces were filled with Endotoxin Free water and incubated at 37°C ± 1° C for one hour. Following incubation and in a biosafety cabinet, 10 mLs of water were extracted from the device into depyrogenated flasks for testing with Limulus Amebocyte Lysate (LAL) reagent.

Results: No more than 1.62 EU/ Device was detected.

Pressure Hold Test

To demonstrate that the CleanLine™ 1.5" Single Use Connector and Hose Barb to T.C. Adapter can maintain integrity at and above normal operating conditions, the connector and adapter were assembled and pressurized with regulated compressed air to 80 psi under both room temperature and 50°C water until bubbles were observed.

Results: Pressure was held at 80 psi. No bubbles were observed at the indicated temperatures and pressures.

Vacuum Hold Test

To demonstrate that the CleanLine™ 1.5" Single Use Connector can maintain integrity under a vacuum level of ~25"Hg, the connector and Hose Barb to T.C. Adapter were assembled and attached to a vacuum pump. The pump was engaged and if the vacuum condition was maintained within 1"Hg for an hour the pass criteria established for the test would be considered to have been met.

Results: Vacuum was maintained with less than 1"Hg loss per hour.

Burst Test on Assembled Connector

To demonstrate that the CleanLine™1.5" Single Use Connector can maintain a maximum pressure prior to becoming mechanically disengaged, the connector was challenged after being pulsed between 28psi and 75psi for 350 cycles over a period of 30 minutes to high pressure.

> *Results*: The CleanLine™ 1.5" Single Use Connector was confirmed to not burst up to 175psi.

Flow Test on Assembled Connector

The Flow Test was conducted to determine the flow rate of water and the differential pressure across the CleanLine™ 1.5" Single Use Connector at a given temperature of 25°C. Pressure gauges placed upstream and downstream of the assembled connector were used in the flow path to determine the differential pressure. The flow was measured from weight change of water emanating from the connector, captured during steady state flow.

> *Result:* The pressure drop induced by a flow of 290 liters per minute and a differential pressure of 0.69 psi.

Material Compatibility

The CleanLine™ 1.5" Single Use Connector material meets USP Class VI, 21 CFR 177.1655, EP 3.1.9, and is Animal Derived Component Free. Each batch is assembled in an ISO-7 Certified Cleanroom and is subject to batch release criteria including Endotoxin and Particulate Inspection. Additionally this guide contains material compatibility information, agency approvals as well as chemical stability data for the fluid process materials of construction.

Test Methods

Microbial Ingress Test on Assembled Connector – Bioburden Testing

Objective:

The purpose of this test is to determine the impact of engaging the CleanLine™ 1.5” Single Use Connector in a variety of environments to confirm that assembly will not compromise the aseptic environment that is created on the interior of the connector post Gamma and Steam Sterilizations respectively.

Procedure:

Seventeen total assemblies were pre-sterilized with either gamma irradiation to a dose level of 50 kGy or steam sterilized at 124°C for 60 minutes with a post vacuum dry cycle that is typical for porous or wet load type of cycles. The sterilized connectors were engaged using aseptic techniques, then injected with Phosphate Buffered Saline and agitated. The contents were then filtered, and then incubated on growth promotion tested Tryptic Soy and Sabauraud Dextrose Agar at 30-35°C for 2-3 days and at 20-25°C for 5-7 days, respectively. The plated filter specimens were then assessed for aerobic and anaerobic growth colony morphology.

Pass/Fail Criteria:

Device failure is indicated by any growth found on the plated filter specimens.

Findings:

All acceptable device samples pass by showing no aerobic and anaerobic growth colony morphology on the plated filter specimens.

References:

- Attachment A1 – Gamma Processing
    - A1a - Certificate of processing (77464A)
    - A1b - Protocol (FS-REF-MIC-001)
    - A1c - Findings (Reports 151545-1 and 151631)
- Attachment A2 – Autoclave Processing Run 1
    - A2a – Certificate of Autoclaving (R-405926-R0)
    - A2b – Protocol (FS-REF-MIC-002)
    - A2c – Findings (160236)
- Attachment A3 – Autoclave Processing Run 2
    - A3a – Certificate of Autoclaving (R-431889-R0)
    - A3b – Protocol (RE-001)
    - A3c – Findings (161600)*

*Note: Test Report 161600 from Microbiological Environments indicated growth on 2 samples. Refine Technology has completed a Non-Conformance Investigation Report (NCR0297) in which the root cause for the deviation was determined to be personnel mishandling the devices. This investigation can be made available upon request

Endotoxin Level – Process Fluid Contact Surfaces

Objective:

The purpose of this test is to determine the level of endotoxin that is on the process fluid contact side of the CleanLine™ 1.5" Single Use Connector after assembly in Refine Technology's ISO-7 Cleanroom.

Procedure:

Four CleanLine™ 1.5" Single Use Connector components were assembled in an ISO-7 Cleanroom Environment. The fluid contact areas were filled with Endotoxin Free water and incubated at 37°C ± 1° C for one hour. Following incubation and in a biosafety cabinet, 10 mLs of water was extracted from the device and transferred in a biosafety cabinet into depyrogenated flasks for testing with Limulus Amebocyte Lysate (LAL) reagent.

Pass/Fail Criteria:

Acceptable endotoxin levels were aligned with given FDA endotoxin limits for implantable medical devices and were expected to meet or exceed the range of no more than 2.15-20.0 EU/device.

Findings:

All four samples were determined to have <0.03 EU/mL which equates to 1.62 EU/device. All four samples passed according to the above criteria.

Reference:

- Attachment B1 - Endotoxin
    - B1a – Protocol (RS-REF-MIC-003)
    - B1b – Findings (161008)

Pressure Hold Test

Objective:

The purpose of the pressure hold test is to demonstrate that the CleanLine™ 1.5” Single Use Connector can operate up to 80 psig, post either gamma irradiation of 50 kGy or steam sterilization (124°C for 60 minutes).

Procedure:

A series of tests were conducted in order to establish maximum operating pressure

To determine maximum operating pressure, the CleanLine™ 1.5” Single Use Connector was assembled with Hose Barb to T.C. Adapters post sterilization (Figure 1). One end of the assembly was capped off while the other side was attached to a pressure line. The devices were pressurized with compressed air under room temperature and 50°C water until bubbles were observed.

(Figure 1)

Step 1: The sterilized complete assembly was immersed in a water bath prior to pressurizing with compressed air from a regulated pneumatic pressure line

Step 2: The assembly was gradually pressurized to 80 psi or until bubbles occurred

Step 3: The same test was performed at an elevated temperature of 50°C

Pass/Fail Criteria:

Failure was denoted when bubbles were observed and pressure reading was recorded to be below 80 psi.

Findings:

A total of twelve trials were conducted to confirm pressure hold data and the results were as expected. For all devices tested, no bubbling was observed from the point between the connector.

Vacuum Hold Test

Objective:

The purpose of the vacuum hold test is to demonstrate that the CleanLine™ 1.5” Single Use Connector can operate under simulated vacuum conditions post either gamma irradiation of 50 kGy or steam sterilization (124°C for 60 minutes).

Procedure:

A series of tests were conducted in order to establish vacuum hold

To determine if the connector could maintain vacuum conditions post sterilization, the CleanLine™ 1.5” Single Use Connector was assembled with Hose Barb to T.C. Adapters post sterilization (Figure 2). One end of the assembly was capped off while the other side was attached to a pressure/vacuum gauge and a valve to the vacuum pump.

(Figure 2)

Step 1: The connection was made, and set up as described above

Step 2: The assembly was gradually brought to approx. 25”Hg

Step 3: Once vacuum was achieved, the valve was closed, the pump was turned off, and the assembly was evaluated for how much vacuum was lost over time (1 hour)

Pass/Fail Criteria:

Failure was denoted if the assembly were to lose more than -1”Hg per hour.

Findings:

A total of ten trials were conducted and the results were as expected. For all assemblies tested, no unit lost more than 1”Hg in 1 hour.

Burst Test

Objective:

The purpose of the pressure hold test is to demonstrate that the CleanLine™ 1.5” Single Use Connector can operate under extreme conditions, determined to be above 100 psig.

Procedure:

To challenge pressure and the sealing ability of the CleanLine™ 1.5” Single Use Connector under extreme conditions, devices were assembled in a similar fashion to Figure 1, however the assembly was placed in a hydrostatic testing chamber, and evaluated for a leak at the flange joint and the capped end of the assembly (Figure 3). A total of six destructive trials were conducted to confirm the burst pressure.

(Figure 3)

Step 1: The assembly was subjected to pressure cycles between 20psi and 75psi for up to 350 cycles.

Step 2: The assembly was pressurized to approximately 80 psi and the pressure was sustained for up to 30 minutes.

Step 3: The assembly was then subjected to elevated pressure until the point of failure in order to determine the burst pressure.

Pass/Fail Criteria:

Failure was denoted when a leak was observed at either the flange or at the capped end of the assembly’s Barb to T.C.

Findings:

The CleanLine™ 1.5” Single Use Connector and Hose Barb to T.C. Adapter assembly was confirmed to not burst up to 175psi.

Reference:

- Attachment C1 - Test Report (659-08-16)

Flow Test

Objective:

The purpose of the test is to determine the maximum flow rate of water and corresponding differential pressure through the CleanLine™ 1.5” Single Use Connector at room temperature.

Procedure:

The CleanLine™ 1.5”Single Use Connector assembly was fitted with pressure gauges placed upstream and downstream of the assembled connector. Flow rate was determined by weight change of a container filled with effluent flow from a test apparatus.

Step 1: A large 50L reservoir filled with room temperature water was placed 3-meters above the connector outlet.

Step 2: Flow was initiated from the reservoir to the outlet of the connector and was simulated using a syphon.

Step 3: Pressure readings were recorded across the assembled connector using calibrated pressure gauges at steady state. The differential pressure and flow rate were measured and recorded.

Pass/Fail Criteria

There is no pass/fail criteria. Observed values are summarized in the below (Figure 4)

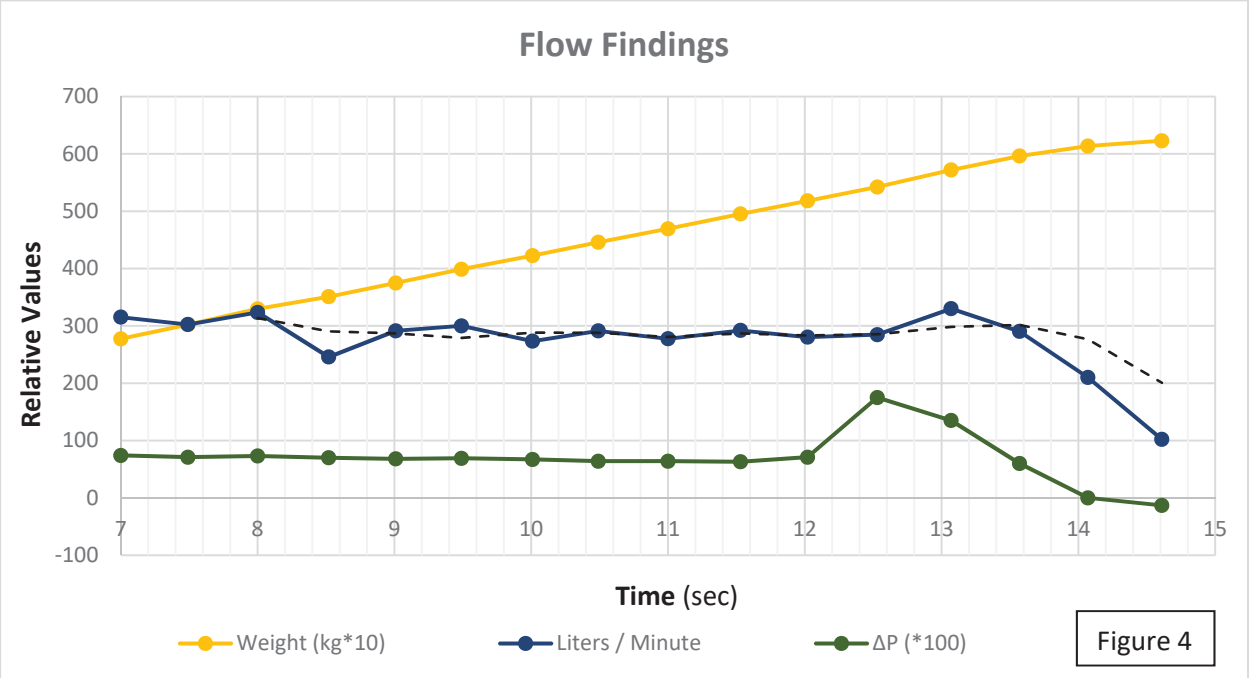

Figure 4

Findings:

16 instances were recorded and calculated at steady state a flow of up to 290 L/min and a maximum differential pressure of 0.69 psi.

Statements

Summary of Product Contact Materials of Construction Agency Approvals:

The process fluid contact materials of construction of the CleanLine™ 1.5” Single Use Connector were selected to have specific industry relevant compatibility data.

The polysulfone used in the manufacture of the CleanLine™ 1.5” Single Use Connector is Ultrason S 3010 NAT from BASF. Agency approvals include and are not limited to USP Class VI, FDA 21 CFR 177.1655, TSE/BSE exceeding EMEA 410/01 Rev.03, NSF 51, as well as various EU and EC requirements.

The membrane material used in the manufacture of the CleanLine™ 1.5” Single Use Connector is Tyvek 1073B from DuPont. Agency approvals include 21 CFR 177.1520, USP Class VI, ISO 10993-5 and 10, ISO 10993-18, USP-85, as well as not containing any animal products.

The silicone used in the manufacture of the CleanLine™ 1.5” Single Use Connector is DOW Corning C6-150. Agency approvals include USP Class VI, ISO 10993-1, EP 3.1.9, and FDA 21 CFR177.2600 as well as not containing any materials of animal origin.

References:

- Attachment D1 - Polysulfone
  - D1a – BASF – USP Class VI
  - D1b – BASF – FDA 21 CFR 177.1655, EC and EU Compliance
  - D1c – BASF – TSE/BSE statement, EMEA 410/01 Rev. 03, NSF 51
- Attachment D2 – Membrane – DuPont – Regulatory Information
- Attachment D3 - Silicone
  - D3a – DOW – USP Class VI, FDA 21 CFR 177.2600, ISO 10993-1
  - D3b – DOW – Animal Origin Statement

Recommended Shelf Life and Storage Conditions Statement:

Ideal storage conditions are to be in an environment void of harsh lighting, any form of radiation, at room temperature, and away from any possible source of liquid water or excessive humidity in the air.

Extractables Testing:

Testing has been completed on the silicone components of the CleanLine™ 1.5" Single Use Connector for substances soluble in hexane, hexane R for phenylated compounds, mineral oils, and residual peroxides per EP 3.1.9. Additional testing has been completed according to 3A-Sanitary 18-03.

Testing of the Polysulfone components of the product is underway and is planned to be reported in a revision of this validation file in June 2017. Chemical Stability charts are provided in this validation file for the user to assess the appropriate application of the CleanLine™ 1.5" Single Use Connector with their specific process fluid's composition, temperature, pH, and saline concentration characteristics.

References:

- Attachment E1 – Silicone Data
    - E1a – DOW – Xiameter Resistance Guide
    - E1b – DOW – EP silicone elastomers for closures and tubing
    - E1c – PAI – Test Results Form – 3A Sanitary 18-03
- Attachment E2 – BASF – Ultrason – Chemical Resistance and Stability