PerfuseCell

Customized Perfusion
Single-Use-Bioreactor

Continuous Biomanufacturing

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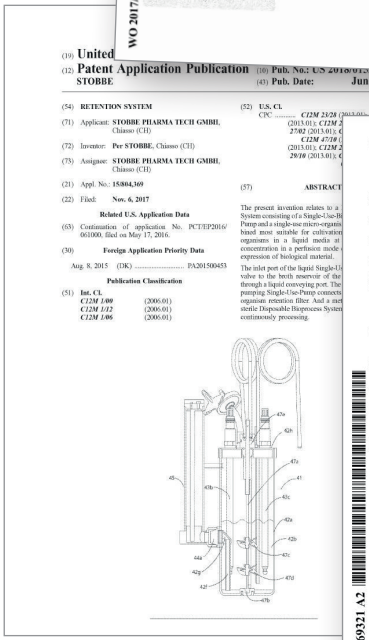
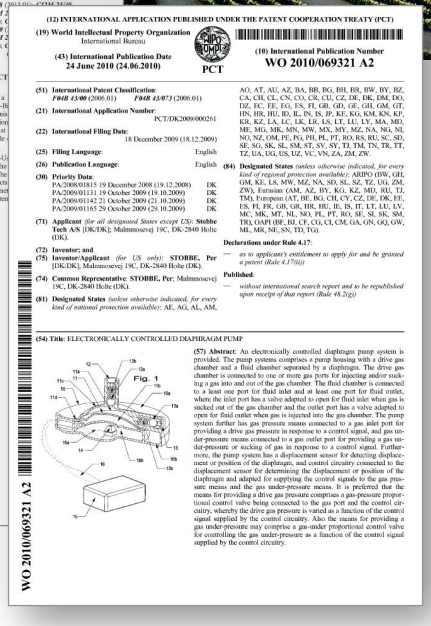
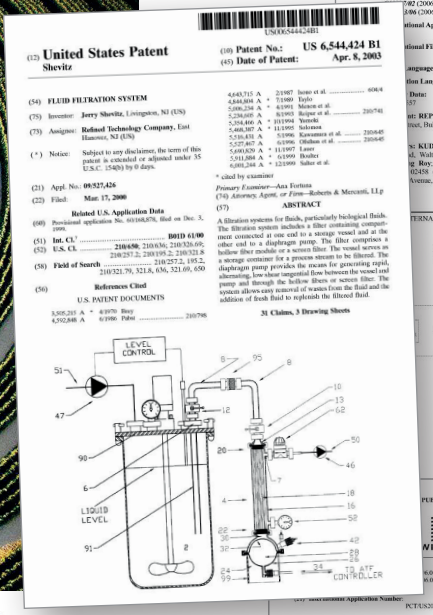
20-22 June 2018

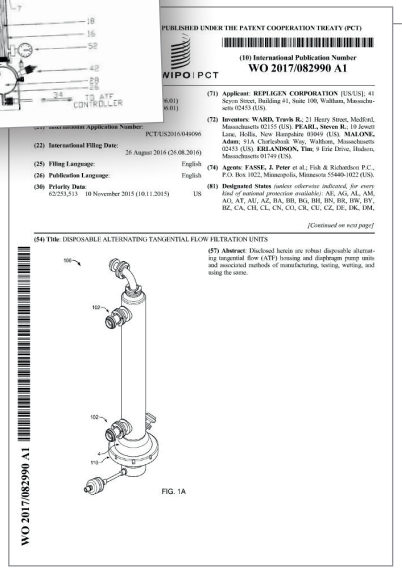
Please let me explain …
Per Stobbe
www.stobbepharma.ch

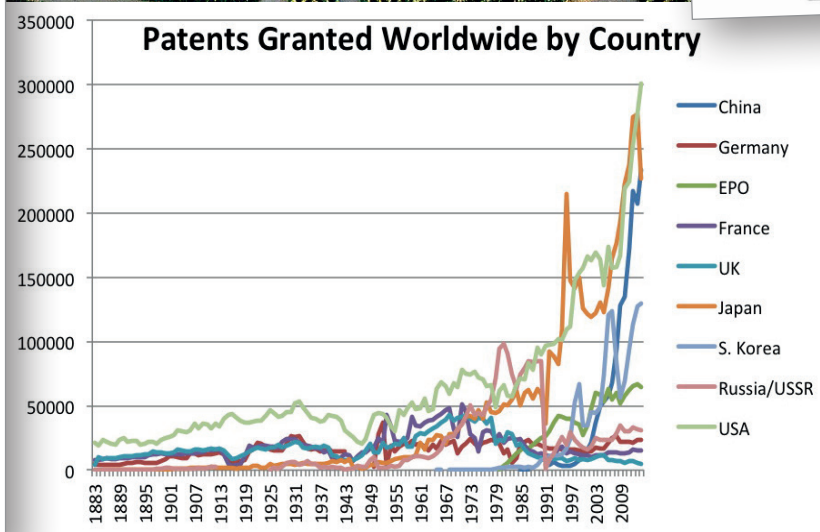
IPR – Intellectual-Property-Right's











Ready to use "right out of the box"

PerfuseCell

The building block's for Perfusion-SUB's

1 SUB
Single-Use-Bioreactor

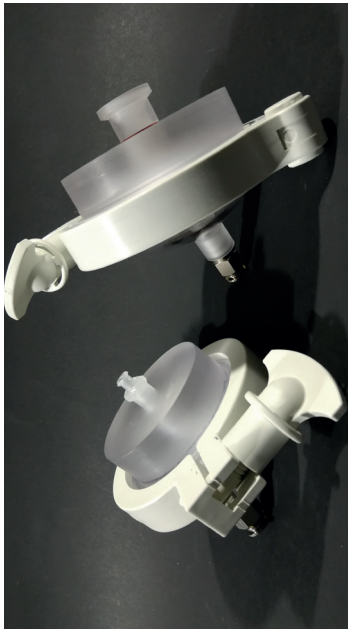
A SUB specifically designed for your application. Adaptable Working Volume, special impeller and aerator, desired length and hose brand, fit your existing PCS, etc.

2 Clio
Single-Use-Pump

Clio in an One-way-Single-Use-Pump (O-SUP) combining the HFF and SUB into the P-SUB.
Clio is a true Positive Displacement liquid pump fully computer controlled.

3 Thalia
Single-Use-Exchanger

Thalia is an Alternating-Single-Use-Exchange (A-SUE) connecting the HFF with the SUB.
Thalia is a true Positive Displacement broth exchanger fully controlled.



4 SUS
Single-Use-Sensor's

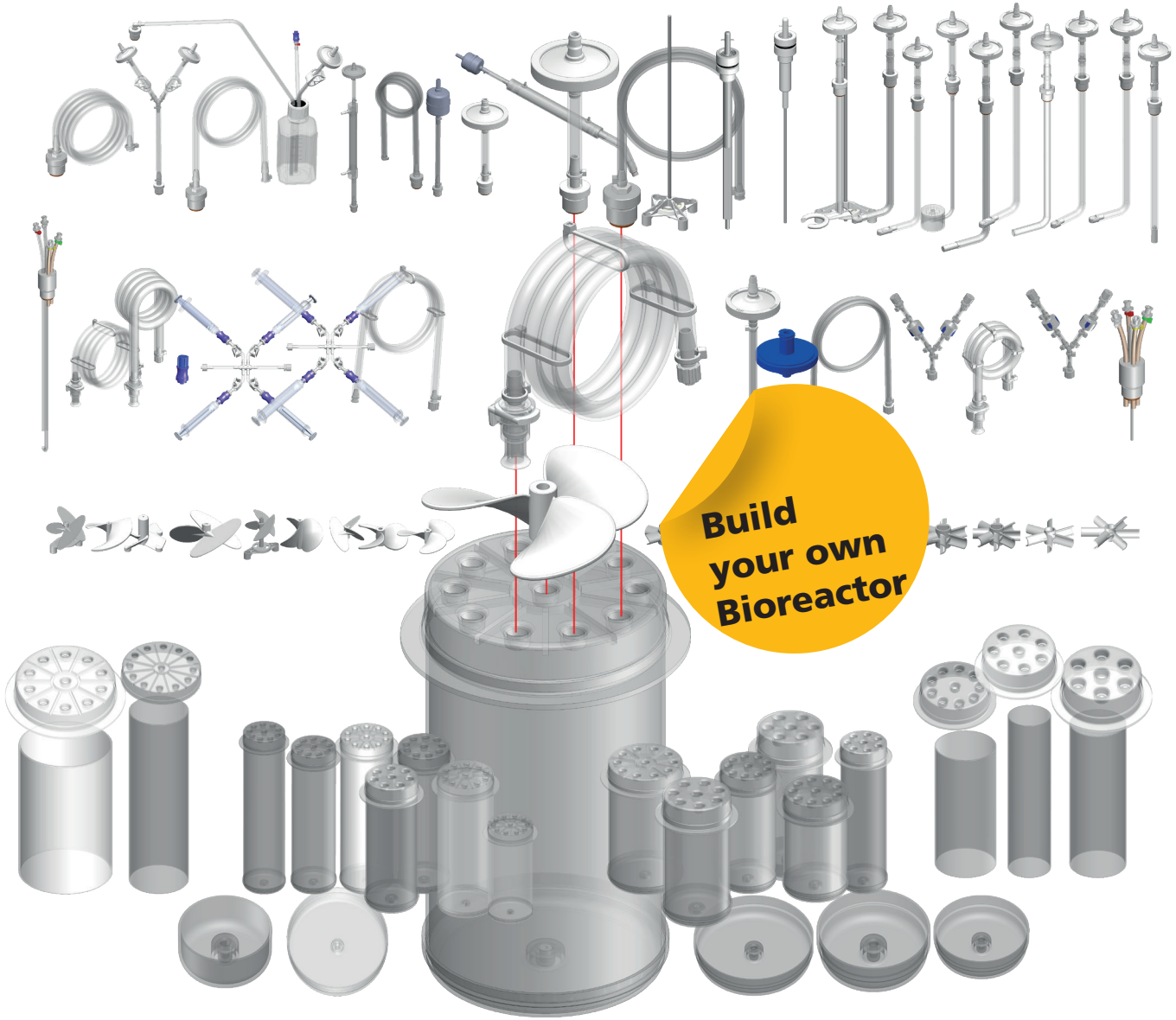
Single-Use-Sensor's which fit your existing Process-Control-System connections.
Parameters measured with VisiFerm, OneFerm, PICO biomass and level.

5 HFF
Hollow-Fiber-Filter

Choose your preferred size Hollow-Fiber-Filter combined with the O-SUP or A-SUE and the SUB.

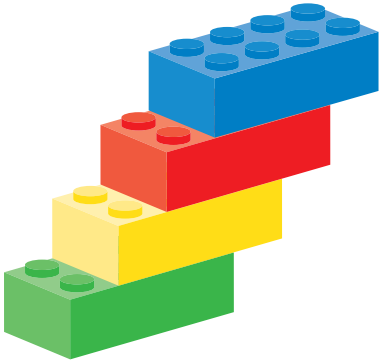
Any type, number and brand of HFF can be added.

❶ What does "Customized" really mean?



Build your next Perfusion-SUB exactly to your needs …

We have more than 5.000 components designed to fit each other. That´s millions of combinations !



If you know Lego® you will like to build with us.

It's all Plug & Play!

❷ The One-way-Single-Use-Pump

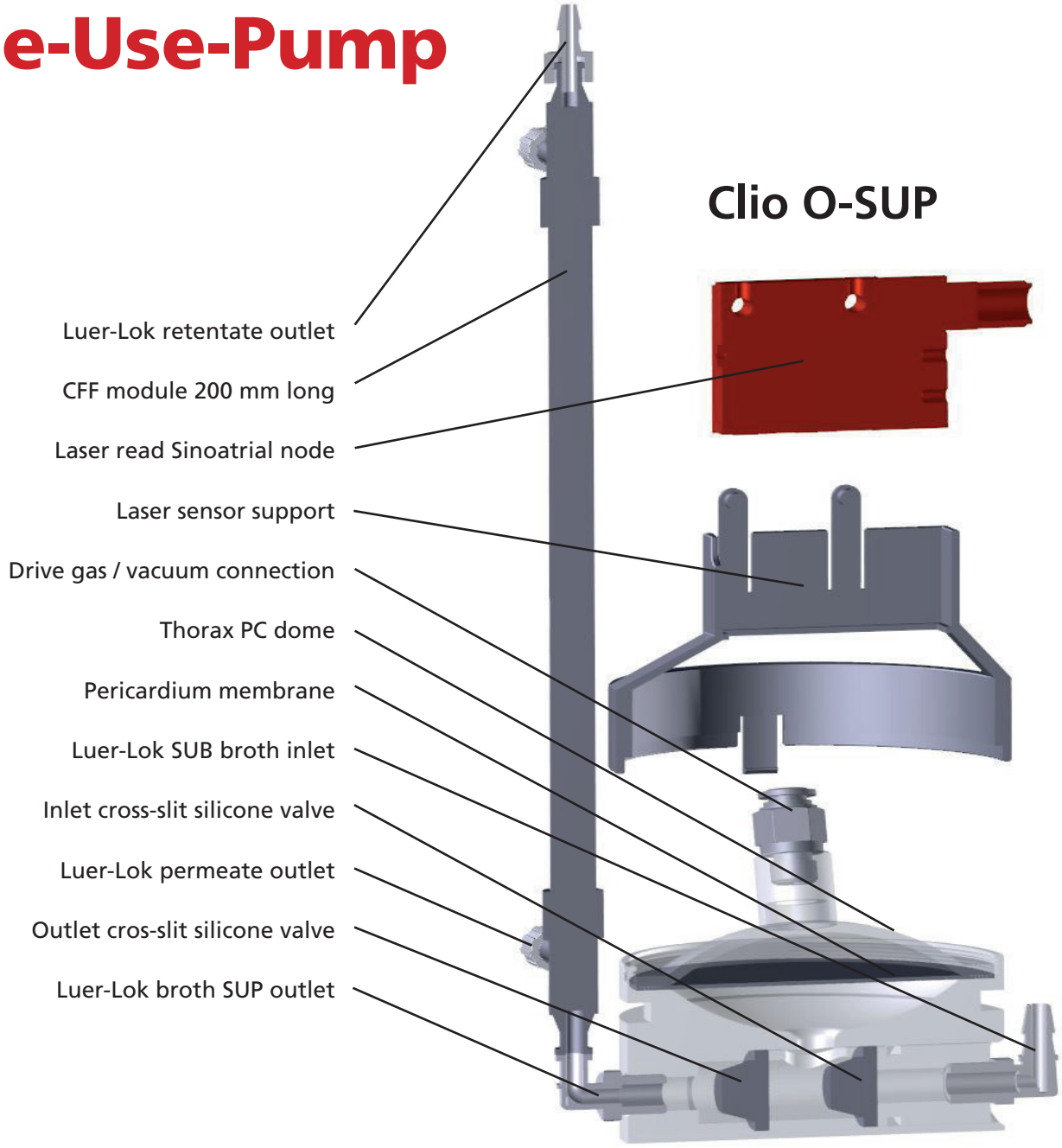
for accurate measurement of both volume and velocity

The O-SUP is a pump arranged inside a Polycarbonate housing with a set of passive liquid conveying valves.

The 1,0 mm thick silicone Pericardium membrane separates the drive gas pressure and / or vacuum from the broth.

The red tri-angular laser sensor read the membrane position with 0,1 mm accuracy at any time. Pressure sensors inside Clotho Drive Unit help calculating online the drive gas pressure. Clotho control via proportional valves and PID loop the wanted membrane position.

Clio can easily be programmed to pump fluids in 1:1000 range over time or by conveyed amount of fluid. Clio is a true Positive Displacement (PD) pump where every stoke is measured accurately independent of the ever dynamic stroke volume. Each stroke duration can vary between seconds and multiple minutes.



PerfuseCell

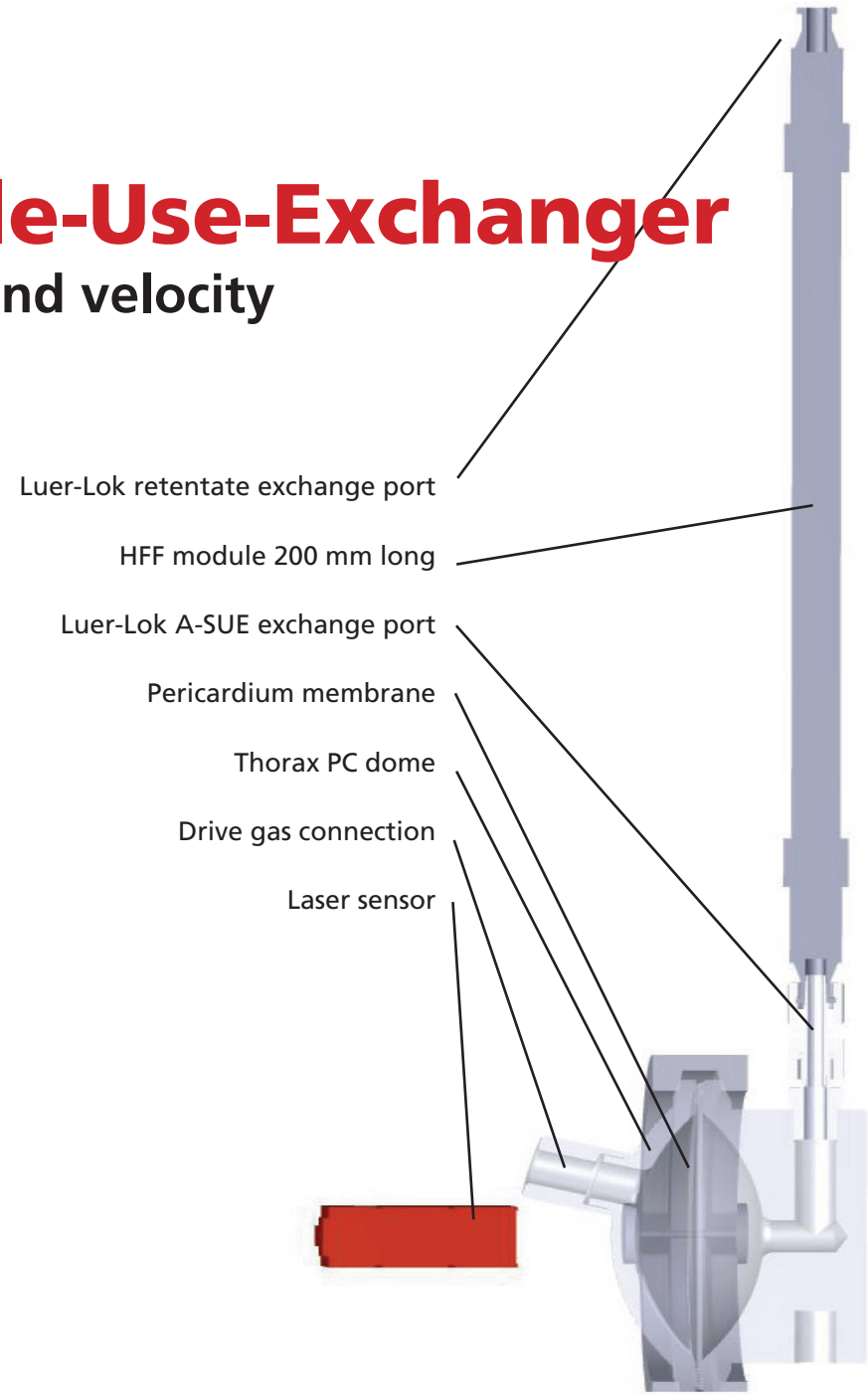
❸ The unique
Alternating-Single-Use-Exchanger
Thalia measure both volume and velocity

The A-SUE is arranged inside a Polycarbonate housing with no connected liquid valves. The A-SUE exchange liquid forth and back.

The 1,0 mm thick silicone Pericardium membrane separates the drive gas pressure and vacuum from the broth.

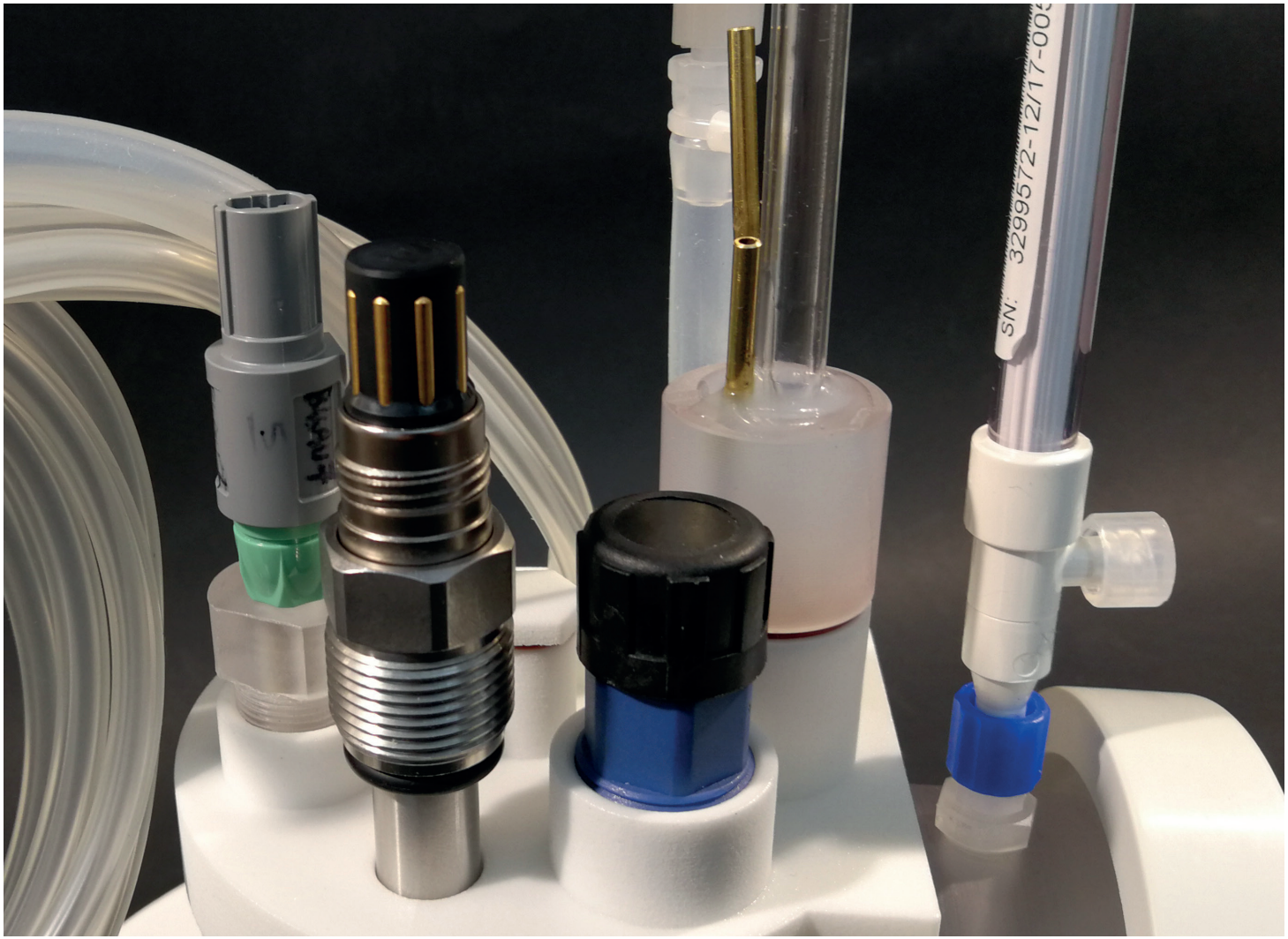
The red tri-angular laser sensor read the membrane position with 0,1 mm accuracy at any time. Pressure sensors inside Clotho Drive Unit participate in online calculation of the needed drive gas pressure. Clotho control proportional valves and hereby in PID loop the wanted membrane position.

Thalia can easily be programmed to convey fluid in 1:1000 range over time or by exchanged amount of fluid. Thalia is a true Positive Displacement (PD) exchanger where every stoke is measured accurately independent of the ever dynamic stroke volume. Each stroke duration can vary between seconds and multiple minutes.



Thalia A-SUE

❹ The unique **Single-Use-Sensor's** measures DO, pH, bio-mass, level



CellMembra-500 and CellRetention-500 as standard include pre-installed Single-Use-Sensor's (SUS) for DO, pH, bio-mass and level. The DO, pH and bio-mass SUS is mounted for lowest possible point of sensing in the broth. Photo show mounted vertically through the head-plate.

CellMembra-3200 and CellRetention-3200 as standard include pre-installed vertically mounted Single-Use-Sensor's (SUS) for DO, pH and level. Bio-mass as a horizontal option at bottom.

For accurate DO measurements we pre-install either VisiWell or PolarWell. Use the optical or polarographic Re-Usable-Sensor supplied with your PCS.

For pH measurements standard PCS cabling with either AK9 or AS8 connector coupled to the pre-installed pH SUS is recommended.

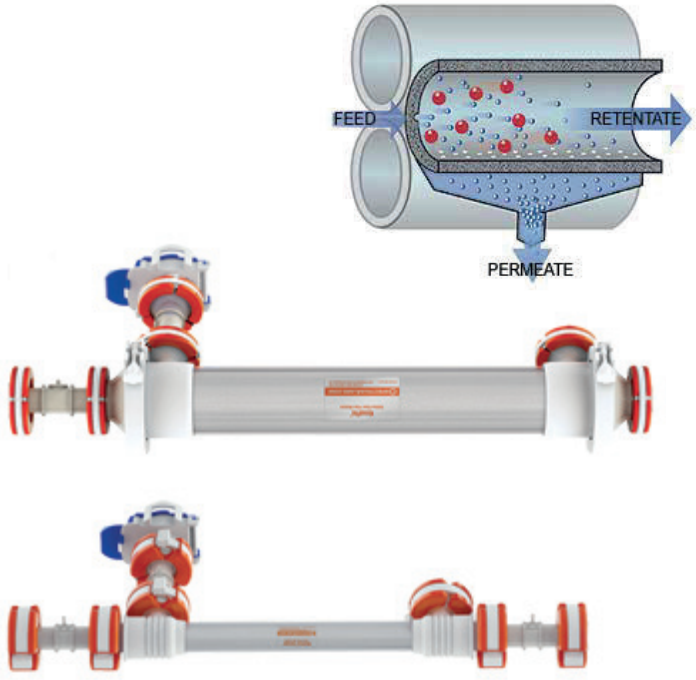
❺ The Hollow-Fiber-Filter

separates at 200 nm

Cross Flow Filtration is an efficient method for filtration and separation of solutions containing biomolecules, or particles such as viruses, bacteria or cellular material. It is a process whereby product flow (broth feed) is directed inside the multiple straw / tube shaped membranes with most of the solution as retentate circulated back into the SUB. A minimum of the broth feed pass tangentially across the membrane as permeate.

The rapid flow of broth along the membrane acts to 'sweep' the surface, reducing concentration polarization. It also prevents build-up of foulants that can plug the pores at the membrane surface. The rapid cross flow creates a pressure drop, which forces some of the feed solution and dissolved molecules that are smaller than the pores in the membrane, through the membrane filter as permeate.

The solution that passes through the membrane is referred to as filtrate or permeate. Molecules or particles larger than the membrane pores are retained in the feed, broth and effectively concentrated in the SUB.



PerfuseCell

Mini P-SUB

integrates Single-Use-Pump, Single-Use-Sensor's and Hollow-Fiber-Filter

CellMembra-500

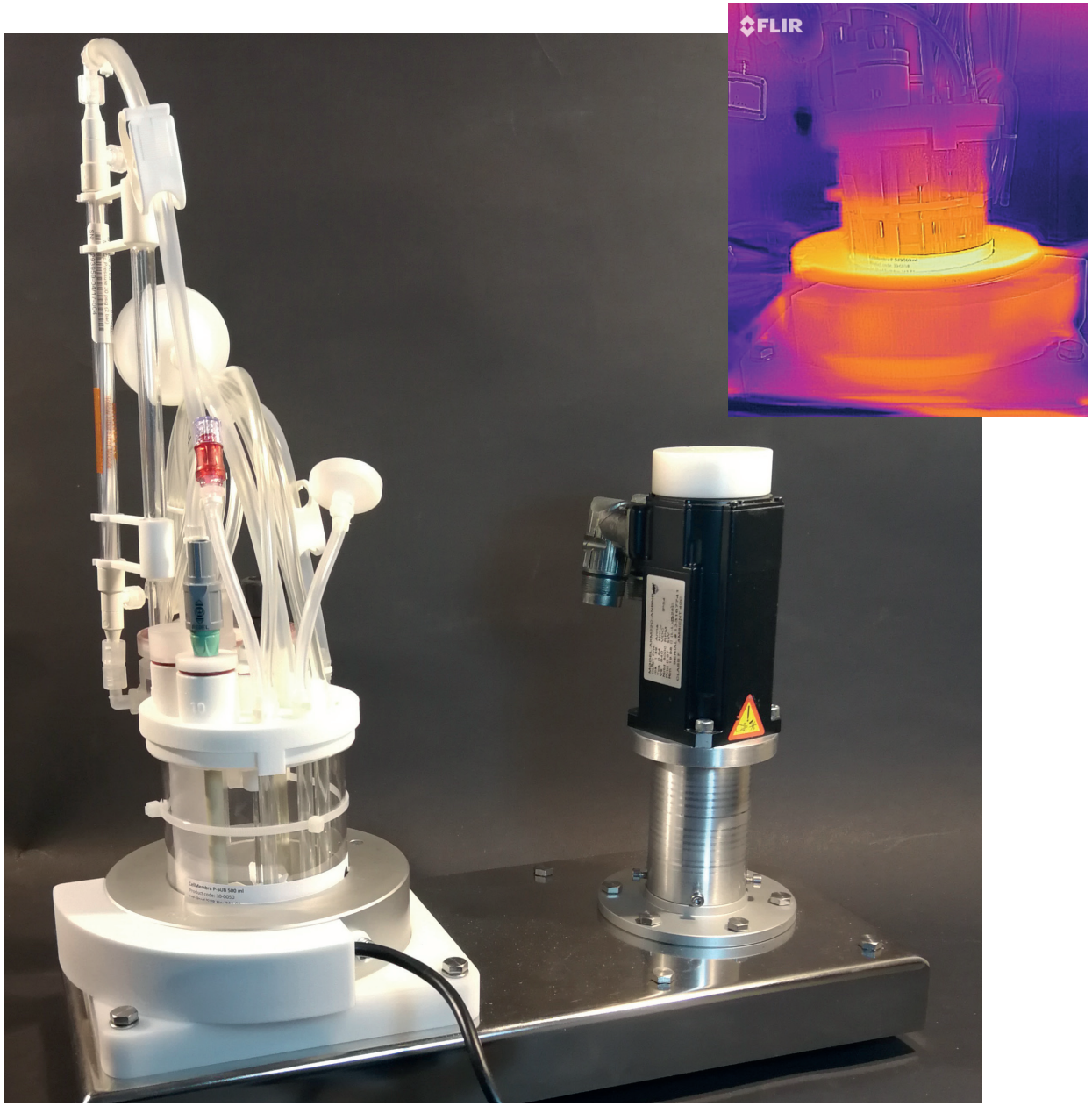
Mini P-SUB for cell retention in perfusion cultivation setup in a fully single-use setup. CellMembra-500 integrates a customized CellVessel Single-Use-Bioreactor (SUB) and a One-way-Single-Use-Pump (O-SUP) and 4 Single-Use-Sensor's combined with the HFF (Hollow-Fiber-Filter).

Features of CellMembra-500:

- CellVessel SUB designed for your applications and setup.
- Supplied with Single-Use-Sensor's (SUS) being DO, pH, bio-mass, and level.
- Pumped volume and obtained velocity accurately measured – no guessing.
- The complete and pre-assembled unit packed in dual film bags and precision irradiated – forget the autoclave.
- Working Volume (WV) range from 100 ml to 400 ml.

Mini P-SUB

driven by standard PCS



CellMembra-500

Mini CellMembra™ P-SUB's may easily be driven by traditional Process-Control-System`s (PCS) servo motor's. The high thermal mass Heating-Support-Foot (HSF-E) insure good PCS PID algorithm regulation. Select either electrical or water thermal control.

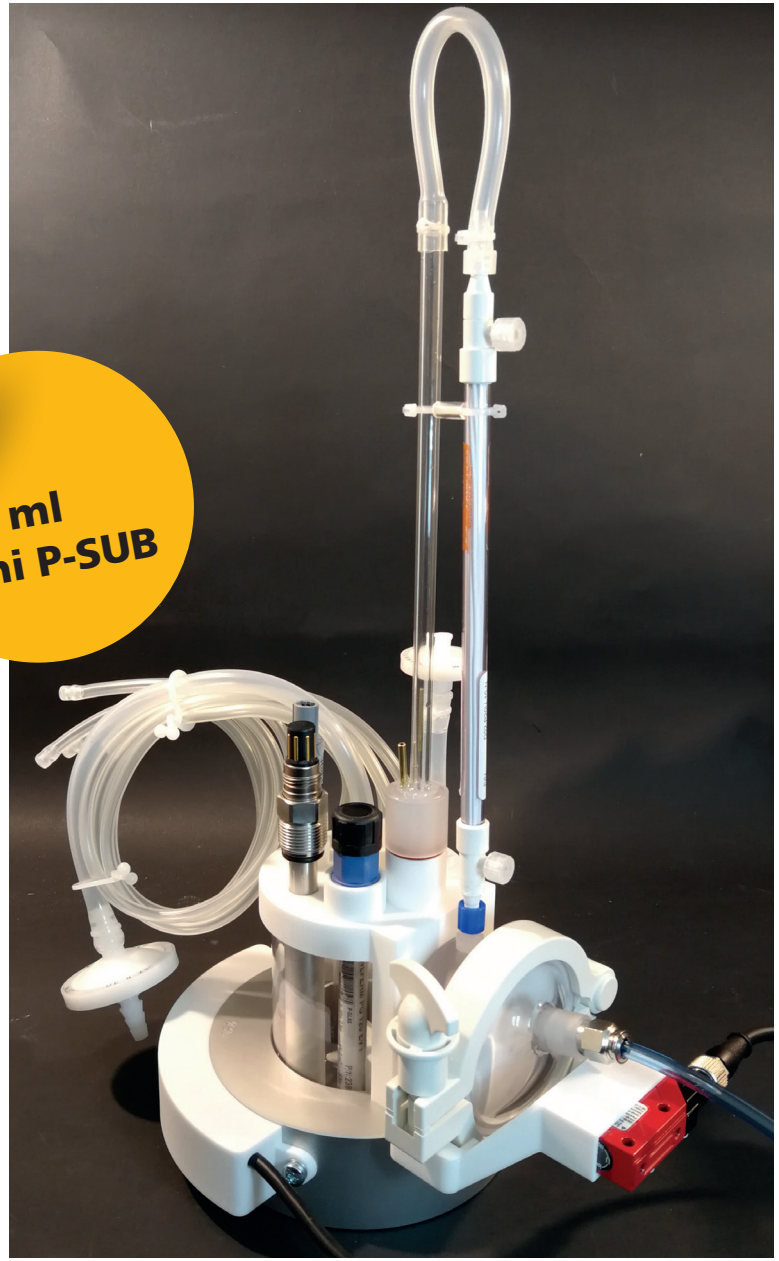
Features of CellMembra-500:

- Select the impeller for operation with your application and PCS setup.
- Single-Use-Sensor`s (SUS) as currently available (DO, pH, bio, level).
- 500 ml Vessel Volume (VV) for Working Volume (WV) ranging from 100 ml to 400 ml.
- The complete and pre-assembled unit packed in dual film bags and precision irradiated – forget the autoclave.

PerfuseCell

Mini P-SUB

with Single-Use-Exchanger, Single-Use-Sensor's, Hollow-Fiber-Filter



CellRetention-500

Mini P-SUB for cell retention in perfusion cultivation setup in a fully single-use setup. CellRetention-500 integrates customized CellVessel Single-Use-Bioreactor (SUB), Alternating-Single-Use-Exchanger (A-SUE), and 4 x Single-Use-Sensor's with the HFF (Hollow-Fiber-Filter).

Features of CellRetention-500:

- CellVessel SUB designed for your applications and setup.
- Supplied with 4 x Single-Use-Sensor's (SUS) being DO, pH, bio-mass, and level.
- Exchanged (alternating) volume controlled and obtained velocity accurately measured and displayed – no guessing.
- The complete and pre-assembled unit packed in dual film bags and precision irradiated – forget the autoclave.
- Working Volume (WV) ranging from 100 ml to 400 ml.

Parallel P-SUB's

designed for any Process-Control-System

Perfusion-SUB-500

Do you need like 4 or 8 or 16 P-SUB's operating in parallel? Mix freely between the 500 or the 3200 size P-SUB's and even CellVessel SUB's? Do you already have 4 or more Process-Control-System's (PCS) available in your lab. Straight forward with all the accessories available from PerfuseCell.

Its all Plug & Play!

- Whatever servo motor you may have the MST can adapt – with agitation for both 500 ml and 3.200 ml VV P-SUB's.
- The width of 4 x P-SUB's mounted in HSF on MST is less than 0,8 meter space on your lab table.
- This setup fits in particular well the DasGip Parallel PCS system with RE30 or RE40 servo motors (PCS pn 76DG04CC or 76DG08CC or 76DG16CC).

Medium size P-SUB

with Single-Use-Pump, Single-Use-Sensor's, Hollow-Fiber-Filter

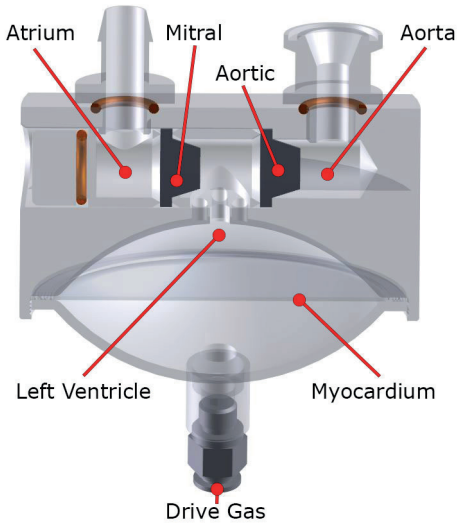
The 3,2 liter Vessel Volume (VV) P-SUB is basically a fully customizable CellVessel expanded into the CellMembra concept

CellMembra-3200

- CellVessel SUB with 3,2 liter Vessel Volume (VV)
- CellVessel SUB ranging 0,4 – 2 liter Working Volume (WV)
- Integrated Clio-100 O-SUP with fully controlled and measured 0 - 100 ml volume per stroke
- Any available HFF can be specified and pre-installed and as many as needed
- SUB with any type of impeller and as many as needed
- Agitation from top (HPD) facilitates RE30, RE40, P100 servo motor with ID25-A adaptor, or Biostat with ID39-B adaptor
- Agitation by Magnetic-Bottom-Drive (MBD) by PerfuseCell Magnetic-Stirrer-Table (MST) by any servo motor. Such as Biostat servo motor with ID39-B adaptor
- Single-Use-Sensor's with connectors which fit your PCS

Medium size P-SUB

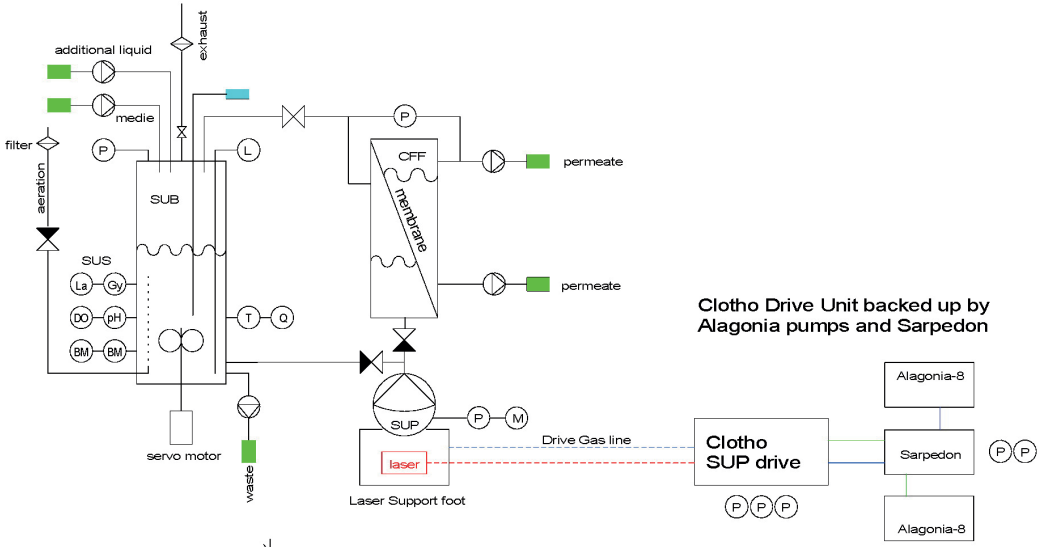
with Single-Use-Pump, Single-Use-Sensor's, Hollow-Fiber-Filter



CellMembra-3200

- CellMembra-3200 is all pre-assembled and ready to use
- O-SUP is Clio-100 with selectable 0 – 100 ml volume per stroke
- O-SUP fully controlled volume and velocity by Clotho
- Fully customized setup and any HFF mono or dual
- Single-Use-Sensor's (SUS) as required (DO, pH, bio-mass, level)
- Compact Clotho Drive Unit is needed
- Alternatively Alagonia-8 pumps and perhaps Sarpedon
- Drive Unit is available in both a single channel and dual channel version within the same U2 cabinet

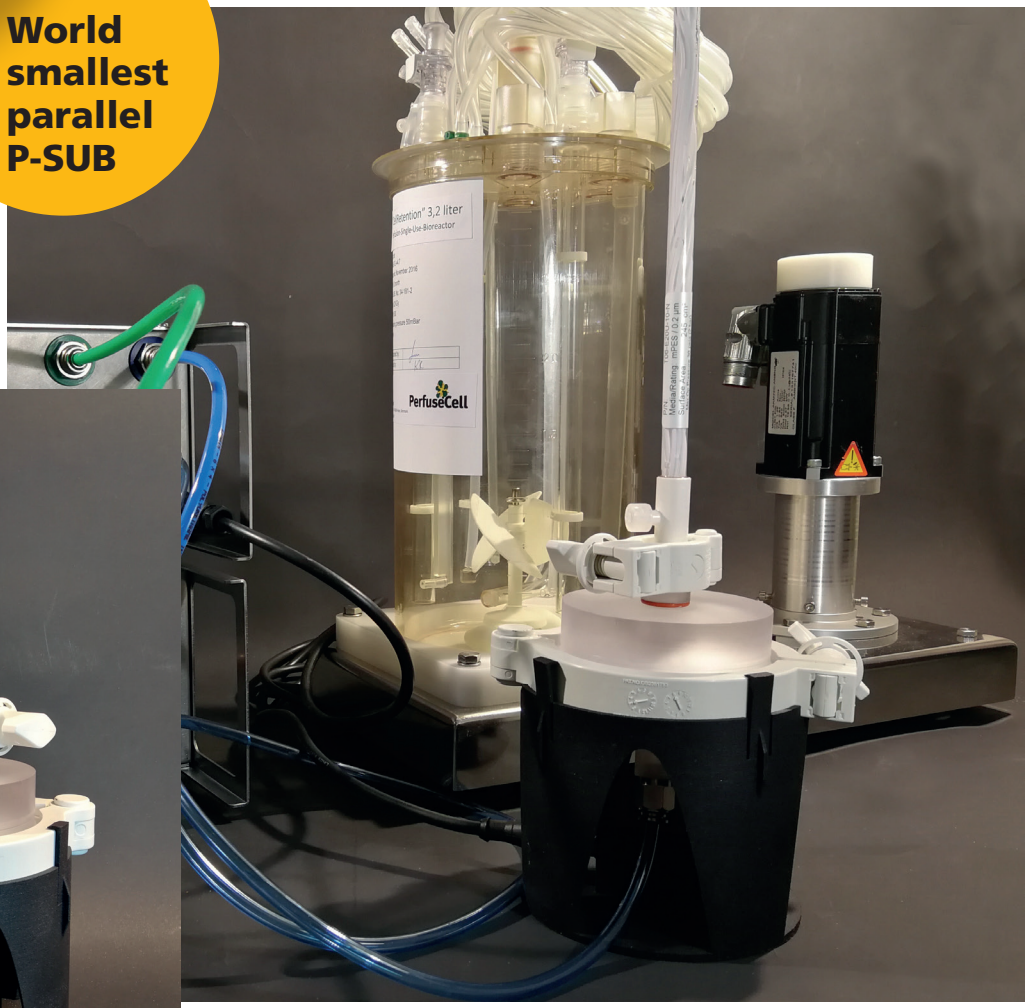
CellMembra Perfusion-SUB integrating Clio O-SUP pump, sensors, valves
Perfusion, cell retention, one direction pulsating flow through CFF

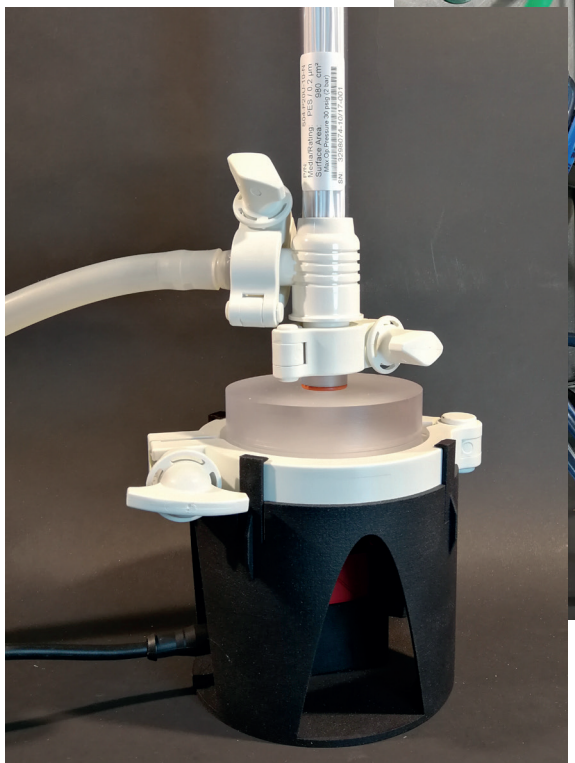


Medium size P-SUB

integrates Single-Use-Exchanger, Single-Use-Sensor's, Hollow-Fiber-Filter

World smallest parallel P-SUB



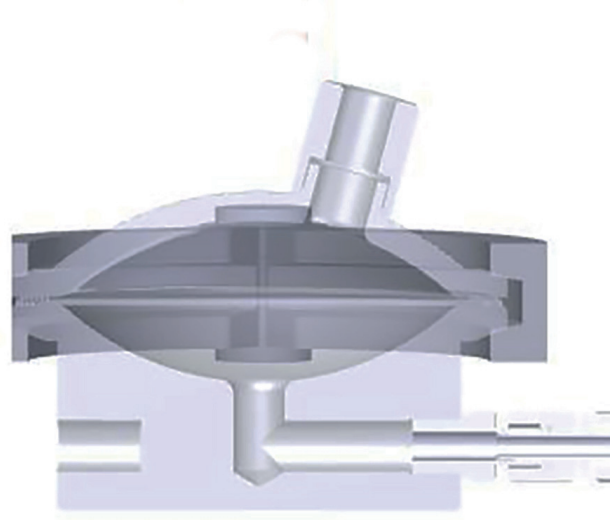


CellRetention-3200

- CellVessel SUB with 3,2 liter Vessel Volume (VV)
- CellVessel ranging 400 ml – 2.000 ml Working Volume (WV)
- Integrated Thalia-100 A-SUE fully controlled and measured 0 - 100 ml volume per stroke
- Any available HFF can be specified and pre-installed and as many as needed
- SUB with any type of impeller and as many as needed
- Agitation from top (HPD) facilitates a range of servo motors with a variety of adaptor's
- Agitation by Magnetic-Bottom-Drive (MBD) by PerfuseCell Magnetic-Stirrer-Table (MST) with any servo motor
- Range of Single-Use-Sensor's with connectors which fit your PCS

Medium size P-SUB

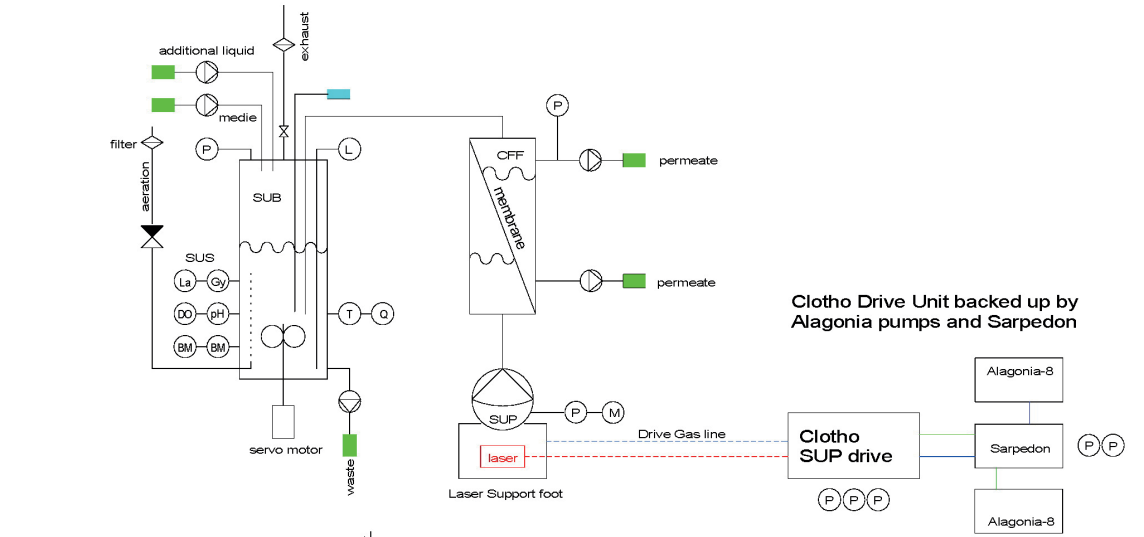
with Single-Use-Exchanger, Single-Use-Sensor's, single-use Hollow-Fiber-Filter



CellRetention-3200

- CellRetention-3200 is all pre-assembled and ready to use right out of the box
- A-SUE is Thalia-100 offering 0 – 100 ml per stroke accurately programmed
- A-SUE fully controlled volume and velocity
- Fully customized setup and any or multiple HFF
- Single-Use-Sensor's (SUS) as required (and available)
- Clotho Drive Unit is needed
- Alternatively Alagonia-8, Alagonia-12 and Sarpedon

CellRetention Perfusion-SUB integrating Thalia A-SUE, Single-Use-Sensors, Cross-Flow-Filter for alternating pulsating flow through CFF



Ultra compact
Clotho-2 Drive Unit
for CellMembra / CellRetention / CellBLU

The portfolio of CellMembra and CellRetention and CellBLU Perfusion-SUB's are all driven by the green Clotho / blue Lachesis software for super accurate control and comprehensive data acquisition.

The ultra compact Clotho-2 Drive Unit is able to control both the Clio One-way-Single-Use-Pump's (O-SUP) and / or the Thalia Alternating-Single-Use-Exchanger (A-SUE) over distances up to 2 meter with 1% accuracy.

The all stainless steel and stackable Hephaestus U2 cabinet measures (in mm):

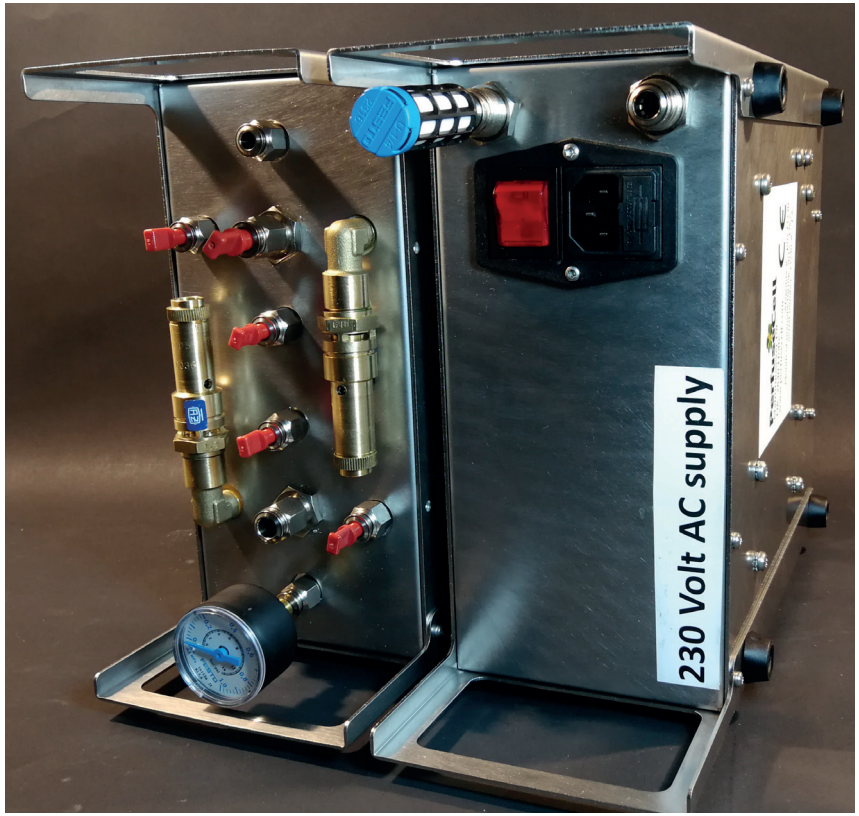
- W: 230
- D: 230
- TD: 295
- H: 110

Clotho Drive Unit and possible accessories

Clotho Drive Unit is housed in ultra compact stainless steel Hephaestus size U2 cabinet.

Clotho-2 facilitate two (red) Laser sensor input and several internal pressure sensors. For independent control of two in parallel and selectable size operating Single-Use-Pump's and / or Single-Use-Exchanger's.

For simple, low noise, ultra compact and fast setup – Alagonia drive gas pump's and Sarpedon manifold / reservior.



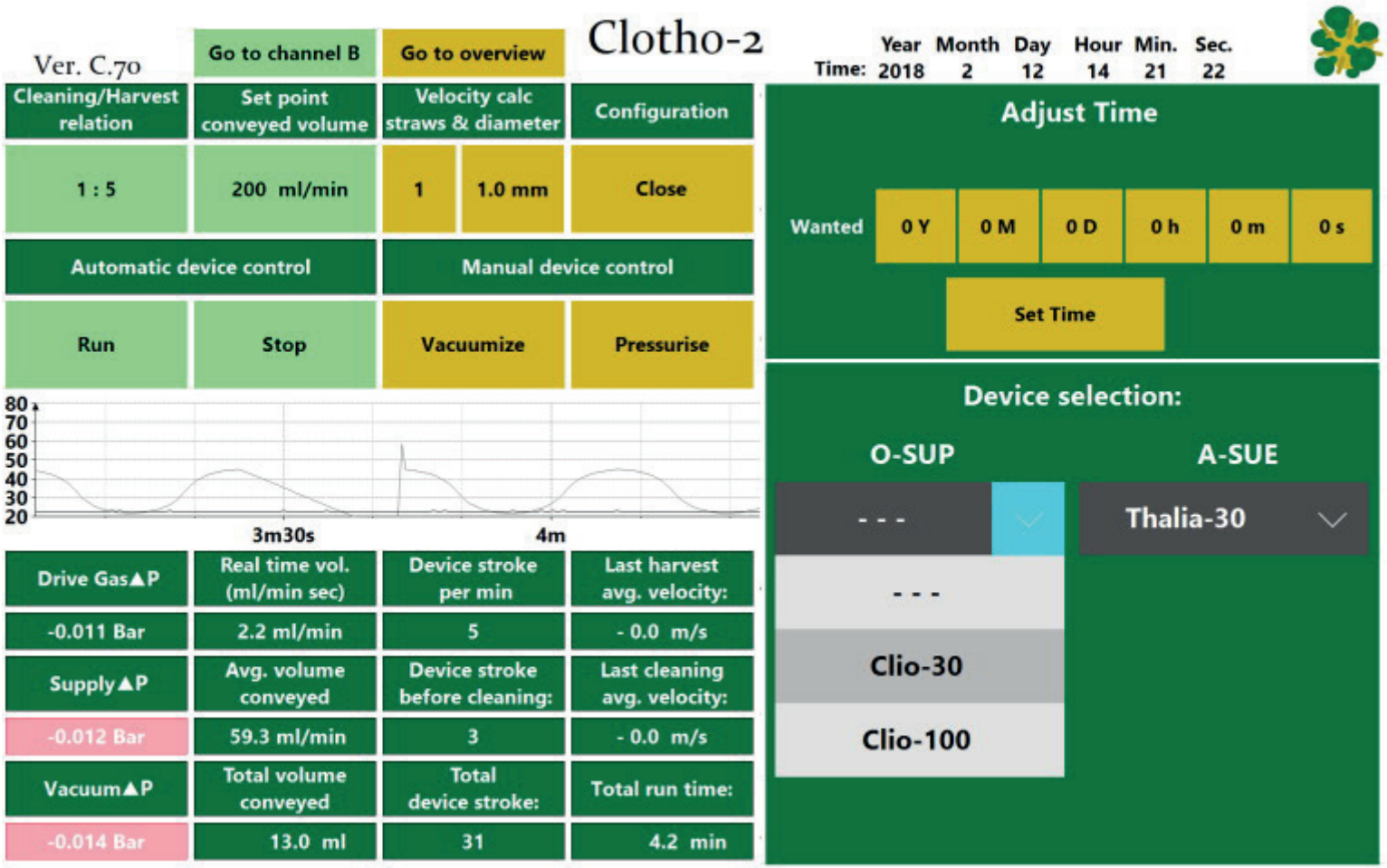
Clotho software

drive both O-SUP and A-SUE

Clotho Drive Unit's contain a webserver displaying online information on the build-in display. The webserver allow the enduser with a smartphone or a PAD to connect to the webserver for programming. Linux runs on a 900 MHz quad-core ARM Cortex-A7 CPU. Clotho software is based on CodeSys PLC platform on top of Linux firmware.

When Clotho is connected to a supply of drive pressure and vacuum source with sufficient capacity, then the spec is:

- Stroke frequency, per minute: 0,5-15
- Stroke duration, seconds: 1-60
- HFF broth velocity, m/s: 0,1-12



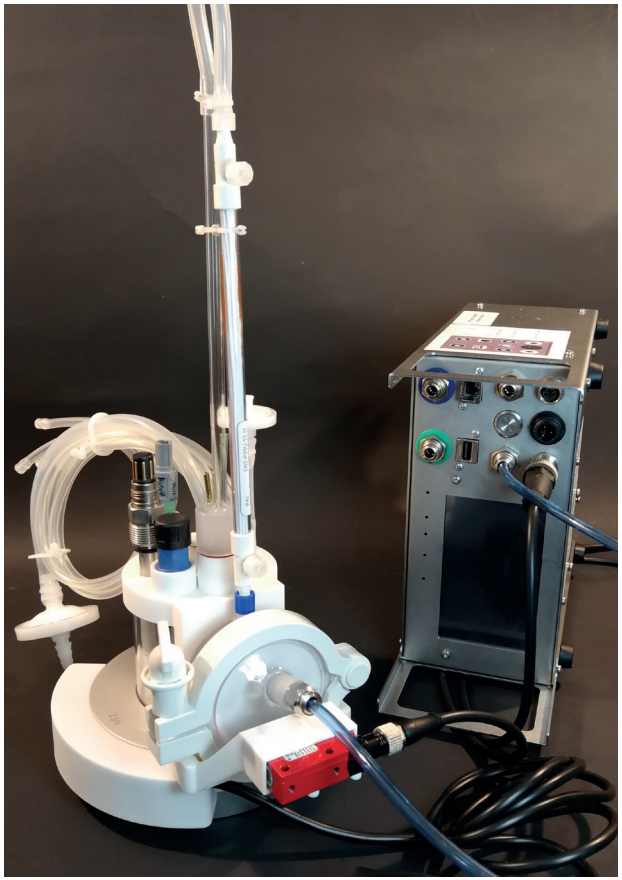
Clotho-2 Drive Unit setup

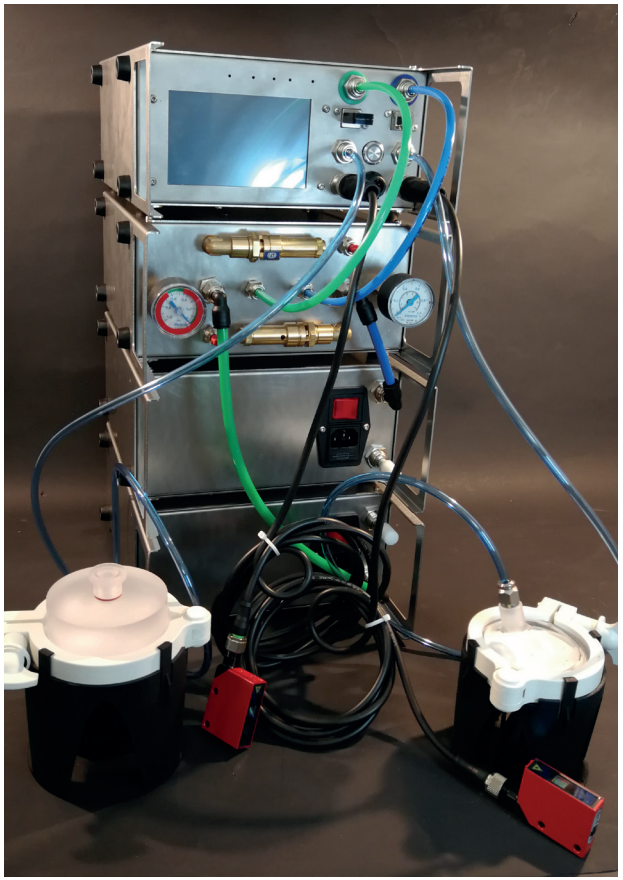
for CellMembra & CellRetention & CellBLU

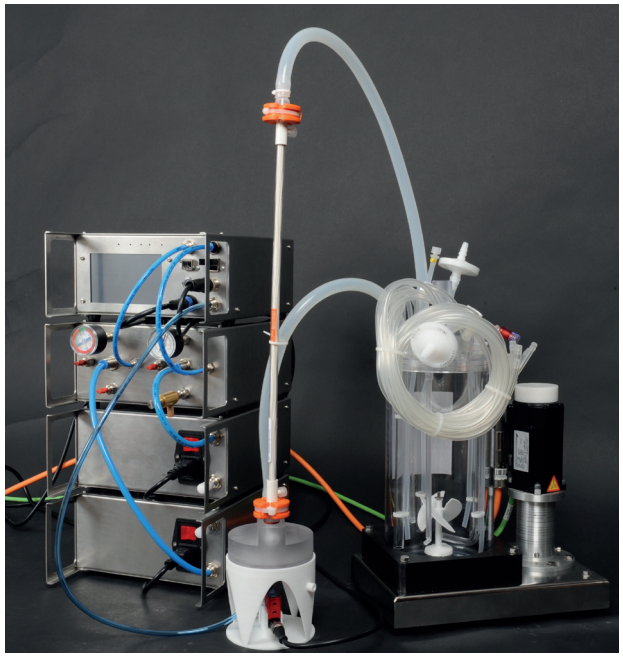
Dual channel fully independent operated by Clotho-2 Drive Unit.

Clotho-2 designed for control of two in parallel operating Single-Use-Pump's and / or Single-Use-Exchanger's.

Shown with Alagonia-8 drive gas pump's and Sarpedon manifold / reservior – all in the same ultra compact Hephaestus U2 cabinet's.

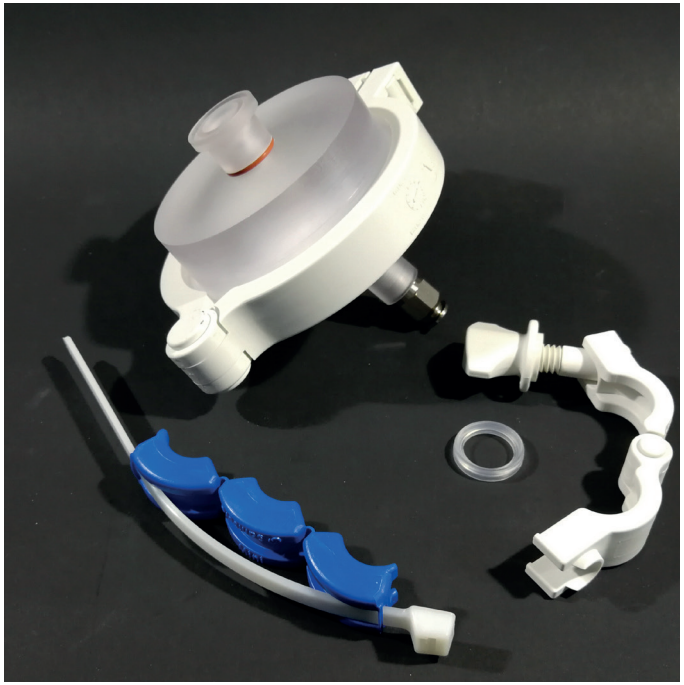






Acessories for P-SUB's

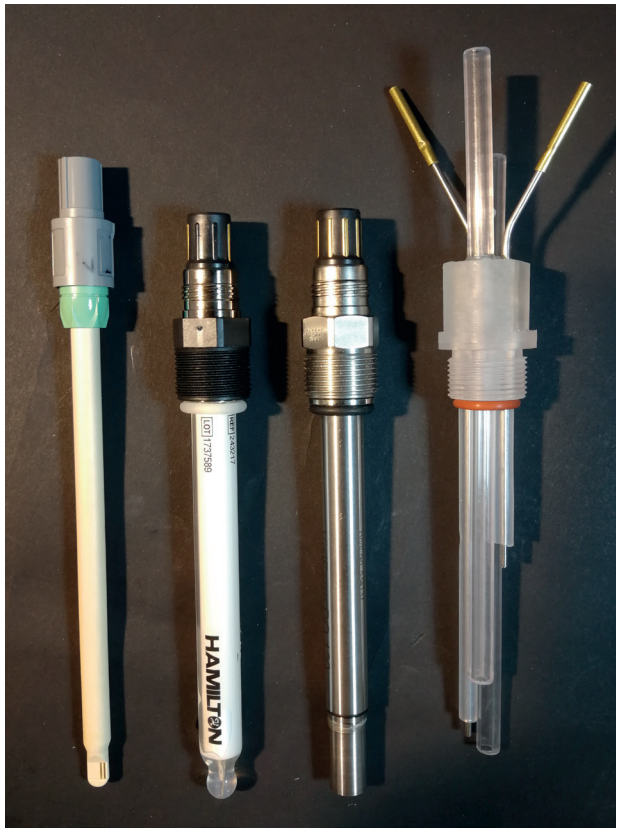
Connecting the HFF to the O-SUP or the A-SUE outlet / inlet port and the SUB ports is easy. PerfuseCell as well as other suppliers offer various connection devices.



HFF – harvest continuously a cell free permeate. Choose from one of your preferred suppliers, such as:

- www.spectrumlabs.com
- www.watersep.net
- www.parker.com/dh-bioprocessing
- www.gelifesciences.com

Capacitance bio-mass, pH and DO and level - all Single-Use-Sensor's – all pre-installed in one package. Here shown in lenght for the 500 ml P-SUBs.



Thank you for your attention