NevoLine™ Upstream platform

Integrated & automated solution for intensified virus manufacturing

UNIVERCELLS Technologies

NevoLine™ Upstream platform

AN INTEGRATED & AUTOMATED SOLUTION

The NevoLine™ Upstream system is a flexible high-capacity, low-footprint automated platform for virus manufacturing under GMP guidelines. It offers an alternative to the traditional paradigm based on stand-alone unit operations. The platform enables intensified processing by integrating all process steps from inoculation to midstream processing to deliver a concentrated, clarified bulk ready for downstream.

Large-scale capacity in a compact module

- Commercial-scale throughput in a 3 m² footprint
- Integration of the intensified scale-X™ nitro bioreactor delivering high cell density

Reliable operations for reproducible performance

- Process automation reducing the number of manual interventions and minimizing risk of human error
- Seamless scalability achieved via the scale-X bioreactor structured fixed-bed design

Rapid manufacturing start-up

- Ergonomic design easing installation and in-process activities
- Continuous processing within a single automated system reducing production time

Flexibility by design

Single system integrating key unit operations for upstream and midstream processing

Configurable single-use assemblies fitting the product needs

Automation system enabling flexible configuration of recipes

MULTIPLE VIRAL APPLICATIONS

- Gene therapies
- Viral vaccines
- Immuno-oncology

DIFFERENT PROCESS CONFIGURATIONS

- **Cell culture** in perfusion or re-circulation
- **Viral production** via infection or transfection
- **Intra- or extra-cellular** product-based process
- **Filtration** in batch or in line
- **Filter configuration** in series or in parallel

ONE SYSTEM FITTING ALL

Drawing upon its expertise in equipment, bioprocessing and automation, Univercells Technologies aims at deploying smart engineering in its development. The company has designed a complete solution were synergies in hardware, single-use and automation lead to a breakthrough integrated design delivering unparalled performance.

The scale-X™ bioreactor range developed by the company combines the principles of intensification and chaining. Integrated in the NevoLine Upstream platform it enables Univercells Technology achieve compact and high throughput large-scale manufacturing.

Ergonomic compact upstream module

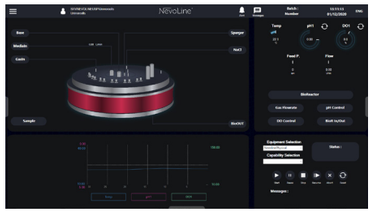
A single hardware designed to fit most process specificities and ease manipulations within a controlled microenvironment.

- Plug & play platform for easy installation and operation
- Uni-directional air flow cabinet
- Integrated HVAC and electrical connections

Single automation system

Automated recipe execution from cell culture to final clarification.

- In-line process control and monitoring
- Single, intuitive HMI for comprehensive system operation
- Recipe configurator to quickly start manufacturing



Comprehensive single-use offering

The NevoLine Upstream platform was designed with flexibility in mind to support different process flows, defined by the single-use assembly configurations

1. Cell culture & viral production
   scale-X™ nitro **200 & 600 m²**
2. Clarification I
3. Product concentration and Diafiltration
4. Clarification II

COMPREHENSIVE SINGLE-USE OFFERING

The NevoLine Upstream platform relies on configurable single-use assemblies adapted to your specific needs. They can be selected to accommodate different process configurations and scales, enabling sequential, continuous or parallel processing for time and footprint optimization.

Customize your process-specific configuration

Cell culture & virus production

Increasing viral productivity

- **Structured fixed-bed bioreactor**
  High viral productivity in a compact system
- **Scale-up within the same module**
  Hardware compatibility to 200m² and 600m² growth surface bioreactors
- **In-line and off-line monitoring**
  Bioreactor fixed-bed and media aseptic sampling

scale-X™ [nitro]

Product concentration & diafiltration

Conditioning product prior to purification

- **Intermediate harvest volume reduction**
  TFF and bioharvest chaining for continuous processing
- **Accomodating process specificities**
  Configurable pressure and pump-based monitoring
- **Adaptable processing mode**
  In-line or batch filtration

Parallel processing resulting in **volume reduction** and therefore overall **footprint**

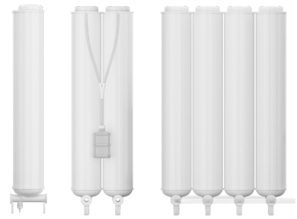
Pre-assembled manifolds according to main process steps to **facilitate installation** and enable a **quick start of manufacturing**

Enables **multi-product manufacture** through manifold and recipe changes

Single or multi-step clarification

Improving product stability and process performance

- **Flexible process integration step**
  Clarification can be defined depending on process requirements
- **Customizable filter selection**
  Fitting main T-caps filters
- **Adaptable filtration capacity**
  Clarification from 1 to 4 filters per bank



Automatic addition of small volumes

Additional instrument not required

- **Flexible reagent management assemblies**
- **Customizable tubing lengths**

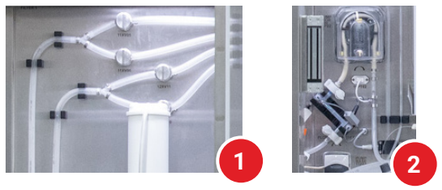
ERGONOMIC UPSTREAM MODULE

The system was designed in consideration of the operator, the product and the manufacturing environment to ease installation and connection to the hardware for a quick start of manufacture.

Easing and accelerating manifold installation and disposal

Guiding structure

The manifolds are guided and held in place via pumps, valves, holders and clips to ease installation step and clear processing space during operations.



Optimized single-use design

Single-use assemblies with pre-fitted manifolds and accessories to ease installation by reducing initial connections and minimizing tube lengths.

Plug-in bioreactor cart

On wheels with integrated heating and agitation, it eases bioreactor handling and installation. The installation of the cart in the platform is facilitated by guiding rails and connection is ensured by a magnetic lock.

Flexible windows

Opening in full for single-use installation & partially for in-operation manipulations such as sampling.

Facilitating in-process activities and reducing operator-related risk

Ergonomic positioning of the unit operations

The NevoLine Upstream system is engineered to reduce risks of injuries and ease remaining manual operations.

Convenient filters venting

Clarification filters venting can be done at low level to facilitate manipulation

Flexible installation and movement of the equipment

System on wheels 5

The system can easily be moved for connection or for maintenance purposes to access the electrical cabinets in back

INTEGRATED SINGLE AUTOMATION SYSTEM

The NevoLine Upstream is operated and monitored by a single controller and software enabling end-to-end continuous upstream and midstream processing.

From initial cell culture to end clarification

The automated end-to-end recipe execution is enabled by the chaining of all unit operations. The use of automated valves to control fluid flows reduces considerably manual operations ensuring process reliability and overall cost reduction.

Ensure process consistency

The controller enables process parameter control & automatic adjustment via sensors included at each step of the process.

- Temperature
- DO
- pH
- Pressure & liquid flow
- Level

Alarms were integrated at each processing steps and can be tracked remotely via the user interface. The system is complemented by an alarm light incorporated on the top center of the hardware.

Fast configuration & process initiation

The controller is pre-loaded with complete recipes defined based on process requirements and built-up with recipe blocks enabling an easy process configuration. Following the ISA 88 standards the user can easily change the recipe without Programmable Logic Controller modifications.

An intuitive user interface developed for quick & remote overview of main unit operations

3 dashboards allow the user to have a quick view and to remotely control the system :

1. Bioreactor for cell culture and viral production
2. TFF and bioharvest for product concentration / diafiltration
3. Enclosure

A P&ID screen allows a direct interaction with all the elements of the system

User can let the phase command or take control of the elements.

Hardware Specifications

NevoLine Upstream module

Parameter	Specification
Dimensions	2653mm x1134mm x 2500mm (+/-10mm) *104" x 45" x 98" (+/-4")*
Weight (empty, without bioreactor cart)	1472kg / 3245lbs
Weight (wetted, approximate with bioreactor cart)	1600kg / 3527lbs
Material of Construction	
Internal process chamber casing	Stainless steel 316L/Brushed 320/ Ra<1.6µm
Outer casing	Stainless steel 316L/Brushed 320/ Ra<1.6µm
Glazing	PMMA (polymethyl methacrylate) mass coloured (Plexiglass)
Internal cabinet floor	Stainless steel mesh
Castors	Stainless, platinum, polyamide and polyurethane
IP Rating	IP54 rated electrical cabinet
Utility requirements	
Power supply	400V, 16A, 3P+N+E 8kW power IP44 UPS (facility supplied)
Instrument air supply	0,22 µm filtered air (clean & dry) Air outlet @ 6 bar (90psi) up to 2L/min 8mm Festo tubing
CO2 supply	0,22 µm filtered gas (pharma grade) CO2 outlet @ 2 bar (30psi) up to 1L/min 8mm Festo tubing
Oxygen supply	0,22 µm filtered gas (pharma grade) O2 outlet @ 2 bar (30psi) up to 1L/min 8mm Festo tubing
Air process supply	0,22 µm filtered air (Pharma grade) Air outlet @ 2 bar (30psi) up to 2L/min 8mm Festo tubing

Process pumps

Pump purpose	Type	Operating range	Tubing ID
Bioreactor Media Inlet	Peristaltic pump	0-2500ml/min	¼" & 3/8"
Bioreactor Media Outlet	Peristaltic pump	0-2500ml/min	¼" & 3/8"
Liquid handling	Quarternary Diaphragm Pump	163ml/min –7.5L/min	3/8"
TFF feed	Quarternary Diaphragm Pump	163ml/min – 20L/min	¾"
Bubble trap	Peristaltic pump	0-2500ml/min	¼" & 3/8"
pH base control	Peristaltic pump	0-42 ml/min	¼"
Additives	Peristaltic pump	0-880ml/min	¼"
Virus addition pump	Peristaltic pump	0-880ml/min	¼"

Process flowmeters

Flowmeter purpose	Operating range
Permeate-waste	0-14L/min ±2%
Bioreactor inlet	0-8L/min

200m² & 600m² bioreactor carts

Parameter	Specifications
Dimensions including handle (W x D x H)	856mm x 1089mm x 982mm *34" x 43" x 39"*
Weight (empty)	177kg / 390lbs
Material of construction	
Casing	Aisi 316L Stainless steel
Castors	Stainless steel, Polyamide, Polyurethane tread

Automation

Automation & software

Control Software Features	Specification
Data management	Data acquisition and storage SQL-based structure, CSV format data export Database management
Network access	Remote access technical support Local WiFi hotspot, VPN
User management	Supervisory control Multiuser Option
Audit trail & alerts	Advanced charting Advanced reporting Process value alarms
Regulatory & quality standards	Recipe control according to ISA-88.01 21 CFR Part 11 compliance GAMP V compliance

Probes and sensors

Probes and sensors purposes	Operating range
Temperature probes	-50°C to +180°C
DO probes	0-300% saturation ±0.1% at 100% (25°C) ±2.5% at 200% Detection (probe): 0.05% saturation
pH probes	pH 3-10 ±0.15 after gamma Drift max 0.1/week at pH 7
High pressure range sensor	0 – 2 bars Input accuracy: 5.5 mbar 0 to 0.4 bar: ±2% of reading 0.4 to 2 bar: ±3% of reading
Low pressure range sensor	0 – 0.69 bar Input accuracy: 0.8 mbar 0 to 0.4 bar: ±2% of reading 0.4 to 0.69 bar: ±3% of reading
Permeate-waste flowmeter	0-14L/min ±2%
Bioreactor inlet flowmeter	0-8L/min ±1%

Single-use assemblies

scale-X™ nitro bioreactor assembly

Component	Parameter	scale-X™ nitro 200	scale-X™ nitro 600
Vessel	Surface area for growth (m²) Dimensions (H[1] x D) Total volume (L) Working volume range (L) Head space Bioreactor dead volume (L) Fixed-bed dead volume (L)	200 184.7 mm x 329.3 mm *7.27"x13.96"* 35 28.9 – 30.6 35 mm / 6.1 L 9.45 9.30	600 383.96 mm x 329.3 mm *15.12"x13.96"* 70 56.8 - 60.15 35 mm / 6.1 L 22.20 21.90
Material of construction	Fixed-bed non-woven fabric and spacer netting Casing	Polyethylene terephthalate (PET) and polypropylene Gamma stable polycarbonate	
Sampling	Fixed-bed sampling Liquid sampling	12 x single-use fixed-bed samples, aseptic sampling ports 1 x single-use assembly connected with multiple falcon tubes	
Impeller	Type Number of blades Material of construction Linear velocity range Maximal agitation speed	Centrifugal pump 10 USP Class VI, ADCF, gamma stable polycarbonate 0,5 -1 cm/s (10 mm Falling Film) 400 RPM	
Bottles	Foam bottle volume	500 mL	
Bags	Base adjustment volume	5 L	
Pre-fitted tubing	Inlet tubing type/internal diameter Outlet tubing type/internal diameter	1/4" 1/4"	

1. From top of carrier sample port to bottom of bioreactor

Clarification assemblies

Parameter	Specification
Composition	The clarification assembly is composed of a series of filters interconnected with tubing. This assembly is an open architecture design, end-users may choose the, size, brand and filter material that suits their process.
Number of filters	Between 1-4 filters connected in series
Number of steps	Single or multistep clarification
Type of filters	Filter must be in a T-style presentation
Tubing ID	Interconnected tubing having an internal ID of 3/8"

Tangential Flow Filtration assembly

Consumable	Parameter	Specification
Bioharvest vessel	Weight (empty) Dimensions (W x D x H) Volume Material of construction	15.3kg / 33.7lbs 500mm x 215.9mm x 679.9mm *19.69" x 8.46" x 26.77"* 55 L Polypropylene
Feed tubing	Internal diameter	3/4"
Permeate tubing	Internal diameter	1/2"
Retentate tubing	Internal diameter	3/8"
Foam trap	Volume	500 mL

Product contact components

Product contact component	Material of construction
Tubing	Platinium cured silicone Thermo plastic elastomer
Liquid handling pump	Polypropylene head, EPDM, and polyethylene
TFF feed pump	Polypropylene head, EPDM, and polyethylene
Connectors & fittings	Polypropylene / PVDF
Flow sensor	Polypropylene
DO probe	PA (Cycloaliphatic polyamide) EPDM VMQ (Silicone elastomer)
pH probe	Glass / VMQ (Silicone elastomer)
Pressure sensors	Polysulfone
Single-use components	USP Class VI <88> Biological Reactivity Tests, In Vivo USP <87> Biological Reactivity Tests, In Vitro ADCF (Animal Derived Component Free) Gamma irradiated to minimum of 25kGy

Installation pre-requisite

Category	Characteristic	Description
Room design consideration	Space requirement	Total length to schedule for the NevoLine Upstream cabinet: 3639mm (*139"*) The media tanks of 600L – 1000L must be connect on the left side of the NevoLine Upstream cabinet and final product tank and waste tank on the right side
HVAC design consideration	Air flow distribution & control Controlled room temperature Controlled relative humidity	Recommended process conditions: minimum clean-room ISO8/Grade D 20 ± 4°C (68°F ±7°F) 30-70%
Architectural consideration	Room construction, flooring, ceiling grid system	No lights, extraction or ventilation air are to be located on the ceiling directly above the UDAF It is recommended to allow a headspace of 200 mm above the system
Network	Connection type	Ethernet RJ45

Univercells Technologies SA
Chemin de la Vieille Cour 56a
1400 Nivelles – Belgium
Tel +32 2 318 83 48
www.univercellstech.com

UNIVERCELLS
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The next evolution of biomanufacturing