Downstream scale-up purification of influenza virus using single-use bioprocessing equipment

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Downstream scale-up purification of influenza virus using single-use bioprocessing equipment

This application note describes a case study where live influenza virus was purified using single-use bioprocessing technology. The GE Healthcare ReadyToProcess™ single-use platform is a flexible manufacturing platform which facilitates easy handling of virus solutions and helps improve productivity. As model system for a live, attenuated influenza virus vaccine, a A/H1N1/Solomon Island strain produced in Vero cells was used. Total process time for the downstream purification was 3 days and the overall scale-up process resulted in production of influenza virus with the same yield and purity as obtained in the laboratory scale.

Introduction

The vaccine manufacturing industry is continuously seeking more flexible and time-saving solutions for a quicker response to pandemic outbreaks (1, 2). For influenza virus, vaccine is traditionally produced in fertilized hen eggs and purified in fixed steel equipment.

In this application note we describe the scale-up of a downstream purification process of cell-based influenza virus, from a 10 L cell culture to the purification from a 50 L culture using ReadyToProcess single-use technology. The ReadyToProcess platform offers a disposable and scalable process solution for fluid handling. Single-use technology reduces the need for time-consuming device preparations, such as cleaning and cleaning validation, and minimizes the risk for cross-contamination, all essential parameters in traditional vaccine manufacturing.

For this study, Vero cells were grown on microcarriers and infected with influenza virus (A/H1N1) (3). Virus particles were subsequently purified using robust and scalable single-use filtration and chromatography techniques. Figure 1 displays an overview of the influenza virus purification process using ReadyToProcess equipment. The downstream scale-up purification process resulted in a similar virus yield and purity as obtained in the laboratory-scale process.

Fig 1. Overview of the production process of whole live influenza virus using ReadyToProcess equipment.

Materials and methods

In the laboratory-scale experiment, standard equipment was used for the downstream purification of influenza virus from a 10 L cell culture. The laboratory-scale, chromatography-based purification process was subsequently scaled up 62.5-fold. In the scaled-up process, ReadyToProcess single-use equipment was used for downstream virus purification from a 50 L cell culture.

An overview of the downstream laboratory-scale and scaled-up purification processes is shown in Figure 2.

Cell culture and infection

Vero cells were cultured in WAVE Bioreactor 20/50 system and WAVE Bioreactor 200 system (GE Healthcare Life Sciences) for the 10 L laboratory-scale culture and the 50 L scaled-up culture, respectively. The cells were grown on Cytodex™ 1 microcarriers (GE Healthcare Life Sciences) with a concentration of 3 g/L and in Dulbecco's modified eagle medium (DMEM)/Ham's F12 (GE Healthcare Life Sciences) supplemented with fetal bovine serum (50 g/L) (GE Healthcare Life Sciences) and Pluronic™ F-68 (2 g/L) (Sigma-Aldrich Co.). Prior to virus infection, cells were washed with serum-free DMEM/Ham's F-12. At a concentration of about 2×10^6 cells/mL, cells were infected with virus at a multiplicity of infection of 4×10^{-3} (the ratio infectious virus particles to number of cells) and a trypsin concentration of 2 mg/L.

Prior to harvest, microcarriers were allowed to settle in the Cellbag™ bioreactor chamber (GE Healthcare Life Sciences). Virus was harvested 3 to 4 d after infection. Time of harvest was based on visual inspection of cytopathic effect and measurement of virus particles.

A more detailed description of the cell culturing and virus infection and harvest is given in the application note 29-0435-48 (3).

Purification of influenza virus using ReadyToProcess

Harvest clarification

The harvest clarification was performed by normal flow filtration in a closed system using ReadyMate™ aseptic connectors and ReadyCircuit disposable tubing assemblies, bags, and sensors (all from GE Healthcare Life Sciences). The outline of the clarification process is displayed in Figure 3. All solutions used in the process were sterile filtered into ReadyCircuit bags before use. Priming of tubing and ULTA Prime GF filter capsules (GE Healthcare Life Sciences) with buffer was performed simultaneously with the calibration of the Watson-Marlow™ pump flow rates (Watson-Marlow Pumps Group, Cornwall, UK).

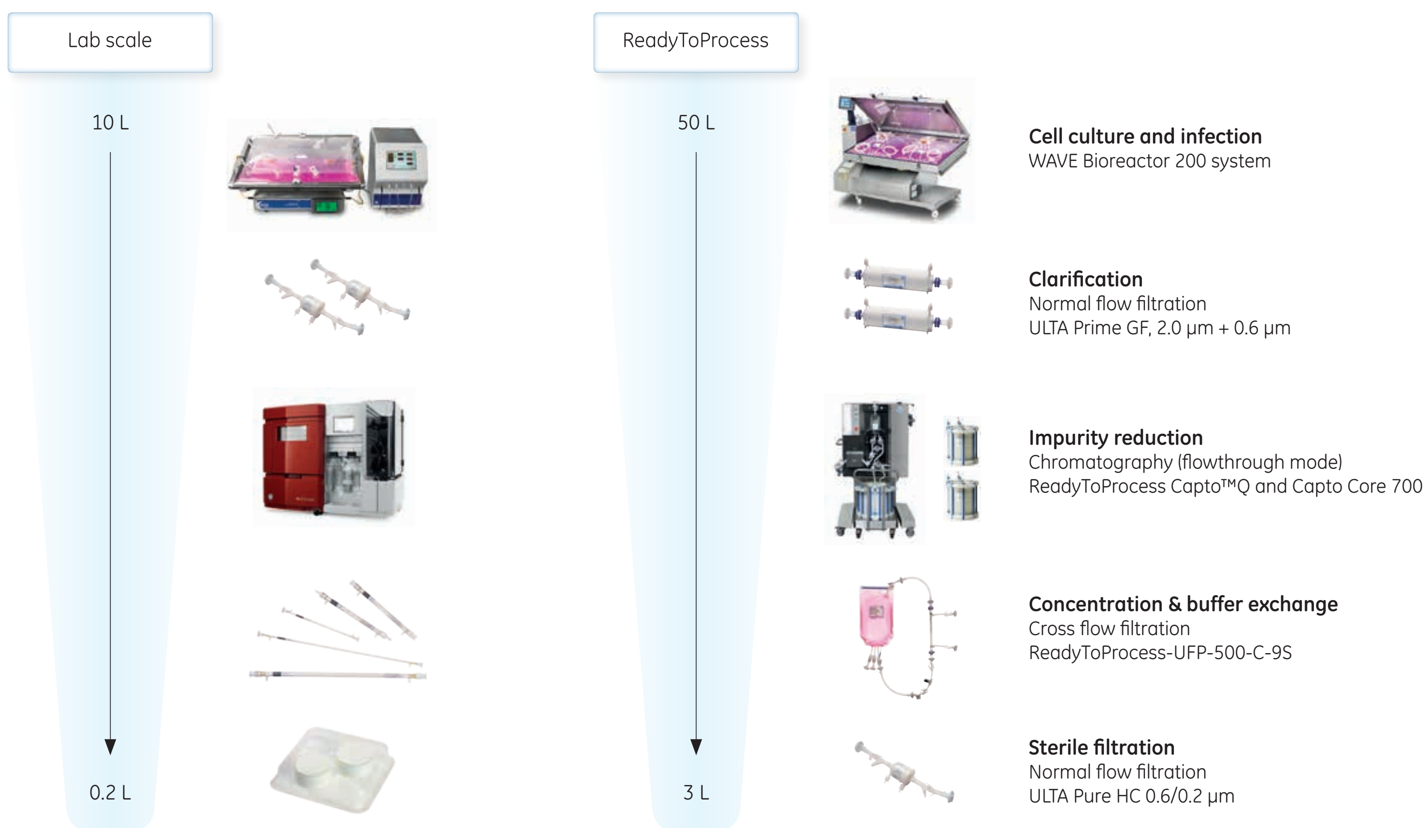


Fig 2. Overview of the downstream scale-up purification of live influenza virus.

Filters:	ULTA Prime GF 2 µm and 0.6 µm ULTA GF 2 µm and 0.6 µm (lab scale)	*Filtration flux rate:*	120 L/m²/h (2.02 L/min)
Buffer:	20 mM sodium phosphate, 0.15 M NaCl, pH 7.2	*Live influenza virus harvest:*	44 L

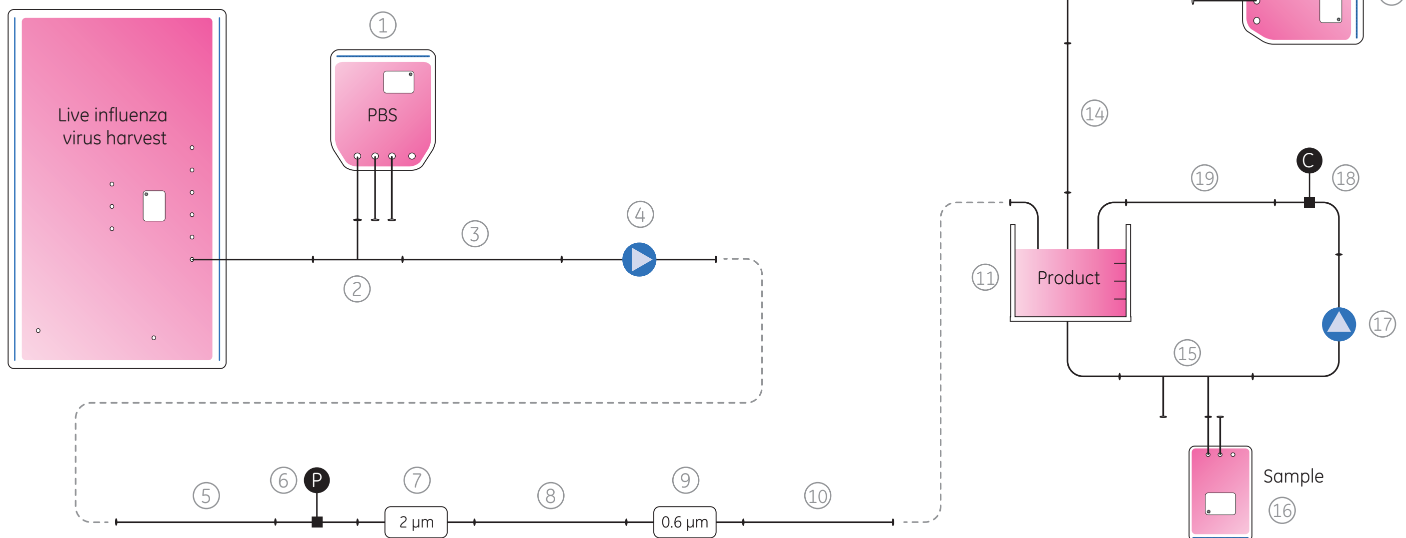


Fig 3. Running conditions and schematic setup of the clarification in the 50 L-scale purification. Further information on numbered items can be found under Ordering information. P = pressure sensor, C = conductivity sensor.

Cell medium containing live influenza virus was transferred by peristaltic pumping (120 L/m²/h) to two serial-connected ULTA Prime GF capsules. PBS buffer was used to prime and rinse the system. The clarified harvest was collected in a 100 L ReadyCircuit bag.

To prepare for the following chromatography purification step, the conductivity was adjusted with 5 M NaCl to approximately 48 mS/cm (0.5 M NaCl). The clarified harvest was mixed by pumping until stable conductivity readings were reached. A sample bag was connected to the mixing circuit allowing sampling via the clave port. Samples were withdrawn and stored at +5°C for hemagglutinin (HA), host cell protein (HCP), and total protein analysis and at -70°C for host cell DNA analysis.

Prestudy of chromatography setup and conditions

The aim of the prestudy was to evaluate how the overall process, including all purification steps used in the scale-up study, was affected by operating columns packed with Capto Q and Capto Core 700 medium (resin) separately or in series. Different flow velocities were tested with live influenza virus in the laboratory scale. The experimental setups of the prestudy are visualized in Figure 4.

The prestudy was performed in flowthrough mode, with 40 mL Capto Q medium in prepacked HiScale™ 16/40 column and 16 mL Capto Core 700 medium in Tricorn™ 10/200 column (all from GE Healthcare Life Sciences). ÄKTAexplorer™ chromatography system (GE Healthcare Life Sciences) was used to operate the chromatography columns and 20 mM Tris, 0.5 M NaCl, pH 7.5 buffer was used for equilibration of the columns.

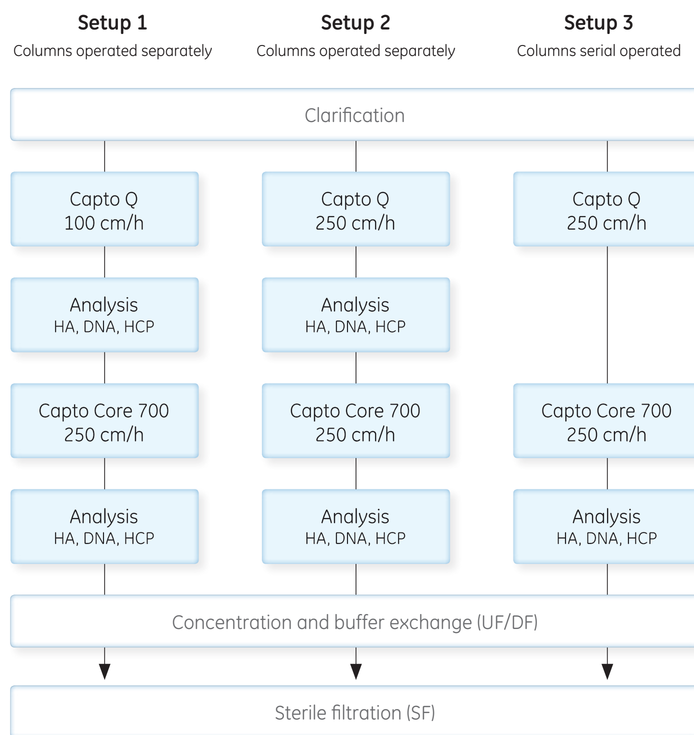


Fig 4. The prestudy was based on three different experimental setups. In setup 1 and 2 Capto Q and Capto Core 700 media columns were operated separately but with the Capto Q step performed at different flow velocities. In setup 3 the columns were operated serially connected. The study was evaluated by comparing process performance (e.g., HA yield and purity).

Outcome of the prestudy

Figure 5 A to D summarizes the results from the prestudy in terms of HA yield (%), host cell DNA-to HA ratio, total protein-to-HA ratio, and HCP-to-HA ratio.

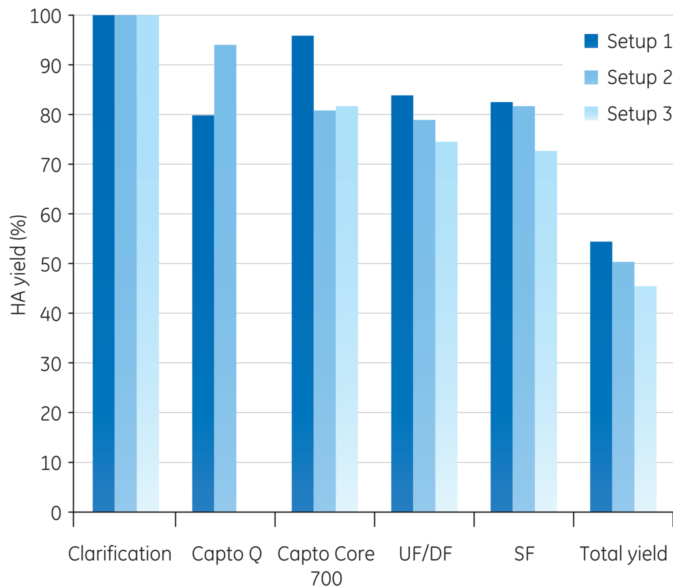


Fig 5A. HA yields for the different prestudy setups described in Figure 4. UF/DF = ultrafiltration/diafiltration, SF = sterile filtration.

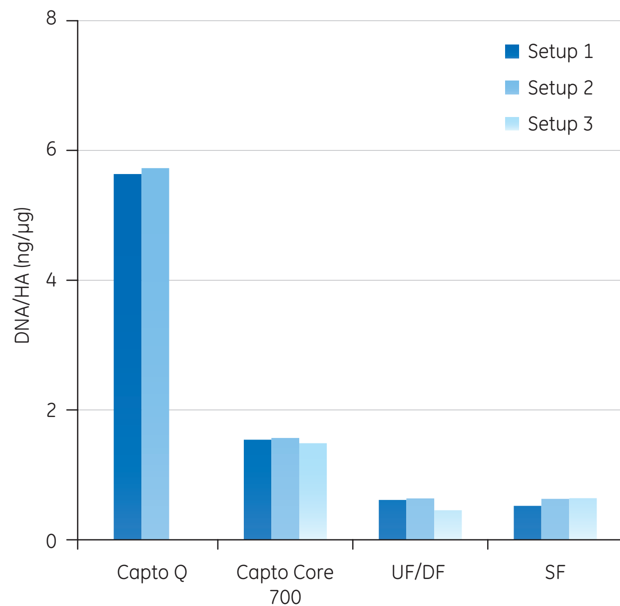


Fig 5B. DNA-to-HA ratio for the different prestudy setups described in Figure 4. The DNA-to-HA ratio after clarification was not determined.

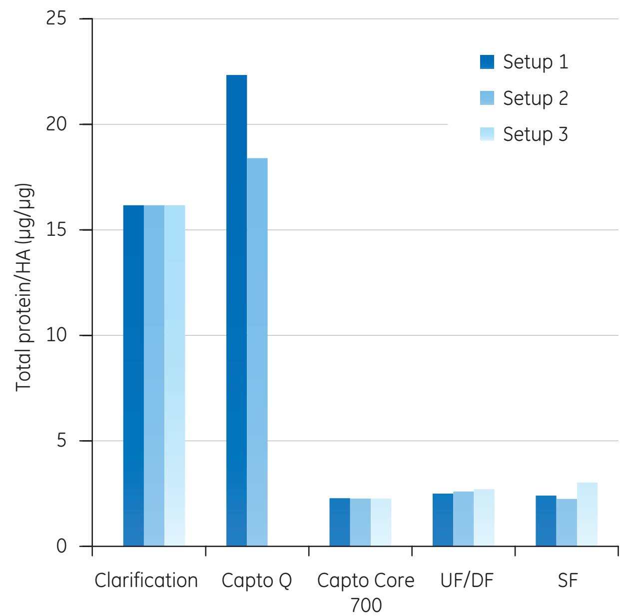


Fig 5C. Total protein-to-HA ratio for the different prestudy setups described in Figure 4.

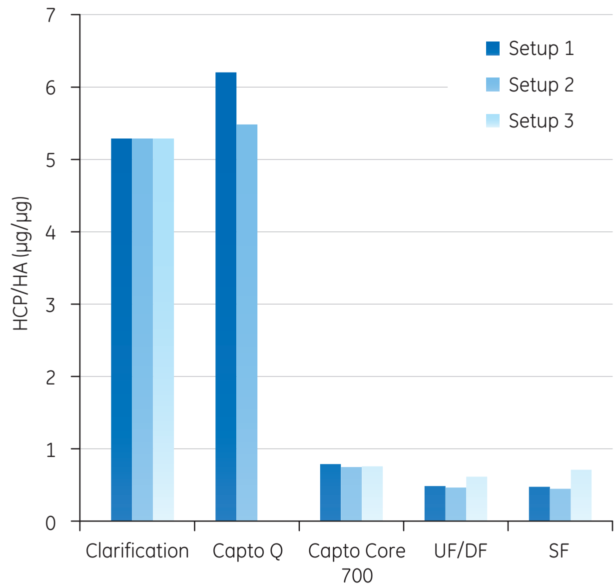


Fig 5D. HCP-to-HA ratios for the different prestudy setups described in Figure 4.

Similar process yield and purity after the last sterile filtration step was obtained in all three setups. To achieve a significant reduction in process time, the laboratory-scale prestudy shows that it is possible to run the chromatography columns in series with similar process yield and purity as when running the columns separately.

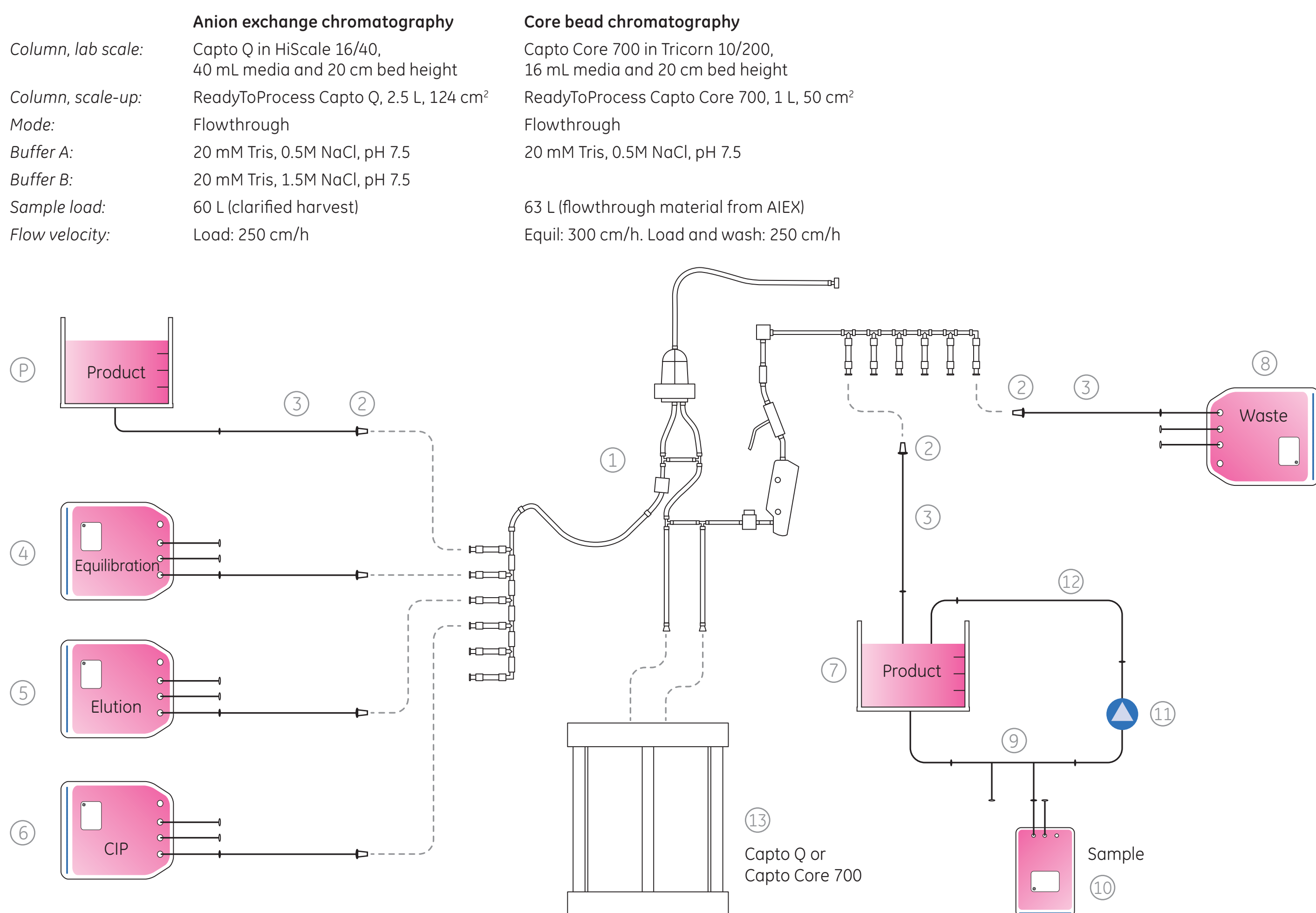
Chromatography

The ÄKTA ready chromatography system (GE Healthcare Life Sciences) together with a 2.5 L ReadyToProcess Capto Q column (GE Healthcare Life Sciences) was used for purification of virus from host cell DNA. By adjusting conductivity to approximately 48 mS/cm (as described above in present study), virus was passed in the flowthrough while the DNA, which is strongly negatively charged, bound to positive Q groups on the matrix. The load of DNA/mL on the Capto Q column was approximately 3.5 µg/mL and the flow velocity was 250 cm/h. Despite the high flow velocity, pressure drop over the column could be kept below 0.7 bar because of the construction of the Capto base matrix.

In the following purification step, impurities, such as HCP and hydrophobic components, were removed in a 1 L ReadyToProcess Capto Core 700 column with 20 cm bed height (GE Healthcare Life Sciences). Capto Core 700 is composed of an inactive shell of agarose and an inner core with a multimodal ligand (octylamine) attached to it. Entities with a molecular weight (M_r) larger than approximately M_r 700 000 will pass outside the bead while smaller entities can diffuse into the bead and bind to the inner core ligand. The binding of impurities to the octylamine ligand are not affected by pH, conductivity, or common buffer compositions. The protein binding capacity of Capto Core 700 is approximately 13 mg ovalbumin/mL medium. Protein load was approximately 7.5 mg/mL medium and the flow velocity was 250 cm/h, giving a column pressure drop of 0.4 bar.

Figure 6 summarizes the running conditions and chromatography setup.

Samples from the chromatography purification steps were collected from the 100 L ReadyCircuit bag via a 250 mL sample bag and stored for subsequent yield and purity analysis as previously described under Harvest clarification.



	Anion exchange chromatography	Core bead chromatography
Column, lab scale:	Capto Q in HiScale 16/40, 40 mL media and 20 cm bed height	Capto Core 700 in Tricorn 10/200, 16 mL media and 20 cm bed height
Column, scale-up:	ReadyToProcess Capto Q, 2.5 L, 124 cm²	ReadyToProcess Capto Core 700, 1 L, 50 cm²
Mode:	Flowthrough	Flowthrough
Buffer A:	20 mM Tris, 0.5M NaCl, pH 7.5	20 mM Tris, 0.5M NaCl, pH 7.5
Buffer B:	20 mM Tris, 1.5M NaCl, pH 7.5	
Sample load:	60 L (clarified harvest)	63 L (flowthrough material from AIEX)
Flow velocity:	Load: 250 cm/h	Equil: 300 cm/h. Load and wash: 250 cm/h

Fig 6. Running conditions and experimental setup of the chromatography steps. Further information on numbered items can be found under Ordering information. AIEX = anion exchange chromatography. CQ = Capto Q, CC 700 = Capto Core 700, CIP = clean-in-place.

Concentration and buffer exchange

The virus concentration and buffer-exchange step included ultrafiltration and diafiltration using a ReadyToProcess hollow fiber cartridge (GE Healthcare Life Sciences).

The virus solution was concentrated from 63 L to 2.7 L by ultrafiltration. By diafiltration, the viral particles were transferred to an appropriate buffer for the final sterile filtration step. Diafiltration was performed by continuously exchanging the retentate with six filter volumes of buffer. Running conditions and experimental setup are illustrated in Figure 7.

Filter, lab scale:	UFP-500-C-9S (lab scale)
Filter, scale-up:	RTPUFP-500-C-9S
Buffer:	20 mM NaP, 0.15 M NaCl, pH 7.2
Share rate:	4.2 L/h, (7600s^{-1})
Flux:	23 L/h, 20 L/m^2/h
Sample load:	Downstream processed sample from the chromatographic steps

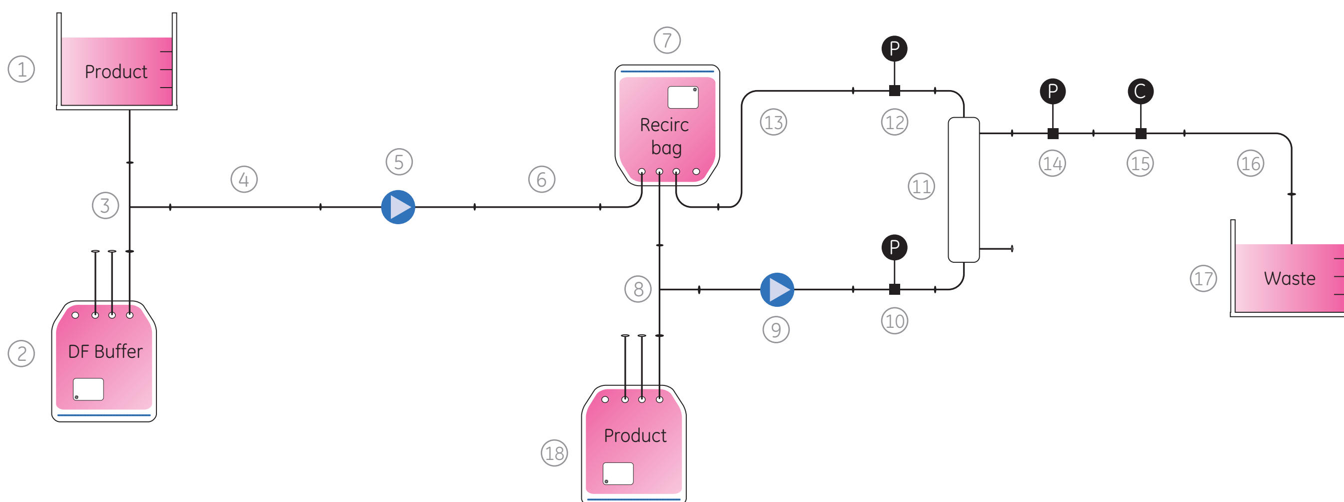


Fig 7. Running conditions and experimental setup of the ultrafiltration and diafiltration (DF) steps. Further information on numbered items can be found under Ordering information. P = pressure sensor, C = conductivity sensor.

Sterile filtration

Prior to sterile filtration, the flow path including tubing, pump, pressure sensor, and filter was primed with buffer to detect any leakage. The experimental setup is displayed in Figure 8.

Filter:	ULTA Pure HC 0.6/0.2 µm
Buffer:	20 mM NaP, 0.15 M NaCl, pH 7.2
Flux:	19 L/h, 186 L/m²/h
Sample load:	Downstream processed sample from the UF/DF steps

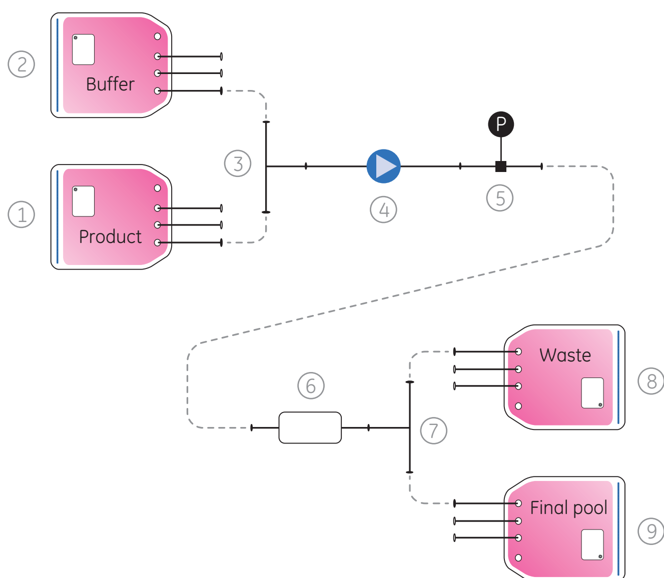


Fig 8. Running conditions and experimental setup of the sterile filtration step. Further information on numbered items can be found under Ordering information. P = pressure sensor, UF/DF = ultrafiltration/diafiltration.

Single-use materials, such as bags, tubing, and filters were treated with 1 M sodium hydroxide and autoclaved before disposal according to local waste treatment routines. However, as the system is closed, inactivation of virus in tubing, bags, and filters might not be needed before disposal.

Analytical methods

Determination of virus content

Samples taken during the infection phase and chromatographic purification were analyzed for virus activity using 50% tissue culture infective dose ($TCID_{50}$), amount of virus particles with Virus Counter 2100 (ViroCyt, Denver, CO, USA), and for HA concentration with Biacore T200 system (GE Healthcare Life Sciences) (4, 5). More detailed descriptions are given in the application note 29-0435-48 (3).

Determination of impurities

Host Cell DNA

Host cell DNA was quantified by quantitative PCR using primers specific to Vero cell gene S4x rRNA. Sample preparation of genomic DNA was performed using illustra™ GFX™ PCR DNA and Gel Band Purification Kit (GE Healthcare Life Sciences). Genomic DNA from Vero cells was purified using illustra tissue and cell genomicPrep Mini Flow Kit (GE Healthcare Life Sciences) and used as reference material.

Total protein assay

Total protein content was measured by Bradford total protein assay (6).

Host cell protein

Host cell protein was quantified using Biacore 200T system with sensor Chip CM5 (GE Healthcare Life Sciences). In-house produced specific polyclonal antibodies against Vero cell lysate proteins were immobilized on the dextran matrix surface of the sensor chip. Samples were injected and HCP were allowed to bind to the immobilized surface antibodies. A calibration curve with Vero cell lysate was included three times in each run: initially, in the middle, and at the end. The calibration curves were used for software normalization for accurate concentration determination of the samples.

Results and discussion

Scale-up study using ReadyToProcess equipment

The outcome from the various steps (i.e., raw harvest, clarification, chromatography, ultrafiltration and diafiltration, and sterile filtration) of the influenza purification process from both 10 L and 50 L production scales is shown in Figure 9 A to E.

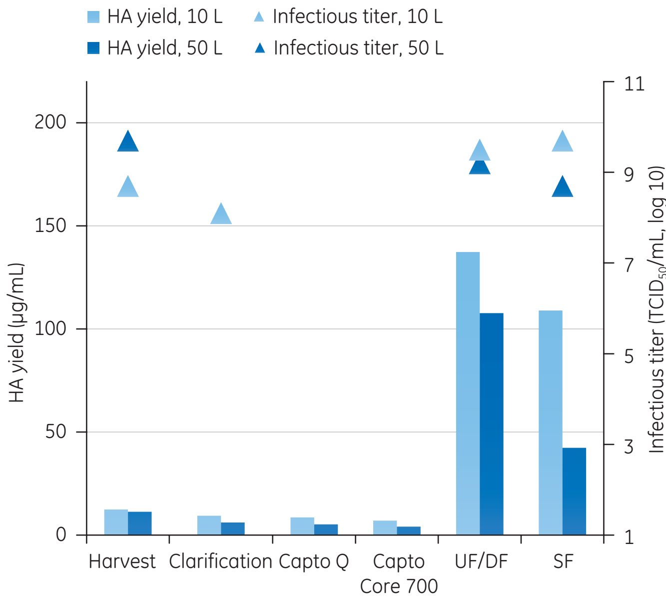


Fig 9A. Summary of HA yields and infectious titer. The infectivity of the virus was retained throughout the process in both scales, as shown by the infectious titer. This is also confirmed by the HA yield and virus particles/mL measured with the Virocyt virus counter.

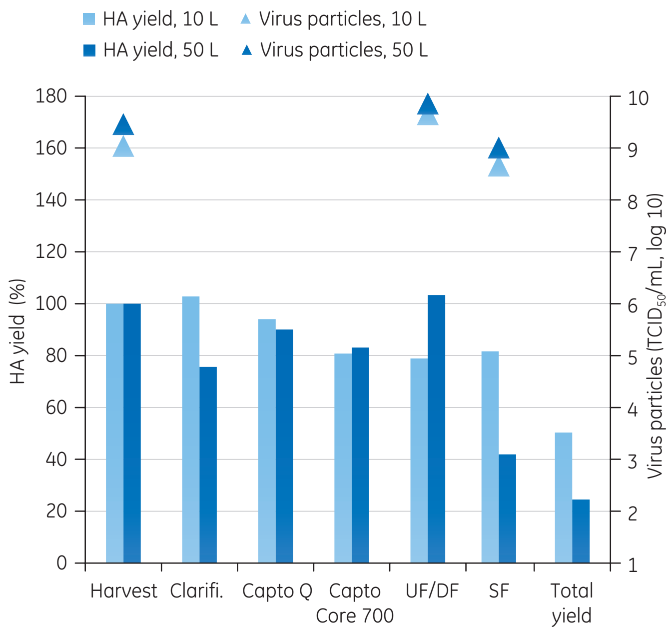


Fig 9B. Summary of HA yield and virus particle amount. Total HA yield over the process was 50% from the 10 L culture and 25% from the 50 L culture.

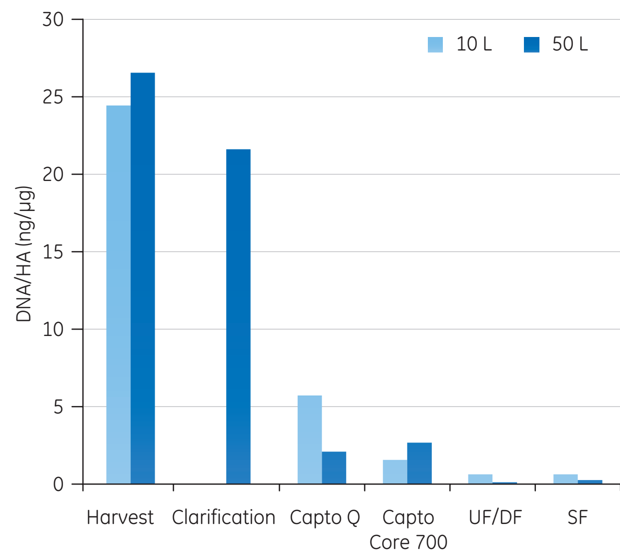


Fig 9C. Summary of DNA-to-HA ratios. The DNA-to-HA ratio after clarification in the 10 L-scale production was not determined.

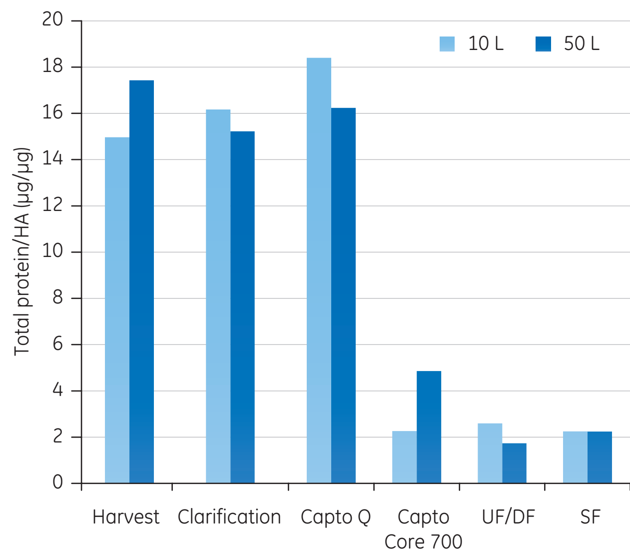


Fig 9D. Summary of total protein-to-HA ratios.

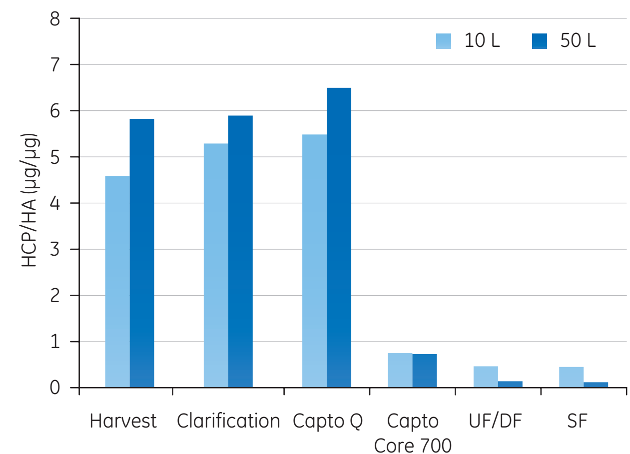


Fig 9E. Summary of HCP-to-HA ratios.

Table 1. Summary of the scaled-up process in doses per liter harvest for the monovalent bulk

	Split-inactivated vaccine[1]	Nasal LAIV[2]
Scale-up output/L harvest	175 doses, each 15 µg HA	3075 doses, each 10^7 $TCID_{50}$ units
Harvest volume to produce 10^6 doses	5760 L	325 L
Protein impurity[3]	30 µg protein/15 g HA	1.5 µg protein/10^7 $TCID_{50}$ units
DNA impurity[4]	3.0 ng/15 µg HA	0.15 ng/10^7 $TCID_{50}$ units

[1] Split-inactivated vaccine contains 3 strains, each 15 µg/HA (e.g., 3 × 15 = 45 µg HA/dose, each 0.5 mL).

[2] Comparison is based on a commercially available specification for a nasal LAIV. A dose of 0.2 mL contains 10^7 fluorescent focus units, which is assumed to be equal to $TCID_{50}$ titer.

[3] WHO guideline for protein impurity: max. 100 µg protein/strain

[4] WHO guideline for DNA impurity: < 10 ng DNA/dose = 3.3 ng DNA/15 µg HA.

The overall process time for the downstream purification in the scale-up study was 3 days, resulting in comparable process yield and purity of influenza virus as obtained in the laboratory-scale experiment. The overall process HA yield was about 25% from the 50 L culture and 50% from the 10 L culture. Differences can be seen between steps and scales that may be explained by variation in analysis methods. The loss in HA and virus yields during the final sterile filtrate step is probably due to the close relation in size of the virus (100 to 120 nm) and the pore profile in the sterile filter.

Comparison to regulatory specifications

As there is no approved cell-based LAIV on the market today, no regulatory requirements in terms of impurities are established. Hence, the output from the scaled-up production is compared to a commercially available specification for a nasal LAIV and a specification for egg-based, split-inactivated influenza vaccine from WHO (8). Study outcome is summarized in Table 1.

Assuming a nasal route of administration and doses of 10^7 infectious particles per 0.2 mL dose, the amount of host cell DNA in the scaled-up production was shown to be below the acceptance level (10 ng/dose) defined by WHO. The host cell protein amount per dose and strain in the scaled-up production was also shown to be below acceptance level of WHO. The outcome from the scaled-up production indicates that it is possible to obtain approximately 3000 doses/L harvest, corresponding to harvests of 325 L for 1 million doses (calculations based on specification for nasal LAIV) and 175 doses/L harvest corresponding to harvests of 5760 L for 1 million doses (calculations based on specification for split-inactivated vaccine).

Conclusions

In this case study, the downstream purification of cell-based influenza virus from a 50 L cell culture using ReadyToProcess single-use technology demonstrates high productivity and efficient removal of host cell derived impurities, with maintained virus infectivity.

Similar process yield and purity was obtained from the scaled-up purification of influenza virus from a 50 L cell culture using ReadyToProcess single-use technology, as from the viral purification from a 10 L cell culture using standard equipment.

The case study described in this application note is not a fully optimized process. Further optimization of the process is necessary prior to use in vaccine manufacturing.

References

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7. Recommendations for the production and control of influenza vaccine (inactivated). *World Health Organization Tech Rep Ser* 927:103. (2005)
8. White paper: Overview of a scale-up of a cell based influenza virus production process using single-use bioprocessing equipment, GE Healthcare, 29-0435-51, Edition AC (2014)

Ordering information

Number*	Product	Description	Code number
	Clarification		
1	20 L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
2	3RMT Jumper .375 in 6 in CF1PK	T-manifold tubing	12-4101-64
3	RMRM Jumper 0.25 in 5' CF1PK	Tubing	12-4101-16
4	PSIL Jumper .375 in ID .563 in OD	Pump tubing. Recommended pump: Watson Marlow series 520	28-9794-32
5	RMRM Jumper 0.25 in 3 ft CF1PK	Tubing	12-4101-15
6	PRES SENS .375 in 6 in RSRM 1PK	Pressure sensor	28-9794-71
7	1XGF0220 2 RM	ULTA Prime GF 2 µm 20" capsule filter terminating with ReadyMate connectors (ReadyCircuit assembly)	12-4100-84
8	RMRM Jumper 0.25 in 3 ft CF1PK	Tubing 3 feet	12-4101-15
9	1XGF9620 2 RM	ULTA Prime GF 0.6 µm 20" capsule filter terminating with ReadyMate connectors (ReadyCircuit assembly)	12-4100-70
10	RMRM Jumper 0.25 in 5 ft CF1PK	Tubing	12-4101-16
11	100L 4 0.75 in port 18 in CF1PK	100 L bag, 4 inlets	12-4102-06
12	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
13	PSIL Jumper .25 in ID .437 in OD	Pump tubing	28-9794-70
14	RMRM Jumper 0.25 in 3 ft CF1PK	Tubing	12-4101-15
15	4RMT Jumper 0.5 in 6 in CF1PK	4-manifold tubing	12-4101-75
16	250 ml 2 .25 in port 1 ft 1 CF1PK	Sample bag, 250 mL	12-4102-26
17	PSIL jumper .5 in ID .75 in OD	Pump tubing Recommended pump: Watson Marlow series 620	28-9794-36
18	Cond sens 0.75 in TCRM 1 PK	Conductivity sensor	12-4102-43
19	RMRM Jumper 0.5 in 5 ft CF1PK	Tubing	12-4101-22
	Chromatography, Capto Q		
	ÄKTA ready system including column trolley and UNICORN		28-906261
1	Low Flow kit, ÄKTA ready		28-9301-82
2	ReadyMate DAC 750 TC		28-9366-94
3	RMRM Jumper .375 in 3 ft CF1PK	Tubing	12-4101-18
4	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
5	10L 3 0.5 in port 1 ft CF1PK	10 L bag, 3 inlets	12-4102-22
6			
7	100L 4 0.75 in port 18 in CF1PK	100 L bag, 4 inlets	12-4102-06
8	50L 4 0.75 in port 18 in CF1PK	50 L bag, 4 inlets	12-4102-29
9	4RMT Jumper 0.5 in 6 in CF1PK	Tubing	12-4101-75
10	250 ml 2 .25 in port 1 ft 1 CF1PK	Sampling bag, 250 mL	12-4102-26
11	PSIL jumper .5 in ID .75 in OD	Pump tubing	28-9794-36
12	RMRM Jumper 0.5 in 5 ft CF1PK	Tubing	12-4101-22
13	ReadyToProcess Capto Q, 2.5 L	AIEX media	28-9017-23

Number*	Product	Description	Code number
	Chromatography, Capto Core 700		
1	Low Flow kit, ÄKTA ready		28-9301-82
2	ReadyMate DAC 750 TC	ReadyMate Disposable Aseptic Connectors	28-9366-94
3	RMRM Jumper .375 in 3 ft CF1PK	Tubing	12-4101-18
4	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
5	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
6	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
7	100L 4 0.75 in port 18 in CF1PK	100 L bag, 4 inlets	12-4102-06
8	50L 4 0.75 in port 18 in CF1PK	50 L bag, 4 inlets	12-4102-29
9	4RMT Jumper 0.5 in 6 in CF1PK	Tubing	12-4101-75
10	250 ml 2 .25 in port 1 ft 1 CF1PK	Sampling bag, 250 mL	12-4102-26
11	PSIL jumper .5 in ID .75 in OD	Pump tubing	28-9794-36
12	RMRM Jumper 0.5 in 5 ft CF1PK	Tubing	12-4101-22
14	ReadyToProcess Capto Core 700, 1L	Core bead media	17-5481-03**
	Clarification & buffer exchange		
1		Bag from chromatographic steps	
2	20L 3 0.5 in port 1 ft CF1PK	20 L bag, 3 inlets	12-4102-24
3	3RMT Jumper .25 in 6 in CF1PK	T-manifold tubing	12-4101-63
4	RMRM Jumper 0.25 in 3 ft CF1PK	Tubing	12-4101-15
5	PSIL Jumper .25 in ID .437 in OD	Pump tubing	28-9794-70
6	RMRM jumper 0.25 in 1 ft CF1PK	Tubing	12-4101-14
7	5L 4 0.375 in port 1 ft CF1PK	5 L bag, 4 inlets	12-4102-21
8	3RMT Jumper 0.5 in 6 in CF1PK	T-manifold tubing	12-4101-66
9	PSIL jumper .5 in ID .75 in OD	Pump tubing	28-9794-36
10	Pres sens 0.75 in TCRM 1PK	Pressure sensor	12-4102-33
11	RTPUFP-500-C-9S	ReadyToProcess hollow fiber cartridges-ultrafiltration 1.15 m^2 surface area; 0.5 mm ID lumen; 60 cm path length	39-0000-54
12	Pres sens 0.75 in TCRM 1PK	Pressure sensor	12-4102-33
13	RMRM Jumper 0.5 in 3 ft CF1PK	Tubing	12-4101-21
14	Pres sens .375 in 6 in RSRM 1PK	Pressure sensor	28-9794-71
15	Cond sens .375 in 6 in RSRM 1PK	Conductivity sensor	28-9794-40
16	RMRM Jumper 0.25 in 3 ft CF1PK	Tubing	12-4101-15
17	200L 4 0.75 in port18 in CF1PK	200 L bag, 4 inlets	12-4102-08
18	5L 4 0.375 in port 1 ft CF1PK	5 L bag, 4 inlets	12-4102-21
	Sterile Filtration		
1		Bag from UF/DF step	
2	5L 3 0.375 in port 1 ft CF1PK	5 L bag, 3 inlets	12-4102-20
3	3RMT Jumper .25 in 6 in CF1PK	T-manifold tubing	12-4101-63
4	PSIL Jumper .25 in ID .437 in OD	Tubing	28-9794-70
5	Pres sens .375 in 6 in RSRM 1PK	Pressure sensor	28-9794-71
6	1XHC9204 2 0.5 ft CF RM	ULTA Pure HC 0.6/ 0.2 µm	12-4100-94
7	3RMT Jumper .25 in 6 in CF1PK	T-manifold tubing	12-4101-63
8	1L 3 0.25 in port 1 ft CF1PK	1 L bag, 3 inlets	12-4102-18
9	5L 3 0.375 in port 1 ft CF1PK	5 L bag, 3 inlets	12-4102-20

* ID number originates from flow schematics in Materials and methods

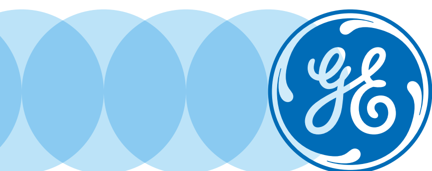
**Capto Core 700 supplied in the RTP format is available via CDP (customized design product)

Related literature	Code number
Microcarrier cell culture principles and methods, handbook	18-1140-62

For local office contact information, visit
www.gelifesciences.com/contact

www.gelifesciences.com/bioprocess

GE Healthcare Bio-Sciences AB
Björkgatan 30
751 84 Uppsala
Sweden



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GE Healthcare UK Limited
Amersham Place, Little Chalfont
Buckinghamshire, HP7 9NA
UK

GE Healthcare Europe, GmbH
Munzinger Strasse 5
D-79111 Freiburg
Germany

GE Healthcare Bio-Sciences Corp.
800 Centennial Avenue, P.O. Box 1327
Piscataway, NJ 08855-1327
USA

GE Healthcare Japan Corporation
Sanken Bldg., 3-25-1, Hyakunincho
Shinjuku-ku, Tokyo 169-0073
Japan

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