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Application Note

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Increased efficiency and product quality with the UniVessel® Single Use bioreactor for CHO fed-batch cultures

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Abstract

The motivation for utilizing single use (SU) bioreactors is the reduced turn-around time and labor required for cleaning and autoclaving traditional glass vessels as well as the associated costs for maintenance and repair. Sartorius' 2L UniVessel® SU has an option for an external water jacket system controlled by Sartorius' BIOSTAT® controllers. In this study, we determined the feasibility of the UniVessel® SU and BIOSTAT® B-DCU II combination by performing detailed comparability studies of cell growth, viability, monoclonal antibody (mAb) productivity and product quality attributes (aggregation, charge variation and glycosylation) using three recombinant CHO cell lines. Comparability was also examined based on power input and agitation. Data show that after optimizing process parameters, the UniVessel® SU with water jacket performed comparably to a jacketed 2L Applikon glass bioreactor.

Introduction

Single use (SU) bioreactors are widely preferred over reusable systems due to their preassembled impellers, filters, tubing and connectors that help to reduce the turn-around times and labor required for cleaning and autoclaving conventional systems. Conversion of an established bench scale bioreactor platform to a SU system requires the selection of a design that replicates its reusable counterpart as closely as possible. Alignment of bench scale SU bioreactor geometry with pilot and production vessels is also critical for scale-down models and late stage process characterization studies. Once a SU bioreactor has been identified, detailed feasibility and comparability studies are required to ensure continuity in the development process. Upon successful completion and implementation, any differences in process performance can then be attributed to the cell line under development rather than to the bioreactor system itself.

Sartorius' UniVessel® SU and Applikon's Water Jacketed Bioreactors

Sartorius' 2L UniVessel® SU stirred tank (STR) bioreactors were recently shown to be directly interchangeable with Sartorius' 2L glass vessels that utilize an electric heating blanket for temperature control (Tappe et al., 2013). Sartorius was the only vendor that offered an external water filled heating | cooling jacket for its SU UniVessel®. Water jacketed bioreactors permit a more reliable and higher performance temperature control than electric heating blankets. Due to this benefit our process development activities utilize Applikon's 3L, glass double-walled jacketed bioreactors, controlled by Sartorius' BIOSTAT® B-DCU II controller. The BIOSTAT® B-DCU II controller has a temperature control module that is designed specifically for connection to water jacketed vessels. Applikon glass jacketed vessels are designed with intake and outlet vents that allow water to be pumped through and recirculated at a constant jacket flow. Piping at the back of the BIOSTAT® B-DCU II controller contains an open overflow routed to the laboratory drain in order to channel fresh water to the jacket when the vessel temperature has to be reduced. The contact area of the double walled glass jacket provides a large surface area for heat transfer and together with temperature control through a PID loop a rapid, precise, gentle and maximum constant temperature is achieved. We routinely utilize Applikon's glass jacketed bioreactors for the implementation of our robust NS0 and CHO cell process development platform that is applicable across a variety of production cell lines for monoclonal antibody (mAb) and bispecific molecules. Since many of our CHO processes require either a single or dual temperature shift a rapid and reliable temperature control via Sartorius' BIOSTAT® B-DCU II controller is critical.

Comparability between the Univessel® SU and Applikon's Reusable Bioreactor

Applikon's 3L glass, jacketed bioreactor is named according to a nominal volume but the actual total and minimum and maximum working volumes correspond to the 2L UniVessel® SU volumes (Table 1). In terms of geometric similarity, critical for maintaining cell culture homogeneity and mixing, both vessels have an aspect ratio (H/Di) of approximately 2 to yield a similar liquid surface area to volume ratio for comparable mass transfer rates at the gas-liquid interface (Table 1). Additionally, similar liquid height leads to comparable residence time of bubbles and oxygen mass transfer rates during sparging. Another important geometric parameter is the impeller to vessel diameter ratio (di/Di) which is similar at approximately 0.5 between the two vessels (Table 1).

Vessel	Applikon 3L	UniVessel® SU 2L
Total Volume (L)	3.2	2.6
Max. Working Volume (L)	2.7	2
Min. Working Volume (L)	0.5	0.6
Max. Liquid Height (H)(mm)	234	273
Vessel Inner Diameter (Di)(mm)	130	131
Impeller Diameter (di)(mm)	60	54
Ratio di/Di	0.46	0.41
Ratio H/Di	1.8	2.08
Power Number	1.5	1.3
Number of Impellers	1	2
Distance between Impellers (mm)	N/A	70
Diameter of Sparger Hole (mm)	1.00	0.5
Number of Holes in Sparger	7	14

Table 1: Geometric parameters of the Applikon Glass and UniVessel® SU

This will help to achieve a comparable flow pattern and power input for culture homogeneity relevant during process feeds, pH control and for a similar dispersion of the sparged air. Another key comparison is the type of impeller. Both vessels possess 3 blade segment impellers to generate axial flow patterns at equivalent pumping rates. The UniVessel® SU impeller is pitched at a 30° angle vs. the Applikon at 45°. Due to its orientation the vortex impeller of the UniVessel® SU generates circulation loops in the downward flow direction identical to our Applikon impeller which is configured with a scoping mixing impeller. The UniVessel® SU consists of a double impeller with a distance of >1.2 times the diameter of the impeller (di), between the two impellers, to ensure that the impellers act independently of each other, while our Applikon vessels are outfitted with a single impeller. An additive power number (Np) can then be used in calculations for a suitable power input. The resulting combined Np (1.3) of the UniVessel® SU impellers is similar to the Np of the single impeller in the Applikon vessel (1.5) (Table 1).

Both have drilled hole L-shaped spargers. The sparger in the UniVessel® SU is below the lowest impeller to ensure adequate gas-bubble dispersion and it differs from the Applikon sparger in that it has twice the number of holes at half the diameter size. While smaller holes generate smaller bubbles for high gas-liquid interface areas and improved oxygen transfer they reduce the efficiency of carbon dioxide (CO_2) stripping. This is unlikely to be a significant issue at small-scale but may become more challenging at larger scale due to the increased hydrostatic pressure and higher solubility of CO_2. To note within the Sartorius family of SU STR bioreactors there is a well-established linear scale-up from the 2L UniVessel® SU system to the 50L BIOSTAT® STR and beyond (Table 2).

SU Bioreactors	UniVessel® SU	BIOSTAT® STR				
Scale (L)	2	50	200	500	1000	2000
Total Volume (L)	2.6	70	280	700	1300	2800
Max. Working Volume (L)	2	50	200	500	1000	2000
Min. Working Volume (L)	0.6	12.5	50	125	250	500
Vessel Inner Diameter (Di) (mm)	130	370	585	815	997	1295
Max. Liquid Height (H) (mm)	240	666	1055	1467	1800	2330
Ratio H/Di	1.8	1.8	1.8	1.8	1.8	1.8
Impeller Diameter (di) (mm)	54	143	225	310	379	492
Ratio di/Di	0.41	1.3	0.38	0.38	0.38	0.38
Distance between Impellers (mm)	70	186	300	403	493	640

Table 2: Geometric similarity and scalability of Sartorius SU STRs

Given dimensional similarity between the water jacketed Applikon 3L glass and 2L UniVessel® SU we ran head to head comparisons between the two using three different mAb producing CHO fed-batch processes. Each CHO process had been extensively developed in Applikon's 3L glass jacketed vessel via platform parameters that were either universal or subject to optimization per cell line (Table 3). In this application note we repeated these established processes and compared jacket temperature control, cellular growth, cell viability, mAb productivity and product quality attributes (aggregation, charge variation and glycosylation). Comparability was examined based on the bioreactor power input and agitation. Additionally, for one of the three CHO cell lines the UniVessel® SU was tested as a scale-down model to the 50L BIOSTAT® STR. Our results show that the 2L UniVessel® SU with an external water jacket was comparable to the glass water jacket system of the 3L Applikon bioreactor in terms of cell growth, viability and productivity. However, we observed a cell line dependent impact on product quality between the UniVessel® SU and Applikon glass vessels. For one of the CHO-cell lines this difference in product quality was reduced between the 2L UniVessel® SU and the 50L BIOSTAT® STR to confer its suitability as a scale-down model to larger scale disposable Sartorius reactors.

Fixed parameters	Parameters to be further optimized
Fed-batch process	Seeding Density
pH & DO set-points	Temperature Shift Criteria
Aeration	Temperature Shift Parameters
Agitation	Feed Schedule

Table 3: CHO Bioprocess Parameters in the Applikon 3L Glass Water Jacketed Reactor

Material

- Raw Materials:
  - Proprietary in-house basal and feed media
  - CHO cell line

- Reusable Stirred Tank Bioreactor:
  - 3L Applikon double walled glass jacketed vessel. Maximum working volume 2.7L

- Single-Use Bioreactor Systems:
  - Sartorius Stedim Biotech UniVessel® SU. Maximum working volume 2L
  - Sartorius Stedim Biotech 50L BIOSTAT® STR. Maximum working volume 50L
  - Sartorius Stedim Biotech CultiBag® RM 20L. Maximum working volume 10L

- Analytical Devices:
  - Beckman Coulter ViCell — Cell counting
  - ABL-805 (Radiometer) — pH, pCO_2, pO_2
  - ABL-805 (Radiometer) — Glucose and lactate
  - Agilent HPLC — mAb titers
  - SEC chromatography — Aggregation
  - CEX chromatography — Size species variants

- Disposable Erlenmeyer Shake Flasks
- CO_2 incubator
- Biosafety Cabinets (BSC)

Methods

Preparation of Bioreactor Seed Cultures

Three recombinant CHO cell lines, CHO-1, CHO-2 and CHO-3 expressing three distinct IgG antibodies were compared. Frozen cells of each cell line were thawed in a chemically defined proprietary medium and were maintained as continuous seed trains for about 2 weeks. The cells were passaged every 3 – 4 days in shake flasks at a seeding density of 8 to 10 × 10^5 cells/mL. These seed train cultures were kept in incubators controlled at 37 °C and 5% CO_2, and were shaken at a speed of 115 rpm until the appropriate biomass was achieved for inoculation of the UniVessel® SU and Applikon bioreactors. CHO-3 was additionally expanded in a seed train that included the single use BIOSTAT Cultibag® RM basic system (20L), to attain sufficient biomass for inoculation of the 50L BIOSTAT® STR. The agitation rate for the Cultibag® RM expansion was 15 rocks/min at an angle of 7°, controlled at 37 °C and 5% CO_2 | air gas mix for a duration of 2 to 3 days.

Set-up of UniVessel® SU

The assembled UniVessel® SU is shown in Figure 1. We opted to integrate conventional pH and DO sensors with a view to purchase a more economical vessel holder without the optoelectronics required to excite the UniVessel® SU's integrated optical pH and DO sensors. Calibrated and autoclaved pH and DO sensors were therefore installed inside the BSC, prior to transfer of the UniVessel® SU to its holder. Necessary connections to media, cell inoculation, feed and base bottles were made using a Terumo tube welder ensuring sterile transfers at the bench. Pre-assembled clamps for each line were color coded to distinguish dip tubes

for harvest and inoculation ports (yellow clamps) from feed and base (white clamps) lines. A Sartorius motor adapter was used to connect the Applikon overhead drive to the UniVessel® SU. The exhaust line had a dual filter assembly with a heater to reduce condensation. The external water jacket's outlet and inlet ports coupled directly to the existing hoses on the BIOSTAT® B-DCU II controller.

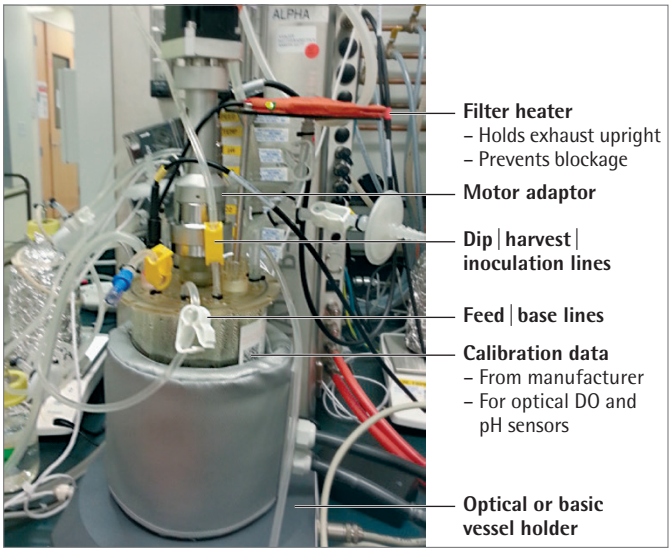

Figure 1: Set up of water jacketed 2L UniVessel® SU

Applikon and UniVessel® SU Bioreactor Parameters

Temperature control loop was switched on to reach set-point at the time of media batching 24 hrs prior to cell inoculation. The PID temperature control loop for the UniVessel® SU was set according to the manufactures' instructions. The culture pH was controlled at 6.9 with a dead band of 0.02 by sodium hydroxide (0.5 M) as base and CO_2 gas as acid. DO was controlled at 40% air saturation by sparging with air and pure oxygen gas, as required. Fed batch cell cultures were seeded in either the Applikon 3L or the UniVessel® SU 2L bioreactor at 10×10^5 cells/mL with an initial working volume of 1.4L. The lower impeller of the UniVessel® SU was completely submerged at the 1.4L inoculum volume. The bioreactor agitation and aeration parameters are summarized in Table 4. Given dimension similarity the UniVessel® SU agitation rate (203 rpm) was computed using the equivalent power specific input P/V (~16.3 W/m³) of the Applikon glass bioreactor at the platform agitation rate of 162 rpm in (Table 4). At this agitation rate the tip speed was very similar in the Applikon glass bioreactor (0.51 m/s) to the UniVessel® SU (0.57 m/s). An equivalent maximum volume of air per volume of liquid per minute (vvm) (0.01 vvm) was maintained in both vessels. At the same volumetric air flow rate (14 mL/min) the gas exit velocity from the UniVessel® SU sparger (8.49 cm/s) was doubled from the Applikon glass bioreactor (4.24 cm/s) due to a decrease in the cross-sectional area of its sparger (Table 4).

	Parameters	Applikon 3L	UniVessel® SU 2L
V	Working Volume (VT) (L)	1.4	1.4
Q	Volumetric Gas Flow Rate (L/min)	0.014	0.014
vvm	Q Normalized to Volume (L)	0.01	0.01
A	Sparger Total Cross Sectional Area (cm²)	0.055	0.027
us	Gas Entrance Velocity (cm/s)	4.24	8.49
	Converting Units (W=joule/sec=kg*m²)/s³)		
V	Volume (m³)	0.0014	0.0014
D	Impeller Diameter (m)	0.06	0.05
Np	Impeller Power Number	1.5	1.3
ρ	Density water (kg/m³)	993	993
	Agitation based on Applikon P/V (16.3 W/m³)		
*N	Agitation (RPM)	162	203

*N = [(V*P/V)/ (Np * D⁵ * ρ)]^(1/3)

Table 4: Determination of agitation and aeration set-points in the Applikon Glass and UniVessel® SU bioreactors

Process parameters for the BIOSTAT® 50L STR are highlighted in Table 5. Scale down agitation rate for the Univessel (170 rpm) was calculated using the BIOSTAT® 50L STR P/V (~9.6) (Table 5).

	Parameters	50L STR	UniVessel® SU 2L
V	Working Volume (VT) (L)	40	1.4
D	Impeller Diameter (mm)	143	54
Np	Impeller Power Number	1.3	1.3
	Converting Units (W=joule/sec=kg*m²)/s³)		
V	Volume (m³)	0.04	0.0014
D	Impeller Diameter (m)	0.143	0.054
ρ	Density water (kg/m³)	993	993
	Agitation based on Sartorius 50L P/V (9.6 W/m³)		
*N	Agitation (RPM)	100	170

*N = [(V*P/V)/ (Np * D⁵ * ρ)]^(1/3)

Table 5: Scale-down agitation rate in UniVessel® SU from 50 L BIOSTAT® STR

KLa measurement

Aeration efficiency of the UniVessel SU vs. the Applikon glass reactor was compared by measuring the KLa using the 'gassing out method'. Cell free reactors were deoxygenated at different working volumes of a 0.1% Pluronic-F68 and antifoam (1%) solution. Nitrogen was replaced by air and the dissolved oxygen concentration was measured with a pre-calibrated DO probe until the DO reached > 50% under the test working volume, agitation, aeration and temperature condition. The air flow was uninterrupted during the switch from nitrogen to air so that consistent

fluid conditions were maintained in the reactor throughout the experiment. By repeating the oxygen stripping process and sparging at different test conditions, the values of KLa as a function of working volume, agitation speed and gas flow rate, were established for each reactor.

Antibody Product Quality Analysis
For product quality analysis, bioreactor harvests were filtered and centrifuged at the end of the fed batch cultures on day 14. mAb was purified from clarified harvest by Protein A (MabSelect Sure, GE) affinity chromatography. Size exclusion chromatography (SEC) was conducted on a Waters HPLC system to determine the percentage of antibody aggregates; i.e. the high molecular weight (HMW) fraction as resolved from the main mAb monomer peak, and low molecular weight (LMW) fragments. Charge variants were determined by cation exchange HPLC (CEX) and imaged capillary isoelectric focusing (icIEF).

Results

More rapid heat transfer was apparent through the double walled Applikon glass vessel compared to the external water jacket of the UniVessel® SU. This difference did not impact the temperature control of CHO-1, -2 and -3 fed batch processes under test that incorporated at least one temperature shift (Figure 2A to C).

In terms of cell culture performance the viable cell density remained similar between the Applikon glass and UniVessel® SU reaching comparable peak viable cell density (VCD) that varied from 150 to 200 × 10^5 cells/mL depending on the cell line (Figure 3A to C). Their respective temperature shift strategies resulted in prolonged stationary phases that did not differ in the time of induction or length of duration between the UniVessel® SU and Applikon vessels (Figure 3A to C). Likewise the cell viability was almost parallel with marginal differences, remaining above 80% for the entire 14 day process (Figure 4A to C). Cell culture performance was also compared in terms of specific nutrient consumption and metabolite production rates. Specific glucose consumption and lactate productions rates followed identical trends between the UniVessel® SU and Applikon glass vessels (Figure 5 and 6). One difference in the glucose consumption rate on day 13 for CHO-3 was attributable to the absence of a glucose feed during the UniVessel® SU run (Figure 5C). Since we have a robust fed-batch platform with high cell viability the cells are minimally lactogenic and the highest lactate production rates correlated with increased glucose consumption during the first 3 days of each CHO process (Figure 5 and 6). Lactate production rates declined to negative values reflective of a metabolic switch to lactate consumption (Figure 6). Moreover, there was no difference in mAb production and near identical titers were obtained between the UniVessel® SU and Applikon glass vessels for each CHO process (Figure 7A to C).

Since the KLa is influenced by variables such as the working volume and number of impellers, we tested these factors at the process agitation rate of 203 and 162 rpm for UniVessel® SU and Applikon glass vessel respectively, at either 1.4 or 2L volumes. These volumes were chosen as they reflected the inoculum, and final post feed volume whereby both impellers of the UniVessel® SU were submerged. We also tested the process aeration (0.01 vvm) and the maximum aeration (0.075 vvm) rate possible calculated from the maximum output of the BIOSTAT® B-DCU controller (150 mL/min) at 2L. Both vessels had similar KLa of 1 h^{-1} at 0.01 vvm for the 1.4L volume at 33 and 37 °C; as expected the KLa was reduced to approximately 0.8 h^{-1} at the higher volume of 2L at 0.01 vvm (Table 6). At 1.4L and 0.07 vvm the UniVessel® SU showed significantly higher KLas at both 33 °C (4 h^{-1}) and 37 °C (6 h^{-1}) compared to the Applikon glass vessel at 33 °C (2.5 h^{-1}) and 37 °C (4 h^{-1}) (Table 6). The higher KLas were attributed to sparger differences and the higher gas entrance velocity compared to the Applikon glass sparger (Table 4). At the 2L volume the impact of the second impeller was apparent only at 37 °C whereby the UniVessel® SU showed higher KLas (4 h^{-1}) than the Applikon glass vessel (2.5 h^{-1}) whereas the KLa was 2 h^{-1} for both vessels at 33 °C (Table 6).

Bioreactor	Parameters			KLa (h^{-1})	
	Volume (L)	Agitation (rpm)	Aeration (vvm)	33 °C	37 °C
UniVessel®	1.4	203	0.01	1.2	1.5
	1.4	203	0.075	4.0	6.0
	2	203	0.01	0.9	1.0
	2	203	0.075	2.0	4.0
Applikon	1.4	162	0.01	1.0	1.2
	1.4	162	0.075	2.5	4.0
	2	162	0.01	0.8	0.9
	2	162	0.075	1.9	2.5

Table 6: Comparison of KLa

Several product quality attributes of secreted mAb were analyzed and compared. On day 14 culture broths were centrifuged, filtered and purified by protein A affinity chromatography. Typical recoveries ≥89% (Table 7) and protein A chromatograms were obtained for the clarified harvests from the UniVessel® SU and Applikon glass vessel (data not shown). HMW aggregates for all the CHO cells lines, as measured by SEC HPLC, were marginally elevated by approximately 1% in the Applikon glass vessel (Table 7).

Cell Line	Bioreactor	Protein A step Recovery (%)	Monomer (%)	HMW (%)	LMW (%)
CHO-1	Univessel®	93	95.1	4.5	0.4
	Applikon	94	93.9	5.7	0.4
CHO-2	Univessel®	96	92.2	7.6	0.1
	Applikon	97	91.6	8.3	0.1
CHO-3	Univessel®	90	95.3	4.7	0
	Applikon	89	93.8	6.2	0

Table 7: Comparison of Protein A step yield and product aggregate Levels

Cation exchange HPLC and icIEF for the separation of the acidic and basic charge variants showed that acidic species were elevated in the Applikon vessel for each CHO product compared to the UniVessel® SU (Table 8). For CHO-2, the difference in acidic species was 4.8% (19.2% for Applikon and 14.4% for the UniVessel® SU) (Table 8). For CHO-1 and CHO-3, the acidic species were approximately 2% higher in the Applikon vessel than in the UniVessel® SU. Furthermore, we tested the UniVessel® SU as a scale-down model to the pilot scale BIOSTAT® 50L STR using CHO-3. Due to geometric similarity between the two scales we matched the BIOSTAT® 50L P/V (9.6 W/m³) to the UniVessel® SU and reduced the agitation rate from 203 to 170 rpm (Table 5). The resulting cell growth, viability and product titers were almost identical between the two scales (Figure 10). Ultimately we found that the acidic species for CHO-3 was more closely matched between the UniVessel® SU (27.2%), BIOSTAT® 50L (pilot) (26.4%) and BIOSTAT®1000L (GMP) (26.6%) runs (Table 8). This is an important observation, pertinent for late stage process characterization studies as the Applikon 3L glass vessel has often faired as a poor scale down model due largely to higher levels of acidic species.

Cell Line	Bioreactor	Fraction of Charge Variants (%)		
		Acidic Species	Main Peak	Basic Species
CHO-1	Univessel®	27.7	65.9	6.2
	Applikon	29.5	64.1	6.2
CHO-2	Univessel®	14.4	71.7	13.9
	Applikon	19.2	66.3	14.5
CHO-3	Univessel®	27.2	60.0	12.9
	Applikon	29.6	54.8	15.6
	BIOSTAT® 50 L STR	26.4	59.0	14.6
	BIOSTAT® 1000L STR	26.6	59.9	13.5

Table 8: Comparison of charge variants

Conclusion

The 2L UniVessel® SU is a feasible single use option that can be directly integrated with our existing BIOSTAT® B-DCU II controllers. Although it took longer for the temperature of the UniVessel® SU to reach set point there was comparability to the Applikon glass vessel in terms of cellular growth, viability and productivity of 3 distinct fed-batch CHO processes. However, differences were noted in product quality attributes for the cell lines compared in this study. Additionally, the UniVessel® SU was a suitable scale-down model for the BIOSTAT® 50L that resulted in similar product quality attributes. Therefore, the UniVessel® SU may serve as a more predicative model than glass 3L bioreactors for late stage process development and characterization studies of large scale Sartorius STR disposable bioreactors.

Reference

Tappe A and Grebe A. White Paper: UniVessel® SU Cultivation of CHO in the single-use bioreactor UniVessel® SU. Sartorius Stedim Biotech GmbH. Publication No.: SBT1021-e. Order No. 85037-545-42. 2014.

Appendix

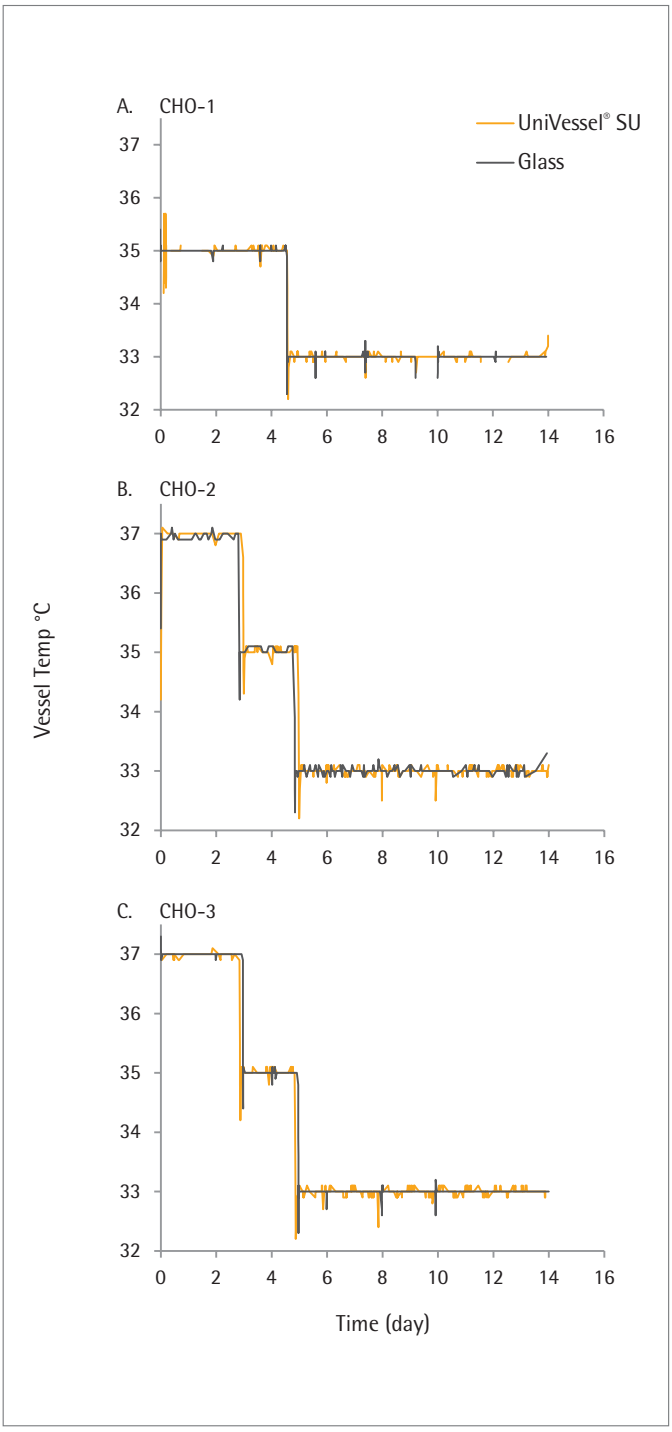

Figure 2: Comparison of on-line vessel temperature control during (a) CHO-1 (b) CHO-2 and (c) CHO-3 processes between UniVessel® SU and Applikon glass vessels with either a single or dual temperature shift

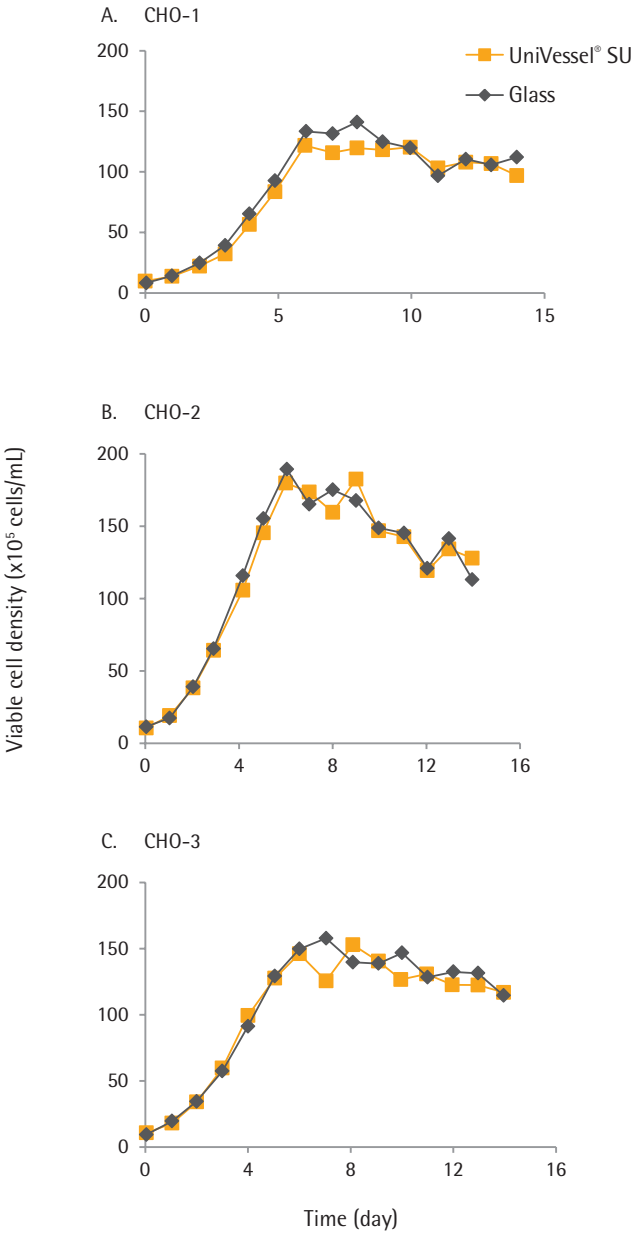

Figure 3: Viable cell density comparison of (a) CHO-1 (b) CHO-2 and (c) CHO-3 between UniVessel® SU and Applikon glass systems

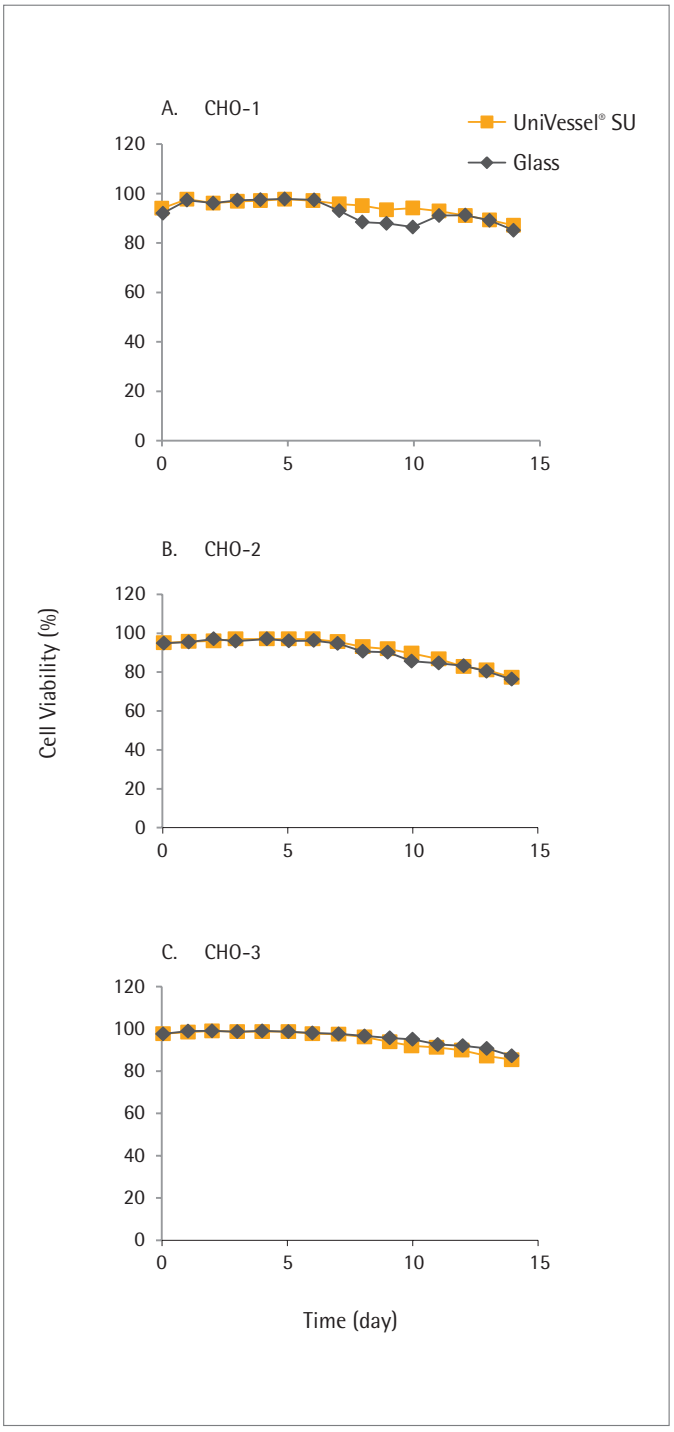

Figure 4: Cell viability comparisons of (a) CHO-1 (b) CHO-2 and (c) CHO-3 in UniVessel® SU and Applikon glass systems

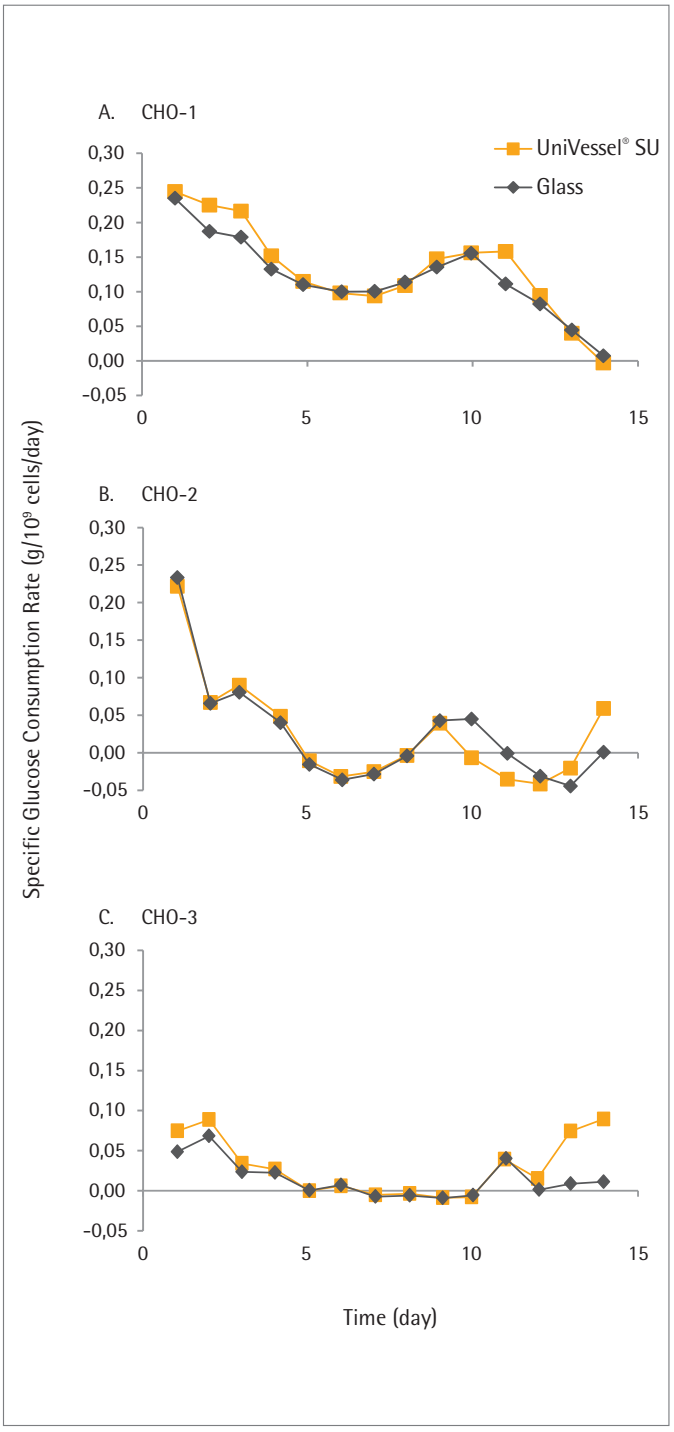

Figure 5: Specific glucose consumption rates of (a) CHO-1 (b) CHO-2 and (c) CHO-3 in UniVessel® SU and Applikon glass systems

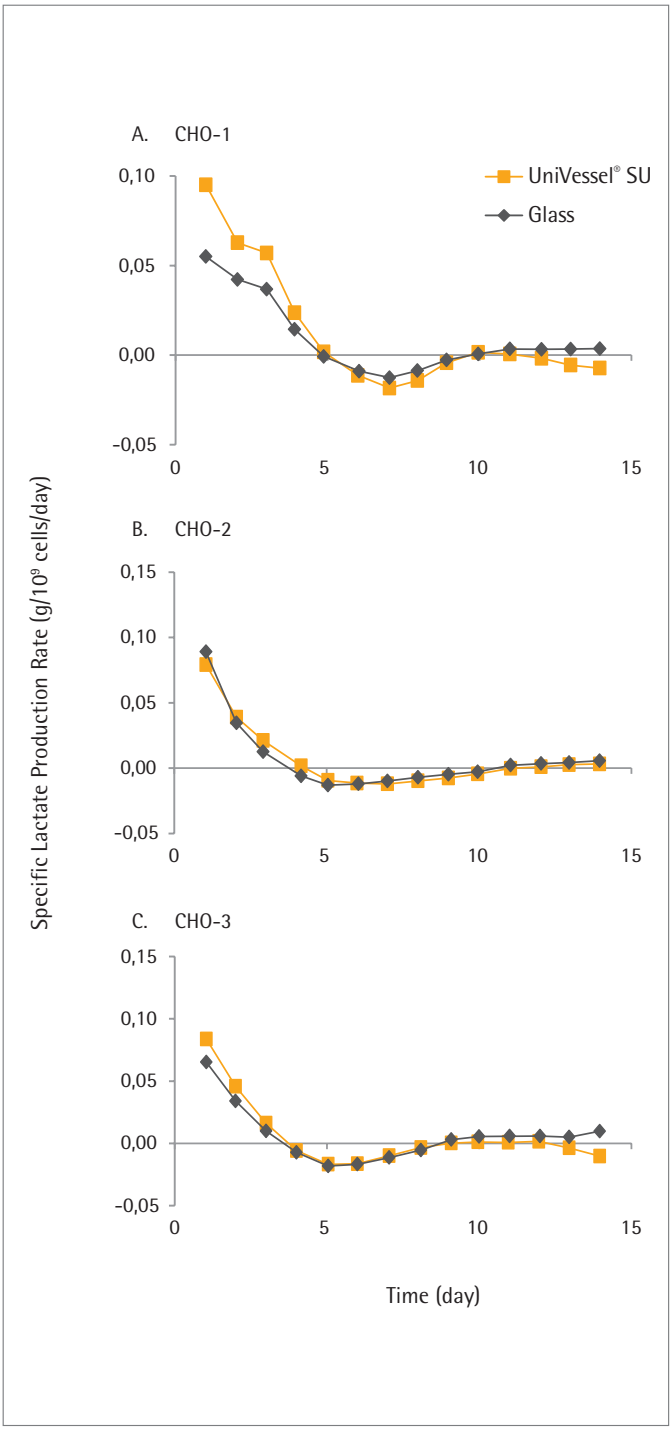

Figure 6: Specific lactate production rates of (a) CHO-1 (b) CHO-2 and (c) CHO-3 in UniVessel® SU and Applikon glass systems

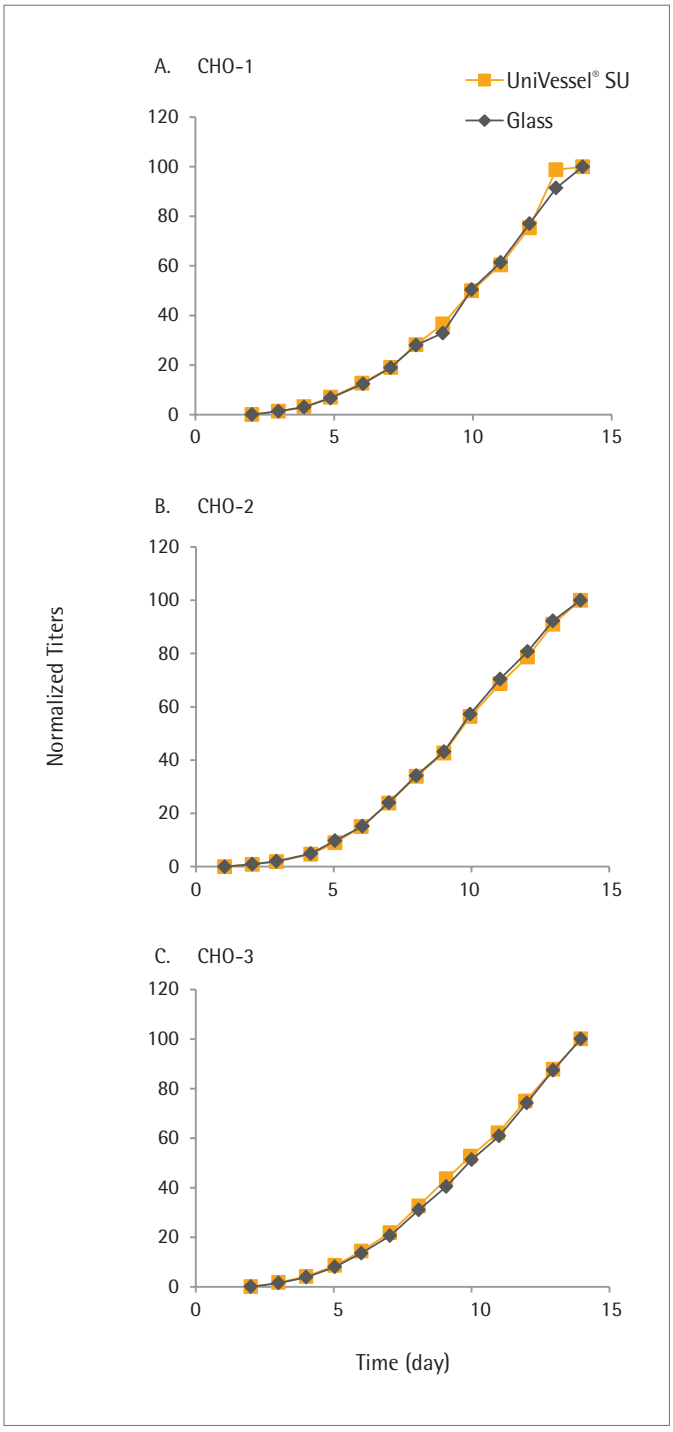

Figure 7: Normalized product titers of (a) CHO-1 (b) CHO-2 and (c) CHO-3 in UniVessel® SU and Applikon glass systems

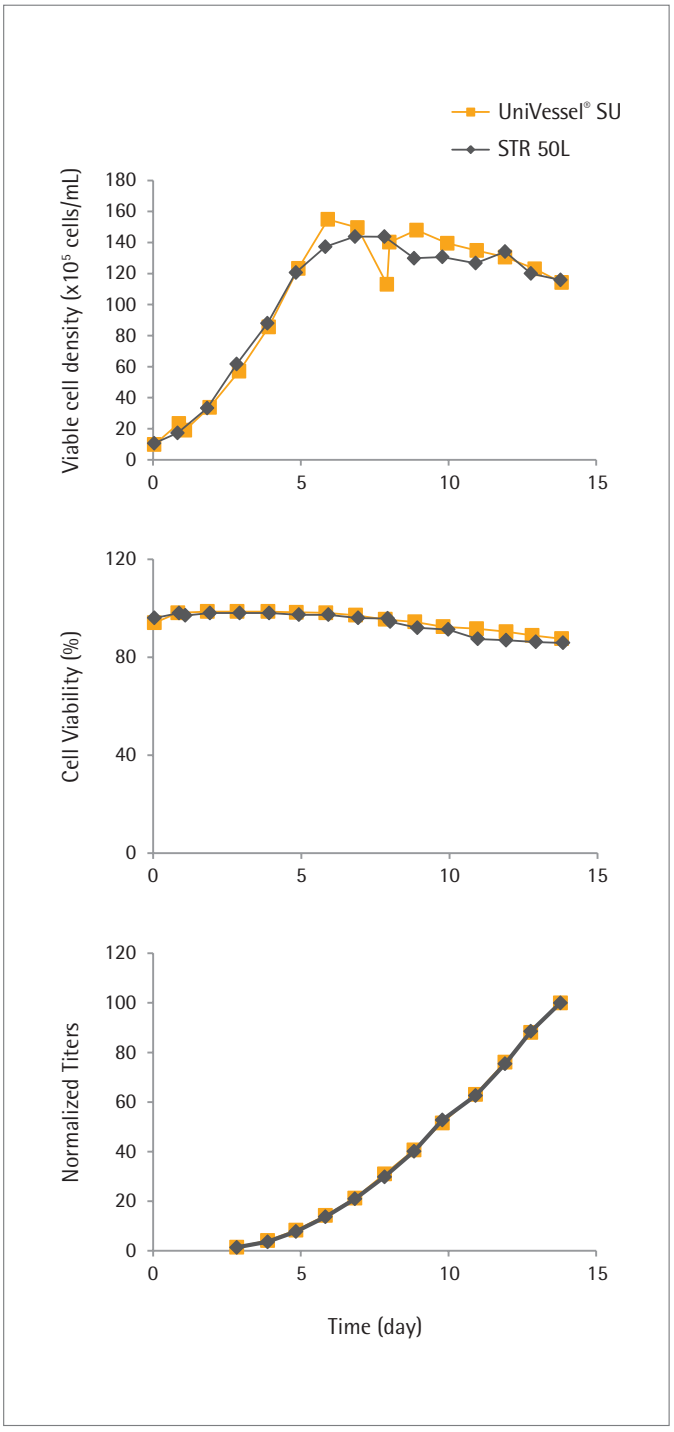

Figure 8: Comparison of CHO-3 (a) viable cell density (b) cell viability and (c) productivity for CHO-3 between the BIOSTAT® 50 L and the UniVessel® SU

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