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Part I: Preconsulting file

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1. DESIGN REQUIREMENTS, V.5

DESIGN REQUIREMENTS

FERMENTER FOR COMPARTMENT III OF THE MELISSA LOOP, EUROPEAN SPACE AGENCY MELISSA PROJECT July 2008

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1. INTRODUCTION

The Melissa loop is a regenerative Life Support System needed to sustain life in Space during long term manned missions.
The Melissa Loop is organized in successive compartments that aim to recover Food, Water and Oxygen from wastes, e.g. CO2 and organic wastes, using light as source of energy.
The Melissa loop shall be tested on ground in the ESA external facility located in Barcelona at the premises of the UAB (Universitat Autonoma de Barcelona)
The different compartments of the Melissa loop shall be installed in a dedicated room for long-term demonstration of the loop efficiency and robustness to regenerate Food, Oxygen and Water from organic wastes.
Among the various compartments of the Melissa loop, the compartment III has been designed to bioconvert NH4+ to NO3- using a mix of bacteria, Nitrobacter and Nitrosomas immobilized on a fixed bead bioreactor.
The Bioreactor shall be redesigned to be operated in strict axenicity during long-term period.
This Design Requirement lists the Design Characteristics of the Bioreactor to be developed and constructed for this application.

2. DOCUMENT OBJECTIVE

This document describes the ESA and SNC-Lavalin Design Requirements for the construction and supply of a Bioreactor for transforming NH4+ into NO3- by using a bacteria mix, Nitrobacter and Nitrosomas immobilized in a Bioreactor. This document contains also the requirements for the ancillary systems, e.g. vessels, pumps, filters, Instrumentation, valves and piping needed for running the bioreactors.
The Bioreactor Design Requirements (DR) are organized in a list form for easy handling of the data in next steps of the project e.g. preparing a book of specifications for the construction and supply of the bioreactor and its ancillary systems (piping, vessels, etc…) The Bioreactor Design Requirements should help in specifying the most appropriate bioreactor for the process to be carried out and should clarify the Requirements of the Bioreactor user allowing time winning when specifying for construction and supply

3. DESIGN REQUIREMENTS

3.1. Bioreactor

1. The microorganisms to be used for fermentation shall be a mix of Nitrobacter and Nitrosomas.
2. The microorganisms shall be immobilized and grown on Biostyr® beads with the average size of 4.1mm.
3. The total volume of the Bioreactor is 8.1 liters
4. The working volume of the Bioreactor is 6.2 liters.
5. The bioreactor shall be run in full axenicity for long period of time (3-5 years)
6. The top and bottom section volumes shall be minimized.
7. The bioreactor shall be made in stainless steel 316L with a surface finish better than 0.4µm (surface roughness) Mirror finish could help in preventing bio-film occurrence (surface finish better than 0.2µ)
8. The bioreactor shall incorporate a vision window on its height to make easy the visualization of the beads.
9. The bioreactor shall incorporate 2 spy holes (fish eyes) for visualization of the top and bottom sections.
10. The top section shall be equipped with a light fixture

11. The Biostyr® bed shall be enclosed in between two removable grids in Stainless Steel 316L.
12. The grid size is about 2mm.
13. The bioreactor shall be equipped with a welded jacket (jacket construction mode to be selected) to control the bioreactor temperature using hot and cold water.
14. The temperature shall be controlled at 28°C +/- 0.1 °C.
15. The total overpressure in the Bioreactor shall be kept lower than 80 mbar.
16. The bottom and top end of the Bioreactor shall be made of 2 Stainless Steel sanitary flanges of the fermentor's diameter. The flanges shall be in Stainless Steel 316L with a surface finish better than 0.4µm (surface roughness) Mirror finish could help in preventing bio-film occurrence.
17. The flanges especially the top flange shall be used as much as possible for locating piping, instrumentation and other relevant connections.
18. The fluids that are necessary for carrying out the fermentation are the sterile feed (Ammonium salts and minerals) the 2 solutions for pH correction and the oxygen gas mixture.
19. The acid to be used for pH correction is 5% H2SO4.
20. The base used for pH correction is Na2CO3 (100g/L)
21. In addition to acid and base, an antifoam solution could be used as appropriate. There will be a reserve port for connecting the antifoam solution if appropriate.
22. For running the fermentor in the long run, the volume of the transferred solutions (entering) shall be equivalent to the volume of the removed solutions (leaving the fermentor)
23. The solution leaving the fermentor is by definition the harvest.
24. In order to create enough liquid movement through the Biostyr beads, the liquid phase above the top grid is recirculated on the bioreactor column via the recirculation loop that ends under the bottom grid.
25. The feed shall be added at the bottom section of the fermentor in the low part of the bottom section.
26. In order to disperse the feed homogeneously through the fermentor beads, the bottom plate of the fermentor receives a magnetic mixer (with external motor and magnetic coupling)
27. The acid and base solutions shall be added at the top section of the fermentor above the top grid near the recirculation loop top penetration.
28. Adding the pH controlling solutions at the fermentor top should minimize the climbing of the biomass towards the pH controlling solutions.
29. The connections should be made preferably in the flanges using mini-clamp or Na-Connect®(brand name of Novaseptic/Millipore).
30. The recirculation loop brings down under the bottom fermentor grid the liquid into which the beads are immerged. It moves the fluid from the top section to the bottom section
31. The recirculation flow of 3.6 L/h is given by the use of a programmable peristaltic pump. If needed this speed can be increased.
32. The recirculation loop feeds the 3 "on line"analyzers to measure Nitrite, Nitrate and Ammonium ions contents in the top section of the bioreactor.
33. The nitrite assay is particularly critical and should be really measured on line on a sample representing the instant status of the bioreactor content in nitrite
34. The recirculation loop shall thus run until the entrance of the analyzers for minimizing dead legs and supplying a representative measure.
35. **The losses of solutions due to sampling and assaying shall be minimized**.
36. Any possibility to recover safely (in full axenicity) some parts of the solutions used for testing or rinsing the measuring cells shall be investigated and installed on the analyzers.
37. The harvest flow is collected at the bioreactor top with a flow rate equal to the sum of the feeds less the flow of the samples taken for "on line" analysis of the Nitrite, Nitrate and Ammonium ions.
38. The harvest flow rate is about 0.5-0.6 l/h, auto-regulating using overflow system.
39. The overflow (harvest) is collected in a small closed and sterilizable intermediate vessel in SS Steel 316 Ra <0.4µm. Variation: the collecting vessel can be a disposable bag ready for use of the wanted volume (light, fully transparent, with all the needed connections)

40. The intermediate vessel is steam sterilizable. Variation: the vessel can be a disposable customized pre-sterilized bag (with all the needed connections)
41. The intermediate vessel is vented by a tubing (silicone tubing if a polyethylene bag is used) linked to the gas exhaust system of the bioreactor (connection before the water condensing system)
42. The harvesting system should be cooled (e.g. through a cooling jacket on the intermediate vessel) in order to prevent the development of the cells that are present in the harvesting system
43. The intermediate vessel volume shall be calculated to give some autonomy in case of bioreactor system failure (e.g. the tangential filtration system downstream) Its total volume should be comprised between 2 and 5 liters (3 to 8 h autonomy)
44. The intermediate vessel is also connected to a peristaltic pump followed by tangential flow filtration system. Tangential Flow filtration will allow a more continuous process, longer lifetime than frontal filtration. With frontal filtration, the lifetime of the filter will be limited depending on cell concentration in the harvest
45. From the tangential flow filtration system, the permeate is connected to the Medium Outlet Vessel D-04.
46. From the tangential flow filtration system, the retentate returns to the intermediate vessel.
47. Connecting piping shall be in Stainless Steel 316L with surface roughness better than 0.4µm. Variation: Silicone tubing can be partly or totally substituted.
48. Tangential filtration can be done using flat membrane systems (cassettes) of hollow fiber cartridges
49. Some Cassettes available presently on the market can be steam sterilized in place (when membranes are stacked into a Stainless steel pack) and allow performing microfiltration down to 0.1µm. Disposable Hollow fiber Ultrafiltration systems (probably with 200kD cut off as best choice) that can be repeatedly sterilized by autoclaving are available commercially for performing tangential filtration. The lumen of the fibers is quite large when comparing with the very narrow space in between the membranes of a cassette so that fouling or clogging is less fast. Disposable Hollow fiber UF cartridges can be back flushed for decompacting/declogging if necessary. Disposable Hollow Fiber cartridge can be discarded when fouled and replace immediately by a similar system in stand by.
50. Very probably the best choice for performing tangential filtration on the long run and in full axenicity is the disposable Hollow Fiber Ultrafiltration system.
51. The hollow fiber cartridge is made of clear plastic (polysulfone) so that the system can be checked visually quite easily at all time.
52. The Hollow fiber material is Polyvinylidenedifluoride
53. The idea is to operate continuously the UF (same flow rate as the harvest flow) The cell concentration in the buffer vessel will gradually increase, until a maximum is reached. It needs to be determined after which time this maximum cell concentration is reached (maximum for the proper operation of the Hollow fiber cartridge) This time is depending of the cells concentration built up and can be related to the pressure drop increase through the hollow fibers.
54. In continuous mode, the Tangential UF system should be set and sized for receiving a total flow rate of 1.5 L/minute and a permeate flow of 0.5-0.6 L/h.
55. The UF loop can be used to remove the free cells from the system by concentrating the retentate and voiding the small residual volume.
56. The full harvesting system could be disposable.
57. The full harvesting system could be totally thrown away in case of unexpected event or when clogged.
58. A redundant sterilizing filter (0.2µ) shall be added on the permeate flow as additional precaution for ensuring the sterility of the harvest sent to the Medium Outlet vessel. This filter can be in a SS cartridge as small as possible. Variation: a disposable polypropylene or alike cartridge can be used instead, in this case the cartridge is smaller and can be supplied already sterile. The disposable filter can be tested in place for integrity after mounting (like a non disposable filter sterilized by SIP or autoclaving)
59. The top section does not contain a level transmitter.
60. A high level switch linked to the control PLC shall stop the feeds to the bioreactor and generate an alarm when activated. Reaching this level means that there is a problem with the harvesting system (or that the flow rate of the feeding fluids is abnormally high)

61. A low level switch for detecting low level occurrence in the top section of the bioreactor (this switch is more useful if the pH correcting solutions are added at the top of the bioreactor)
62. The Bioreactor shall be equipped with a third circuit for backwashing.
63. This third circuit shall be independent from the previous ones (recirculation and harvest)
64. Backwashing is needed for de-compacting the beads and de-channeling the bioreactor because of the bioreactor operation (channeling and compacting create areas in the beads with low oxygenation)
65. Backwashing is opposite to the recirculation loop (from bottom section to top section
66. The backwashing connections are made on the bottom flange and the top flange (bottom penetration in the side wall is acceptable if the bottom flange cannot be used)
67. Backwashing is operated at the rate of 36 L/h at a very low frequency depending of the pressure build up in the bioreactor bed.
68. The bioreactor shall be equipped with a connection in the top section (flange) to be used for sending Oxygen pulses to decompact the beads and to release the biomass not fixed strongly onto the Biostyr beads.
69. At completion of Oxygen pulses, the backwashing circuit is started for completing the effect of the oxygen pulses.
70. Oxygen pulses and backwash release cells. These cells shall be collected by the Hollow Fiber UF cartridge operated in concentration mode allowing concentration of the free cells.
71. The bioreactor oxygenation is realized by injection of Oxygen through a dedicated circuit at the bottom of the fermentor.
72. The connecting point is made in the bottom flange.
73. The oxygen injecting system is designed for a flow rate of 3.000 ml/min (nominal).
74. The injecting tip should be equipped with a ceramic fritted disc (steam sterilized in place) rated at about 1 µ for generating micro-bubbles (the disc is inserted in the connecting Na connect clamp).
75. The minimum oxygen supply shall corresponds to a ratio of 11 mol O2/mol NH4+
76. The bottom and top section and or flanges shall contain reserve connecting points to be used for easy modification of the Bioreactor configuration as appropriate

3.2. Bioreactor sterilization

The bioreactor and its ancillaries (piping, valves, filters, instrumentation and other components) shall be steam sterilized in one run (or a very limited number of runs depending of the P&ID configuration) before starting the fermentation process. In addition, bits of the system should be sterilizable separately in order to allow preventative maintenance, replacement of parts of the system that have failed or are no more usable (clogged filters, etc) A Functional Analysis shall determine all the bits of the systems that shall be steam sterilizable in place at request and the level of automation and control (control and monitoring) needed for these sterilization runs.

Variations: bits of systems (e.g. the harvesting system) could be made of disposable systems (customized as appropriate) that are supplied sterile ready for use and with connectors suitable for aseptic connection in non-classified rooms. This is quite easy for installation and rapid for replacement in case of troubleshooting. Also it is transparent and lightweight. All the disposable systems can be tested in place for integrity if applicable (when they include sterilizing filters)

3.3. Bioreactor loading

After steam sterilization of the Bioreactor and its ancillaries, the reactor shall be loaded aseptically with the Biostyr beads. After successful loading, the beads shall be loaded with the Nitrosomas and Nitrobacter bacteria.

3.3.1. Biostyr loading

Biostyr beads are not steam sterilizable. They have been previously packed and sterilized by gamma irradiation. The package selection is crucial for loading aseptically without external contamination. The aseptic loading operation is depending of the Biostyr package and shall be adapted to the pack that will be used. Additional information from ESA/UAB are needed for finalizing the Biostyr loading design.
The underneath proposal is one way of performing the loading aseptically.

77. The Biostyr loading shall be performed using the principle of the alpha/beta ports 'La Calhene" type.
78. Loading should be made easier if the container is (with the exception of the alpha connecting system) a soft bag mechanically resistant as available on the market.
79. Loading is made by connecting the Biostyr pack to the system at the alpha beta ports and pushing the bead into the bioreactor with compressed air.
80. The Biostyr loading line is connected to the fermentor just under the top grid by a dedicated tri clamp connection immediately followed by a membrane valve.
81. The Biostyr loading line has been previously steam sterilized and allows on line sterile filtration of the used compressed air.

3.3.2. Bacteria loading

The preparation of bacteria is available ready for use in a closed container.
Preferably the closed container should be a polyethylene bag of suitable volume.
The aseptic loading operation is depending of the Bacteria package and shall be adapted to the pack that will be used. Additional information from UAB/ESA is needed for finalizing the Bacteria loading design.
The underneath proposal is one way of performing the loading aseptically.

The bacteria container is aseptically connected to the top compartment of the reactor by the intermediate of a SIPable device (connector) connected to the recirculation loop.
The connector device is Sterilized In Place by steam.
If the bag contains a microorganism slug, the additional transferring liquid can come from another bag aseptically connected to the bag containing the microorganisms.
After mixing, the fluid containing the microorganisms is transferred to the bioreactor by using the recirculation pump.
As appropriate, the loading bag can be rinsed to remove the residual microorganisms as appropriate
After successful loading, the connector can be sterilized again for safe disconnection and disposal of the microorganisms loading system.

3.4. Bioreactor Installation

The reactor shall be installed in an environmental controlled area together with other equipment belonging to other Compartments of the Melissa project. A proposal has been made by SNC- Lavalin for improving the actual facility to be used for installing the Melissa loop (see Audit Report, Universitat Autonoma de Barcelona, Installations for housing the compartments of the Melissa project, July 21 2008)
The area for installation is very limited in space. The bioreactor and its ancillary systems should be installed on a stainless steel skid (minimum AISI 314) on wheels that has been studied in terms of ergonomics. All the manual operations shall be easy to be done in aseptic conditions and their execution shall be guided by instructions on the PC screen and acknowledged by the operator after execution.
Calibration, replacement of components, cleaning and sanitation shall be considered when designing the skid.
The skid shall be designed to hang the reservoirs of acid/base/antifoam and all the necessary components for running and sterilizing the system. The footprint of the system shall be minimized.
All connections with utilities and drainage shall also be optimized

The skid shall be capable of passing through a door 130 cm wide and 240 cm high with minimum dismounting if any.
Variation: possibly, the skid could be designed with the accompanying Hepa Filter coverage and air guides for improving the aseptic manipulations to be carried out. This option consists in covering the skid footprint with a laminar flow providing sterile air over the skid and providing more Sterility Assurance during the connections, disconnections, repairs and preventative maintenance and any interventions in general onto the bioreactor system

3.5. Gas exhaust system

82. A gas exhaust condenser shall be installed in the gas exhaust system before the gas vent sterilizing filter to prevent water condensation in the exhaust filter.

3.6. Piping

The Stainless Steel piping required for this application corresponds to the highest standard available on the market.
Extra smooth piping is needed to minimize or slowdown the appearance of biofilm.
Extra smooth means Ra<0.4 µm.
Variation: mechanical polishing to this surface finish could be complemented by electropolishing for providing Ra<0.2µ.
Small diameter “seamless” piping shall be selected for this application. Suppliers like Dockweiller, Neumo or Biobore shall be contacted. The seamless standard US OD tubes should correspond to the smallest diameters available
¼ inch tubes (6.35mm x 0.91) are available with Ra<0.4µm (0.2 µm electro-polished)
Tri-clamp ferrules are available in similar diameters and quality in US OD as well as 45 and 90 degree bends, Y-pieces, crosses, tees and reducers. For these small diameters tubing, bending could be acceptable (instead of welded tees, etc.) Similarly, Instrument tees are available for very small diameter in Standard US OD (starting from ½ “OD tubes) with 1 ½ and 2” TC.
Piping shall be automatically orbital welded wherever possible. Welds shall be 100% controlled (as much as possible) with appropriate endoscope.
When welding is not desired (e.g. for instrumentation, bioreactor connections) triclamp connection shall be substituted. For bioreactor or vessel connection, Na Connect connection could be substituted especially for enhancing cleanability (less shadowing effect) and steam sterilization (air pocket prevention) efficiency..
Variation: Silicone tubing can be substituted partly to SS tubing as appropriate. Such tubing can be replaced easily and exists in smaller diameters. Also it is more or less transparent.

3.7. Membrane Valves/cavity free ball valves

On-Off Valves shall be sanitary membrane valves. A few valves could be preferably sanitary ball ones (the ones on the steam lines) The decision to use ball valve shall be taken case by case according to a risk/benefit evaluation.
Membrane shall withstand steam sterilization (PVDF with EPDM back cushing)

3.8. Non return valves

Non return valves should be used only when strongly indicated. Sanitary design is required.

3.9. Safety valves

Sanitary safety valves shall be installed where needed in the system. Such sanitary valves shall be sufficient for the application when compared to rupture disks.
Variation: Rupture discs are better absolute barriers to microorganism contamination from outside to inside. On the contrary, in case of pressure burst, the rupture disc is totally destroyed

3.10. Regulating valves

Manual valves that could be used to set the flow should be preferably sanitary seat valves and not needle valves.
Flow Regulating valves
Regulating valves (like the one use for regulating the Oxygen flow in the Bioreactor) shall be pneumatic sanitary angle valve "Samson" type or alike (Jordan) The valves shall be capable of regulating the flow in the specified range. Metal part shall be in SS 316L with Ra<0.8µ. They shall withstand steam sterilization if included in lines that shall be steam sterilized. They shall be self draining.
Pressure regulating valves
A pressure regulating valve shall be used to keep the bioreactor pressure at set point during use.
The valve shall be designed, constructed and installed in order to ensure complete protection against bacteria spreading and leakage. Such a valve shall be installed after the gas exhaust condenser and gas exhaust sterilizing filter and shall be adapted to the pressure control range.

3.11. Steam traps

Excellent Cleanability, air venting capability, absence of water retention, good sterile barrier characteristics are mandatory for this application. Balance Pressure Thermostatic steam traps are theoretically the most suitable for this application.

3.12. Pumps

Fluids are moved by pressure differentials and pumps. Gas are preferably moved by gas pressure (oxygen)
For liquids, pumps are preferred.
Basically two types of pumps are usable for this application. The peristaltic pump and the membrane pump.
Pump selection shall be discussed with the fermentor constructor.
The highest level of Quality shall be selected.
Our preference goes to the peristaltic pump for its ease of preventative maintenance.
Membrane Pumps shall be in Stainless Steel 316L with the best surface finish available (<0.5µm)
Membrane pumps shall be steam sterilizable in place where appropriate and self-draining.
Membrane pumps should also be available with disposable and sterile head.

3.13. Heat exchangers

The gas exhaust system shall include a cooling exchanger (double tube type) for condensing the moisture contained in the bioreactor gas exhaust. The system should use Chilled Water as cooling media.
The fermentor shall be equipped with a jacket for process temperature control.
The harvesting intermediate vessel shall be cooled for preventing the development of cells within the harvest system.

3.14. Sterilizing filters

The compartment III system shall be run in full axenicity (no contamination or cross contamination) in the long run (3-5 years). For avoiding any external contamination of the bioreactor coming from the feeding fluids, gases or vent, these lines should be equipped as closed as possible of the bioreactor with sterilizing filters.
In principle, to guarantee the highest probability of axenicity, these filters shall be Steam Sterilized In Place.
After sterilization and cooling, they shall be checked for integrity. Gas filters shall be checked for integrity by the Water Intrusion Test (manual) provided that the cartridge and filter volume is large enough for testing in place.
Filters used for sterilizing liquids shall also be checked in place for integrity by gas diffusion test after being wet. 200cm2 is the minimum filter surface that can be checked for integrity by the gas diffusion test. Smaller filter surfaces are integrity tested with the bubble point test.
Variation: disposable, pre-sterilized filtration system can be used instead of SS systems provided they are mounted on the lines aseptically using connecting systems designed for use in non classified environment. Such systems after assembling can be tested for Integrity In Place. For such disposable filters, the integrity test in place is normally not needed (test already made by the supplier)
Potential advantages are a shorter time for restarting the system, less validation (sterilization validation) transparency and lightweight.

Filters in parallel with isolating valves
Shall be considered if the filter can be clogged by the media passing through it and/or if short replacement time allows continuing the run without consequences.
This is particularly interesting on the gas filtration line after the condensing system.
Filters in serial
Serial filters can be interested if there is no way of checking the filter integrity in place after steam sterilization and or if higher Sterility Assurance Level is wanted.
However, it increases the pressure loss in the system. A risk evaluation shall be done case by case because the system shall not be over designed.
Gas filtration
The filters assembly (frame plus filter) shall withstand large range of pressure variation without failure of microbial retention capability. They shall be **hydrophobic** and carefully selected for the specified flow and pressure range.
They shall be preferably of cartridge type with a carter made in stainless steel 316 with Ra <0.8 µm. They shall be self-draining, steam sterilized in place and tested for integrity in place.
Variation: disposable pre-sterilized filtration system can be used.

83. Gas filtration (on oxygen lines with minor other components like C02 and Nitrogen) shall be doubled (in parallel) after the gas condensing system because clogging can occur due to the possible moisture content of the gas.
84. Before bioreactor entrance a double gas filtration system is also preferable for ensuring the continuous oxygen supply to the bacteria.

Liquid filtration
Liquid Filtration cartridge requires air elimination upstream (by vent manual opening) for being operated. **This operation means a significant risk of contamination of the upstream media.**
Liquid filtration concern filtration of the feed, of the solutions for pH control (the antifoam solution if applicable), the harvest after the UF cartridge and the samples taken by the “on line” analysers.
Base, acid and antifoam filtration
A single filter (no filter in parallel or in serial) should be sufficient on the acid and base supply (and antifoam if applicable). The cartridge material and cartridge assembly shall be carefully selected to withstand long exposure to the products. In theory, PVDF and PES can be used for filtration of sodium Carbonate and H2SO4 solutions.

Fluorodyne DFL membrane cartridges are said to have excellent compatibility with sodium carbonate solutions. Possible Upstream contamination due to gas venting before use is not a problem for these applications.

Variation: use of bags for storage of the solutions supported on hangers connected to weight cells

Feed Filtration

85. The feed is aseptically filtered at the entrance of the feeding vessel so that a double serial or parallel filtration seems not justified. Additionally, the system is operated in batch so that time is available for intervention in case of troubleshooting. A single filter is sufficient for this application provided the feed media has been already filtered on 0.2µ filter.

Possibly, the feed can be contaminated upstream because of the vent opening at start of the liquid filtration

Harvest filtration

86. Harvest filter comes in redundancy with the UF cartridge.

Contamination upstream (in between the UF cartridge and the filter can occur at vent filter opening at start of the filter use. A single filtration shall suffice for this application.

Variation:

Use of pre-sterilized disposable filtration systems for all or some of the liquid filtration

Filtration of samples for automated analyzers

87. The feeding line to the analyzers contains a single sterilizing filter added to prevent any contamination coming from the analyzers operation and to allow the accurate measurement of the ions (no or quite limited dead volume)

3.15. Sampling ports/devices

The addition of SIPable sampling devices for sampling and testing the system off line shall be considered. Sampling could be interested

- On the bioreactor media (to be taken to measure free cells)
- On the feed
- Perhaps on the harvest after UF and sterile filtration.

In case such sampling ports are considered mandatory for monitoring the system performance, the type of sampling valves shall be studied carefully in order not comprising the axenicity by the sampling methodology. Sampling ports location will be finalized when the P&ID's will be in the near final stage of design

3.16. Instrumentation

3.16.1. Flow measurements

Gas:

Mass flowmeter shall be used for this application. The equipment accuracy and range shall be compatible with the flow rate that is currently applied. The equipment shall resist to corrosion that could be induced by moisture.

Liquid

Mass flowmeter shall also be used for this application. They shall be made in stainless steel 316L with the best Ra available (<0.4µm). They shall be self- draining and Steam Sterilizable In Place. The equipment accuracy and range shall be compatible with the flow rate that is currently applied.

3.16.2. Temperature measurement

Thermowell shall be used for temperature measurement in the top and bottom sections and in the beads section. Accuracy and range shall be compatible with the process. Pt 100 sensors shall be preferably used and shall be installed for easy calibration and recalibration. All parts in contact with the product shall be in Stainless Steel 316L. Favorite suppliers are Fabritius and Thermibel.

3.16.3. Pressure measurement

Metal Diaphragm Pressure sensor shall be selected for this application. The membrane shall resist to steam sterilization and pressure shocks. Stainless steel 316L with the best Ra available shall be selected. Favorite supplier is Endress Hauser.

3.16.4. pH measurement and control loop.

Retractable pH sensors shall be used for this application. The sensors should be steam sterilizable without process interruption. A pH sensor shall be installed in the bottom and top chamber of the bioreactor. The control system shall comprise a calibration menu for ease of calibration. The system Standard Operating Procedure shall indicate the calibration procedure and restart procedure in full axenicity (after SIP). The pH measurements shall be used by the PLC to activate the acid or base peristaltic pumps for reaching the specified pH range.

3.16.5. Oxygen measurement and control

Retractable D.O sensors shall be supplied for measuring the Oxygen Concentration under and above the BioStyr beads. The sensors should be steam sterilizable without process interruption. The control system shall comprise a calibration menu for ease of calibration. The system Standard Operating Procedure shall indicate the calibration procedure and restart procedure in full axenicity.
The control system shall analyze the difference in Oxygen concentration between the bottom and top compartment. Oxygen incoming flow shall be adapted accordingly by the Control System.

3.16.6. Differential Pressure measurement

The fermentor shall contain a pressure differential transmitter using 2 Pressure sensors, one being placed under the bottom grid of the Fermentor (in the bottom section) and the other one being placed in the top section in the liquid phase for detecting clogging of the packed bed due to excessive bio-film formation.
When the high-pressure limit is reached, the Control system shall trigger the oxygen pulses and the following steps (backwashing and free cell removal using the UF cartridge system)

3.16.7. Level measurement and control loop

The harvest is removed from the bioreactor by overflow and gravity.
There is thus no need of using a level detector associated with a level controller in the top section of the bioreactor.
Anyway, in order to detect a high level problem in the top section of the bioreactor a High level switch linked to the control PLC should be considered.
A similar low level switch does not seem needed to detect a low level in the top section of the Bioreactor unless the pH correcting solutions are added in the top section of the bioreactor.

The intermediate vessel used for collecting the harvest by gravity requires a way of knowing and controlling automatically the levels inside.
It is assumed that the collected solutions will not foam substantially in this vessel.
Consequently, the level could be controlled by a capacitance sensor. Alternatives to be discussed (considered) are balances or weight cells and ultrasound (foam occurrence)

3.16.8. . Conductivity measurement

Conductivity measurements are to be performed in the bottom and top section of the bioreactor.
They are used to monitor the conductivity of the feed to follow in some way the ionic content of the feed. The top compartment contains also a second conductivity sensor in the gas space for initiating the antifoam pump and supply as required (optional)

3.16.9. Weight measurement

Weight cells are used under the acid and base container (also optionally under the antifoam) to monitor the content of these containers. Weight cells are linked to the control system.
Weight cells or balances can also be used for level control in the harvest intermediate vessel.

3.16.10. Other measurements

These measurements are made by on-line analyzers on the recirculation loop after removal of the cells by frontal filtration. These measurements are linked to the particular Nitrification process. Ions that are measured are residual NH4+, nitrites and nitrates. The limit of detection and Quantification shall be quite low for measurement of NH4+ and Nitrite. Sensing methodology is not known by SNC-Lavalin.
The developers/suppliers of these systems shall give their feed requirement and characteristics (dimensions, connection type) for allowing their connections to the bioreactor system.

3.16.11. On line biomass measurement

This measuring system is developed in a parallel study and should allow monitoring the evolution of the Biomass within the packed bed during Long Term Operation (e.g. by FPCR measurement)
The system could require up to 3 sampling devices respectively at the bottom, medium and top part of the Biostyr bead.
The Bioreactor shall include the 3 relevant connection ports. Information about the requirements for these ports shall be provided by ESA to SLP.

3.17. Bioreactor control system

The bioreactor and its ancillaries shall be microprocessor controlled. The control system consists of a microprocessor and a Scada supervision system. The associated software is developed by others and shall permit control of suitable process variables via control loops, set points and alarms. It shall also permit in situ calibration operations and control of all pumps, harvest system, recirculation loop, backwashing loop, instrumentation, Biostyr® loading and bacteria loading. It shall allow to quick scroll through all the operating parameters. It shall allow data records and trends analysis. A suitable Automation Requirements/Functional Analysis shall be developed for that particular application.

3.18. Disposable equipment versus Non Disposable

The Bioreactor is run with the use of various ancillaries that should allow perfect functionality and axenicity during long runs.
Such key ancillaries are the feed systems and the harvesting system.
In addition, all the fluids entering the bioreactor shall be sterilized by Cartridge Filtration, all the fluids leaving the Bioreactor and sent to the next compartment (Medium Outlet Vessel D-04) or to the on line analyzers shall also be aseptically filtered
All these systems can be:

- Non disposable basically with Stainless Steel housing
- Disposable basically in polymeric material (silicon, Polyethylsulfone, PVDF, etc)

These systems are compared in the next table in terms of advantages and disadvantages

Disposable systems	Non disposable systems
Lightweight	Heavy

Disposable systems	Non disposable systems
Transparent	Opaque
Easy and requiring a short time for start up	Requires cleaning, assembly and sterilization before use
Numerous spares can be kept in stock (10 and even more) without requiring a large storage place	Only a few spares could be kept
Some systems allow aseptic connections in non clean environment (non classified environment)	Not applicable
System configuration is easily changed if the selected design does not give full satisfaction	Harder and longer
Requires less qualification/validation time	More Validation e.g. filters are not so easy to sterilize efficiently in place
Filters can be tested for integrity in place	Filters can be tested for integrity in place
Filter assembly (cartridge plus housing) can be delivered with a quality certificate	Not possible for the assembly
In case of troubleshooting with the running bioreactor, restart should be done after repair/exchange faster than with non disposable	Slower
Disposable complex systems can be customized by potential suppliers and supplied tested and ready for use	Not applicable
Disposable systems are steam sterilisable out of place (in case of need)	Non disposable systems are steam sterilisable in place or out of place

In addition to all these advantages of the disposable items, there are additional reasons due to the UAB available utilities/equipment that could make the use of disposable components more suitable.

- The existing steam generator does not provide “Clean Steam” that’s to say steam without endotoxins, without trapped particles and chemicals (in droplets)
- The existing generator does not provide dry steam and steam without Non Condensable Gases. Such Steam Quality is important to guarantee steaming efficiency.
- The existing autoclaves are quite old and for two of them without recording of sterilization parameters.
- The existing autoclaves should probably also be inappropriate for special delicate cycles that require strict control of pressure during the sterilization phases.

All the previous advantages and considerations justify SNC-Lavalin recommendation to use disposable equipment as much as possible taking also account of the project planning.

The investment linked to the project could be also substantially decreased by the use of disposable items

Consequently, at this project stage, we recommend the use of disposable items for the following Bioreactor subsystems:

- The buffering system supplying suitable samples to the automated analyzers (filter, bag, pipe)
- The harvesting system (the full system or parts)
- The acid and base feed starting from the peristaltic pump down to the Bioreactor.
- The optional antifoam feed
- The part of the NH4+ feed outlet from the peristaltic pump to the sterilizing filter

Such proposal shall be challenged by risk analysis to be performed during the preconsulting, ordering/construction phase depending noteworthy of what is exactly available on the market in terms of disposable systems.
Such risk analysis can also be influenced by the possible modifications/improvements that could be done on the UAB facilities, utilities and autoclaves;

For small volume disposable tank, level control could be controlled advantageously by balance or equivalent external instrumentation.

4. LIST OF ATTACHMENTS

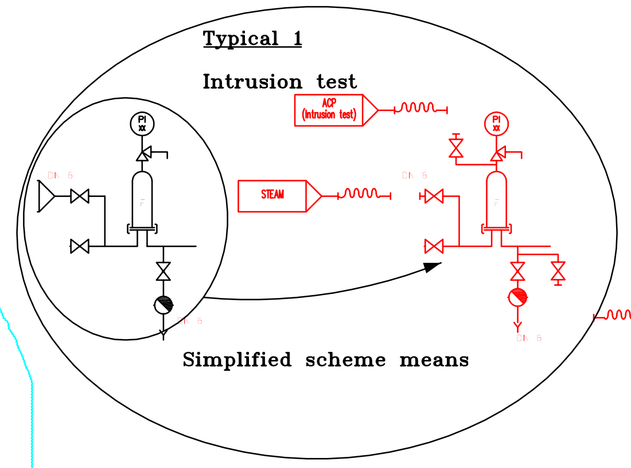
Attachment N°	Title
7006354121001	P&ID of the nitrification bioreactor system *
Melissa technical note 78.61	UAB Technical Specifications for the re-design of the compartment III pilot reactor Final issued on 20/05/07.
2	Audit Report, Universitat Autonoma de Barcelona, Installations for housing the compartments of the Melissa project, July 21 2008

2. PID, Rev. B

X X X X | A | B | C | C | N N N

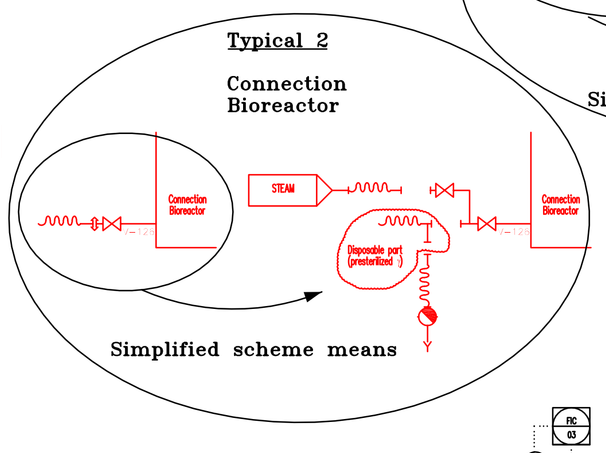
Typical 1

Intrusion test



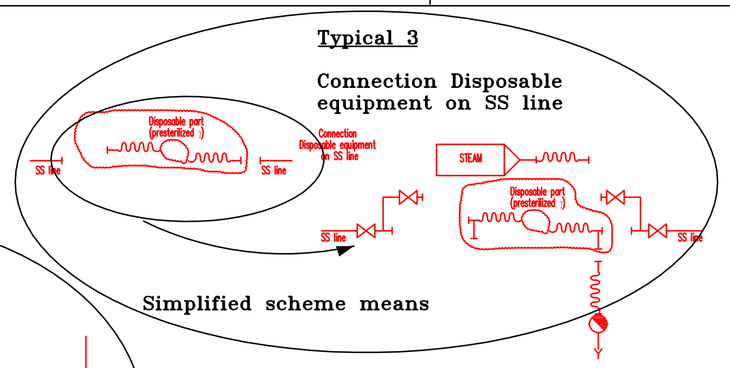
Typical 2

Connection Bioreactor



Typical 3

Connection Disposable equipment on SS line



REMARKS

1. All filters to be foreseen with all necessary connections for water intrusion test

2. Sampling points will be decided after finaliz ation of the design

3. Acid and base : possibility to connect at top or bottom

4. Need of bed discharge to be confirmed by ESA

5. Cyan dashed lines = spare for future (will not be implemented at start)

6. Blue = disposable items

7. Battery limits
   - UAB = UAB supply
   - SS = Supplied by vessel/ Bioreactor supplier
   - DISP = Supplied by supplier of Disposable items

8. All necessary reducers, T and connection pieces not shown. To be foreseen by supplier

ANTI-FOAM SYSTEM : ALL CONNECTIONS TO BE FORESEEN FOR FUTURE INSTALLATION

Modulating valve should be considered

TO BE FINALIZED

SPARE FOR GAS ANALYZER

PIPING MATERIAL CLASS
Spec & Size (OD x Th mm)

INDICATIVE DIMENSIONS

Metric / DIN 11866

Tubing 316L DN4 (6 x 1) or 1/4"
Tubing 316L DN6 (8 x 1) or 3/8"
Tubing 316L DN8 (10 x 1) or 1/2"
Tubing 316L DN10 (12 x 1) or 1/2"
Tubing 316L DN15 (18 x 1.5) or 3/4"

REV	DRAWN	CH'D	DATE	DESCRIPTION OF REVISION
B	J.VU	F.SMAL	05.12.08	FILE PRECONSULTATION
A	J.VU	F.SMAL	18.11.08	FOR PRECONSULTATION PHASE

PRELIMINARY ☐

RELEASED FOR
☐ information ☐ design ■ price inquiry
☐ approval ☐ take-off ☐ material order

REFERENCE DRAWING N° TITLE

RELEASED FOR CONSTRUCTION
☐ complete ☐ with holds

THIS DRAWING SUPERSEDES/IS SUPERSEDED BY DRAWING N ° :

SNC-LAVALIN PHARMA APPROVAL	VISA	NAME	DATE	REV
DRAWN		J.VU	05.12.08	B
CH'D				
SL/RES				
P.E.				
P.M.		F.SMAL	05.12.08	B

CUSTOMER APPROVAL	VISA	NAME	DATE	REV

CUSTOMER : ESA - UAB

INSTALLATION : MELISSA - RE-DESIGN COMP III

TITLE : P&ID of the nitrification bioreactor system

SNC·LAVALIN Pharma

SCALE ON A1 NONE

701014 41 21 001 B

X X X X | A | B | C | C | N N N | Z

FILENAME:$12345678901234567890
SYSTEM:$1234567890

3. TECHNICAL DATASHEET: VESSEL 30L, Rev. A

V — Technical datasheet: Vessel 30L

Item N° D-03 & D-04

Applicable to: Proposal ☒ Purchase ☐ As built ☐

Installation:	ESA – Melissa Loop	Unit:	Compartment III
Service:	Medium Feed Vessel	Quantity:	2
Manufacturer:	(*)	Type:	Sanitary sterile, vertical, cylindrical, jacketed

Fluid: Process: Water 99% + Ions, 10°C, pH 5-8.
Sterilized in Place with Clean Steam

DESIGN DATA

	Operating	Design	Test	Units
Temperature :	Min. /Nom. /Max. : 0 /10 /134 °C	Vessel: 152 °C		°C
Pressure :	Min. /Nom. /Max. : 0 /0,08 /2,5	Vessel:-1/3; Jacket: -1/2,5	Vessel:(*)	barG
Vol. mass :	1000			kg/m3

Full flat top plate (sanitary flange)	**Volumes:**	**Weight:**
Gasket in EPDM	- Working: vessel 30 L	- Weighing electronic system: ~~yes~~/no
Fixation by bolts and nuts	- Total : Vessel (*) L	- Empty: (*) kg
Round bottom end	**Jacket Surface:** Yes (on the cylindrical part)	- In operation: (*) kg
		- Full of water: (*) kg

MATERIALS (*)

1	**Head** SS 316L (DIN1.4404)	5	**Support** ss 304 (DIN 1.4301)	9	**Internals** ss 316L (DIN 1.4404)
2	**Shell** SS 316L (DIN 1.4404)	6	**Gaskets** EPDM	10	**Jacket** ss 316L (DIN 1.4404)
3	**Nozzles** SS 316L (DIN 1.4404)	7	**Bolts** SS 304		
4	**Flanges** SS 316L (DIN 1.4404)	8	**Nuts** SS 304		

NOZZLES LIST

Noz	size	Sch.	Service	Connection Type	Connection Face
N1	DN10	PN10	Media Inlet with Filter	TC	Top
N2	(*)	PN10	Pressure Safety Valve (1)	TC	Top
N3	(*)	PN10	Level Indicator	TC	Top
N4	DN15	PN10	Vent Filter + Manometer	TC	Top
N5	(*)	PN10	Sight glass with lamp	Flange	Top
N6	(*)	PN10	Level Transmitter	TC	Top
N7	(*)	PN10	Spare (3)	TC	Top
N8	(*)	PN10	Spare (3)	TC	Top
N9	DN10	PN10	Jacket Outlet (4)	Welded	Side
N10	DN10	PN10	Jacket Inlet (4)	Welded	Side
N11	(*)	PN10	Temperature probe (5)	Thermowell	Side
N12	(*)	PN10	Level Switch Low (**)	NA-connect®	Bottom
N13	DN10	PN10	Bottom Outlet (6)	Welded	Bottom
N14	(*)	PN10	Spare	Ingold	Bottom
N15	(*)	PN10	Manometer (membrane)	TC	Top

FABRICATION AND INSPECTION

Code
Legal requirements: 97/23/CE
and according to PED
Wall thickness to be calculated by supplier accordingly
Non destruc. tests : 100% X-ray radiography on longitudinal
100% on circular welds, 100% on intersections
Inspection by: Notified body
Finish of welds: same finish as other internal parts of vessel
Inside finishing: Ra ≤ 0,4 µm or Mirror polished (≤0,2)(**)
Passivation: Yes
Outside finish: Ra ≤1,2 µm – Bright polish
Insulation : No

General notes

- Bolt holes in flanges: to be discussed
- Name plate to be supplied: yes/~~no~~, in SS, welded
- Lifting lugs to be supplied by manufacturer yes/~~no~~

REMARKS

(1) Set point: 3barg & 152°C, SS316L
(2) Manhole: Sanitary flange, gasket in EPDM body.
Borosilicate glass, torical gasket EDPM body, light: 24V (Metaglass, Canty or equiv.) - Built in manhole
(3) With blind plate
(4) Must be able to maintain media at 15°C with cold water.
(5) To be mounted on the cylindrical part at the lowest position.
(6) Steam sterilized In Place (see typical drawing 2)

FOR INSTRUMENTATION, REFER TO SPECS
(*) to be completed by Supplier (**) Optional

Visa	XH				
Rev.	A				
Date	26/11/08				

CLIENT: ESA/UAB

PROJECT: 701014

SNC-LAVALIN

Doc. n°: 701014.41.60.001

Sheet: 1/1
Rev.: A

4. TECHNICAL DATASHEET: BIOREACTOR 8L, Rev. A

V	Technical datasheet: Bioreactor 8L	Item N°	C-01

Applicable to:	Proposal ☒	Purchase ☐	As built ☐	
Installation:	ESA – Melissa Loop	Unit:	Compartment III	1
Service:	Bioreactor for Nitrification	Quantity:	1	2
Manufacturer:	(*)	Type:	Sanitary sterile, vertical, cylindrical, jacketed	3
Fluid:	Process: Water (99%) + ions, Bacteria : Nitrobacter + Nitrosomomas, 28°C, pH 8.1.			4
	Sterilized In Place with Clean Steam			5

DESIGN DATA

	Operating	Design	Test	Units	
Temperature :	Min. /Nom. /Max. : 0 /28 /134	Vessel: 152		°C	8
Pressure :	Min. /Nom. /Max. : 0 /0,08 /2,5	Vessel:-1/3 ; Jacket: -1/2,5	Vessel:(*)	barG	9
Vol. mass :	1000			kg/m3	10

	Volumes: Reactor must be made of 3 flanged parts	**Weight:**	11
	- Top section (harvest side) : 0,49 L – Φ : 120 mm	- Weighing electronic system: ~~yes~~/no	12
Height of middle section; 556 mm	- Middle section (reactor) : 6,17 L – Φ: 120 mm	- Empty: (*) kg	13
Each reactor section must be	- Bottom section (feeding side): 1,48 L – Φ: 120 mm	- In operation: (*) kg	14
Separated by a 2mm mesh grid	**Jacket Surface:** Yes (on the middle section)	- Full of water: (*) kg	15

MATERIALS (*)

1	**Head** SS 316L (DIN1.4404)	5	**Support** ss 316L (DIN 1.4404)	9	**Internals** ss 316L (DIN 1.4404)	17
2	**Shell** SS 316L (DIN 1.4404)	6	**Gaskets** EPDM	10	**Jacket** ss 316L (DIN 1.4404)	18
3	**Nozzles** SS 316L (DIN 1.4404)	7	**Bolts** SS 304 minimum			19
4	**Flanges** SS 316L (DIN 1.4404)	8	**Nuts** SS 304 minimum			20

NOZZLES LIST

Noz	size	Sch.	Service	Connection Type	Connection Face
N1	DN4	PN10	Culture Medium Inlet	NA-co/TC (7)	Bottom S
N2	DN4	PN10	Base inlet	NA-co/TC (7)	Bottom S
N3	DN4	PN10	Acid inlet	NA-co/TC (7)	Bottom S
N4	DN4	PN10	Backwashing outlet	NA-co/TC (7)	Bottom S
N5	DN25	PN10	Biomass sensor C	Ingold (5) (8)	Middle
N6	DN25	PN10	Biomass sensor C1	Ingold (5) (8)	Middle
N7	DN25	PN10	Biomass sensor B	Ingold (5) (8)	Middle
N8	DN25	PN10	Biomass sensor B1	Ingold (5) (8)	Middle
N9	DN25	PN10	Biomass sensor A	Ingold (5) (8)	Middle
N10	DN25	PN10	Biomass sensor A1	Ingold (5) (8)	Middle
N11	DN10	PN10	Jacket Inlet	Welded	Side
N12	DN10	PN10	Jacket Outlet	Welded	Side
N13	DN4	PN10	Backwashing outlet	NA-co/TC (7)	Top S
N14	(*)	PN10	Level Switch Low (**)	NA-connect®	Top S
N15	(*)	PN10	Temperature probe	Thermowell	Top S
N16	(*)	PN10	Level Switch Low (**)	NA-connect®	Top S
N17	(*)	PN10	Spare (3)	NA-co/TC (7)	Top
N18	DN8	PN10	Steam inlet	NA-co/TC (7)	Top
N19	(*)	PN10	Spare (conductivity)	Ingold (8)	Top
N20	(*)	PN10	L-209 Air/Oxygen outlet	NA-co/TC (7)	Top
N21	(*)	PN10	Pressure sensor	NA-co/TC (7)	Top
N22	DN40	PN10	Light (2)	Flush	Top
N23	DN6	PN10	Air/Oxygen pulse	NA-co/TC (7)	Top
N24	(*)	PN10	Conductivity sensor	Ingold (8)	Top
N25	(*)	PN10	DO2 sensor	Ingold (8)	Top S
N26	(*)	PN10	pH sensor	Ingold (8)	Top S
N27	(*)	PN10	Harvest outlet	NA-co/TC (7)	Top S
N28	(*)	PN10	Differential pressure	NA-co/TC (7)	Top S
N29	DN4	PN10	Recirculation outlet	NA-co/TC (7)	Top S
N30	DN25	PN10	Biostyr intlet (3)	NA-co/TC (7)	Middle
N31	(*)	PN10	Temperature probe	Thermowell	Top S
N32	DN40	PN10	Biostyr discharge (**)	NA-co/TC (7)	Middle
N33	DN4	PN10	Recirculation inlet	NA-co/TC (7)	Bottom S
N34	(*)	PN10	Differential pressure	NA-co/TC (7)	Bottom S
N35	(*)	PN10	Conductivity sensor	Ingold (8)	Bottom S
N36	(*)	PN10	DO2 sensor	Ingold (8)	Bottom S
N37	(*)	PN10	pH sensor	Ingold (8)	Bottom S

FABRICATION AND INSPECTION

Code

Legal requirements: 97/23/CE and according to PED

Wall thickness to be calculated by supplier accordingly

Non destruc. tests : 100% X-ray radiography on longitudinal

100% on circular welds, 100% on intersections

Inspection by: Notified body

Finish of welds: Same as bioreactor

Inside finishing: Ra ≤ 0,4 µm or Mirror polished (**)

Passivation: yes

Outside finish: Ra ≤1,2 µm – Bright polish

Insulation : No

General notes

- Bolt holes in flanges: to be discussed
- Name plate to be supplied: yes/~~no~~, in SS, welded
- Lifting lugs to be supplied by manufacturer ~~yes~~/no

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V	Technical datasheet: Bioreactor 8L	Item N°	C-01

N38	DN6	PN10	Air/Oxygen inlet (9)	NA-connect®	Bottom		61
N39			Magnetic stirrer		Bottom		62
N40	(*)	PN10	Pressure Safety Valve (1)	NA-co/TC (7)	Top		63
N41	DN6	PN10	Steam Condensate	NA-co/TC (7)	Bottom	Machined in the thickness of the plate to create lower point	64
N42	DN40	PN10	Spy hole (4)	Flush	Bottom S		65
N43	(*)	PN10	Vision window (4)	Flush	Middle		66
N44	DN40	PN10	Spy hole (4)	Flush	Top S		67
							68
							69
							70
							71
							72

REMARKS 73

(1) Set point: 3barg & 152°C, SS316L 74

(2) Light : Sanitary type, Borosilicate glass, torical gasket EDPM body, light: 24V (Metaglass, Canty or equiv.+ lighting 75

(3) With blind plate 76

(4) Sanitary type, Borosilicate glass, torical gasket EDPM body 77

(5) Type “Ingold” : ID : 25 mm, length : 40 – 50 TBC according attachment “Biomass sensors for final CIII configuration.pdf” 78

(6) Sanitary type, drainability by gravity must be guaranteed 79

(7) NA-connect® or Tri-clamp connection 80

(8) With Ingold cap coupling 81

(9) With ceramic disk 82

Height of bottom section 150mm 83

Height of top section: minimum , in theory, 50mm 84

FOR INSTRUMENTATION, REFER TO LIST 85

(*) to be completed by Supplier (**) Optional 86

Visa	XH					**CLIENT:** ESA/UAB
Rev.	A					
Date	26/11/08					**PROJECT: 701014**

5. QUESTIONNAIRE/CHECK-LIST: BIOREACTOR SYSTEM SUPPLIER, Rev.1

1. DOCUMENT OBJECTIVE

This document is a check list prepared in order to evaluate the possible scope of supply of the potential bioreactor system supplier and to fix the scope of supply attended from each supplier.
The document will be used also to indicate the potential suppliers Company name and address and the identification and details on the contact person(s)

2. COMPANY AND CONTACT IDENTIFICATION

Company Name			
Address			
Country			
Contact person			
Tel			
Mobile			
Email			
Other			
By and date			

3. QUESTIONNAIR/CHECK LIST

Human resources	
Material Resources (e.g. for piping lines)	
Experience in Bioreactor supply	

Experience in Biotec and pharmacy	
Commitment to project	
Pumps supply and installation	
Weight cells supply and installation	
Agitator supply and installation	
Electric board supply and installation	

Instrumentation Supply and Installation	
Pneumatic system supply and installation (small box)	
Miscellaneous	
By and date	

6. MACRODESCRIPTION OF DISPOSABLE AND SS ITEMS, Rev. 2

PRECONSULTATION PHASE

Macro-description of disposable and Stainless Steel items within the compartment III of the Melissa loop

EUROPEAN SPACE AGENCY
MELISSA PROJECT
November 2008

Publication Record

VERSION NO.	DESCRIPTION	DATE	BY
Rev 1	Initial issue	28-Nov-2008	Francis Smal
Rev 2	Change of disposable sets configuration	5- Dec-2008	Francis Smal

TABLE OF CONTENTS

1. INTRODUCTION

The Melissa loop is a regenerative Life Support System needed to sustain life in Space during long term manned missions.
The Melissa Loop is organized in successive compartments that aim to recover Food, Water and Oxygen from wastes, e.g. CO2 and organic wastes, using light as source of energy.
The Melissa loop shall be tested on ground in the ESA external facility located in Barcelona at the premises of the UAB (Universitat Autonoma de Barcelona)
The different compartments of the Melissa loop shall be installed in a dedicated room for long-term demonstration of the loop efficiency and robustness to regenerate Food, Oxygen and Water from organic wastes.
Among the various compartments of the Melissa loop, the compartment III has been designed to bioconvert NH4+ to NO3- using a mix of bacteria, Nitrobacter and Nitrosomonas immobilized on a fixed bed bioreactor.

The Bioreactor shall be redesigned to be operated in strict axenicity (absence of foreign micro-organisms contamination) during long-term period.

2. DOCUMENT OBJECTIVE

This document indicates macroscopically which components of the compartment III are disposable and which ones are in stainless steel. The document justifies also why these choices have been made. This document is to be used in complement of the P&ID 701014 RevF prepared by SNC-Lavalin for this project.

3. P&ID COLOUR CODE

The components in black ink on the P&ID have to be supplied in stainless steel
The components in blue have to be supplied in Disposable material
The components in green are optional equipment that are not part of any supply (disposable or stainless steel) but for which the connections to the bioreactor systems have to be foreseen. These connections are in stainless steel.

4. STAINLESS STEEL COMPONENTS

The following components of the compartment III shall be constructed in Stainless Steel and are Steam Sterilized In Place.

- The bioreactor
- The Upstream Medium Feed Vessel 30 L useful volume (ref D-03) and its ancillary equipment.
- The Downstream Medium Feed Vessel 30 L useful volume (ref D-03) and its ancillary equipment.
- The gas (oxygen) line complete
- The recirculation loop up to the connecting valve and clamp just at the entrance of the ions analyzers (NH4+, NO2- and NO3-.
- The cooling/heating systems for the Bioreactor, the vessel jackets and the gas condenser exchanger for condensing the moisture in the gas mixture leaving the bioreactor.

4.1. The bioreactor C-01

The bioreactor has to be done in stainless steel 316L with a surface finish better than 0.4µm. TIG orbital automated welding has to be performed. The other connections are Tri-clamp, Na-Connect or sanitary flanges as indicated in the component list being part of the bidding file.
The bioreactor is made of 3 large pipe sections:

- The central section houses the polystyrene beads onto which the nitrifying bacteria are immobilized and maintained just alive without significant growth.
- The bottom section receives the feeds entrance (pH correcting solutions, the NH4+ feed and the oxygen feed) It contains also the magnetically coupled agitator (Novaseptic or equivalent) and the steam condensate low point evacuation (machined in the bottom flange)
- The top section houses the harvest collecting system (by overflow)

Before use, the bioreactor has to be steam sterilized in place. The bioreactor is not insulated.
The connection between the bottom flange (or the top flange) and the central flange have to be made by large Ttriclamp or sanitary flanges to be dismountable.

All the sections receive various instrumentations that are used to survey the correct operation of the Bioreactor. The instrumentation is described in the instrumentation list that is part of the bidding file. The instrumentation fixed onto the bioreactor can be dismounted and with an angle of about 15/30° with respect to the horizontal plane (with a few exception like well for T sensors or dP instrumentation to check the pressure drop throughout the polystyrene beads)

The top and bottom section receive practically all the bioreactor penetration points (connections) except the polystyrene loading connection that is placed in the central section.

The central section has a cooling/heating jacket to maintain the bioreactor media at about 28°C (using cold and hot water) The bioreactor is not insulated.

The central section houses the polystyrene beads onto which the nitrifying bacteria are immobilized and maintained just alive without significant growth.

The central section shall house six instrumentation ports (characteristics are given in the instrumentation list) to monitor the biocharge distribution on the height of the polystyrene beads.
This instrumentation is not part of the supply.

The instrumentations and the penetration points can be located on the top and bottom flange or on the cylinder. The location on the P&ID on the flanges or on the cylinder is indicative and can be modified if more adequate.

The bottom section shall receive an oxygen connection aimed to produce micro-bubbles in the Bioreactor fluid. The classical way of introducing Oxygen in the bioreactor is through a sparger designed for generating small bubbles. We suggest replacing this system by a micro-porous ceramic disc (to be placed on a Na connect port) to generate micro-bubbles in the bioreactor bottom section.
The potential suppliers should investigate the feasibility and advantages disadvantages of this proposal.

The polystyrene beads are enclosed within two stainless steel 316L sieves with mesh size of about 2mm.
The sieves are expected to be removable.

4.2. The vessels D-03 and D-04 upstream and downstream the bioreactor.

These two vessels are identical and are used to collect the bioreactor feed (coming from the previous Melissa compartment) and to collect the harvest from this bioreactor;
These two vessels are described in specific data sheets. The limits of supplies for these two items are indicated on the P&ID.
The feeding line from the D-03 vessel to the bioreactor contains a peristaltic pump that requires a section of silicone tubing for its operation.
The pump flow rate is about 0.6 L/h

4.3. The gas (oxygen) lines

The oxygen (gas) supply line is in fact a loop because the oxygen not used by the cells is recycled into the system. The necessary balance is supplied by an oxygen supply connected onto the loop. As indicated on the P&ID, the loop is also connected on Nitrogen and Carbon dioxide gas supply.
The gases take moisture from the bioreactor media when passing through it (removed from the exhaust gas by a cooling condenser) and collect the C02 generated by the cell growth within the bioreactor.
The regulating valve XV02 keeps the gas pressure at set point within the bioreactor.
The circulator CC 01(see data sheet) is used to give the necessary pressure throughout the gas feed.
The gas pressure is kept constant at the bioreactor entrance through the use of the mechanical Pressure regulator PCV04.

When the bioreactor internal pressure is too high due to the growing of bacteria or when channeling in the beads is responsible for presence of residual NH4+ or N02 in the harvest, the operator has to correct the situation by generating oxygen pulses at counter current of the bioreactor flow (XV 336 is closed and XV337 creates Oxygen pulses at counter current)

After a few pulses, the oxygen supplies returns in standard (routine) mode and the backwash circuit is activated (high liquid flow rate at counter current) to complement the action of the oxygen pulses.

The dechanneling/decompacting operations followed by the backwashing are supposed to be very rare events (operated once or twice per year)
The free cells released by these operations are collected by the overflow systems and sent to the harvest system where the cells are concentrated and removed aseptically.
The gas lines contain 2 sets of 2 sterilizing filters mounted in parallel to ensure non stop supply of gases to the bioreactor (one filter of each set of 2 is in use and the other is in standby)

4.4. The recirculating loop

The loop increases the liquid flow throughout the bioreactor to bring to the cells more nutriments and to remove with better efficiency the metabolites and cells debris coming from the cells.
The loop runs until the entrance of each ion automated analyzer to minimize the dead volume upstream the measuring cells. The sampling at each analyzer port is controlled by an automated valve that prevents simultaneous sampling allowing sampling of only one ion only at a given time.
The membrane valve is followed by a frontal disk filter 0.2 µm (possibly stacked disks) to remove the free cells before the analysis.
From and including the filter, the line to the analyzer is disposable and as short as possible and is designed for aseptic change of the filter when the sample flow is no more sufficient.
There is no obvious solution that considers low dead volume and safe aseptic change of the filter.

4.5. The vessel and bioreactor jacket and the heat exchangers for temperature control

The jacket on the vessels and on the bioreactor shall be in Stainless Steel 316L (see relevant data sheets)

The bioreactor jacket shall maintain the bioreactor content during routine operation at 28°C ± 0.2°C.
For doing that the thermo-fluids are supplied at the following temperature:

- The cooling water: XXXXXXX °C
- The heating water: YYYYYYY °C

The pH correcting solutions are supplied to the bioreactor at room temperature (<25°C) at a very low rate (less than 10ml /24h while the ammonium feed is supplied at the rate of 0.6L/h at the temperature of XX°C

The D03-D04 vessel jacket shall maintain the vessels contents during routine operation at XX°C ± Y°C.
When empty, the D03 vessel (upstream) is filled at the rate of X ml/h from the previous compartment; The incoming liquid is at °C.
The D04 vessel (downstream) is supplied at the continuous rate of 0.5-0.6 L/h by harvest at 28°C

The D03-DO4 jacket cooling fluid is chilled water 7-13°C

4.6. The gas condenser

The gas condenser located at the exit of the bioreactor is used to remain the moisture in the gas mixture leaving the bioreactor. The gas condenser shall be in Stainless Steel 316L and is cooled by constant flow of chilled water. The condenser shall be calculated to cool the exhaust air to less than 15°C when leaving the condenser.

5. DISPOSABLE COMPONENTS

The following components of the compartment III shall be disposable: received already sterile (γ irradiated) ready for use or sterilized locally by autoclaving after assembly of the disposable components.

- The H2SO4 line (pH correcting system): typical in preparation
- The Na2CO3line (pH correcting system): typical in preparation
- The Biostyr loading line: typical in preparation
- The microorganisms loading line: typical in preparation
- The liquid back-flush line: typical in preparation
- The harvesting system: typical in preparation

For that purpose, SNC-Lavalin is preparing with potential suppliers (Millipore, Pall and Sartorius) short description of these various) to define the content of these lines and get prices for supplying the items.

5.1. The H2SO4 and the Na2CO3 lines

These 2 lines are identical and are supplied sterile ready for use except the liquid solutions that shall be added aseptically. The lines supply the bioreactor with the pH correcting solutions needed for its operation.
A third line identical is mounted empty to be used for supplying the antifoam solution if needed but more probably to replace temporarily the supply of 1of the 2 pH correcting solutions in case of trouble shooting.

The connection to the bioreactor is realized on the relevant Triclamp equipped with a “Colder type “device allowing the’ steam sterilization in place of the connection.

The lines are made of:

- The bag (1 or 2 liters) that shall receive the pH correcting solutions, each bag equipped with at least 2 connections and positioned on weight cells.
- The disposable tubing leading the liquid to the bioreactor thanks to a peristaltic pump: the line encloses the tubing for the operation of the peristaltic pump, the disposable sterilizing filter in PVDF or PES filter piping

5.2. The Biostyr loading line

This line is used once only at the start of the Bioreactor. It is thus easily justified to load the Biostyr with a disposable line.

This line could contain the following component from upstream to downstream

- The Triclamp connection to connect the system to the Compressed Air source

- The tubing (1 inch) to the sterilizing filter allowing Compressed air sterilization
- A tee with the vertical branch connected to a 10 liter bag containing the required quantity of Biostyr
- The tee is prolongated by a one inch tubing up to the colder (>1/2 inch) to make the SS/Disposable connection on the bioreactor.

The inner diameter should be large enough to avoid blockage by the beads.
The system works by Venturi effect. The loading system is removed after Biostyr loading

5.3. The Microorganisms loading system

This system is used once only at the start of the Bioreactor. It is thus easily justified to load the Microorganisms with a disposable line. It is attached to the recirculation line

The microorganisms loading system is attached to the Triclamp and the manual valve MV-461. The SS/disposable connection is steam sterilized in place (Colder)

This line could contain the following component

- The intermediate bag (1-2L) to receive the 2 bacterial suspensions for loading the bioreactor. The bag has two connections.
- The Luer connection to load the micro-organisms suspensions e. g through syringe or tubing (by gravity). The loading operation is done for suspension 1 and 2 under laminar flow.
- The connection to be attached to the recirculation line and including at its end a “colder” union to allow Sterilization In Place of the Disposable/SS connection.

The loading system is removed after loading.

The loading set can be supplied sterile and ready for use.

5.4. The back flush loop

The back flush line is used very rarely (estimated to once or twice a year)

The disposable line could be prepared by the user and sterilized by autoclaving. Alternatively it can be supplied fully gamma irradiated by Millipore, Pall or equivalent.

The recirculating set shall be ended by 2 Colder unions allowing Steam Sterilization In Place of the Disposable set /SS connections. The Silicone central tube can be inserted in the peristaltic pump to be used for back flushing and contains also an Opticap or alike filter for collecting the cells released by the back flush.

At the end of the back flush, the disposable system is removed and a new one is reloaded.

This way of doing avoid keeping the cell solution stagnant in the back flush line when not in use and allows easy recovery of the cells released by the back flush. This allows removing the cells rapidly to minimize the cell concentration increase in the harvest line due to the backflush.

5.5. The harvesting system

The harvesting system is the most complex part of the bioreactor system; The harvest system shall remove the free cells from the harvest, shall be operated without interruption (as much as possible) and shall be robust.

Basically there are 2 systems that will be designed in parallel;
The system 1 separates the cell by frontal filtration
The system 2 separates the cell by tangential Ultrafiltration

For these two systems, the crude harvest leaves the bioreactor by overflow and arrives in a small intermediate vessel of 1 to 5 liters. From this buffering vessel, the harvest is pumped via a peristaltic pump trough a frontal or tangential (ultra)filtration system removing the cells at the rate of 0.5-0.6 L/h in the permeate.
In the case of tangential Ultrafiltration, the majority of the upstream flow (the retentate) is sent back to the 1-5 liter intermediate vessel where the cells are thus concentrated.
SNC-Lavalin is preparing a typical and a separated description of these two different disposable harvesting systems for discussion with the potential suppliers of disposable equipment and finalization of the designs.
At this stage, the Bioreactor harvesting SS line ends at two triclamps loated at a convenient place around the bioreactor where the 2 disposable systems can be added (one in operation and one in standby). The line removing the harvest by gravity is in Stainless Steel to be sure of the perfect operation of the gravity collect.

7. PROJECT DESCRIPTION AND ORGANISATION PLANIFICATION, Rev. 2

PRECONSULTATION PHASE

PROJECT DESCRIPTION, ORGANISATION AND PLANNING

EUROPEAN SPACE AGENCY
MELISSA PROJECT
November 2008

Publication Record

VERSION NO.	DESCRIPTION	DATE	BY
Rev 1	Initial issue	27-Nov-2008	Francis Smal
Rev 2	Revised list of bidding file content	5-Dec-2008	Francis Smal

TABLE OF CONTENTS

1. INTRODUCTION

The Melissa loop is a regenerative Life Support System needed to sustain life in Space during long term manned missions.
The Melissa Loop is organized in successive compartments that aim to recover Food, Water and Oxygen from wastes, e.g. CO2 and organic wastes, using light as source of energy.
The Melissa loop shall be tested on ground in the ESA external facility located in Barcelona at the premises of the UAB (Universitat Autonoma de Barcelona)
The different compartments of the Melissa loop shall be installed in a dedicated room for long-term demonstration of the loop efficiency and robustness to regenerate Food, Oxygen and Water from organic wastes.
Among the various compartments of the Melissa loop, the compartment III has been designed to bioconvert NH4+ to NO3- using a mix of bacteria, Nitrobacter and Nitrosomas immobilized on a fixed bed bioreactor.

The Bioreactor shall be redesigned to be operated in strict axenicity (absence of foreign micro-organisms contamination) during long-term period.

2. DOCUMENT OBJECTIVE

This document describes the approach of the European Space Agency and its partners (UAB, SNC-Lavalin, Sherpa, etc) for the in time Procurement of the Compartment III Bioreactor and ancillary components.

3. PROJECT TECHNICAL FILE

The technical characteristics of the Bioreactor system have now been decided so that the Bioreactor and its ancillaries can be described and specified in order to select the supplier that will receive the contract.

A few potential bioreactor suppliers will be contacted to determine their capability for designing, constructing and supplying the bioreactor and its ancillaries according to the planning proposed by SNC-Lavalin and the European Space Agency.

For that purpose, SNC-Lavalin is assembling a project file describing the equipment to be supplied, the accompanying documentation, the tests to be done as FAT and SAT and the planning of the supplies. The project file contains also the component list, the instrumentation list and the bill of quantities to get comparable quotation from the potential suppliers.
See the table hereafter to have an overview of the data that will be supplied to get the price of the supply
As it can be seen in the next table, the bioreactor automation/supervision is not included in the scope of the bioreactor supplier.

SNC-Lavalin Deliverables	List of deliverables	Availability Comment
Bioreactor Description	- Bioreactor systems Design requirements - Melissa project description - List of Bioreactor subsystems out of scope	Available Available Available
Requisition sheets for preconsulting	- Data sheets Vessels 30 L - Data sheet Bioreactor - P&ID - Simplified piping specs - Description of the Bioreactor Sub systems out of scope (with respect to P&ID) see 701014_Disposable_SS_compo_Rev2 - List of Documentation to be supplied - Commissioning tests	Available Available Available Available Available Available Available
List of components/ bill of quantities	- Component list - Instrumentation list - BOQ	Available Available Use component list
Definition of disposable Subsystems (1)	- List of systems - Schematics - Description	Available In preparation 12/12/08 Available (simplified)
Project Organization	- Project description, organization and planning - Responsibilities	Available 09/12/08
URS Automation(2)	- I/O list - URS automation	12/12 16/01/2009

(1) Out of scope of the bioreactor system manufacturer, not supplied during the preconsultation phase.
(2) The software and hardware supply is out of the scope of the bioreactor supplier

4. BIOREACTOR SYSTEM LAYOUT

The bioreactor system should be supplied on a skid.
The supply shall ideally contain all the Stainless steel piping linking the various components to be supplied. It shall also contain the needed Compressed Air Pipes and the Solenoid valves to operate the valves and the other components requiring the use of Compressed Air.
The solenoid valves shall of course be supplied in a board in stainless steel being part of the skid that should also contain some equipment needed for operating the magnetically coupled agitator (variable speed drive) and the pumps.

5. PRECONSULTING POTENTIAL SUPPLIERS

The Bioreactor suppliers are contacted by SNC-Lavalin on behalf of the UAB/ESA to determine their capability for designing, constructing and supplying the bioreactor and its ancillaries according to the planning proposed by SNC-Lavalin and the European Space Agency.
The contact and discussions with the potential suppliers shall allow selecting the supplier that is the most indicated for supplying the bioreactor system.

The key parameters for deciding are:

- **The budgetary price given by the supplier.**
- **The capability of supplying the bioreactor at the date agreed that shall be not later than May 16 2009**
- **The commitment/interest of the supplier for the project that should guarantee the quality of the supply and the respect of the agreed planning.**
- The level of technical input that the supplier can bring in the process (the bioreactor system is not a standard system)

6. PRECONSULTATION CALENDAR

The preconsultation phase starts week 48 and shall be finished to the latest on week 51.
Suppliers quotations shall be in the hands of SNC-Lavalin to the latest on Thursday December 18 2008.

SNC-Lavalin will supply the consulted suppliers not later than December 4 2008 with the complete project file that should help them to prepare their quotation and to assess the feasibility of the proposed planning of supply. Parts of this file shall be available beginning of week 49 (December 2)

Manufacturer activities during preconsultation	Manufacturer deliverables during the preconsultation	Availability at SNC-Lavalin offices in Brussels
Budget determination	- Budget proposal - Key personnel supposed to work on the project	Not later 18/12
Planning of supply	- Planning as expected at this stage of the project. - Written engagement showing supplier will and resources to deliver the Bioreactor system at the agreed date - Highlight of project milestones to succeed in providing the system at due date - Comments/advices to shorten the delivery time (e.g. electropolishing increases the delay of supply by X days)	Not later 18/12
Technical inputs and challenge	- At any time during the preconsultation	NA

At the end of the preconsultation phase, the potential suppliers shall take the firm written engagement to supply the Bioreactor at due date and to put enough resources on the project to deliver the bioreactor in due time

It is strongly attended (we would strongly appreciate) from the potential suppliers to inform SNC-Lavalin as soon as possible during the preconsultation phase if they are not in a position to supply the Bioreactor at due date (May 16)

7. DESIGNING, CONSTRUCTING, TESTING AND SUPPLYING THE BIOREACTOR SYSTEMS

Assuming that the preconsultation phase is finished on December 18, SNC-Lavalin shall finish the evaluation of the preconsulted suppliers and the written justified recommendation of the supplier to UAB/ESA for December 29.

Assuming these dates are fulfilled, the ESA/UAB organization shall pass the order not later than January 21 2009.
The engineering, constructing, testing, commissioning and shipping shall be finished to the latest on May 16 2009.
This makes thus a total of 16 weeks.

The planning challenge is thus quite hard and shall be assessed very carefully during the preconsultation phase.
The potential suppliers shall take the firm written engagement to supply the Bioreactor in due date and to put enough resources on the project to deliver the bioreactor in due time

All the components shall certainly be defined and ordered by the selected supplier within the 2 weeks following the bioreactor order.
The bioreactor shall be supplied to the University of Barcelona to the latest on May 20. The unpacking and installation on site shall follow immediately and shall be completed on May 25 to the latest.

8. ACCOMPANYING THE MANUFACTURER

SNC-Lavalin shall assist/advice/supervise the Bioreactor manufacturer in all the phases of the manufacturing to take immediately the technical decisions allowing the project to advance according to the agreed planning.
SNC-Lavalin should assist the manufacturer by the presence of one of its employees at the manufacturer site especially at the time of ordering the various systems components (valves, instrumentation, etc.) by the bioreactor supplier and at the most acute phases of construction of the main systems.
During the engineering phase, SNC-Lavalin shall also be very present for the definition of the systems layout.

FAT can be performed during the progress of the system assembly by the supplier when SNC-Lavalin is present on site. That should decrease the time needed for corrections and modifications.

SAT (at unpacking of the delivered items on site) shall be quite brief and shall consist in verifying that the systems have not been damaged during shipment and are correctly installed on the site.
At receipt on site, the supplier shall proceed immediately with installation on site and the assembly (if applicable) of the subsections of the skid.

9. INSTALLATION ON SITE

The manufacturer shall be responsible for the positioning on site of the skid and its components (and reassembly if applicable) and the execution under supervision of the very limited SAT.
It will be decided during the conversations of the preconsultation phase with the potential suppliers if the potential suppliers perform the connections of the skid onto the tie in points foreseen for the Utilities.
This concerns mainly the connection to the steam supply and the Oxygen, C02 and N2 supplies.
It concerns also the connections to the Instrument Compressed Air and to the fluids used for cooling and heating the jackets of the Bioreactor systems.

Presently, it is assumed that a Spanish company will install the utilities lines needed for the project before the installation on site of the bioreactor system and that this company will realize the connections of the utilities to the skid items.

8. SAT PROTOCOL, Rev. 1

APPROVAL OF PROTOCOL

ISSUED BY SNC-LAVALIN Name & function		Signature	Date
Prepared by			
Approved by			

MANUFACTURER APPROVAL Name & function		Signature	Date
Approved by			
Approved by			
Approved by			

Identification of SAT file	SAT

TABLE OF CONTENTS

1. OBJECTIVE

Verify on Bioreactor system site that the Bioreactor system has been installed at the foreseen location as indicated and that the bioreactor system has not been damaged during shipment or site installation.

2. IDENTIFICATION OF THE TESTED EQUIPMENT

This protocol concerns the SAT of the UAB/ESA Bioreactor and ancillary systems of the C3 Compartment of the Melissa loop.

EQUIPMENT: Bioreactor and ancillary systems	
Manufacturer	
Year of construction	
TAG number	
Room installation identification	

3. RESPONSIBILITIES

3.1. Vendor responsibilities

- The Vendor shall approve the SAT protocol in advance
- The Vendor is responsible for the execution of the test described in this protocol. The vendor shall supply the personnel and equipment needed for performing the tests. The vendor and SNC-Lavalin will fill the test sheets. The vendor will add all the prints and any related documents relevant to the performed tests
- The Vendor will execute all the necessary adjustments, modifications, additions agreed upon during or after the SAT performance and described in the deviation sheets of the punch list.

3.2. SNC-LAVALIN responsibilities

- SNC-LAVALIN is responsible for the preparation and the approval of the SAT protocol.
- SNC-LAVALIN is responsible for test witnessing.
- SNC-LAVALIN is responsible of the approval of the SAT report and punch list.

3.3. UAB/ESA responsibilities

- UAB/ESA is responsible for Approval of the SAT protocol and reports and of the punch list.

4. DEFINITIONS

– **Critical instrumentation:**
  Any instrumentation controlling and/or recording a process-parameter.

– **Non-critical instrumentation:**
  Instrumentation not controlling nor recording a process-parameter. This instrumentation is used primarily for convenience, operator ease or maintenance.

– **Deviation:**
  Deviation is a test result that is not in compliance with the acceptance criteria. Any deviation requires an investigation, corrective action or justification.

5. PROCEDURE

5.1. Procedure: general

- Perform and document the SAT tests as outlined in this protocol. Indicate and justify all not applicable tests (N/A) Attach any printouts and relevant documentation to the SAT report. The attached document should be referenced to the relevant section of the SAT document and must be clearly labelled with the protocol number, section or form number, date of tests and executors.
- If a test has already be adequately performed and documented, affix test report to the SAT document while indicating its existence in the SAT report at the corresponding worksheet.
- Approve any referenced worksheet or protocol before using it.
- If a vendor protocol is used instead or complementary to the SAT protocol, indicate clearly the link between the vendor protocol and the SAT document.

5.2. Documentation: general

- Only the use of **blue ink** is permitted to write during test performance, unless otherwise stated on the applicable Test Form.
- Report the results in the spaces provided in the SAT protocol and test forms. Corrections made to data entered in a field must be made by crossing out the mistake using a single line and then initialling and dating the correction (=GMP requirement) using blue ink.
- If it is not possible to report the results in the space provided, external documents (documents not inherently being part of this protocol like: lists, drawings, copies of supplier documentation, calculation sheets …) may be used. These documents should be appended and be referenced to the relevant section of the SAT document and must be clearly labelled with the protocol number, section or form number, date of test and executors signature. External documents attached to this protocol will be labelled "*Annex #0X to the protocol XXX*" and referenced on the first page.

5.3. Raw data generation and deviations documentation

- Identify the persons who generate/ report data relative to this protocol in the relevant section of this document.
- Identify the used measuring equipment in the relevant section of this document.
- Report "on line" (directly) the tests results (= raw data) on this document and on the provided test forms where applicable.
- When checking drawings, a colour code may be used:
  - Yellow highlighting indicates that the checked item complies with the drawing.
  - Red highlighting or red ink indicates that the checked item does not comply with the drawing or document and is not accepted by the person entering the results on the document. The non compliance must be recorded on the Punch List and must be physically corrected and rechecked.
  - Other coding conventions may be described on the testing documents.
- For each test or inspection, the appropriate column must be checked for compliance (PASS OR Y) or non compliance (FAIL OR N) with the specification and/ or acceptance criteria. The column 'Value / Document / Remark' will be used to document the numerical raw data, the identification and the location of external document or any supporting comments. Upon completion of each test or inspection, the person conducting the test will identify him/herself and fill in the test date.

During test performance, any Deviation to the acceptance criteria must be reported on **SAT Deviation Form**, attachment #02 of this protocol. A deviation must be understood as a failure to fully comply with the acceptance criteria or specification.

5.4. Test forms

Tests forms are used to better report the results of certain tests.

5.4.1. Procedure & Acceptance criteria

Each single Test Form contains a detailed Title, Objective, Method, Acceptance Criteria, Test equipment, Results and Test status.
Each page is provided with boxes for the signature and date of Test performer and Checker.
The procedure for completing these Test forms is described in the following section.

5.4.2. Working method for completing "TEST FORMS"

Only the use of **blue ink** is permitted to write during test performance, unless otherwise stated on the applicable Test Form.
Perform the tests detailed in the SAT Protocol, and record the results in the spaces provided in the attachments.

If it is not possible to perform a test as described in the Test Form, and no alternative method can be found, the reason why the test could not be performed
Any comments on the test method, the results or any unusual occurrence during validation should be written on the Test form – section "Comment

5.4.3. SAT Deviation Form (Attachment #02)

During test performance, any deviation must be reported on **SAT Deviation Form**, **attachment #02** of this protocol
Numbering:
To each Deviation Form, a sequential number is attributed which is referenced in the column Deviation Nber of the form
Handling of Deviations:
On each Deviation Form, the entire "deviation cycle" is managed:

- Description of the deviation
- Corrective actions
- Documented evidence of corrective actions resolution
- Mutual sign-off (SNC-Lavalin and Supplier name) of the Deviation form; when all deviations have been satisfactorily resolved

5.5. SAT completion and approval

Sign-off of this form implicates that all tests outlined in this protocol are completed, reconciled, documented and attached to this protocol. All **SAT Deviation Forms** are to be filed at the end of the SAT Report, just in front of the **SAT Completion and Approval** sheet (the SAT completion and approval sheet being the last page of the SAT Report while all Deviation Forms are just before this page).

6. ATTACHMENTS

ATTACHMENT #	TITLE
#02	SAT Deviation Form
#05	Test form: Piping & Instrumentation Diagram (P&ID) Verification
#06	Test Form: General Arrangement Verification (layout)
#15	SAT Completion and Approval

7. REFERENCES (DOCUMENTS & DRAWINGS) USED FOR SAT

DOCUMENT IDENTIFICATION	REV	TITLE	STATUS/ DATE	LOCATION

8. IDENTIFICATION OF PEOPLE PERFORMING THE TESTS & INSPECTION

NAME	INITIALS	SIGNATURE	DATE	JOB TITLE / COMPANY

9. TEST EQUIPMENT USED

List all instrumentation used for SAT performance in the hereafter table.

INSTRUMENT IDENTIFICATION	INSTRUMENT DESCRIPTION	CALIBRATION DATE	VALID UNTIL	INSTRUMENT OWNER

10. TESTS SHEETS

10.1. Documentation

10.1.1. Review of Supplier Documentation	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Use the relevant FAT documentation sections and check that any missing documentation at the time of FAT performance has been added, is relevant and complete. Document the findings					
By:			Date:		

10.2. Inspections/Verifications

10.2.1. Overall skid inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
The D03 and 04 Vessels are installed as indicated and are not damaged by transport of installation.				Not applicable	
Report any findings on the relevant P&ID and or GAD drawing and attach the drawing(s) to the SAT report					
By:			Date:		

10.2.2. Vessel D03-04 inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
The other bioreactor system is installed as indicated and is not damaged by transport of installation.					
Report any findings on the relevant P&ID and attach the drawing to the SAT report. Use attachment 05 and or 06 to summarize the findings					
By:			Date:		

10.2.3. Bioreactor inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
The bioreactor is installed as indicated and is not damaged by transportation or installation on site					
Report any findings on the relevant P&ID and attach the drawing to the SAT report. Use attachment 05 and or 06 to summarize the findings					
By:			Date:		

10.2.4. Components inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Verify all system components (mechanical, instrumentation, electrical, piping, valves, relief & safety valves,) are correctly installed and not damaged					
Report any findings on the relevant P&ID and attach the drawing to the SAT report. Use attachment 05 and or 06 to summarize the findings					
By:			Date:		

10.2.5. Pneumatic system inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Verify all pneumatic system integrity and installation and confirm that the pneumatic system is not damaged by transport or installation					
Report any findings on the relevant pneumatic schematics and attach the doc to the SAT report					
By:			Date:		

11. DEVIATION FORMS SUMMARY

Number of Deviation forms attached to this document	
All Deviations justified or corrected	Y/N
Comments:	

12. TEST FORMS SHEETS

12.1. ATTACHMENT #02: SAT Deviation Form

Document any deviations noted during the SAT using this Form. Include the corrective actions of these items and/or any outstanding item that will require future corrective actions. After the satisfactory completion of these items, sign the "Deviation Form Completed" section".

SAT Deviation form n°:		**Reference (attachment n°):**	
Raised by:		**Date raised:**	
Deviation:			
Corrective actions:			
Corrective actions approved/ Deviation Form Completed	Signature	Date	
SNC-LAVALIN			

12.2. ATTACHMENT #05: Test form: Piping & Instrumentation Diagram (P&ID) Verification (First)

Objective:
This section details the tests that will be performed to ensure that the pipe work has been installed in compliance with the "Approved As Built "Piping and Instrumentation Diagrams (P&ID's).
The Piping and Instrumentation Diagram (P&ID) will be used to ensure that all components are present and connected in the correct sequence, that they are labelled, accessible for maintenance and that the pipe work slope, branch length and drainage points are correct.

Method:

1. Obtain a copy of the "Approved As Built" drawing and register the information about the drawing into the results section.
   Inspect the valves, instrumentation and other components against the P&I Diagram.
   - ✓ Mark with a highlighter pen (**fluo yellow**) each detail on the P&I D when it has been verified as present and correctly installed. Any required corrections to the drawing should be made on the drawing with a **red** pen. If it is not possible to verify a detail the reason should be written on the drawing beside the item in **red** ink.
   - ✓ Verify that all piping is tagged with service and direction of flow at acceptable intervals; at change of direction. When services are supplied at different pressures, piping should be labelled with maximum pressure.
   - ✓ Confirm that all piping systems that are in contact with media can be drained. Locate each drainage, sample and take off point present in the distribution line and confirm whether or not it is self-draining. If the point is self-draining write the words "**DRAINS OK**" using a **blue** pen and initial the comment on the P&I D at the relevant point. All points that retrain water must have the words "**DOES NOT DRAIN**" written in **red** pen by the relevant point. Add to the P&I D using a **red** pen any drain lines, sample points or take off points not marked, and then test them as detailed above.
   - ✓ Measure and record on the drawing using a **blue** pen, the length of each dead leg in the system, measured from the centreline of the main to the midpoint of the branch valve. If there are any dead legs greater than six times the nominal diameter of the dead leg pipe, sign it with the text „ **Dead Leg** "using a **red** pen. Append the calculation of the dead legs to the report.
   - ✓ If it is not possible to check the length of a dead leg, investigate draining, or measure the air gap between an outlet and the drainpipe, write the reason on the drawing beside the item to which it applies in **red** ink.
2. Any deviation shall receive a sequential identification that should be written on the P&I D beside the item to be corrected and in the relevant deviation form. Any deviations should be documented in a "Deviation Form" (Attachment # 02). The Deviation form has to be numbered and referenced

Entered by (sign):		Date	

ATTACHMENT #05:
Test form: Piping & Instrumentation Diagram (P&ID) Verification (Cont'd)

Method (Cont'd):
1. Sign and date the P&I D and endorse the fully marked-up P&I D with "SAT DRAWING CHECK"

Acceptance criteria:
1. All components are present and correctly installed and in the positions shown on the P & I Diagram. All components are present and with correct tag-number.
2. All piping is tagged with service and direction of flow at acceptable intervals; at change of direction, every valve and each side of a wall or floor penetration, when services are supplied at different pressures, piping are be labelled with maximum pressure.
3. All systems are drainable. The system drainage, sample, and take off points are self-draining and do not leave stagnant water or product remaining.
4. There are no dead legs in the system greater than six times the internal branch pipe diameter in the circulation and draining systems, measured from the centreline of the main to the midpoint of the branch valve.
5. The marked-up P&ID is attached to the SAT File.

Test Equipment:
Any equipment used must be listed underneath:

Entered by (sign):		Date	

ATTACHMENT #05:
Test form: Piping & Instrumentation Diagram (P&ID) Verification (Cont'd)

Results:				
	Reference number	**Revision**	**Date of approval**	**Visa**
P & I Diagram				
Criteria			**Satisfies Yes/No**	**Visa / Date**
1. All components are present and correctly installed and in the positions shown on the P & I Diagram. All components are present and identified as in P&ID				
2. All piping is tagged with service and direction of flow at acceptable intervals; at change of direction. When services are supplied at different pressures, piping must be labelled with maximum pressure.				
3. All systems are drainable. The system drainage, sample, and take off points are self-draining and do not leave stagnant water or product remaining.				
4. There are no dead legs in the system greater than six times the internal branch pipe diameter in the circulation and draining systems, measured from the centreline of the main to the midpoint of the branch valve.				
5. The marked-up P&ID is attached to the SAT File				
Comments:				
Test status: Conform / Not Conform				
Reference here the numbers of the Deviation Forms				

Entered by (sign):		Date	

12.3. ATTACHMENT #06:
Test Form: General Arrangement Verification (First)

Objective:
This review is performed using the **"General Arrangement drawings"** (equipment layout) Installation, critical dimensions, general layout, alignment and interconnection wire lengths are checked.

Method:
The General Arrangement Verification Record is used to record the verification. Upon a successful inspection of the General Arrangement, the inspector will place a « **Yes** » in the Piping, Dimensions, and Layout columns. If the inspection identifies a non conformity, enter a « **No** ». In case of **No**, Deviation Forms (attachment #02) is completed and referenced in the Test Status section of this Test Form.

Acceptance criteria:
There is no difference between as built documents and installed equipment.

Test Equipment:
Any equipment used must be listed underneath:

Results:

Drawing number	Revision	Piping	Dimensions	Layout	Visa Date

Entered by (sign):		Date	

ATTACHMENT #06:
Test Form: General Arrangement Verification (Last)

Comments:	
Test status: Conform / Not Conform	
Reference here the numbers of the Deviation Forms	

Entered by (sign):		Date	

12.4. SAT Completion and Approval

Verify that all tests required by the protocol are completed successfully unless justified in the Deviation forms and that all tests results are reported in the SAT report. Verify that all amendments and deviations are documented, approved and attached to the SAT report.

Signatures in the blocks below indicate that all items in the SAT Protocol of the Bioreactor systems are reviewed and found to be acceptable. Signatures also indicate that all deviations have been satisfactorily resolved or have been included in an approved Action Plan and that the Bioreactor system is ready and authorized for Shipment to the installation site.

SNC-LAVALIN APPROVAL Name & function		**Signature**	**Date**
Approved by			
Approved by			

UAB/ESA APPROVAL Name & function		**Signature**	**Date**
Approved by			
Approved by			
Approved by			

9. FAT PROTOCOL, Rev. 1

APPROVAL OF PROTOCOL

ISSUED BY SNC-LAVALIN Name & function		**Signature**	**Date**
Prepared by			
Approved by			

MANUFACTURER APPROVAL Name & function		**Signature**	**Date**
Approved by			
Approved by			
Approved by			

Identification of FAT file	FAT

TABLE OF CONTENTS

1. OBJECTIVE

Verify at the manufacturer's Factory that the Bioreactor system has been constructed, tested and documented according to the ordering file, the "For Construction" approved Drawings and Documents" and current Good Manufacturing Practices (cGMP's)

2. IDENTIFICATION OF THE TESTED EQUIPMENT

This protocol concerns the FAT of the UAB/ESA Bioreactor and ancillary systems of the C3 Compartment of the Melissa loop.

EQUIPMENT: Bioreactor and ancillary systems	
Manufacturer	
Year of construction	
TAG number	

3. RESPONSIBILITIES

3.1. Vendor responsibilities

- The Vendor shall approve the FAT protocol in advance
- The Vendor is responsible for the execution of the test described in this protocol. The vendor shall supply the personnel and equipment needed for performing the tests. The vendor and SNC-Lavalin will fill the test sheets. The vendor will add all the prints and any related documents relevant to the performed tests
- The Vendor will execute all the necessary adjustments, modifications, additions agreed upon during or after the FAT performance and described in the deviation sheets of the punch list.

3.2. SNC-LAVALIN responsibilities

- SNC-LAVALIN is responsible for the preparation and the approval of the FAT protocol.
- SNC-LAVALIN is responsible for test witnessing.
- SNC-LAVALIN is responsible of the approval of the FAT report and punch list.

3.3. UAB/ESA responsibilities

- UAB/ESA is responsible for Approval of the FAT protocol and reports and of the punch list.

4. DEFINITIONS

– **Critical instrumentation:**
Any instrumentation controlling and/or recording a process-parameter.

– **Non-critical instrumentation:**
Instrumentation not controlling nor recording a process-parameter. This instrumentation is used primarily for convenience, operator ease or maintenance.

– **Deviation:**
Deviation is a test result that is not in compliance with the acceptance criteria. Any deviation requires an investigation, corrective action or justification.

5. PROCEDURE

5.1. Procedure: general

- Perform and document the FAT tests as outlined in this protocol. Indicate and justify all not applicable tests (N/A) Attach any printouts and relevant documentation to the FAT report. The attached document should be referenced to the relevant section of the FAT document and must be clearly labelled with the protocol number, section or form number, date of tests and executors.
- If a test has already be adequately performed and documented, affix test report to the FAT document while indicating its existence in the FAT report at the corresponding worksheet.
- Approve any referenced worksheet or protocol before using it.
- If a vendor protocol is used instead or complementary to the FAT protocol, indicate clearly the link between the vendor protocol and the FAT document.

5.2. Documentation: general

- Only the use of **blue ink** is permitted to write during test performance, unless otherwise stated on the applicable Test Form.
- Report the results in the spaces provided in the FAT protocol and test forms. Corrections made to data entered in a field must be made by crossing out the mistake using a single line and then initialling and dating the correction (=GMP requirement) using blue ink.
- If it is not possible to report the results in the space provided, external documents (documents not inherently being part of this protocol like: lists, drawings, copies of supplier documentation, calculation sheets …) may be used. These documents should be appended and be referenced to the relevant section of the FAT document and must be clearly labelled with the protocol number, section or form number, date of test and executors signature. External documents attached to this protocol will be labelled "*Annex #0X to the protocol XXX*" and referenced on the first page.

5.3. Raw data generation and deviations documentation

- Identify the persons who generate/ report data relative to this protocol in the relevant section of this document.
- Identify the used measuring equipment in the relevant section of this document.
- Report "on line" (directly) the tests results (= raw data) on this document and on the provided test forms where applicable.
- When checking drawings, a colour code may be used:
  - Yellow highlighting indicates that the checked item complies with the drawing.
  - Red highlighting or red ink indicates that the checked item does not comply with the drawing or document and is not accepted by the person entering the results on the document. The non compliance must be recorded on the Punch List and must be physically corrected and rechecked.
  - Other coding conventions may be described on the testing documents.
- For each test or inspection, the appropriate column must be checked for compliance (PASS OR Y) or non compliance (FAIL OR N) with the specification and/ or acceptance criteria. The column 'Value / Document / Remark' will be used to document the numerical raw data, the identification and the location of external document or any supporting comments. Upon completion of each test or inspection, the person conducting the test will identify him/herself and fill in the test date.

During test performance, any Deviation to the acceptance criteria must be reported on **FAT Deviation Form**, attachment #02 of this protocol. A deviation must be understood as a failure to fully comply with the acceptance criteria or specification.

5.4. Test forms

Tests forms are used to better report the results of certain tests.

5.4.1. Procedure & Acceptance criteria

Each single Test Form contains a detailed Title, Objective, Method, Acceptance Criteria, Test equipment, Results and Test status.
Each page is provided with boxes for the signature and date of Test performer and Checker.
The procedure for completing these Test forms is described in the following section.

5.4.2. Working method for completing "TEST FORMS"

Only the use of **blue ink** is permitted to write during test performance, unless otherwise stated on the applicable Test Form.
Perform the tests detailed in the FAT Protocol, and record the results in the spaces provided in the attachments.

If it is not possible to perform a test as described in the Test Form, and no alternative method can be found, the reason why the test could not be performed
Any comments on the test method, the results or any unusual occurrence during validation should be written on the Test form – section "Comment

5.4.3. FAT Deviation Form (Attachment #02)

During test performance, any deviation must be reported on **FAT Deviation Form**, **attachment #02** of this protocol
Numbering:
To each Deviation Form, a sequential number is attributed which is referenced in the column Deviation Nber of the form
Handling of Deviations:
On each Deviation Form, the entire "deviation cycle" is managed:

- Description of the deviation
- Corrective actions
- Documented evidence of corrective actions resolution
- Mutual sign-off (SNC-Lavalin and Supplier name) of the Deviation form; when all deviations have been satisfactorily resolved

5.5. FAT completion and approval

Sign-off of this form implicates that all tests outlined in this protocol are completed, reconciled, documented and attached to this protocol. All **FAT Deviation Forms** are to be filed at the end of the FAT Report, just in front of the **FAT Completion and Approval** sheet (the FAT completion and approval sheet being the last page of the FAT Report while all Deviation Forms are just before this page).

6. ATTACHMENTS

List of attachments:

ATTACHMENT #	TITLE
#02	FAT Deviation Form
#05	Test form: Piping & Instrumentation Diagram (P&ID) Verification
#06	Test Form: General Arrangement Verification (layout)
#08	Test form: Power, Electrical utilities Verification
#10	Test form: Critical Instrument List Verification
#15	FAT Completion and Approval

7. REFERENCES (DOCUMENTS & DRAWINGS) USED FOR FAT

DOCUMENT IDENTIFICATION	REV	TITLE	STATUS/ DATE	LOCATION

8. IDENTIFICATION OF PEOPLE PERFORMING THE TESTS & INSPECTION

NAME	INITIALS	SIGNATURE	DATE	JOB TITLE / COMPANY

9. TEST EQUIPMENT USED

List all instrumentation used for FAT performance in the hereafter table.

INSTRUMENT IDENTIFICATION	INSTRUMENT DESCRIPTION	CALIBRATION DATE	VALID UNTIL	INSTRUMENT OWNER

10. TESTS SHEETS

10.1. Preliminary/ Review of Documentation

10.1.1. Supplier Pre-FAT tests	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
If applicable, review the supplier pre-FAT tests: * Protocol					
* Report					
* Remarks					
By:			Date:		

10.1.2. Third Party Approval Pressure vessel certification	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
PED certification is available * Certificate number:					
The system is CE labelled * Certificate number:					
By:			Date:		

10.1.3. Third party approval Electrical	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Notified body certificate is available * Certificate number:					
By:			Date:		

10.1.4. Supplier Documentation Check	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Verify that the documentation requested in the Bioreactor Doc List is supplied in adequate format and quantity					
Lists and type of components (instruments, valves, filter, spare parts, etc.) are available and conform to the specification					
"For Construction" drawings are in compliance with the specifications and have been approved by the Engineer					
Materials certificates (AISI 316 L) are available. Certificates numbers are listed.					
Surface roughness certificates are available (Ra<0.4µm) Certificates numbers are listed.					
Drawings are in DWG format.					
Vessel, line, jacket safety valves are calibrated. Certificate numbers:					
By:			Date:		

10.1.5. Welding documentation			N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Welders list and certification is available					
Welding inspection file is available and in conformity with the specifications					
By:			Date:		

10.1.6. Cleaning & Passivation	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Internal system surfaces (in contact with the process fluids)are cleaned and passivated * Passivation certificates:					
By:			Date:		

10.1.7. Critical instruments documentation	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
The list of the critical instruments is available					
Verify the critical instrumentation list for accuracy, completeness and information content. Use the **attachment 10** of this document to report the test results					
By:			Date:		

10.2. Inspections/Verifications

10.2.1. Overall skid inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
The D03 and 04 Vessels have provisions for lifting by a crane				Not applicable	
Jacket, cladding, insulation materials conform to the specification					
Jacket and insulation are totally enclosed					
The bioreactor and the vessels D-03 and D-04 are completely self draining by gravity					
A nameplate with the requested information is permanently attached to the bioreactor and each of the 30 L tanks					
By:			Date:		

10.2.2. Vessel D03-04 inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Each vessel connection conforms to the specifications and cGMP in terms of location, type, dimension, material and construction * Process					
* Utilities					
* Vents					
* Instruments					
* Sight glass					
* Spray ball					
Each component and entry point is easily accessible for cleaning, maintenance and repair.					
Filter cartridges: *Check filter compatibility					
*Verify SIP (sterilisation in place) capability					
*Verify cartridge installation					
*Verify integrity test ports					
By:			Date:		

10.2.3. Bioreactor inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Each bioreactor connection conforms to the specifications and cGMP in terms of location, type, dimension, material and construction					
* Process					
* Utilities					
* Vents					
* Instruments					
* Sight glass					
Each component and entry point is easily accessible for cleaning and maintenance.					
* Verify SIP (sterilisation in place) bioreactor capability					
Air filter cartridges:					
* Check filter compatibility					
* Verify cartridges installation					
* Verify SIP cartridges/filter capability installation					
* Verify integrity test ports					
By:			Date:		

10.2.4. Components & P&ID inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Verify all system components (mechanical, instrumentation, electrical, piping, valves, relief & safety valves,) are tagged					
Check (P&ID) drawings using the **attachment 05** of this document					
By:			Date:		

10.2.5. Piping & connections inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Piping and connections conform to cGMP in terms of dead legs, support, drainability, …					
By:			Date:		

10.2.6. Valves inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
All valves are located as on relevant P&ID and are identified accordingly					
Valves conform to the cGMP and specification in terms of type, materials, size, installation, access for maintenance, …					
By:			Date:		

10.2.7. Critical instruments inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Verify the critical instrumentation installation and connection.					
By:			Date:		

10.2.8. Dimension inspection	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Use the **attachment 06** to report the results					
Use appropriate General Arrangement Drawing(s) (GAD) and the P&ID's if relevant to report the verifications and results					
By:			Date:		

10.2.9. Surface roughness	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Internal surfaces: Ra < 0.4 µm * Vessel D03				Max = µm	
* Vessel D04					
* Bioreactor				Max = µm	
* Piping					
* Valves				Max = µm	
* Ancillaries:				Max = µm	
By:			Date:		

10.2.10. Electrical Test	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Identify the electrical cabinet and verify the presence of the relevant electrical diagram in the cabinet.					
The electrical system has been successfully inspected using the **attachment 08** of this document.					
The electrical cabinet contains the items needed for operating the agitator, the pumps, sight glass light and is protected to IP54 level.					
15% reserve space is available.					
By:			Date:		

10.3. Functional Evaluation

10.3.1. Vessel D03 integrity test	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Isolate vessel by closing all valves					
Fill vessel with water and pressurise to 2 bar, the maximum pressure drop after 60 min is 40mbar					
By:			Date:		

10.3.2. Vessel D04 integrity test	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Isolate vessel by closing all valves					
Fill vessel with water and pressurise to 2 bar, the maximum pressure drop after 60 min is 40mbar					
By:			Date:		

10.3.3. Bioreactor integrity test	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Isolate Bioreactor by closing all valves					
Fill bioreactor with water and pressurise to 2 bar, the maximum pressure drop after 60 min is 40mbar					
By:			Date:		

10.3.4. Pneumatic Test	PASS	FAIL	N/A	VALUE / DOCUMENT / REMARK	DEV NBER
Identify the Pneumatic cabinet and verify the presence of the relevant schematics inside the cabinet.					
All solenoid valves are identified, linked to the relevant pneumatic valves and operational when tested with Compressed air.					
15% reserve space is available.					
By:			Date:		

11. DEVIATION FORMS SUMMARY

Number of Deviation forms attached to this document	
All Deviations justified or corrected	Y/N
Comments:	

12. TEST FORMS SHEETS

12.1. ATTACHMENT #02: FAT Deviation Form

Document any deviations noted during the FAT using this Form. Include the corrective actions of these items and/or any outstanding item that will require future corrective actions. After the satisfactory completion of these items, sign the "Deviation Form Completed" section".

FAT Deviation form n°:		**Reference (attachment n°):**	
Raised by:		**Date raised:**	
Deviation:			
Corrective actions:			
Corrective actions approved/ Deviation Form Completed	Signature	Date	
SNC-LAVALIN			

12.2. ATTACHMENT #05: Test form: Piping & Instrumentation Diagram (P&ID) Verification (First)

Objective:
This section details the tests that will be performed to ensure that the pipe work has been installed in compliance with the "Approved As Built "Piping and Instrumentation Diagrams (P&ID's).
The Piping and Instrumentation Diagram (P&ID) will be used to ensure that all components are present and connected in the correct sequence, that they are labelled, accessible for maintenance and that the pipe work slope, branch length and drainage points are correct.

Method:

1. Obtain a copy of the "Approved As Built" drawing and register the information about the drawing into the results section.
   Inspect the valves, instrumentation and other components against the P&I Diagram.
   - ✓ Mark with a highlighter pen (**fluo yellow**) each detail on the P&I D when it has been verified as present and correctly installed. Any required corrections to the drawing should be made on the drawing with a **red** pen. If it is not possible to verify a detail the reason should be written on the drawing beside the item in **red** ink.
   - ✓ Verify that all piping is tagged with service and direction of flow at acceptable intervals; at change of direction. When services are supplied at different pressures, piping should be labelled with maximum pressure.
   - ✓ Confirm that all piping systems that are in contact with media can be drained. Locate each drainage, sample and take off point present in the distribution line and confirm whether or not it is self-draining. If the point is self-draining write the words "**DRAINS OK**" using a **blue** pen and initial the comment on the P&I D at the relevant point. All points that retrain water must have the words "**DOES NOT DRAIN**" written in **red** pen by the relevant point. Add to the P&I D using a **red** pen any drain lines, sample points or take off points not marked, and then test them as detailed above.
   - ✓ Measure and record on the drawing using a **blue** pen, the length of each dead leg in the system, measured from the centreline of the main to the midpoint of the branch valve. If there are any dead legs greater than six times the nominal diameter of the dead leg pipe, sign it with the text „ **Dead Leg** "using a **red** pen. Append the calculation of the dead legs to the report.
   - ✓ If it is not possible to check the length of a dead leg, investigate draining, or measure the air gap between an outlet and the drainpipe, write the reason on the drawing beside the item to which it applies in **red** ink.
2. Any deviation shall receive a sequential identification that should be written on the P&I D beside the item to be corrected and in the relevant deviation form. Any deviations should be documented in a "Deviation Form" (Attachment # 02). The Deviation form has to be numbered and referenced

Entered by (sign):		Date	

ATTACHMENT #05:
Test form: Piping & Instrumentation Diagram (P&ID) Verification (Cont'd)

Method (Cont'd):
1. Sign and date the P&I D and endorse the fully marked-up P&I D with "FAT DRAWING CHECK"

Acceptance criteria:
1. All components are present and correctly installed and in the positions shown on the P & I Diagram. All components are present and with correct tag-number.
2. All piping is tagged with service and direction of flow at acceptable intervals; at change of direction, every valve and each side of a wall or floor penetration, when services are supplied at different pressures, piping are be labelled with maximum pressure.
3. All systems are drainable. The system drainage, sample, and take off points are self-draining and do not leave stagnant water or product remaining.
4. There are no dead legs in the system greater than six times the internal branch pipe diameter in the circulation and draining systems, measured from the centreline of the main to the midpoint of the branch valve.
5. The marked-up P&ID is attached to the FAT File.

Test Equipment:
Any equipment used must be listed underneath:

Entered by (sign):		Date	

ATTACHMENT #05:
Test form: Piping & Instrumentation Diagram (P&ID) Verification (Cont'd)

Results:				
	Reference number	**Revision**	**Date of approval**	**Visa**
P & I Diagram				
Criteria			**Satisfies Yes/No**	**Visa / Date**
1. All components are present and correctly installed and in the positions shown on the P & I Diagram. All components are present and identified as in P&ID				
2. All piping is tagged with service and direction of flow at acceptable intervals; at change of direction. When services are supplied at different pressures, piping must be labelled with maximum pressure.				
3. All systems are drainable. The system drainage, sample, and take off points are self-draining and do not leave stagnant water or product remaining.				
4. There are no dead legs in the system greater than six times the internal branch pipe diameter in the circulation and draining systems, measured from the centreline of the main to the midpoint of the branch valve.				
5. The marked-up P&ID is attached to the FAT File				
Comments:				
Test status: Conform / Not Conform				
Reference here the numbers of the Deviation Forms				

Entered by (sign):		Date	

12.3. ATTACHMENT #06:
Test Form: General Arrangement Verification (First)

Objective:
This review is performed using the **"General Arrangement drawings"** (equipment layout) Installation, critical dimensions, general layout, alignment and interconnection wire lengths are checked.

Method:
The General Arrangement Verification Record is used to record the verification. Upon a successful inspection of the General Arrangement, the inspector will place a « **Yes** » in the Piping, Dimensions, and Layout columns. If the inspection identifies a non conformity, enter a « **No** ». In case of **No**, Deviation Forms (attachment #02) is completed and referenced in the Test Status section of this Test Form.

Acceptance criteria:
There is no difference between as built documents and installed equipment.

Test Equipment:
Any equipment used must be listed underneath:

Results:

Drawing number	Revision	Piping	Dimensions	Layout	Visa Date

Entered by (sign):		Date	

ATTACHMENT #06:
Test Form: General Arrangement Verification (Last)

Comments:	
Test status: Conform / Not Conform	
Reference here the numbers of the Deviation Forms	

Entered by (sign):		Date	

12.4. ATTACHMENT #08:
Test form: Power, Electrical utilities verification (First)

Objective:
The objective of this test is to check the electrical board(s) and electrical connections

Method:
Proceed to the Test Form section "Results" in order to check all the requirements indicated in the Acceptance criteria section. Carry out all wiring connection check. Check electrical connections both sides. In case a deviation is found, use the Deviation Form to report it (attachment #02)

Acceptance criteria:
1. The electrical connection diagrams are available in the electrical boards.
2. The board is identified.
3. The electrical board official inspection certificate is available
4. Wirings are unambiguously identified: identification on wire and terminals.
5. All components of the board are identified.
6. There are no temporary fix-ups, jumps and alike.
7. All components are used for system operation (no dead components).
8. 15% reserve space is available

Test Equipment:
Any equipment used must be listed underneath:

Entered by (sign):		Date	

ATTACHMENT #08:
Test form: Power, Electrical utilities verification (Last)

Results:

Tests	Yes / No	Visa / Date
The electrical connection diagrams are available in the electrical board		
The electrical board official inspection certificate is available		
The board is identified		
Wirings are unambiguously identified		
All board components are identified		
There are no temporary fix-ups, jumps and alike (Yes = absence; No = presence)		
All components of the boards are used for system operation (no dead components)		
15% reserve space is available		

Comments:

Test status: Conform / Not Conform	
Reference here the numbers of the Deviation Forms	

Entered by (sign):		Date	

12.5. ATTACHMENT #10:
Test form: Critical Instrument List and Verification (First)

Objective:
To establish the Critical Instrument List for the Equipment Name using the ID number on the P&ID.
To verify that the supplier Critical Instrument List indicates instrument Manufacturer, Type, Model, Serial Number, Range and reference for ordering

Method:
1. From the study of equipment P&ID, Layout, documentation and from the process knowledge, verify and approve the vendor critical instrumentation list for the Equipment Name.
2. For each critical instrument of the Equipment Name, check that the required information is mentioned on each item of the list: instrument Manufacturer, Type, Model, Serial Number, Range and reference for ordering
3. Check for each critical instrument if a valid calibration certificate from the supplier is present.
   If a calibration certificate is present, include this calibration certificate in the Calibration File at its appropriate Location.
4. Check the presence of a complete relevant data sheet for each critical instrumentation and that the datasheet indicated the P&ID Identification of the instrumentation

Acceptance criteria:
1. All instrumentation that controls or records the system function has been identified and is listed in the Critical Instrument List. This list is approved
2. For each critical instrument listed, all the requested information is entered in the list
3. Each critical instrumentation is supplied with a valid calibration certificate.
4. Complete relevant data sheets are available for each critical instrumentation and that the data sheet is annotated with the relevant P&ID number of the instrumentation.

Test Equipment:
Any equipment used must be listed underneath:

Entered by (sign):		Date	

ATTACHMENT #10:
Test form: Critical Instrument List and Verification (Last)

Results:		
	Yes / No	**Visa / Date**
All instrumentation that controls or records the system function has been identified and is listed in the Critical Instrument List. This list is approved.		
For each critical instrument listed, all the requested information is entered in the list (instrument Manufacturer, Type, Model, Serial Number, Range and reference for ordering)		
Each critical instrumentation is supplied with a valid calibration certificate.		
Complete relevant data sheets are available for each critical instrumentation and that the data sheet is annotated with the relevant P&ID number of the instrumentation.		

Comments:	
Test status: Conform / Not Conform	
Reference here the numbers of the Deviation Forms	

Entered by (sign):		Date	

12.6. FAT Completion and Approval

Verify that all tests required by the protocol are completed successfully unless justified in the Deviation forms and that all tests results are reported in the FAT report. Verify that all amendments and deviations are documented, approved and attached to the FAT report.

Signatures in the blocks below indicate that all items in the FAT Protocol of the Bioreactor systems are reviewed and found to be acceptable. Signatures also indicate that all deviations have been satisfactorily resolved or have been included in an approved Action Plan and that the Bioreactor system is ready and authorized for Shipment to the installation site.

SNC-LAVALIN APPROVAL **Name & function**		**Signature**	**Date**
Approved by			
Approved by			

UAB/ESA APPROVAL **Name & function**		**Signature**	**Date**
Approved by			
Approved by			
Approved by			

10. CLEAN STEAM SUPPLY, Rev.1

SNC-LAVALIN

CLEAN STEAM SUPPLY FOR BIOREACTOR OF COMPARTMENT III

701014 PROJECT

Compartment III of Melissa loop

UAB/ESA Barcelona

REV	DATE	MODIFICATIONS/REVISIONS	Prepared by	Verified by	Approved by
1	2/12/08	Initial issue	F. Smal		

SNC·LAVALIN Pharma

DOCUMENT NR. :6067 42 60 006

701014 Clean Steam Supply

TABLE OF CONTENTS

1. CLEAN STEAM SUPPLY

For starting and routine use of the bioreactor of the compartment III, clean steam is required for ensuring the various sterilization in place that are necessary.

The steam shall be supplied by a steam line that is capable of supplying 15 Kg/h of clean steam at the pressure of maximum 2.5 bar.

The line pressure should be manually set to the target value (2.1-2.5 bar) through a mechanical manual Pressure regulator.

The feeding line should end by a drainable manifold where 4 manual connections of sterilizing pipes can be done.
This systems allows thus to sterilize in place 4 different systems via 4 removable soft tubes designed for withstanding steaming in place at 2.5 Bar. These tubing are commercially available.

The 4 connections are Triclamp connections.

Each Tri clamp connection is preceded by a manual on off ball valve and a needle valve to set and optimized the steam flow for sterilization performance (without damaging the system to be sterilized)

The flow is expected to be bigger to sterilize the 40 liters vessels than the very small volume at the interface of the disposable and stainless steel sections.

1 Connection could be set for sterilisation of the 40 liters vessels and perhaps the bioreactor.
The other ones should be set for sterilisation of very small volume (filters, sections of pipes, Stainless steel connection to Disposable)

11. SMALL CABLING, PNEUMATIC SYSTEM, Rev.1

SNC-LAVALIN

SMALL CABLING, PNEUMATIC SYSTEM

701014 PROJECT

Compartment III of Melissa loop

UAB/ESA Barcelona

REV	DATE	MODIFICATIONS/REVISIONS	Prepared by	Verified by	Approved by
1	2/12/08	Initial issue	F. Smal		

SNC·LAVALIN Pharma

DOCUMENT NR. :6067 42 60 006

701014 Small Cabling, Pneumatics

TABLE OF CONTENTS

1. SMALL CABLING

The Bioreactor manufacturer shall include in its supply the Stainless Steel electric board (minimum AISI 304) to house the electrical components needed to feed the motors and lights included in the bioreactor supply;

- The bioreactor mixer (bottom section)
- The peristaltic pumps to be included in the supply (each equipped with remote speed control input 4-20 mA)
- The other pumps needed for the bioreactor operation.
- The weight cells used for the bioreactor operation.
- The light included in the bioreactor supply
- The circulator CC1 (KNF brand) on the oxygen loop.

The board shall be compliant with CEN regulations and CE labelled.
It shall contain 15% reserve space.

2. PNEUMATIC SYSTEM

The bioreactor supplier shall include in its supply the pneumatic systems to operate the bioreactor.
The manufacturer will supply a dedicated Stainless steel board (minimum AISI 304) to locate the solenoid valves used to operate the pneumatic valves of the bioreactor.
The manufacturer shall install, mark and test the pneumatic tubing (Festo type) from the valves (on-off and regulating) to the solenoid valves.
The board shall contain 15% reserve space.

The supplier of the bioreactor control system shall supply the control system for operating these solenoid valves.

3. PERISTALTIC PUMPS

The pumps shall be equipped with PC interface allowing remote speed control (4-20 mA input) and with manual potentiometer.

- The pump P-04 is used to feed the bioreactor with the ammonium solutions. The pump flow rate is controlled by the Control system (supervising system) and the routine flow rate is 0.6Liters per hour. The pump shall be selected to supply the nominal flow at about 60% of its speed using a silicone tubing diameter in the middle range of the pump.

- The pumps P-02, P-03 and P-08 are used to supply the sodium carbonate and sulphuric acid solutions to control the pH of the solution in the Bioreactor. The pumpP-08 is used for the optional antifoam solution but shall be supplied and installed on the skid to be used as reserve pump in case of failure of the 2 other ones. The operation of these two pumps is supervised by the control system. Their flow rate is intermittent and very low. Supply of pH correcting solutions is done more or less drop by drop and should be in the range of 1-10 ml per 24 hours.

- The pump P-07 is used for backwashing. The pump flow rate is manually adjusted to about 36 L/h. The pump shall be selected to supply the nominal flow at about 60% of its speed using a silicone tubing diameter in the middle range of the pump.

- The pump P-06 is used for recirculation bioreactor solution throughout the bioreactor. The pump flow rate is controlled by the Control system (supervising system) and the routine flow rate is 3.6 Litres per hour. The pump shall be selected to supply the nominal flow at about 60% of its speed using a silicone tubing diameter in the middle range of the pump.

- The pump P-01 is used for harvesting. The pump P-01 selection depends of the method used for separating the free cells in suspension in the harvest from the solution. Harvesting should be done by tangential filtration of frontal filtration. In case frontal filtration is used, the pump shall be the same as P-04. In case tangential Ultrafiltration, the flow rate is much higher because a high percentage of the flow rate is resent back to the pump feed. The attended pump flow rate is about 80l/h variable and controlled by the supervising system. The pump shall be selected to supply the nominal flow at about 60% of its speed using a silicone tubing diameter in the upper range of the pump.

4. THE OTHER PUMPS

These pumps are:

- The circulating pump needed for temperature control of the jacket of the bioreactor.
- The circulator CC1(KNF brand) on the oxygen loop

The pump for the jacket has to be calculated by the Bioreactor supplier taking account of the jacket construction and calculation, the operational set point (28°C) the temperature of the cooling and heating water included in the T regulating loop and the characteristics of the Stainless Steel exchangers.

The jacket panoply hardware is included in the supply (heat exchangers E03 and E02, piping, pump, T instrumentation and expansion vessel)

We are waiting information from the UAB Barcelona about the temperature and flow rate of the cooling and heating fluids.

The circulator CC1 (KNF brand) on the oxygen loop is described in the relevant data sheet provided in the preconsultation file.

12. TUBING SPECIFICATIONS, Rev.1

SNC-LAVALIN

TUBING SPECIFICATIONS

701014 PROJECT

Compartment III of Melissa loop

UAB/ESA Barcelona

REV	DATE	MODIFICATIONS/REVISIONS	Prepared by	Verified by	Approved by
1	2/12/08	Initial issue	F. Smal		

SNC·LAVALIN Pharma

DOCUMENT NR. :6067 42 60 006

701014 Tubing Specs

TABLE OF CONTENTS

TECHNICAL CONTRACT SPECIFICATIONS

1. ENGINEERING AND CONSTRUCTION STANDARDS

The tubing shall be in compliance with the following standards, codes, laws (edition in force):

- ASTM 270 « Standard Specification for seamless and Welded Austenitic Stainless Steel Sanitary Tubing »
- ASTM 269 « Standard Specification for Seamless and Welded Austenitic Stainless Steel Tubing for General Service » (for the unspecified specifications in the ASTM 270)
- Guide to Inspections of High Purity Water Systems (F.D.A., July 1993)

2. GENERAL TECHNICAL SPECIFICATIONS

2.1 CONSTRUCTION MATERIAL

All parts in contact with the process liquids and gases, except gaskets and membrane of valves must be AISI 316L stainless steel

Finishing:
- inside (contact with the Process Water)
  Ra < 0,4 µ
- outside: not important (e.g. 180 grit finish). For the vessels and bioreactor: Ra ≤1,2 µm – Bright polish

2.2 TUBING

The tubes will be seamless tubes or welded tubes.
Tubing and fittings have to be supplied with a material certification sheet for construction material, standards in force, and surface roughness. Provide pre-cleaned and capped tubing. Handle material in such a way to prevent introduction of contaminants into the piping system.

a) Tolerances: minimum tolerances to assure proper alignment for automated welding - following ASTM A270 and ASTM A 269
b) Standard: Imperial (OD) or ISO according availability
c) Favourite suppliers: Dockweiller, Neumo or Biobore according best availability.

2.3 VALVES

- All steel wetted surface in 316L stainless steel
- Interior finish: as specified for tubing (Ra ≤ 0.4µm)
- Self drainage
- Welded to tubing or clamps
- Favourite suppliers: Gemu, Saunders or ITT according best availability

2.3.1 Diaphragm valves, point of use valves

- 316L Stainless steel forged body
- EPDM Membrane

2.3.2 Regulating valves

Sanitary ends (clamps)
Gasket material to be specified
Favourite suppliers: Samson, Jordan

2.4 FITTINGS (TEE, ELBOWS, CLAMPS, ETC.)

Material, wall thickness and finishing as specified for tubing.

2.5 WELDINGS

Automated TIG orbital welding.
Manual welding is authorised when automated welding is not technically possible.

2.6 GASKETS

EPDM or Viton
Steam sterilizable

2.7 CALIBRATED ORIFICES

Not applicable.
In case of need, use restricted orifices without dead zone (e.g. available from Neumo)

2.8 SAMPLING VALVE

Membrane valve with mini-clamp, blind plate and small chain.

2.9 PUMPS

Peristaltic pumps with variable speed motor drive (PLC controlled) selected to provide the specified flow at about 60% of maximum speed, with low shearing effect.
Favourite supplier: (Ismatec, Quattro, Watson-Marlow others according availability).

2.10 HEAT EXCHANGER (GAS CONDENSER)

Seamless tubes only: Double concentric tube or double tube sheet.
Surface in contact with process fluid 316 L non electropolished (Ra $\leq$ 0,4 µ)
Fully drainable
Connections by: Tri-clamp
All necessary fittings to remove the cooling or heating water from the exchanger to allow efficient steam sterilisation, when steam sterilisation is specified.

2.11 VESSELS, BIOREACTOR

Inside surface: 316 L Ra<0.4µm.
Vessel must be totally drainable.
No spray ball.
Vessels must be equipped with vent filter (0,2 µm hydrophobic) installed in such a way as to prevent condensate from being trapped. Designed for SIP and WIT in place.
The model must be approved by the customer.
The bioreactor is not insulated.
See relevant data sheets for additional information;

2.12 SENSORS

Required sensors (Temperature, Pressure, Conductivity, Flow meter...) in contact with the process waters must be:
- Sanitary type
- Connected by Na Connect or tri-clamp as specified in Instrumentation List
- Thermowell mounted (temperature sensor only)

The length of the electrical connections must be long enough to allow the calibration of the sensors.

2.13 INSULATION

Not applicable
except for Chilled water piping.

2.14 INSTALLATION CONCEPT

The installation (pump, loop, line, tubing...) shall be designed to meet the following parameters:

- No dead leg ≥ 6D = 6 x the internal diameter of the smallest pipe (measured from the axis of the pipe in use)

2.15 EXECUTION

The tubing must be provided pre-cleaned and capped.
The prefabricated parts must be stored cleaned and capped to prevent introduction of contaminants into the piping system.
The bending of the tubes is allowed up to and including DN 10. Use of fittings is preferable.

2.16 DRAINAGE

- The whole installation must be completely drainable
- The slope tubing to the low points must be 1% minimum, preferably 1,5 to 2 %
- The membrane valves must be positioned to be fully drainable
- During sterilisation, the relevant steam trap(s) is(are) preceded by a movable T sensor for recording the sterilisation temperature.

2.17 CERTIFICATION:

Welders shall be certified to the used welding procedures for the applicable material in accordance with a European standard of Qualification (to be approved).

Welders shall be certified in the use of the specific equipment and material being used in the welding process.

2.18 WELDING PROCEDURE

Perform Automatic TIG orbital welding. The use of a machine with printout of the welding parameters is preferable.
Develop a set of acceptable parameters for the tubing that will be welded, subject to approval.
Manual welding may be used only when automated welding is not technically possible.
Do not use ferrous material, tools or equipment (carbon steel cutting tools) in the fabrication or installation of systems.

2.19 INSPECTION

Examine each external weld visually to ensure there are no surface defects, and record.
Examine each interior weld and adjacent areas, visually if possible, and record.
Examine the interior weld with endoscope:
- 20 % of the automatic welds, minimum one test per day and per change of welding's parameters.
- 100 % of the manual welds.

Document and log each weld as follows:
- Provide the "as built" isometric view with the number, location and type of welds (manual, automatic)
- Engrave each weld with a number
- Location, number and date of weld
- Name of welder
- Name of inspector
- Identification of used endoscope
- Video tape of 20% of automatic welds, of 100% of manual welds.
- One sample of automated welds per day and per change of the welding parameters.
- Printout of the welding parameters.

3. PRESSURE TESTS

The pressure tests must be done before cleaning and passivation.
A first test must be executed during 1 hour with an inert gas.
The second test must be hydraulic with DI water, during 6 hours, without loss of the initial pressure.
The test pressure must be 1,5 X the used pressure.

4. CLEANING AND PASSIVATION

For the passivation operation, a by-pass must be installed for the equipment that is electropolished if any.
All gaskets to be replaced after passivation:

4.1 CLEANING

Cleaning is mandatory.
Operate according to a written pre-approved procedure.

Record and log cleaning dates and steps.

4.2 PASSIVATION

Passivation is mandatory. Use a 15-20 % weight/weight nitric acid solution in water.
Circulate at least 1 hour. Operate according to a written pre-approved procedure.
Do not use Fluorhydric acid for passivation.
Record and log passivation dates and steps.
Drain the system completely, and collect the solution according to local regulation.
By-pass pipes for all equipment shall be shown in the supplier drawings.

4.3 RINSING

Fill the system with DI water, circulate for 15 minutes, flush each use point outlet and equipment connection until the pH of discharge water is equal to the inlet pH.
Record and log cleaning dates and steps.
Drain the system completely, and collect the solution according to local regulation.

5. IDENTIFICATION

All system components (pump, vessel, instrumentation, valves, heat exchangers,...) must be tagged.
The tag number must be the number of the P&I.

13. DOCUMENTATION LIST, Rev.1

1. DOCUMENT OBJECTIVE

The objective of this document is to define the list of documentation that has to trace the procurement, design, construction and installation, FAT, and SAT of the UAB/ESA bioreactor and its ancillary systems in Stainless Steel. The documentation concerns the hydraulic, pneumatic and control instrumentation of the system. The hardware/software for system supervision is not included.

The objective of this document is also to define by whom the different sections of the documentation have to be prepared.

2. ABBREVIATIONS

S = Supplier or Vendor
E = Engineering company (SNC-lavalin)
U = UAB/ESA
NA= Non applicable

3. RESPONSIBILITIES

- In the "issued by" column, when a single Abbreviation S or E or U is used, the mentionned organization (U, S or E) is responsible for preparing the protocol, reports, raw data, punch list and whole documentation file.
- When 2 or more organizations are mentioned in the "issued by" column, the balance between the organizations has to be fixed case by case.

4. DEDICATED DOCUMENTATION LIST

- This standard documentation list is used to prepare, by equipment (vessel, bioreactor, etc;) a dedicated documentation list to be included in the supplied file.

5. FACTORY ACCEPTANCE TESTS

To be performed according to the requirements of the purchase order.

6. SITE ACCEPTANCE TESTS

To be performed according to the requirements of the purchase order.

ENGINEEERING FILE

Section	Engineering file sections		Document in file	Issued by
1	TABLE OF CONTENT		Sections and sub sections as mentioned here	S
2	BIDDING REQUIREMENTS	01	Bidding File, URS, mail and E-mails	E
		02	Bidding Drawings	
3	ORDERING DOCUMENTS	01	Purchase order, bids comparisons, meeting reports with vendor	U/E
		02	Supplier Quotation, mail and Emails (follow up)	S
4	"FOR EXECUTION" APPROVED DOCUMENTS	01	Components list and data sheets	S
		02	Design Calculations (PSV Calculations, third party approval)	S
		03	Control system Specifications	S
5	"FOR EXECUTION" APPROVED DRAWINGS	01	Dra&wing list	S
		02	P&ID's	S
		03	Skid/layout drawing	S
		04	Mechanical drawings	S
		05	Pneumatic drawings	S
		06	Electrical drawings (agitator, pumps)	S
		07	Other drawings (civil works) NA	NA
6	AS BUILT DRAWINGS	01	List of "As built" Drawings	S
		02	P&ID's	S
		03	Skid/layout drawing	S
		04	Mechanical drawings	S
		05	Pneumatic drawings	S
		06	Electrical drawings (agitator, pumps)	S
		07	Other drawings (civil works) NA	NA
		08	Electronic support of all the drawings	S
7	AS BUILT DOCUMENTS	01	Components list and data sheets	S
		02	- Vessels	S
		03	- Reactor	S
		04	- SS lines and loop	S
		05	- instrumentation	S
		06	- others	S
8	OPERATIONS AND MAINTENANCE DOCUMENTATION	01	Operation and maintenance manuals	S
		02	Installation instruction	
		03	Consumables list with supplier references	S
		04	Spare parts list with manufacturer part numbers	S
		05	Training Documentation	S
		06	Set points, Alarm values, functional parameters	NA
		07	Copy of program	NA

COMMISSIONING FILE

Section	Commisioning file sections		Document in file	Issued by
1	TABLE OF CONTENT		Table of content of the commissioning file	S
2	PROJECT CHANGES	01	Change (control) documents and related documents	S
3	FACTORY ACCEPTANCE TESTS (FAT)	01	FAT tests protocols	S
		02	FAT tests reports	S/E/U
4	SITE ACCEPTANCE TESTS	01	SAT tests protocols	S
		02	SAT tests reports	S/E/U
5	EXTENDED PIPING/WELDING DOCUMENTATION	01	Slopes verification	S
		02	Welding procedure and Qualification	S
		03	Welders Qualification	S
		04	Welding book	S
		05	Cleaning/passivation procedures and reports	S
6	EQUIPMENT/SUPPLIER CERTIFICATES	01	Instrumentation Calibration certificates, PSV certificates	S
		02	PED compliance (certificate)	S
		03	CE compliance (certificate)	S
		04	Material certificates	S

14. INSTRUMENTATION AND COMPONENT LIST, Rev.A

ESA - Projet 701014

INSTRUMENTATION and COMPONENT LIST

For list of valves see table 701014 41 60 004

TAG		Description	Op Range	Brand	Ref n°	Rem
Tag Line / System			C-01	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)			NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	10/ 28/ 130	Yes
C	001	see 701014_41_60_002 DS Bioreactor					
CD	001	Air Condenser (cold water)	~200 l / h	(*)	(*)	Cold water temperature to be supplied by UAB
D	005	Expansion Vessel (thermostatization)	(*) l/h	(*)	(*)	temperature to be supplied by UAB
DO2E	001	Dissolved O2 element	0 to 100% acc 1%	Mettler Toledo	Infit (*)	(1) (2) + SIP
DO2E	002	Dissolved O2 element	0 to 100% acc 1%	Mettler Toledo	Infit (*)	(1) (2) + SIP
DO2T	001	Dissolved O2 transmitter (see corresponding element)				
DO2T	002	Dissolved O2 transmitter (see corresponding element)				
DPT	001	Differential Pressure transmitter	0 to 3 bar	Endress+Hauser	Deltabar(*)	(1) (2) + 4-20 mA
L	105	Flow element + transmitter	45 to 450 l/h	Krohne	H250	(1) Alu is acceptable
L	106	See corresponding FE				
L	107	Future (out of scope)				
OPT LSHH	001	Level switch (Vibrating horizontal)	Contact	Endress+Hauser	Liquiphant M FTL (*)	(1) (2) OPT = In option
OPT LSL	001	Level switch (Vibrating horizontal)	Contact	Endress+Hauser	Liquiphant M FTL (*)	(1) (2) OPT = In option
P	005	Circulating Pump	0 to 350 l/h	(*)	(*)	
PE	001	Pressure element + transmitter	0 to 1000 mbar	Endress+Hauser	Cerabar (*)	(1) (2)
PHE	001	pH element + transmitter	pH 0 to 14	Endress+Hauser	Cleanfit H (*)	(1) (2)+ Retractable (steril + calibr)
PHE	002	pH element + transmitter	pH 0 to 14	Endress+Hauser	Cleanfit H (*)	(1) (2)+ Retractable (steril + calibr)
PHT	001	see corresponding pHE				
PHT	002	see corresponding pHE				
PSV	001	Pressure relief valve on vessel	-1 to +3 bar	Grayel	(*)	(1) + with connection to safe location

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
PT	001	see corresponding PE				
TE	005	Temperature element + transmitter	4 to 250°C	Endress+Hauser	(*)	(1) (2) + 4-20 mA; Dismountable
TE	006	Temperature element + transmitter	4 to 250°C	Endress+Hauser	(*)	(1) (2) + 4-20 mA; Dismountable
TT	005	see corresponding TE				
TT	006	see corresponding TE				
XE	001	Conductivity element + transmitter	c = 0,1 cm-1 (0,04 à 500 µS/cm)	Endress+Hauser	Condumax (*)	(1) (2) + 4-20 mA; Retractable (steril + calibr)
XE	002	Conductivity element + transmitter	c = 0,1 cm-1 (0,04 à 500 µS/cm)	Endress+Hauser	Condumax (*)	(1) (2) + 4-20 mA; Retractable (steril + calibr)
XE	003	Future (out of scope)				
XT	001	see corresponding XE				
XT	002	see corresponding XE				
XT	003	Future (out of scope)				
YT	001	Out of scope (ordered by ESA)				

Tag Line / System	D-03	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	5/ 8/ 130	Yes

D	003	See 701014_41_60_001 DS Vessel 30L				
LI	002	Level indicator (from corresponding LT)				Digital display on skid
LT	001	Level transmitter (capacitive)		Endress+Hauser	(*)	(1) (2) + 4-20 mA
OPT LSL	003	Level switch (Vibrating horizontal)	Contact	Endress+Hauser	Liquiphant M FTL (*)	(1) (2) OPT = In option
PI	003	Pressure Indicator (Manometer)	-1 to +3 bar	Same as selected filter housing	(*)	(1) (2) Aseptic membrane type + connection for water intrusion test
PSV	002	Pressure relief valve on vessel	-1 to +3 bar	Grayel	(*)	(1) + with connection to safe location
TE	002	Temperature element + transmitter	4 to 250°C	Endress+Hauser	(*)	(1) (2) + 4-20 mA; Dismountable
TT	002	see corresponding TE				

Tag Line / System	D-04	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	5/ 8/ 130	Yes

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
D	004	See 701014_41_60_001 DS Vessel 30L				
LI	003	Level indicator (from corresponding LT)				Digital display on skid
LT	002	Level transmitter (capacitive)		Endress+Hauser	(*)	(1) (2) + 4-20 mA
OPT LSL	004	Level switch (Vibrating horizontal)	Contact	Endress+Hauser	Liquiphant M FTL (*)	(1) (2) OPT = In option
PI	022	Pressure Indicator (Manometer)	-1 to +3 bar	Same as selected filter housing	(*)	(1) (2) Aseptic membrane type + connection for water intrusion test
PSV	004	Pressure relief valve on vessel	-1 to +3 bar	Grayel	(*)	(1) + with connection to safe location
TCV	003	Temperature Control Valve	0 to 300 l/h	Samson	(*)	
TE	003	Temperature element + transmitter	4 to 250°C	Endress+Hauser	(*)	(1) (2) + 4-20 mA; Dismountable
TT	003	see corresponding TE				

Tag Line / System	L-100	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Air	DN15	3	0,1/ 0,6/ 1	-1/ 0/ 1	10/ 20/ 130	Yes

F	005	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)

Tag Line / System	L-101	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	10/ 20/ 130	Yes

F	004	Liquid filter ; 0,22µm ; SiPable	0 to 10 l / h	Millipore or equiv	(*)	(2)

Tag Line / System	L-103	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No

TCV	202	Temperature Control Valve	0 to 300 l/h	Samson	(*)	

Tag Line / System	L-104	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	DN4	1	0,1/ 0,6/2	-1/ 0,08/ 3	5/ 8/ 130	Yes

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
F	003	Liquid filter ; 0,22µm ; SiPable	0 to 10 l / h	Millipore or equiv	(*)	(2)
FE	001	Flow element + transmitter	0 to 2l/h	(*)	(*)	(1) (2)
FT	001	see corresponding FE				
NRV	155	Non return valve process	0 to 2 l/h	Staitech	HCV 02	(2)
P	004	Peristaltic Pump multichannel, variable speed	0 to 1000 ml/h	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER

Tag Line / System	L-105	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
NA2CO3 (100g/l)	DN4	2	0,001/0,01/0,10	-1/ 1/ 3	10/ 20/ 50	No

F	002	Liquid Filter ; 0,22µm ; 1 ml/min	0 to 100 ml / h	Millipore or equiv	(*)	(3)
P	003	Peristaltic Pump (acid/base) multichannel, variable speed	0 to 10 ml/h (10 ml/24h)	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER
WI	002	Acid/Base Bottle weight indicator (+ weighing scale)	0 - 40kg (precision 10g)	Sartorius or equivalent	(*)	All SCALE in the scope of the BIOREACTOR SUPPLIER
WT	002	Weight Transmitter (see corresponding indicator)				

Tag Line / System	L-106	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
H2SO4 5%	DN4	2	0,001/0,01/0,10	-1/ 1/ 3	10/ 20/ 50	No

F	001	Liquid Filter ; 0,22µm ; 1 ml/min	0 to 100 ml / h	Millipore or equiv	(*)	(3)
P	002	Peristaltic Pump (acid/base) multichannel, variable speed	0 to 10 ml/h (10 ml/24h)	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER
WI	001	Acid/Base Bottle weight indicator (+ weighing scale)	0 - 40kg (precision 10g)	Sartorius or equivalent	(*)	All SCALE in the scope of the BIOREACTOR SUPPLIER
WT	001	Weight Transmitter (see corresponding indicator)				

Tag Line / System	L-109	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	DN4	2	1/ 80/ 100	-1/ 0,08/ 3	10/ 28/ 50	No

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
P	001	Peristaltic Pump multichannel, variable speed	0 to 150 l/h	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER
TTF	001	Disposable Harvest system				Disposable scope
TTF	002	Disposable Harvest system				Disposable scope
WI	005	Weighing scale + indicator for TTF	0 - 40kg (precision 10g)	Sartorius or equivalent	(*)	All SCALE in the scope of the BIOREACTOR SUPPLIER
WT	005	Weighing scale + indicator for TTF	0 - 40kg (precision 10g)	Sartorius or equivalent	(*)	All SCALE in the scope of the BIOREACTOR SUPPLIER

Tag Line / System	L-111	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	DN4	2	0,1/0,6/ 2	-1/ 0,08/ 3	10/ 28/ 50	No

P	009	Peristaltic Pump multichannel, variable speed	0 to 1000 ml/h	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER

Tag Line / System	L-113	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Compressed Air	DN25	2	50/ 200/ 250	0/0,2/0,5	ambiante	No

F	014	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(3)

Tag Line / System	L-200	Disposable Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Media (Water 99% + ions)	DN4	2	10/ 36/ 50	-1/ 0,08/ 3	10/ 28/ 50	No

P	007	Peristaltic Pump multichannel, variable speed	0 to 60 l/h	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER

Tag Line / System	L-201	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 50	No

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
HX	002	Heat Exchanger		(*)	(*)	Thermostatic unit - to be proposed by supplier
HX	003	Heat Exchanger		(*)	(*)	Thermostatic unit - to be proposed by supplier

Tag Line / System	L-202	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No

TCV	705	Temperature Control Valve see Heat exchanger

Tag Line / System	L-204	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	30/ 60/ 80	No

TCV	704	Temperature Control Valve see Heat exchanger

Tag Line / System	L-210	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

F	006	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)

Tag Line / System	L-211	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

F	007	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)

Tag Line / System	L-212	Bioreactor Supplier Scope			
used for :	Dim :	Material Class	Flow (l/h)	Pressure range (bar)	Temperature (°C)	SiP
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

NRV	338	Non return valve clean gas	0 to 300 L/h	Staitech	HCV 02	(2)

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
Tag Line / System			L-214	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 20/ 50	No
NRV	339	Non return valve clean gas	0 to 300 L/h	Staitech	HCV 02	(2)
Tag Line / System			L-215	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
CO2 gas			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 20/ 50	No
FCV	005	Flow Control Valve non sterile gas	0 to 500 l/h	Emerson	Baumann 83000	
FE	005	Flow element + transmitter	45 to 450 l/h	Krohne	H250	(1) Alu is acceptable
FT	005	See corresponding FE				
PCV	003	Pressure Control Valve non sterile gas	0 to 2 bar	Tescom or equiv	(*)	(1)
Tag Line / System			L-216	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
O2 Gas			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 20/ 50	No
FCV	004	Flow Control Valve non sterile gas	0 to 500 l/h	Emerson	Baumann 83000	
FE	004	Flow element + transmitter	45 to 450 l/h	Krohne	H250	(1) Alu is acceptable
FT	004	See corresponding FE				
PCV	002	Pressure Control Valve non sterile gas	0 to 2 bar	Tescom or equiv	(*)	(1)
Tag Line / System			L-217	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
N2 Gas			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 20/ 50	No
FCV	003	Flow Control Valve non sterile gas	0 to 500 l/h	Emerson	Baumann 83000	
FE	003	Flow element + transmitter	45 to 450 l/h	Krohne	H250	(1) Alu is acceptable
FT	003	See corresponding FE				
PCV	001	Pressure Control Valve non sterile gas	0 to 2 bar	Tescom or equiv	(*)	(1)

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
Tag Line / System			L-218	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
CC	001	Mini diaphragm compressor	0 to 5 l/min	KNF	N86		
FCV	007	Flow Control Valve non sterile gas	0 to 500 l/h	Emerson	Baumann 83000		
FE	007	Flow element + transmitter	45 to 450 l/h	Krohne	H250	(1) Alu is acceptable	
FT	007	See corresponding FE					
NRV	325	Non return valve clean gas	0 to 300 L/h	Staitech	HCV 02	(2)	
PCV	004	Pressure Control Valve clean gas	0 to 2 bar	Tescom or equiv	(*)	(1) (2)	
PT	002	Pressure transmitter	0 to 2 bar	Endress+Hauser	PTP35	(1) (2)	
Tag Line / System			L-219	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
F	008	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)	
Tag Line / System			L-220	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)			DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
F	009	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)	
Tag Line / System			L-222	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)			DN4	1	1/ 3,6/ 5	-1/ 0,08/ 3	10/ 28/ 50	No
P	006	Peristaltic Pump multichannel, variable speed	0 to 6000 ml/h	Ismatec or Masterflex or Watson Marlow or equiv	(*)	All PUMPS in the scope of the BIOREACTOR SUPPLIER	

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

TAG		Description	Op Range	Brand	Ref n°	Rem
Tag Line / System			L-223	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)			DN4	1	0,1/0,6/2	-1/ 0,08/ 3	10/ 28/ 130	Yes
F	011	Liquid filter ; 0,22µm ; SiPable	0 to 10 l / h	Millipore or equiv	(*)	(2)	
FE	006	Flow element + transmitter	0 to 2l/h	(*)	(*)	(1) (2)	
FT	006	see corresponding FE					
Tag Line / System			L-232	**Bioreactor Supplier Scope**		
used for :			*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Air			DN15	3	0,1/ 0,6/ 1	-1/ 0/ 1	10/ 20/ 50	Yes
F	012	Air Filter ; 0,22µm ; SiPable	0 to 200l / h	Millipore or equiv	(*)	(2)	

(*) To be defined by supplier - (1) Calibration certificate - (2) Material certificate - (3) Integrity certificate
Material Class : 1 = SS 316L Ra 0,4 µm Process - 2 = Disposable - 3 = SS 316L Ra 0,8 µm Clean gas - 4 = SS 304L Ra 1,2 µm Utilities

15. CHARACTERISTICS AND LIST OF VALVES, Rev.A

SNC·LAVALIN Pharma

ESA - Projet 701014

Characteristics and List of Valves

For list of Instrumetation and other components see table 701014 41 60 003

Valve Tag	Description					
Tag Line / System	C-01					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	10/ 28/ 130	Yes
MV005		Manual valve				
MV106		Manual valve				
MV126		Manual valve				
MV206		Manual valve				
MV450		Manual valve				
MV454		Manual valve				
Tag Line / System	D-03					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	5/ 8/ 130	Yes
MV154		Manual valve				
Tag Line / System	D-04					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	5/ 8/ 130	Yes
MV603		Manual valve				
MV605		Manual valve				
MV606		Manual valve				
MV611		Manual valve				
MV613		Manual valve				

Valve Tag	Description

Tag Line / System	L-100					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Air	DN15	3	0,1/ 0,6/ 1	-1/ 0/ 1	10/ 20/ 130	Yes
MV 141		Manual valve				
MV 142		Manual valve				
MV 144		Manual valve				

Tag Line / System	L-101					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	NA	1	0,1/ 0,6/ 2	-1/ 0,08/ 3	10/ 20/ 130	Yes
MV 145		Manual valve				
MV 146		Manual valve				
MV 147		Manual valve				
MV 148		Manual valve				

Tag Line / System	L-102					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV 149		Manual valve				

Tag Line / System	L-103					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV 151		Manual valve				

Tag Line / System	L-104					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	DN4	1	0,1/ 0,6/2	-1/ 0,08/ 3	5/ 8/ 130	Yes
MV 156		Manual valve				
MV 157		Manual valve				
MV 159		Manual valve				
ST 003		Steam Trap				

Valve Tag	Description					
Tag Line / System	L-120					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV 143		Manual valve				
ST 001		Steam Trap				
Tag Line / System	L-121					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
ST 002		Steam Trap				
Tag Line / System	L-122					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV 152		Manual valve				
Tag Line / System	L-123					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water or Condensate	DN10	1	0,1/ 1/ 250	-1/ 1/ 3	10/ 28/ 130	Yes
MV 153		Manual valve				
Tag Line / System	L-124					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV 158		Manual valve				
Tag Line / System	L-125					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Vent	DN6	4	0,1/ 1/ 10	-1/ 0/ 1	5/ 15/ 30	No
MV 150		Manual valve				

Valve Tag	Description					
Tag Line / System	L-201					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 50	No
MV714		Manual valve				
MV716		Manual valve				
Tag Line / System	L-202					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV706		Manual valve				
Tag Line / System	L-203					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV703		Manual valve				
Tag Line / System	L-204					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	30/ 60/ 80	No
MV702		Manual valve				
Tag Line / System	L-205					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	30/ 60/ 80	No
MV701		Manual valve				
Tag Line / System	L-207					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV313		Manual valve				

Valve Tag	Description					
Tag Line / System	*L-208*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV314		Manual valve				
Tag Line / System	*L-210*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
MV316		Manual valve				
MV318		Manual valve				
MV322		Manual valve				
Tag Line / System	*L-211*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
MV315		Manual valve				
MV317		Manual valve				
MV320		Manual valve				
Tag Line / System	*L-212*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
MV334		Manual valve				
Tag Line / System	*L-213*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes
XV002		Automated valve				
Tag Line / System	*L-218*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

Valve Tag	Description
MV326	Manual valve
XV336	Automated valve

Tag Line / System	L-219					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

MV329	Manual valve
MV331	Manual valve
MV337	Manual valve

Tag Line / System	L-220					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

MV328	Manual valve
MV330	Manual valve
MV335	Manual valve

Tag Line / System	L-221					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Mixed Gas (mainly O2)	DN6	3	50/ 180/ 250	-1/ 0,08/ 3	10/ 28/ 130	Yes

XV337	Automated valve

Tag Line / System	L-222					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	DN4	1	1/ 3,6/ 5	-1/ 0,08/ 3	10/ 28/ 50	No

MV405	Manual valve
MV407	Manual valve
MV460	Manual valve
XV631	Automated valve NH4
XV632	Automated valve NO3
XV633	Automated valve NO2

Valve Tag	Description					
Tag Line / System	*L-223*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Media (Water 99% + ions)	DN4	1	0,1/0,6/2	-1/ 0,08/ 3	10/ 28/ 130	Yes
MV502		Manual valve				
MV503		Manual valve				
MV504		Manual valve				
MV505		Manual valve				
MV506		Manual valve				
MV508		Manual valve				
MV509		Manual valve				
Tag Line / System	*L-225*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water drain	DN10	1	0,1/ 1/ 250	-1/ 1/ 3	10/ 28/ 130	No
MV715		Manual valve				
Tag Line / System	*L-226*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Vent	DN6	4	0,1/ 1/ 10	-1/ 0/ 1	10/ 28/ 130	No
MV717		Manual valve				
Tag Line / System	*L-227*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV601		Manual valve				
ST601		Steam Trap				
Tag Line / System	*L-228*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water drain	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No
MV311		Manual valve				

Valve Tag	Description					
Tag Line / System	L-229					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Vent	DN6	4	0,1/ 1/ 10	-1/ 1/ 1	10/ 28/ 130	No
MV312		Manual valve				
Tag Line / System	L-232					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Air	DN15	3	0,1/ 0,6/ 1	-1/ 0/ 1	10/ 20/ 50	Yes
MV608		Manual valve				
MV609		Manual valve				
Tag Line / System	L-234					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV321		Manual valve				
ST009		Steam Trap				
Tag Line / System	L-235					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV319		Manual valve				
ST008		Steam Trap				
Tag Line / System	L-236					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Drain	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV333		Manual valve				
Tag Line / System	L-237					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Drain	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV327		Manual valve				

Valve Tag	Description					
Tag Line / System	*L-238*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV336		Manual valve				
ST005		Steam Trap				
Tag Line / System	*L-239*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV332		Manual valve				
ST004		Steam Trap				
Tag Line / System	*L-240*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Inoculum	DN4	1	10/ 36/ 50	-1/ 0,08/ 3	10/ 28/ 5010/ 28/ 130	Yes
MV461		Manual valve				
MV462		Manual valve				
Tag Line / System	*L-241*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV507		Manual valve				
ST006		Steam Trap				
Tag Line / System	*L-242*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Condensate	DN6	1	0,1/ 1/ 10	-1/ 1/ 3	10/ 28/ 130	Yes
MV610		Manual valve				
Tag Line / System	*L-243*					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Vent	DN6	4	0,1/ 1/ 10	-1/ 0/ 1	5/ 15/ 30	No

Valve Tag	Description
MV 604	Manual valve

Tag Line / System	L-244					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water	DN10	4	0,1/ 1/ 10	-1/ 1/ 3	5/ 15/ 30	No

Valve Tag	Description
MV 607	Manual valve

Tag Line / System	L-245					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Water or Condensate	DN10	1	0,1/ 1/ 250	-1/ 1/ 3	10/ 28/ 130	Yes

Valve Tag	Description
MV 612	Manual valve

Tag Line / System	L-246					
used for :	*Dim :*	*Material Class*	*Flow (l/h)*	*Pressure range (bar)*	*Temperature (°C)*	*SiP*
Pure Steam	DN8	1	50/ 200/ 250	-1/ 1/ 3	15/ 130/ 150	Yes

Valve Tag	Description
MV 171	Manual valve