Building a Fully Single-Use Process: High Productivity Protein A Membrane Devices that Complement Disposable Upstream Technology

AGC Biologics

GORE

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Abstract

An intensified and fully single-use downstream operation was demonstrated to process a monoclonal antibody cell culture harvest at a manufacturing scale. A focus of the study was the first published demonstration of Protein A membrane capture chromatography using commercial, GMP-compliant devices with sufficient productivity to enable fully utilized, single-use purification at the 2000 L bioreactor scale. Critical quality attributes established with incumbent resin purification were met and scaling from lab scale devices was demonstrated. The results of the study were combined with previously published data to show the potential for high productivity affinity capture sufficient to cover up to 10 g/L titers at the 2000 L scale.

Introduction

Single-use technologies are benefiting the downstream processing of antibody-based therapeutics by reducing labor intensive cleaning processes, decreasing product changeover times in multi-product facilities, reducing cross-contamination risks and minimizing bioburden. For example, single-use membrane-based Ion Exchange Chromatography (IEX) columns have demonstrated high flow rate, high-capacity performance for improved polishing operations over traditional resin columns.[1,2] Additionally, single-use Tangential Flow Filtration (TFF) systems have demonstrated high yield, economical, low-risk buffer exchange and product concentration over incumbent multi-use TFF systems.[3]

The affinity capture step in downstream processing has been challenging to convert to a high productivity, fully utilized single-use operation. Protein A affinity chromatography has long been established as the primary antibody capture step in downstream purification. Traditionally, the Protein A binding ligand has been immobilized onto the surface of highly porous resin beads. These resin beads are then packed into columns that demonstrate high capacities with highly selective binding and long cycling lifetimes. However, mass transport limitations governed by operating pressure constraints result in oversized and underutilized columns.[4] Specifically, process time limitations dictate large bed volume columns that can only be cycled to a fraction of their lifetime. This limitation dictates either disposing of underused resin or the process of expensive storage, cleaning and revalidation operations. Conversely, membrane-based Protein A chromatography columns demonstrate true single-use capability by enabling significantly higher productivity over packed bed columns.[5,6] Productivity is expressed as the mass of antibody, per unit bed volume, and per unit time. Sufficiently high productivities enable smaller bed volume columns to be cycled to full column lifetime across time periods sufficient to maintain product quality for a given bioreactor batch.

Ideally, the performance characteristics of membrane chromatography columns should be capable and scalable from laboratory scale (e.g., drug discovery and process development) through manufacturing scale. With many therapies being developed for more targeted and smaller populations, more molecules are being manufactured in smaller batch sizes. The 2000 L bioreactor size is often ideal for manufacturing in multi-product facilities, considering the flexibility of fast turnaround times and the ability to scale out if needed.

One example of membrane-based Protein A chromatography is the GORE® Protein Capture Devices with Protein A. These devices incorporate a composite membrane enabling high binding capacity at fast flow rates. These devices are currently commercialized in pre-packed formats from 1 mL to 1 Liter bed volumes with the potential to parallel manifold into larger sizes.

The objective of this study was to demonstrate the capability for an intensified, fully single-use downstream processing of a fed-batch cell culture harvest producing a representative monoclonal antibody (mAb) at industrial scale. The primary focus is on demonstrating the integrated performance of parallel manifolded, commercially available Gore 1 Liter Devices, resulting in 2 liters of total bed volume. Specifically, the aim is to culture approximately 500 L of antibody harvest and purify said harvest adequately demonstrating the feasibility of a full 2000 L batch. Successful demonstration of the capture step includes matching or exceeding critical quality attributes established from an appropriate Protein A resin column control purifying the same cell culture harvest.

Experimental

Figure 1 below diagrams the process flow for the 500 L study. Details of each unit operation follow.

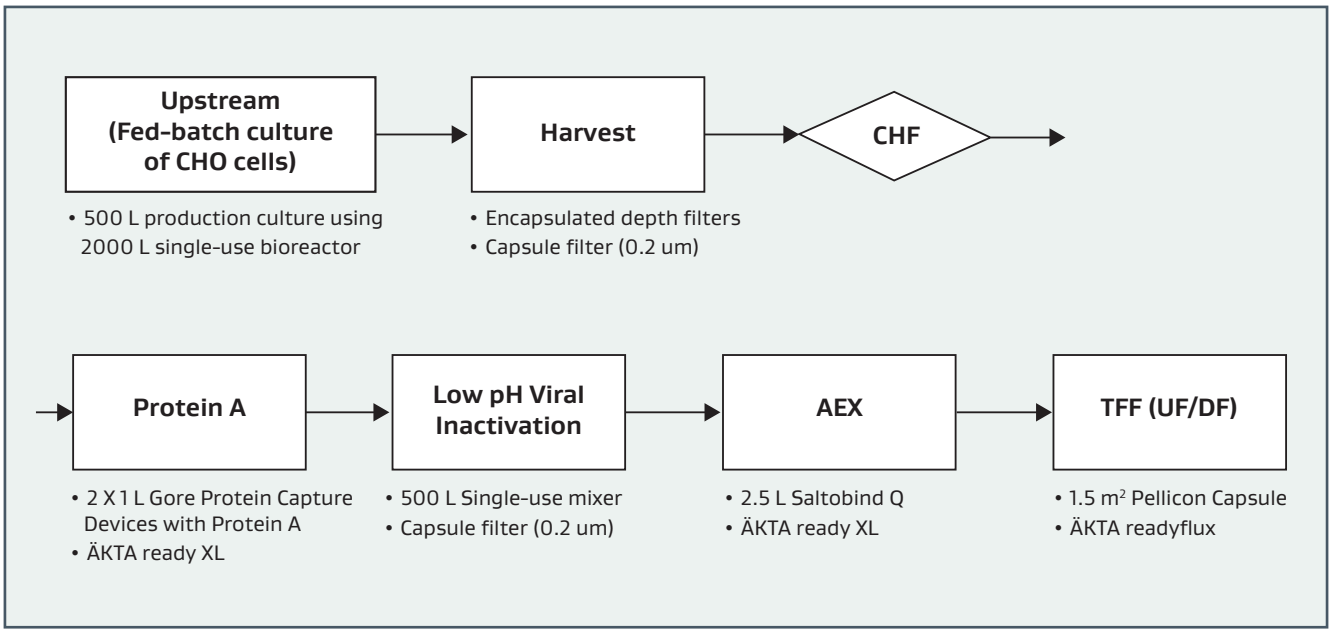

Fig. 1. Process flow diagram for the fully single-use mAb production process

Clarified Harvest

A target volume of approximately 500 L of a monoclonal antibody (mAb) expressing CHO cell culture harvest was processed in an N-stage 2000 L bioreactor. This harvest was then clarified using a two-stage cartridge depth filter followed by a 0.2 µm capsule sterile filtration. In order to establish benchmark performance targets for the Protein A capture step, this same harvest lot was aliquoted for separate purification using lab scale columns.

Protein A Affinity Capture – Manufacturing Scale

Affinity capture was performed on a Cytiva® ÄKTA ready™ XL chromatography system incorporating a single-use 3/4" flow kit. Two commercially available, GMP-compliant, Gore 1 L Device (PROA303) were parallel manifolded together and integrated into the chromatography system as shown in Figure 2. In order to reduce buffer usage and improve chromatographic transitions, the flow kit air trap was bypassed during use in favor of the integrated air trap system that is built into the Gore devices (Gore Document PB10126).

Fig. 2. Pictures of parallel manifolded 2 X 1 Liter Gore Devices with integration into chromatography system.

The cycling protocols used for cycles 1-10 and 11-19, respectively, are summarized in Tables 1 and 2.

Table 1. Chromatography Method for Gore device cycling with 2 minute CIP.

Step	Buffer	Step Duration (MV)	Residence Time (min)	StepTime (min)
Equilibration	Tris-HCl buffer	3.00	0.20	0.60
Load	Cell Culture Harvest Fluid	11.60	0.40	4.66
Wash 1	Tris-HCl Buffer	1.43	0.40	0.57
Wash 2	Tris-HCl + NaCl buffer	3.00	0.20	0.60
Pre-elution wash	Tris-HCl buffer	3.00	0.20	0.60
Elution	Sodium Acetate buffer	3.75	0.20	0.75
Clean in Place (CIP)	0.1 N NaOH	5.00	0.40	2.00
Re-Equilibration	Tris-HCl Buffer	3.00	0.20	0.60
Total time (per cycle)				10.38

Table 2. Chromatography Method for Gore device cycling with 1.2 minute CIP.

Step	Buffer	Step Duration (MV)	Residence Time (min)	StepTime (min)
Equilibration	Tris-HCl buffer	3.00	0.20	0.60
Load	CHF[*1]	11.60	0.40	4.66
Wash 1	Tris-HCl Buffer	1.43	0.40	0.57
Wash 2	Tris-HCl + NaCl buffer	3.00	0.20	0.60
Pre-elution wash	Tris-HCl buffer	3.00	0.20	0.60
Elution	Sodium Acetate buffer	3.75	0.20	0.75
Clean in Place (CIP)	0.1N NaOH	3.00	0.40	1.20
Re-Equilibration	Tris-HCl Buffer	3.00	0.20	0.60
Total time (per cycle)				9.58

The difference in protocols between Tables 1 and 2 reflect a reduction in the Clean in Place (CIP) contact time as it was desired to evaluate the impact of this phase on performance to increase productivity. The load volume reflects an estimated Dynamic Binding Capacity at 10% Breakthrough ($DBC_{10\%}$) of 25 g/L at 24 seconds residence time (SRT) based on prior work with this molecule using a 1 mL Gore Device; loading was performed to 80% of $DBC_{10\%}$ at 24SRT. The elution fractions were triggered at 50 mAU A280 limits for both elution start and end. Elution fractions were collected in 20 L single-use bags which were then aliquoted for analysis.

Protein A Affinity Capture – Lab Scale

In order to establish benchmark critical quality attribute targets for the Protein A capture step, harvest aliquots were purified using a 5 mL HiTrap MabSelect SuRe™ Protein A resin column (Cytiva p/n 11003493). This column was cycled four times using the same buffer scheme and cycling steps as the Gore device except that all steps were performed at a 3-minute residence time and loading DBC was set to 30 mg/mL, based on prior work with this molecule and resin (AGC Biologics unpublished data). The cycle time was 133.4 minutes.

In order to have a lab scale membrane device reference, a 3.5 mL GORE Device (PROA102) was cycled 10 times using the protocol in Table 2.

The above lab scale purification was performed on an ÄKTA avant 25 chromatography system.

Low pH Viral Inactivation, Neutralization and Filtration

Elution fractions were pooled into a 200 L single-use bag with integrated magnetic mixer (Pall, 6404). The pool pH was lowered and held for a prescribed time for Viral Inactivation (VI). After the hold, the VI pool was titrated back to pH for anion exchange chromatography. The neutralized VI pool was then filtered through capsule filters incorporating a sterile filtration element.

Anion Exchange Chromatography

The filtered elution volume was further purified using a single-use Sartobind® Q Jumbo 2.5 L membrane anion exchange column (Sartorius p/n 96IEXQ42D3NSS) in flow-through mode. Note that previous work demonstrated that this chromatography step was sufficient to meet quality goals and that further polishing (e.g., Cation Exchange Chromatography) was not necessary (AGC Biologics unpublished data).

Ultrafiltration/Diafiltration

Desired drug substance concentration and formulation buffer exchange was performed using an ÄKTA readyflux™ tangential flow filtration system incorporating single-use Pellicon® capsules with a 1.5 m^2 Ultracel® 30 kDa Membrane (Millipore Sigma p/n PCC030C15C).

Analytical Characterization of Downstream Steps

- Cell culture harvest mAb concentration was quantified with an Octet® RED 96e (FortéBio) using Protein A Dip and Read Biosensors. Elution mAb concentrations were measured with a NanoDrop™ One (Thermo Fisher Scientific).
- Product-related impurities were quantified using HPLC Size Exclusion Chromatography (SEC) on an Agilent 1100 platform. Products were isocratically separated at a 0.3 ml/min flow rate on a TSKgel± SuperSW mAB HTP column coupled with a Diode Array Detector. Peaks were analyzed to quantify percent of high and low molecular weight species in relation to the target mAb main peak.
- Host Cell Proteins (HCP) were quantified using ELISA (Cygnus kit #F550-1 with ProteinSimple Ella™ cartridges) following manufacturer protocols. HCP concentrations were normalized to mAb concentration and expressed as ng/mg (ppm). Log Reduction Value (LRV) was subsequently determined in relation to cell culture harvest HCP values.
- Leached Protein A was quantified using a Protein A ELISA kit from Repligen Bioprocessing (p/n 9000-1). The ELISA was performed using the “Dilute and Go” extraction according to the manufacturer’s instructions. Concentrations were normalized to mAb concentrations and LRV’s calculated from cell culture harvest values.
- Host-cell DNA were quantified using qPCR. Host-cell DNA concentration were normalized to mAb concentration as pg/mg and removal efficiencies at each chromatography step were evaluated by Log Reduction Value (LRV).

Results

Harvest

The target 500 L of cell culture harvest was successfully grown and clarified using a 2000 L single-use bioreactor platform. The target mAb titer was measured to be 1.72 g/L. The starting cell culture harvest HCP concentration was measured to be 160,187 ppm.

Manufacturing Scale Protein A Capture

The 2 L Gore device was used to successfully purify approximately 441 L of the clarified cell culture harvest over a total of 19 cycles. Using the cycling protocols listed in Tables 1 and 2, unyielded productivities were calculated to be 123 g/L/h over cycles 1-10 and 133 g/L/h over cycles 11-19.

Figure 3 overlays the UV280 chromatogram traces for the 19 cycles.

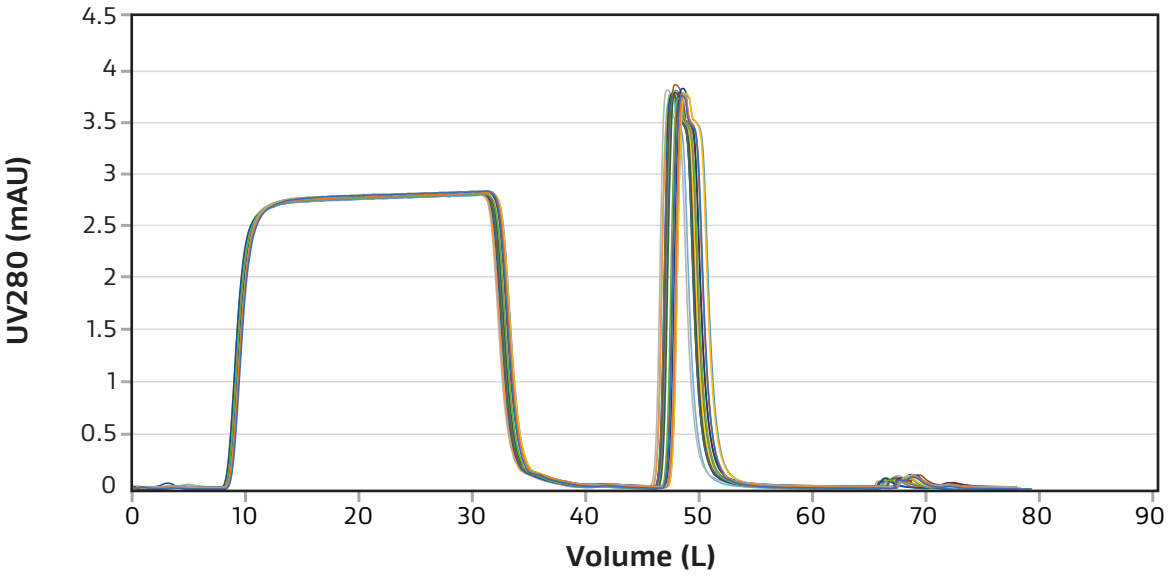

Figure 3. Ultraviolet absorbance signal (A280) overlays of the 19 cycles peformed on the Gore 2L device.

The chromatograms indicate acceptable phase transitions and consistent performance over the 19 cycles. The spikes in the elution peaks may be related to detector saturation limits.

Figure 4 exhibits delta column pressure traces over the 19 cycles for both the equilibration step and the elution step (where the highest cycle pressures were observed).

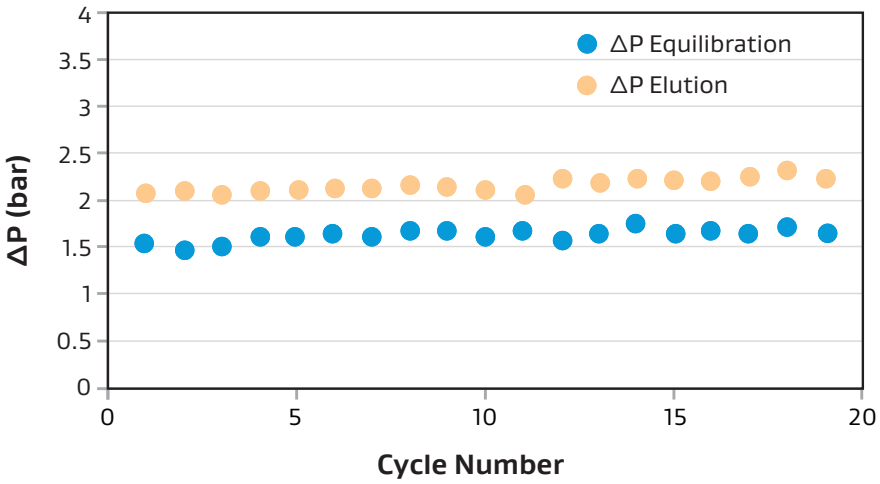

Figure 4. Column pressure drop traces for the Gore 2 L device measured at equilibration as well as peak pressure drop at measured at elution.

All pressure data were well within 4 bar system limits. The relatively flat slopes suggest minimal column fouling occuring during the course of cycling. Also, the reduction in CIP contact time at cycle 11 did not appear to significantly impact pressure rise.

Figure 5 shows elution yields, as calculated from load titer and elution concentration data.

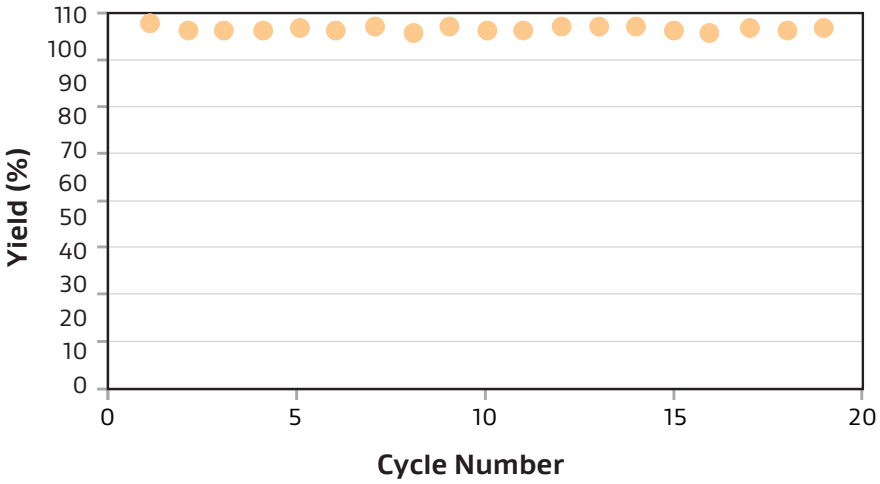

Figure 5. Elution yields of the mAb measured over the 19 cycles of the Gore 2 L device.

Figure 5 suggests consistent yields over the course of cycling. Calculated yields over 100% are likely a measurement artifact of the two different analytical methods used to determine product concentration in purified eluate vs. clarified harvest fluid.

Figure 6 shows elution volume data over the course of cycling including both collected volume as triggered by 50 mAU triggers as well as calculated elution volumes from chromatograms using 100 mAU triggers.

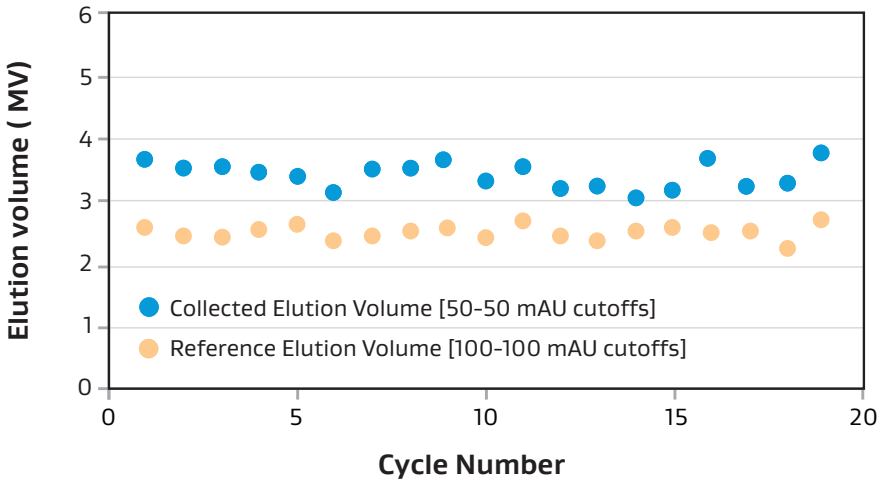

Figure 6. Elution volumes for the Gore 2L device. Collected elution volumes reflect measured volumes in elution bags as triggered by 50 mAU triggers in the cycling protocols. The 100-100 mAU reference elution volumes are calculated based on chromatogram elution widths and membrane volume.

The data in Figure 6 indicate consistent and sharp elution volume performance over the course of cycling. The 100-100 mAU cutoff volumes provide a reference to compare preference for maximum mAb capture vs. maximum elution mAb concentration.

Figure 7 shows HCP LRV values as a function of harvest cycle.

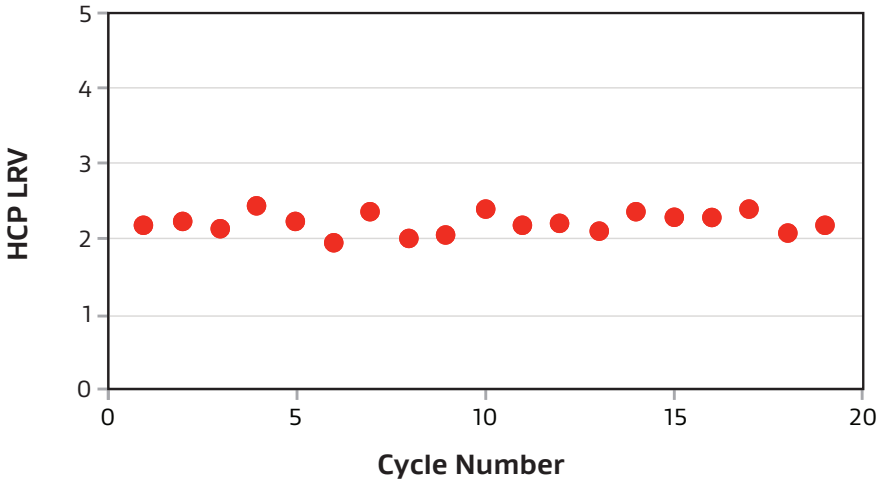

Figure 7. Calculated Host Cell Protein Log Reduction Values in the Gore 2L device elutions over the course of 19 cycles.

The data in Figure 7 suggest high and consistent HCP reduction with an average of a 2.22 LRV.

Figure 8 shows leached Protein A concentration in parts per million (ng/mg-mAb) as a function of harvest cycle.

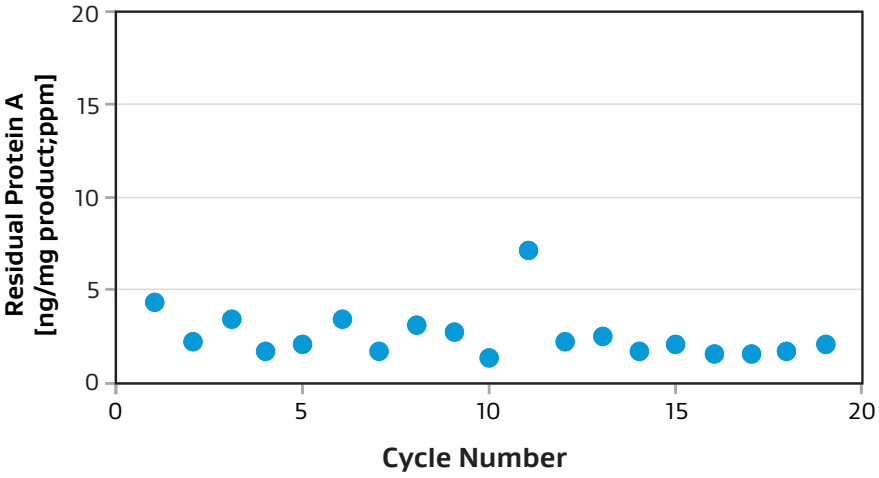

Figure 8. Leached Protein A concentrations measured in the elutions from the Gore 2L device over the course of 19 cycles.

The data in Figure 8 suggest consistently low leached Protein A values, averaging to 2.67 ppm. A process interruption before cycle 11 may have resulted in an assignable cause for the somewhat higher value at that point.

The Host-cell DNA in the pooled elution was removed at 3.37 LRV relative to the concentration in the harvest fluid. This value is considered comparable to the DNA removal performance in the purification of typical mAbs using conventional resin-based Protein A columns,[7] suggesting that it was efficiently removed by the Gore Device (Table 4).

Size Exclusion Chromatography (SEC) was performed on the pooled elution. The main peak fraction (target mAb) was calculated to be 93.9%, within the specifications of the final product of the mAb in this study, and the high molecular weight fraction (aggregation) was calculated to be 6.1%, less than in the resin-based Protein A column eluate using the same harvest fluid.

Lab-Scale Protein A Capture

Aliquots of the cell culture harvest were purified with laboratory-scale columns to provide benchmark performance targets as well as a scaling reference for the GORE Device. Table 3 below summarizes calculated productivity, elution volume and process/product impurity data from the Protein A resin column control as well as a 3.5 mL Gore Device in relation to the previously discussed 2 L Gore Device data.

Table 3: Lab scale Protein A resin column and the Gore Device performance/quality comparison to manufacturing scale Gore device.

Attribute	5 mL Protein A Resin column	3.5 mL Gore Device with Protein A	2 L Gore Device with Protein A
Productivity (g/L/h)	13.8	132.8	132.6
Average elution volume [100-100 mAU cutoff]	2.72	1.84	2.68
Elution HCP (LRV)	2.03	2.12	2.22
Elution Protein A (ppm)	4.28	5.25	2.49
Average SEC Product Quality (% main/%HMW)	89.9 / 10.1	93.3 / 6.7	93.9 / 6.1

Productivity calculations indicate a consistent 10X increase in productivity for the GORE Devices compared to the resin column. Otherwise, chromatographic performance as well as process and product impurity data were comparable between the two GORE Devices and the Protein A resin control.

Single-use Downstream Performance Characterization Summary

Table 4 summarizes step yields, step productivities, and pooled HCP, Protein A and SEC characterization data for the affinity capture, VI, AEX and TFF steps.

Table 4. Comparison of step yield, productivity, and process/product quality data for the downstream unit operations. Purity data were analyzed from the final pool at each operation.

			HCP			Host Cell DNA	SEC-HPLC (%)	
Step	Step Yield (%)	Step Productivity	ppm	Step LRV	Residual Protein A [ppm]	Step LRV	Main	HMW
Harvest (Filtration)	-	–	160,187	-	-	-	-	-
Protein A Affinity (Gore Protein A)	103.8	132.6 $g\ L^{-1}\ h^{-1}$	830	2.29	2.49	3.37	93.9	6.11
Viral Inactivation (Single-use Mixer)	-	–	915	-	2.36	-	92.6	7.37
Anion Exchange (Sartobind Q)	88.9	189.2 $g\ L^{-1}\ h^{-1}$	72	1.10	2.20	1.70	92.1	7.89
TFF: UF/DF (Pellicon Capsule)	104.4	72.0 $g\ m^{-2}\ h^{-1}$	99	-	2.42	-	93.9	6.05

Discussion

The experimental approach set forth herein established a high productivity, manufacturing scale mAb production platform process utilizing fully disposable upstream and downstream components, demonstrated with 500 L of CHO cell culture harvest manufactured in a 2000 L single-use production suite. The findings, inclusive of cycle-to-cycle pressure rise, elution volume, yield, productivity, and other quality attributes can be readily extended to bioreactor batch sizes of 2000 L. Serving an industry whose foundation is risk mitigation,[8] the successful use of disposable/single-use downstream processing components in this study further demonstrated (1) the elimination of column packing/unpacking, (2) the elimination of column validation testing and associated chemical consumption, and (3) the elimination of operator intervention and time investment in packing, unpacking, cleaning, and storing columns and resins. Elimination of these elements in this study thereby reduced contamination risk in the production suite.

The equivalency study conducted between a 5 mL Protein A resin column and a 3.5 mL GORE Device demonstrated comparable mAb purification results using the same culture supernatant on a small scale. The Gore membrane devices at both manufacturing and lab scales demonstrated 10 times higher productivity compared to the resin control.

In the 2000 L production suite scale Protein A affinity capture step, two GMP-compliant production scale 1 L GORE Devices were used in parallel. Nineteen rapid chromatography cycles were performed to purify the mAb from approximately 450 L of culture harvest fluid. Since this Protein A membrane device allows for a much higher flow rate process than conventional resin-based columns, the time required for one cycle was roughly 10 minutes or less, so the process time for 19 cycles was 3.2 hours. Also, in combination with the single-use chromatography system, the entire Protein A operation was completed well within one workday (~ 8 hours), including preparation and cleanup of the equipment and inter-cycle operations. The A280 chromatograms, mAb yield, HCP reduction, and leached protein A were acceptable and stable over all 19 cycles, demonstrating that production scale GORE Devices enable critical quality attributes to be achieved while increasing productivity by an order of magnitude. By way of reasonable extrapolation leveraging Gore's validated product claim of cycling durability to at least 100 cycles (Gore Document PB10133), the results with two parallel manifolded 1 L Gore Devices demonstrate the potential to purify 2000 L of this culture harvest fluid in roughly 85 cycles. This equates to 14.2 hours of total Protein A process time in the full 2000 L bioreactor batch size scenario.

This demonstrated performance, inclusive of parallel manifolding, can be combined with additional configurations suggested by Gore and supported by Gore publications to predict several scenarios at the 2000L scale as outlined in Table 5.

Table 5: 2000 L Culture Harvest Fluid Protein A Purification Scenarios[1] Using GORE Protein Capture Devices with Protein A

Bioreactor Batch Size (L)	Titer (g/L)	GORE Device Configuration	Cycles[2] Needed to Clear Bioreactor	Total Time per Cycle[3] (min)	CIP Time per Cycle (min)	Total Bioreactor Clearance Time (h)	Productivity (g/L/h)[4]
2000	1.5	1 L	94	14.8	0.5	23.2	130
				16.3	2	25.5	118
				17.3	3	27.1	111
2000	3	2 x 1 L parallel manifold	94	9.5	0.5	14.8	203
				11.0	2	17.2	175
				12.0	3	18.7	160
2000	6.4	4 x 1 L parallel manifold	100	6.7	0.5	11.1	289
				8.2	2	13.6	236
				9.2	3	15.3	210
2000	10	4 x 1 L parallel manifold	157	5.8	0.5	15.0	334
				7.3	2	18.9	265
				8.3	3	21.5	233
				10.3	3	26.7	187

1. Assumes $DBC_{10\%}$ of 40 g/L at 30 SRT, loading to 80% of DBC10% at 30 SRT, non-loading steps at 7 SRT.

2. GORE Protein Capture Devices with Protein A are validated to 100 cycles and demonstrated to 200 cycles; see Gore documents PB10133 and PB12594, respectively, for details.

3. Range of total time per cycle is inherently higher for lower titers due to increased time needed for loading low titer harvest to 80% of $DBC_{10\%}$

4. The Gore Productivity Calculator (Gore document PB11711) can be used to model a wide range of additional scenarios.

In all of the Viral Inactivation, Anion Exchange Chromatography, and UF/DF processes that followed the Protein A process, single-use devices were used. In the AEX process, the single-use Sartobind Q membrane device also allowed for a high flow rate process with a high productivity of 189.2 g L^{-1} h^{-1}, and in combination with the single-use chromatography system, the operation time from preparation to completion of the process was only comfortably within 4 hours. It was further confirmed that HCP and Host cell DNA were removed sufficiently in Anion Exchange Chromatography in Flow Through mode using the Sartobind Q. We have also confirmed that by adding the Sartobind S, cation exchange membrane unit operation, HCP can be further reduced to less than 10 ppm (data not shown), and various combinations of membrane devices are possible depending on the molecule to be produced and the desired quality. The UF/DF process using single-use TFF capsule membranes operated similarly to conventional flat-sheet TFF cassettes, with acceptable results in terms of process yield and buffer exchange, with a demonstrated high productivity of 72.0 g/m^2/h. The TFF process employing the single-use TFF system was completed comfortably within 8 hours, including preparation activities.

Conclusions

The findings herein established a high productivity, manufacturing scale antibody production platform utilizing fully disposable upstream and downstream processing components, featuring commercial manufacturing scale 1 L Gore Devices, demonstrated in a 2000L single-use production suite. Further, the Protein A capture step equivalency study conducted between a 5 mL Protein A resin column and a 3.5 mL Gore Device demonstrated comparable mAb purification results using the same culture supernatant on a small scale, with the Gore devices demonstrating 10 times higher productivity at both manufacturing and lab scales relative to the resin control. GORE Devices enable critical quality attributes to be achieved while increasing productivity by an order of magnitude. The findings are readily extendable to multiple scenarios enabling harvest volumes of 2000L at titers ranging to 10 g/L to be purified.

The findings indicate that a fully disposable upstream and downstream platform process in antibody production is real, demonstrates improved production speed and order-of-magnitude higher productivity, and can reduce risk in biologics manufacturing.

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