BIOTECH

Validation Guide

USTR 2911

Cadence® Inline Concentrator With Delta and Omega™ Membranes

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1 Introduction

1.1 Purpose of this Document

This document provides validation support information for Cadence Inline Concentrator (ILC) modules with Cetrarate™ and Centrasette™ cassettes with Delta and Omega membranes. The document includes summary data from tests conducted for biological safety, extractables, chemical compatibility, physical and performance attributes, as well as usage conditions.

The data contained in this guide was generated under standard conditions as specified. The methods and information contained in this guide are designed to provide the user with an acceptable approach for validation of Cadence ILC modules under actual conditions of use.

Using the information and methods in this validation guide, the end-user should be able to prepare procedures for actual use of the Cadence ILC modules which can be validated to ensure consistent performance and to meet regulatory requirements.

If needed, Pall Corporation offers technical support to customers to develop, troubleshoot, and validate Cadence ILC module procedures.

1.2 Validating a Filtration Process—General Concepts

Tangential flow filtration (TFF) membrane cassettes play an essential role in purifying, concentrating, and separating biopharmaceutical solutions and products. For example, established TFF applications include concentrating human plasma fractions, downstream processing of enzyme and protein solutions, and harvesting mammalian or bacterial cells. To ensure these TFF processes result in safe and efficacious products, the U.S. Food and Drug Administration requires validation of these processes.

The FDA defines validation as "…establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributes." [Current Good Manufacturing Practice (cGMP) for Finished Pharmaceuticals, U.S. **Code of Federal Regulation** (CFR) Title 21 Food and Drugs, Part 210.3: Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General; Definitions (21 CFR 210.3)]. With respect to a TFF process, validation involves providing assurance that the filtration process operates reproducibly and consistently.

The first step in Cadence ILC process validation is to create a functional design specification. Users base the functional design specification on the requirements of the TFF process and thedata generated during pilot scale runs. A functional design specification should include operational protocols. The operational protocols should be consistent with the performance limits outlined in this Validation Guide and the Cadence ILC module User Guide (Pall document reference USD 2841) found at www.pall.com/procedures.

The second step is to design and develop a Cadence ILC process that enables the direct scale-up of the specifications established during pilot or bench-scale runs. Three stages of process validation are typically followed: Installation Qualification (QP), Operational Qualification (OP), and Performance Qualification (PQ).

Installation Qualification (IQ)

An Installation Qualification verifies that the Cadence ILC module's operating instructions and certificate of conformance were received, and that the installation of the Cadence ILC module was completed in accordance with the operating instructions.

Operational Qualification (OQ)

During an operational qualification, validation personnel test and document the range and operational limits of the filtration process with a Cadence ILC module in place. An Operational Qualification does not have to be conducted in a user's manufacturing area.

Validation personnel normally simulate worst-case production conditions for these Operational Qualification studies, using water or other surrogate process fluid. The goal is to deliberately trigger alarm conditions. As part of the Operational Qualification, validation personnel also verify and document procedures such as flushing and sanitizing that are associated with the operation of the Cadence ILC module.

Performance Qualification (PQ)

Performance qualification involves testing the Cadence ILC process during production of the final product under actual operating conditions including installation, sanitization, conditioning, concentration, product recover and post-use sanitization (if necessary) etc. Critical elements of a performance qualification include verifying chemical compatibility between the final product and the wetted components of the filtration system, and the retention characteristics of the filtration system.

Data from a performance qualification is derived from the filtration process using the actual product and process conditions. Therefore, it provides the most meaningful process validation data. PQ may not necessarily provide data on the operation of the module at the design limits(maximum pressure, etc.), as the process may never reach these limits.

Manufacturers of regulated products must develop and submit protocols, qualification documents, and validation documents for their specific product to be granted approval to manufacture and market their product.

2 Cadence Inline Concentrator Modules

2.1 Packaging

Cadence ILC modules are double bagged to protect the modules from damage and contamination. Both the inner and outer clear plastic bags are heat sealed.

Each bagged Cadence ILC module is packed in boxes with protective foam inserts along with a Certificate of Quality. The care and use guide and safety data sheet can be found online at www.pall.com/procedures.

2.2 Labeling and Product Identification

Product labeling and individual serial numbers ensure definitive identification of Cadence ILC modules and traceability of module components.

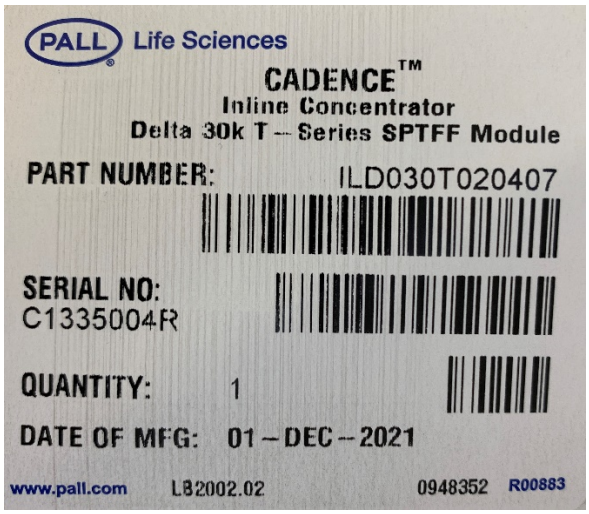
Product labels are included on the packaging box and on the plastic bag. Production identification information is also printed on the side of each module. The module serial number,included in all three locations, enables traceability of components.

The labels (Figure 1) on the box and bag include the following information:

- Manufacturer’s name
- Product name
- Part number
- Serial number
- Quantity
- Date of manufacture

Figure 1

Bag and box label for Cadence ILC modules



Each module includes the following information printed on it (Figure 2):

- Module membrane area
- Part number
- Serial number
- www.pall.com/patents
- Port names
- Maximum operating pressure

Figure 2

Information printed on each side of the Cadence ILC module

TOP PLATE FRONT SIDE EXAMPLE LASER MARKING

SERIAL #: C3123001R	RETENTATE	PART#: ILD030T020407

BOTTOM PLATE FRONT SIDE EXAMPLE LASER MARKING

FEED	Maximum Operating Pressure: 4.1 barg (60 psig)

TOP PLATE BACK SIDE EXAMPLE LASER MARKING

0.13 SQ.M / 1.4 SQ.FT	PERM 2

BOTTOM PLATE BACK SIDE EXAMPLE LASER MARKING

http://www.Pall.com/patents	PERM 1

Example top and bottom plate laser marking for a Cadence ILC module with 30 kiloDalton (kDa) Delta membrane and T02 format cassette.

2.3 Part Numbers

A module's part number identifies its purpose and design elements. For example, a Cadence ILC module with Delta 10 kDa regenerated cellulose membrane in a T01 cassette format has part number ILD010T010407.

IL	Inline concentrator
D or OS	The module is made using cassettes with Delta (D) or Omega (OS) membrane
010	The NMWC of the membrane in kDa
T01	T-series cassette format used in the module
04	4-in-series flow path
07	The total number of cassettes is 07

Part numbers and their associated models are shown in Table 1.

Table 1

Cadence ILC module characteristics and dimensions

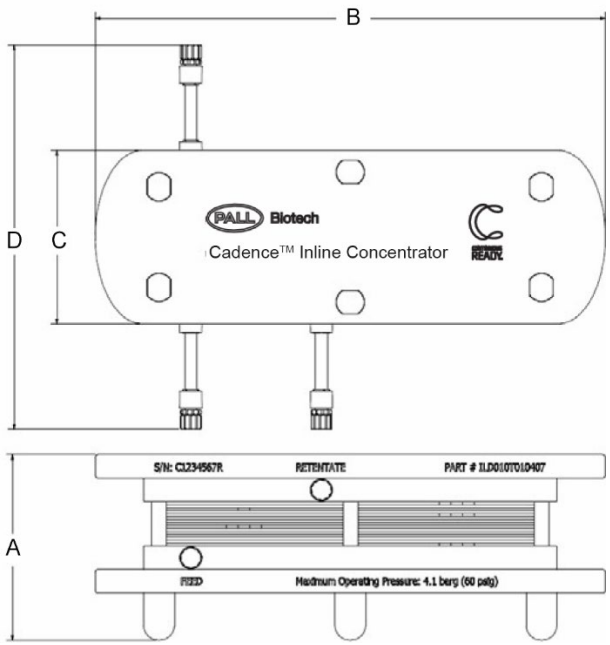
Module Part Number	Area (m^2)	Estimated Minimum Holding Volume (mL)	Total Module Weight kg (lbs)	A Height cm (in.)	B Length cm (in.)	C Width (Plate) cm (in.)	D Approx. Width (Cap to Cap) cm (in.)	Port Connector Type
ILD010T010407								
ILD030T010407								
ILOS010T010407								
ILOS030T010407	0.065	20	2.1 (4.7)	9.8 (3.8)	27.4 (10.8)	9.3 (3.7)	20.7 (8.2)	Female Luer
ILD010T020407								
ILD030T020407								
ILOS010T02047								
ILOS030T02047	0.13	40	2.2 (4.9)	10.5 (4.1)	27.4 (10.8)	9.3 (3.7)	20.7 (8.2)	Female MPC
ILD010T120407								
ILD030T120407								
ILOS010T120407								
ILOS030T120407	0.7	200	3.9 (8.5)	20.3 (8.0)	27.4 (10.8)	9.3 (3.7)	20.7 (8.2)	Female MPC
ILD010T060407								
ILD030T060407								
ILOS010T060407								
ILOS030T060407	3.5	1300	16.9 (35)	27.2 (10.7)	28.9 (11.4)	24.1 (9.5)	51.4 (20.2)	Female MPX

See Figure 3 for dimension references.

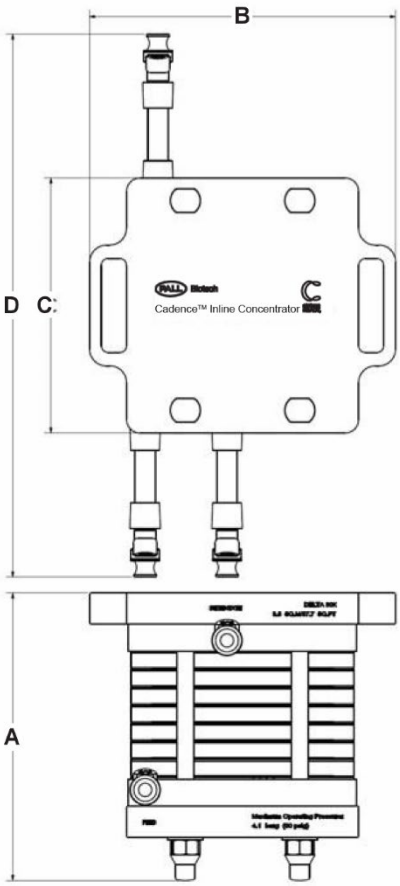
Figure 1

Cadence ILC module dimensions for T01/T02, T06, and T12 cassette formats

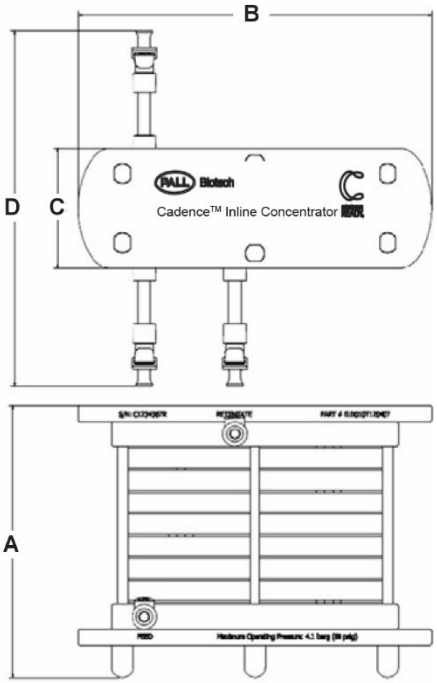
T01 and T02 module configurations



T06 module configuration



T12 module configuration



2.4 Serial Numbers

The serial number on the package labels and printed on each Cadence ILC module enables the determination of the following:

- C = Cadence module
- Second digit is the last digit of the year of manufacture (e.g., for 2019, it is "9")
- Next three digits are the Julian date (e.g., 01-JAN is '001' and 01-FEB is '032')
- Next three digits are the cassette # or module # of the day, starting with 001
- Last digit R represents the facility where the product was assembled

Hence, if needed, Pall Corporation can trace the source of individual components used tomanufacture each module.

3 Materials of Construction

The materials of construction in the flow path of the Cadence ILC modules with T-series Centramate and Centrasette cassettes with Delta or Omega membrane are detailed in this section.

Materials of construction biosafety conformance summary is in Section 9.

- Membranes:
    - Delta membranes are cast from cellulose resins on a polypropylene substrate
    - Omega membranes are cast from polyethersulfone (PES) resins on a polyolefin substrate
- Screens:
    - The screens used to separate the membrane layers in T-series cassettes are manufactured from polypropylene
- Support Layer:
    - The Delta membrane in T-series cassettes contains an additional support layer manufactured from polyolefin fiber
- Cassette Encapsulant:
    - The encapsulant used in T-series cassettes is polyurethane with a white pigment (TiO_2)
- Permeate Seals, Gaskets, and Tubing:
    - The permeate seals, gaskets, and tubing are made from platinum-cured silicone rubber
- Top and Bottom Manifolds:
    - The top and bottom manifolds in the Cadence ILC modules are constructed of high-density polyethylene.
- Connectors:
    - The connectors used in the Cadence ILC modules are made from polypropylene (Luer) and polysulfone (MPC/MPX)

4 Integrity Testing

4.1 Principles

The module integrity test measures the Forward Flow rates with air at specified pressures to determine the integrity of membrane module. The air Forward Flow rate is a measure of air diffusion through the liquid in the membrane pores, air flow through potential defects, plus air leakage around seals. The test identifies gross defects in the membrane or cassette seals.

During integrity testing, compressed air is applied to the feed port. The retentate port is closed,and both permeate ports are opened. Hence, the compressed air must flow through the membrane (and potential defects) and out of the open permeate ports.

4.2 Specifications

The integrity test specifications for the Cadence ILC modules are shown in Table 2.

Cadence ILC modules with Delta membrane are integrity tested at a test pressure of 4.1 barg (60 psig). The maximum air flow rate is 538 standard cubic centimeters per minute per square meter (sccm/m^2) (50 sccm/ft^2).

Cadence ILC modules with Omega membrane are integrity tested at test pressure of 2.1 barg (30 psig). The maximum air flow rate is 1600 sccm/m^2 (150 sccm/ft^2).

Nitrogen can be used in place of air.

Table 2

Cadence ILC module integrity test parameters

Module Part Number	Membrane Type	Test Pressure	Membrane Area (m^2)	Forward Flow Limit (sccm)
ILD010T010407			0.065	35
ILD010T020407			0.13	70
ILD010T120407			0.7	380
ILD010T060407	Delta, 10 kDa		3.5	1900
ILD030T010407			0.065	35
ILD030T020407			0.13	70
ILD030T120407			0.7	380
ILD030T060407	Delta, 30 kDa	4.1 barg (60 psi)	3.5	1900
ILOS010T010407			0.065	100
ILOS010T020407			0.13	210
ILOS010T120407			0.7	1100
ILOS010T060407	Omega, 10 kDa		3.5	5600
ILOS030T010407			0.065	100
ILOS030T020407			0.13	210
ILOS030T120407			0.7	1100
ILOS030T060407	Omega, 30 kDa	2.1 barg (30 psi)	3.5	5600

4.3 Obtaining Reliable and Reproducible Results

For best integrity test results, Pall Corporation recommends the use of dedicated integrity analyzers that incorporate mass flow meters. When performing integrity testing, use only instrument- quality air or nitrogen from cylinders. Fluctuations in house air or nitrogen supplies, as well as changes in temperature, can result in inconsistent measurements. Failing to fully wet-out the membrane in the Cadence ILC module prior to performing the membrane integrity testing can result in high Forward Flow values.

5 Shelf Life

The recommended shelf life of new, unopened Cadence ILC modules stored in their respective preservative solution (5% ethanol + 1% sodium diacetate for modules with Delta membrane; 0.3 N sodium hydroxide for modules with Omega membrane) is expected to be at least three years from the date of manufacture.

To achieve satisfactory performance, it is recommended that the Cadence ILC modules be stored unopened in the original packaging, at ambient temperature and protected from direct light.

Users should test the membrane integrity prior to use. For further shelf-life information, please contact your Pall Corporation representative.

6 Compatibility with Sanitizing Agent

Please see the User Guide for the Cadence Inline Concentrator (Care and Use Procedures) for appropriate selection of compatible sanitizing agents (Pall document reference USD 2841).

7 Operating Pressures and Temperatures

Cadence ILC modules are intended to operate between 20 and 40 °C up to a feed pressure of 4.1 barg (60 psig). Note that devices can be operated at lower temperatures, but this should be validated by the user.

To demonstrate stability to these conditions and to simulate alternating processing and cleaning cycles, Pall Corporation tested Cadence ILC modules using recirculating deionized water. The modules were subjected to five 24-hour cycles at 20 °C at 4.1 barg (60 psig) with four-hour hot cycles at 40 °C at 4.1 barg (60 psig) in-between.

In addition, Pall Corporation subjected Cadence ILC modules to an eight-hour cycle at 4 °C at 4.1 barg (60 psig) and an eight-hour cycle at 40 °C and 4.1 barg (60 psig).

7.1 Results

The modules remained integral throughout the temperature/pressure limit studies. Results show that Cadence ILC modules can operate at 20-40 °C at a feed pressure of 4.1 barg (60 psig). Devices can beoperated at lower temperatures, but this should be validated by the user.

8 Extractables

Please contact your Pall Corporation representative if you require information about extractables characterization of Cadence ILC modules with Delta or Omega membrane.

9 Biocompatibility Conformance

9.1 Summary

The materials of construction in the flow path in the Cadence ILC module were evaluated in terms of biological safety. All materials met the requirements of United States Pharmacopeia (USP) <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 °C Plastics (USP 88), and UPS <87> Biological Reactivity Test, *In Vitro,* Cytotoxicity (USP <87>) (L929 Minimum Essential Medium (MEM) Elution Cytotoxicity, and Hemolysis Test). In addition, the fluid path components do not contain materials of construction that are considered Bovine Spongiform Encephalopathy (BSE) or Transmissible Spongiform Encephalopathies (TSE) risk materials according to current legislation and guidelines (reference European CPMP EMEA/410/01 and CFR, Title 21 Food and Drugs, Part 189.5: Prohibited Cattle Materials.

9.2 Materials of Construction Conformance

- Delta membrane and substrate, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
    - Membrane regenerated from cellulose resin that meets:
        - CFR Title 21 Food and Drugs, Part 175.300: Resinous and polymeric coatings (21 CFR 175.300).
        - CFR Title 21 Food and Drugs, Part 175.380: Xylene-formaldehyde resins condensed with 4,4' – isopropylidenediphenol- epichlorohydrin epoxy resins (21 CFR 175.380).
        - CFR Title 21 Food and Drugs, Part 175.390: Zinc-silicon dioxide matrix coatings (21 CFR 175.390).
        - CFR Title 21 Food and Drugs, Part 176.170: Components of paper and paperboard in contact with aqueous and fatty foods (21 CFR 176.170).
        - CFR Title 21 Food and Drugs, Part 177.1210: Closures with sealing gaskets for food containers (21 CFR 177.1210).
        - CFR Title 21 Food and Drugs, Part 182.90: Substances migrating to food from paper and paperboard products (21 CFR 182.90).
    - Polypropylene substrate meets:
        - CFR Title 21 Food and Drugs, Part 177.1520: Olefin polymers (21 CFR 177.1520).
- Omega membrane and substrate, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
    - Membrane made from polyethersulfone (PES) that meets:
        - CFR Title 21 Food and Drugs, Part 177.2440: Polyethersulfone resins (21 CFR 177.2440).
    - Polyolefin substrate meets:
        - 21 CFR 177.1520
- Plant-Origin Kosher Glycerin (used as humectant in membrane formulation, removed with flushing):
    - GRAS CFR Title 21 Food and Drugs, Part 182.1320: Glycerin (21 CFR 182.1320).
    - CFR Title 21 Food and Drugs, Part 175.105: Adhesives (21 CFR 175.105).
    - 21 CFR 175.300.
    - CFR Title 21 Food and Drugs, Part 175.320: Resinous and polymeric coatings for polyolefin films (21 CFR 175.320).
    - 21 CFR 175.380.
    - 21 CFR 175.390.
    - CFR Title 21 Food and Drugs, Part 176.210: Defoaming agents used in the manufacture of paper and paperboard (21 CFR 176.210).

- 21 CFR 177.1210.
- CFR Title 21 Food and Drugs, Part 177.2420: Polyester resins, cross-linked (21 CFR 177.2420).
- CFR Title 21 Food and Drugs, Part 178.3120: Animal glue (21 CFR 178.3120).
- 21 CFR 182.90.
- CFR Title 21 Food and Drugs, Part 182.99: Adjuvants for pesticide chemicals (21 CFR 182.99).

- Polypropylene screens, meets:
  - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
  - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
  - 21 CFR 177.1520.
- Polyolefin fiber support layer, meets
  - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
  - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
  - 21 CFR 177.1520.
- Polyurethane encapsulant, meets:
  - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
  - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
  - Materials listed in CFR Title 21 Food and Drugs, Parts 175.105 to 175.300 (21 CFR Parts 175.105-175.300).
  - Materials listed in CFR Title 21 Food and Drugs, Parts 177.1680 to 177.2600 (21 CFR Parts 177.1680-177.2600).
- Polyethylene manifolds, meets:
  - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
  - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
  - 21 CFR 177.1520.
- Silicone gaskets, meets;
  - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
  - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
  - CFR Title 21 Food and Drugs, Part 177.2600: Rubber articles intended for repeated use (21 CFR 177.2600).

- Silicone tubing, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
    - 21 CFR 177.2600.
- Silicone permeate seals, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
- Polypropylene Luer connectors, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - USP <87> Biological Reactivity Test, *In Vitro*, Cytotoxicity (L929 MEM Elution Cytotoxicity and Hemolysis Test).
    - 21 CFR 177.1520.
- Polysulfone Colder connectors, meets:
    - USP <88> Biological Reactivity Test, *In Vivo*, for Class VI - 70 ˚C Plastics.
    - Internal Organization for Standardization (ISO) 10993-5 *Biological evaluation of medical devices Part 5: Tests for in vitro cytotoxicity* (ISO 10993-5 Cytotoxicity) (L929 MEM Elution Cytotoxicity and Hemolysis Test)

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