
MGT
INDUSTRIES LTD

Cell Culture Bio-Reactor System

Operating Manual

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POB 367, Maalot, Israel 2101301
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The WEEE symbol indicates that this system contains electrical and electronic components which must be collected and disposed of separately.

Never dispose of electrical and electronic waste in general municipal waste.

Collect and dispose of separately.

Make use of the return and collection systems and components available to you, or use your local recycling program. Contact your local authority or place of purchase to find out what options are available.

Electrical and electronic equipment contain hazardous substances which, when disposed of incorrectly, may leak into the ground. This can contribute to soil and water pollution which is hazardous to human health and endangers wildlife.

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1. INTRODUCTION

1.1. About this guide

This guide will allow you to quickly use the MGT bio-reactor system. Please note that this guide is an integral part of system, and must be reviewed prior to the use of the system. Carefully read and follow all indications in the instructions.

This manual also provides information about the systems service and maintenance; please note that all maintenance in the system must be performed by authorized personal **ONLY** after adequate training.

1.2. Legal disclaimer

MGT will not be held responsible for any failure, breakdown, and/or accidents due to lack of knowledge and non-application of the rules contained in this manual. The same applies to the execution of changes, variations and/or installation of accessories that are not authorized in advance. The machines are subject to changes and may appear different from those depicted; this does not affect the text contained within these instructions.

MGT will not be held responsible for any use of the system that is not complies with local regulation (food safety, electricity safety, environment safety, employee's safety etc.).

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2. SAFETY INSTRUCTIONS

2.1. General Safety Precautions

The system contains electrical elements, and as such, direct water spray on these components should be avoided during normal and cleaning operations.

2.2. Electrical Hazards

- For its routine operation the system operates under different live voltages (24, 240, 380 volts) - appropriate safety measures must be in place.
- Before conducting any maintenance activities – Shut down main power supply to the system, use designated shutoff switch.
- Switching off power supply to the specific element that is being serviced could be acceptable – use extra prudence and discretion.
  - ➢ Always visibly mark and lock power source access to prevent inadvertent switching the power on.
- Any electricity related activities on the system including testing, connecting disconnecting etc. must be performed by a certified electrician.
- No changes in electrical or control elements should be performed without written preapproval of MGT (failure do so will result with the system warranty to be voided).

2.3. Chemical/Mechanical Hazards

- Leakage – The system contains many liquid piping and steam lines; there are different types of liquids running through the system. As such, during routine operations and over time, some leakage may be expected.
  - Once a leakage is noticed, system operation should be **stopped**, and appropriate maintenance and repair activities should be done ASAP by a trained and authorized personnel only.
  - Some liquids may be hazardous and corrosive – use appropriate protective gear. Consult Material Safety Data Sheet (MSDS) when dealing with these materials which should be provided by site's safety responsible person.
  - Some of the equipment such as tanks and pipes may contain **high pressured** and/or **hot** liquids and/or steam - beware of potential splashing hazards associated with this equipment.
- Moving Parts - The system contains moving parts such as stirrers, pump impellors etc.
  - When performing any maintenance operations or repairs on these components: shut down power supply in a manner that precludes switching-on accidentally during these activities, clearly mark the equipment that is being serviced.

    Reminder: Always visibly mark and lock power source access to prevent inadvertent switching the power on.

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- Do not put any objects in the direct path, or that might interfere at any way with the movement of these components.
- Keep airways around the motors clear to allow sufficient ventilation, do not cover.

- Accessways – Maintain clear accessways around the system that will allow:
  - Easy and convenient access to the system for normal operations, including the supply and transport of materials to and away from the system.
  - Fast evacuation of an injured person in case of an accident.
  - Clear path to the main electrical shutoff switch.

2.4. Personnel Protection & Protective Gear

Normal operation of the system involves some hazards to the personnel, however, risks can be reduced and avoided by using personal protective gear and awareness.

- Use safety goggles – to protect against mechanical and chemical hazards
- Use protective gloves – especially when dealing with specific materials – consult MSDS per specific material as needed.
- Dealing with steam piping and other heated elements – use heat proactive gloves.
- Safety shoes are recommended within the system's workspace.
- Eye/face washes and emergency showers should be located and operational in close vicinity to the system.
- Appropriate Fire extinguishers (suited for electrical fires) and other firefighting measures should be in the immediate proximity of the system and its electricity cabinets. Personnel must be trained to use these measures in the case of a fire.

2.5. Decommissioning

If the system or parts of it are decommissioned:

- Clearly mark on the system and the control panel that the system is not in service and should not be switched on.
- When putting the system out of service for a prolong period of time – disconnect or shutoff the main power supply and mark it accordingly.

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3. System Description

The system designed for the production of cell culture meat in a fed-batch process followed by a continuous profusion process which including media treatment and recycling. The system has the capabilities of running a full CIP (Clean in place) process, which includes all the vessels and piping, and a SIP (Sterilization in place) process for the sterile zone.

The system includes 4 vessels equipped with agitators and instrumentation, which controlled by a PLC with an integrated software, allowing the operator to control and track every process and operation.

The Process divided into sterile zone, which includes two bio-reactors and the peripheral equipment and piping, and a non-sterile zone which includes the media preparation vessel and the rejuvenation vessel.

The main units of the system are:

- "T1" – Media Preparation vessel
- "T2" – Bio-Reactor
- "T3" – Bio-Reactor
- "T4" – Rejuvenation vessel
- Temp control Skid (X4)
- Pumps stand (X4)
- Mass flow controller stand
- CIP Loop
- Control Cabinet + HMI working station

See figures 1 and figure 2 for the positioning of each unit.

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4. MAIN HARDWARE UNITS – TECHNICAL SPECIFICATION

4.1. "T1" – Media Preparation Tank

Description	Value	Units
Type	Atmospheric, Double-Jacket, Isolated	-
Internal Diameter	800	mm
Cylinder Height	900	mm
Bottom Type	Torispherical	-
Cover Type	Torispherical	-
Material of Construction	Inside: SS-316,, Ra<0.5 outside: SS-304, Mirror polish	-
Full Capacity	530	Liter
Working Capacity	150 - 400	Liter
Tank Working Pressure	Atmospheric	-
Jacket Working Pressure	1	Bar
Number of spray balls / size	2 / 28 mm	-
Agitator	Marine type ⌀350mm	-
Agitator power	1.5	kW
Cover Fittings	○ Agitator ○ Manway ⌀400 mm ○ Atmospheric breather ○ PW inlet. ○ CIP inlet with spray ball. ○ Spare socket with plug (X2)	-
Bottom Side Fittings	○ PT100 temperature sensor ○ conductivity sensor ○ pH Sensor ○ Sample valve ○ Spare socket with plug (X1)	-
Bottom Fittings	○ Tank bottom Valve ("Zero Valve")	-

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4.2. "T2" & "T3" – Bio-Reactor

Description	Value	Units
Type	Pressure/Vacuum, Double-Jacket, Isolated	-
Internal Diameter	600	mm
Cylinder Height	1,200	mm
Bottom Type	Torispherical	-
Cover Type	Flat Flange	-
Material of Construction	Inside: SS-316,, Ra<0.5 outside: SS-304, Mirror polish	-
Full Capacity	360	Liter
Working Capacity	40 - 300	Liter
Tank Working Pressure	(-1) - 3	Barg
Jacket Working Pressure	0 - 3	Barg
Number of spray balls / size	2 / 28 mm	-
Agitator	3 adjustable impellers	-
Agitator power	2.2	kW
Cover Fittings	○ CIP inlet with spray ball. ○ Pressure gauge ○ Pressure transmitter ○ Foam level probe ○ Vent ○ Rupture disk ○ Sight Glass 3" ○ Deep pipe ○ Spare socket with plug (X1)	-
Top Side Fittings	○ Sterilizable ports X 7 ○ Overlay inlet ○ Ring Sparger inlet	
Bottom Side Fittings	○ PT100 temperature sensor ○ conductivity sensor ○ pH Sensor ○ Insight Sensor ("Biomass") ○ Dissolved Oxygen Sensor ○ Sample valve ○ Sight Glass 1" ○ Micro sparger inlet ○ ATF port ○ Spare socket with plug (X1)	-

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Bottom Fittings	○ Agitator ○ Tank bottom Valve (“Zero Valve”)	-

4.3. “T4” – Rejuvenation Tank

Description	Value	Units
Type	Atmospheric, Double-Jacket, Isolated	-
Internal Diameter	800	mm
Cylinder Height	900	mm
Bottom Type	Torispherical	-
Cover Type	Torispherical	-
Material of Construction	Inside: SS-316,, Ra<0.5 outside: SS-304, Mirror polish	-
Full Capacity	530	Liter
Working Capacity	150 - 400	Liter
Tank Working Pressure	Atmospheric	-
Jacket Working Pressure	1	Barg
Number of spray balls / size	2 / 28 mm	-
Agitator	Marine type ⌀300mm	-
Agitator power	1.5	kW
Cover Fittings	○ Agitator ○ Manway ⌀400 mm ○ Atmospheric breather ○ PW inlet. ○ CIP inlet with spray ball. ○ Spare socket with plug (X2)	-
Bottom Side Fittings	○ PT100 temperature sensor ○ conductivity sensor ○ pH Sensor ○ Sample valve ○ Spare socket with plug (X1)	-
Bottom Fittings	○ Tank bottom Valve (“Zero Valve”)	-

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4.4. Temp Control Skid – For T2 & T3 (“high Pressure”)

Description	Value	Units
Type	High Pressure - Two PHE in a row	-
Working Temp	0-135	C
Working Pressure	0-3.5	Barg
Circulation Pump flow rate	2,000	l/m
Circulation Pump motor rate	0.37	kW
PHE cooling Capacity	22,000	Kcal/hr
PHE Heating Capacity	24,000	Kcal/hr
Temperature indication	Jacket inlet, Chiller outlet	-
Jacket waterב compensation	Auto – pressure valve	-
Safety	○ Pressure Relief Valve ○ Expansion tank	-

4.5. Temp Control Skid – For T1 & T4 (“low Pressure”)

Description	Value	Units
Type	Low pressure - Two PHE in a row	-
Working Temp	0-100	C
Working Pressure	0-1	Barg
Circulation Pump flow rate	2,000	l/m
Circulation Pump motor rate	0.37	kW
PHE cooling Capacity	22,000	Kcal/hr
PHE Heating Capacity	24,000	Kcal/hr
Temperature indication	Jacket inlet, Chiller outlet	-
Jacket waterב compensation	Auto – pressure valve	-
Safety	○ Pressure Relief Valve ○ Expansion tank	-

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4.6. Pump stand – For T2 & T3

There is one stand next to each tank. each stand includes the pump as per the list below:

Description	Value
Type	5 pumps
Pump type / flow	Analog/ 0 - 3,500 ml/m
Pump type / flow	Analog / 0 - 2,040 ml/m
Pump type / flow	Analog / 0 - 2,040 ml/m
Pump type / flow	Analog / 0 - 2,040 ml/m
Pump type / flow	Analog / 0 - 2,040 ml/m

4.7. Pump stand – For T1 & T4

There is one stand next to each tank. each stand includes the pump as per the list below:

Description	Value
Type	3 pumps
Pump type / flow	Analog / 0-3,500 ml/min
Pump type / flow	fixed / 0-510 ml/min
Pump type / flow	fixed / 0-510 ml/min

4.8. Mass flow controller stand

There is one stand for all the MFC – used for T2 & T3 – each set of MFC include the MFC as bellow:

Description	Value
Gas / flow	Air#1 / 1-300 l/min
Gas / flow	Air#2 / 0-10 l/min
Gas / flow	Oxygen#1 / 1-100 l/min
Gas / flow	Oxygen#2 / 1-100 l/min
Gas / flow	Nitrogen / 1-100 l/min
Gas / flow	CO2 / 1-100 l/min

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4.9. CIP Loop

Fully automatic CIP process for all tanks and piping.

Description	Value
Type	Aseptic design, zero dead leg, verification of cleaning cycle
CIP pump type	Centrifugal, Self-Priming, Self-drain, ultra clean
Pump flow rate / Pressure	4,000 l/hr / 2 bar
Control Instrumentation	Temperature, Conductivity, flow rate
Washing cycles	First Wash, Detergent, second Wash, Acid, Last Wash, Air purging
Washing plans	Adjustable by the operator
Temp Control	0 - 90 C

4.10. Control System & HMI

Description	Value
HMI Software	WinCC (Tia Portal 16)
HMI	Siemens, 19”, flat panel touch screen
PLC	Siemens, SIMATIC S7-1500
IO	DI, DQ, AI, AQ, RTD, Profibus
Switch	SCALANCE XB008 , 8 ports
PC	Intel® Core™ i Standard-Size, Automation Computer with 4 xGbE, 1 x mPCIe, 1 x HDMI, 1 xDP, 4 x USB 3.0, and 4 x COM
Remote Control	Via Secomea (for technician use only)
Pneumatics	Festo VTUG

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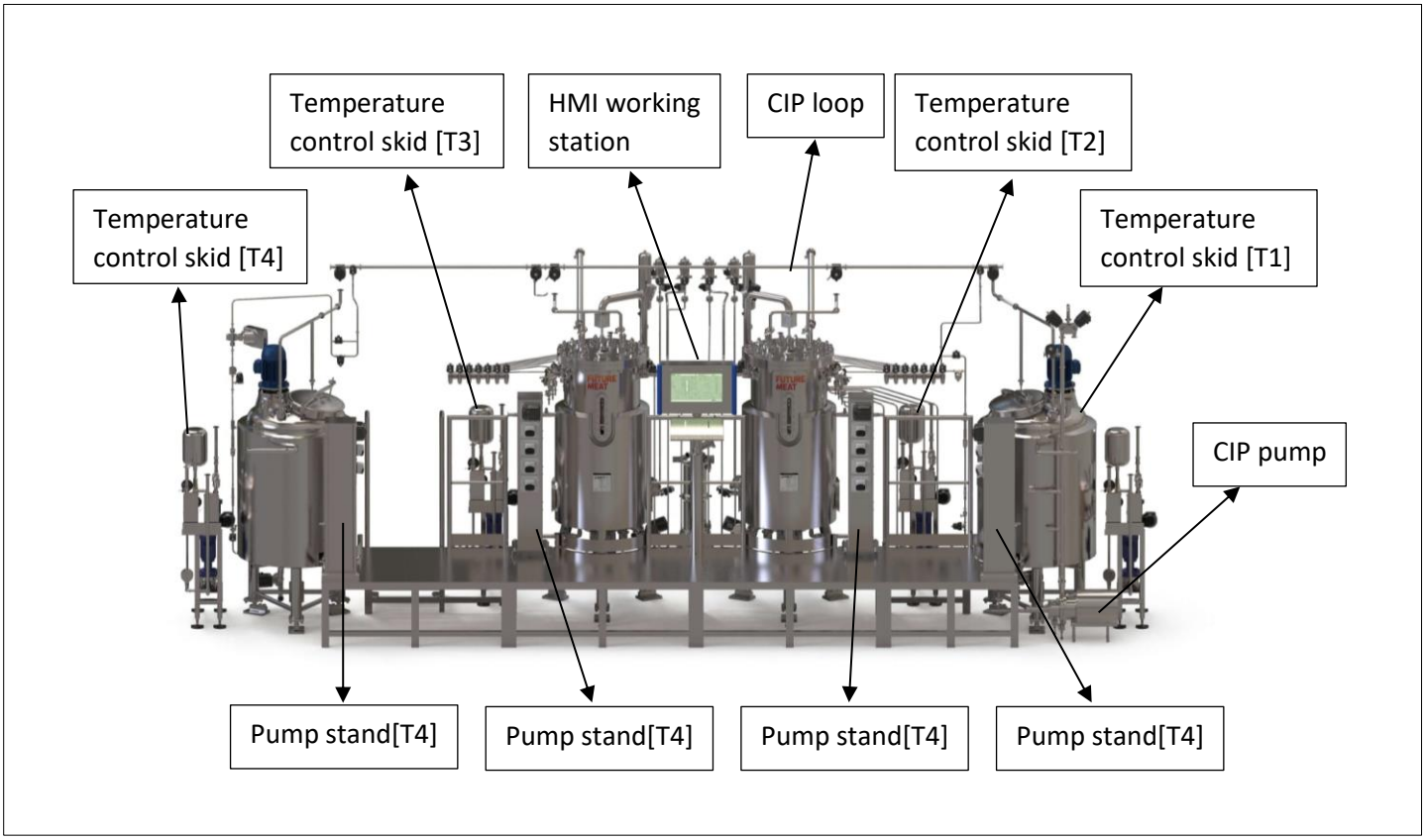

Figure 1:System front view

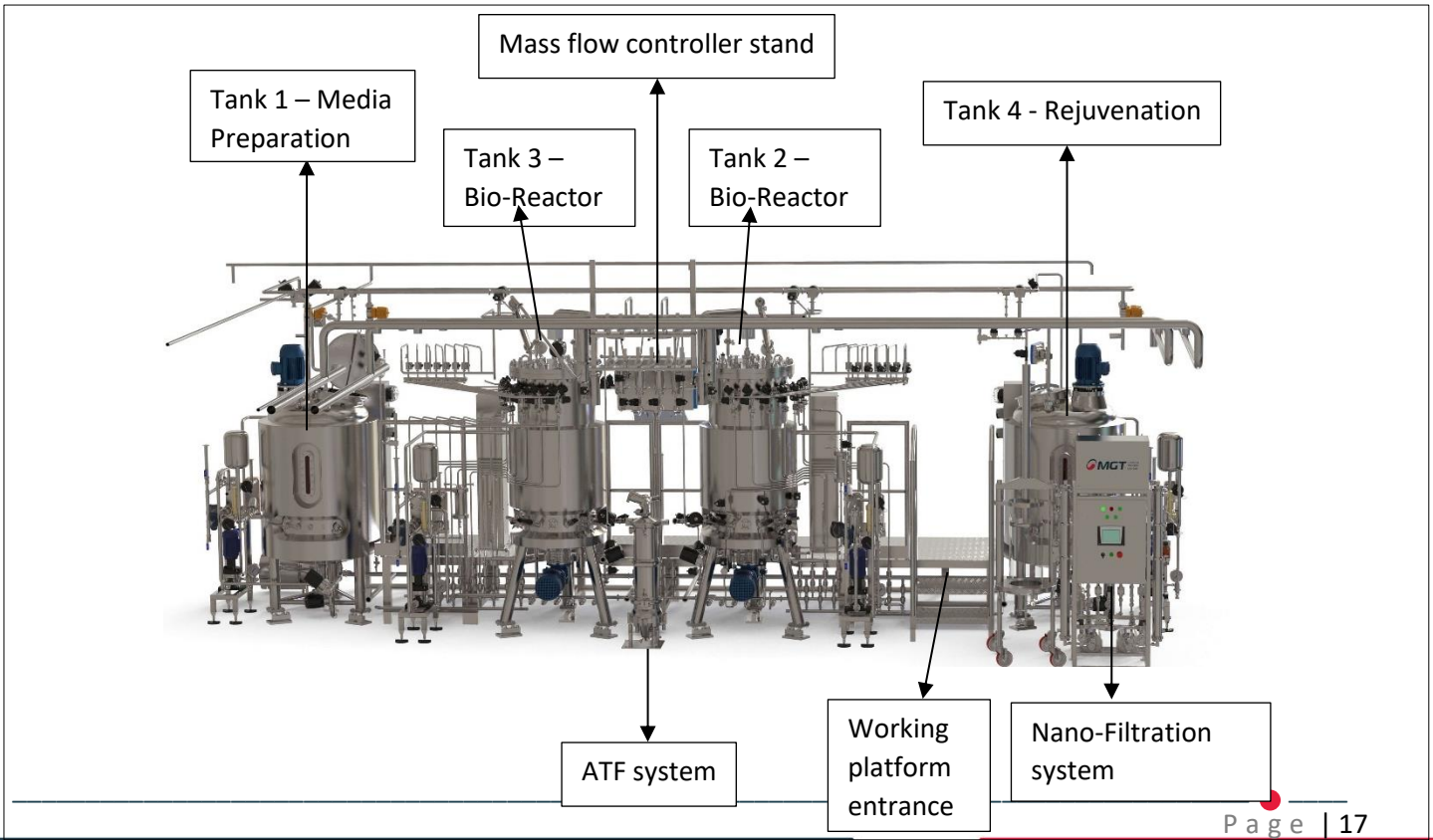

Figure 2: System Back view

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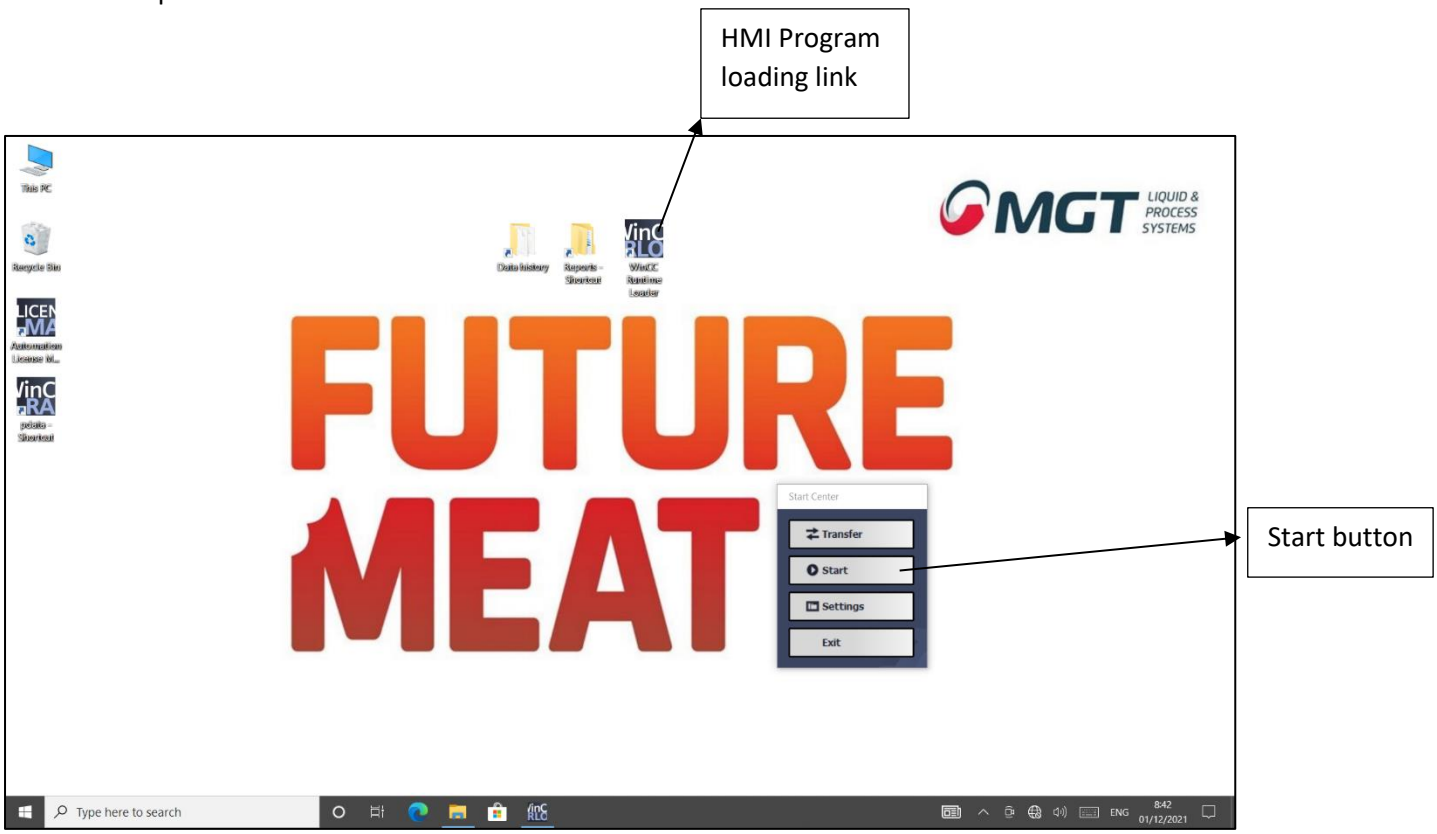
5. HMI - General Operating Behavior

The control system is based on Siemens software and hardware – the PLC located in the main control cabinet and connected to a PC and to a touch screen that located in the HMI working station.

The HMI program is running on windows environment. So, while exiting the HMI program the operator will enter to “standard” windows environment.

5.1. Starting the HMI program

In order to enter the HMI program, the operator should double click on the link: “wincc run time”, and then press the start button.



5.2. Switching on/off

The control system stores all parameters which are adjustable by the operator (setpoint, calibration parameters, etc.) in a battery buffered memory. Hence these parameters are still available when the system is switched off and restarted again.

3 cases of switching-off or power failure, respectively, are differentiated:

- Shut down due to mains failure or **Switching „off“ and „on“ using the mains switch** at the front main control cabinet.
- **Shut down of HMI only** due to mains failure.

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- **Emergency cut-off** via the „SHUT-DOWN "-key at the HMI working station or at the main control panel.

5.2.1. Switching "off" and "on"

The control system is switched-on or off, respectively, via the mains switch on the front panel of the control cabinet, or shut down of the main control cabinet due to mains failure. After being switched-on (again) the system will start at (return to) a defined state of operation:

- All controllers are "off" actuators are in rest position
- All timers are "off" (stopped)
- All Process are "off" (SIP for example)

5.2.2. Shut Down of HMI Only/ Exit HMI program

In case of circuit brake of the HMI supply or exit the HMI program, only the HMI is turned off, while the PLC and all the equipment are not affected. In this case, the operations that are currently running will not stop and will not be affected. After being switched-on (again) the HMI will start automatically and will come back to the last operating screen.

5.2.3. Emergency cut-off

In order to activate the emergency cut-off, there is need to press the emergency button. Located on the front main control panel and on the front of the HMI working station.

While the emergency button is pressed (active), the control system screens an alarm message, and all outputs are switched over to their predefined safe state. Other active functions of controllers, timers, profiles, recipes and sterilization are not affected.

The emergency cut-off can be released by releasing the emergency button. Then all outputs are reactivated.

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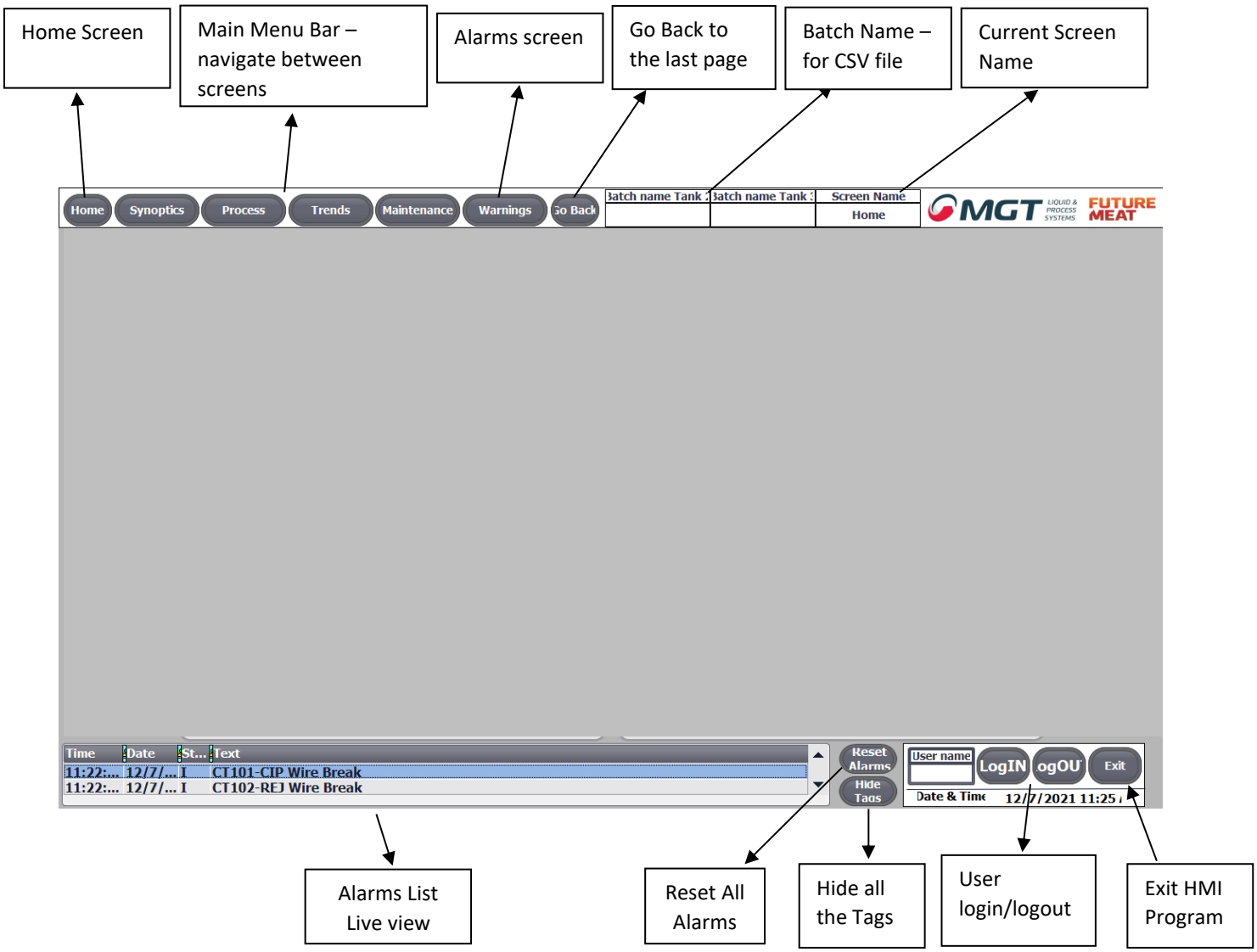
5.3. HMI General Operation

The control system has a remote touch screen, located in the working station which is on the production line platform. The touch screen design for operation of the entire system. it has integrated touch keys where the operator can select the menus and the related operations, enter data and select and switch-over the modes of operation. In general, the HMI is operated simply by pressing the screen at the position of the screened keys.

5.3.1. Operating Screen Navigation



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5.3.2. Main menu bar

The main menu bar is located on the upper part of the screen and allow the operator to navigate between all the screens. The Menu bar include 6 main tabs:

- **Home**: general view of the system - monitoring the sensors of each of the 4 tanks.

  By clicking the tab, the screen will open.

- **Synoptics**: Screen for manual control of the valves and motors in the system, fault inspection and special operations. By clicking the tab, a list of screens will open:
  - Tank no.1
  - Tank no.2
  - T2 additives
  - Tank no.3
  - T3 Additives
  - Tank no.4
- **Process**: The operating screens of the system, through which it is possible to start an automatic process. By clicking the tab, a list of screens will open:
  - CIP
  - SIP
  - Media Preparation
  - Cultivation T2
  - Cultivation T3
  - Rejuvenation
- **Trends** – Pre-defined process trends. By clicking the tab, a list of screens will open:
  - T2
  - T3
- **Maintenance**: a screen for calibration of the equipment and other maintenance operations. By clicking the tab, a list of screens will open:
  - Calibration Pumps
  - Schedules
  - Explorer
- **Warnings –** alarm list which the operator can monitor all of the alarms and warnings. By clicking the tab, the screen will open:

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- **Go Back –** by clicking the tab the last screen will open.

5.3.3. Inputs

- **Numerical inputs**

When clicking on a place for input numerical value, the pop-screen below will be open.

Enter the values by clicking the numbers. Press enter key in order to save the value.

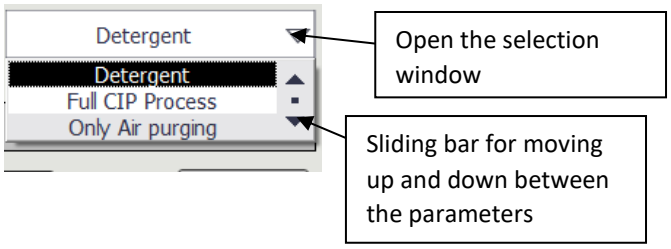
- **Text Inputs**

When clicking on a place for input text, the pop-screen below will be open.

Enter the text by clicking the letters. Press enter key in order to save the value.

- **Sliding bar**

When entering a selection window, the operator can slide up and down by clicking the arrows.



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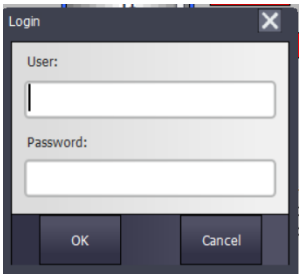
5.3.4. **Users- Login/logout**

There is one available user that can be logged in by the operator.

The system doesn't have restrictions for users, and most functions can be operated without the need to be logged in as a user.

If a function is selected, which is password-protected (required user logging), then a pop-up screen will automatically appear. The default setting for the user and password are:

- User: fm
- Password: 123



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6. HOME SCREEN

The “Home” screen design only for monitoring the tanks controls.

It is possible to see the present values of all the controlled functions in each tank, in addition the operator has a status bar which he can see the process that is currently running (CIP , SIP , Pressure test ,Cultivation , Perfusion)

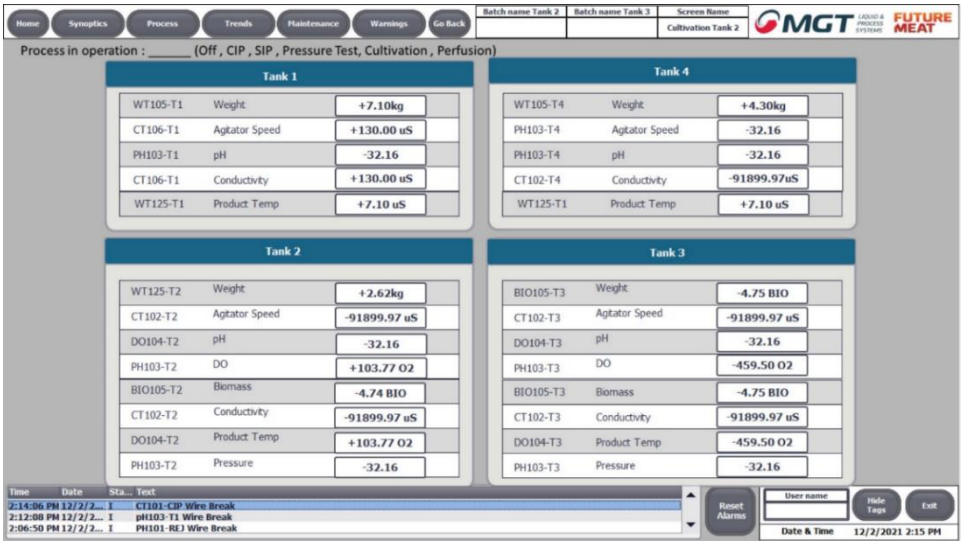
By clicking the heading of each window, the operator can enter the process screen of the relevant tank.

Tank 1 → “Media preparation” screen

Tank 2 → “Cultivation tank 2” screen

Tank 3 → “Cultivation tank 3” screen

Tank 4 → “Rejuvenation” screen



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7. SYNOPTIC SCREENS

7.1. General

There are 6 synoptic screens, divided according to the positioning of the equipment.

- Tank no.1 – operation of T1 and CIP pump.
- Tank no.2 - operation of T2.
- T2 additives – operation of the inlet ports to T2, including pop up screen for controlling the Steam-Bridge application.
- Tank no.3- operation of T3.
- T3 Additives - operation of the inlet ports to T2, including pop up screen for controlling the Steam-Bridge application.
- Tank no.4 - operation of T3 and the sterile steam main inlet.

The synoptic screens allow the user to monitor the operation of the automatic processes and to control each unit in manual mode.

**** Be aware! - there are no restriction for manual mode operation.**

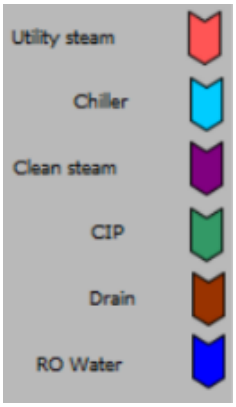
7.2. Understanding the synoptic screens:

The synoptic screens are similar to a P&ID drawing, so the operator will get a better understanding of the process when needed, especially when a manual operation is required. The positioning of the equipment in the synoptic screens are similar to the installation positioning, so that the operator can "connect" between the HMI and the field.

The lines represent the piping and allow the operator to understand the direction of flow.

The line colors allow the operator to identify the medium that flow in the specific pipe.

line color legend: (located in the right end of each synoptic screen)



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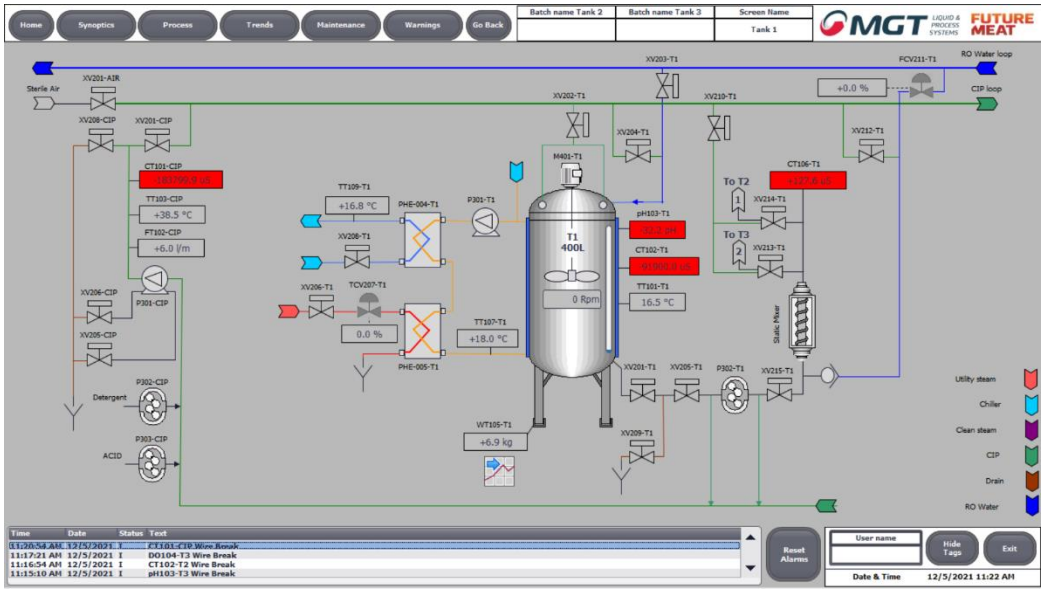
Example of a Synoptic Screen: (T1)



7.3. Equipment Operation State:

The operator can identify the state of each equipment by the color of the symbol and the color of the tag name.

- Off/Close – symbol colored in grey
- On/Open – symbol colored in green
- Auto mode – tag name colored in black
- Manual mode – tag name colored in yellow
- Eror/Warning– symbol colored in red

7.4. Manual mode operation:

Changing the equipment state to manual mode is designed for technicians and senior operators.

**** Be aware! - there are no restriction for manual mode operation.**

Each equipment has a pop-up screen (face plate) that allow the operator to:

- Control the valves and motors in the system.
- Allow manual mode operation.
- Fault inspection and special operations.

In order to enter the face plate, the operator should click on the equipment symbol.

In order to exit the face plate, the operator should click on the X in the top right of the window.

7.4.1. When the operator clicks on an ***on/off valve***, the following window will open:

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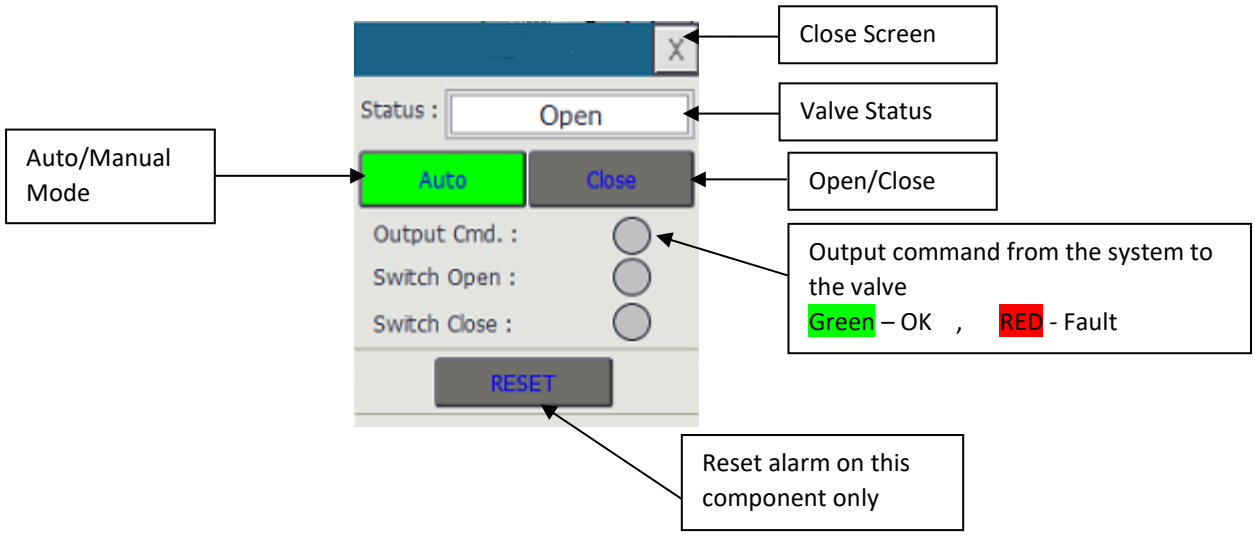
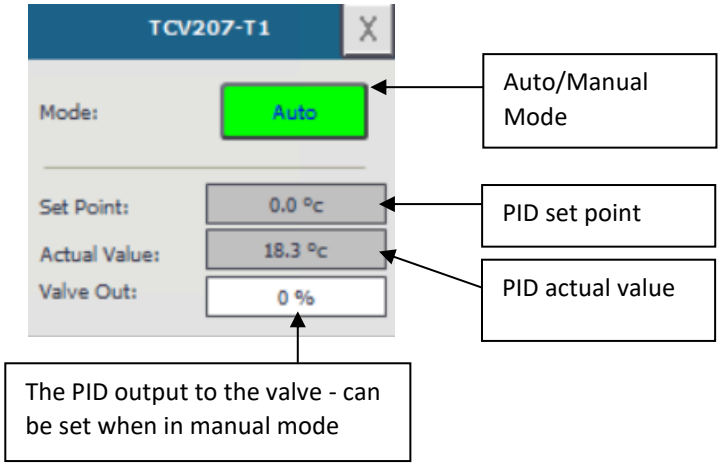
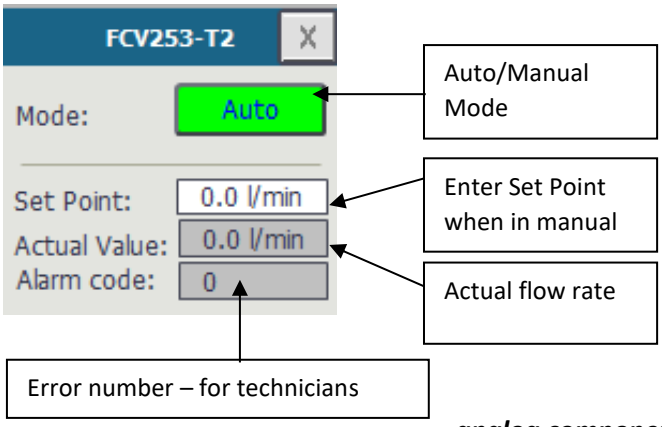


7.4.2. When the operator clicks on a ***proportional valve***, the following window will open:



7.4.3. When the operator clicks on ***MFC***, the following window will open:



7.4.4. When the operator clicks on an ***analog component***, the following window will open:

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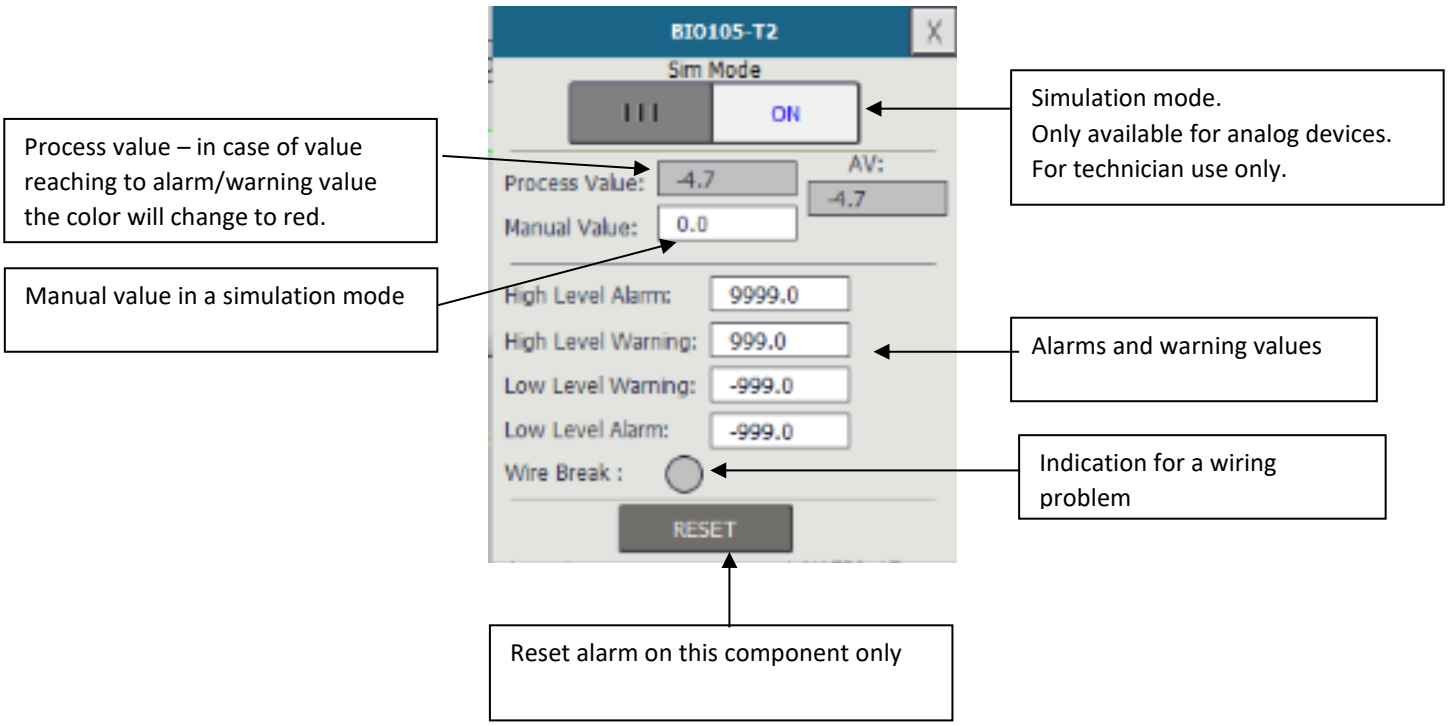
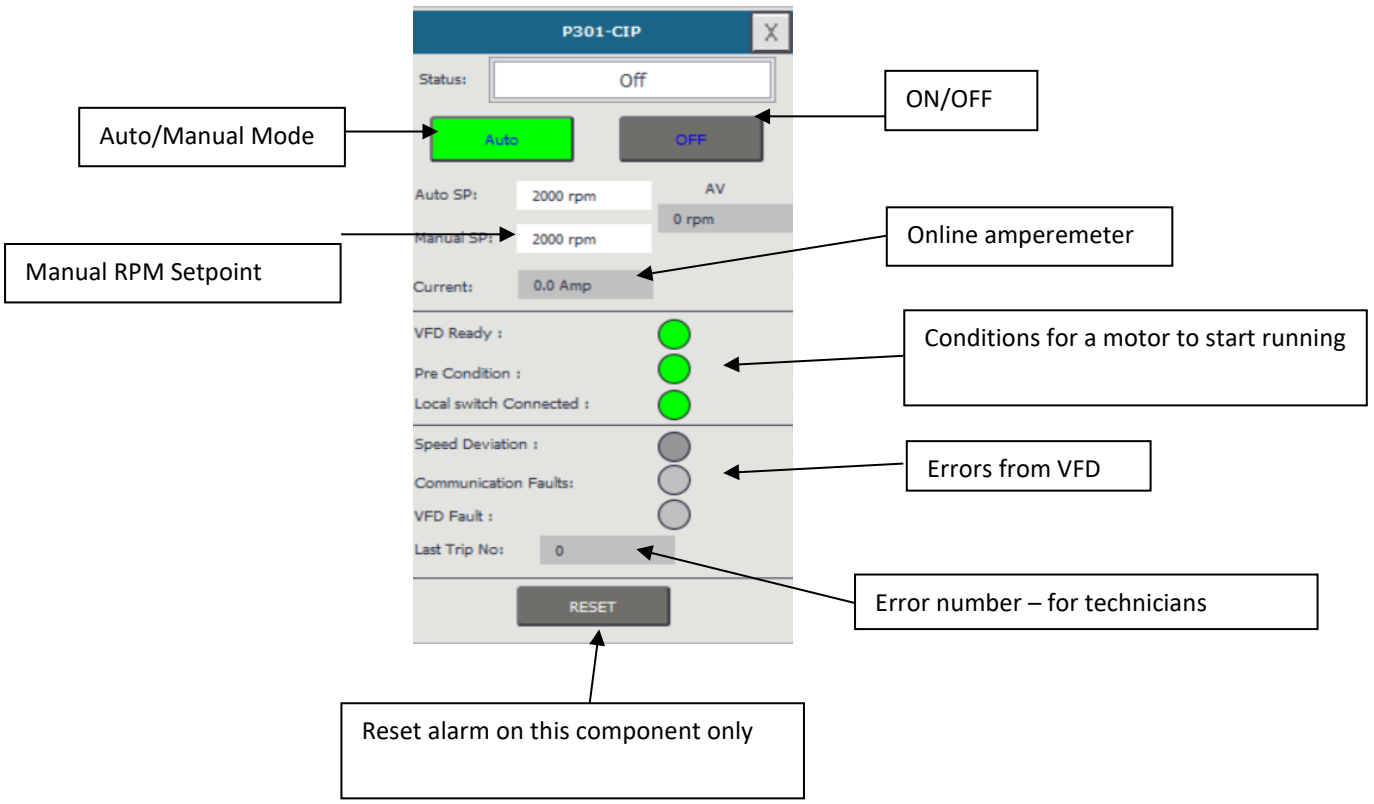


7.4.5. When the operator clicks on a ***VFD motor*** component, the following window will open:



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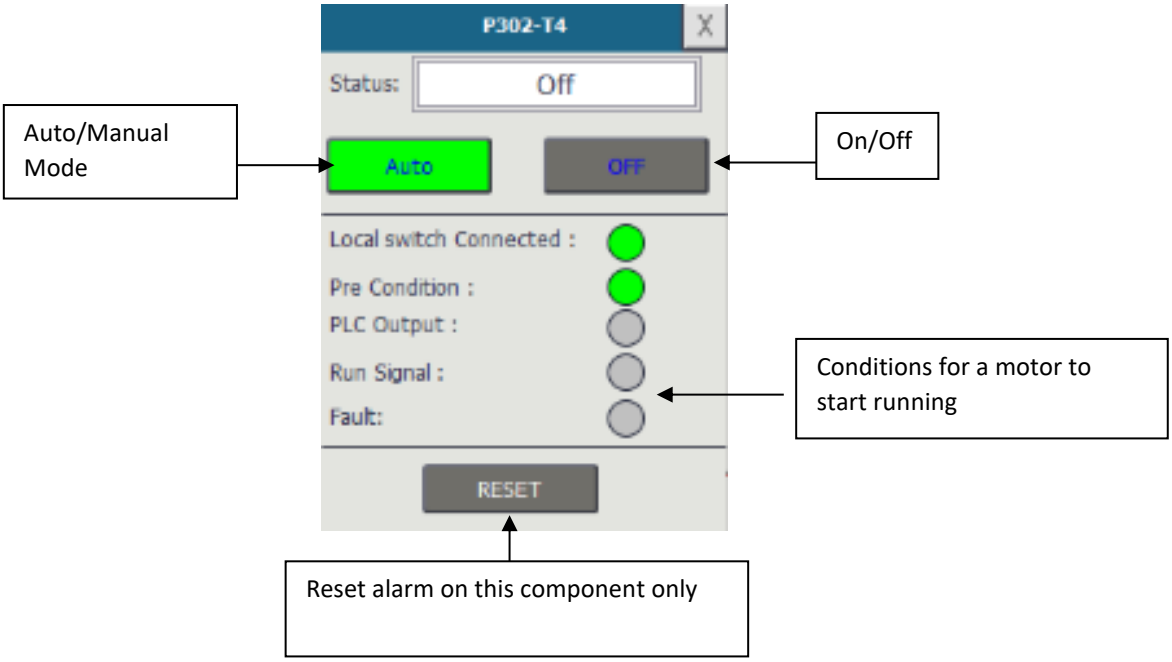
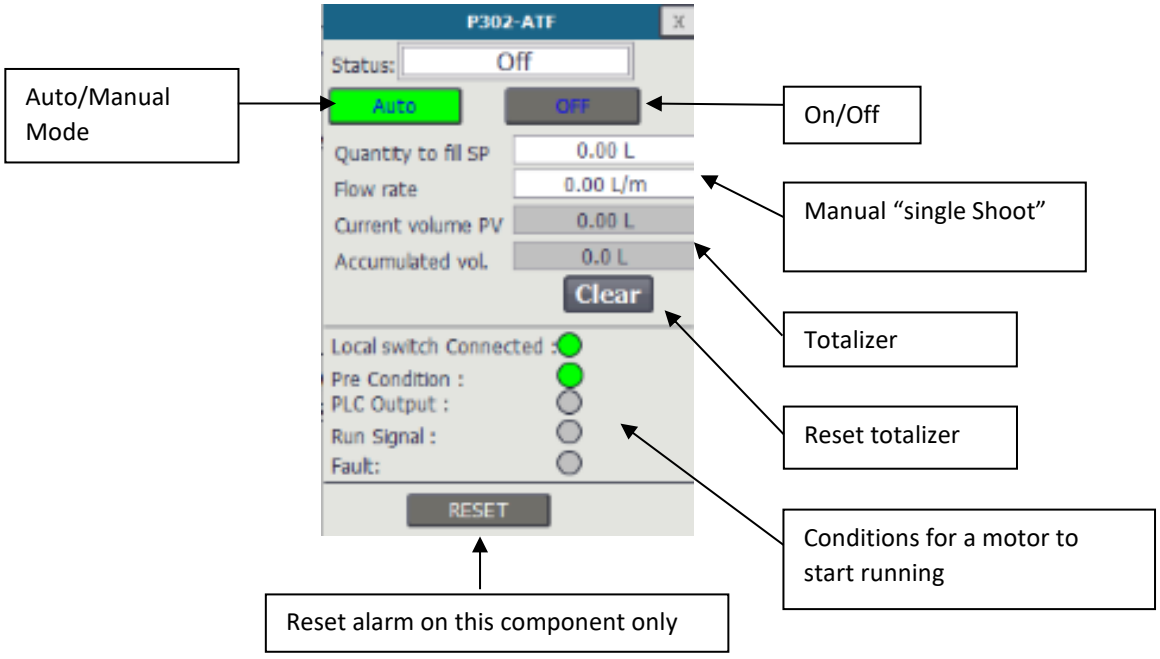
7.4.6. When the operator clicks on a ***on/off motor*** component, the following window will open:



7.4.7. When the operator clicks on an ***analog dosing pump***, the following window will open:
*See dosing pump features for more details.



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8. Process Menu - CIP

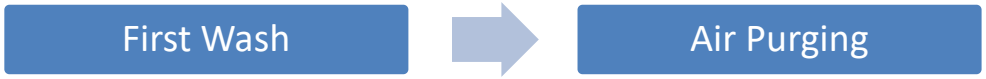
The CIP process is a fully automatic cleaning process of the system, the process design to clean the tanks and the peripherical piping and instrumentation.

The operator can choose the tanks to be washed, the washing program and the washing cycles for each tank.

8.1. CIP Program – Process Flow Diagram:

- Full CIP

- First Wash only



- Detergent only

- Acid only

- Air Purging Only

8.2. Process Sequence

There are 2 main sequences for the CIP process:

- **Wash sequence** – identical sequence for the first, second and last wash.
- **Cleaning agent sequence** – the same sequence for detergent and acid.

The sequence variables can be changed by the parameters table in the operation screen, it is possible to change the time and cycle of each sequence as well as the cleaning agent concentration, washing temperature and flow rate.

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8.2.1. Wash Sequence:

Filling T1 → Preparation T1 → Circulation T1 → Drain T1 → Drain Timer T1 → Filling T1 → transfer to T2→ Preparation T2 → Circulation Additives T2 → Circulation T2 → Drain T2 → Drain Timer T2 → Filling T1 → transfer to T3→ Preparation T3 → Circulation Additives T3 → Circulation T3 → Drain T3 → Drain Timer T3 → Filling T1 → transfer to T4 → Preparation T4 → Circulation T4 → Drain T4 → Drain Timer T4

8.2.2. Cleaning agent Sequence:

Filling T1 → Preparation T1 → Circulation T1 → transfer to T2→ Preparation T2 → Circulation Additives T2 → Circulation T2 → transfer to T3→ Preparation T3 → Circulation Additives T3 → Circulation T3 → transfer to T4 → Preparation T4 → Circulation T4 → Drain T4 → Drain Timer T4

8.2.3. Sequences operation:

- Filling – open PW valve and fill the tank with water. Filling ends when weight reaching “water quantity” SP.
- Preparation - Circulation of the liquid on the tank until the flow-rate, conductivity and temperature values are reaching the required set-points.
- Circulation – the washing procedure – circulation of the liquid until the timer reaches the “time” SP.
- Drain – drain the liquid by using the pump. Drain end when tank weight reach “empty tank tolerance” SP.
- Drain timer – drain the leftovers by gravitational flow. Drain ends when timer reach SP.
- Transfer to – transferring the liquid to the next tank – transfer end when weight SP is reached or when transferring tank is empty.

8.2.4. Special Note:

- Tank combination: The operator can choose whether he want to run a “full CIP” process or only run the process on some of the tanks. When not choosing the “full CIP” the process ends without the air purging process.
- Process Cycle: A washing process can be repeated by choosing the number of cycles.

  The sequences are updated according to the chosen tank combination and number of cycles.

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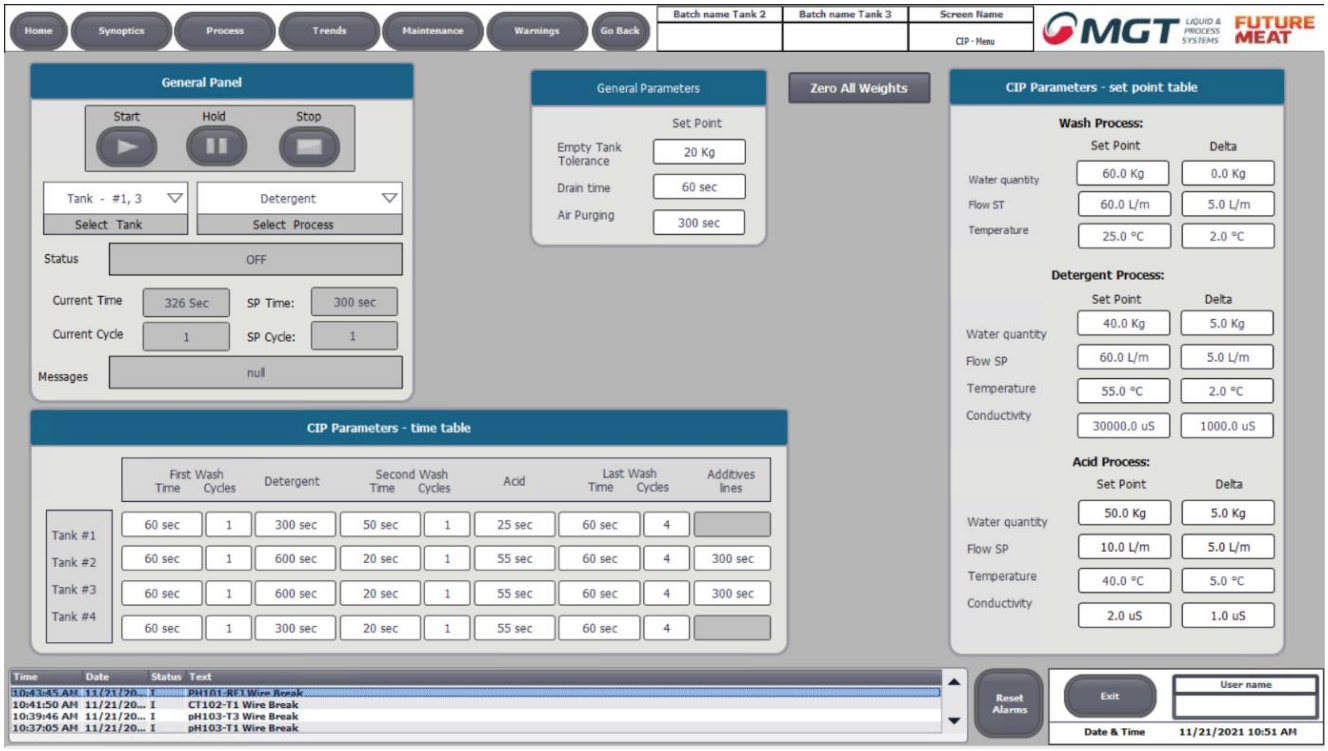
8.3. CIP Operation Screen: Process → CIP



8.3.1. General Panel:

- Start – start the process.
- Pause- pause the process, click again for resume the process from the same point.
- Stop – stop the process.
- Select tank – choose the tank combination for the process.
- Select process- choose the CIP program for the process.
- Status – showing the operation that currently in process.
- Timers – showing the current and set-point time of the operation that currently in process.
- Message – showing warnings and alarms.

8.3.2. General Parameters:

- Empty tank tolerance [kg]: the tank weight that signals an empty tank (for pump safety).
- Drain time [sec]: timer for draining the tanks after the “empty tank tolerance” is reached.
- Air purging time [sec]: the total time of the air purging process.

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8.3.3. CIP Parameters - Time Table:

Enter the time and number of cycles for each process and for each tank.

- Additives lines: the time for washing the peripherical pipes of tank 2 and tank 3.

8.3.4. CIP Parameters – Set Point Table:

- Water Quantity [liter]- the amount of water to be used in the process (wash, detergent, acid).
- Flow-rate [l/min] – set the minimum flow rate for the process. (Wash, detergent, acid).
- Temperature [◦C] – set the required temperature for the process. (Wash, detergent, acid).
- Conductivity [µS/cm] - set the required conductivity for the process. (Detergent, acid).

Be aware: Only if the 3 parameters (flow-rate, temperature, conductivity) will be higher than the set-point, the process will start counting the circulation time.

8.3.5. Process monitoring:

- Monitor the process progression through the ***General Panel*** tab:
  - Status – showing the operation that currently in process.
  - Timers – showing the current and set-point time of the operation that currently in process.
  - Cycles - showing the current and set-point cycle of the operation that currently in process.
  - Message – showing warnings and alarms.
- Monitor the process progression through the ***Time Table*** tab:
  - Yellow color header will indicate the procedure that is currently in process.

8.3.6. Process verification:

The verification of the process is done by limiting the timer counting of the circulation process to be active only if the: flow-rate, conductivity and temperature values are within the required set-point range. In case of not achieving the set-point range, the process will be paused automatically by one of the warnings alarms (see troubleshoot), so the operator will have the ability to fix the problem and continue the process from the same point. in case of process done, the operator can be sure that the washing is complete as per the requirements.

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8.3.7. Starting CIP process:

- Precaution
  - Equipment reaches high temp: > 55 ◦C.
  - Chemical hazards.
  - Wear personal protective equipment during the process.

- Check list before starting the CIP process
  - ✓ Verify all CIP piping are connected (change from process piping to CIP piping).
  - ✓ Take off all the gas filters from the filter housing.
  - ✓ Close tight the manway cover of Tank 1 and Tank 4.
  - ✓ Check the level of additives (base, Acid).
  - ✓ Verify all tanks are empty and/or press Zero to clear the tank weight if necessary.
- Step by step instruction
  - Step 1 – select the tanks combination [“select tanks”].
  - Step 2 – select washing program [“select program”].
  - Step 3 – fill the process parameters [“CIP parameters”, “time table” ,“general parameters”].
  - Step 4 – press “play” button.

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9. PROCESS MENU - SIP

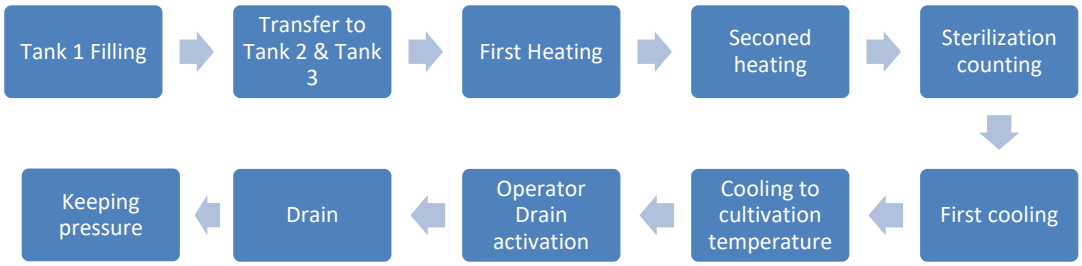
The SIP process is a fully automatic sterilization process of the bio-reactors (T2, T3) and the peripheral piping and instruments.

The SIP is a “full tank wet process” – it means the process is performed by heating up PW in the bio-reactors and created saturated sterile steam.

The SIP process is a predefined sequence, the operator can change the sequence variables from the parameters list.

A pressure test function is controlled through the SIP screen and can be programed by the operator to activate automatically the SIP process in case of a successful pressure test.

9.1. SIP Process Sequence



9.1.1. SIP Sequence operations:

- Filling – PW valve opened and T1 filled with water. Filling ends when T1 weight reaching T1 filling SP.
    - T1 filling SP is a calculated value which takes into consideration the current volume of each tank and the required volume to fill in T2 and T3.
- Transfer to – transferring the liquid from T1 to T2 and T3– transfer ends when T2 weight, T3 weight are reaching the “water filling” SP.
- First heating- heating the tanks with the vent valve open until reactors temp sensor reaching the “first heating temperature” SP.
- Second heating –heating the tanks while all valves are closed in order to raise the pressure and creating the steam. Operation ends when reactors temp sensor reaching the “sterilization heating temperature” SP.
- Sterilization counting – the time of sterilization process. Operation ends when all the temperature sensors reached the “sterilization time” SP or when the heating timer reached the “process fail time” SP.
- First cooling – cooling the tanks with cold water in the jacket. Operation end when reactors temp sensor reaching the “first cooling temp” SP.

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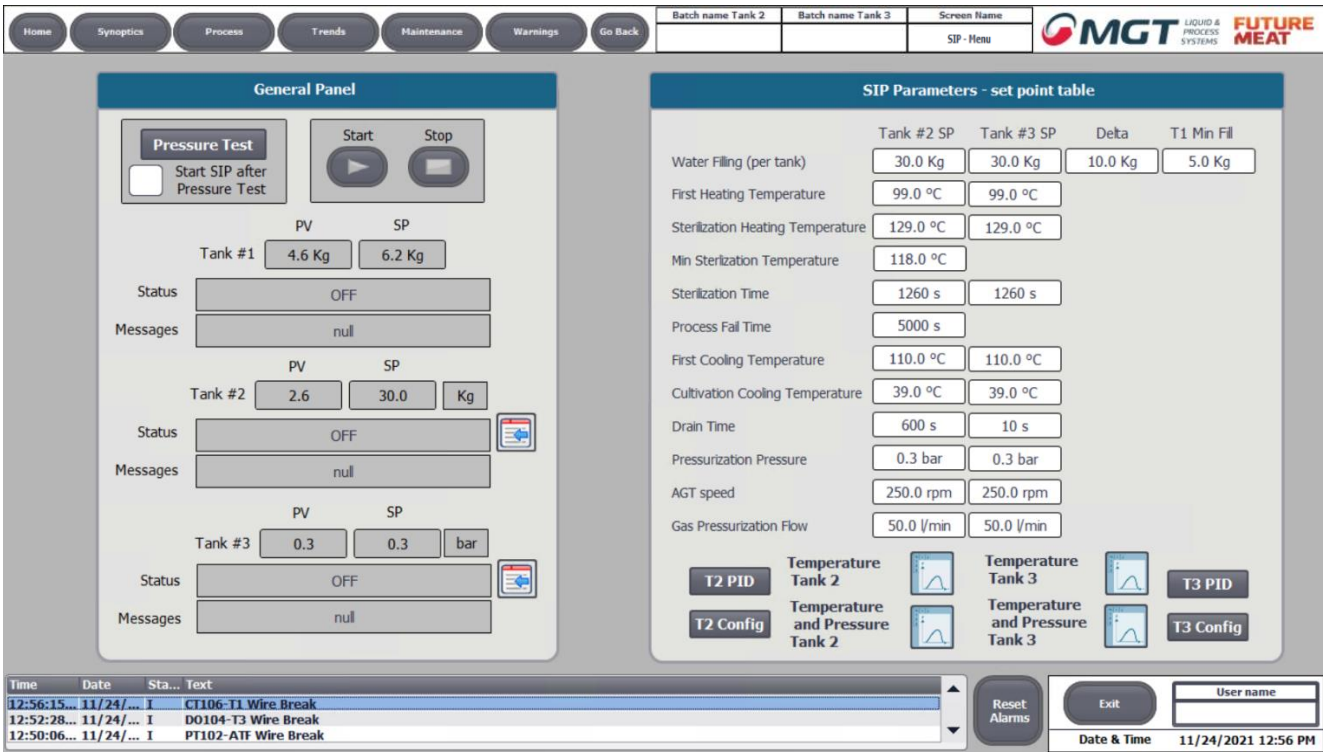
- Cooling to cultivation temp – continue the cooling operation and adding air flow to the tanks to maintain positive pressure and to improve the cooling process. Operation end when reactors temp sensor reaching the “cultivation temp” SP.
- Operator Drain activation – after reaching the cultivation temp. the operator will need to approve the drain operation. By clicking the drain icon, the drain operation will start.
- Drain – drain the leftover water through a sterile port (Harvest). Process end when timer reaching the “drain time” SP.
- Keeping pressure- at the end of the SIP process, a positive pressure is kept in the bio-reactor automatically by introducing sterile air to the bio-reactors. Operation ends when the operator clicks the STOP button.

9.2. SIP Operation Screen: Process → SIP



- First heating temp [◦C]: the temp which all peripheral valve will close and the pressure in the tank will start raise.
- Sterilization heating temp [◦C]: the temp which the peripheral valves will open and the peripheral temperature will start heat up.
- Min. sterilization temp [◦C]: the min temperature for counting the sterilization temp.
- Sterilization time [sec]: the time for sterilization process.
- Process fail time [sec]: the maximum time for heating.

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- First cooling temp [◦C]: the temperature which the vent valve open and the sterile air flow to the bio-reactor.
- Cultivation cooling temp [◦C]: Drain will be possible only when the reactor temperature will get to this temperature.
- Drain time [sec]: the time for the drain of the leftover water.
- Pressurization pressure [Bar]: the pressure that the bio-reactor will maintain from the moment of reaching the first cooling temp.
- AGT speed [RPM]: the agitator speed during the process.
- Gas Pressurization Flow [liter/min]: the sterile air flow-rate from the moment of reaching the first cooling temp.

9.2.3. SIP Process monitoring:

It is possible to monitor the process through the ***General Panel*** tab, according to the description below:

- Status – showing the operation that currently in process.
- Timers – showing the current and set-point value of the operation that currently in process.
- Message – showing warnings and alarms.
- Pressure Test tab – green symbol – pressure test running, red symbol- pressure test fault, grey symbol – pressure test off. Monitoring the pressure test process in the pressure test parameters tab. * see "pressure test operation screen"

In addition, the operator can monitor the process through the temperature table tab.* see – "SIP Process Verification".

9.2.4. SIP process verification:

There are 12 temperature sensor that are monitoring during the SIP process.

11 sensors are in the peripheral area and 1 sensor is in the bio-reactor.

The sterilization counter count only when the temperature is higher than the ***min. sterilization temp*** parameter.

Each one of the sensors has a timer, while the process is running, the status is ***in process***, in case of reaching the sterilization time, the status of the specific sensor will change to ***Done***, in case of reaching the process fail time parameter without reaching the sterilization time, the status will change to ***Fail***.

In the end of the process, the operator will know which sensor doesn't reach the sterilization time and will be able to decide if he runs the SIP process again or only preform local steam bridge.

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Select	Name	Time [AV]	Total Time	Temp	Status
☐	Media From T1	0 s	0 s	+20.1 °C	OFF
☐	Glucose	1027 s	1030 s	+20.4 °C	OFF
☐	Anti foam	1260 s	1980 s	+19.9 °C	Done
☐	Innculum	1260 s	2985 s	+20.0 °C	Done
☐	Rej. From T4	1260 s	1415 s	+21.9 °C	Done
☐	Feed	1027 s	1030 s	+20.2 °C	OFF
☐	Base	1260 s	2499 s	+20.0 °C	Done
☐	Mix Filter	0 s	0 s	+19.8 °C	OFF
☐	O2 Filter	1260 s	1368 s	+19.5 °C	Done
☐	Harvest	0 s	0 s	+20.1 °C	OFF
☑	Sampling Valve	500 s	512 s	+20.0 °C	Done
☐	DO Sensor	1260 s	1322 s	+18.8 °C	Done
☐	pH Sensor	1260 s	1361 s	+19.6 °C	Done
☐	ATF	0 s	0 s	+20.6 °C	OFF
☐	AGT Seal	0 s	0 s	+18.7 °C	OFF

Temperature sensor monitoring table

9.2.5. Starting SIP process:

- Precaution
  - Equipment reaches high temp: >130 ◦C
  - High Pressure in the bio-reactor and the peripherical piping: >1.5 bar
  - Wear personal protective equipment during the process.
  - Never touch tanks and piping equipment during the process.
  - Never disassembly a valve or pipe during the process.

- Check list before starting the SIP process:
  - ✓ Verify all manual valves (HV-003: HV-008, HV:0014) are close or replacement elbow are installed.
  - ✓ Install sterile filter cartridge.
  - ✓ Preform Pressure test
  - ✓ Verify that the bio-reactor are empty and clean.
  - ✓ Verify that the tanks are empty and/or press Zero to clear the tank weight if necessary.

- Step by step instruction:
  - Step 1 – fill the process parameters.
  - Step 2 – if pressure test is required prior to the SIP process, go to section 9: “pressure test process”
  - Step 3 – If only SIP process is required - Press the start button.

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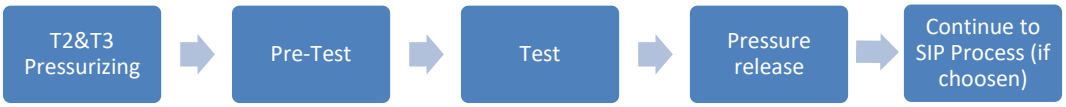
10. PRESSURE-TEST PROCESS

The pressure test process is an automatic process to check if there are leakages from the sterile boundary of the system.

The pressure test operation is done from the SIP screen.

10.1. Pressure Test Sequence:



10.1.1. Pressure test sequence operations:

- Pressurizing- introducing air to the bio-reactors to increase the pressure. Operation ends when the bio-reactor pressure is reaching the "Test Pressure" SP.
- Pre-Test – a pre-test is performed before the pressure test. Operation ends when timer is reaching the "pre-test time" SP.
- Test – The pressure test is performed. Operation ends when timer reaching the "test duration" SP.
- Pressure release- at the end of the process the vent valve is open gradually until the bio-reactor pressure reaching 0 Bar.

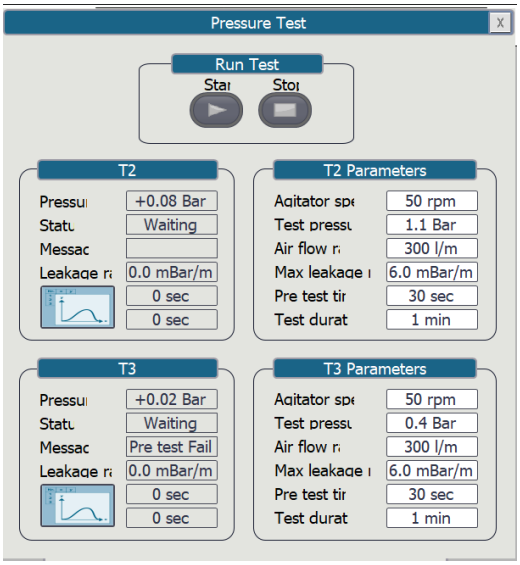
10.2. Pressure test- Operation Screen: Process → SIP → Pressure test

10.2.1. General Panel:

- Start – start the process.
- Stop – stop the process.

10.2.2. Parameters:

- Agitator speed [RPM]: the agitator speed during the process.
- Test pressure [Bar]: the pressure to reach for starting the test.
- Air flow rate [l/min]: the sterile air flow rate during the pressurization process.
- Max. leakage rate [mbar/min]: the maximum allowable pressure loss during the test.



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- Pre-test time [min]: the time for the pre-test operation.
- Pressure test duration [min]: the time for the pressure test operation.

10.2.3. Pressure test - Process monitoring

It is possible to monitor the process through the ***T2 and T3*** tabs, according to the description below:

- Pressure- showing the present value of the pressure in the bio-reactors.
- Status – showing the operation that currently in process.
- Message – showing warnings and alarms.
- Leakage rate – showing the pressure loss during the process. (the leakage rate is reset when process moving form pre-test to pressure test operation)
- Timers – counting the time of the pre-test and the pressure test operations.

In addition, the operator can monitor the process from the main SIP screen according to the color of the pressure test tab – green symbol – pressure test running, red symbol- pressure test fault, grey symbol – pressure test off.

10.2.4. Pressure test process verification:

It is possible to verify the process status during the process operation and at the end of the process.

The process message and status will be kept until the operator is clicking the stop button.

10.2.5. Starting the pressure test process:

- Precaution
  - High Pressure in the bio-reactor and the peripherical piping: >1 bar
  - Never disassembly a valve or pipe during the pressure test operation.

10.2.6. Check list before starting the pressure test process

- ✓ Verify all manual valves (HV-003: HV-008, HV:0014) are close or replacement elbow are installed.
- ✓ Install sterile filter cartridge.
- ✓ Verify that the bio-reactor are empty and clean.

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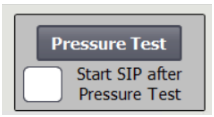
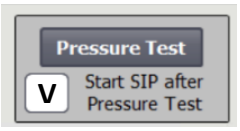
10.2.7. Step by step instruction:

- Only pressure test.
  - Step 1 – enter the SIP screen.
  - Step 2 – verify there is no “V” in the tab for auto start SIP Process.
  - Step 4 - enter the pressure test pop-up screen (click on the Pressure test tab).
  - Step 5 - fill the pressure test process parameters.
  - Step 6 - click the Play button.



- Pressure test with SIP starting automatically
  - Step 1 – enter the SIP screen.
  - Step 2 - Mark “V” in the tab for auto start SIP process.
  - Step 3 - fill the SIP process parameters.
  - Step 4 - enter the pressure test pop-up screen (click on the Pressure test tab).
  - Step 5 - fill the pressure test process parameters.
  - Step 6 - click the Play button.



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11. STEAM-BRIDGE PROCESS

A fully automatic local sterilization process of a single or multiple sections in the system. Allowing the operator to sterilize parts of the system while in production process.

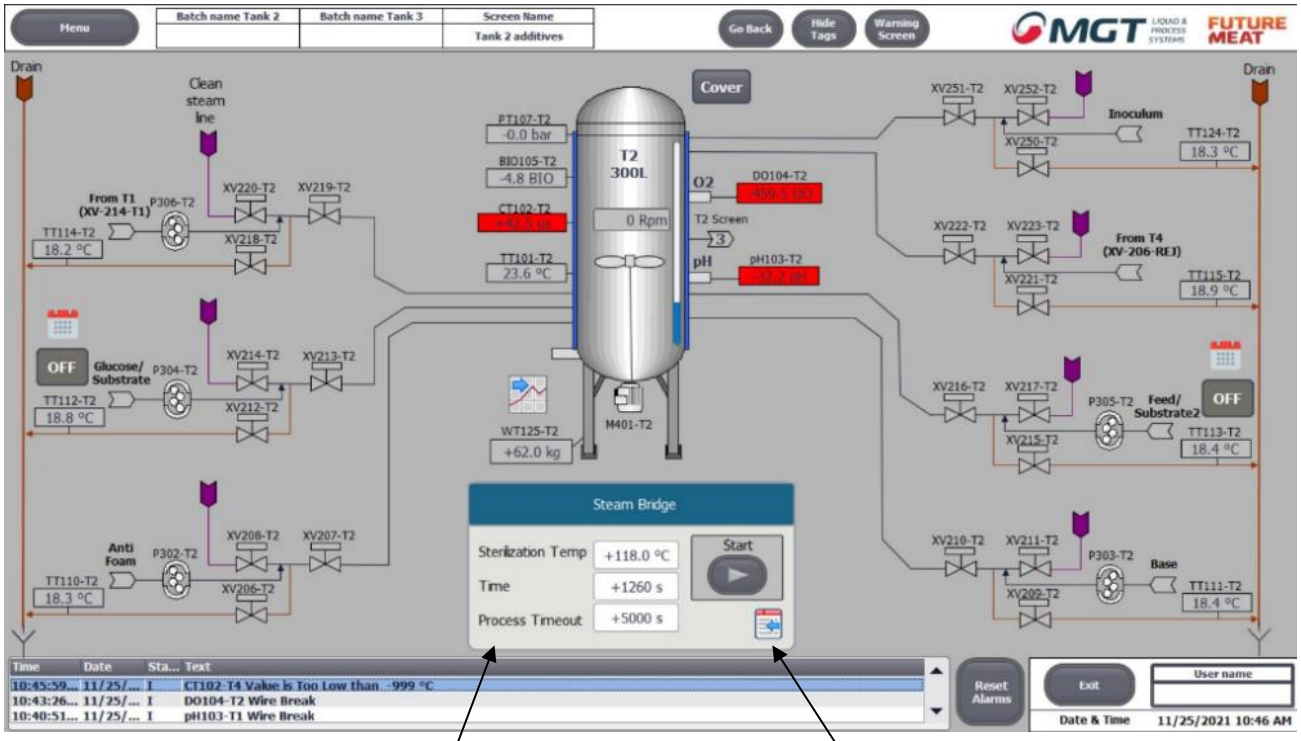
The operator can choose the section that he would like to sterilize from the steam bridge table.

11.1. Steam-bridge Sequence:

The operator can choose from a table the pipe section that he would like to sterilize. It is possible to choose multiply sections. While the steam-bridge is in operation the relevant steam and condensate valves are open and a timer start counting the sterilization process for each section separately. The timer will count only if the temperature of the relevant temperature sensor is higher than the "sterilization temperature" SP.

While the process is running, the status is in process, in case of reaching the "sterilization time", the status of the specific sensor will change to ***Done***, in case of reaching the "process fail time" parameter, the status will change to ***Fail***.

11.2. Steam-bridge operation screens: Menu → Tank 2/3 Additives → Steam bridge



Steam-bridge operation screen

Click to open the steam bridge table

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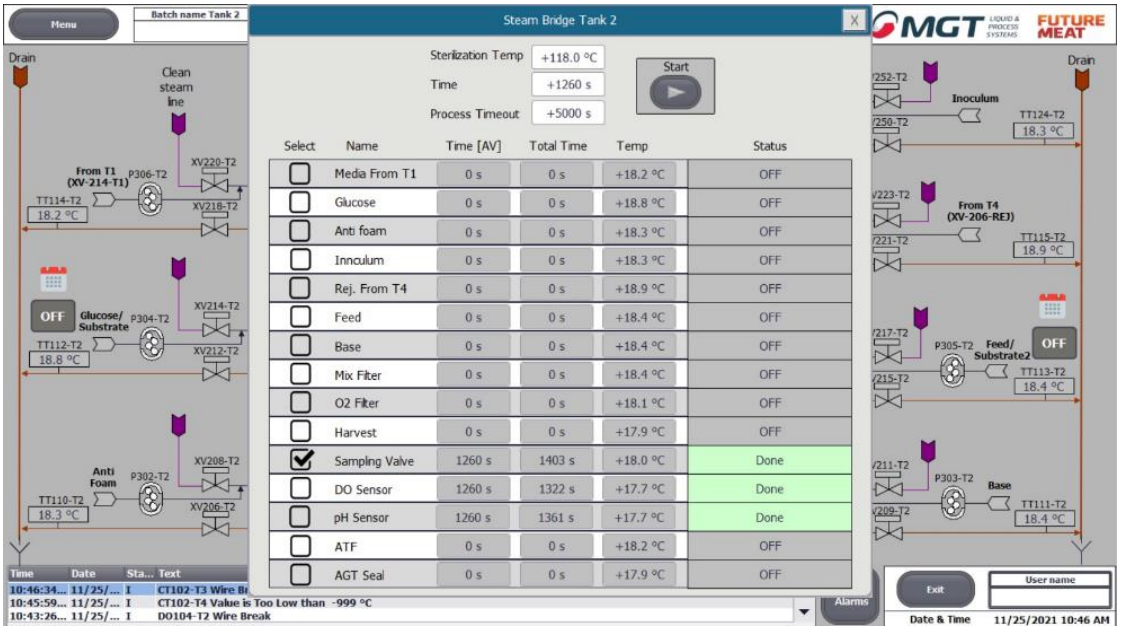

11.2.1. General Panel:

- Start – start the SIP process. . Click again to Stop the process.
- Sterilization temp – the min temperature for counting the sterilization process.
- Time – the time for the sterilization process.
- Process timeout [sec]: the maximum time for heating.

11.2.2. Steam bridge table:

- Select: the operator selects the section that will perform the sterilization process.
    - It is possible to select multiple section.
- Name: the name of the section.
- Time: counter for the time that the specific section was above the sterilization temp.
- Total time: counter for the total time of the process.
- Temp: the present value of the specific temperature sensor.
- Status: In process, Done, Fail

11.2.3. Process monitoring:

The operator can monitor the process in the steam bridge table (Status, timers, temp).

open by clicking the icon: 

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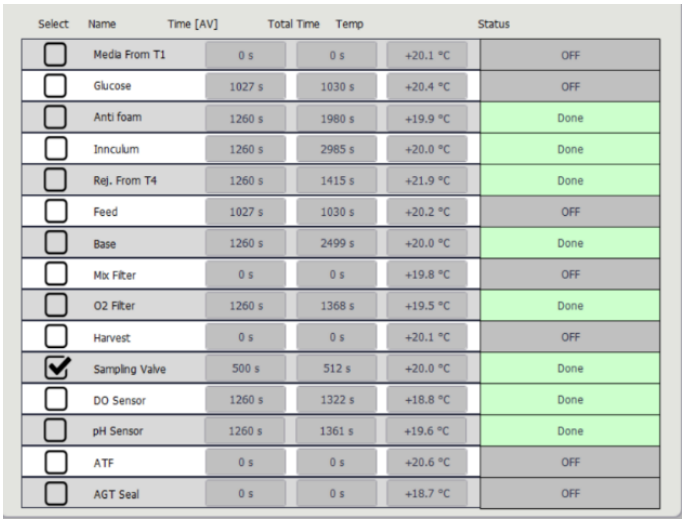
11.2.4. Sterilization process verification:

Each section has a temperature sensor that is monitored during the steam-bridge process.

The sterilization counter count only when the temperature is higher than the min. sterilization temp parameter.

Each one of the sensors has a timer, while the process is running, the status is ***in process***, in case of reaching the sterilization time, the status of the specific sensor will change to ***Done***, in case of reaching the process fail time parameter without reaching the sterilization time, the status will change to ***Fail***.

At the end of the process, the operator has the full list of the sections with the status of each one.



Select	Name	Time [AV]	Total Time	Temp	Status
☐	Media From T1	0 s	0 s	+20.1 °C	OFF
☐	Glucose	1027 s	1030 s	+20.4 °C	OFF
☐	Anti foam	1260 s	1980 s	+19.9 °C	Done
☐	Innculum	1260 s	2985 s	+20.0 °C	Done
☐	Rej. From T4	1260 s	1415 s	+21.9 °C	Done
☐	Feed	1027 s	1030 s	+20.2 °C	OFF
☐	Base	1260 s	2499 s	+20.0 °C	Done
☐	Mix Filter	0 s	0 s	+19.8 °C	OFF
☐	O2 Filter	1260 s	1368 s	+19.5 °C	Done
☐	Harvest	0 s	0 s	+20.1 °C	OFF
☑	Sampling Valve	500 s	512 s	+20.0 °C	Done
☐	DO Sensor	1260 s	1322 s	+18.8 °C	Done
☐	pH Sensor	1260 s	1361 s	+19.6 °C	Done
☐	ATF	0 s	0 s	+20.6 °C	OFF
☐	AGT Seal	0 s	0 s	+18.7 °C	OFF

11.2.5. Starting Steam-Bridge process:

- Precaution:
  - Equipment reaches high temp: >130 ◦C
  - Wear (PPE)personal protective equipment during the process.
  - Never touch tanks and piping equipment during the process.

- Check list before starting the SIP process:
  - ✓ Verify that the section that will perform the operation is ready in terms of valves positioning and instrumentation.

- Step by step instruction:
  - Step 1 – Open the steam bridge table.
  - Step 2 – Fill the process parameters.
  - Step 3 – Choose the units to perform the process.
  - Step 4 – Press the start button

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12. PRODUCTION PROCESS - GENERAL

The Production process involves a set of processes that works simultaneously according to the mode of operation. The operator has the flexibility to operate a single process or multiply processes, according to his needed.

The process starts with the cultivation mode, which involves the use of tank no.1 for fresh media preparation and the use of the two bio-reactors in a fed-batch process.

According to the operator decision, the process changed to prefusion mode, which is a continuous process that involves the use of all the system units.

- Tank no.1 – concentrated fresh media dilution
- Bio-reactors – continuous process with ATF filtration and media recovery
- Tank no. 4 – media rejuvenation and media balancing
- ATF – cultured media filtration
- Nano-filtration – media rejuvenation

12.1. Cultivation & Prefusion PFD:

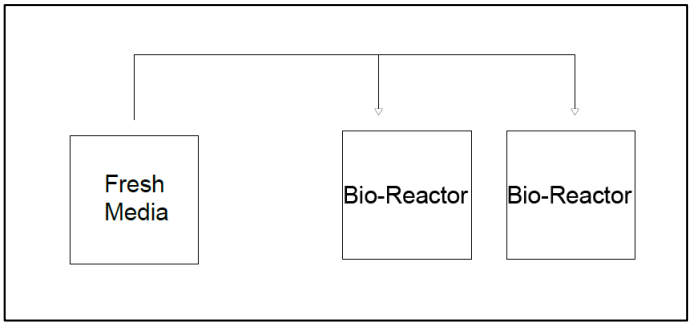

Figure 3: Cultivation mode

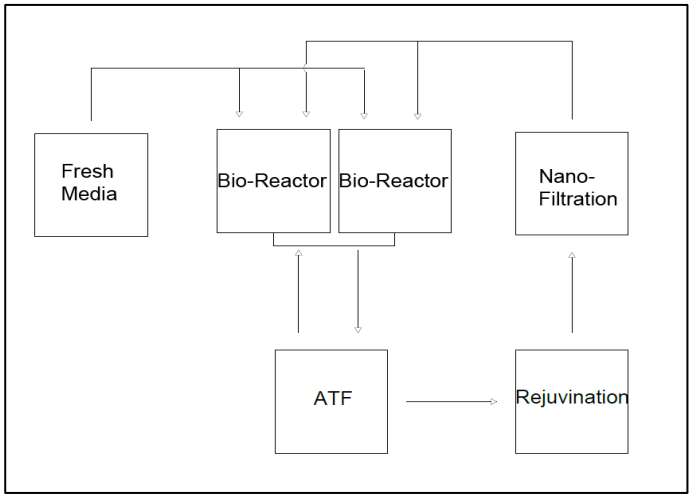

Figure 4:Prefusion mode

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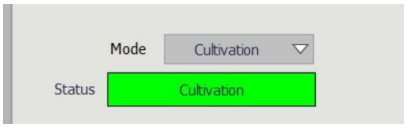
12.2. Cultivation/Prefusion mode

The mode of the production process is pre-condition for some of the process in the "media preparation" and "rejuvenation" screens, and therefore it should be set before operating the control functions.

The setting of the operation mode can be done in both screens ("media preparation", "rejuvenation"). The operator should enter the mode in the selection bar and choose the process mode.



- **Be aware** - process that include the bio-reactor in their loop of operation also required that the main cultivation screen will be in "***Play***" mode.

12.3. Control loops - General

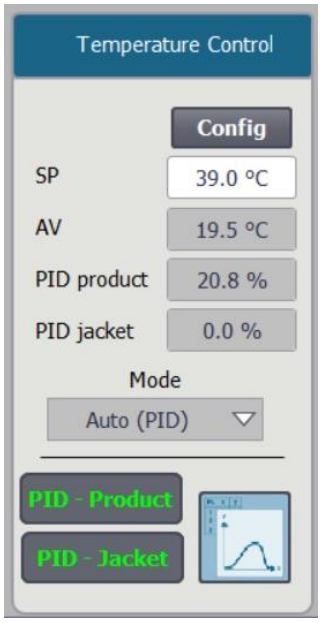
The control loops in the system operate either as PID controllers, setpoint controllers or on/off controllers and are adapted to the related control loops. The controller structure (PID) can be parametrized, if necessary and it is possible to switch over between the operating modes.

In the controller main screen, you can enter set-point value, actual values, operating modes and controller outputs. In the configuration screen you can enter to a more advance parameters and to adjustt the PID parameters, dead band and other advance configuration depending on the specific control loop.

12.3.1. Controller Operation in General

In general, the operation of all the controllers is almost the same. Operation includes the necessary changes of the setpoints, of the controller modes and of the controller outputs. Additional controller settings not required for routine operation, and can be done via the configuration functions.

An example of Control loop operating screen:



- Config: open advance configuration screen
- SP: enter the set-point
- PV: the present value
- PID output- the output of the controller
- Mode: select the mode of operation:
  - Off – control loop switched off
  - Auto (PID) - controller in PID operation
  - Auto (Cascade) - controller in Master/Slave operation
  - Schedule - controller in PID operation with set-point changing according to a predefine schedule
- PID Tab – open the PID configuration screen
- Trend symbol: open the PID trend screen

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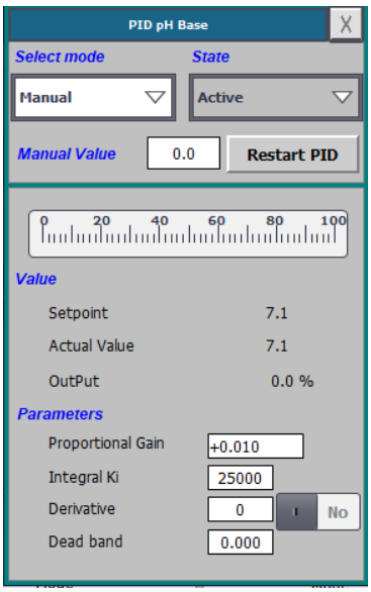
12.3.2. PID Controller Configuration Screen



- Select mode:
  - Off - controller switched off with defined output
  - Auto - controller in operation
  - Manual - manual control of controller
- State – display the state of the controller (active/not active)
- Manual value - set the output value when in manual mode
- Restart PID – restarts the PID in case of error
- Value – display the SP, PV and output
- Parameters –
  - Proportional Gain- Input of proportional gain factor
  - kI - Input of the time response of the integral action
  - Derivative - Input of the time response of the deviation action

    *can be turn off in case of not in use.
- dead band: input of the dead band. Symmetrically for to the SP.

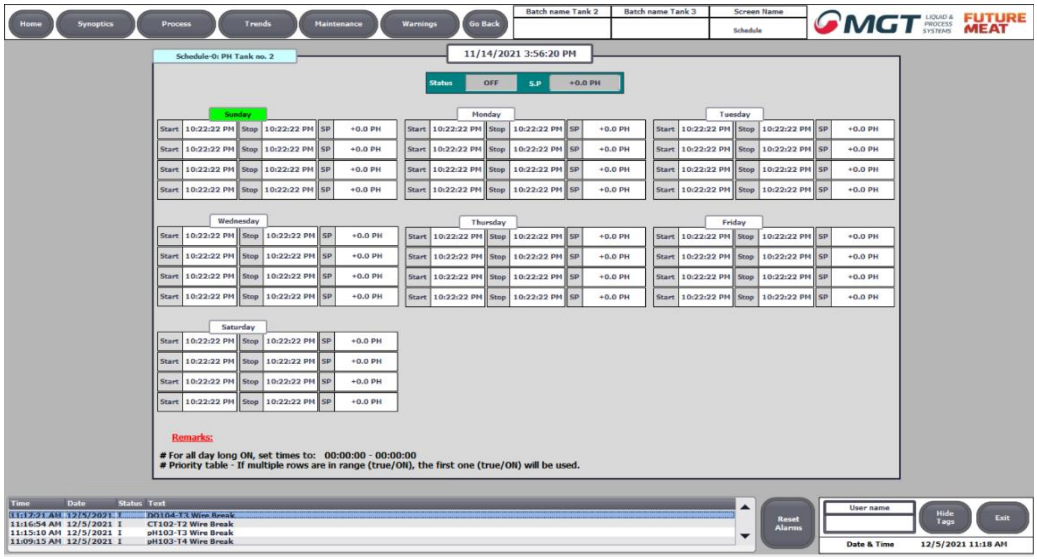
12.3.3. Controller in Schedule mode

When schedule mode is available there will be an icon  in the controller general screen.

By clicking the icon, the schedule settings screen will open.

The schedule mode allowing the operator to change the set-point value automatically according to a weekly schedule.

- It is possible to set 4 different values for each day of the week.
- For all day long ON – set times to: 00:00:00 – 00:00:00
- Priority table – if multiply rows are in the same range, the first row will be used.



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12.4.Before starting production processes:

- Check list before starting any production process:
    - ✓ Verify the system is clean and sterile (CIP and SIP are done).
    - ✓ Verify all Process piping are connected including single use piping.
    - ✓ Verify all the sterile filter cartridge are installed.
    - ✓ Calibrate the sensors and pumps.
    - ✓ Calibrate the tank weight.

- Shifting from SIP process to Production process

  Usually, the production process will start after preforming an SIP process. At the end of the SIP process, a positive pressure is kept in the bio-reactors to eliminate the risk of contamination. In order to keep the sterility when shifting between the process. It is recommended to follow the steps below:

    - Step 1: Go to Cultivation screen
    - Step 2: Set all control loops to OFF
    - Step 3: Set the Set-Point for the pressure control and switch from OFF to AUTO(PID)
    - Step 4: Go to SIP screen
    - Step 5: Turn off the SIP Process (click on Stop button)
    - Step 6: Go to Cultivation screen
    - Step 7: Turn ON the Cultivation process (click on Start button)

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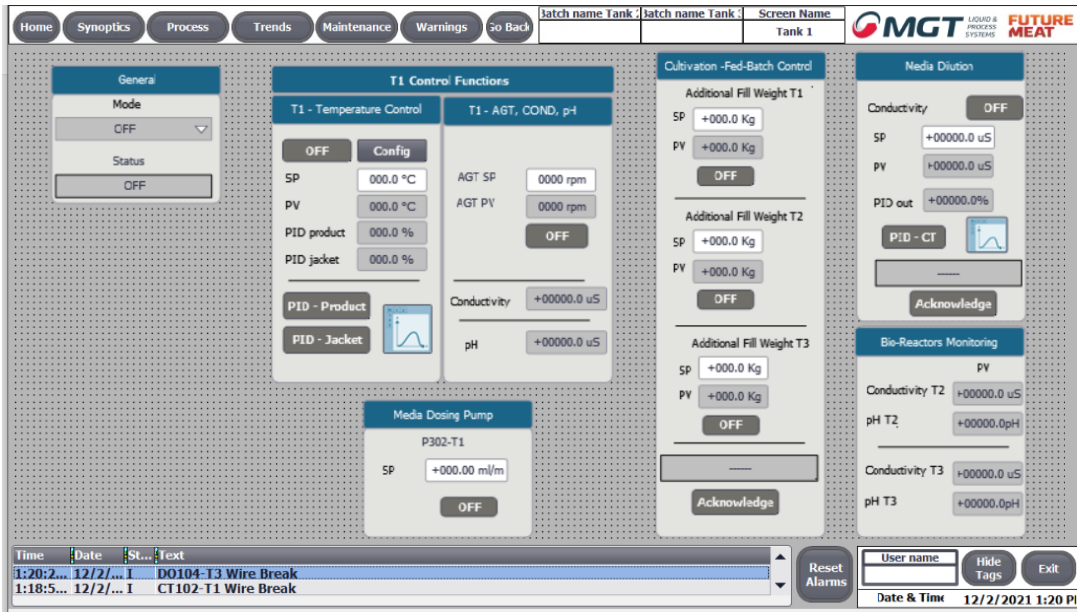
13. PROCESS MENU - MEDIA PREPARATION:

The process of media preparation is done in Tank no. 1. It is a semi-automatic process, the operator set the amount of water to fill, the agitation speed and the desire temperature, and introduce the additives manually through the manhole.

When the media is ready, according to the operator decision, the operator can choose the weight of media to transfer to each of the bio-reactors. The filling process is done automatically.

It is possible to dilute the media inline during the transferring of media to the bio-reactor. This is done by dosing PW to the transferring line. The dilution is controlled by PID controller, which triggers the opening percentage of a proportional valve.

13.1. Media Preparation Screen: Process → Media Preparation



The screen divided to blocks, each one controlled a different function in the process.

13.1.1. General:

- Mode – choose the mode of operation – Off, Cultivation, Prefusion
- Status – sowing the current status of the process. (Green for operation and red for alarm)

13.1.2. Tank 1 – control functions:

- AGT – set the agitator speed. (Agitation control)
- Temp T1 – set the desired temperature for T1. (Temperature control)
- Conductivity and pH – Present value for monitoring

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13.1.3. Cultivation – Fed-Batch:

- Additional fill weight T1 – set the weight to be filled in T1.
- Additional fill weight T2 – set the weight to be transferred from T1 to T2.
- Additional fill weight T3 - set the weight to be transferred from T1 to T2.

Be aware – the set-point value is the additional weight (PV+SP).

13.1.4. Media Dosing pump:

- P302-T1 – set the flow rate for transfer the media from T1 to the bio-reactors.

13.1.5. Media dilution:

- Conductivity – enter set-point for the required diluted media conductivity.
- PID output – display of the PID output – sets the PW valve opening

13.1.6. Bio-reactor Monitoring: display of the conductivity and pH in the bio-reactor during the media dilution process.

- Conductivity T2
- pH T2
- Conductivity T3
- pH T3

13.2. Step by step instruction: Media Preparation/transferring/dilution

- Step 1 – enter to media preparation screen.
- Step 2- turn on the tank 1 general control loops (only if required)
- Step 3 – enter the set point for filling tank 1 and turn it ON
- Step 4 – Add materials manually according to the recipe
    - In case of transferring media to T2 & T3 - continue to next step
- Step 5 – set the mode of operation to: “cultivation”
- Step 6 – enter the flow-rate for the transferring pump and turn the pump ON
- Step 7 - enter the set point for filling tank 2 & tank 3 and turn it ON
    - In case of media dilution - continue to next step
- Step 8 – make sure the main cultivation process is in “play” mode (in cultivation screen)
- Step 9 – set the mode of operation to: “prefusion”
- Step 10 -Enter the conductivity SP and turn the control ON

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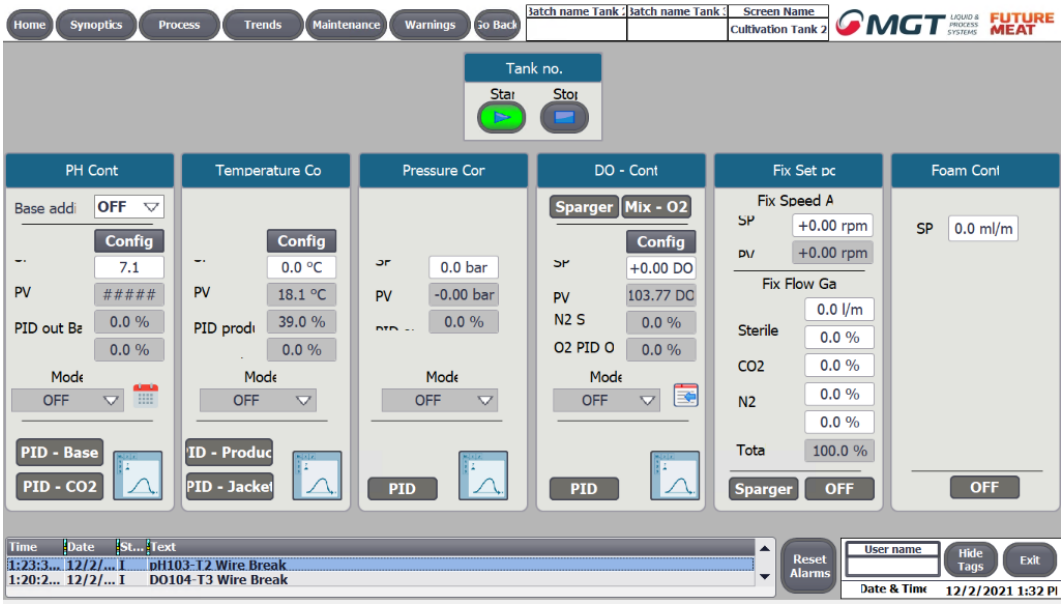
14. PROCESS MENU – CULTIVATION TANK 2 / TANK 3:

The cultivation operating screens are similar for both bio-reactors, therefore we use for this manual only the tank 2 screens.

The screen divided to blocks, each one controlled a different function of the bio-reactor control.

- **Be Aware**- the "start" button of the cultivation screen is a precondition for other control function of the system.

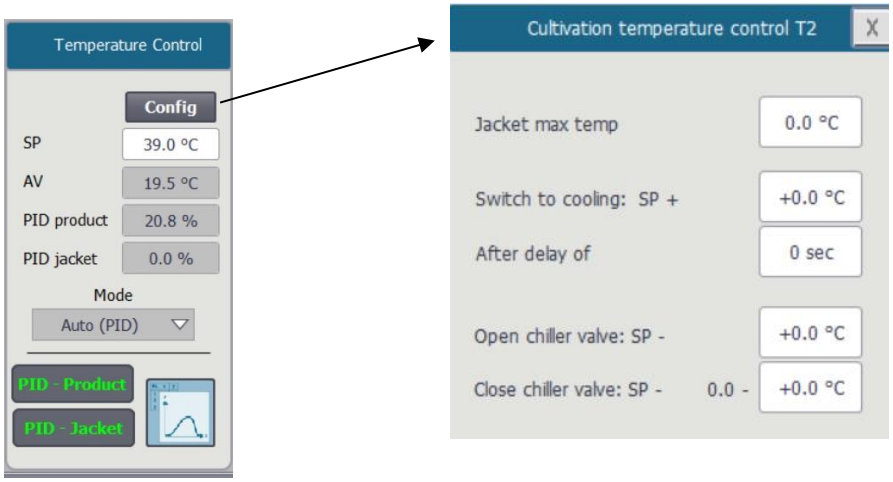


14.1. Temperature Control:

The temperature is controlled via a cascade control with a master controller for the vessel temperature and a slave controller for the jacket temperature. The output of the slave controller controls the steam valve.

There are different modes for the control functions- fast heating, slow heating and cooling mode.

14.1.1. Main operation screen: *see "general controller operation" for more details.



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14.1.2. Special Feature: “Config”

- ❖ **Be aware** – advance configuration, for experienced operator or technician use only.

By clicking the config button, a pop-up window will open with the advance configuration settings.

The setting is for controlling the cooling mode.

- Jacket max temp: set the max temp for the jacket
- Switch to cooling: the temperature that will trigger the switching from heating to cooling.
- After delay of: delay time when reaching the switching temp.
- Open chiller valve: when in cooling mode - the temp that will trigger the chiller valve to open.
- Close chiller valve: when in cooling mode - the temp that will trigger the chiller valve to close.

14.2. Agitation Control:

The speed of the agitator motor is controlled via an external, extra motor controller (VFD). the adjustment of all the agitator parameters is done in the external controller. The control function of the agitator works as a setpoint controller and supplies the analog setpoint signal to the external controller.

When operation is done through the DO cascade control, the agitator speed controller is operated as a slave controller in the DO cascade control loop.

*For screen and parameters see “DO control”.

14.3. Gassing control:

All the gases supply are controlled via an external mass-flow controller. Each gas control function works as a setpoint controller. It supplies the analog setpoint signals to the external mass-flow controller. The menu at the control system is used for entering the setpoints and screen of the flowrate. signal coming from the mass-flow controller. For DO control the airflow controller can be switched over to be slave controller in the DO cascade control loop.

*For screen and parameters see “DO control”.

14.4. pH Control:

The pH - control function works in PID - behavior. There are 2 PID, one for base addition, which triggers the base pump and valves, and one for CO2 addition, which triggers the mass flow controller and gas inlet valves.

There is a split range between the two PID operation, which allows a simultaneous control of both the acid and base supplies.

Special Features:

- Dead bend operation - the acid and base control signals remain „off“ as long as the deviation of the actual value lies within the parametrized dead band. This feature prevents unnecessary dosage of acid or base.

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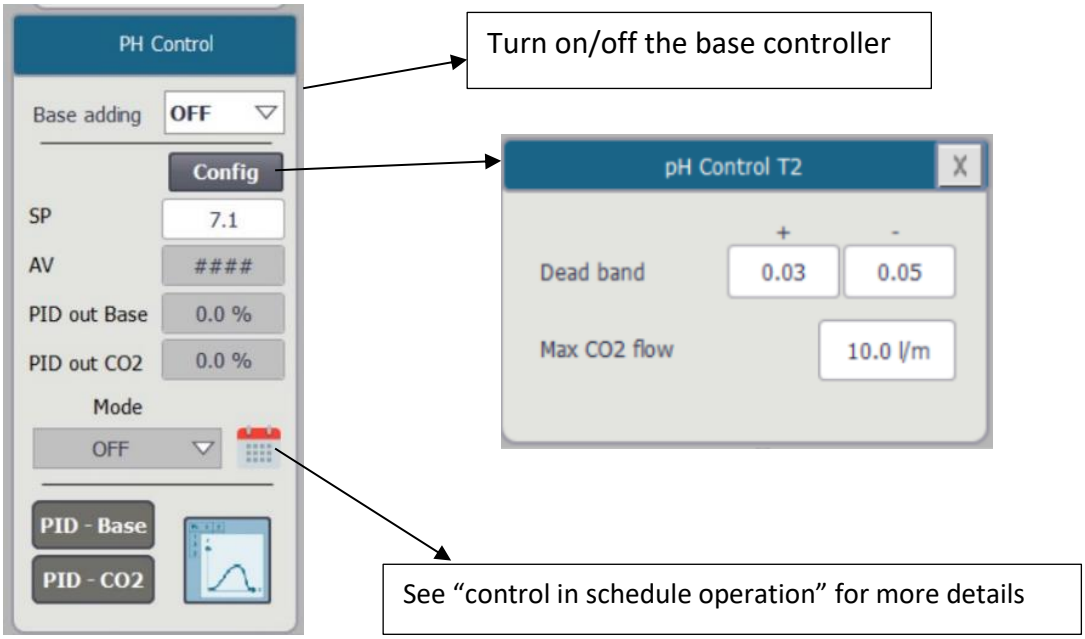
- The dead band value is not symmetrical and can be adjusted manually by the operator in order to achieve the most stable and economical operation.
- CO2 flow limit – limit the maximum flow rate of the CO2 to prevent high flows and set-point overshoot.
- Base control off mode – having the ability to turn off the base controller if needed (usually before the inoculation).

14.4.1. Main Operating screen:



14.4.2. Special feature- “Config”:

❖ **Be aware** – advance configuration, for experienced operator or technician use only.

By clicking the config button, a pop-up window will open with the advance configuration settings.

- Dead Band: set the dead band for CO2 and base addition (SP+ xxx , SP-xxx).
- Max CO2 flow – set the max flow rate of the CO2 [1-100 l/m]

*For PID screen see “general operation screen”

**For schedule screen See “control in schedule operation”

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14.5. DO Control

The DO can be controlled in manual mode (i.e., “fix set point”) or in auto mode.

14.5.1. Manual mode (i.e., Fix set-point)

Manually operation of the agitator and the gassing control.

The operator can set the gas mix by enter the total flow rate and the percentage of each gas, choose the gassing outlet location – sparger or overlay for the mix gas, and mix or micro for the oxygen gas, and set the agitator speed.

The controller will calculate the required gas flow rate for each gas, and will send the set point for the mass flow controller.

By choosing the gas outlet location, the relevant valves will open/close.

In manual mode there is need to press the ON/OFF button in order to start the operation.

14.5.2. Auto mode (i.e., Cascade control):

The cascade DO control function works as a PID controller for increasing the DO and as pulsation control for decreasing the DO.

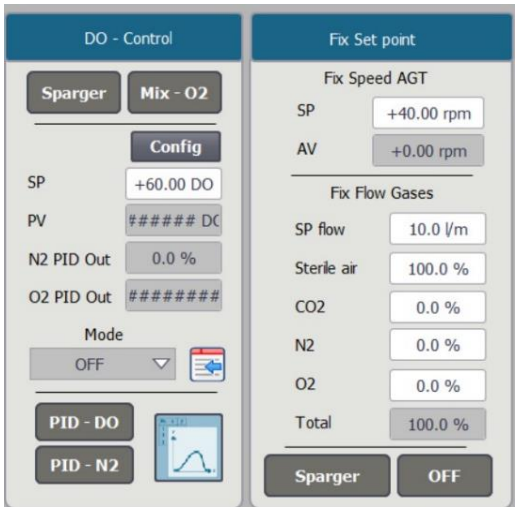
When there is a demand for O2 – the DO PID controller output triggers the supply of air, O2 and agitator speed according to the “DO priority table”. In the “DO priority table” the operator define the range of operation and the priority for each supply (air, O2, agitator).

When there is need to decrease the DO, nitrogen is introduced by a manner of pulsation, the control of this process is done by a “Pulse table”. In the “Pulse table” the operator can define all the variables of the N2 pulsation control and to define the operation of the control based on the process need.

Such a control strategy allows to keep the DO value constant over prolonged periods of the process.

The two controllers (DO, N2) are adjusted independently of each other in order to allow maximum adaptation to the process, and maximum flexibility to the operator.

14.5.3. Main operating screen:



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14.5.4. Special feature: gas outlet location: The operator can choose manually the outlet flow location for the mix gas and for the oxygen by pressing the buttons:

- Sparger / Overlay – choose where the mix gas will flow – sparger or overlay.
- Oxygen-mix / Oxygen-micro- choose if the oxygen gas will flow to the mix or to the micro sparger.

14.5.5. Special feature: DO priority table:

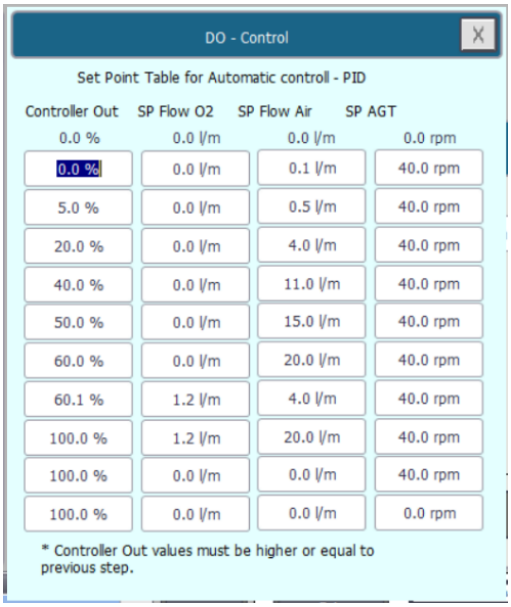
❖ **Be aware –** advance configuration, for experienced operator or technician use only.

The operator can set the operation range of the controlled elements according to the PID controller output.

The first raw in the table indicate the present value of each element.

❖ **Be Aware:**

- Controller output: Always enter values in ascending order.
- Set-point: the values in the table must be fitted to the process, otherwise the controller will not work well.



14.5.6. Special Feature: N2 pulse table:

❖ **Be aware** – advance configuration, for experienced operator or technician use only.

The operation is divided to two section – one for low oxygen demand (O2 flow<0.5 l/m) and one for high oxygen demand (O2 flow>0.5 l/m).

In each table the operator can enter the range of operation according to the distance of the PV from the SP, the N2 maximum flowrate, the pulse and pause duration.

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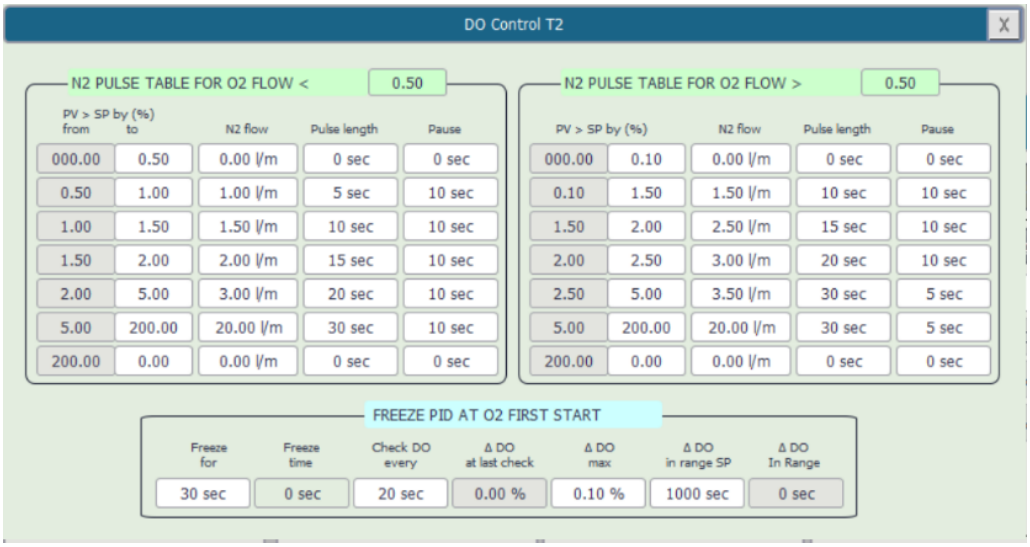
In addition, it is possible to freeze the DO PID operation in the transition phase, when oxygen gas starting to take part in the cascade operation.

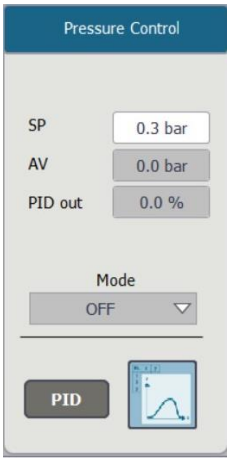


14.6. Pressure control:

The pressure control works as a PID controller with continuous output. The corresponding analogue output signal 4…20 mA controls a continuous control valve in the exhaust line via an I/P converter.

- **Be aware -** When the pressure controller is switched off, the control valve fully close.

14.6.1. Main operating screen:



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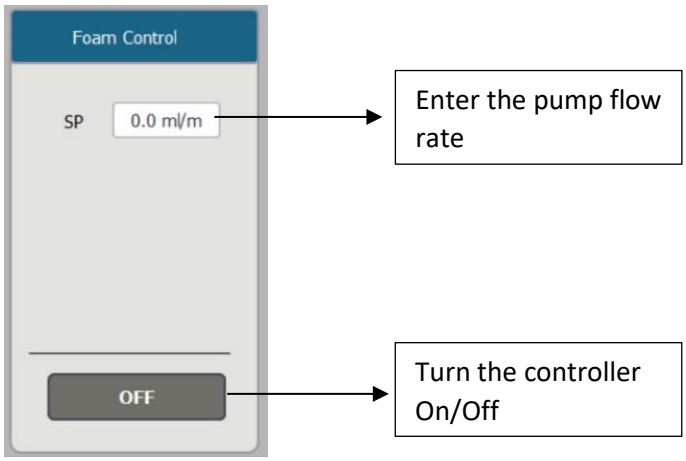
14.7.Foam Control:

When foam comes into contact with the antifoam sensor, the foam measurement amplifier generates a limit value signal for the antifoam controller. This signal is active as long as foam has contact with the probe. The sensitivity of the foam detection can be adjusted via the foam controller. The digital output of the antifoam control function triggers a dosing pump to supply antifoam agent to the culture. The pump is switched on and off according to the demand, the pump flow-rate can be adjusted manually in the control screen.

14.7.1. Main operating screen:



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15. PROCESS MENU - REJUVENATION

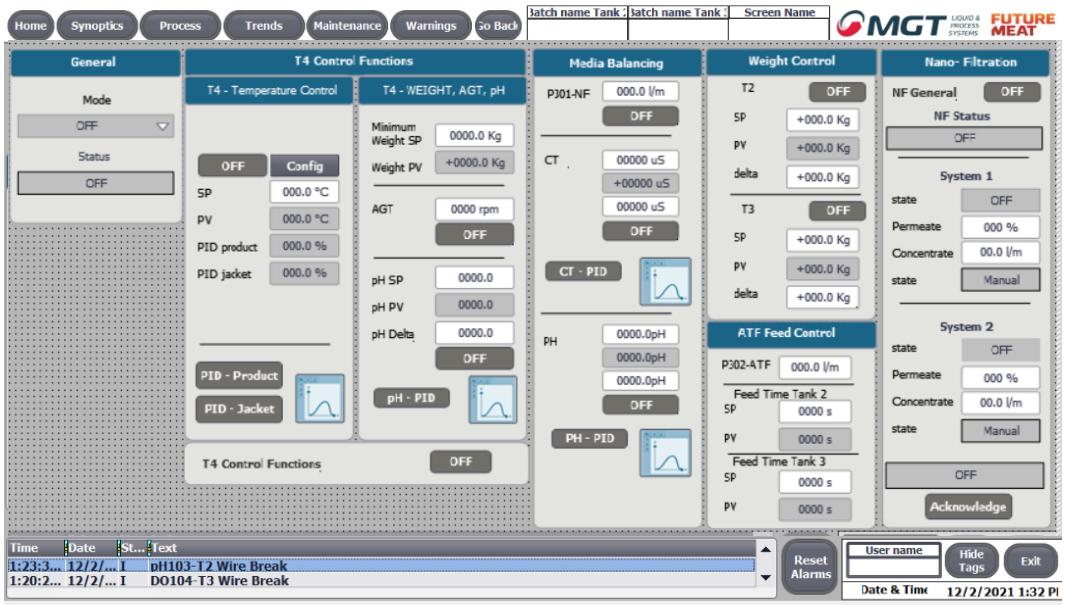
The process of rejuvenation is performed during the prefusion mode of operation.

The process involves the filtration of the cultured media from the bio-reactors, treatment of the filtered media, and recycling the media back to the bio-reactors based on a weight control function.

The treatment of the used media is done in a series of controlled operations, acidification in tank no. 4, transferring to nano filtration system and finally transferring the media back to the bio-reactor through an inline media conditioning.

The operation of all the controlled function of the rejuvenation process is performed in the rejuvenation screen.

15.1. Rejuvenation operating screen: Process → Rejuvenation



The screen divided to blocks, each one controlled a different function in the process.

15.1.1. General:

- Mode – choose the mode of operation – Off, Cultivation, Prefusion.
- Status– sowing the current status of the process. (Green for operation and red for alarm).

15.1.2. Tank 4- control functions:

- Min weight – set the minimum weight for the operation of the control loops in T4. Below this weight the controls will not start.
- AGT – set the agitator speed. (Agitation control)
- pH – set the desired pH value in T4. This will trigger the Acid pump operation.

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- pH delta - The dead band for the operation of the pH control. It is symmetrical to the set-point.
- Temp – set the desired temperature for T4. (Temperature control)

  For more detailed regarding the temp control – see “cultivation temp control”.

15.1.3. Weight control:

keeping the weight in the bio-reactor at a constant range (set point+-delta) by makeup rejuvenated media.

- Keep weight T2 – set the weight that should be kept in T2.
- Keep weight T3 – set the weight that should be kept in T3.
- Delta – The dead band for the operation of the weight control. It is symmetrical to the set-point.
  - For example: SP=100kg, Delta=10kg: the weight control will not operate when PV is in the range of 90-110 kg.

15.1.4. Media balancing

- Transferring pump:
- pH control:
- Conductivity control:

15.1.5. Nano-Filtration:

The nano filtration system is a stand-alone system. The full operation of the system is done from the local HMI. However, there is an option to control over basic operation through the MGT HMI.
In order to have the control from the MGT HMI, the operator should change to remote mode and auto mode, in the local HMI.

15.1.6. ATF Feed control

The function in the “ATF feed control screen” are for controlling the ATF filtrate pump flow rate and the feed valves timers.

- P-302-ATF – enter the required flow rate for the ATF filtrate pump (supply to tank 4)
- Feed time Tank 2 – the opening time for the ATF feed valve in tank 2.
- Feed time Tank 3 - the opening time for the ATF feed valve in tank 3.

In order to control remotely the ATF system there is an option to connect remotely to the ATF HMI from the MGT HMI by screen mirroring (Process → ATF).

- **Be aware**: in order to start any control function you need to click to “ON” button next to the control block.

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15.2.Step by step instruction: Rejuvenation Process

- Step 1 – enter to rejuvenation screen.
- Step 2- set the mode to prefusion.
- Step 3 – set the controls function.
- Step 4 – turn on the control function that should operate
  - ❖ **Be aware:** make sure the main cultivation process is in “play” mode (in cultivation screen)

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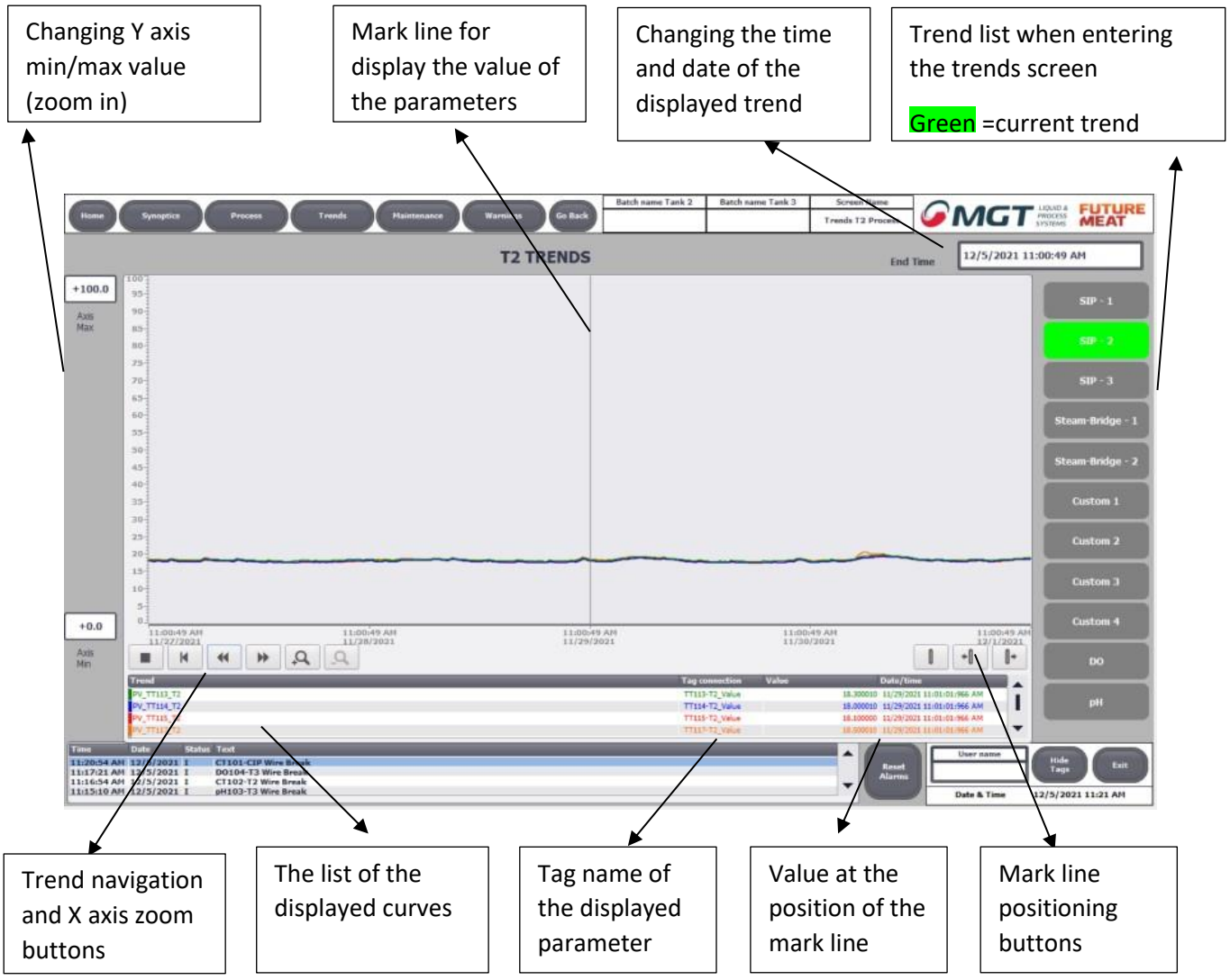
16. TRENDS

The are several predefine trends for monitoring the process and the control function of the system.

When navigate in the different screens, it is possible to enter a trend, whenever there is the “trend” icon, by clicking the “trend” icon.

In addition, there is a trend screen for each bio-reactor, entering the screens is from the main menu bar.

16.1.Trend screen operation



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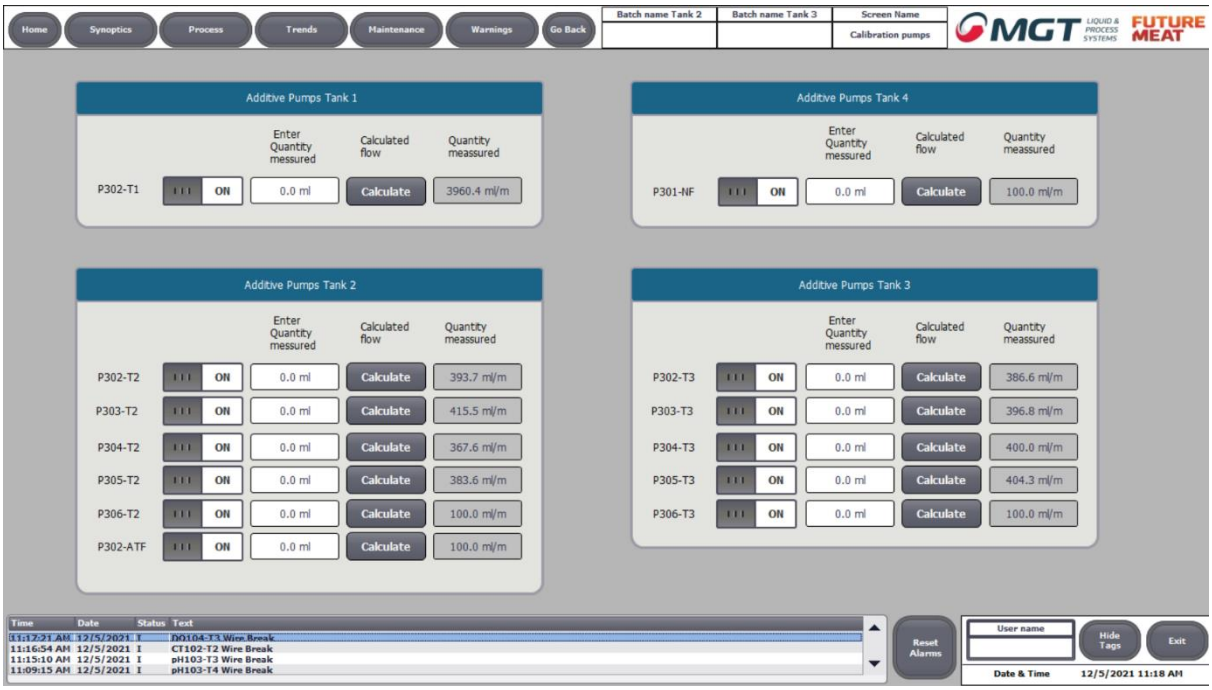
17. MAINTENANCE - CALIBRATIONS

17.1. Dosing pumps – Maintenance→ pumps calibration

For monitoring of the corrective material consumption, the dosing times of the pumps are totalized and used as process values. The control system converts the dosing times into delivered volumes considering the specific flowrates of the pumps. The dosing counters can be zeroed at any time via the pump operating screen.

The flowrates are calculated automatically during the calibration process from the measured running time and the entered delivery volume. The calibration of the dosing pumps is being done through the HMI operating program.

17.1.1. Calibration pump- operating screen



17.1.2. Calibration of a Pump – step by step:

❖ **Be aware:** For calibration always use tubing of the same type and dimensions as for the delivery of media during the process.

- Step 1: fill the tubing with water. For this you can manually activate the pump.
- Step 2: fill a measuring beaker with a certain volume of water
- Step 3: Place one end of the tubing into the beaker with the water and the other end into an empty measuring beaker.
- Step 4: Enter the value to the “enter quantity measured” tab.
- Step 5: Start the calibration process by sliding the ON/Off button.

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- Step 6: Stop the calibration process when the beaker is empty.
- Step 7: press the “calculate” button in order to complete the calibration of the pump.

The control system automatically calculates the flowrate considering the internally recorded running time and the measured volume.

17.2. Electrodes Calibration

All the electrodes can be calibrated through the ARC air application/software via Bluetooth connection.

Follow the ARC air operating manual for preforming the calibration.

17.3. Weight controller calibration

The tanks weighing system can be configured and recalibrated through the weight controller that is located in the main control cabinet.

Follow the supplier operating manual for preforming the calibration.

It is possible to “zeroing” the weight through the HMI program via the weight operation screen.

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18. MAINTENANCE – DATA EXPORT

18.1. Data exporting

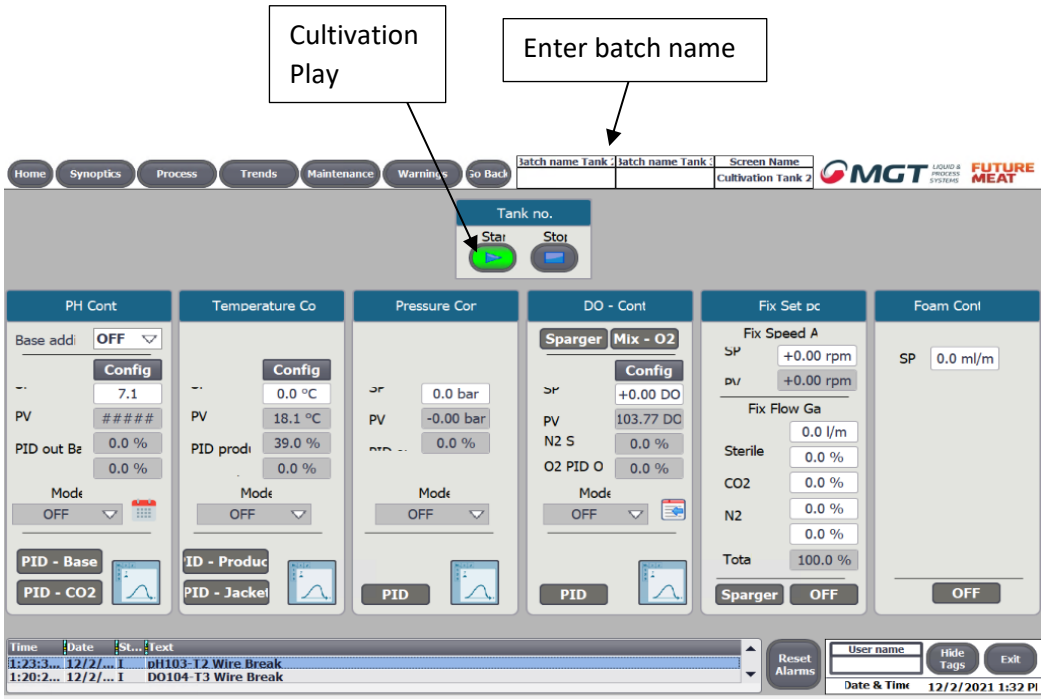
The process data is saved on the PC as a CSV file and can be copied to a USB flash drive.

There are two methods of logging the data of the system:

18.1.1. **History log files:** The data is saved during all the time. the files are being creating automatically according to their capacity. The files will be saved for 3 years, after 3 years the new files will overwrite the oldest file.

The history files are located in the history library in the PC. ["C:\History\Logs "]

18.1.2. **Batch Log files**: A batch log file include only batch relevant data (predefine) , which organized to be easily converted to graphical view in Excel.
The batch log file is being created when the operator is pressing the "Start" button in the cultivation screen, the file stop saving the data when the operator is pressing the "Stop" button in the cultivation screen.
For each Cultivation tank (T2 / T3) there is a separated log file.
In case the operator enter a batch name , the log file will have the same name.



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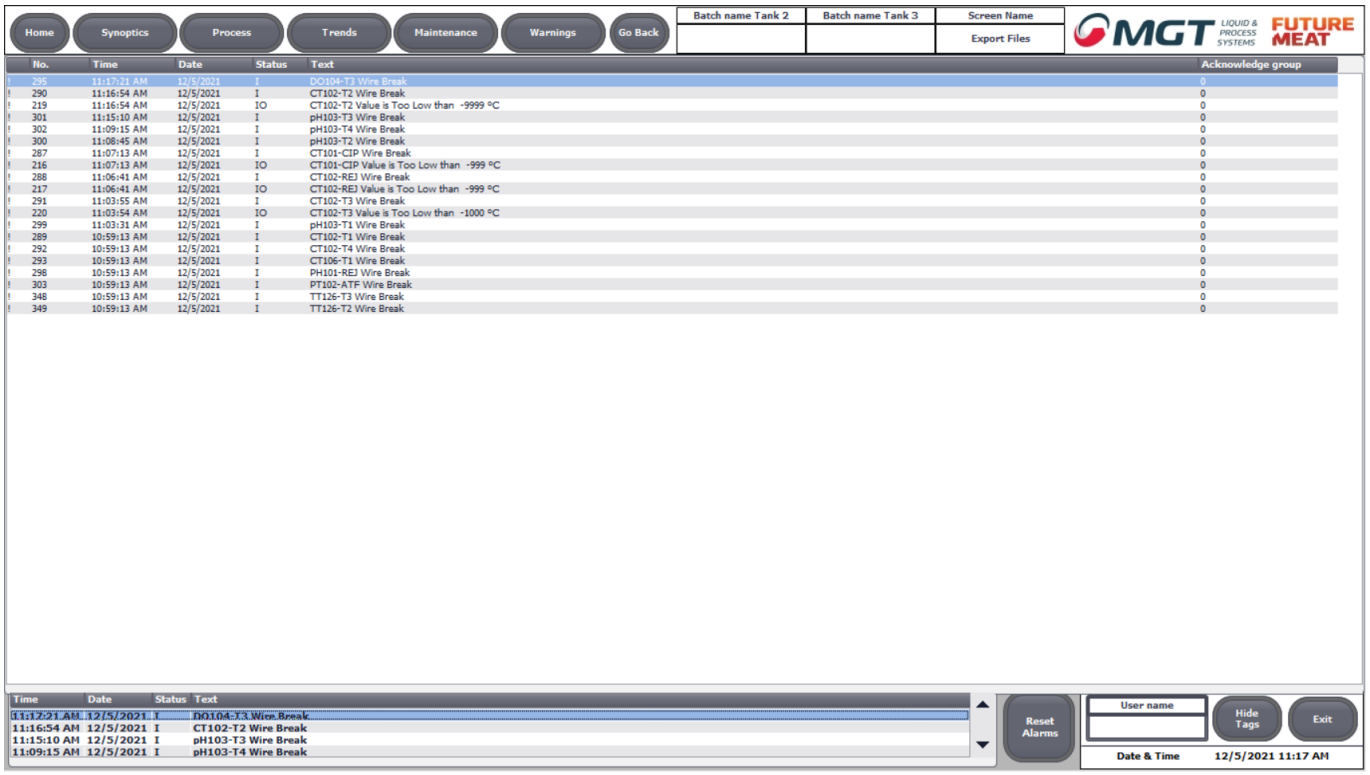
19. WARNINGS SCREEN

The warning screen design to store and monitor all the active warnings in the system.

The operator can see the time and date and the warning description.

Entering the warning screen is from the main menu bar.

In addition, there is a live warning list, located in the bottom of each screen. So the operator can be alert immediately even during other process operations.



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20. TROUBLESHOOT

20.1.CIP process - Warnings

Warning message	Meaning	Possible Cause
Device Fault	Motor fault	-electric fault
Heating taking too long	The heating process of one of the tanks takes more than 20 minutes.	-Steam supply low pressure -Steam valve fault -Circulation pump fault
Filling taking too long (for tank 1)	The filling process of tank no. 1 takes more than 5 minutes.	-no pressure in water feed line - water feed valve isn't open/partially open
Filling taking too long (all tanks)	The transferring process takes more than 5 minutes.	-Supply tank is empty -CIP pump fault - Valve fault
Conductivity taking too long	The conductivity doesn't reach the set-point after more than 5 minutes.	-No detergent/acid in the storage tank -Dosage pump or pipe fault
Flow taking too long	The CIP pump flow-rate doesn't reach the set-point after more than 5 minutes.	-CIP pump fault - Valve fault - Air enters the pipe/pump
Draining taking too long	The draining process to the tank empty tolerance weight is taking more than 5 min	- tank load cell fault -CIP pump fault - Valve fault

20.2.SIP process - Warnings

Warning message	Meaning	Possible Cause
Device Fault	Motor fault	-electric fault
Draining taking too long	The draining process to the tank empty tolerance weight is taking more than 5 min	- tank load cell fault -CIP pump fault - Valve fault
Heating taking too long	The heating process to sterilization process temp is taking more than 1 hour.	-Steam supply low pressure -Steam valve fault -Circulation pump fault

20.3.Pressure test – Warning

Warning message	Meaning	Possible Cause
Pressurizing taking too long	The pressurizing stage is taking too long (dp <=100 mbar/min)	- High-rate air leaking - Inlet Air pressure too low
Test taking too long	The test is taking more than 1 hour.	-general fault

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Heating taking too long	The heating process to sterilization process temp is taking more than 1 hour.	-Steam supply low pressure -Steam valve fault -Circulation pump fault

20.4.Cultivation Fed-Batch - Warnings

Warning message	Meaning	Possible Cause
Not in Cultivation mode	The process required to be in the cultivation mode for running	- The operation mode is not set correctly
Not enough media in tank 1	There is not enough media in tank 1 for feeding the bio-reactors	- Not enough media is prepared - Load cell fault - Feeding set point fault
Main cultivation state - Off	The process required the main cultivation process to be operate	- The "play" button in the cultivation screen is not active.

20.5.Weight control - Warnings

Warning message	Meaning	Possible Cause
Not in Prefusion mode	The process required to be in the "prefusion" mode for running	The operation mode is not set correctly
Not enough media in tank 1	There is not enough media in tank 1 for feeding the bio-reactors	- Not enough media is prepared - Load cell fault - Feeding set point fault
Main cultivation state - Off	The process required the main cultivation process to be operate	- The "play" button in the cultivation screen is not active.

20.6.Nano-Filtration -Warnings

Warning message	Meaning	Possible Cause
Cultivation mode	The process required to be in the "prefusion" mode for running	The operation mode is not set correctly or the process running in cultivation mode.
Warning – high pressure system 1	See NF system manual	See NF system manual
Warning – high pressure system 2	See NF system manual	See NF system manual
Warning – high pressure system 1&2	See NF system manual	See NF system manual
Warning – Pressure out of range PT102-ATF	The ATF filtrate pressure is out of range. Flow to T4 is not OK. Therefore, the NF process is in risk.	ATF filter is blocked

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21. MAINTENANCE & SERVICE INSTRUCTION

❖ **Be aware:** For detailed instruction of service and maintenance of specific equipment one should look in the specific equipment manual.
In the print version attachment, there are only the selected parts maintenance and

21.1. Recommended periodic general maintenance list

In order to ensure the proper operation of the system, we recommended to follow the instruction in the table below, as well as the detailed manufacturer instruction of each of the installed equipment.

Procedure	Description	Frequency
Checking for leakage from Piping and instruments	Visual inspection of the system	1/day
Checking the tanks surface condition	Visual inspection for corrosion or calcium precipitation Visual inspection of the surface cleanliness	1/week
Checking the valves operation	Checking that the valves are operated correctly. Check the pneumatic air pressure.	1/week
Checking the CIP cleaning agent piping condition	Visual inspection – replace piping if necessary	1/week
Steam filter cleaning	Open the filter house and clean the filter cartridge	1/month
Vent filter cleaning	Open the filter house and clean the filter cartridge	Prior to each cultivation running.
Instrumentation checking	- compare the sensors reading with lab sample - compare the pressure reading with the pressure gauge. - compare temperature sensors with calibrated sensor - check foam level indication is OK -	1/month
Pumps general checking	- Check visually for leakages - Check noise during operation - Check flow and pressure are according to the pump curve	1/month
Checking the double jacket water makeup operation	- Verify correct pressure - Check pressure reducing valve operation	1/month
Checking the agitator mechanical seal operation	- Check visually for leakages - Check abnormal noise during operation - Check the steam condenser: float switch, valves and pressure	1/month

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Agitators general checking	- Check for abnormal noise during operation - Check motor heat during operation	1/month
Checking the removable impellers condition	- Tight the screws of the removable impellers	1/3 month
Checking the rupture Disk condition	- Visually checking	1/3 month
Checking the Expansion tank condition	- Visually checking - Pressure checking	1/3 month
Checking the double jacket PRV operation	- Check operation manually by lifting the arm - Check the spring visually	1/3 month
Checking the steam traps operation	- visually checking - manually test the steam trap operation. - Verify no abnormal steam escaping during operation	1/3 month
preform general cleaning of the system	- Clean the tanks and the surrounding equipment with suitable cleaning material	1/6 month
Checking the control cabinet, HMI cabinet, and instrumentation electrical connections	- Clean with Air - Check for loos cables - Check for corrosion - Tight connection - Check earth connections in the system- tight if necessary	1/year

21.2. Bio-reactor cover lifting

When necessary, there is a need to open the bio-reactor cover for inspection of the inner parts and the flange O-ring. This is done by pneumatic lifting system which is installed on the bio-reactor.

1.1.1. Step by step instruction

- Precaution:
    - Chemical hazards.
    - Wear personal protective equipment during the process.
    - Heavy loads
- Check list before starting any production process:
    - ✓ Verify the system is clean.
    - ✓ Verify no pressure in the reactor (vent valve open)
    - ✓ Verify the reactor is not warm

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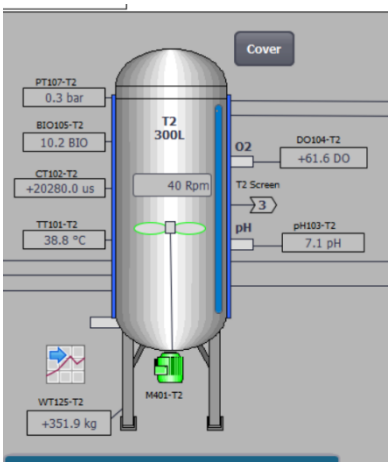
- Step 1: dismantle the CIP piping.
- Step 2: disconnect the foam probe and lift it out.
- Step 3: dismantle the vent condenser.
- Step 4: open all the flange bolts.
- Step 5: enter the synoptic menu → tank2/3 additives.
- Step 6: press the cover symbol.
- Step 7: In order to open the cover – use the manually lift handle located under the HMI display.
  It is a 3 positions operator: use it gently to lift the cover slowly and to replace it back in the position.
  - Upper position – cover go up.
  - Middle position – cover stop.
  - Down position – cover go down.
- Step 8: push the cover gently to remove it from the tank.



In order to close back the cover work according to the same steps but in the opposite order (start from step 8) below:

❖ **Ba aware:**

- on the cover and on the reactor flange there is a line mark, make sure the lines are in front of each other while the cover is close.
- Before closing the cover, check the O-ring condition and make sure it seats perfectly in his position.

Cover Lifting handle[T3]

Cover Lifting handle[T2]

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22. SUPPORT AND MORE INFORMATION

You can contact us for more information and assistance at:

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23. ATTACHMENTS LIST

- PROJECT DRAWINGS
  - P&ID Drawing
  - Layout Drawing
  - Electrical Drawings
- BIO-REACTORS PRESSURE TEST AND CERTIFICATES
- EQUIPMENT MANUALS
- QUALITY AND CALIBRATION CERTIFICATES

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