



Designed in  
Singapore

VACCI X CELL  
ADHERENT BIOPROCESSING SPECIALIST

# Hybrid Bioreactor<sup>®</sup>

Changing Perspective from Discovery to Delivery



7L Hybrid Bioreactor

**ESCO**<sup>®</sup>  
Healthcare



"Discovery to Delivery"

# Hybrid Bioreactor

## Your Four in One Bioreactor

### ► Applications

Research and Development/ Scale up Studies  
 Media Development  
 Human Vaccines  
 Animal Vaccines  
 Monoclonal Antibodies  
 Biosimilars/ Biobetters  
 Cell Therapy  
 Gene Therapy  
 Diagnostics  
 Pre-Screening



For users under Research and Development that needs single-use vessel for adherent culture, the CelCradle™ benchtop bioreactor system is the perfect choice. The CelCradle™ bottle is ready to use and is pre-packed with BioNOC™ II macrocarrier making it cost effective. One (1) CelCradle™ Bottle is equivalent to up to 20 roller bottles.

Small Scale Secreted Biologics Production  
 Secreted Virus (e.g. Rotavirus or Hog Cholera)  
 Secreted Extracellular Vesicles (e.g. Exosomes)  
 Proteins/ Recombinant Proteins  
 Virus Like Particles (VLPs)  
 Viral Vectors (e.g. AAV/LV or Simian Immuno-deficiency Virus)

For users under pilot/production scale who choose to use either single-use or multiple use vessel for adherent culture, Vaccixcell offers the TideCell® bioreactor system which is the world's largest linearly scalable bioreactor, from seed preparation in CelCradle™ to 5000 liters with closed automated cell harvesting.



► Cells

Cells			
Anchorage dependent		Human Derived Cell lines	
	3T3		Hepatocytes
	COS		Hepatic stellate cells
	Human Osteosarcoma		human diploid cell lines
	MRC-5		Mesenchymal Stem Cells - Umbilical cord derived - umbilical wharton's jelly - adipose derived - dental plaque - bone marrow
	BHK		fibroblasts
	VERO		Stroma
	CHO		HELA
	rCHO	Hybridomas	
	HEK 293		DA4.4
	HEK 293T		123A
	rHEK 293		127A
	rC 127		GAMMA
Insect			67-9-B
	TN-368		
	SF9	Fungi	
	rSF9	Yeast	
	Hi-5		
Viruses		Bacteria and Fungi	
Viral Vectors			
	Adeno-associated Virus (AAV)		
	Lentivirus		
Virus Like Particles		Yeast	

► Process Modes

Batch

All the ingredients are fed together at the start of the operation. It is relatively easy to maintain aseptic conditions because the number of additions is limited.

Fed-batch

The system can run in fed-batch mode controlling and regulating addition of important ingredients like glucose at appropriate stages of the batch. It increases the opportunity for optimizing environmental conditions of the cells.

Perfusion

It can be performed in the Hybrid bioreactor by connected feed and harvest vessel to the reactor vessel

- **Feed vessel** – contains fresh culture media to be added to the reactor vessel
- **Harvest vessel** – empty vessel used to contain media that is pumped out of the reactor vessel

100% Media Exchange

With feed and harvest tanks in tide motion, 100% media exchange can be provided to allow 100% fresh new media for virus to propagate making system ideal for production of secreted biologics

► Key Features

- Automated control of pH, DO, aeration, foaming, temperature, agitation, and level
- Glass water jacketed vessel heats to 37°C (±) 0.3 in just 30 minutes
- Inoculation and sampling in a closed system
- Working volume of up to 50 L
- Touch Screen HMI Controller. One touch screen HMI controller can be connected and control up to four (4) utility stations making DOE recording and analysis easier





# Hybrid Bioreactor Control Unit – Hive of Activity



## Hybrid Bioreactor

The VacciXcell Hybrid Bioreactor is a unique and multifunctional bioreactor system for your research and development. The control unit opens an innovative technology and robust flexibility suitable for your changing requirements. Whether adherent or suspension, choose your cultivation chamber from our range of multiple-use vessels:

- Conventional stirred tank autoclavable vessels
- Tide-motion matrix vessel

## Best Companion

Since the system can perform four (4) types of culture namely: adherent culture using macrocarriers, adherent culture using microcarriers, suspension culture and fermentation. Researchers can easily compare how one cell line performs or reacts to one type of culture method as compared to another.

## Configurable Design

Esco VacciXcell offers configuration for your bioreactor to match your specific needs. Hybrid Bioreactor offers comfort and convenience for flexible and scalable options from 1L up to 50L stainless steel vessel for secreted biologics production and from 0.1L up to 5,000L for adherent scale production all in the same 3D tide motion.

## Guaranteed World Class Quality

Esco VacciXcell Hybrid bioreactor is proven and tested for reliable quality. It is sold & serviced globally by Esco's 25 direct sales/service offices, factories and trained sales & service partners.





## Tide Motion Matrix Vessel

Our proven autoclavable borosilicate glass is available in both 1 Liter and 7 Liter suitable for your laboratory needs. The matrix vessel contains the carriers, BioNoc™ II, to which the cells adhere to and grow; it is oscillated up and down by air pressure to submerge and emerge the carriers in the nutrient medium.

### ► Benefits

- Optimizes our patented tide-motion principle that is proven effective and linearly scalable up to 5,000 liters
- 5.5g of BioNOC™ II has enough surface area to culture up to  $10^9$  cells
- Ability to scale up for large scale production

### ► Main Applications

- Adherent culture (Insect, Plant and etc.)
- Research and Development
- Laboratory-scale production
- Process development, optimization and characterization

## Stirred Tank Reactor Vessel

Our proven autoclavable borosilicate glass is available in both 1 liter and 7 liter suitable for your laboratory needs. The stirred tank reactor vessel is suitable for suspension culture. Easily switch from adherent to suspension by replacing the matrix basket with baffle in the reactor vessel.

### ► Benefits

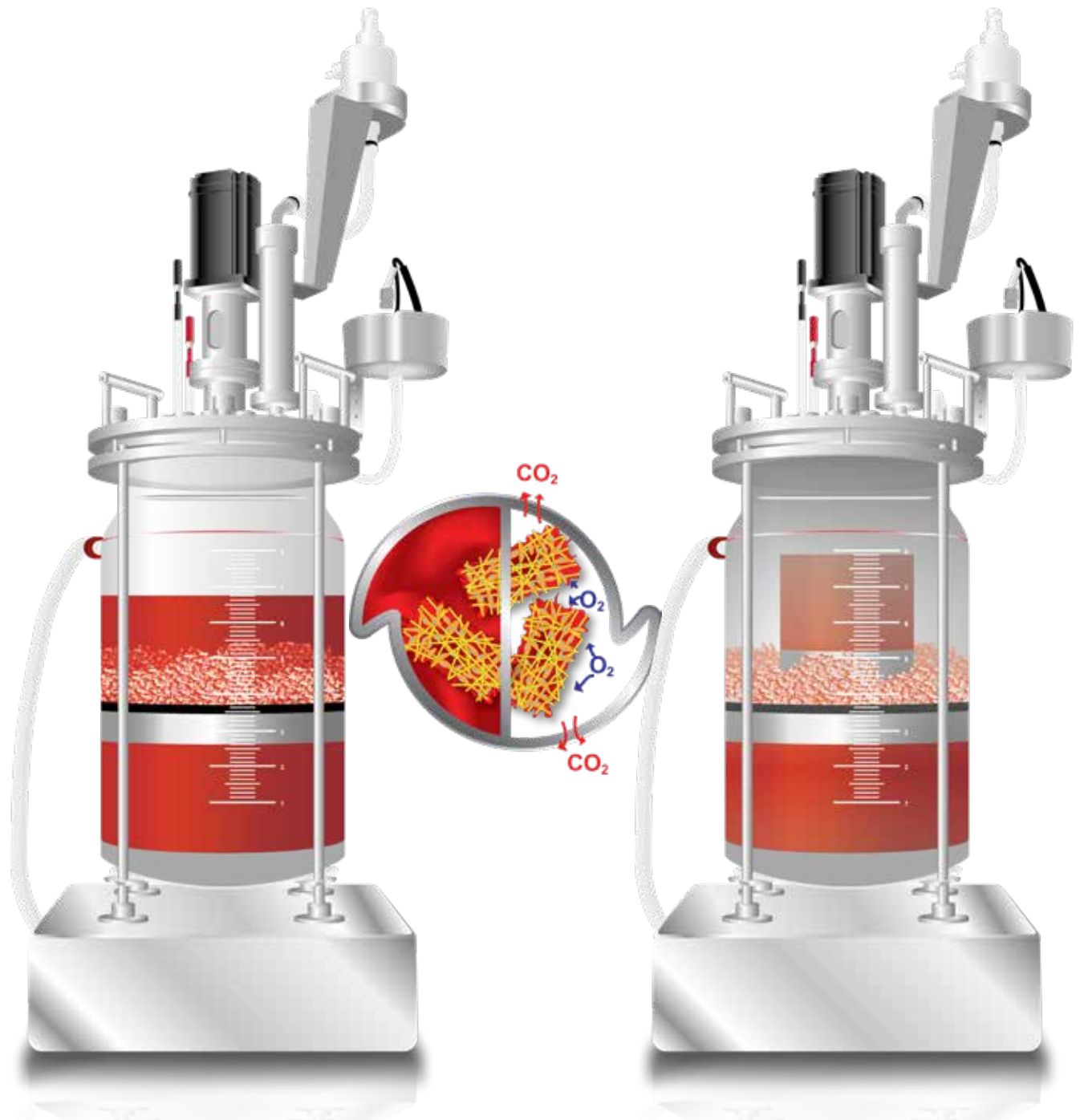
- Proven scalable stirred tank design
- Extensive performance and simplifies suspension/fermentation culture with easy steps

### ► Main Applications

- Suspension culture (Insect, Plant and etc.)
- Research and Development
- Laboratory-scale production
- Process development, optimization and characterization



## Tide Motion Technology Advantage



### Total Nutrition

- ✓ Matrices are submerged into the culture medium
- ✓ Eliminates nutrient starvation



### Total Aeration

- ✓ Direct exposure of matrices in the air
- ✓ Oxygen can penetrate the matrix bed

## WHY TIDE MOTION TECHNOLOGY

The gentle vertical oscillation of the medium creates a dynamic interface between the air and the adherent cells in the culture medium. Tide motion provides the cells with an environment that has low shear stress, high aeration and nutrition levels, zero foaming, and no oxygen limitation. This efficient nutrient and oxygen transfer produces high cell density yield that is linearly scalable

VacciXcell's tide motion system is intended for the culture of adherent or anchorage-dependent cells to be used for various applications.

### ► Benefits

- Large Surface Area (BioNOC™ II)
- High Productivity
- Low Downstream Processing Costs
- No Oxygen Limitation
- Low-shear Stress
- Zero Foaming
- Difficult Viruses
- Isolator Capability
- Continuous processing
- Immortal cell lines
- Linearly scalable from 1 L up to 50 L stainless steel for secreted biologics production and 0.1L up to 5,000 L for adherent scale-up production

### ► Main application

- cell banking
- cell culture-based vaccine production
- biologics production
- cell therapy
- gene therapy
- diagnostics





# Hybrid Bioreactor

## Exceeding your Expectations



### Reactor Vessel

The double-jacketed reactor vessel is made of borosilicate glass that guarantees safety, quality, and durability. The head plate, sparger, shaft and impellers are made of stainless steel 316L making it rigid, heat-proof, acid-proof, and alkali-proof.



### Chiller

A machine equipped to remove heat from a liquid via vapor compression cycle. The cooled water will be transported from the chiller to the double jacketed water vessel. The temperature can be as low as 7°C that are perfect for culturing specific viruses such as those used in fish vaccines.



### Control Unit

The Hybrid bioreactor's control unit allows users to easily configure culture parameters while also allowing continuous data and result tracking. Culture parameters are embedded and can effortlessly switch to different culture modes.



### BioNOC™ II

VacciXcell's BioNOC™ II is a low fiber content macrocarrier that acts as the packed bed component of the tide motion system in the bioreactor. It is a 100% PET fibrous culture matrix with stability of up to 5 years that has enough surface area to culture up to  $10^9$  cells. BIONOC™ II macrocarriers are placed inside the matrix vessel of the hybrid bioreactor.





### Connections for Sensors and Ports

All inlet and ports e.g. processed gases are located on the rear panel of the bioreactor's control unit. All connections are marked with the same names used in the reactor vessel for fast and efficient identification.



### Connections for External Accessories

Hybrid bioreactor makes it easy for the user to attach all cables and supplies to the reactor vessel. The couplings are properly named to match the corresponding labels in the head plate.



### Touch Screen HMI

8.4" touch screen HMI creates a comfortable working environment. The PLC-Base control structure increases performance, flexibility and reliability of the whole system. The main culture screen is a real time dynamic display that allows users to switch between automatic and manual control of parameters.



### Peristaltic pumps

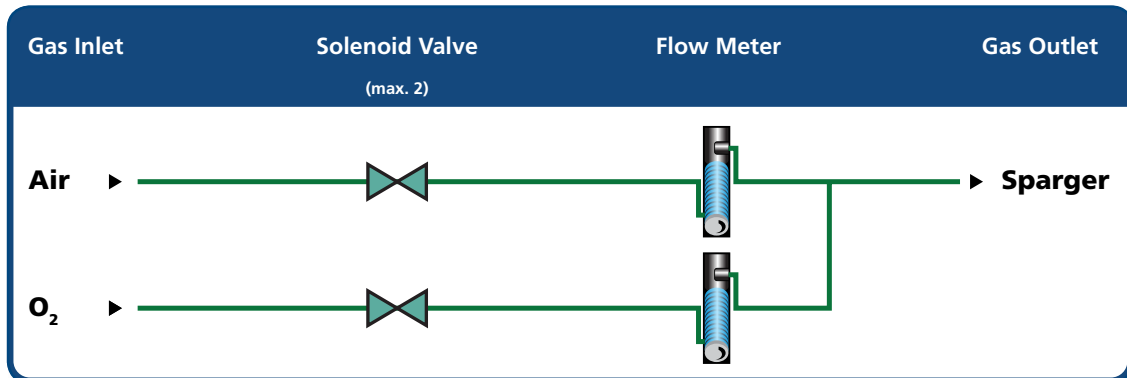
It is used to pump in liquids in the bioreactor. The hybrid bioreactor control unit has 4 function-assigned peristaltic pumps. Choose between pumps for feeding and harvesting of media or acid/base agents addition.

# Aeration Strategies

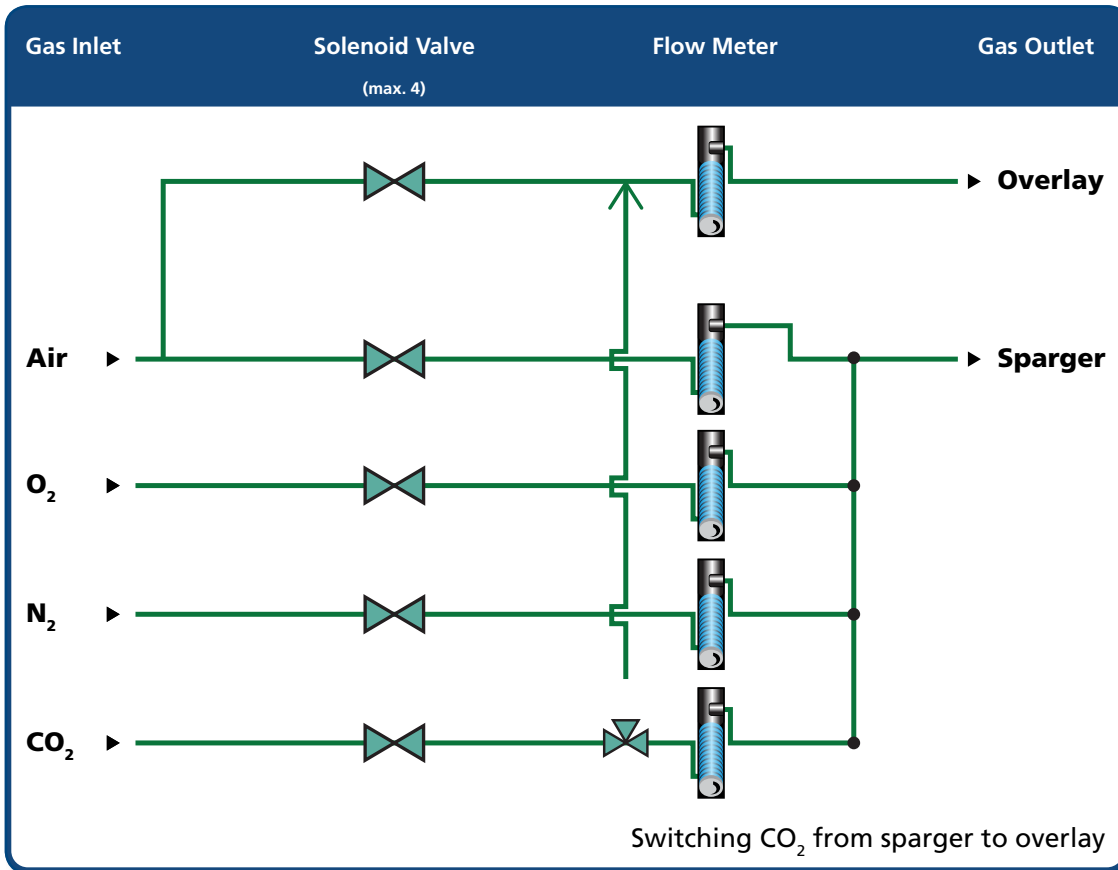
## Microbial Applications in Suspension Reactor Vessel

Different controller and configurations within the system enable air circulation techniques utilizing air or oxygen or O<sub>2</sub> enrichment of air.

The standard built-in solenoid valves located in the control unit, in combination with a rotameter (flow meter) ensures reliable gas supply for culture applications. The parameters may be adjusted by the user based on their pre-determined protocol to maintain stable gas flow rate which save both time and operational expense.



## Cell Culture Applications in Matrix Reactor Vessel



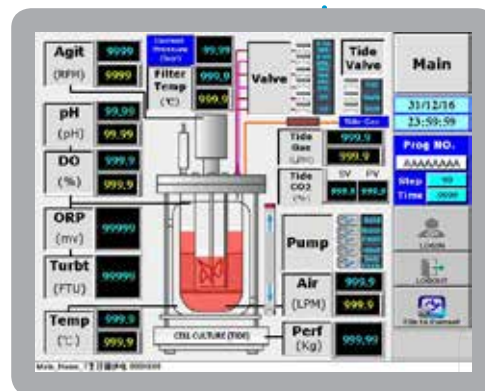
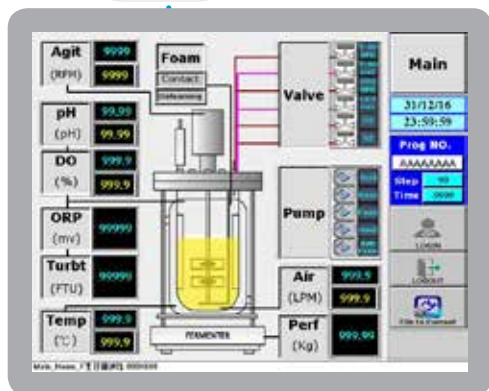
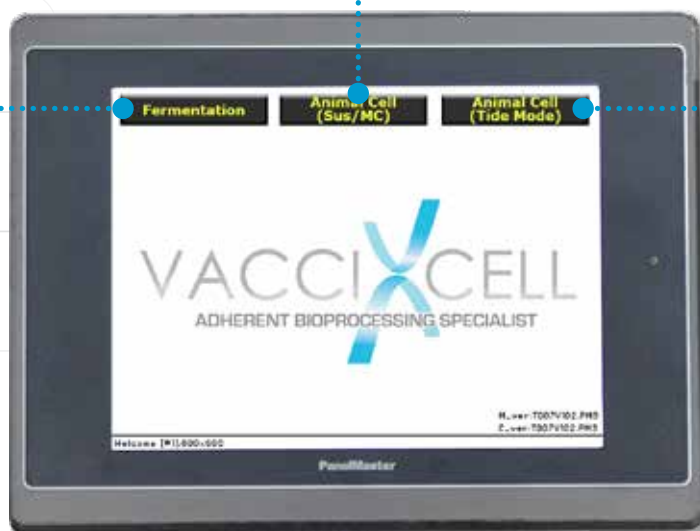
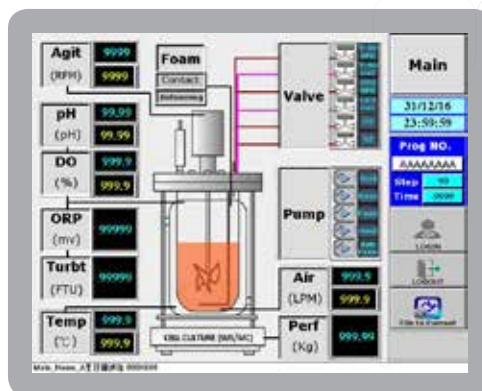
Gas lines are connected to its corresponding solenoid valves and rotameters deliver accurate and flexible control of gas flow.

The Hybrid Bioreactor HMI control page allows the user to switch amongst sparger and overlay for the CO<sub>2</sub> and Air (vent air for adherent culture) gas supply or pH control. Efficient gas exchange is achieved through the tide motion principle. Tide Motion uses this upward and downward liquid flow to provide both oxygen and nutrients to the adherent cells being cultured. The gentle vertical oscillation of the culture medium creates a dynamic interface between air and culture medium on the surface of the cells, providing the cells with an environment that is of low shear stress, high aeration and nutrition levels, zero foaming, and no O<sub>2</sub> limitation.

# Main Page

## Easy Switch for Every Mode

The Vaccixcell hybrid bioreactor gives its users exactly the option by being able to try out four (4) different types of culture namely: adherent culture using macrocarrier, adherent culture using microcarrier in a stirred tank environment, suspension culture and fermentation. By being able to do the design of experiment (DOE) using these four types of culture in one system, data gathering and analysis would be easier and more efficient, resulting in lower total cost and shorter process development period.







## Perfusion Processing Control

The different peristaltic pumps of the hybrid bioreactor can be programmed to perform different functions such as acid/base addition, feeding and harvesting. The hybrid can operate continuously for an extended periods of time at high cell density

DO Control (Select SEQ or SYN):

SEQ	DO+	DO-	Status Indicator	
Step 1	AG	N2	AG+	AG-
Step 2	V-AIR	N2	Air+	Air-
Step 3	O2	N2	V-Air+	N2+
Step 4	O2		O2+	

	HI	PV(sec)	LO	Time(sec)	Step Value
Agit	100		60	10.0	10
Air	5.0	Ref.	0.0	0.1	5.0
V-Air	5.0	0.0	9999.9	1.0	1.0
O2	5.0	0.0	9999.9	1.0	1.0
N2	5.0	0.0	9999.9	1.0	1.0

**DO Control**

07/04/17

14:59:13

AG	0
TP	35.8
pH	8.83
DO	0.2
Air	0.0
Perf	9.99

Prog NO.

AAAAAAAA

File to Current

## Automatic DO Control

The DO Control Page contains parameters that can be set for advanced controlling of DO injected to the culture medium. Modifications on the parameter setting of DO from agitation rate to gases injected in the reactor vessel provides specific set point for control.

The sequence of the parameters are steps to be followed by the system to keep the gas flow rate constant. It shall operate until the preferred aeration strategy is reached. This gives the user a flexible configuration for better processing requirement.

## Automatic pH Control

pH requirement can be met through setting parameters. These parameters can be acid/base addition or by CO<sub>2</sub> aeration and base addition. The hybrid bioreactor is equipped for setting parameters in different culture modes.



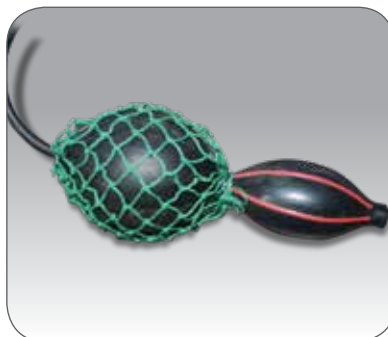
## Seeding, Feeding and Harvesting



### Seeding



Prepared seed for inoculation  
(1 L volume)



The inoculum from the seeding vessel  
is pumped through the bioreactor via  
balloon pump



Inoculum (seed) is pumped into  
the seeding port located inside the  
reactor vessel

## Programmable Peristaltic Pump

The different peristaltic pumps of the hybrid bioreactor can be programmed to perform different functions such as acid/base addition, feeding and harvesting.



Having programmable pumps allows hybrid to have:

- one (1) feed and one (1) harvest pump or,
- two (2) feed pumps

By having two (2) feed pumps, processes such as fed batch culture can be done with twice flow rate, giving more options to end users

### ▶ Feeding

- Feeding is the predetermined or controlled addition of nutrients into the bioreactor under culture operations.
- Allows a degree of control on the process and operations of hybrid bioreactor. It can control the rate of growth of the microorganisms or the concentration of the biomass by controlling parameters such as frequency of feed and concentrations of feed.

### ▶ Harvesting

- Harvesting is performed by separating the cell culture from the growing medium or harvesting secreted products in the bioreactor through the harvesting port.



# Technical Specifications

## Hybrid Bioreactor Control Unit

Control Unit Weight	
Single	80 kg (177lbs)
Control Unit Dimensions	
Single	W460x D 637 x H 903 mm
Utility Connections	
Power Supply	220 volts, max power consumption 5A
Gases	4x6mm external tubing diameter Gas supply pressure, 10psi oil & moisture-free
Water	Water supply pressure- 1.5 M Flow rate up to 10-12 lpm Minimum temperature 13-14°C L/S 35 Silicone for tubing
Control Unit	
Housing	Stainless Steel, AISI 304
Display	HMI
Resolution	800x600
SCADA Communication	Ethernet
Safety valve gas pressure	10 psi for Matrix Reactor Vessel and Suspension Vessel
Water inlet pressure reduction	0.15bar, integrated pressure control
Motor Drive	
Direct Drive	Power: 400W

## Reactor Vessel

Reactor Vessel Material	
1 Liter and 7 Liter vessel Total Volume: 1.5L and 8.2L	Borosilicate glass
14 Liter vessel	Borosilicate glass/Stainless Steel
25 Liter vessel	Stainless Steel
50 Liter vessel	Stainless Steel
Vessel Dimensions	
1 Liter	D 116 x H 148 mm
7 Liter	D 190 x H 320 mm
14 Liter	D 240 x H 450mm

(scale up sizes for 1L-50L vessel is applicable for Tide Motion Principle only)



Sensor   Measurement Range   Display Accuracy	Description		
Temperature	PT-100 class A ; Deviation: $\pm(0.15+0.00  t )$ ; 0°C-100°C		
Dissolved oxygen	Measurement Principle	Amperometric/ Polarographic	
	<b>Working Conditions</b>		
	Pressure resistance measurement	0.2-6 bar absolute (2.9-87.0 psi absolute)	
		Mechanical pressure resistance	
	Mechanical pressure resistance	max. 12 bar absolute (174.0 psi absolute)	
		Measuring temperature range	
	Measuring temperature range	0...80°C (32...176 °F)	
	Temperature range	-5...140°C (23...284°F) (autoclavable)	
	<b>Construction</b>		
	Temperature compensation	Automatic with built-in RTD	
	Cable connection	VarioPin (IP 68) straight or angled K8S straight (digital ISM sensors)	
	O-ring material	Silicone FDA and USPP VI approved	
	Membrane material	PTFE/Silicone/PTFE (reinforced with steel mesh)	
	Wetted metal parts	Stainless steel	
		Special material on request	
	Surface roughness of wetted metal parts (ISO 1320:1992)	N5 (< 0.4µm [16in])	
	Quick disconnect interior body	Standard	
	Cathode	Pt	
	Anode	Ag	
	Guard ring	No	
	<b>Dimensions</b>		
	Sensor diameter	12 or 25 mm (0.47" or 0.96")	
	Immersion length (a) for 12 mm sensor	70, 120, 220, 320, 420 mm. (2.8, 4.7, 8.66, 12.6, 16.54")	
	Immersion length (a) for 25 mm sensor	80, 160, 260, 360 mm (3.15, 6.3, 10.24, 10.17")	
	<b>Performances</b>		
	Detection limit	6ppb	
Accuracy	≤ ±(1% + 6 ppb) of reading in liquids		
Response time at 25°C/77°F (air – N2)	98% of final value <90s		
Sensor signal in ambient air (25°C/ 77°F)	50...110nA		
Residual signal in oxygen-free medium	<0.1% of the signal in ambient air		
Maximum flow error	≤ 5%		

Sensor   Measurement Range   Display Accuracy	Description	
Dissolved oxygen (cont'd)	<b>Certification</b>	
	EHEDG, 3A	Yes
	3.1B (EN 10204.3/1.b)	Yes
	ATEX certificate	Yes
	FM Approval	Yes
	FDA/USP VI	Yes
	Quality control	Yes
pH	Measuring range	pH 0...14
	Temperature	0...80°C for operation 0...140°C for sterilization
	Pressure resistance	Up to overpressure of max. 6 bar (87psi)
	Reference system	Argenthal (Ag/AgCl)
	Reference electrolyte	Gel electrolyte
	Diaphragm	1 ceramic diaphragm
	Glass membrane	HA, high alkali glass quality
	Glass shaft	Ø12 mm
	Plug head	K8S, Pg 13.5 thread
Foam Control	Teflon insulated stainless steel	
Level	Teflon insulated stainless steel	
Turbidity	<b>Dimension</b>	W 270 x D 200 x H 300 mm
	Measuring principle	Backscatter, 1-fiber
	Sensor material	DIN 1.4435 (316L)
	Sensor diameter	12 mm
	Insertion length	120, 205, 297, or 407 mm
	Process connection	Pg 13.5
	<b>Measuring range:</b>	
	Formazin Turbidity Units	10...40000 FTU
	Suspended Solids (Diatomaceous earth as reference)	0...250 g/L
	<b>Design:</b>	
	Cable connectors	SMA
	Cable lengths	3m (10ft) optical
	Cable type	Duplex HCS fiber, fixed

Sensor   Measurement Range   Display Accuracy	Description	
Turbidity (cont'd)	<b>Wetted parts:</b>	
	Metals	DIN 1.4435 (316L)
	Plastic	None
	O-ring	Viton-FDA
	Sapphire spigot for fiber protection	None
	Sapphire window for fiber protection	None
	<b>Working conditions:</b>	
	Pressure range	0...6 bar (0...87psi)
Redox	<b>Dimension</b>	W 270 x D 170 x H 230 mm
	Measuring range	pH 0...12
	Temperature	0...100°C in operation 0...130°C for sterilization
	Pressure resistance	From vacuum up to a process pressure of max 2.5 bar (36psi)
	Reference system	Argenthal (Ag/AgCl)
	Reference electrolyte	Pressurized gel electrolyte
	Diaphragm	1 ceramic diaphragm
	Glass shaft	Ø12 mm
	Plug head	K8S, Pg 13.5 thread
	RM load cells	Weight: 100 kg Dimensions: (in mm) 330 X 330

Vessel Sizing and Volume		
Model	M-1000	M-5000
Total Volume (L)	1.5	8.2
Maximum Working Volume (L) for Suspension Culture	0.6-1.1	4.5-7
Depth (mm)	116	190
Height (mm)	148	320
Recommended BioNOC II Matrix volume [ml]	180	1000
Recommended amount BioNOC II Matrix in grams	10	55
Aspect Ratio	1:2.5 (for suspension) 1:3 (for microbial culture)	

Specifications* of VXL Hybrid Bioreactor	Adherent Cell Culture		Suspension Cell Culture		Fermentation		Microcarrier-Based Cell Culture	
	Model	M-1000	M-5000	M-1000	M-5000	M-1000	M-5000	M-1000
Vessel Material	Borosilicate Glass							
Temperature Range	20 °C-70 °C Precision: 0.1 °C	10 °C-70 °C Precision: 0.1 °C	20 °C-70 °C Precision: 0.1 °C	10 °C-70 °C Precision: 0.1 °C	20 °C-70 °C Precision: 0.1 °C	10 °C-70 °C Precision: 0.1 °C	20 °C-70 °C Precision: 0.1 °C	10 °C-70 °C Precision: 0.1 °C
Baffle	N/A		YES		YES		N/A	
Top Stirrer Motor	10-1200rpm							
Impeller speed	25-200rpm		50-1200 rpm		50-1200 rpm		25-400 rpm	
Impeller Design**	Small 6-Blade Rushton Turbine		3-Pitched-Blade Turbine and 3-Marine-Blade Propeller		Large 6-Blade Rushton Turbine		3-Pitched-Blade Turbine and 3-Marine-Blade Propeller	
Ventilation	Ring Sparger		Micro-Sparger		Ring Sparger		Ring Sparger	
Drive Method	Tide: KNF brushless motor with air pump, controlled by PID or constant voltage direct drive. Mixing: Top direct servo motor with PID/PWM control				Mixing: Top direct servo motor with PID/PWM control			
Condenser	Stainless steel condenser with 0.2 um disk type or cartridge type filter							
pH Range	pH 4-14 Precision: 0.01							
DO Range	0-100 % Precision: 0.01%							
Aeration	10L/min Precision: 2%							
Emerging Time	0-100mins		N/A					
Submerging Time	0-100mins		N/A					
Liquid Level Control	High Level Sensor		Electronic Scale					
Sampling	liquid: sampling bottle; matrix: sample port		liquid: sampling bottle					
Foaming Control	N/A		YES		YES		YES	
Control Unit	8.4" HMI							



## North America

### USA

#### Esco Technologies, Inc.

##### Lab Division

903 Sheehy Drive, Suite F, Horsham, PA 19044, USA

Toll-Free USA and Canada: 1-877-479-3726

Tel: 215-441-9661

Fax: 484-698-7757

Email: [eti.sales@escoglobal.com](mailto:eti.sales@escoglobal.com)

Website: <http://escolifesciences.us>

##### Pharma Factory

2512 Metroprolitan Dr, Suite 120-B

Feasterville-Treose, PA 19053-6738

Tel: +1 215-322-2155 - Ext 1101

Email: [eti.pharma@escoglobal.com](mailto:eti.pharma@escoglobal.com)

Website: [www.escopharma.com](http://www.escopharma.com)

## Europe

### UK

#### Esco Gb Ltd

##### Lab Division

Unit 21 Shortwood Business Park,

Shortwood Close, Hoyland,

Barnsley, S74 9LH.

Tel: +44 (0) 1226 361529

Fax: +44 (0) 1226 741709

Email: [egb.ops@escoglobal.com](mailto:egb.ops@escoglobal.com)

Website: [www.escolifesciences.eu](http://www.escolifesciences.eu)

##### Pharma Division

Unit 2 R-Evolution @ Gateway 36,

Kestrel Way, Barnsley,

S70 5SZ

Tel: +44 (0) 1709 761669

Mobile: +44 (0)7823 775585

Email: [egb.pharma@escoglobal.com](mailto:egb.pharma@escoglobal.com)

Website: [www.escopharma.com](http://www.escopharma.com)

## Germany

#### Esco Medical

Dr. Sanjay Bhojwani

Regional Sales Manager

Germany, Austria, Switzerland

Email [sanjay.bhojwani@escoglobal.com](mailto:sanjay.bhojwani@escoglobal.com)

## Italy

#### Esco Technologies S.r.l.

Legal office: Via Giuseppe Mazzini 114/B,

00195, Rome, Italy

Operative office: Via Nomentana, 935,

00137, Rome, Italy

Tel +39 06 37513715

Fax +39 06 89281096

Email [marcello.bagli@escoglobal.com](mailto:marcello.bagli@escoglobal.com)

## Russia

#### Esco Russia

Building 4, 8, Novovladikinskii proezd

Moscow, Russian Federation

Email [slava.kodisov@escoglobal.com](mailto:slava.kodisov@escoglobal.com)

Website [escolifesciences.ru](http://escolifesciences.ru)

## Asia Pacific

### Singapore

#### Esco Micro Pte Ltd

21 Changi South Street 1 Singapore 486777

Tel: +65 65420833

Fax: +65 65426920

Email: [mail@escoglobal.com](mailto:mail@escoglobal.com)

Website: [www.escoglobal.com](http://www.escoglobal.com)

### China

#### Beijing

Room 701, Building C, the Triumph Center, No. 170

Beiyuan Road,

Chaoyang District, Beijing

Tel: +86 (10) 5823 6368

Fax: +86 (10) 5823 6369

**Shanghai**

Room 1211, Jiahe International Building, No.1, Lane 66,  
Huayuan Road,  
Hongkou District, Shanghai  
Tel: +86-21-60951955

**Guangzhou**

Room 908, West Tower, Ocean Pearl Building,  
No.21 Huali Road, Zhujiang New City,  
Tianhe District, Guangzhou, China 510623  
Tel: +86 (20) 3837 3621

**Chengdu**

Rm. 1-406, Building No. 2, Shangding International  
Building,  
No.27 4th Block, South Renmin Road,  
Chengdu City, Sichuan, China  
Tel: +86 (28) 8553 6219  
Website: <http://escolifesciences.cn>  
Email: [mail@escolifesciences.cn](mailto:mail@escolifesciences.cn)

**Hong Kong****Esco Technologies (Hong Kong) Limited**

Room 1705, New Tech Plaza,  
No. 34 Tai Yau Street, San Po Kong,  
Kowloon, Hong Kong  
Tel : +852 3628 3986  
Fax : +852 3186 2821  
Email: [mail@escolifesciences.hk](mailto:mail@escolifesciences.hk)  
Website: <http://escolifesciences.hk>

**India****Esco Biotech Pvt. Ltd.****Mumbai**

111-114, Agarwal B2B Commercial Centre, Dhruv Park,  
Off Link Road  
Kanchpada, Malad (W), Mumbai - 400 064  
Tel: + 91 22 2844 3636 / 2880 3636 / 2889 1375 / 2889  
3535  
Fax: +91 22 2889 3636 / 2880 3738  
Email: [info@escobiotech.in](mailto:info@escobiotech.in)

**Bangalore**

No. 1021, 1st floor,  
1st Main, 4th Block, Opp. Suguna Hospital,  
Dr. Rajkumar Road, Rajaji Nagar, Bangalore - 560 010  
Tel: +91 80 2340 1544  
Fax: +91 80 2340 1545  
Email: [bangalore@escobiotech.in](mailto:bangalore@escobiotech.in)

**Delhi**

Flat No. 504, 5th Floor, Vikrant Tower-4,  
Rajendra Place New Delhi 110 008  
Tel: +91 11 2575 9033/34  
Fax: +91 11 4576 9306  
Email: [delhi@escobiotech.in](mailto:delhi@escobiotech.in)

**Indonesia****PT Esco Utama**

Taman Tekno BSD Blok H6 no 10,  
Serpong, Tangerang 15314  
Tel: +6221 29 666 565 / 301  
Fax: +6221 29 666 302  
Email: [theresia.wibisono@escoglobal.com](mailto:theresia.wibisono@escoglobal.com)  
Website: <http://escolifesciences.co.id>

**Japan****Esco Japan Co., Ltd**

2-1-10 Nankoukita  
Suminoe-ward, Osaka City  
Osaka, Japan  
Fax: +81-6-6537-1626  
Email: [eiji.uenaka@escoglobal.com](mailto:eiji.uenaka@escoglobal.com)  
Website: <http://jp.escoglobal.com>

**Malaysia****Esco Micro (M) Sdn. Bhd.****Selangor**

No. 15, Jalan Sungai Buloh 27/101A,  
Persiaran Klang, HICOM 27 Industrial Park,  
40400 Shah Alam Selangor, Malaysia  
Tel: 03 5103 8480  
Fax: 03 5614 3385  
Email: [malaysia@escoglobal.com](mailto:malaysia@escoglobal.com)

**Melaka**

13-1, Jalan Melaka Raya 32, Taman Melaka Raya 1  
75000 Melaka  
Tel: 606-284 0007  
Fax: 606-283 0288  
Website: <http://my.escoglobal.com>

## Philippines

### **Esco Philippines, Inc.**

R-7 Ground Floor, Tower B  
Two E-com Center, Bayshore Ave.  
Mall of Asia Complex  
Pasay City, Philippines 1300  
Tel : +632-828-1527  
Email: philippines@escoglobal.com

## South Korea

### **Esco Korea Micro Pte Ltd**

#206, Byucksan Digital Valley 8-Cha, 70,  
Gyeongin-ro 71-gil, Yeongdeungpo-gu, Seoul,  
Republic of Korea  
Tel: +82-2-830-0482  
Fax: +82-2-830-0491  
Email: info@escoglobal.co.kr  
Website: <http://www.escoglobal.co.kr>

## Taiwan

No. 112, Sec. 2, Qingfeng Rd., Zongli Dist.,  
Taoyuan City 320, Taiwan  
Tel: +886 34533220  
Fax: +886 34532770  
Email: mail@escolifesciences.tw  
Website: <http://escolifesciences.tw>

## Thailand

### **Esco Lifesciences (Thailand) Co., Ltd.**

30 NP Building 4th Floor,  
Soi Rama IX 55 (Wisetsuk4),  
Rama IX Road,  
Suanluang, Suanluang, Bangkok 10250  
Tel : 02-187-2216  
Fax : 02-187-2207  
Email: customerservice2.th@escoglobal.com  
Website: <http://escolifesciences.co.th>

## Vietnam

### **Esco Vietnam Company Ltd.,**

#### **Hanoi**

7th Floor, No. 8, Alley 15, Trung Kinh Street,  
Trung Hoa Ward, Cau Giay District, Hanoi, Vietnam  
Tel: +844 62691460  
Fax: +844 62691461  
Mobile phone: +84904165623/ +84977966188  
Email: vietnam@escoglobal.com

### **Ho Chi Minh**

No. 14 - Lot G3, Street No. 53, Tan Quy Dong Settlements,  
Tan Phong Ward, District 7, HCMC, Vietnam  
Tel: (+84) 8 3776 0363  
Fax: (+84) 8 3776 0343

## Middle East/ North Africa

### Bahrain

#### **Esco Micro Middle East Representative Office**

Flat 26, Building 589  
Road 1111, Block 711,  
Tubli, Kingdom of Bahrain  
Tel : 0097336526145  
Email: middleeast@escoglobal.com

## South Africa

### South Africa

#### **Esco Technologies Pty Ltd**

Physical address:  
Unit 2 Landmark Park,  
17 Landmarks Avenue,  
Kosmosdal Extension 11,  
Centurion,  
0157  
Email : sonja.strydom@escoglobal.com  
Tel #: +2711 314 3184

#### **Direction postal:**

**Esco Technologies Pty Ltd**  
Postnet Kyalami Suite 37 P/BAG, X11  
Halfway House  
Gauteng  
1685  
Website: <http://za.escoglobal.com>

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21 Changi South Street 1 • Singapore 486 777  
Tel +65 6542 0833 • Fax +65 6542 6920 • mail@vaccixcell.com  
www.vaccixcell.com