SOURCE™ 30Q and 30S

SOURCE 30Q and 30S are from the GE range of BioProcess™ resins for ion exchange chromatography (IEX). SOURCE resins are developed for rapid, high resolution, preparative separations. They are based on porous, rigid, monodispersed, ~ 30 µm diameter polystyrene/divinyl benzene particles, designed to meet the demands of today's industrial bioprocessing for performance, reliability and scaleability.

Table of Contents

Read these instructions carefully before using the products.

Safety

For use and handling of the products in a safe way, refer to the Safety Data Sheets.

1 BioProcess resins

BioProcess chromatography resins are developed and supported for production scale chromatography. BioProcess resins are produced with validated methods and are tested to meet manufacturing requirements. Secure ordering and delivery routines give a reliable supply of resins for production scale. Regulatory Support Files (RSF) are available to assist process validation and submissions to regulatory authorities. BioProcess resins cover all purification steps from capture to polishing.

2 Characteristics

SOURCE 30Q and 30S provide excellent flow rates with a minimum back pressure to allow short cycle times and high productivity.

The controlled pore size distribution of SOURCE 30Q and 30S gives a high binding surface area, providing high loading capacity for a wide range of biological molecules.

The high physical and chemical stability of the matrix prevents bed compression and formation of fines, and allows efficient maintenance procedures for increased lifetime. These characteristics, together with the high batch-to-batch reproducibility and reliability of supply, make SOURCE 30Q and 30S ideal for scaling up in industrial production.

SOURCE 30Q and 30S are designed for intermediate purification and final polishing steps. When high-resolution separation is needed use a smaller bead, such as SOURCE 15Q and 15S. Table 1 summarizes the characteristics of SOURCE 30Q and 30S. Figure 2 (p. 17) shows typical pressure/flow characteristics.

Table 1. Characteristics of SOURCE 30 Q and SOURCE 30 S.

Matrix	Spherical and monodisperse, porous, rigid, polystyrene/divinyl benzene particles	
Type of ion exchanger	Q: R-O-CH_2-CHOH-CH_2-O-CH_2-CHOH-CH_2-$N^+(CH_3)_3$ S: R-O-CH_2-CHOH-CH_2-O-CH_2-CHOH-CH_2-SO_3^-	
Mean particle diameter [1]	~ 30 µm	
Dynamic binding capacity, Q_{B50}	SOURCE 30S: ~ 80 mg Lysozyme/mL resin [2] SOURCE 30Q: ~ 45 mg BSA/mL resin [3]	
	SOURCE 30Q	**SOURCE 30S**
pH stability, operational [4]	2 to 12	2 to 13
pH stability, CIP [5]	1 to 14	1 to 14
pH ligand fully charged [6]	Entire pH range	Entire pH range
Chemical stability	Stable to commonly used aqueous buffers, 1.0 M HCl, 50% acetic acid, 70% ethanol, 30% isopropanol/0.5 M NaOH, 1.0 M NaOH [7], 0.5% Tween	
Autoclavability	20 min at 121°C in H_2O, pH 7, 1 cycle	
Recommended maximum operating flow velocity [8]	2000 cm/h	
Recommended operating flow velocity	300 to 1000 cm/h	
Operating temperature	4°C to 40°C	
Delivery conditions	SOURCE 30Q: 20% ethanol. SOURCE 30S: 20% ethanol and 0.2 M sodium acetate	

1 Monodisperse size distribution.

2 Dynamic binding capacity at 50% breakthrough by frontal analysis at a mobile phase velocity of 300 cm/h in a PEEK 7.5/50 column at 5 cm bed height (1 min residence time) for Lysozyme in 20 mM Sodium phosphate, pH 6.8.

3 Dynamic binding capacity at 50% breakthrough by frontal analysis at a mobile phase velocity of 300 cm/h in a PEEK 7.5/50 column at 5 cm bed height (1 min residence time) for BSA in 20 mM BisTrisPropane, pH 7.0.

4 pH range where resin can be operated without significant change in function.

5 pH range where resin can be subjected to cleaning- or sanitization-in-place without significant change in function.

6 pH range where ligand is fully charged; although the ligand is fully charged throughout the entire pH range, only use the resin within the stability ranges.

7 1.0 M NaOH should only be used for cleaning purposes.

8 Will depend on the pressure specification of the chromatographic system used. A flow velocity of 2000 cm/h will give a pressure drop of approximately 10 bar at a bed height of 10 cm.

3 Packing columns

Treat SOURCE with care and avoid "digging" or stirring directly in sedimented resin or packed beds as this can generate fines. Resuspend stored SOURCE by shaking in a container.

A packed bed in a column is best removed by dismantling the upper end- piece and pumping in liquid from the opposite end.

Suspend SOURCE 30Q in 20% ethanol, SOURCE 30S in 20% ethanol and 0.2 M sodium acetate for packing.

Recommended columns

General

Purifying biological macromolecules by IEX is a typical high selectivity technique where the difference in retention for the molecules to be separated can be substantial at any specific pH and ionic strength.

Therefore, relatively short columns can be used if the selectivity of the adsorbent is exploited in an optimal way. Typical bed heights range from 3 to 15 cm, which reduces back pressure and allows high throughput.

To exploit the resolving power of SOURCE 30Q and 30S, use columns with a well-designed flow distribution system at the column inlet and outlet. To minimize zone spreading, the flow distribution must be effective without resulting in large mixing volumes.

The column should have a pressure stability of at least 0.3 MPa (3 bar, 43 psi). Filters which prevent the passage of particles are also essential.

In many production situations, stringent hygiene requirements put additional demands on column design.

The FineLINE™ columns designed by GE will meet these requirements. With a hydraulically controlled adapter, it also allows fast and efficient packing in large-scale applications (see later). Packing takes about 10 minutes with excellent performance and reproducibility.

Recommended Lab-scale columns

Column	i.d. (mm)	Bed volume (mL)	Bed height (mm)
FineLINE Pilot 35	35	29 to 140	30 to 150
Tricorn 5/20	5	0 to 0.5	0 to 26
Tricorn 5/50	5	0.2 to 1.1	8 to 56
Tricorn 10/20	10	0.0 to 2.1	0 to 26
Tricorn 10/50	10	0.0 to 0.44	0 to 56
Tricorn 10/100	10	3.6 to 8.4	46 to 106
Tricorn 10/150	10	7.6 to 12.3	96 to 156
Tricorn 10/200	10	11.5 to 16.2	146 to 20
Tricorn 10/300	10	19.4 to 24.1	246 to 306

Recommended Production-scale columns

Column	i.d. (mm)	Approx bed volume (mL)	Bed height (mm)
FineLINE 70	70	580	30 to 150
FineLINE 70L	70	1200	50 to 300
FineLINE 100P	100	1200	30 to 150
FineLINE 100PL	100	240	50 to 300
FineLINE 200P	200	470	30 to 150
FineLINE 200PL	200	940	50 to 300
FineLINE 350P, PFR, 2 µm	350	14 400	30 to 150
FineLINE 350PL, EPDM, 10 µm	350	28 800	50 to 300

4 Packing procedures

Tricorn 10/100

Step	Action
1	Assemble the column (and packing reservoir if necessary).
2	Eliminate air from the column dead spaces by flushing the end piece and adapter with 20% ethanol. Make sure no air has been trapped under the column net. Close the column outlet leaving the net covered with 20% ethanol.
3	Resuspend SOURCE resin in its container by shaking (avoid stirring sedimented resin). A slurry concentration of up to 60% can be used for packing (in 20% ethanol).
4	Pour the slurry into the column in one continuous motion. Pouring the slurry into the packing glass tube in a slow motion will minimize the introduction of air bubbles.
5	Connect the end-piece to the packing tube, or the adapter and connect the column to a pump. Avoid trapping air bubbles under the adapter or in the inlet tubing.
6	Open the bottom outlet of the column and let SOURCE sediment by pumping 20% ethanol through the column at a flow rate generating a back pressure of 10 bar for a Tricorn 10/100 column. This corresponds to a volumetric flow rate of approximately 20 mL/min for a Tricorn 10/100 at a bed height of 10 cm.
7	When the resin bed is stabilized, close the bottom valve and stop the pump.
8	Carefully place the top filter on top of the bed before fitting the adapter.
9	With the adapter inlet disconnected, screw the adapter down approximately 2 mm into the resin bed, allowing the packing solution to flush the adapter inlet.
10	Connect the pump, open the bottom outlet and continue packing. The bed will be further compressed at this point forming a space between the bed surface and the adapter.

Step	Action
11	Disconnect the column inlet and lower the adapter approximately 2 mm into the resin bed. The column is now ready to use.

FineLINE 100 and FineLINE 200

FineLINE columns allow an extremely simple, rapid and reproducible packing procedure whereby SOURCE is packed at the same time as the adapter is adjusted into position at the correct pressure on top of the bed.

Two different valves are needed, an adjustable pressure relief valve and a 4-port (2-way) valve mounted on the lower column outlet. The columns are used with 6 mm ID tubing and 25 mm OD clamp connectors, gaskets and blind plates (stop plugs).

Step	Action
1	Assemble the column. Add 20% ethanol to the bottom of the column and drain the column outlet by opening the bottom valve. Close the bottom valve. Connect a tube to the suction side of a pump. Place the tube on top of the net and start the pump to extract any remaining air bubbles trapped under the net. Leave the net covered with 20% ethanol.
2	Resuspend SOURCE resin by shaking the container (avoid stirring sedimented resin).
3	Pour the slurry carefully into the column. Top up with 20% ethanol to approximately 1.0 cm or 2.5 cm below the rim for FineLINE 100 and FineLINE 200 respectively.
4	Connect the adapter and column lid. Avoid trapping air bubbles under the adapter by slightly tilting the adapter while mounting. Block the tubing at the top of the adapter rod with a blind plate.
5	Connect the pump to the inlet of the hydraulic chamber with the pressure relief valve in line. Remove air from the chamber by pumping liquid through it.
6	Switch off the pump and block the hydraulic chamber outlet with a blind plate.

Step	Action
7	Adjust the pressure relief valve to 0.6 MPa (6 bar, 85 psi) for FineLINE 100 and 0.4 MPa (4.0 bar, 57 psi) for FineLINE 200 while running the pump against the closed inlet of the hydraulic chamber. The pump used should be able to provide a flow velocity of at least 20 cm/min through the column, at the stipulated pressure.
8	Open the lower column outlet and the inlet of the hydraulic chamber. The adapter now moves down as the bed is packed at a constant hydraulic pressure, continuously regulated by the pressure relief valve.

NOTICE

Make sure that the pressure relief valve is correctly adjusted, otherwise the weakest seal in the system will leak when its limit is exceeded.

9	When the adapter has reached its lowest position, continue running the pump for one more minute. In the meantime, secure the adapter with the locking bar. Do not use tools to fasten the screws. Close the column outlet and the inlet to the hydraulic chamber. Stop the pump.
10	Start running the column with an upward flow to remove any residual air trapped in the adapter. The column is now ready to use.

5 Removal of fines

The high physical stability of SOURCE prevents the formation of fines under normal working conditions and after repeated repacking of the resin under the mild and reproducible conditions used with FineLINE columns.

However, mechanical stirring of sedimented resin or repeated compression of a packed bed can create fines. For example, repeated packing with conventional flow pressure procedures can create fines since the bed is subjected to several compression and expansion cycles.

Fines generated in this way can be removed with the following procedure.

Step	Action
1	Make a 50% slurry of the resin in 20% ethanol
2	Allow the slurry to sediment for 2.5 hours.
3	Decant or siphon off the supernatant containing the fines.
4	Resuspend the sedimented material to the original slurry volume using 20% ethanol
5	Repeat this procedure four times.

6 Evaluation of packing

To check the quality of the packing, and to monitor this during the working life of the column, we recommend that you determine the number of theoretical plates per meter (N/m) and the peak asymmetry factor (A_s).

A well packed column can be expected to give values in the following range:

N/m > 11 000

A_s 0.8–1.5

However, it is of utmost importance to realize that the calculated plate number will vary depending on the test conditions and should therefore be used as a reference value only. The most important thing is that conditions and equipment are kept constant so that results are comparable. Changes in solute, solvent, eluent, sample volume, flow rate, liquid pathway, temperature, etc. will influence the results.

If an acceptance limit is defined in relation to column performance, the column plate number can be used as part of the acceptance criteria for use and re-use of columns.

Conditions

Sample volume:	1.0% of bed volume
Sample conc.:	2.0 M NaCl in water
Eluent:	0.5 M NaCl in water
Flow rate:	60 cm/h
Detection:	Conductivity

Calculate the number of theoretical plates per meter (N/m) as follows:

$N/m = 5.54 (V_e/W_{1/2})2 \times 1000/L$

Calculate the peak asymmetry factor as follows:

$A_s = b/a$

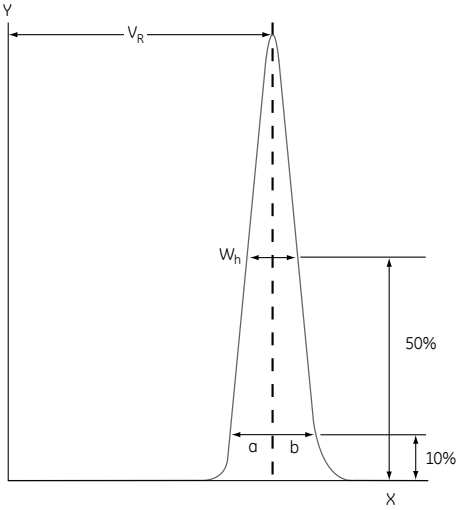

Fig 1. A typical test chromatogram showing the parameters used for HETP and A_s calculations. X = Volume; Y = Absorbance

V_e = Volume eluted from start of sample application to peak maximum

$W_{1/2}$ = Peak width at half of peak height

L = Bed height in mm

a = 1st half peak width at 10% of peak height

b = 2nd half peak width at 10% of peak height

7 Method design and optimization

The main purpose of optimizing a chromatographic step is to reach the predefined purity level with highest possible product recovery by choosing the most suitable combination of the critical chromatographic parameters.

In process chromatography, this must be accomplished as quickly and easily as possible for good productivity and process economy.

The following sections are guidelines for optimizing the critical operational parameters which affect the efficiency and use of an IEX step.

Binding conditions

The most common procedure is to allow the molecule(s) of interest to bind to the ion exchanger and then separate them from the contaminating molecules by applying a continuous or step-wise increase in the ionic strength of the eluting buffer. In some cases it can be useful to choose conditions where a contaminant is bound and the product of interest flows through instead.

Selectivity during adsorption to the ion exchanger is optimized by careful selection of pH and ionic strength of the start buffer. pH is selected according to the isoelectric point of the molecule of interest. For maximum selectivity and capacity, optimal pH would be approximately 1 to 2 pH units away from the isoelectric point, on that side of the isoelectric point where the isoelectric points of the bulk of the contaminating molecules are positioned. A pH far from the isoelectric point of the molecule of interest will give stronger binding and increased capacity but can have a negative effect on selectivity by binding contaminants. The choice of optimal pH will always be a balance between selectivity and capacity.

The buffer system should be selected to give maximum buffering power at the lowest possible ionic strength to ensure high binding capacity of the molecule of interest. To achieve this, the pKa of the buffer should not be more than 0.5 pH units away from the pH being used. Generally, 10 mM buffer is the minimum desirable level. Ideally, one of the buffering species should also be uncharged, and so not contribute to the ionic strength.

Buffering ions should not interact with the adsorbant. The charged form(s) of buffer should be of the same sign as the substituents on the adsorbant. If not, undesirable and unpredictable pH changes can occur in the microenvironment adjacent to the adsorbed proteins. This can cause changes in strength of interaction and, at worst, denaturation. It is less important to observe when higher concentrations of buffer can be used.

In large-scale applications, economic considerations often limit the choice to acetate, citrate, phosphate, or other inexpensive components, even for anion exchangers.

Table 2. Suggested buffers for use with SOURCE 30Q.

Buffer	Concentration	pKa (25°C)
N-methylpiperazine	20 mM	4.8
Piperazine	20 mM	5.7
bis-Tris	20 mM	6.5
Triethanolamine	20 mM	7.8
Diethanolamine	20 mM	8.9
Ethanolamine	20 mM	9.5
Glycine	20 mM	9.9
1,3-diamino-propane	20 mM	10.5
Piperidine	20 mM	11.1

Table 3. Suggested buffers for use with SOURCE 30S.

Buffer	Concentration	pKa (25°C)
Citrate	50 mM	3.1
Formate	50 mM	3.8
Acetate	50 mM	4.8
Malonate	50 mM	5.7
MES	50 mM	6.2
Phosphate	50 mM	7.2
HEPES	50 mM	7.6
BICINE	50 mM	8.4

Elution

Elution from ion exchangers is usually accomplished by applying a continuous or step-wise increase in the ionic strength of the eluting buffer. This weakens the electrostatic interaction between the bound molecule and the adsorbent.

Elution by pH gradients is not generally very successful. This is because, unless there is a very high buffering capacity, the attempt to change the pH by applying a pH gradient is frustrated by the buffering power of the molecules adsorbed on the column and, in case of weak ion exchangers, the buffering of the adsorbent groups themselves. However, for step-wise increases, pH elution can be quite successful. The pH change will be delayed compared with the new buffer front because of these titrations, but eventually the bound molecule is desorbed, coincident with a rapid pH change.

Simple linear gradients are the first choice for screening experiments. With experience, a shallower gradient in the area where the molecule elutes can be advantageous. A steep gradient is best used in areas where contaminating molecules are eluted. Such complex gradients offer maximum flexibility in terms of combining resolution with speed during the same separation.

Elution is normally achieved with salt gradients up to 0.5 to 1.0 M sodium chloride with a gradient volume of approximately 10 column volumes.

Stepwise elution is often preferred in large-scale applications since it is technically more simple and reproducible than elution with continuous gradients. Step-wise elution will also decrease buffer consumption, shorten cycle times and allow the molecule of interest to be eluted in a more concentrated form.

Resolution vs productivity

When IEX chromatography is used for intermediate or final polishing, the focus is to maximize selectivity and resolution to meet the predefined requirements.

If a linear gradient is used during elution, careful optimization of the gradient improves resolution. If a step elution procedure is used, the resolution is optimized by optimizing the eluting strength and volume of the steps. For improvement of resolution during desorption, increase the efficiency of the system by increasing the bed height. The highest resolution can be achieved with short a separation time which reduces dilution of the product.

After the binding and eluting conditions are optimized for resolution, throughput can be maximized by optimization of sample load and flow rate.

Maximum loading capacity is defined by running a series of experiments with gradually increased sample load. Optimal conditions will be the maximum sample load that provides a resolution that meets the predefined purity requirements.

Flow velocity

SOURCE 30Q and 30S can be used in lab-scale columns at flow velocities up to 2000 cm/h with ÄKTA™ or HPLC systems. This is useful for lab-scale preparative applications and for scouting different separation conditions at small-scale.

When scaling up, it is important to consider practical issues such as pressure limitations of large-scale equipment, difficulties of liquid handling and process control at very high volumetric flow rates.

Typically, linear flow velocities in the range 300 to 1000 cm/h will provide the desired resolution, productivity and product yield with convenient large-scale separation times of a few minutes to one hour.

The flow/pressure characteristics of the SOURCE 30 matrix are shown in Figure 2.

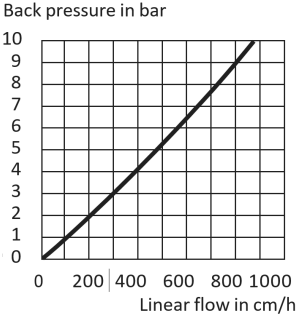

Fig 2. Pressure/flow characteristics of the monodispersed SOURCE 30 matrix. The pressure/flow data were determined in a 200 mm i.d. column with a bed height of 14.9 cm

Regeneration

Normally a separation cycle is followed by washing the column with a high ionic strength buffer (e.g., containing 1 to 2 M NaCl) and/or changing pH, to remove strongly adsorbed substances from the column.

To prevent a slow buildup of contaminants on the column over time, more rigorous cleaning protocols can be used on a regular basis.

8 Cleaning-in-place (CIP), sanitization and sterilization

CIP

CIP is the removal of tightly bound, precipitated or denatured substances generated in previous purification cycles. When contaminants accumulate on the column they can affect the chromatographic properties of the column. Severe fouling can block the column, increase back pressure and reduce flow rate. To remove:

- Ionically bound substances, wash the column with 0.5 bed volumes of a 2 M NaCl at a flow velocity of 40 cm/h, contact time 10 to 15 minutes, reversed flow direction.
- Precipitated substances, hydrophobically bound substances and lipoproteins, wash the column with 1 M NaOH at a flow velocity of 40 cm/h, contact time 1 to 2 hours, reversed flow direction.
- Strongly hydrophobically bound proteins, lipoproteins and lipids from the column, wash with 70% ethanol or 30% isopropanol at a flow velocity of 10 to 40 cm/h, reversed flow direction. Apply increasing gradients to avoid air bubble formation when using high concentrations of organic solvents.

Alternatively, wash the column with 2 to 4 bed volumes of 0.1% to 0.5% of a nonionic detergent in a basic or acidic solution. Always remove detergent with 70% ethanol or 30% isopropanol, contact time 1 to 2 hours after treatment.

After washing the column, equilibrate with at least 3 bed volumes of start buffer before use.

Use the CIP protocols as guidelines for a specific feed material, however we recommend CIP every 5 cycles during normal use. Depending on the nature of the contaminants, use different protocols in combination. If fouling is severe the protocols can need further optimization.

Sanitization

Sanitization reduces microbial contamination of the bed to a minimum.

Wash the column with 0.5 to 1.0 M NaOH at a flow velocity of approximately 40 cm/h, contact time 30 to 60 minutes.

To sanitize a FineLINE column packed with SOURCE follow the procedure below.

Step	Action
1	Apply 2.5 column volumes of 1.0 M NaOH at a flow velocity of 250 cm/h, using upward flow through the column.
2	Change flow direction and apply another 2.5 column volumes of 1.0 M NaOH with downward flow through the column.
3	Stop the pump and allow to stand for 60 minutes.
4	Re-equilibrate the column with start buffer.

Sterilization

For sterilization, dismantle the column and autoclave the resin at 121°C for 20 minutes.

9 Storage

Store SOURCE 30Q in 20% ethanol, SOURCE 30S in 20% ethanol and 0.2 M sodium acetate at 4°C to 30°C, to avoid microbiological growth. Storage in 0.01 M NaOH [1] can be used as an alternative to ethanol. After storage, equilibrate with at least 3 bed volumes of start buffer before use.

[1] In most cases, no long term stability data has been generated by GE Healthcare Life Sciences in 0.01 M NaOH. In some cases, accelerated studies at elevated temperature indicate that storage in 0.01 M NaOH can be a viable option but no guarantees can be made regarding retained function of the product.

10 Scaling up

Scalability must be designed-in during the development phase and is done after the IEX step has been optimized at laboratory scale.

Design-in of scalability addresses the design and optimization of the step (robustness, simplicity, costs, capacity etc.), and the choice of chromatography resin (chemical stability, physical stability, particle size, cost etc.).

Scale-up is performed by increasing the diameter of the column. Parameters that remain constant include bed height, flow velocity, sample volume in relation to bed volume, and the ratio gradient volume/bed volume. The larger equipment used in scale-up can cause deviations from a method optimized at small-scale. Therefore, check the solvent delivery system and monitoring system and minimize the effects of liquid delays and volume changes in the flow path. The increased length and diameter of outlet pipes can also cause zone spreading in larger systems.

Scale-up from a 2.2 mL lab-scale column to a 1.6 L production-scale column is demonstrated in Figure 3.

Column: (a) Small-scale column; ID 7.5 mm; 2.2 mL (b) Production-scale column, ID 200 mm; 1.57 L
Sample: Mixture of chymotrypsinogen, cytochrome C and lysozyme
Sample load: 0.32 mg/mL resin
Start buffer: 20 mM sodium phosphate, pH 6.8
Elution buffer: 20 mM sodium phosphate + 0.5 M NaCl, pH 6.8 Flow velocity: 300 cm/h
Gradient: 0–100% B; 20 column volumes

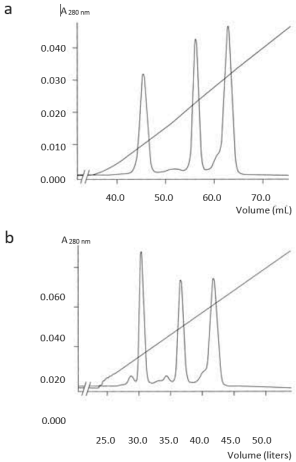

Fig 3. Separation of a mixture of model proteins on SOURCE 30S showing a 700-fold scale-up from a lab-scale column (a) to a production-scale column (b).

11 Ordering information

SOURCE resins	Quantity	Product code
SOURCE 30Q	50 mL	17127501
	200 mL	17127502
	1 L	17127503
	5 L	17127504
SOURCE 30S	50 mL	17127301
	200 mL	17127302
	1 L	17127303
	5 L	17127304

Columns and accessories	Product code
Tricorn 10/100 (ID 10 mm)	28406415
Tricorn glass tube 10/300	18115318
Tricorn 5/20	28406408
Tricorn 5/50	28406409
Tricorn 10/20	28406413
Tricorn 10/50	28406414
Tricorn 10/150	28406416
Tricorn 10/200	28406417
Tricorn 10/300	28406418
FineLINE 70	18115298
FineLINE 70L	18115299
FineLINE 100P	11002798
FineLINE 100PL	11002799
FineLINE 200P	11003114
FineLINE 200PL	11003115
FineLINE 350P, PFR, 2µm	11002792
FineLINE 350PL, EPDM, 10µm	11002785
Packing connector 10–10	18115323
Packing equipment 10/100	18115325
FineLINE Pilot 35	18110202
FineLINE 100 (ID 100 mm)	18110535
Column stand (FineLINE 100)	18103110
FineLINE 200 (ID 200 mm)	18110577
Column stand (FineLINE 200)	18103120
Relief valve	18110536
Bottom valve (4-port; 2-way)	18575701

The SOURCE range also includes ion exchange resins based on ~ 15 µm particles (SOURCE 15Q and 15S), hydrophobic interaction chromatography resin, and reversed phase chromatography resins. Some are also available in small scale prepacked RESOURCE™ columns.

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