PALL Biotech

Validation Guide

USTR 3316

Cadence™ Inline Diafiltration Modules with Delta and Omega™ Membranes

Filtration. Separation. Solution.SM

Contents

1 Introduction

1.1 Purpose of this Document

This document provides validation support information for Cadence inline diafiltration modules (ILDF) with Centramate™ cassettes with Delta and Omega membranes. The document includes summary data from tests conducted for biological safety, 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 ILDF 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 ILDF modules which can be validated to ensure consistent performance and to meet regulatory requirements.

If needed, Pall Biotech offers technical support to customers to develop, troubleshoot, and validate Cadence ILDF 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 buffer exchange for final drug substance, desalting or buffer exchange before or after column chromatography, and small molecule contaminant removal. To ensure these TFF processes result in safe and efficacious products, the FDA requires validation of these processes.

The U.S. Food and Drug Administration 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, 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 ILDF process validation is to create a functional design specification. Users base the functional design specification on the requirements of the TFF process and the data 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 ILDF module User Guide (Pall document reference USD3256) found at **www.pall.com/procedures**.

The second step is to design and develop a Cadence ILDF 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 (IQ), Operational Qualification (OQ), and Performance Qualification (PQ).

Installation Qualification (IQ)

An installation qualification verifies that the Cadence ILDF module's operating instructions and certificate of conformance were received and that the installation of the Cadence ILDF 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 ILDF 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 another 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 ILDF module.

Performance Qualification (PQ)

Performance qualification involves testing the Cadence ILDF process during production of the final product under actual operating conditions including: installation, sanitization, conditioning, diafiltration, product recovery 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 Diafiltration Modules

2.1 Packaging

Cadence ILDF 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 ILDF 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

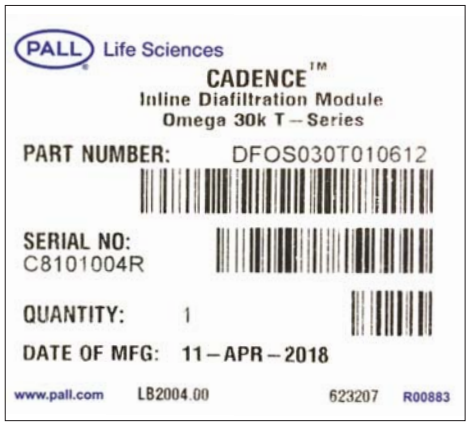
Product labeling and individual serial numbers ensure definitive identification of Cadence ILDF modules and traceability of module components.

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 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 ILDF modules



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

- Company name
- Part number
- Serial number
- www.pall.com/patents
- Port names

Figure 2
Information printed on each side of the Cadence ILDF module

TOP PLATE FRONT SIDE EXAMPLE LASER MARKING

Retentate	DF Buffer	P/N: DFOS030T010612

BOTTOM PLATE FRONT SIDE EXAMPLE LASER MARKING

Feed

TOP PLATE BACK SIDE EXAMPLE LASER MARKING

S/N: C8101004R	Permeate 2

BOTTOM PLATE BACK SIDE EXAMPLE LASER MARKING

http://www.pall.com/patents	Permeate 1

Example top and bottom plate laser marking for a Cadence ILDF module with 30 kDa Omega membrane and T01 format cassette

2.3 Part Numbers

A module's part number identifies its purpose and design elements. For example, a Cadence ILDF module with Delta 30 kDa regenerated cellulose membrane in a T01 cassette format has part number DFDC030T010612.

DF	Inline diafiltration module
DC or OS	The module is made using cassettes with Delta (DC) or Omega (OS) membrane
030	The NMWC of the membrane in kDa
T01	T-series cassette format used in the module
06	6-stage flow path
12	The total number of cassettes is 12

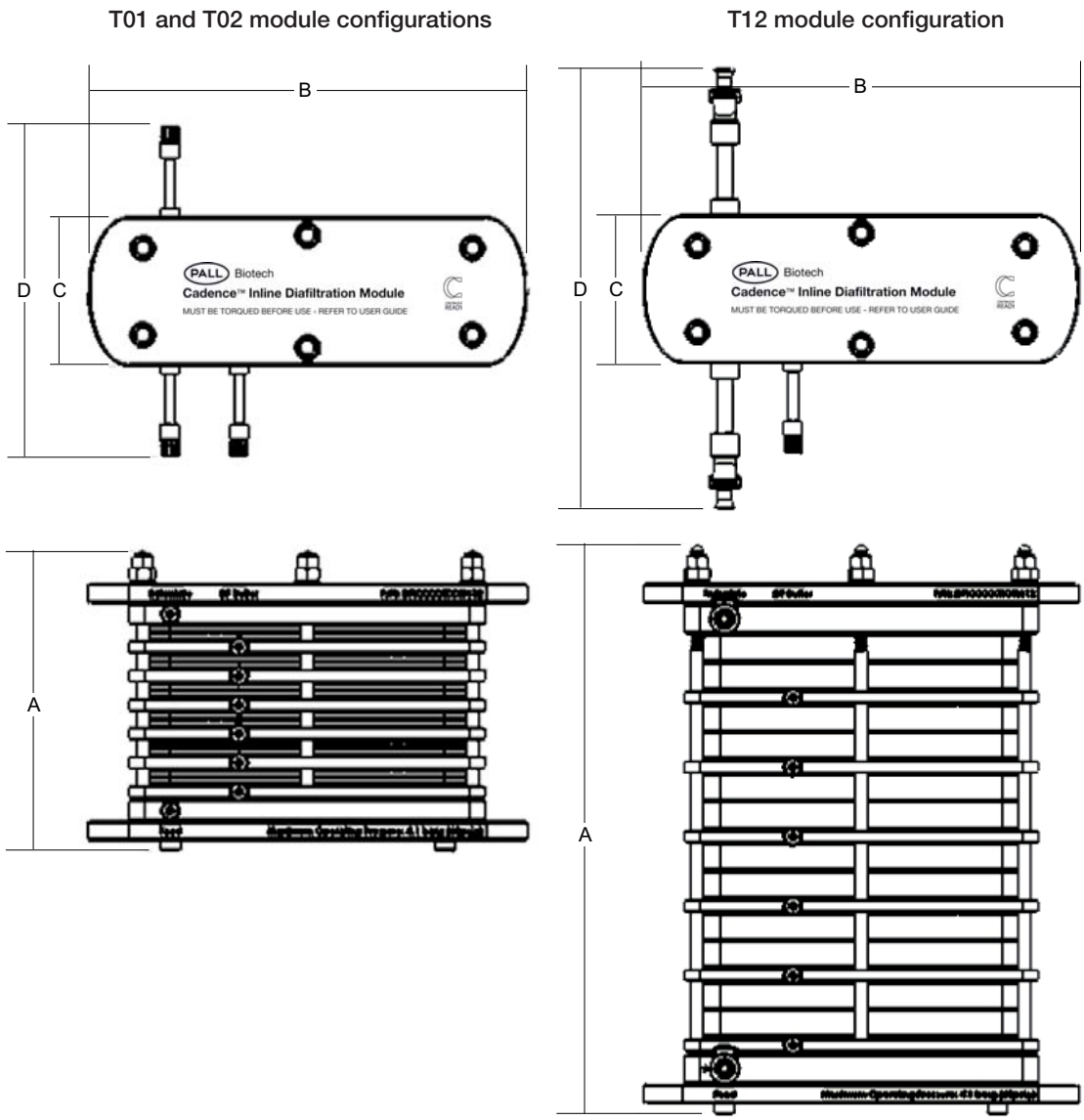
Part numbers and their associated modules are shown in Table 1.

Table 1
Cadence ILDF 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
DFDC030T010612	0.11	25	3.58 (7.9)	17.1 (6.7)	27.4 (10.8)	9.3 (3.7)	20.6 (8.1)	Female Luer
DFOS030T010612								
DFDC030T020612	0.22	50	3.80 (8.4)	18.7 (7.4)			20.6 (8.1)	Female Luer
DFOS030T020612								
DFDC030T120612	1.2	200	6.07 (13.4)	35.7 (14.1)			27.7 (10.9)	Female MPC & female Luer
DFOS030T120612								

See Figure 3 for dimension references

Figure 3.
Cadence ILDF module dimensions for T01/T02 and T12 cassette formats



2.4 Serial Numbers

The serial number on the package labels and printed on each Cadence ILDF 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 Biotech can trace the source of individual components used to manufacture each module.

2.5 Tubing Sets

The following tubing sets are available for Cadence ILDF modules:

Table 2
Tubing sets for Cadence ILDF modules

Part Number	Description
5390-0565M	Cadence ILDF T01/T02 PharmaPure◆
5390-0565N	Cadence ILDF T01/T02 Sta-Pure◆
5390-0565P	Cadence ILDF T12 PharmaPure
5390-0565Q	Cadence ILDF T12 Sta-Pure

3 Materials of Construction

The materials of construction in the flow path of the Cadence ILDF modules with T-series Centramate cassettes with Delta or Omega membrane and tubing sets are detailed in this section. Materials of construction biosafety conformance summary is in Section 9.

ILDF Modules

- **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**
  Delta T-series cassettes contain 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 Module 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 ILDF modules are constructed of high density polyethylene.
- **Connectors**
  The connectors used in the Cadence ILDF modules are made from polypropylene (Luer) and polysulfone (MPC).

Tubing Sets

- **Pump Tubing**
  PharmaPure tubing is made from thermoplastic elastomer. Sta-Pure tubing is made from platinum-cured silicone and expanded polytetrafluoroethylene.
- **Additional Tubing**
  All additional tubing is made from platinum-cured silicone.
- **Hose Barb Connectors**
  The hose barb connectors used in the Cadence ILDF modules are made from polypropylene (Luer) and polysulfone (MPC).
- **Sensors**
  The pressure and conductivity sensors contain polysulfone.

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 diafiltration buffer feed and retentate ports are 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 ILDF modules are shown in Table 3. Prior to integrity testing, Cadence ILDF modules must be tightened to a torque of 5.6-7.9 Nm (50-70 in-lbs) according to the pre-use conditioning instructions in the user guide.

Cadence ILDF 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 ILDF 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 3
Cadence ILDF module integrity test parameters

Module Part Number	Membrane Type	Test Pressure	Membrane Area (m^2)	Forward Flow Limit (sccm)
DFDC030T010612	Delta, 30 kDa	4.1 barg (60 psig)	0.11	60
DFDC030T020612			0.22	120
DFDC030T120612			1.2	640
DFOS030T010612	Omega, 30 kDa	2.1 barg (30 psig)	0.11	170
DFOS030T020612			0.22	350
DFOS030T120612			1.2	1900

4.3 Obtaining Reliable and Reproducible Results

For best integrity test results, Pall Biotech 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 ILDF 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 ILDF modules stored in its 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 1 year from the date of manufacture.

To achieve satisfactory performance, it is recommended that the Cadence ILDF modules be stored unopened in the original packaging, at ambient temperature 4 - 25 °C and protected from direct light.

Shelf life studies are ongoing. Users should test the membrane integrity prior to use. For further shelf life information, please contact your Pall Biotech representative.

6 Compatibility with Sanitizing Agent

Please see the User Guide for the Cadence inline diafiltration modules (Care and Use Procedures), USD3256 at **www.pall.com/procedures** for appropriate selection of compatible sanitizing agents.

7 Operating Pressures and Temperatures

Cadence ILDF are intended to operate between 20 and 40 °C up to a feed pressure of 4.1 barg (60 psig). Note that devices may be operated at lower temperatures but this should be validated by the user. Prior to operation, Cadence ILDF modules must be tightened to a torque of 5.6-7.9 Nm (50-70 in-lbs) according to the pre-use conditioning instructions in the user guide.

To demonstrate stability to these conditions and to simulate alternating processing and cleaning cycles, Pall Biotech tested Cadence ILDF modules using recirculating deionized water. The modules were subjected to two (2) cycles of 24 hours at 15 °C at 4.1 barg (60 psig) followed by 2 hours at 45 °C at 4.1 barg (60 psig).

Results

The modules remained integral throughout the temperature/pressure limit studies. Results show that Cadence ILDF modules can operate at 20-40 °C at a feed pressure of 4.1 barg (60 psig).

8 Extractables

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

9 Biocompatibility Conformance

9.1 Summary

The materials of construction in the flow path in the Cadence ILDF module were evaluated in terms of biological safety. All materials met the requirements of USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C plastics and Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity. In addition, the fluid path components do not contain materials of construction that are considered BSE or TSE risk materials according to current legislation and guidelines (reference European CPMP EMEA/410/01 and Code of Federal Regulations, Title 21 part 189.5).

9.2 Materials of Construction Conformance

Cadence ILDF TFF Modules

- 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*) L929 MEM Elution Cytotoxicity, and Hemolysis Test. Membrane regenerated from cellulose resin that meets 21 CFR 175.300; 21 CFR 175.380; 21 CFR 175.390; 21 CFR 176.170; 21 CFR 177.1210; and 21 CFR 182.90. Polypropylene substrate meets 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*) L929 MEM Elution Cytotoxicity, and Hemolysis Test. Membrane made from polyethersulfone (PES) that meets 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 21 CFR 182.1320. Also 21 CFR 175.105; 175.300; 175.320; 175.380; 175.390; 176.179; 176.210; 177.1210; 177.2420; 178.3120; 182.90; 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*) L929 MEM Elution Cytotoxicity, Hemolysis Test, and 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*) L929 MEM. Elution Cytotoxicity, Hemolysis Test, and 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*) L929 MEM Elution Cytotoxicity, and Hemolysis Test, and 21 CFR 175.105, 175.300, 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*) L929 MEM Elution Cytotoxicity, Hemolysis Test, and 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*) L929 MEM Elution Cytotoxicity, Hemolysis Test, and 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*) L929 MEM Elution Cytotoxicity, Hemolysis Test, and 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*) 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*) L929 MEM Elution Cytotoxicity, Hemolysis Test, and 21 CFR 177.1520.
- Polysulfone Colder connectors— Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics, ISO 10993-5 Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity, and Hemolysis Test.

Tubing Sets

- PharmaPure Tubing (5390-0565M and 5390-0565P) — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics, USP <87> Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity, and Hemolysis Test.
- Sta-Pure Tubing (5390-0565N and 5390-0565Q) — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics and USP <87> Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity.
- Additional Tubing — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics, USP <87> Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity, and 21 CFR 177.2600.
- Polysulfone Connectors — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics, 10993-5 Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity, and Hemolysis Test.
- Polypropylene Connectors — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics, either USP <87> or 10993-5 Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity, and 21 CFR 177.1520.
- Sensors — Meets USP <88> Biological Reactivity Test (*in vivo*) for Class VI-70 °C Plastics and 10993-5 Biological Reactivity Test (*in vitro*) L929 MEM Elution Cytotoxicity.

PALL Biotech

Corporate Headquarters
Port Washington, NY, USA
+1 800 717 7255 toll free (USA)
+1 516 484 5400 phone

European Headquarters
Fribourg, Switzerland
+41 (0)26 350 53 00 phone

Asia-Pacific Headquarters
Singapore
+65 6389 6500 phone

Visit us on the Web at www.pall.com/biotech
Contact us at www.pall.com/contact

International Offices
Pall Corporation has offices and plants throughout the world in: Argentina, Australia, Austria, Belgium, Brazil, Canada, China, France, Germany, India, Indonesia, Ireland, Italy, Japan, Korea, Malaysia, New Zealand, Norway, Philippines, Poland, Russia, Singapore, South Africa, Spain, Sweden, Switzerland, Taiwan, Thailand, United Kingdom, and Vietnam. Distributors in all major industrial areas of the world. To locate the Pall office or distributor nearest you, visit **www.pall.com/contact.**

The information provided in this literature was reviewed for accuracy at the time of publication. Product data may be subject to change without notice. For current information consult your local Pall distributor or contact Pall directly.

© 2018, Pall Corporation. Pall, PALL, Cadence, Centramate, and Omega are trademarks of Pall Corporation. ***Filtration.Separation.Solution*** is a service mark of Pall Corporation. ♦Pharmapure is a trademark of Saint-Gobain Performance Plastics Corporation. STA-PURE is a trademark of W. L. Gore & Associates. ® indicates a trademark registered in the USA and ™ indicates a common law trademark.

Filtration. Separation. Solution.SM

11/18, PDF, GN18.10116 USTR 3316