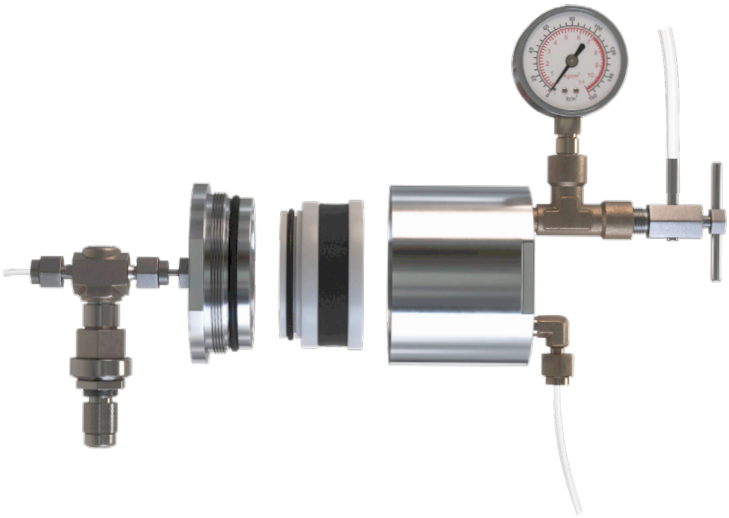
SILICYCLE Inc.

E-PAK® Laboratory Scale Housings

INSTALLATION AND OPERATION MANUAL



E-PAK cartridge housings are intended for use in a controlled environment and should be setup and operated in accordance to this manual. Read the entire installation manual prior to operating your E-PAK® vessel. This manual does not supersede any local plant policies, codes or procedures.

E-PAK Introduction

E-PAK is a family of radial flow adsorption cartridges developed specifically for pharmaceutical processings.

Created with proprietary technology, E-PAK cartridges provide rapid adsorption kinetics at flow rates and processing capacities suitable for laboratory, pilot and commercial operations. They are designed for use with both organic and aqueous solvents, and incorporate design features useful for the production of active pharmaceutical ingredients (*API*).

Features and Benefits

- Proven cartridge design ensures rapid, simple and reliable technology
- High adsorption capacity and flow rate
- Fixed-bed design ensuring safer handling, clean-up and disposal
- Large adsorbent capacity in small area footprint increases product recovery and reduces solvent requirements

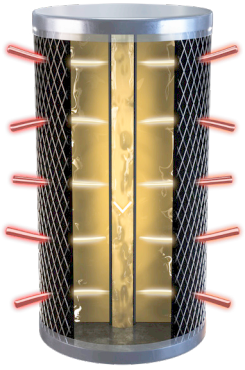
Sorbents for E-PAK Cartridges

E-PAK cartridges are available in a range of sorbents to accommodate the broad range of processing requirements. Other adsorbents are available upon request.

Sorbents for E-PAK		
Active Adsorbents (*typical loading*)	**For Removal and/or Recovery of:**	**pH Operation**
Silia*MetS* Thiol (*1.2 mmol/g*)	**Pd, Ag, Hg, Os, Ru,** Cu, Ir, Pb, Rh, Se and Sn	2 to 9
Silia*MetS* DMT (*0.5 mmol/g*)	**Pd, As, Ir, Ni, Os, Pt, Rh, Ru, Se,** Cd, Co, Cu, Fe, Sc and Zn	
Silia*MetS* Imidazole (*0.96 mmol/g*)	**Cd, Co, Cu, Fe, Ir, Li, Mg, Ni, Os, W, Zn,** Cr, Pd and Rh	
Silia*MetS* AMPA (*0.8 mmol/g*)	**Al, Ce, Dy, Er, Eu, Gd, Ho, La, Lu, Mn, Nd, Ni, Pm, Pr, Sb, Sn, Tb, Tm, V, Yb**, Co, Cu, Fe, Mg and Zn	
Silia*Bond* Amine (*1.2 mmol/g*)	**Pd, Cr, Pt, W, Zn,** Cd, Co, Cu, Fe, Hg, Ni, Pb, Ru, Sc and Se	
Silia*MetS* Diamine (*1.28 mmol/g*)		
Silia*MetS* Triamine (*1.11 mmol/g*)		
Silia*MetS* TAAcONa (*0.41 mmol/g*)	**Ca, Cd, Cs, Cu, Fe, Ir, La, Li, Mg, Ni, Os, Rh, Sc, Sn**, Cr, Pd, Ru, Se and Zn	
Silia*Bond* Cyano (*1.38 mmol/g*) **& Florisil**	Various organic molecucles	
Silia*Bond* Propylsulfonic Acid SCX-2 (*0.63 mmol/g*)	Amines & anilines, ion exchange	
Silia*Flash* Bare Silica	Very vast range of organic impurities, metals, pigments...	
Activated Carbon Silia*Carb* CA	Precious metal catalysts & colors	1 to 13
Activated Carbon Silia*Carb* HA		
Activated Carbon Silia*Carb* VA		
Activated Carbon Silia*Carb* VW		

Best scavenged metals in bold.

Out-to-in radial flow-through cartridge



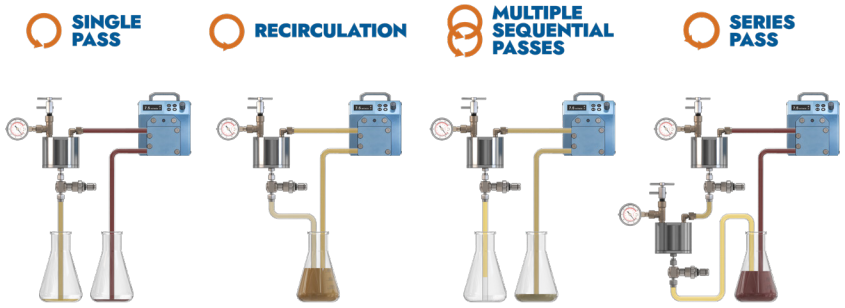
E-PAK cartridges are manufactured using a proprietary technology and chemically stable materials in most common organic solvents. They have been tested and found satisfactory for use with the following commonly used solvents:

- 2-Butanone
- Dichloromethane
- Ethanol
- Ethyl acetate
- Heptane
- Methanol
- MTBE
- N-ethyl-2-pyrolidone
- Tetrahydrofuran (*at room temperature*)
- Toluene (*at room temperature*)

Various Ways of Using E-PAK

Depending on the application and how you prefer to work, E-PAK cartridges can be used in different ways as shown below on all housing sizes (lab, pilot and commerical scale).

For a single pass usage, we suggest to run at very low flow rate compared to recirculation process, which can be run at higher flow rate.



Silia*MetS*® E-PAK Portfolio

Lab Scale

Lab scale cartridges are designed to facilitate small samples evaluation. Testing with loose media can be done with samples as small as a few milliliters and is normally done before cartridge testing to identify the formula with the highest capacity to remove contaminants with the highest recovery.

Lab Scale Cartridges				
Cartridge Size Diameter × Height (*cm*)	Typical Flow Rate Range (*mL/min*)	Pressure Drop with w/1 cP Fluid (*psig*)	Typical Media Weight	
			Silia*Flash*, Silia*MetS* & Silia*Bond* (*g*)	Silia*Carb* (*g*)
5 × 1	1 - 20	≤ 5	8	5
5 × 10	10 - 200	≤ 5	75	50
5 × 25	25 - 500	≤ 15	200	125

Note: Faster flow rates can be used for the lab scale cartridges depending on the application or the scavenging difficulty (*1 cm up to 100 mL/min, 10 cm up to 500 mL/min and 25 cm up to 1 L/min*).

Pilot and Commercial Scale

E-PAK pilot scale cartridges provide rapid processing for volumes from 10 to hundreds of liters, and can establish the parameters upon moving to larger scales, since E-PAK achieve true linear scalability.

E-PAK commercial scale cartridges provide rapid processing for manufacturing operations needing to process batch sizes of > 1,000 liters or can be adapted for continuous operation using a duplex design.

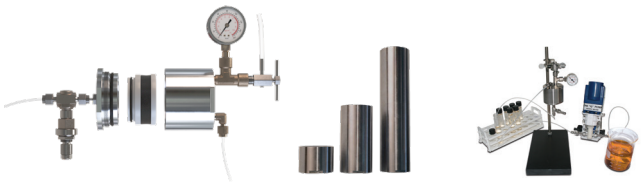
Pilot & Commercial Scale Cartridges				
Cartridge Size Diameter × Height (*cm*)	Typical Flow Rate Range (*L/min*)	Pressure Drop with w/1 cP Fluid (*psig*)	Typical Media Weight	
			Silia*Flash*, Silia*MetS* & Silia*Bond* (*kg*)	Silia*Carb* (*kg*)
Pilot Scale				
16.5 × 12.5 cm	0.10 - 2.5	≤ 10	0.87	0.55
16.5 × 25 cm	0.25 - 5	≤ 10	1.75	1.10
Commercial Scale				
16.5 × 50	0.50 - 10	≤ 10	3.50	2.10
16.5 × 100	1 - 20	≤ 10	7.00	4.10

Both pilot and commercial cartridges are provided with a Code 8 (*closed top & open bottom end caps-bottom with double 2-222 Teflon® encapsulated Viton® o-ring*) cartridge sealing configuration. To meet commercial processing requirements, E-PAK cartridges can be operated in parallel for increased capacity.

Housings

Lab Scale

- Various housing lengths available (*for 1 cm, 10 cm and 25 cm cartridges*)
- Made in stainless steel 316L or Hastelloy C276
- Pressure rating for housing 150 psi
- Easy housing conversion for all lengths by changing the bowl
- Operated with standard pump



Pilot and Commercial Scale

- Various housings available for simultaneous operation of 1 to 12 cartridges (*for 12.5 cm, 25 cm, 50 cm and 100 cm*)
- Made in stainless steel 316L or Hastelloy C276
- Pressure rating for housing 150 psi
- Can be operated in parallel to process batch sizes of ≥ 1,000 L
- ASME and PED 2014/68/EU, CE compliant

How to Calculate the Amount of Scavengers to Use?

The equivalent method

The equation below will result in a number of g of Silia*MetS* to use.

$$\frac{\square\ \text{mg}}{\text{kg}} \times \square\ \text{kg} \times \frac{1\ \text{mol}}{\square\ \text{g}} \times \frac{1\ \text{g Silia}\textit{MetS}}{\square\ \text{mmol}} \times \square\ \text{equiv} = $$

- Concentration of the residual metallic or organic impurity to be scavenged (*ppm or mg/kg*)
- Quantity of the product to be treated (*kg*)
- MW of the impurity to be scavenged (*g/mol*)
- Exact loading of the Silia*MetS* in *mmol/g* (*found on the CoA or on the bottle*)
- Number of equivalents you want to add to your mixture

For example, if you need to scavenge **800 g of material** containing 500 ppm of Pd (*MW of Pd: 106.42 g/mol*) with a Silia*MetS* Thiol with a loading of 1.2 mmol/g and you want to add 4 equivalents, this would mean a cartridge with 12.5 g of Silia*MetS* is needed.

$$\frac{500\ \text{mg}}{\text{kg}} \times 0.800\ \text{kg} \times \frac{1\ \text{mol}}{106.42\ \text{g}} \times \frac{1\ \text{g Silia}\textit{MetS}}{1.2\ \text{mmol}} \times 4\ \text{equiv} = 12.5\ \text{g}$$

The weight/weight method

The amount of sorbent required is estimated using the percentage weight/weight of the sorbent/crude

$$\square\ \text{kg} \times \square\ \% \left(\frac{\text{Sorbent}}{\text{Crude}}\right) = \square\ \text{g of sorbent}$$

- Quantity of the product to be treated (*kg*)
- Percentage of weight/weight desired (*20 % is a good starting point*)

For example, if you have 10 kg of crude product to treat, and you want 20 % weight/weight of sorbent, you will need 10 x 20 % = **2 kg.** Then you need to select the E-PAK cartridge for this weight, in this case it will be a 16.5 X 50 cm that has 3.5 kg of silica based adsorbant and 2.1 kg of activated carbon (*see Tables on page 3*).

Scale-Up Calculation

Although there are always exceptions, scale-up projections based on a linear extrapolation of adsorbent mass have proven to be quite accurate when test conditions including contact time, temperature, solvent type and contaminant and compound levels are held constant. The following table shows the scale-up/relative change in mass between lab, pilot and commercial size E-PAK cartridges available with scavengers.

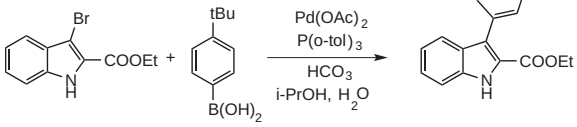
Scale-Up Calculation for Various Adsorbents							
Cartridge Sizes (Typical Loading)	**5 x 1 cm**	**5 x 10 cm**	**5 x 25 cm**	**16.5 x 12.5 cm**	**16.5 x 25 cm**	**16.5 x 50 cm**	**16.5 x 100 cm**
Typical scale-up Factor	-	10	25	110	220	440	875
Mass of Activated Carbon (*g*)	5	50	125	550	1,100	2,100	4,100
Mass of Silica (*g*)	8	75	200	875	1,750	3,500	7,000
# mmol Silia*MetS* AMPA (*0.8 mmol/g*)	6.4	60	160	700	1,400	2,800	3,600
# mmol Silia*MetS* Diamine (*1.28 mmol/g*)	10.2	96	256	1,120	2,240	4,480	8,960
# mmol Silia*MetS* DMT (*0.50 mmol/g*)	4.0	38	100	438	875	1,750	3,500
# mmol Silia*MetS* Imidazole (*0.96 mmol/g*)	7.7	72	192	840	1,680	3,360	6,720
# mmol Silia*MetS* TAAcONa (*0.41 mmol/g*)	3.3	31	82	359	717	1,435	2,870
# mmol Silia*MetS* Triamine (*1.11 mmol/g*)	8.9	83	222	971	1,942	3,885	7,770
# mmol Silia*MetS* Thiol (*1.20 mmol/g*)	9.6	90	240	1,050	2,100	4,200	8,400
# mmol Silia*Bond* Amine (*1.20 mmol/g*)	9.6	90	240	1,050	2,100	4,200	8,400
# mmol Silia*Bond* Cyano (*1.38 mmol/g*)	11.0	103	276	1,207	2,415	4,830	9,660
# mmol Silia*Bond* SCX-2 (*0.63 mmol/g*)	5.0	47	126	551	1,102	2,205	4,410
Bed Volume (cm^3)	18.8	188	470	2,375	4,750	9,500	19,000
Recommended Flow Rate (*mL/min*)	7.5	75	190	950	1,900	3,800	7,600
Typical Flow Rate Range (*mL/min*)	1 - 20	10 - 200	25 - 500	100 - 2,500	250 - 5,000	500 - 10,000	1,000 - 20,000
Approximated Tank Volume (mL)	50	200	450	2,500	5,000	11,600	23,300
Minimum System Flushing (mL)	150	600	1,350	7,500	15,000	35,000	70,000

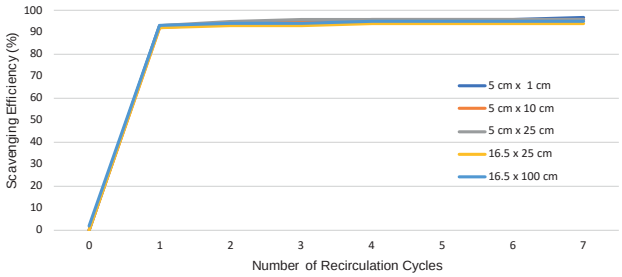
Measurement Methodology:

- Scale-up Factor: mass of silica / 8 g (*smallest size*)
- Mass of Activated Carbon (*g*): amount of Silia*Carb* in the cartridge
- Mass of Silica (*g*): Amount of Silia*MetS* / Silia*Bond* in the cartridge
- # mmol Silia*MetS* / Silia*Bond* XXX (*X.X mmol/g*): silica mass x typical loading of Silia*MetS* / Silia*Bond*
- Bed Volume (cm^3): total volume of the cartridge without the volume of the hole
- Recommended Flow Rate (*mL/min*): for residence times of 2.5 minutes
- Typical Flow Rate Range (*mL/min*): for residence times from 1 to 20 minutes. Faster flow rate can be used for some applications.
- Minimum System Flushing: corresponds to 3 tank volumes measured experimentally with the cartridges inside the housing. The volume of solvents needed for conditioning can vary depending on experimental conditions. It is recommended to do a minimum of 3 system flushing before use.

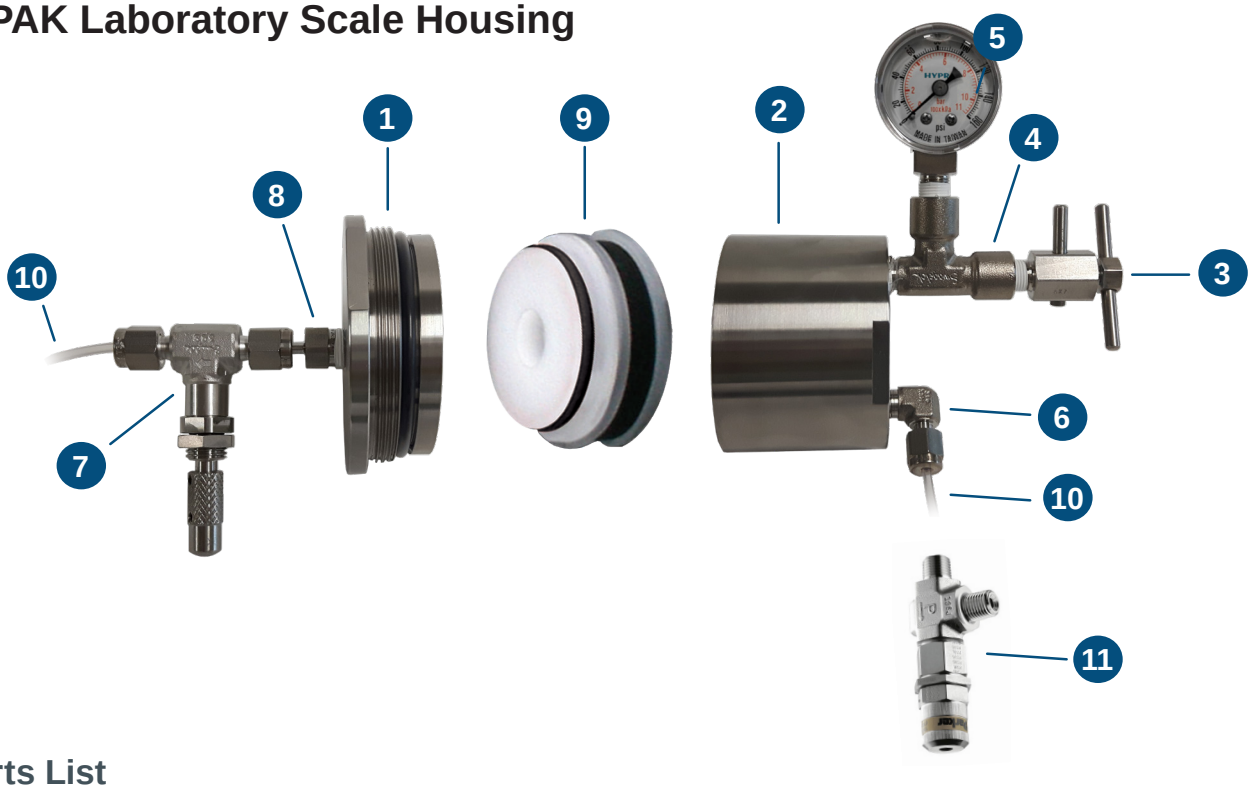
Scale-Up Linearity Demonstration

Using the Suzuki-Miyaura reaction shown below, with ≈ 12 molar equiv, scale-up reactions were performed with E-PAK from lab to commercial scale. As you can see, each format behaved similarly in terms of efficiency and kinetics.

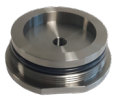




E-PAK Laboratory Scale Housing



Parts List

ITEM #	PICTURE	DESCRIPTION	ITEM #	PICTURE	DESCRIPTION
1		Base with O-Ring	7		Metering Valve
2		Bowl	8		1/8” NPT to 1/8” Compression Fitting
3		Bleed Valve	9		E-PAK® Lab Cartridge
4		Street T	10		1/8” OD Tubing
5		Pressure Gauge	11		Relief Valve w/t - Fitting 1/4” Compression Tube
6		Inlet Elbow			

Safety

E-PAK lab systems are intended for use in a controlled lab environment. It is the operator’s responsibility to ensure that the system is set up in strict accordance with this manual and otherwise in a manner that takes into account possible safety hazards of the materials being evaluated.

Inspection and Assembly

For convenience, we have preassembled the E-PAK lab housing prior to shipment.

1. Assemble and inspect the unit for loose fittings or damage. If needed, use teflon tape to assemble the street t (*#4*) and inlet elbow (*#6*) to the bowl (*#2*). Tighten any fittings that may have loosened during shipment. Contact our customer service if any components are damaged or missing.
2. Verify that the pressure gauge (*#5*) indicates 0 psi. If the gauge does not read 0, please contact us.
3. Separate the housing base (*#1*) from the bowl (*#2*).
4. Select a cartridge (*see Cartridge Selection page 3*) and insert it into the base (*#1*) with a slight rotating motion using light pressure.
   Tip: if the test cartridge is difficult to insert, moisten cartridge o-ring with compatible solvent.
5. Reassemble by inserting the housing base (*#1*) into the bowl (*#2*) and rotating clockwise until snug, being careful to avoid cross threading.
   Tip: in most cases, hand tightening will be sufficient to seal the base to the bowl. If leakage occurs, a strap wrench can be used to tighten further. When housing will be used to test an acidic solution, apply a single wrap of Teflon® tape to the base thread to protect against metal gauling of the threads.
6. Secure the housing assembly to a laboratory ring stand. The air bleed valve (*#3*) should be at the top of the assembly. Insert the tubing from the air bleed valve (*#3*), if you have one, securely into a suitable container that will collect the fluid exiting the valve during air purge operation.
7. Temporarily remove the pre-installed metering valve (*#7*) from the housing base.
   Note: the metering valve is removed until the system has been flushed to prevent plugging of its small orifice.
8. Using supplied tubing (#10) as shown in the diagram on page 6, connect housing inlet to pressure relief valve (#11) and then the pressure relief valve to pump outlet, pump inlet to feed reservoir and housing outlet to outlet reservoir.

Operation

System Flush

1. Ensuring that the selected E-PAK cartridge has been installed, flush the system using a compatible solvent. This will remove loose silica/carbon fines and other particulates from the system that could plug the back pressure control valve. This is best accomplished using solvent delivered at ≥ 10 mL/min.
2. Use bleed valve (*#3 also called vent valve*) to remove trapped air from the housing then close the valve and pump at least three reactor volume of solvent through the system. The solvent should be collected and discarded.
   Note: verify that the metering valve (*#7*) has been removed so that the solvent will not flow through the valve.
   Typical reactor volume per cartridge size: 1 cm = 50 mL, 10 cm = 200 mL, 25 cm = 450 mL.
3. Following solvent flush, use a small adjustable wrench to reconnect the metering valve (*#7*) to the housing base (*#1*) and reconnect outlet tubing.

Step-By-Step Operation

1. Once that all assembly and preparation steps have been completed, fully open the metering valve (*#7*).
2. Set the pump to a low flow rate (*i.e. 5 mL/min*).
3. Fully open the air bleed valve (*#3*) on top of the head.
4. Turn the pump on and watch for test fluid exiting from the bleed valve.
   Tip: over the course of the test run, additional gas produced due to degassing from pump action can accumulate in the housing, periodically this gas should be removed through the bleed valve to prevent interference with even flow distribution through the adsorbent cartridge.
5. When the bleed valve (*#3*) begins discharging liquid, indicating that all air has been bled from the system, close the bleed valve.
6. Observe the pressure gauge (*#5*) after closing the bleed valve (*#3*). Pressure should increase slowly. If pressure increases rapidly, immediately shut the pump off and disassemble the cartridge housing and inspect for blockage. If no blockages are identified, consider feed material characteristics; high viscosity or high solids can create pressure difficulties.
   Tip: we recommend that users pre-filter test solutions containing a large amount of insoluble solids.
7. If pressure increases slowly it will usually stabilize below 5 psi at a pump setting of 5 mL per minute for 5 X 1 cm setup. If pressure and/or flow are not in the target range, slowly adjust metering valve (*#7*) and pump setting as necessary. When using multiple housings in series, repeat steps 1 through 6 for each housing.
8. Begin sample loading on the cartridge and collection at intervals according to desired data needs or circulate the solution for the number of desired runs. If running multiple sequential passes, make sure that you stop the pump while you still have liquid in the tubing going to the housing before transfering the clean solution for another pass through and start step 8 again.
   Tip: during sample collection, periodically monitor flow and pressure, adjusting metering valve and pump setting as necessary to maintain target range.

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Silia*Bond*® − Chromatographic Phases
Silia*Sep*™ − Flash Cartridges
Silia*Plate*™ − TLC Plates
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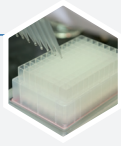
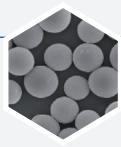
SAMPLE PREPARATION

Silia*Prep*™ − Silica-based SPE Cartridges & Well Plates
Silia*PrepX*™ − Polymeric SPE Cartridges & Well Plates
R&D Services − Custom Column Packing and Extraction & Purification

ANALYTICAL & PREPARATIVE CHROMATOGRAPHY

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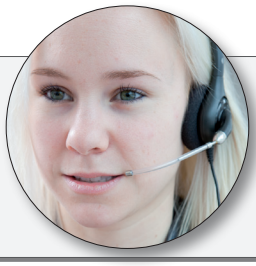

SILICYCLE

SiliCycle Inc.
2500, Parc-Technologique Blvd,
Quebec City (Quebec) G1P 4S6
CANADA

Phone: **+1 418.874.0054**
Toll Free **+1 877.745.4292** (*North America only*)
Fax: **+1 418.874.0355**

Email: **info@silicycle.com**
Website: **www.silicycle.com**

Overseas Offices

SiliCycle Europe	europe@silicycle.com
SiliCycle India	india@silicycle.com
SiliCycle Shanghai	contact@silicyclechina.com

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