# Ovalbumin removal in egg-based influenza vaccine production using Capto Core 700

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# Ovalbumin removal in egg-based influenza vaccine production using Capto™ Core 700

**This application note demonstrates the performance of Capto Core 700 chromatography medium (resin) as an alternative for ovalbumin removal in the production of egg-based influenza vaccine. Ovalbumin removal and haemagglutinin (HA) recovery were determined after the Capto Core 700 step in combination with ultrafiltration and diafiltration (UF/DF). The process performance was compared with that of zonal ultracentrifugation (UC), a technique traditionally used for ovalbumin removal in influenza vaccine purification. The results show that an influenza purity that meets the regulatory requirements was achieved with both methods. The two methods were also compared in terms of productivity and equipment cost at different scales. The process economic model demonstrates higher productivity at all scales and a more cost-effective production at process scale for the Capto Core 700 process, when compared with the zonal UC process.**

## Introduction

Influenza virus causes both seasonal epidemics and occasionally severe worldwide pandemics. Vaccination is an effective prevention strategy for protection of large populations. To meet the annual needs, efficient and cost-effective vaccine production is required. Investing in a domestic influenza vaccine production could further increase the availability and the ability for many countries to meet the urgent needs in a pandemic situation.

Today, influenza vaccine is primarily produced in embryonated hen eggs and the purification processes has been essentially unchanged for the past decades. Industrial processes for manufacturing of influenza vaccine are commonly based on a combination of zonal UC and different filtration steps. However, modernization of legacy vaccine processes can help meet the requirements for increased productivity and cost-efficiency in the production of influenza vaccine.

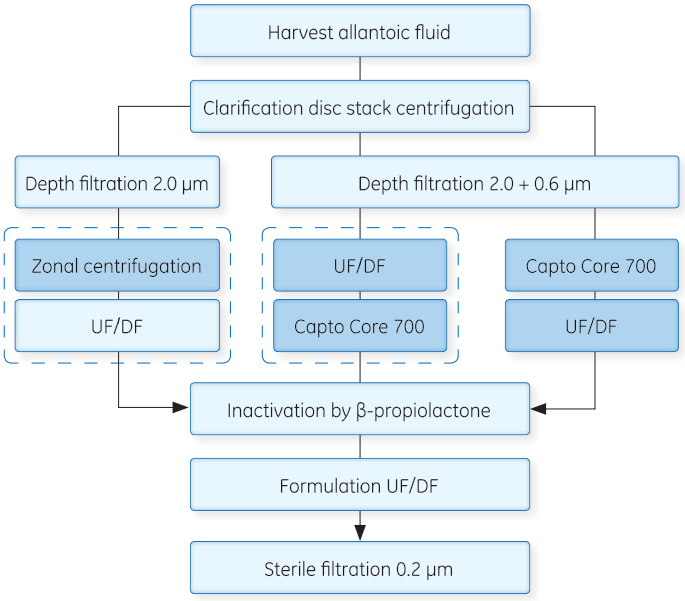



**Fig 1.** Schematic illustration of the purification processes for egg-based influenza virus. Ovalbumin removal and HA recovery in the Capto Core 700 (CC700) processes were compared with those in the Zonal UC process (marked in dark blue). The purification steps included in calculation of process economy are marked with dotted lines.

For egg-based vaccines, ovalbumin is the main impurity, corresponding to approximately 60% of the total protein content (1). Ovalbumin needs to be removed, as it can cause severe allergic reactions. According to WHO, the recommended ovalbumin content should be below 1 µg ovalbumin/vaccine dose (2).

In this work, static and dynamic binding capacities of Capto Core 700 for ovalbumin were determined. Furthermore, the performance of Capto Core 700, in terms of ovalbumin removal and HA recovery, was compared with that of zonal UC (Fig 1). The experimental work was performed in collaboration with Intravacc, an institute with a long history

in influenza vaccine product and process development. In addition, a model for calculation of process economy was designed to compare productivity and capital cost at pilot and process scales for the two purification methods.

### *Capto Core 700 chromatography media*

The Capto Core 700 medium consists of an inactive shell and a ligand-activated core. The octylamine ligands in the core of the bead are multimodal, being both hydrophobic and positively charged. The core is surrounded by an inert outer shell, consisting of cross-linked agarose. Pores in the shell allow smaller molecules ($M_r$ < 700 000) to enter and be captured in the core, while larger entities, such as virus particles, pass in the flowthrough (Fig 2).

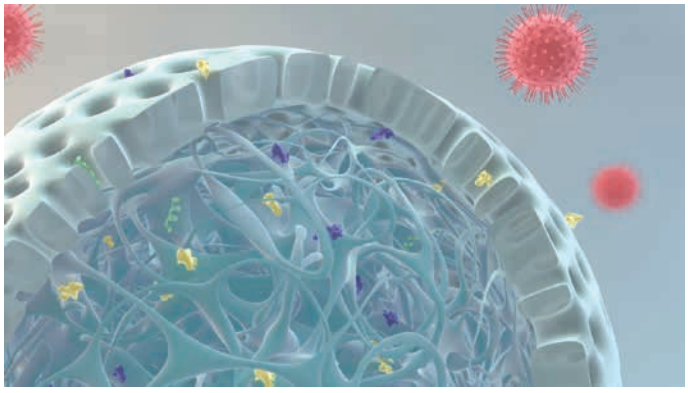


**Fig 2.** Schematic view of Capto Core 700 showing a bead with an inert shell and a ligand-containing core. Pores in the shell allow small proteins and impurities (colored green, yellow, and blue) to enter and be captured in the core, while virus particles (red) and other larger entities ($M_r$ > 700 000) pass in the flowthrough.

## Material and methods

### *Determination of static binding capacity (SBC)*

To investigate the effect of sample pH and ionic strength on protein binding, the SBC of Capto Core 700 for ovalbumin (Sigma-Aldrich Corp., St. Louis, MO, USA) was evaluated in PreDictor™ filter plates filled with 10 µL medium per well (available on demand). For ovalbumin sample preparation and for equilibration of the PreDictor plates, 20 mM phosphate, pH 6.5, 7.0, 7.5, and 8.0 as well as 20 mM Tris, pH 7.5, 8.0, and 8.5 buffers with either 150 mM or 1 M NaCl were used (Fig 3). The amount of ovalbumin recovered in the combined flowthrough and wash solution was compared with the amount of ovalbumin in the sample and the difference was stated as the SBC. All experiments were performed in triplicate (Fig 3).

### *Determination of dynamic binding capacity (DBC)*

The DBC of Capto Core 700 for ovalbumin was evaluated in duplicate, on three separate Tricorn™ 5/50 columns (column volume (CV) approximately 1 mL), using the ÄKTA™ explorer 10 system. For ovalbumin sample preparation and column equilibration, 20 mM Tris-HCl, 150 mM NaCl, pH 7.5 was used. All columns were loaded with ovalbumin (3 mg /mL) at a flow velocity of 100 cm/h, equivalent to a residence time of 3 min. DBC was determined at 10% breakthrough (DBC10%), the point where 10% of unbound ovalbumin was detected in the flowthrough.

### *Propagation of virus in hen eggs*

Pilot-scale virus inoculations (approximately 10 000 eggs) were performed with two different strains of influenza: A/Uruguay/716/2007 (H3N2) and A/Puerto Rico/8/1934 (H1N1). Each virus batch was prepared using embryonated hen eggs cultivated in 36°C and infected at day 11. The allantoic fluid was harvested 72 h post infection (approximately 100 L pooled volume).

### *Clarification of allantoic fluid*

Clarification was performed by continuous centrifugation using a disk stack separator (GEA Westfalia Separator Nederland B. V., Cuijk, The Netherlands) followed by filtration using two parallel 10 inch 2.0 µm ULTA™ Prime filter capsules. The part of the allantoic fluid intended for chromatographic experiments was additionally filtered through a 0.6 µm ULTA prime GF to protect the column from possible aggregates.

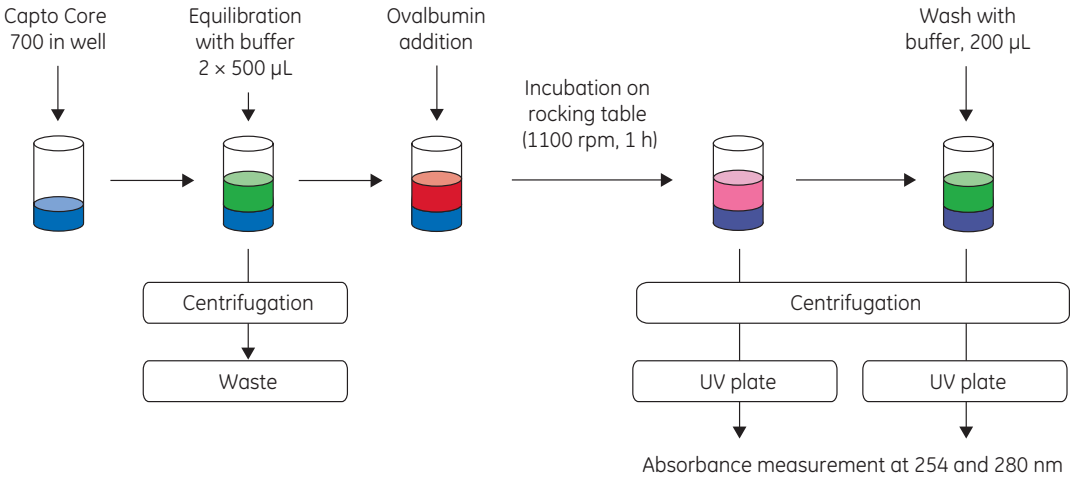



**Fig 3.** Schematic illustration of the evaluation of SBC of Capto Core 700 medium for ovalbumin in PreDictor plates.

## *Zonal UC process*

An eKII centrifuge (Alfa Wassermann, Woerden, The Netherlands) with K3rotor (3.2 L) was used for zonal UC at 20°C. A sucrose gradient was created using 0.125 M citrate buffer, pH 7.8 and a 60% sucrose solution. The clarified allantoic fluid was loaded at an initial flow rate of 4.8 L/h with a constant speed of 15 000 rpm (16 350 × g), which gradually was increased to 18 L/h and 35 000 rpm (89 000 × g) over 7 h. After centrifugation, a peristaltic pump was used to collect the virus-containing fraction at a sucrose content between 35% and 47%. In the zonal UC process, 70 L allantoic fluid was processed, resulting in a final volume of 471 mL, equivalent to a concentration factor of 149.

## *Capto Core 700 process*

### UF/DF

A hollow fiber cartridge with 0.085 $m^2$ filter area, 1 mm lumen diameter, 750 000 nominal molecular weight cut-off (NMWC) (model number UPF -750E-4X2MA) was connected to a 504U pump (Watson-Marlow Pumps Group, Cornwall, UK). The filter was run at a shear rate of 3500 $s^{-1}$ and an approximate flux of 35 L/$m^2$/h. The process material was first concentrated 20× and then 10-fold diafiltered for buffer exchange to phosphate buffered saline (PBS). The filter load was 88 L/$m^2$ for the A/Uruguay/716/2007 (H3N2) strain and 112 L/$m^2$ for the A/Puerto Rico/8/1934 (H1N1) strain.

### Capto Core 700 chromatography

For chromatography using Capto Core 700 medium, a HiScreen™ column (4.7 mL CV, 10 cm bed height) was used in the experiments including influenza strain A/Uruguay/716/2007 (H3N2), whereas a HiScale™ 16 column (15 mL CV, 7.5 cm bed height) was used in the experiments including the A/Puerto Rico/8/1934 (H1N1) strain. Both columns were operated using the ÄKTA explorer 10 system. Columns were equilibrated with PBS. A flow velocity corresponding to 6 min residence time was selected. Sample (10 CV) from UF/DF was loaded on the columns and the flowthrough was collected.

In addition, a reversed Capto Core 700 process was performed by loading 12.5 CV of clarified allantoic fluid on a Capto Core 700 HiScale 50/20 column (200 mL CV, 10 cm bed height) before the UF/DF procedure (performed as above).

Between runs, the columns were washed with PBS followed by cleaning in place (CIP) with 1 M NaOH + 27% 1-propanol. The total contact time for CIP was 30 min.

## *Analytical methods*

### Haemagglutinin (HA)

HA concentration was determined by a single-radial immunodiffusion (SRID) assay according to the method described by Wood *et al.* (3). All reagents were supplied by NIBSC, Potters Bar, London, UK.

### SDS-PAGE analysis

SDS-PAGE analysis was performed according to the method described by Harvey *et al.* (4). Virus was inactivated by β-propiolactone treatment. Virus proteins were deglycosylated by incubation with PNGase F enzyme (New England Biolabs, Ipswich, USA) at 37°C overnight. SDS-PAGE analysis of 5 µg of sample, taken before and after deglycosylation, was performed using the Gold precast gel system (Lonza, Basel, Switzerland). All samples were mixed with water and loading dye and denatured in the presence of dithiothreitol by heating to 100°C for 5 min prior to loading on the gel. Gel separation was performed at 140 V for 1 h. The gels were stained using the Colloidal Blue Stain Kit (Invitrogen, Bleiswijk, The Netherlands) and scanned using an in-gel imaging system (Isogen, De Meern, The Netherlands). Gel spots from each major band were excised for protein identification by liquid chromatography-mass spectrometry (LC-MS) analysis. The gel spots were destained with acetonitrile in ammonium bicarbonate prior to in-gel tryptic digestion overnight. The dried digestion products were subjected to nano-scale LC-MS as described by Meiring *et al.* (5) and the acquired data was compared against the protein database UniprotKB/SwissProt (http://www.uniprot.org).

### Ovalbumin

Ovalbumin concentration was measured using a commercially available ELISA kit (Seramun Diagnostica, Wolzig, Germany).

# Results and discussion

## *SBC of Capto Core 700*

The SBC of Capto Core 700 for ovalbumin was reduced only to a minor extent by increasing the pH and conductivity (Fig 4). Increasing the pH of the phosphate buffer from 6.5 to 8.0 or of the Tris buffer from 7.5 to 8.5 resulted in a SBC reduction to 88% of the maximum capacity. The SBC was shown to exceed 16 mg ovalbumin/mL medium for all conditions tested, which in many cases can eliminate the need for sample adjustment (pH or conductivity) prior to load.

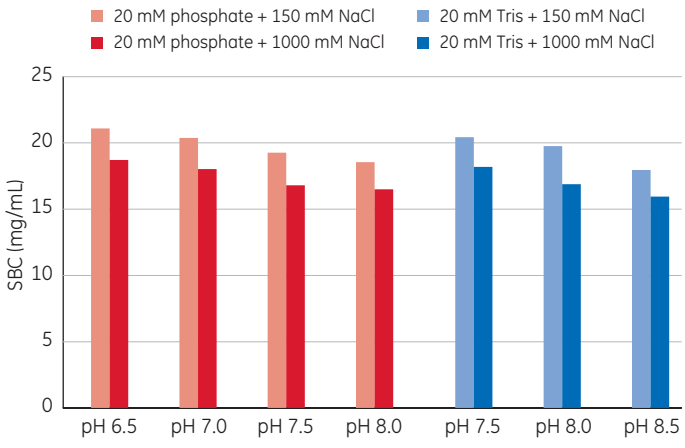



**Fig 4.** SBC of Capto Core 700 for ovalbumin in different pH and conductivities.

## DBC of Capto Core 700

The DBC of Capto Core 700 at 10% breakthrough (DBC10%) and 3 min residence time was 14.1 mg ovalbumin/mL medium in duplicate runs on three separate columns (Table 1). The results are in agreement with the SBC data, indicating strong binding of ovalbumin to the Capto Core 700 medium.

**Table 1.** DBC10% of Capto Core 700 for ovalbumin (average of duplicate runs performed on three separate columns)

| Experiment | DBC (mg/mL) |
|---|---|
| 1 | 12.6 |
| 2 | 14.8 |
| 3 | 14.9 |
| average | 14.1 |

## HA recovery in pilot-scale experiments

HA recovery (%) for the zonal UC process was 80%. However, for the Capto Core 700 process, comprising both the Capto Core 700 chromatography and the UF/DF step, the HA recovery was between 57% and 69% (Table 2).

**Table 2.** Comparison of results from influenza virus purification using zonal UC and Capto Core 700 (average of duplicate runs)

| A/Uruguay/716/2007 (H3N2) | Zonal UC | UF/DF + Capto Core 700 | Capto Core 700 + UF/DF |
|---|---|---|---|
| HA recovery (%) | 80* | 57 | 61 |
| Ovalbumin log reduction factor | 4.2 | 4.3 | 3.9 |
| Ovalbumin (ng)/dose (45 µg HA) | 12 | 11 | 25 |
| **A/Puerto Rico/8/1934 (H1N1)** | | | |
| HA recovery (%) | 80* | 66 | 69 |
| Ovalbumin log reduction factor | 4.1 | 4.0 | 4.3 |
| Ovalbumin (ng)/dose (45 µg HA) | 59 | 82 | 54 |

* The HA amount obtained in the SRID assay after zonal UC was estimated to 80% of the amount in the clarified harvest.

## Ovalbumin removal in pilot-scale experiments

Ovalbumin was reduced 12 000 times (log reduction factor 4.1) both by the zonal UC process and the Capto Core 700 process. The results were similar for both influenza strains investigated.

Figure 5 shows ovalbumin removal in the Capto Core 700 process for A/Puerto Rico/8/1934 (H1N1), when performing UF/DF prior to the Capto Core 700 step. Approximately 80% of the ovalbumin was removed by UF/DF. The Capto Core 700 step removed an additional 99.9% of the remaining ovalbumin, giving less than 0.015% ovalbumin in the final sample.

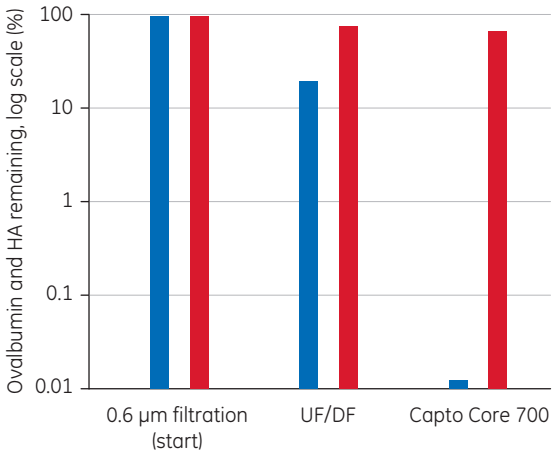



**Fig 5.** Ovalbumin removal from clarified allantoic fluid, containing the A/Puerto Rico/8/1934 (H1N1) influenza strain, by UF/DF followed by a Capto Core 700 chromatography step.

In the zonal UC process, the ovalbumin content was reduced from an initial concentration of 63 500 ng/mL to 610 ng/mL for the A/Uruguay/716/2007 (H3N2) strain, resulting in an amount of ovalbumin per dose (45 µg HA) of 12 ng. For the A/Puerto Rico/8/1934 (H1N1) strain, the amount of ovalbumin per dose was 59 ng. These results are significantly lower than the WHO target of ≤ 1000 ng ovalbumin per 45 µg HA (2).

In the Core 700 process (UF/DF followed by chromatography), ovalbumin was reduced from 51 200 ng/mL to 70 ng/mL. The resulting average amount of ovalbumin per dose was 11 ng, which is similar to the results achieved for the A/Uruguay/716/2007 (H3N2) strain using zonal centrifugation. For the A/Puerto Rico/8/1934 (H1N1) strain, the ovalbumin amount per dose was 82 ng. When the Capto Core 700 process was performed in the reverse order (chromatography followed by UF/DF), the ovalbumin amount per dose was lower, approximately 54 ng for A/Puerto Rico/8/1934 (H1N1) and 25 ng for A/Uruguay/716/2007 (H3N2).

For A/Puerto Rico/8/1934 (H1N1), the ovalbumin removal was less efficient when concentrating the allantoic fluid before loading onto the chromatography column. This outcome might be attributed to impurity aggregation caused by concentration in the UF/DF step, which might lead to less efficient impurity removal.

As summarized in Table 2, performing UF/DF prior to chromatography improves ovalbumin removal for A/Uruguay/716/2007 (H3N2). For A/Puerto Rico/8/1934 (H1N1), ovalbumin removal was more efficient in the reversed process, performing chromatography prior to UF/DF. For both influenza strains, the most efficient ovalbumin removal obtained with the Capto Core 700 process are comparable with the results from the zonal UC process. A chromatogram showing ovalbumin removal in the Capto Core 700 process for A/Uruguay/716/2007 (H3N2) is displayed in Figure 6.

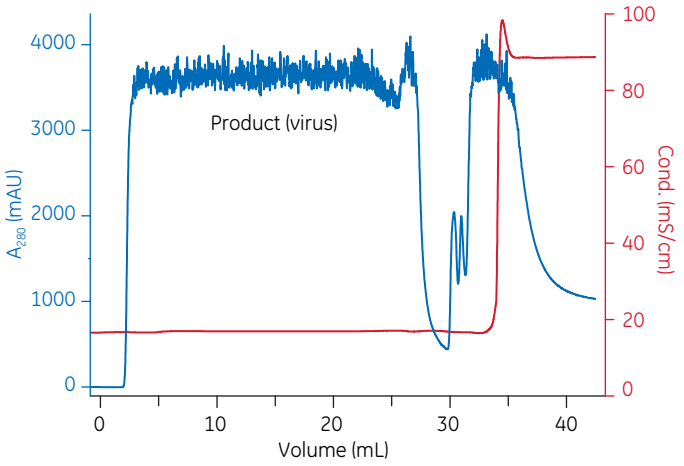
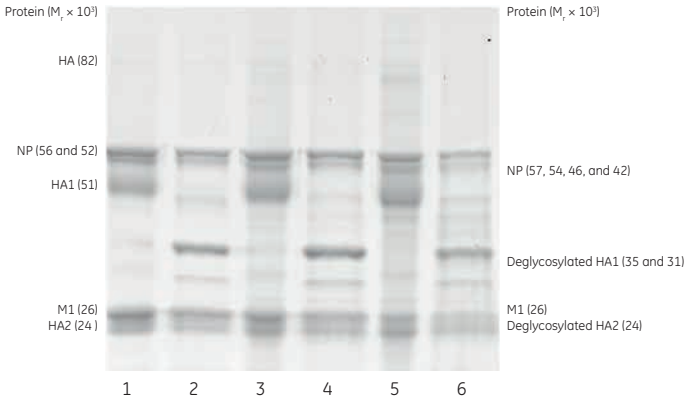



**Fig 6.** Impurity removal for A/Uruguay/716/2007 (H3N2) using Capto Core 700 HiScreen column. Virus particles passed in the flowthrough, while ovalbumin and other smaller impurities were captured in the bead core and subsequently eluted in the CIP procedure.

## SDS-PAGE

SDS-PAGE analysis gives a qualitative picture of proteins present in a sample. Glycosylated proteins generate smearing bands in SDS-PAGE gel analysis. As HA, like many other virus proteins, is glycosylated, samples were subjected to deglycosylation prior to SDS-PAGE analysis to obtain more distinct gel bands. Analysis by SDS-PAGE revealed an almost identical banding pattern when comparing material derived from the zonal UC and Capto Core 700 processes, indicating a similar virus purity profile for both processes (Fig 7).




Lane 1: zonal UC
Lane 2: zonal UC (PNGase F treatment)
Lane 3: UF/DF + Capto Core 700
Lane 4: UF/DF + Capto Core 700 (PNGase F treatment)
Lane 5: Capto Core 700 + UF/DF
Lane 6: Capto Core 700 + UF/DF (PNGase F treatment)

**Fig 7.** SDS-PAGE analysis of whole, inactivated A/Puerto Rico/8/1934 (H1N1) virus concentrates, before and after deglycosylation. Weak bands corresponding to neuraminidase (NA) and nonstructural proteins (NSP) were also detected in each lane (not indicated). Hemagglutinin = HA, hemagglutinin 1 = HA1, hemagglutinin 2 = HA2, nucleoproteins = NP, matrix protein = M1.

## Process economic model

To compare costs for ovalbumin removal using Capto Core 700 versus zonal UC, a side-by-side comparison of the different techniques was made. The calculations compare hardware investments, process time, and costs for disposables, labor, and buffers. The results are stated as costs per dose, cost per batch, and doses/process time.

It was assumed that similar process steps were required before and after the ovalbumin removal steps included in the comparison. The calculation assumes virus production in 10 000, 100 000, and 300 000 eggs, equivalent with 100 L, 1000 L, and 3000 L harvested allantoic fluid, respectively. Based on the obtained HA recovery shown in this work using either the zonal UC or the Capto Core 700 process, the recoveries in the process economic model were estimated to 90% after clarification, 80% after the Capto Core 700 or the zonal UC step, and 80% after UF/DF (6) (Fig 8).

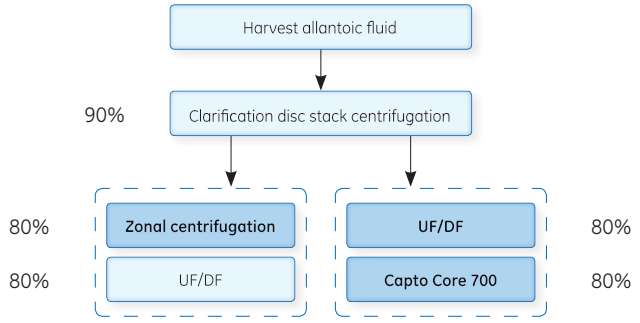



**Fig 8.** Estimated recoveries for the purification steps included in the process economic model.

Costs for equipment and consumables, including filters, buffer bags, chromatography media, columns, filter- and chromatography skids, were all based on pricing of GE Healthcare products. Single-use bags were selected for sample and buffer storage up to 500 L. For larger volumes, stainless steel vessels were selected. Facility-related costs, QC/QA costs, and system validation costs were not included. Additionally, it was not considered that the purified influenza virus will have different concentrations after the two purification procedures, which would impact equipment size further down the process until the final formulation step. General assumptions and costs are summarized in Table 3. The model gives an indication of advantages and disadvantages of the different purification techniques.

**Table 3.** General assumptions and process costs

| General assumptions | | | |
|---|---|---|---|
| Annual production | 80 batches/year | | |
| Buffer storage | single use < 500 L<br>stainless steel > 500 L | | |
| Material | influenza virus from allantoic fluid, 3 µg HA/mL | | |
| Dose | 15 µg/strain/dose, pandemic situation | | |
| Buffer cost | 2 USD/L (incl. buffers, cleaning solutions) | | |
| Labor cost/person | 100 USD/h (incl. hands-on preparations and process monitoring) | | |
| Depreciation | 10 years | | |
| Interest rate | 10% | | |
| **UF/DF** | | | |
| Filter membrane | Hollow fiber 500 C | | |
| Reuse of fiber | 10 times | | |
| Flux | 25 L/m$^2$/h | | |
| Shear rate | 5000 s$^{-1}$ | | |
| Filter load | ~ 100 L/m$^2$ | | |
| **Capto Core 700** | | | |
| Investigated scale (L) | 100 | 1000 | 3000 |
| Process time (h) | 11 to 13 | 11 to 13 | 11 to 13 |
| UF/DF system | UniFlux™ 30 | UniFlux 400 | UniFlux 400 |
| Capto Core 700 volume | 0.2 L | 2 L | 6 L |
| Columns | AxiChrom™ 50/300 column | AxiChrom 100/300 column | AxiChrom 100/300 column |
| System | ÄKTApilot™ system | ÄKTAprocess™ system | ÄKTAprocess system |
| Equilibration | 7* CV | | |
| Sample load | 11 mg ovalbumin/mL medium (80% of ovalbumin† DBC) | | |
| Sample residence time | 4 min | | |
| Wash | 5 CV | | |
| CIP | 10* CV | | |
| Reuse of chromatography medium | 20 times | | |
| **Zonal centrifugation** | | | |
| Investigated scales (L) | 100 | 1000 | 3000 |
| Process time (h) | 24 | 30 | 49 |
| Ultracentrifuge | eKII centrifuge (Alfa Wassermann) with rotor K3 (3.2 L) | | |
| No. of ultracentrifuges | 1 | 5 | 5 |
| No. of cycles/UC | 1 | 1 | 3 |
| Load/run | 100 L | 200 L | 200 L |
| Load flow rate | 25 L/h | 25 L/h | 25 L/h |
| UF/DF system | QuixStand™<br>bench top system | UniFlux 10 | UniFlux 10 |

* Required volumes of equilibration buffer and CIP solution depend on buffers/solution type and must be investigated for each specific case and feed. Volumes could be significantly reduced following an optimization of the process.

† It was assumed that ovalbumin contributes to approximately 60% of the total protein content (1) and that 80% of the ovalbumin from the clarified harvest was removed in the UF/DF step prior to the chromatography step.

### *Process economic outcome*

As shown in Figures 9 to 11, the total operational cost/batch is lower for the zonal UC process than for the Capto Core 700 process at 100 L pilot scale. At 1000 L and 3000 L scales, however, when multiple ultracentrifuges are required for zonal UC, the total operational cost is lower for the Capto Core 700 process than for the zonal UC process. The operational cost/dose is lower for the Capto Core 700 process at all scales.

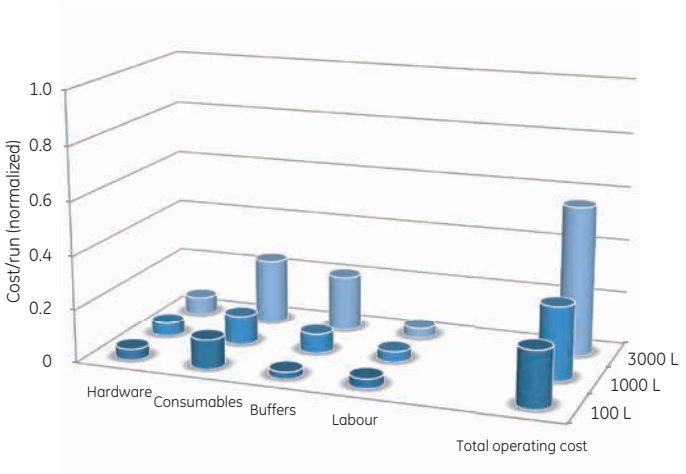



**Fig 9.** Operational costs (normalized) at different scales for the combination of UF/DF and Capto Core 700 chromatography.

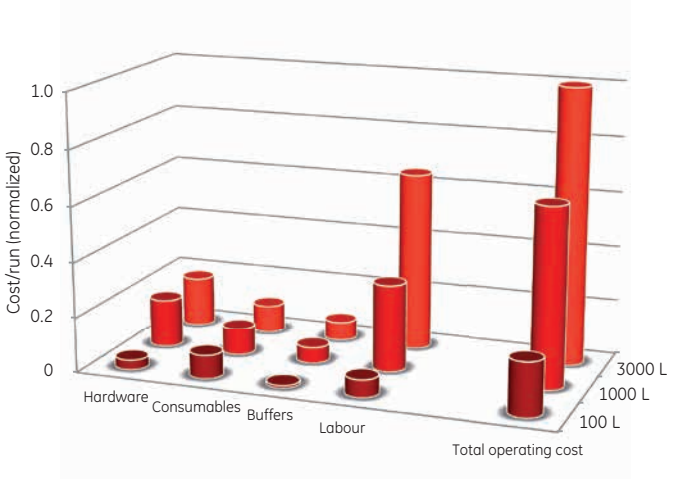



**Fig 10.** Operational costs (normalized) at different scales for the combination of zonal UC and UF/DF.

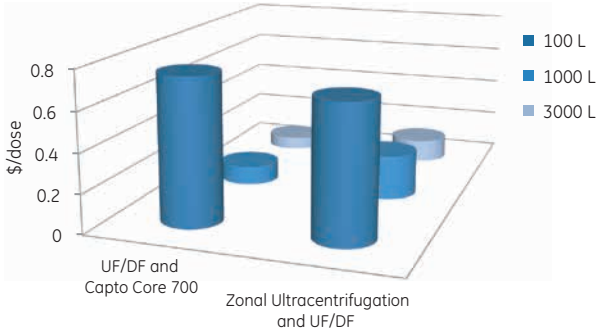



**Fig 11** Operational cost (USD)/dose for the Capto Core 700 and the zonal UC processes at 100 L, 1000 L, and 3000 L scales.

As shown in Figure 12, the productivity of the Capto Core 700 process is twice as high for the 100 L scale and up to four times higher at 3000 L scale, as compared with the zonal UC process.

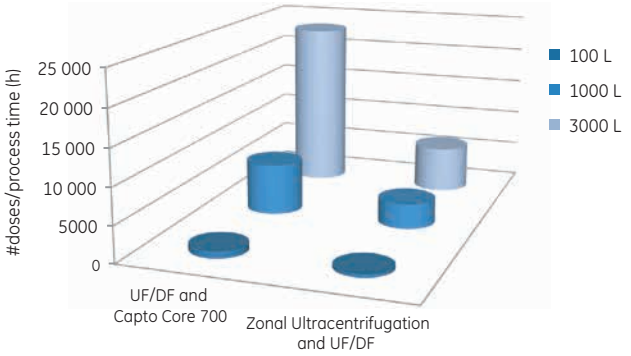



**Fig 12.** Productivity stated as the number of doses/process time (h) for Capto Core 700 and zonal UC processes at 100 L, 1000 L, and 3000 L scales.

The process time is 11 to 13 h for the Capto Core 700 process regardless of process scale. Substantially longer process time is required for the zonal UC process, which is even more evident at larger scales. Process time for the zonal UC process at the 100 L, 1000 L, and 3000 L scales are 24, 30, and 49 h, respectively. Accordingly, the labor cost is substantially higher for the zonal UC process than for the Capto Core 700 process.

In summary, the productivity is higher and operational cost/dose is lower for the Capto Core 700 process at all scales. At process scale (3000 L), the Capto Core 700 process can deliver four times as many doses/h at half the operational cost.

## Conclusion

The main focus of this study was to investigate the performance of Capto Core 700 chromatography medium as ovalbumin scavenger in the purification of egg-based influenza virus. The result was compared with the traditionally used zonal UC technique. Both methods generated a virus purity that meets regulatory requirements. SDS-PAGE analysis shows an almost identical banding pattern when comparing samples from Capto Core 700 and zonal UC process steps, indicating a similar impurity removal.

Capto Core 700 exhibits high protein binding capacity over wide pH and conductivity ranges and can thus be used at different stages of a purification process without the need of sample conditioning prior to the run. As shown in this work, the Capto Core 700 step can be incorporated before or after the UF/DF steps with similar results. However, by reducing the sample volume in a UF/DF step prior to the chromatography step, less Capto Core 700 medium is required. Running unconcentrated feed on the Capto Core 700 column, on the other hand, can improve impurity removal. This strategy can, for example, be used in cases were the impurities tend to aggregate when concentrated during UF/DF, leading to less efficient purification in the subsequent chromatographic step.

The Capto Core 700 process can be a viable alternative to zonal UC for ovalbumin removal and can offer substantial cost benefits at larger production scales where time and productivity are key considerations. Capto Core 700 exhibits high loading capacity and the purification process can be performed at high flow rates. The combination of these two factors has a strong influence on the overall process economy. A Capto Core 700 step in combination with UF/DF can deliver twice as many doses per process hour at a 1000 L process scale and a four-fold number of doses per process hour at 3000 L scale compared with zonal UC in combination with UF/DF.

As the combination of Capto Core 700 and UF/DF is easily implemented and scaled, this process for ovalbumin removal could be an alternative to take into consideration for actors interested in expanding domestic influenza virus production capacity for rapid response to pandemic outbreaks.

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## Ordering information

| Product | Size | Code number |
|---|---|---|
| Capto Core 700 | 25 mL | 17-5481-01 |
| Capto Core 700 | 100 mL | 17-5481-02 |
| Capto Core 700 | 1 L | 17-5481-03 |
| Capto Core 700 | 5 L | 17-5481-04 |

| Prepacked columns | Size | Code number |
|---|---|---|
| HiTrap Capto Core 700 | 5 × 1 mL | 17-5481-51 |
| HiScreen Capto Core 700 | 1 × 4.7 mL | 17-5481-15 |

| Related literature | Code number |
|---|---|
| Capto Core 700, data file | 28-9983-07 |
| The use of Capto Core 700 and Capto Q ImpRes in the purification of human papilloma virus like particles, application note | 29-0983-01 |
| Purification of influenza A/H1N1 using multimodal Capto™ Core 700, application note | 29-0003-34 |


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

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





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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