Biotech

Instructions for Use Part B: Software

USD3311

iCELLis® 500+ Bioreactor Control System

Part Number: ICL500CSSSIP

Filtration. Separation. Solution.SM

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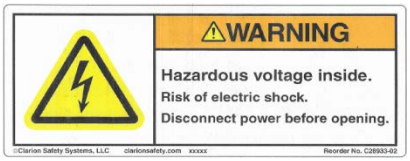
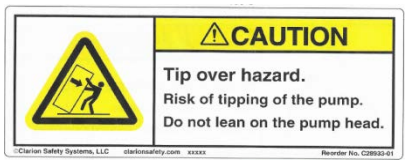
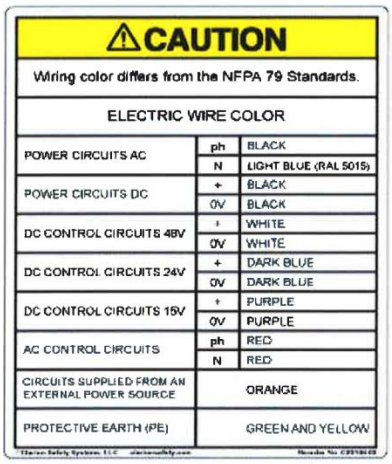
1. Warnings

1.1 Hazard Icons

The following icons are used in this Instruction for Use to point out hazards resulting from the utilization of the system described.

The documentation must be carefully reviewed where these icons are present.

	**General icon for DANGER, WARNING, CAUTION or ALERT** This symbol notifies general risk or specific procedures, which if not followed correctly, can result in injury of personnel or damage to equipment.
	**Electrical Shock WARNING icon** This symbol notifies a risk of electric shock.
	**Crush WARNING icon** This symbol notifies a risk of a crushing event.
	**Hot Surface WARNING and CAUTION icon** This symbol notifies a risk of burn or hot surface.
	**Magnetic field DANGER icon** This symbol notifies a risk linked to magnetic fields.
	**WARNING Risk of hand entanglement and crush** These symbols notify a risk of hand entanglement. Red icon is displayed on peristaltic pumps.
	**Information icon** This symbol is used to highlight useful information, and indicate that caution should be exercised while working on the system.
	**CAUTION Do not cover during operations** Safety pressure relief valve output. Do not cover during operations.
	**WARNING Hazardous voltage inside** Risk of electrical shock. Disconnect power before opening the doors.
	**CAUTION Tip over hazard** Risk of tipping of the high speed pumps. Do not lean on the pump head of the accessories.

	**CAUTION Surface may be hot inside.** Risk of burn. Allow to cool before opening the bag pre-heater.
	**CAUTION Strong magnetic field.** Interaction with metallic objects may produce Pinch Hazards. Persons with medical implants KEEP BACK 12 in. (30 cm) from the agitator shaft.
	**CAUTION wiring color differs from the NFPA 79 Standards.** The electric wire color used in the iCELLis 500+ control system is listed on the label and conformed to the IEC 60445.

1.2 Hazard Level

Hazard icons are used in combination with the following danger level indications:

DANGER!	Will lead to severe injuries or death
WARNING!	May lead to severe injuries or death
CAUTION!	May lead to light or moderate injuries
ALERT!	May lead to material damage
IMPORTANT!	May lead to inconsistency in system utilization

Hazard or information icons may be supplemented with specific description or instructions.

2. Software Warning Messages

	**IMPORTANT!** Utilization of iCELLis 500+ bioreactor software must be done only by authorized persons trained to operate the iCELLis 500+ bioreactor system.
	**IMPORTANT!** Modification of the iCELLis 500+ bioreactor software configuration settings should only be done by trained and experienced users with appropriate access level to the system.
	**ALERT!** Risk of damage to the process and/or data! When using an external keyboard or mouse make sure it is not laying on the bioreactor as it will impact the measurement of bioreactor weight by load cells and affect other loops cascaded to the weight.
	**ALERT!** Risk of damage to the process and/or equipment! Heating bioreactor with Temp. 1 or Temp. 2 for reference sensor, in empty and/or non-agitated bioreactor will result in local overheating of bioreactor shell and/or media and cells. The temperature control unit (TCU) should be used to preheat the double-jacket when the bioreactor is empty or when the agitation is stopped. Starting heating without agitation in bioreactor will trigger a warning message.
	**ALERT!** Risk of damage to data! Simulation mode allows changes to the state of sensors and actuators or simulating process values. This mode must never be used during a GMP batch to guarantee data authenticity. It is the responsibility of the user to ensure appropriate access level to simulation mode.
	**WARNING!** Risk injury to personnel! In simulation mode the iCELLis 500+ bioreactor system will still activate actuators placed under AUTO or MANUAL control based on control settings and process values. Make sure your simulation settings are compatible with equipment use. E.g. No operator interacting with the equipment, no tubing in peristaltic pumps, etc.
	**ALERT!** Risk of damage to process! Do not use CLEAN PULSE button during a process as this would damage cells below biomass probe.
	**ALERT!** Risk of damage to process! Note that setting the polestar module to SETUP mode interrupts all channels measurement (pH1, pH2, DO1 and DO2) and this will display the last value measured. Any on-going regulation will continue with the last received value.
	**ALERT!** Risk of damage to the process! It is recommended to calibrate DO prior to pH to get the most accurate DO reading. It is particularly the case for 2-points calibration procedure.
	**ALERT!** Risk of damage to process! Incorrect settings of control loops can result in inconsistent behavior of regulations and can impact process parameters. Factory settings for PID in the iCELLis 500+ bioreactor have been developed to cover standard applications. PID settings can be optimized for a specific application, however it will require strong theoretical knowledge of control loop regulation and time-consuming experimental testing with iCELLis 500+ bioreactor system before finding stable and optimized parameters. Control loops settings modification is the user's responsibility.
	**WARNING!** Risk of injury to personnel and/or damage to equipment! TCU pump stage has direct impact on pressure in the double-jacket. Special care must be taken when modifying this parameter.
	**ALERT!** Risk of damage to process! Incorrect settings in MAINTENANCE menu will lead to inconsistent behavior of hardware elements and could impact process. Hardware settings must be changed only by trained persons using reliable reference sensors.

	**ALERT!** Risk of damage to the equipment/process! Even though the alarms can be manually suppressed, failure to observe an alarm message could result in damage to the device.
	**ALERT!** Risk of damage to equipment/data! Incompatibility between user's knowledge and granted access level may lead to incorrect use of the equipment and potential corruption of equipment settings or recorded data. It is the responsibility of the user to grant access levels to user in accordance with their training and role.
	**ALERT!** Risk of damage to equipment/data! Polestar USB key should be in shutdown mode and ejected before shutting down the PC. Shutting down the PC without ejecting Polestar USB key may cause corruption of the USB key.
	**ALERT!** Risk of damage to data! SHUTDOWN PC and RESTART PC commands will interrupt data recording by the iCELLis 500+ bioreactor Control System and could affect data authenticity in the frame of GMP batch record.
	**ALERT!** Risk of damage to the process! Do not change the HMI screen while the calibration of any Polestar sensor is ongoing. There is a risk that the calibration could not be finished. Wait until the success message for the Polestar calibration appears. If the HMI screen is changed during calibration, then the calibration must be performed again.

3. Preliminary Remarks

This Instructions for Use manual is intended to describe and explain the iCELLis 500+ bioreactor software functions in standard configuration and general operating conditions.

The figures, illustrations, parameters values and settings shown in this document are only examples and should not be used for a given application. Exact settings are provided through configuration documents or should be obtained empirically for a specific application.

IMPORTANT!
Utilization of the iCELLis 500+ bioreactor software must only be performed by authorized persons trained to operate the iCELLis 500+ bioreactor system operation.

The iCELLis 500+ bioreactor system and software factory settings have been optimized for most operating conditions. However, users may want to modify or optimize system configuration for a specific application or environment and this user manual describes configuration parameters accessible to end users.

IMPORTANT!
Modification of iCELLis 500+ bioreactor software configuration settings should only be done by trained and experienced users with appropriate access level to the system.

All the passwords available for the customers are listed in a different document provided by Pall. This document is the passwords list.

All the information regarding the backup and restoring of the system can be obtained in the ‘Disaster Recovery Plan’ document, which can be obtained by contacting Pall.

The entire software was validated using a risk based analysis attending the GAMP 5 guidelines. In case of an update of the developed software, a new software validation of the impacted systems will be performed, based on a risk analysis, according to the GAMP 5 guidelines.
The software validation is not provided by Pall to the customers. If required by the customer, a meeting can be arranged, where the original software validation documents can be presented.

This Instruction for Use has been released for the iCELLis 500+ bioreactor software version 1.03 and following versions.

4. Introduction to the iCELLis 500+ Bioreactor Control System

4.1 Structure of the iCELLis 500+ Bioreactor Control System

The iCELLis 500+ bioreactor control system is composed of the hardware, or equipment part, and an industrial computer running with Windows♦ 10 operating system (OS). The hardware includes sensors monitoring process values (PV), actuators such as peristaltic pumps, mass flow Control Systems (MFC), stirrer, heaters and the Programmable Logic Control System (PLC). The PLC contains an operating program which integrates PVs to calculate actuators state and outputs (ON/OFF, open/close, speed, …) to control the process. The industrial computer hosts the iCELLis 500+ software. Its functions can be divided in 3 modules:

- The Human Machine Interface (HMI) displays process data and equipment parameters on a touchscreen and allows interactions between users and the supervisory control module. It also allows creation of reports based on database content;
- The supervisory control module allows control of the PLC at different levels: manual control of actuators, automatic control through pre-programmed regulation loops and their parameters or complete automated control sequence through a recipe;
- The data acquisition system archives process data, equipment parameters, actions performed by users through the HMI and instructions sent by supervisory control module to the PLC through the process to store them in a secured SQL database for further reporting.

The iCELLis 500+ software is thus both a HMI and a Supervisory Control and Data Acquisition (SCADA) software, specifically designed for the iCELLis 500+ bioreactor control system.

Relationships between these components and the rest of the environment are schematically described in Figure 1.

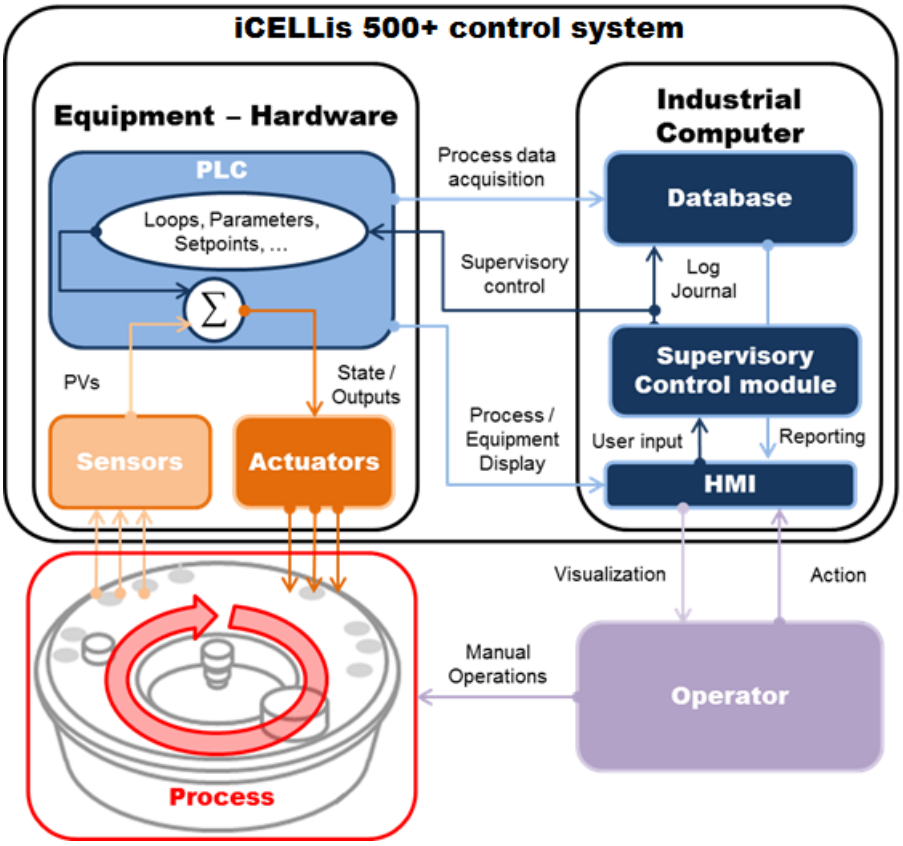


Figure 1: Relationship between process, iCELLis 500+ bioreactor control system hardware, software and operator

4.2 Compatibility with Guidance for Electronic Records and Signatures

Users of the iCELLis 500+ bioreactor system subjected to current GMP may choose to record and maintain iCELLis 500+ process information electronically. In this case their computerized systems must comply with guidelines such as 21 CFR Part 11 in US, or EudraLex vol. 4, Annex 11, in Europe.

The iCELLis 500+ bioreactor system has been designed to be compatible with requirements of these guidelines by:

- Allowing system access to authorized individuals only by use of electronic signatures;
- Recording all process relevant information and audit trail in batch records;
- Insuring data authenticity by use of operational system checks and device checks.

The electronic specifications of the iCELLis 500+ software alone cannot constitute a data management system. It is the user's responsibility to integrate the iCELLis system into their own data management system, to configure signature policy, batch record content etc. and to submit it for validation by the required authorities.

5. iCELLis 500+ Bioreactor Software Overview and Operation Principles

5.1 Screen Layout, Status and Navigation

5.1.1 General Layout

The HMI screen layout is composed of 3 main layers (Figure 2): HEADER, WORKING AREA and FOOTER. The HEADER displays general information about the equipment and process. The FOOTER is dedicated to navigation and is only accessible when a valid user is logged into the system. The WORKING AREA populates depending on the menu item selected. When applicable, the WORKING AREA displays TAB selection and PAGE selection buttons to navigate within a menu (Figure 2). These areas will be described in the following sections.

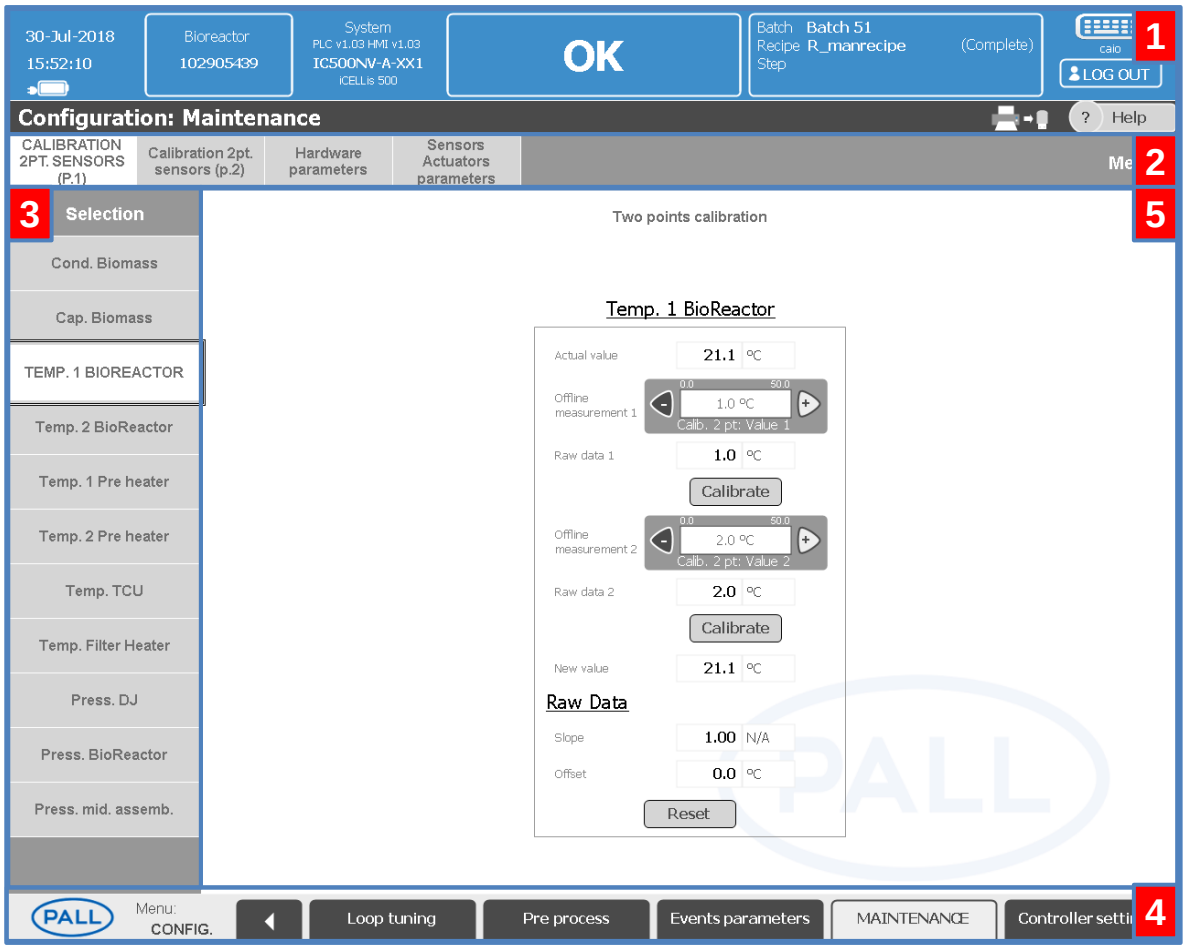


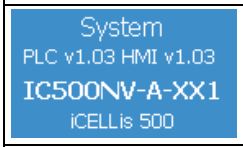
Figure 2: General screen layout – 1) HEADER, 2) TAB selection pane (if applicable), 3) PAGE selection pane (if applicable), 4) FOOTER, 5) WORKING AREA.

5.1.2 HEADER and System Status

The HEADER is composed of 2 ribbons. The top ribbon displays the following from left to right (Table 1):

- System information: Date and Time, Bioreactor Name, System ID and software version;
- System and process status, shortcut to active Event;
- Batch and Recipe information, shortcut to Recipe: Execution Screen;
- KEYBOARD button, current User logged, LOG IN/OUT button.

Table 1: HEADER icons and keys descriptions

Icon	Name – Function
	*DATE AND TIME* Date and time are synchronized with computer's date and time. *BATTERY PACK icon* This icon indicates the status of the safety battery pack of the computer allowing correct PC shutdown in case of power failure.
	*BATCH INFORMATION button* Allows input of user-defined batch information. Refer to Section 12.1 Editing Run Information for more information.
	*SYSTEM VERSION and SYSTEM NAME*PLC and HMI software versions currently installed on the equipment and computer name of the industrial PC present inside the iCELLis 500+ machine.
	*STATUS button* When status is different from OK, shortcut to corresponding events page.
	*RECIPE SUMMARY button* Shortcut to Recipe: Execution menu.
	*KEYBOARD button* Calls screen keyboard. Not visible when keyboard is displayed.
	*LOGIN button* Allows Login IN or OUT and displays currently logged user name above button.
	*MENU bar* Indicates the current WORKING AREA being displayed
	*PRINT button* Generates a print screen of the current active screen. Print screen is saved as a PNG file on the hard drive (top icon) or on USB external storage device (bottom icon).
	*HELP button* Calls the Help menu where the system manual and other helpful documents can be found.

The iCELLis 500+ software automatically detects the connection of storage devices to the computer's USB port and selects it for further file saving (print screens or Recipe file export). MAKE SURE NO EXTERNAL STORAGE DEVICES ARE CONNECTED TO THE SYSTEM DURING STARTUP.
Do not forget to unplug storage devices when not in use.

The top ribbon displays 5 different states depending on ongoing-process and equipment status: OK (Blue), INTERLOCK (Red), ALARM (Red), HARDWARE (Orange) and WARNING (Orange). The display priority of the status is as follows:

INTERLOCK > ALARM > HARDWARE > WARNING > OK

When the system status is different from OK, the status message becomes a shortcut for the corresponding Event page. Events and Alarms are detailed in Section 13: EVENTS: Alarms and Journal.

The bottom ribbon does not change with state and displays the following from left to right:

- The pathway and name of the current WORKING AREA;
- PRINT button;
- HELP button.

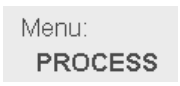
5.1.3 FOOTER and Navigation in The Menus

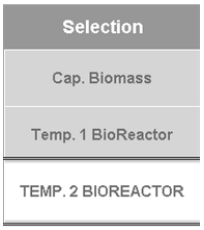
The FOOTER layer is dedicated to the navigation of the software menu tabs. It displays the following from left to right:

- Pall logo, service button, allowing verification of system connections status;
- Parent menu of current navigation location;
- BACK arrow button;
- MENU NAVIGATION buttons.

Additional navigation keys can be displayed in the WORKING AREA to display more pages or separate tags. These keys are detailed in Table 2 together with FOOTER keys.

Table 2: FOOTER and additional navigation keys description

Icon	Name – Function
FOOTER	
	*PLC and ESD STATUS indicator* Left side of logo: PLC connection status. Opens PLC connection status box. Right side of logo: Critical interlock ESD status. Opens Interlock ESD status box. Refer to section 13.2.4 for further information on PLC connection status and ESD status popup.
	*CURRENT PARENT MENU* The previous menu tab.
	*BACK button* Allows going back to the previous menu tab.
	*MENU NAVIGATION buttons* Allows navigating within menu tabs.

WORKING AREA Additional navigation keys	
	*TAB buttons* Allows navigating from tab to tab within a menu or submenu.
	*PAGE buttons* Allows navigating from page to page within a tab of a menu or submenu.

Fonts and background of navigation keys change when selected:

- MENU NAVIGATION buttons
  - Selected: Black upper case fonts, light grey background.
  - Non-selected: White lower case fonts, dark grey background.
- TAB and PAGE buttons
  - Selected: Dark grey upper case fonts, white background.
  - Non-selected: Dark grey lower case fonts, grey background.

From the HMI, user can access the following menus:

- HOME menu, displaying the summary of sensors
- PROCESS menu, dedicated to operations of the equipment during a run;
- RECIPE menu, dedicated to the creation, validation and execution of recipes;
- CONFIGURATION menu, dedicated to equipment settings;
- BATCHDATA menu, dedicated to the creation of batch reports;
- EVENTS menu, dedicated to the management of alarms and other events.

Menus can contain submenus that are displayed in the FOOTER during navigation. When the browsing reaches a branch with no more submenus it toggles the WORKING AREA. Navigation can continue through pages and tab selection. The menu hierarchy from the HMI interface to different submenus is highlighted in Figure 3.

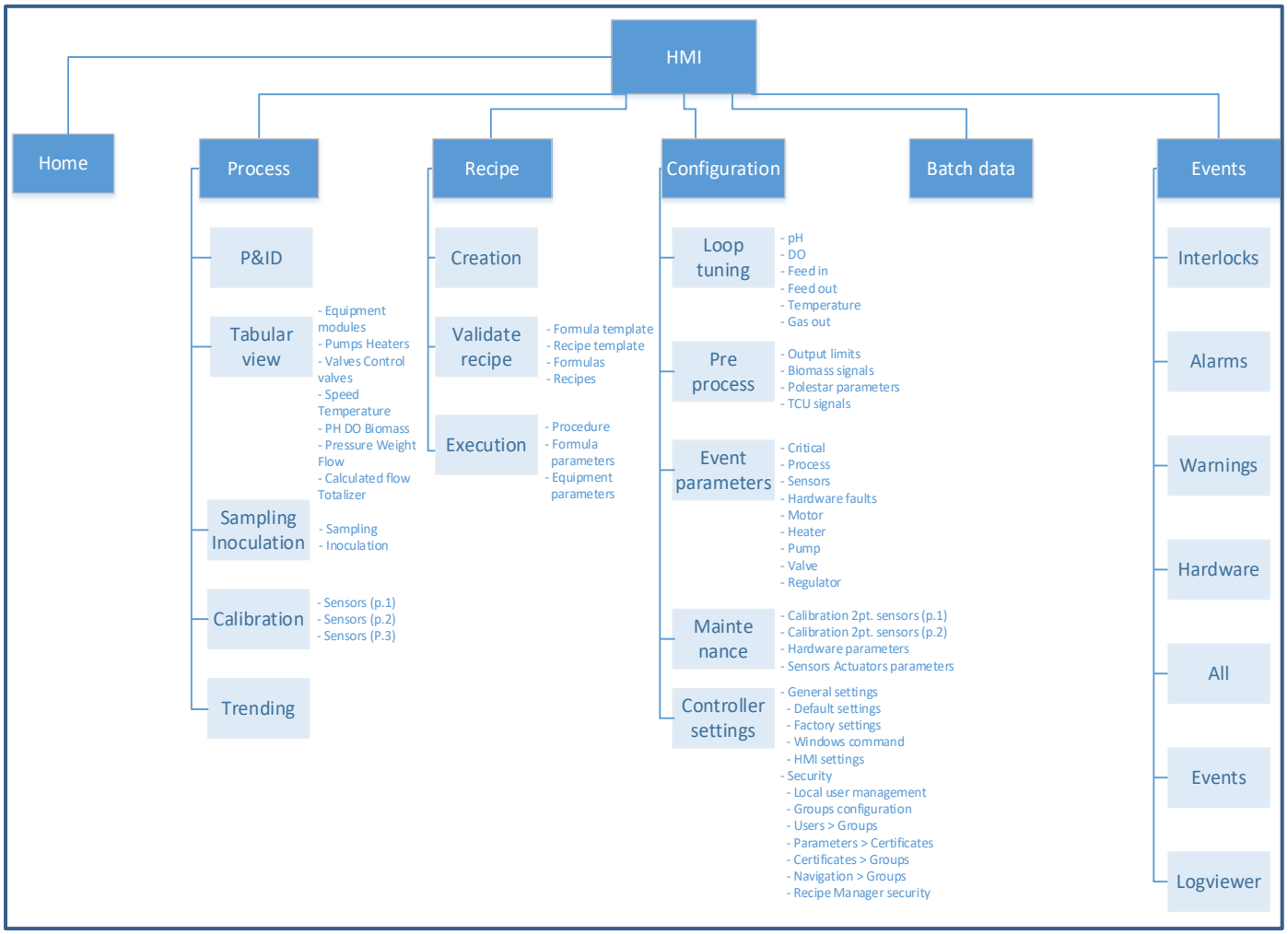


Figure 3: Tree view of menu and submenus in the iCELLis 500+ bioreactor software

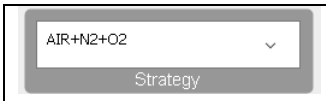
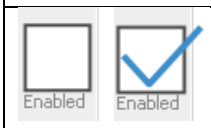
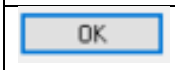
The permanent shortcuts contained in the HEADER and pointing to Events pages and Recipe menus (see Table 1) are not shown in this tree view.

5.2 Selection Keys and Keyboards

The WORKING AREA layer displays several functional elements requiring selection keys for value/state selection, numerical input, confirmation and actions. These keys are standardized across menus and are detailed in Table 3.

Table 3: Selection keys overview

Icon	Name - Function
Standby (OFF) STANDBY (ON)	*Action buttons* Used for single step action, application of settings, confirmation of value, state reset … Button state will be either OFF or ON.
Start / STOP No Access / Access	*Dual toggles button* In these examples 'STOP' and 'Access' states are selected.
NO ACCESS | ACCESS | SINGLE SIGN | DUAL SIGN	*Multiple toggles button* In this example 'ACCESS' is the selected state.

	*Dropdown list selection key* Select the white field to roll out selection list and select desired value.
	*Numerical set-point box* Value with units (N/A if no unit). Value can be changed by using '-' and '+' buttons (last digit single step) or by selecting the white field and entering the value using the screen numerical keypad or external USB-plugged keyboard. The authorized MIN and MAX values are indicated on both sides above the input box.
	*Check boxes* Used to enable alarms thresholds. Disable state is unchecked (left icon) and enabled state is checked (right icon).
	*Windows OS confirmation keys* Used for actions related to system security e.g. signature verifications.

Selection keys change when activated:

- Selected, active: white upper case fonts, dark grey background.
- Non-selected, inactive: dark lower case fonts, light grey background.

Some actions require the use of a keyboard, such as entering names and password of signatures and introducing comments. The touchscreen keyboard appears on screen when the field to be completed is selected (Figure 4A). The keyboard can also be called with the Keyboard button in the HEADER. Optionally users can connect an external keyboard through the USB port.

Similarly, numerical set-point boxes automatically pop-up a numerical keypad on the screen when selected (Figure 4B).

A) B)

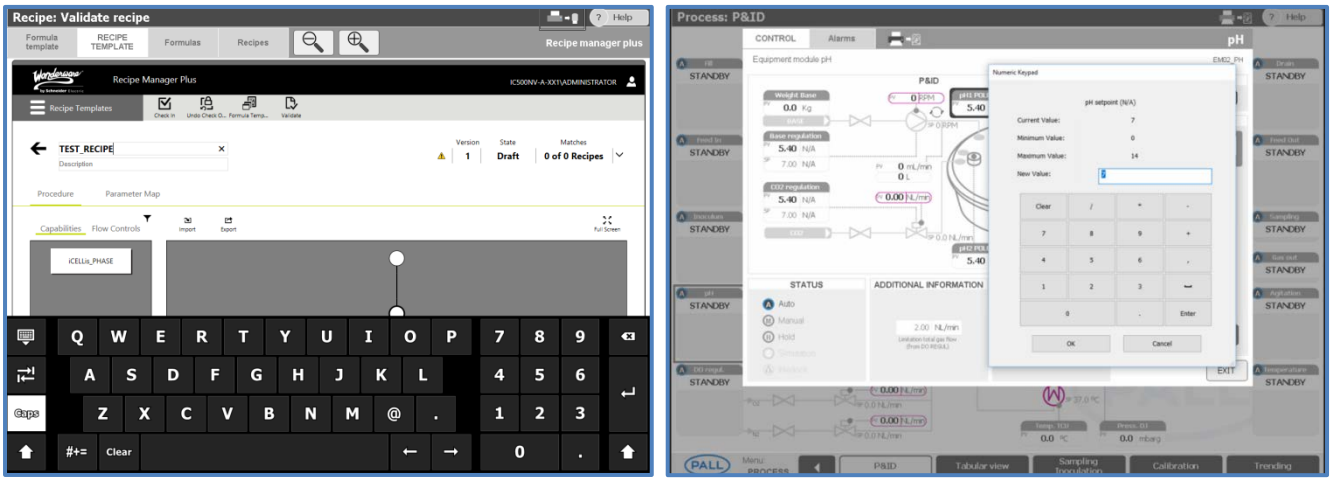


Figure 4: Touchscreen keyboard and numerical keypad on screen – A) Keyboard on recipe menu screen, B) Numerical keypad after selection of a set-point in an EM dialog box.

ALERT!
When using an external keyboard or mouse make sure it is not laying on the bioreactor as it will impact the measurement of bioreactor weight by load cells and affect other loops cascaded to the weight.

With a touchscreen keyboard, external keyboard or touchscreen numerical keypad, make sure you confirm your entry by pressing ENTER before any other action or your entry will not be validated.

5.3 Start-Up of the System and Login

When switching ON the iCELLis 500+ bioreactor control system the computer automatically starts, initiates Windows OS and loads the iCELLis 500+ software in full screen mode (Figure 5).

If an interlock or an alarm is active at system startup, the system directly goes to the corresponding mode and alarm horn can sound. Go to the Events menu to acknowledge the horn and stop sound.

If the computer is ON but the iCELLis 500+ bioreactor HMI is closed, it can be started by selecting the WindowViewer icon in the Windows bar. Please note that the software should boot up automatically during power up. If it does not, wait 5 minutes and then contact the system administrator/expert.

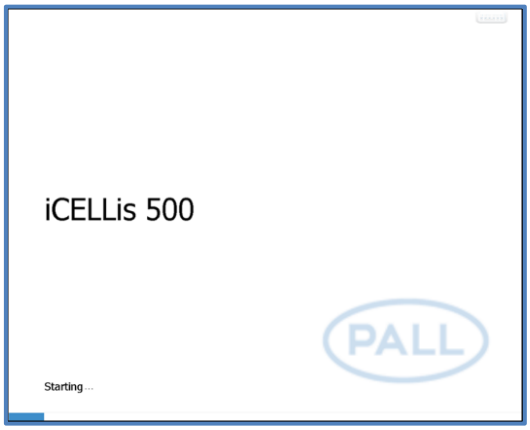


Figure 5: iCELLis 500+ bioreactor software loading screen

The software will then display the HOME screen.

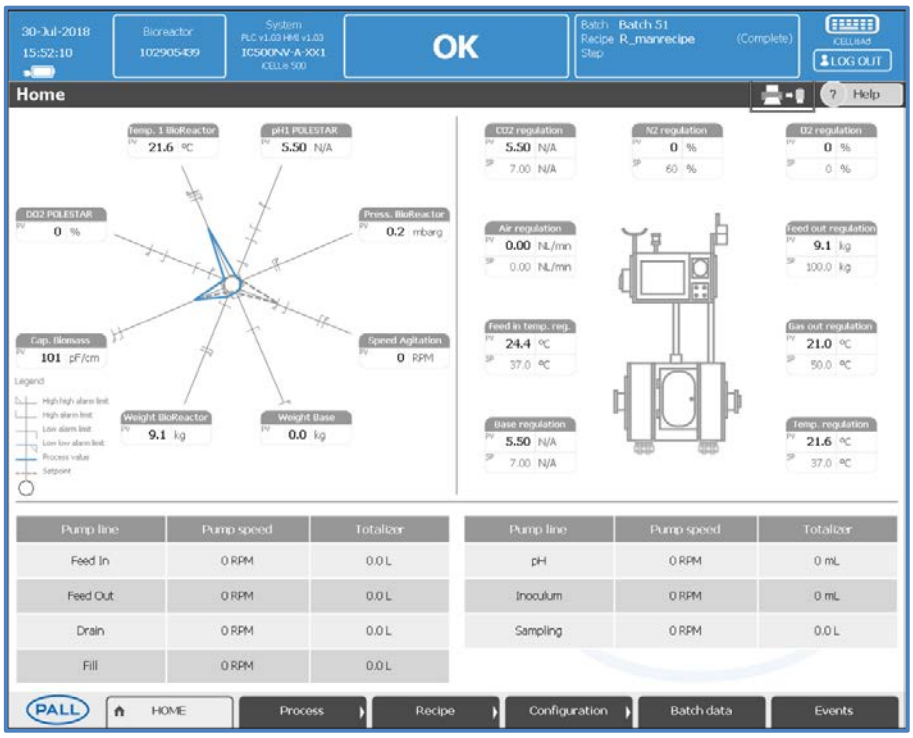


Figure 6: HOME screen at equipment start-up (after successful login)

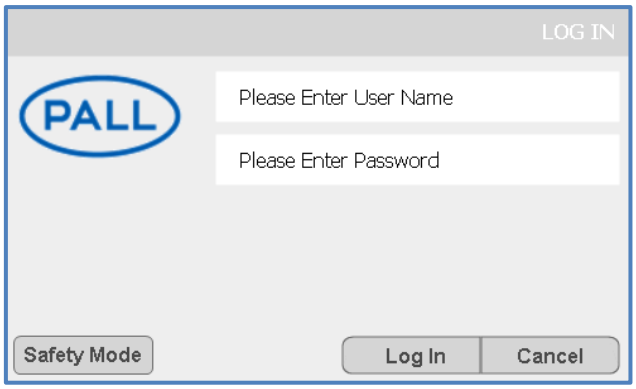


Figure 7: LOG IN dialog box

After the iCELLis 500+ touch screen has been inactive for a certain period of time, it will display the Home screen and there will be no navigation buttons available on the footer, until a user has logged in. Only the LOG IN button will be active on the screen.

Use the LOG IN button in the HEADER to open the Login dialog box (Figure 7). Enter the User Name and Password in the designated fields then select the LOG IN button to confirm or CANCEL to exit the Log in. The SAFETY MODE button directs User to a password reset window if the password has expired.

User Name and Password can be obtained and setup by your system administrator. When a user is logging in for first time, the user will be asked to change their password. For more details about user management, refer to Section 14 Security, Users and Groups Management.

By default, automatic log out occurs after 10 min without action on the touchscreen. This delay can be modified in the General Settings in the Control System Settings menu detailed in Section 15.

6. Process Visualization

6.1 HOME Screen

The HOME screen (Figure 8) is displayed at system start-up, when a user is logged out or when accessed at the root of the navigation tree via the Home button. After successfully logging in, a user will see the navigation menu in the footer.

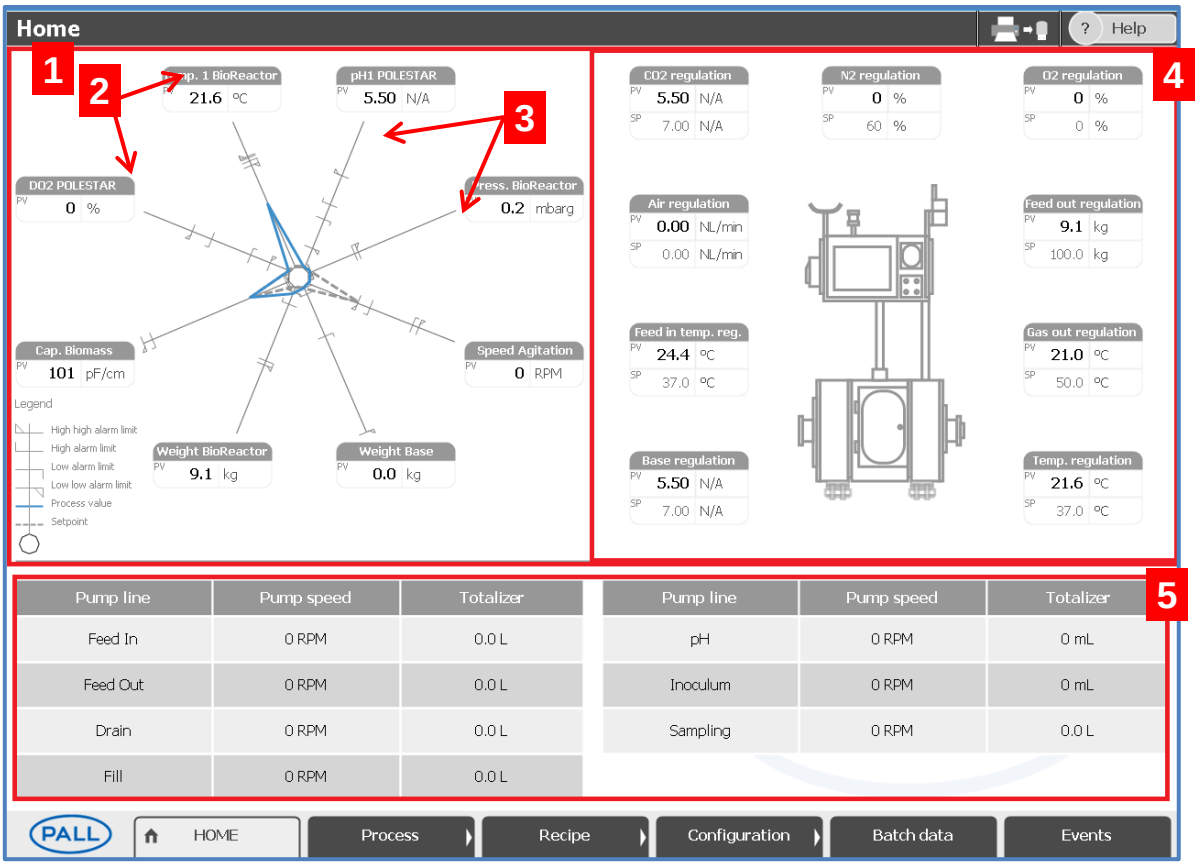


Figure 8: Home screen – 1) Culture main parameters radar chart, 2) Culture parameter sensor boxes with PVs and units, 3) Display axis with PV (blue), SP (dash grey) and alarm limits (see legend), 4) Regulation control loops status, 5) Pumps status table.

The HOME screen gives a quick overview of the main culture parameters in the form of a radar chart displaying PV and SP for these parameters (Figure 8-1). If multiple sensors are available for a given parameter, the graph displays only the one selected for regulation. The HOME screen also displays the control loops status (Figure 8-2) and pumps status in the form of a table (Figure 8-5).

Elements displayed on the HOME screen are not shortcut to other menus or submenus.

Note that Alarms are visible on the HOME screen with colored frame around the parameter box causing the alarm. For more information about alarms visualization refer to Section 13.1

6.2 TABULAR VIEW Screen

Navigate to PROCESS: TABULAR VIEW and continue navigation with TAB buttons at the top of the screen (Figure 9). This menu allows quick visualization of the iCELLis 500+ bioreactor control system elements through tables grouped in pages by element types:

- Equipment modules: shows selected strategies, set points, Process values, etc.
- Pumps Heaters: shows information about status of pumps and heaters actuators
- Valves Control valves: shows information about status of safety valves and MFC actuators
- Speed Temperature: shows the motor speed and pumps as well as the process values of the temperature sensors
- pH DO Biomass: shows process values of pH, DO and Biomass sensors
- Pressure Weight Flow: shows process values for pressure/weight sensors & flow measurement of gases
- Calculated Flow Totalizer: shows totalizer values for inlet/outlet pumps

Like the HOME screen, elements displayed in this menu are not active and do not allow any action. The main purpose of tabular view is to have all process related parameters easily available at one place.

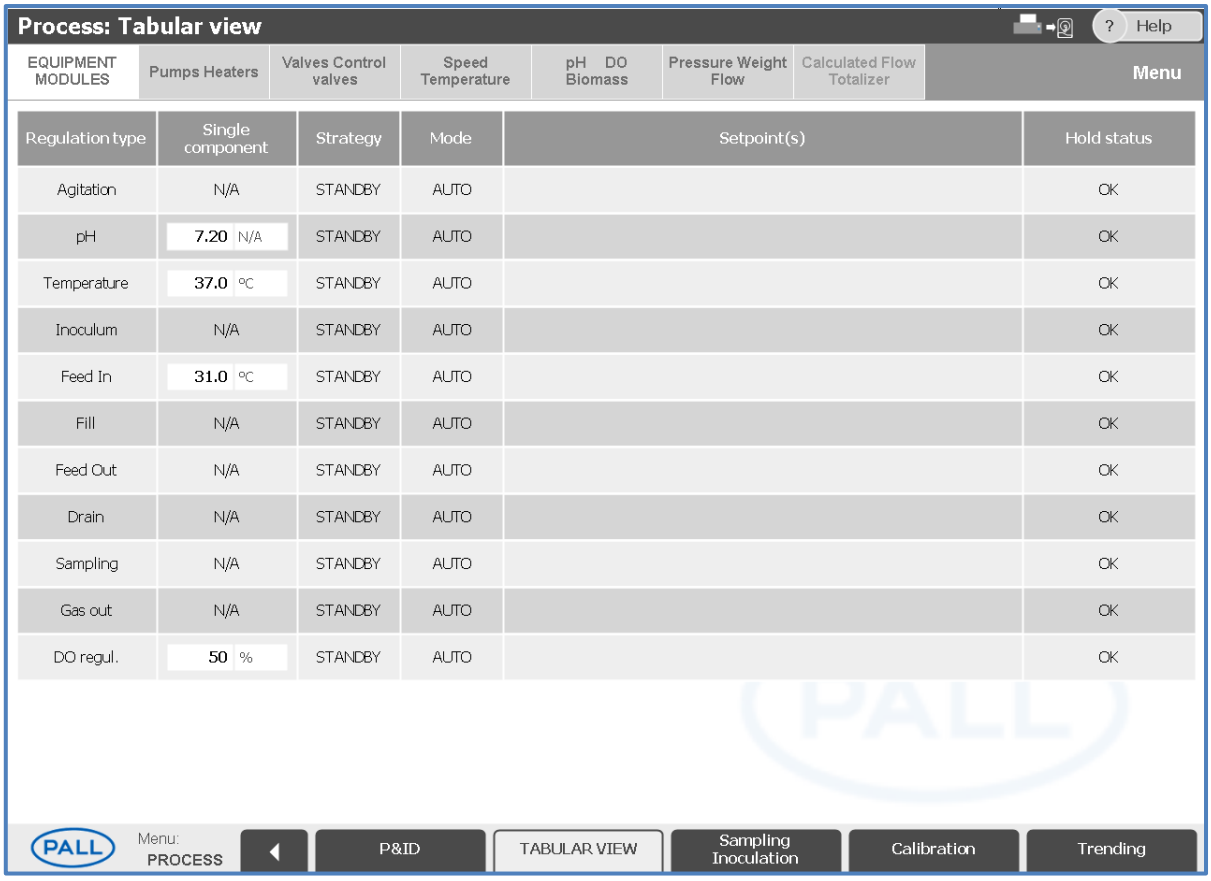


Figure 9: Tabular view screen, equipment Modules tab

6.3 Trends

Trending screens offer the possibility to visualize the trends of recorded values of system parameters. Two trending screens are accessible in the system:

1. TRENDING screen allows selection and display configuration of several parameters
2. SENSOR TREND is a time-fixed trend for a single sensor reached by selecting the sensor to open the Sensor Configuration (a quick trend).

6.3.1 TRENDING Screen

Navigate to PROCESS: TRENDING. The graph displays time on the x-axis and selected parameters on the y-axis (Figure 10).

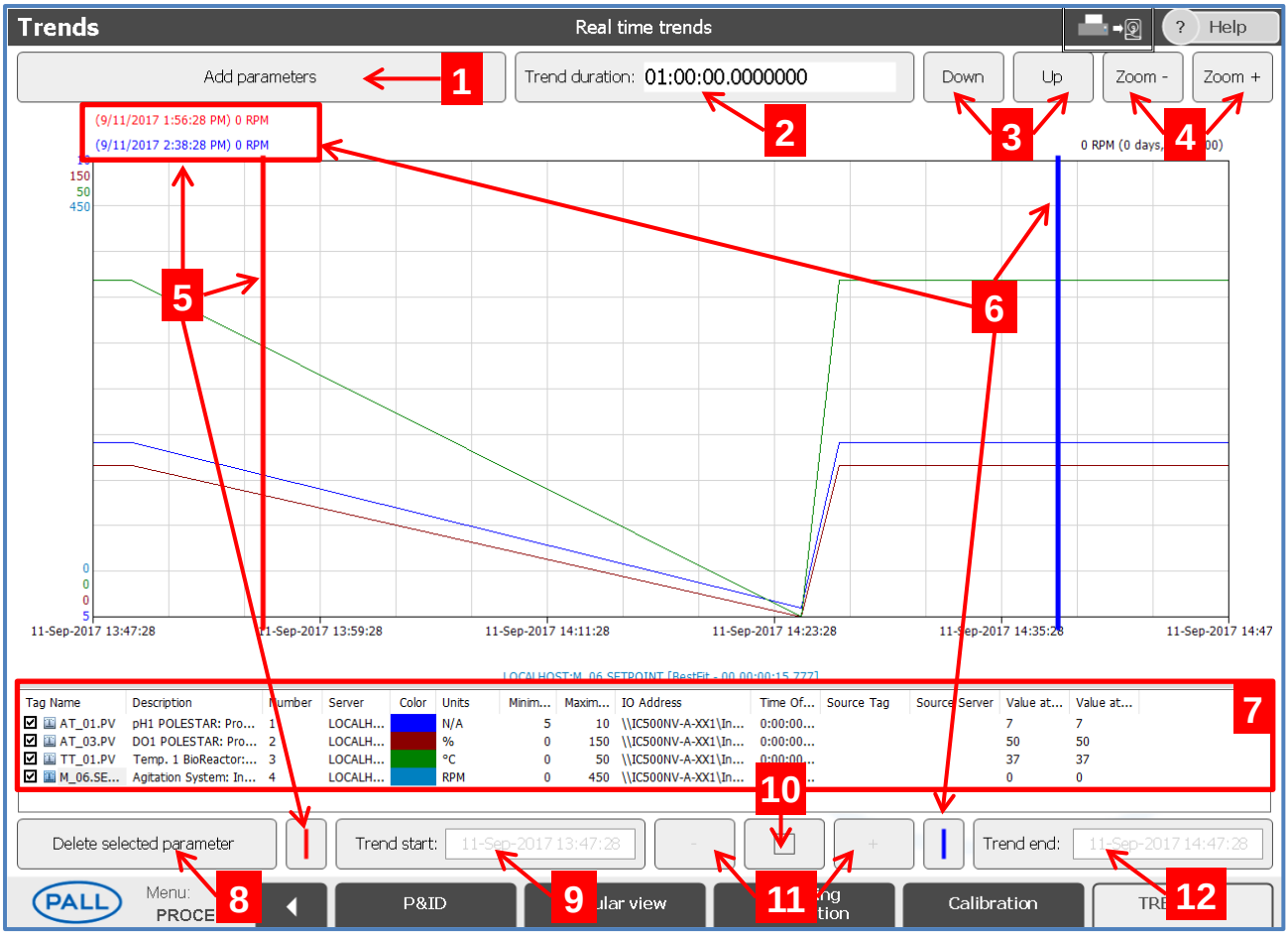


Figure 10: TRENDING screen and main functions – 1) ADD PARAMETER button, 2) Trend duration time selection, 3) Up and Down buttons sliding graph on y-axis, 4) Zoom In or Out on y-axis, 5) X1 axis (red bar), value (red text) and position button, 6) X2 axis (blue bar), value (blue text) and position button, 7) List of displayed parameters (with X1 and X2 values at right end), 8) DELETE PARAMETER from trending button, 9) Trend Start time direct setting, 10) Shift between static and live time axis, 11) Change time (backward or forward) on time axis (horizontal), 12) Trend End time direct setting.

A live trend can be viewed by selecting the PLAY button (Figure 10-10). In live-time mode a user can modify the time axis by selecting a duration between 30 minutes and 2 weeks (Figure 10-2). By selecting the stop button, the trend will enter static-time mode where it is possible to set the time axis to ant time range with TREND START/END and +/- buttons (Figure 10-9/11/12).

Displayed parameters are visible in a list below trending area (Figure 10-7). User can add or remove a system parameter using the ‘Add parameters’ button (Figure 10-1). The parameter selection dialog box will open (Figure 11).

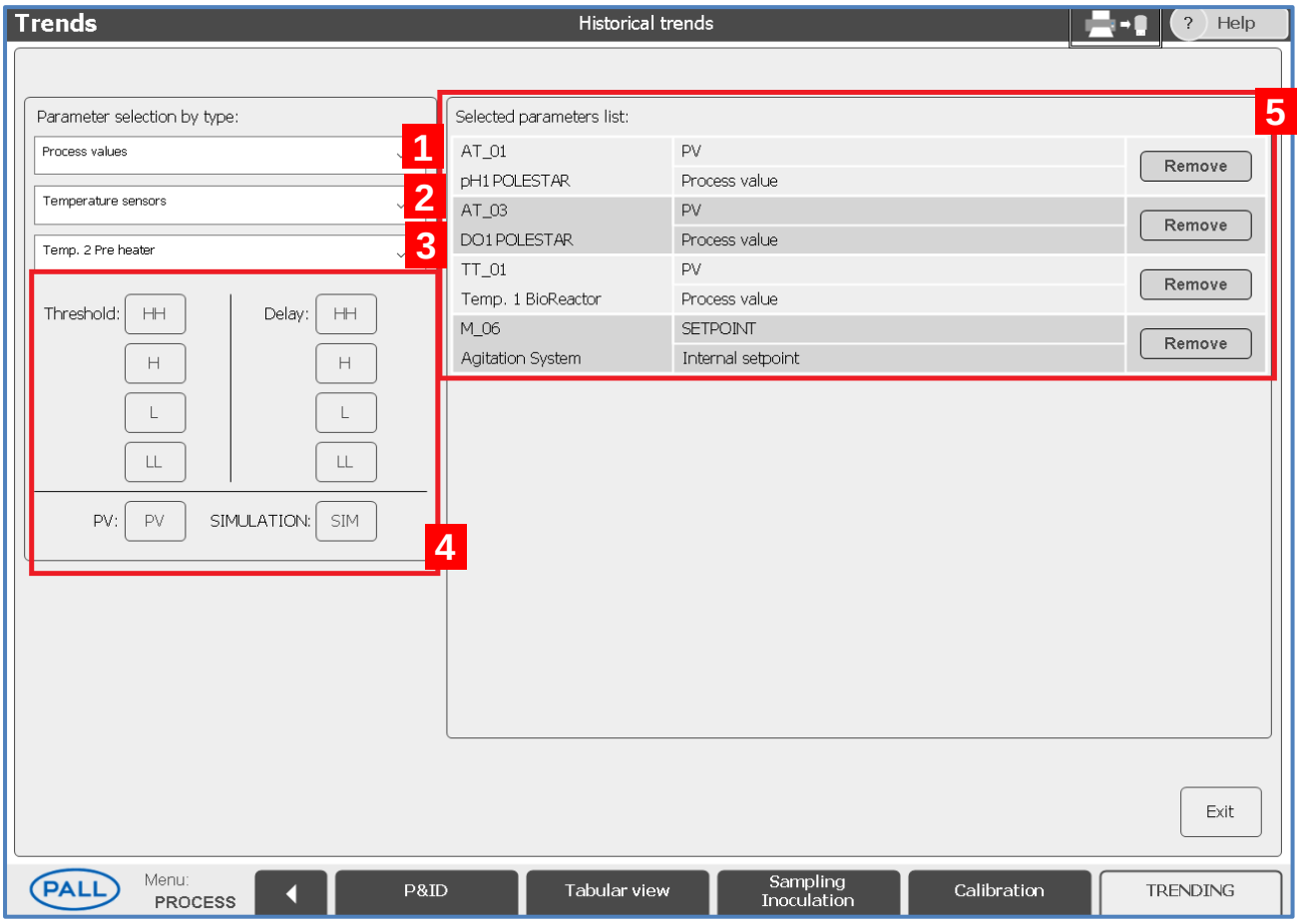


Figure 11: Parameter selection dialog box – 1) Parameter type, 2) Parameter family, 3) Parameter component, 4) Parameter data type, 5) Selected parameter list with REMOVE button.

Parameters are sorted by Parameter type > Parameter family > Parameter component. Once the parameter component has been defined, the user must select one data type among the refined list proposed and the parameter data is automatically added to the SELECTED PARAMETERS list (Figure 11-5) and to the trend view. The SELECTED PARAMETERS list provides a quick description of each parameter. The REMOVE button allows deletion of a parameter from the list and trend view.

6.3.2 Sensors Trends in Sensor Configuration Box

From the P&ID screen or within the EM dialog box, selecting a sensor box opens the Sensor Configuration box (Figure 12). This box displays a trend of the sensor process value for the last 5 hours. When enabled, alarms thresholds will also be displayed on the graph. The X and Y axes cannot be changed.

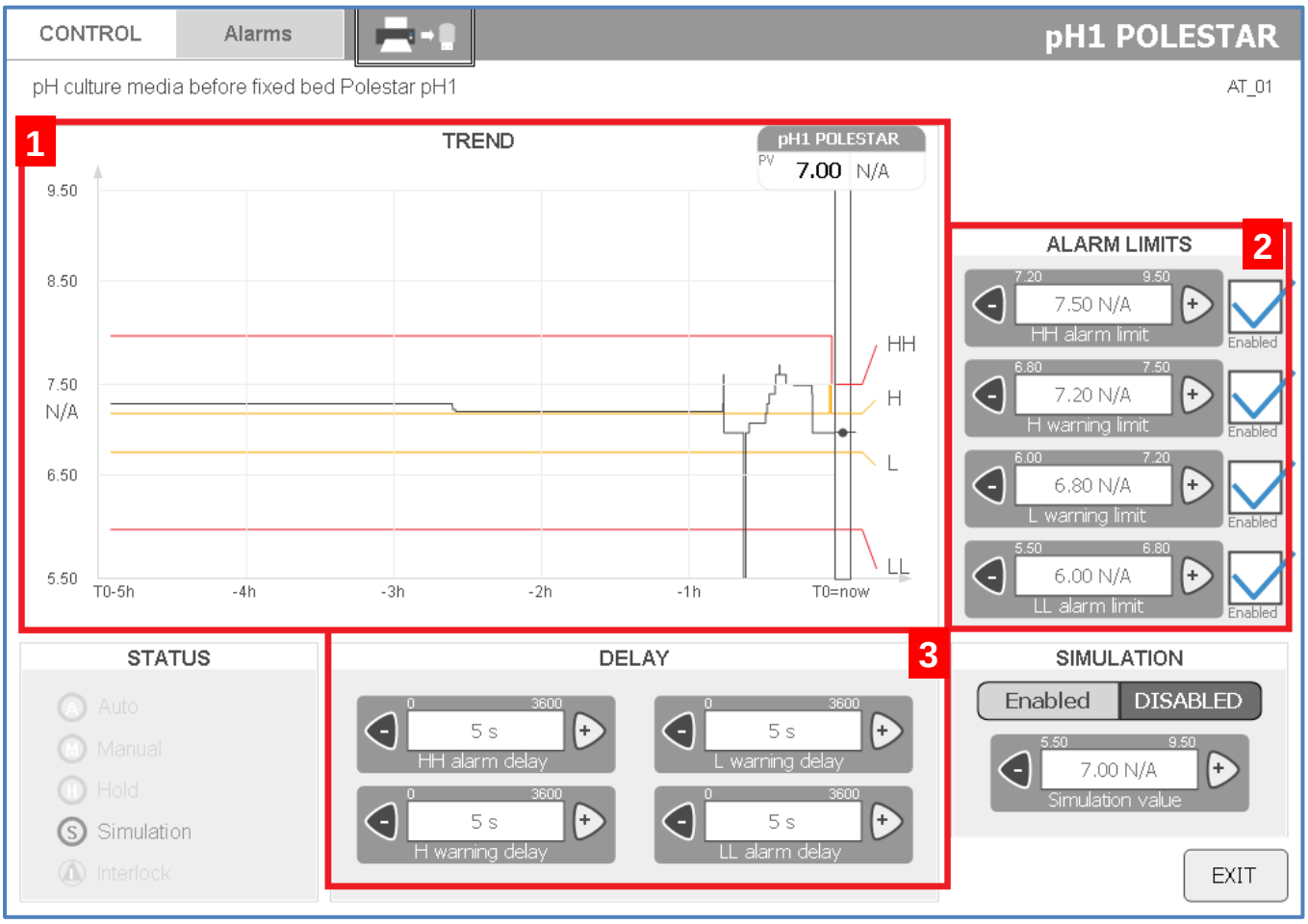


Figure 12: Sensor configuration box – 1) Sensor measure trend over last 5 hours, 2) Alarm limits set-point boxes and Enabled checkboxes, 3) Alarms delay set-points.

6.4 Main P&ID

Navigate to PROCESS: P&ID. This screen is a simplified Piping and Instrumentation Diagram (P&ID) of the iCELLis 500+ bioreactor system (Figure 13). It shows the bioreactor flanked by actuators and sensors of the system.

On each sides of the screen the Equipment Module (EM) boxes are displayed. EM on the left are dedicated to flows going IN the bioreactor while EM on the right are dedicated to flows going OUT of the bioreactor, except for the Agitation and Temperature EM which are also on the right. EM boxes are linked to the bioreactor by lines that cross sensors, actuators and totalizers related to or controlled by the EM (except for sensors physically attached to the bioreactor which are displayed on the top of the screen).

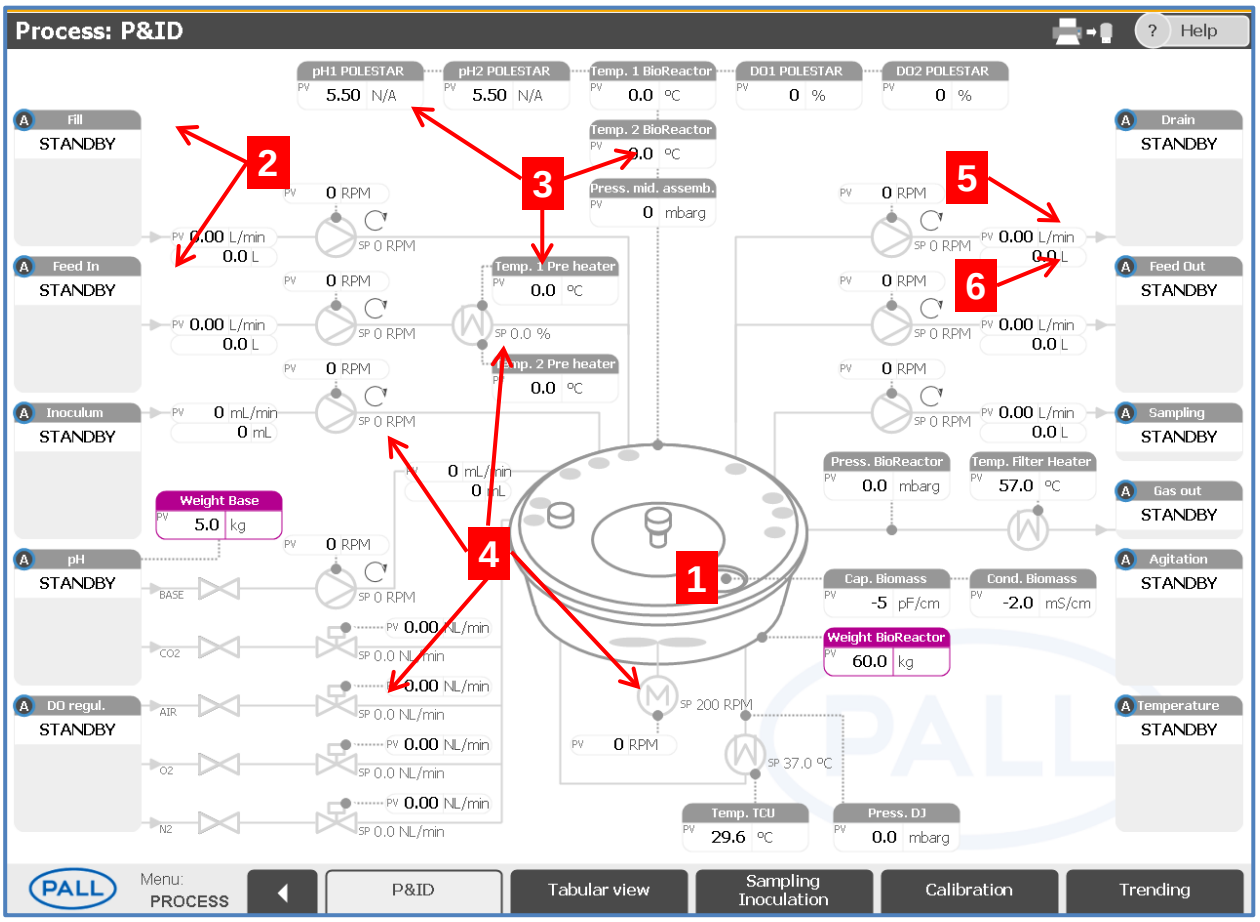
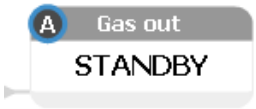
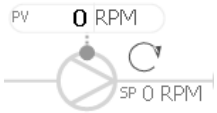


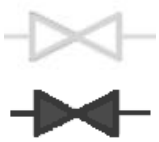
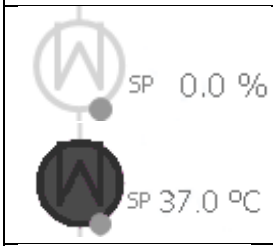
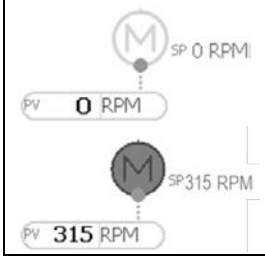
Figure 13: P&ID screen – 1) iCELLis bioreactor, 2) EM boxes, 3) Sensor boxes, 4) Actuators icons, 5) Flow rates for pump, 6) Flow totalizers of the pump.

Icons and boxes displayed on the P&ID screen show the elements state (ON/OFF, under alarm or interlock, etc.) and give access to control parameters of the selected element. The main states of icons and boxes of P&ID screen are detailed in Table 4.

Note that other states can be indicated by the icons on the P&ID screen such as Manual mode, Simulation mode and Alarms. For more information, refer to the corresponding sections.

Table 4: P&ID icon name and function

Icon states	Name - Function
	*Equipment Module Box* Equipment Module (EM) name and mode are displayed on top. Selecting this box will open the corresponding EM dialog box. For more details about EM see Section 7.1 Equipment Module Box.
	*Sensor box* Sensor box displays the sensor name on top, and process value (PV) with the measured unit on the bottom. Selecting this box will open the Sensor configuration tab in the related EM dialog box.
	*Pumps* Pump icons include visualization of pump state, pump direction diagram (rounded arrows), pump speed set-point (SP) and pump speed feedback value (PV in box). Selecting the icon will open the Actuator configuration tab for the corresponding EM dialog box.

	Pump OFF = Light grey; Pump ON = Dark grey
	*Valves* Pinch valve (for Base) or solenoid valve (for gas) icons are simple as they only display the CLOSED/OPEN state indicated by a color shift. Selecting the icon will open the Actuator configuration tab for the corresponding EM dialog box. Valve CLOSED = Light grey; Valve OPEN = Dark grey
	*MFC* Gas mass flow Control System icon includes visualization of the MFC capacity utilization (dark fill), flow set-point (SP) and flow process value (PV in box). Selecting the icon will open the Actuator configuration tab for the corresponding EM dialog box. MFC OFF = Light grey; MFC ON = Dark grey + Dark grey filling
	*Heaters and TCU* This icon is used for heating elements including the TCU; It includes a visualization of heater state and displays the set-point (SP) in temperature or in percentage of heating power output (%). Selecting the icon will open the Actuator configuration tab for the corresponding EM dialog box. Heater OFF = Light grey; Heater ON = Dark grey
	*Agitation motor* Agitation motor icon includes visualization of the motor state, motor speed set-point (SP) and motor speed feedback (PV in box). Selecting the icon will open the Actuator configuration tab for the corresponding EM dialog box. Motor OFF = Light grey; Motor ON = Dark grey

7. Process Control: Equipment Modules

In the iCELLis 500+ bioreactor control system, regulation loops and regulation cascades are predefined in the Control Systems and cannot be modified by the User. The EM is a combination of one or several control loops and actuators sharing the same process sensors and interlocks. Each actuator or control loop is assigned to one and only one EM. EM can be operated in MANUAL mode by setting each actuator set-point manually or in AUTO mode by selecting a process value set-point (such as pH or DO) and a strategy to maintain this set-point. When using the EM in auto mode, the control loops and actuators are guided by the strategy selected in the EM.

Sensors, actuators and totalizers related to an EM are accessible in the EM dialog box. There are 11 preconfigured Equipment Modules in the iCELLis 500+ system detailed below.

SAMPLING and INOCULATION EM are also accessible through a dedicated submenu in PROCESS: SAMPLING INOCULATION.

7.1 Equipment Module Box

EM boxes are visible on the P&ID screen and displays the EM state information. The EM displays the control mode (AUTO or MANUAL) and if a control is active the EM box displays the applied strategy and its color shifts from light to dark grey (Figure 14). If an on-going recipe is on hold, the status will shift to HOLD (H) and will override the auto control mode until the Recipe is resumed.

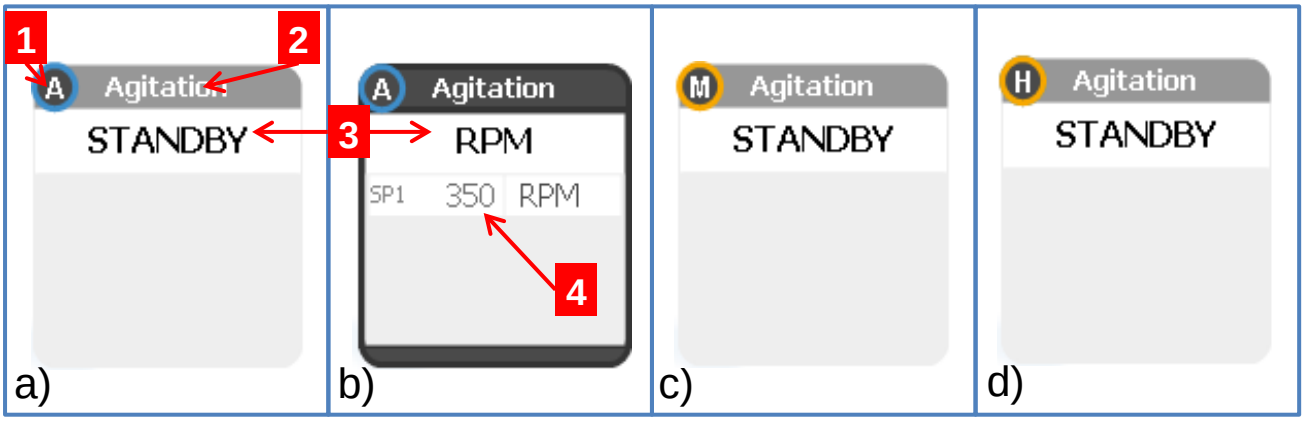


Figure 14: EM box in the P&ID screen – A) EM inactive (STANDBY), B) EM active in AUTO mode, C) EM active in MANUAL mode, D) EM on hold, 1) EM control mode: automatic = A, manual = M, hold status = H, 2) EM name, 3) EM applied strategy (STANDBY if not active), 4) Control set-points related to applied strategy.

Selection of the EM box in the P&ID screen will open the corresponding EM dialog box.

7.2 Equipment Module Dialog Box Operation Principles

7.2.1 EM Dialog Box Overview

The EM dialog box displays a simplified P&ID with the same functional element icons and boxes that are on the main P&ID screen but limited to elements related to the selected EM. Surrounding the diagram are control and command settings (Figure 15). After changes are applied to the EM the user must close the dialog box with the EXIT button to return to the main P&ID screen.

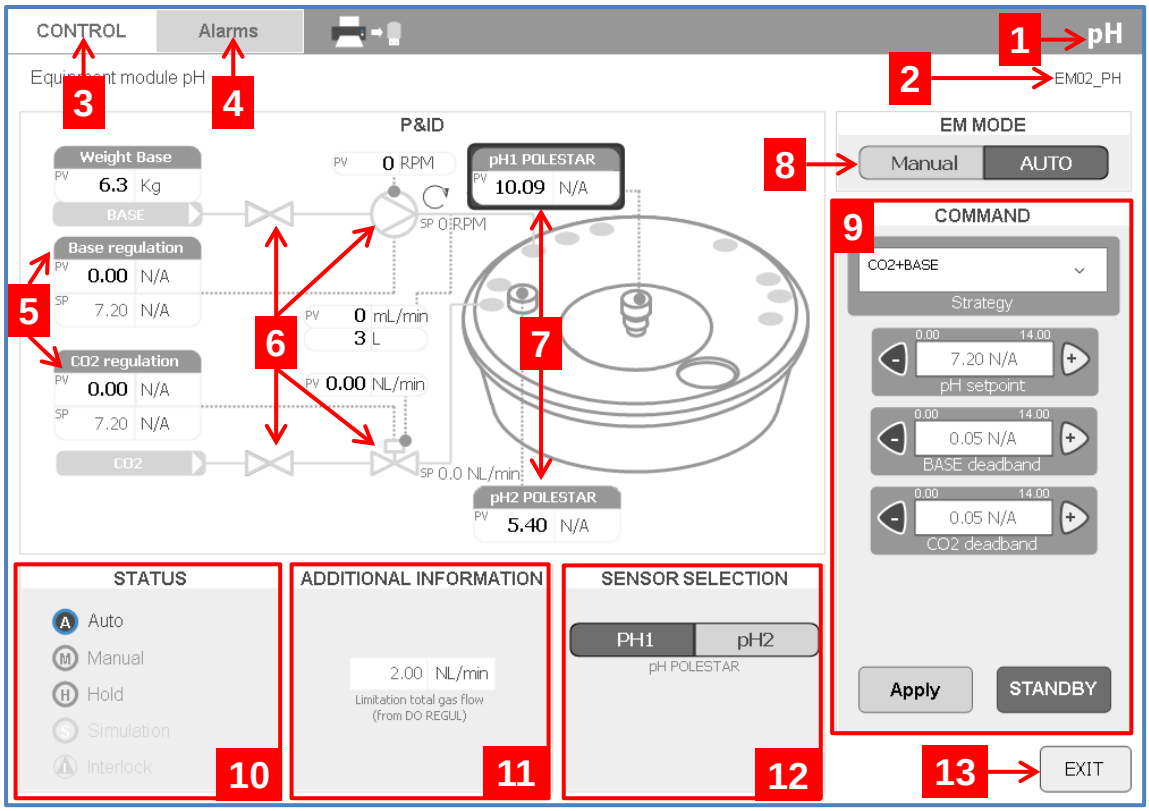


Figure 15: Equipment module dialog box structure – 1) EM name, 2) EM tag name, 3) CONTROL page button (displayed), 4) ALARMS page button, 5) Control Loops, 6) EM actuators – opens ACTUATOR CONFIGURATION page, 7) EM sensors – opens SENSOR CONFIGURATION page, 8) MANUAL/AUTO switch button, 9) EM COMMAND settings, 10) EM status, 11) ADDITIONAL INFORMATION (visible only if applicable), 12) SENSOR SELECTION for reference PV regulation, 13) EM dialog box EXIT button.

Note that the simplified P&ID in the EM dialog box displays both process sensors used as reference for process control (if applicable) and sensors used to trigger interlocks affecting actuators of the EM.

7.2.2 ACTUATOR CONFIGURATION Tab

When the user directly selects an actuator from the main P&ID screen or from the simplified P&ID in the EM dialog box, the related ACTUATOR CONFIGURATION tab opens in the EM dialog box (Figure 16). To operate actuators manually, the user must first put the EM in Manual mode Figure 15-8).

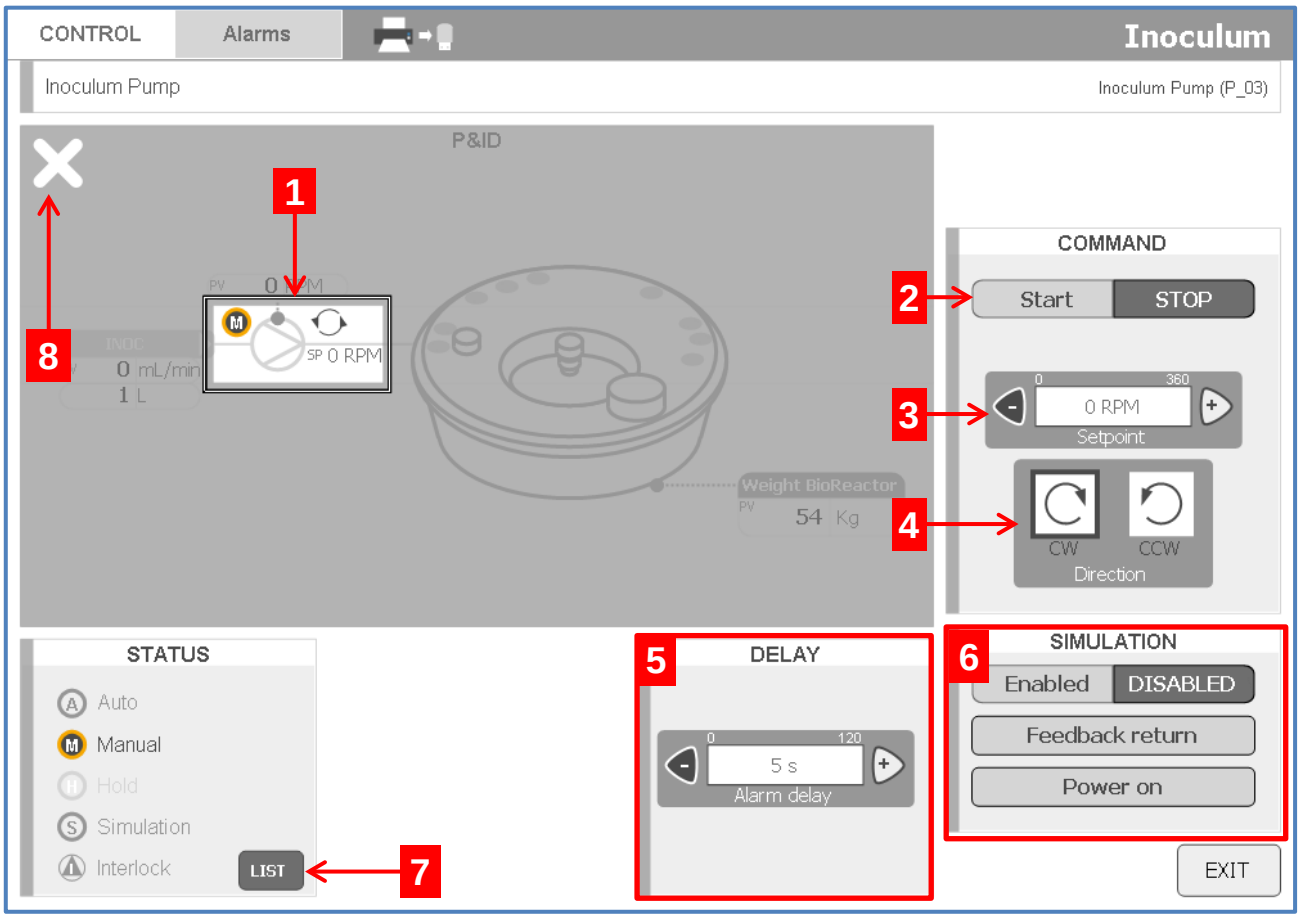


Figure 16: Inoculum pump ACTUATOR CONFIGURATION tab – Selected actuator, 2) START/STOP switch (OPEN/CLOSE for valves), 3) Actuator set-point (Not applicable for valves), 4) Pump direction button (only for pumps), 5) Actuator alarm feedback delay, 6) Actuator simulation settings, 7) Actuator interlocks list. 8) Close actuator configuration view.

In addition to the actuator settings detailed in the MANUAL control mode section (Section 7.3.2), the ACTUATOR CONFIGURATION tab gives access to the Actuator Feedback Alarm delay (Figure 16-5; see Section 13.4 EVENTS Parameters), Simulation state settings (Figure 16-6; see Section 7.15 EM SIMULATION Mode) and the list of Interlocks related to the selected actuator (Figure 17).

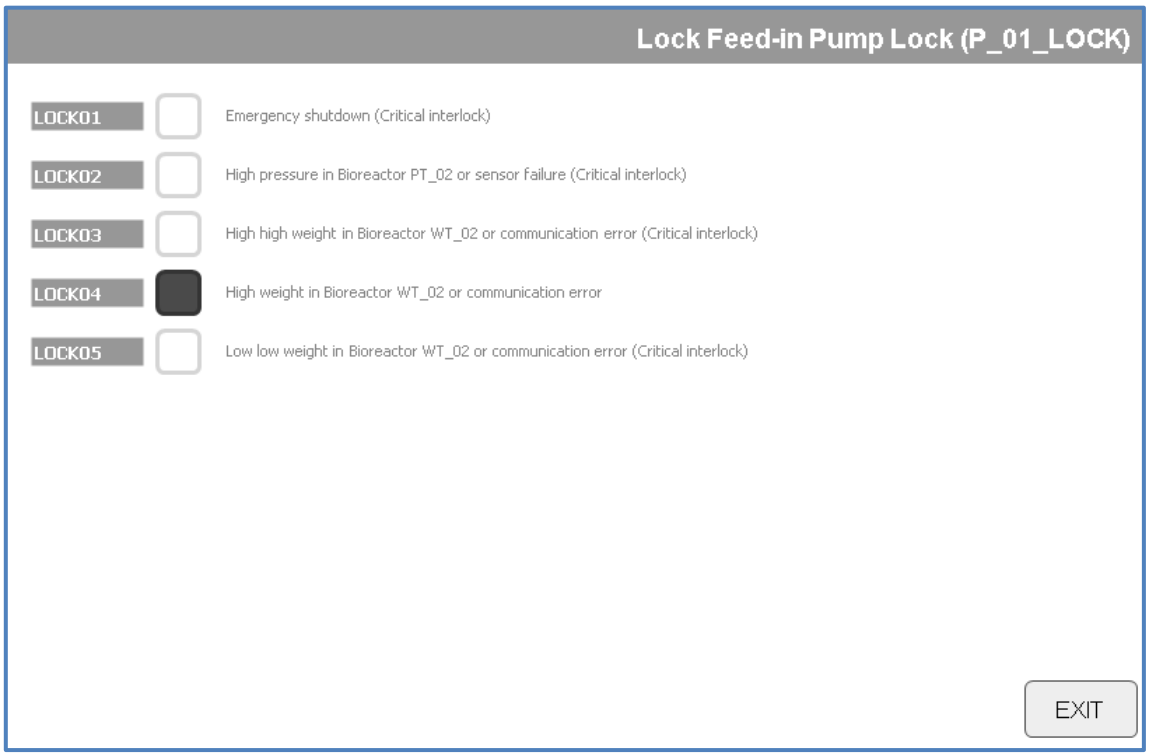


Figure 17: Interlocks list of FEED-IN pump. 'High weight in bioreactor' interlock is active

If an actuator is blocked by an interlock and several interlocks exist for this actuator, the interlock list allows the identification of the active interlock.

7.2.3 SENSOR CONFIGURATION Tab

The SENSOR CONFIGURATION tab (Figure 18) is accessed by selecting a sensor box on the P&ID screen or in the EM dialog box. The SENSOR CONFIGURATION tab displays a pre-defined trend of the sensor measurements from the previous 5 hours including visualization of the alarms thresholds if alarms are enabled. The alarm Limits can be modified in this tab as well as Alarm Delays. Simulation settings for a sensor are also accessible from this tab (see Section 7.15 EM SIMULATION Mode).

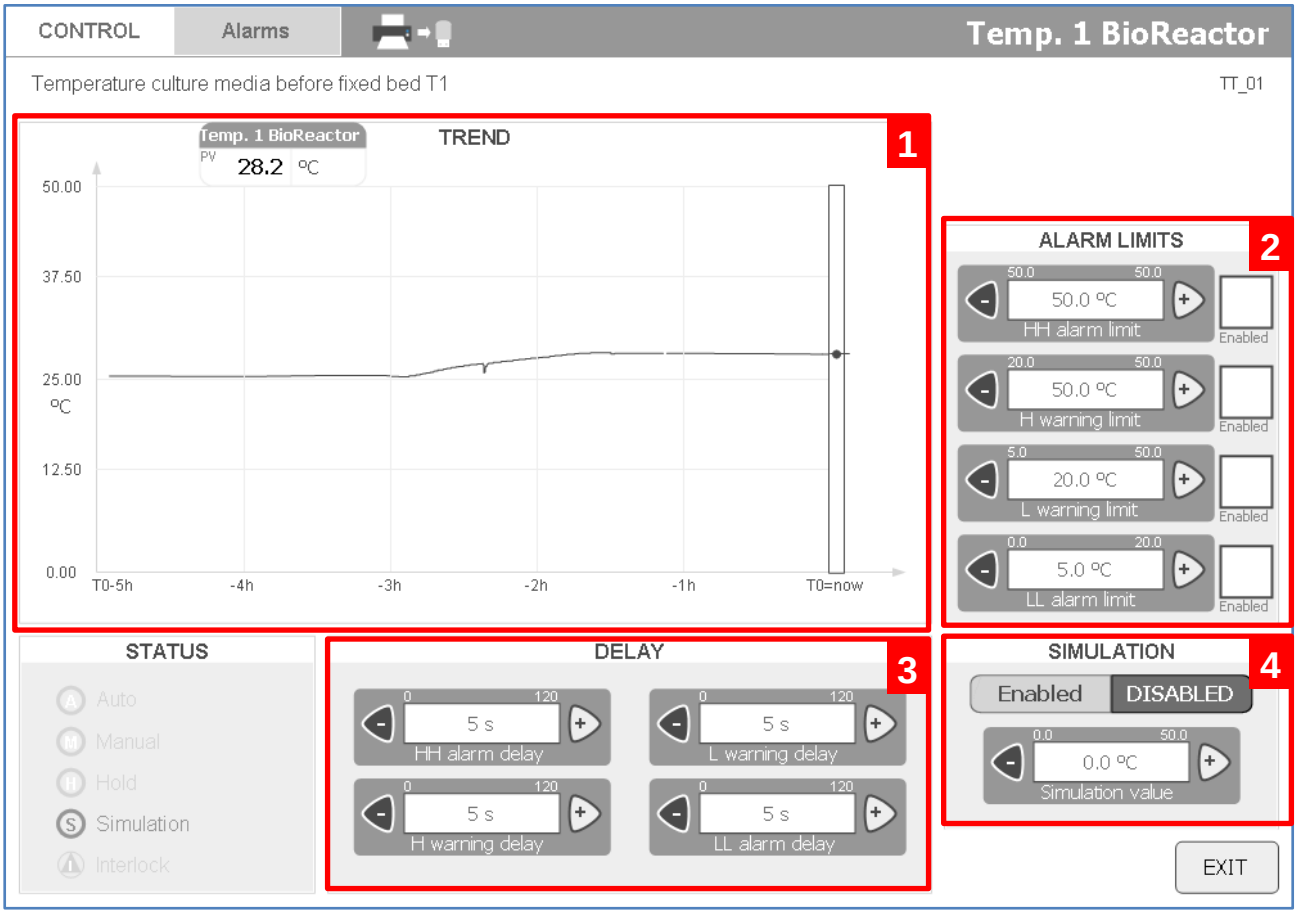


Figure 18: Sensor configuration tab in EM dialog box – 1) Sensor auto-trend window over the last 5 hours, 2) Alarm limits set-point and enabling checkbox, 3) Alarm delay set-points, 4) Simulation state settings.

7.3 EM AUTO and MANUAL Control Modes

7.3.1 EM AUTO Control Mode

Equipment Modules can be set to MANUAL or AUTO mode (Figure 15-8). In AUTO mode control loops and actuators are slaves of the EM. Control loop's settings entered in the EM COMMAND field (Figure 15-9) guides the actuators and control loops to achieve the desired set point defined by selected strategy of EM. The COMMAND settings are composed of a command strategy (dropdown list) and one or several set-points (numerical inputs). Some EM also have ADDITIONAL COMMANDS settings or ADDITIONAL INFORMATION displayed (Figure 15-11 & 12). In AUTO mode the regulation will control the process value. If several sensors are available for measuring the process value, the user can choose which reference sensor will be used by the control loop (Figure 15-12).

The command must be confirmed with the APPLY button to start regulation. When the EM is active (APPLY button active), changing a set-point will be directly applied without further confirmation unless a signature is required. The EM control is stopped by selecting the STANDBY button and all actuators and control loops linked to that EM will go to their standby state. AUTO mode strategies and SP for each EM are detailed in Sections 7.4 to 7.14.

In AUTO control mode, it is still possible to access the ACTUATOR CONFIGURATION tab of the pumps to set pump direction (Figure 16-4).

7.3.2 EM MANUAL Control Mode

In MANUAL mode, the user can directly set the output of actuators. To activate manual control, use the MANUAL/AUTO switch in the corresponding EM dialog box (Figure 19). The EM COMMAND settings will no longer be available and all actuators and control loops shift to the MANUAL COMMAND settings, with 'M' symbols displayed next to all the actuators and control loop icons under the specified EM on the P&ID screen (Figure 13-c) and in the EM dialog box (Figure 19) as well as next to the Control System boxes on the HOME screen.

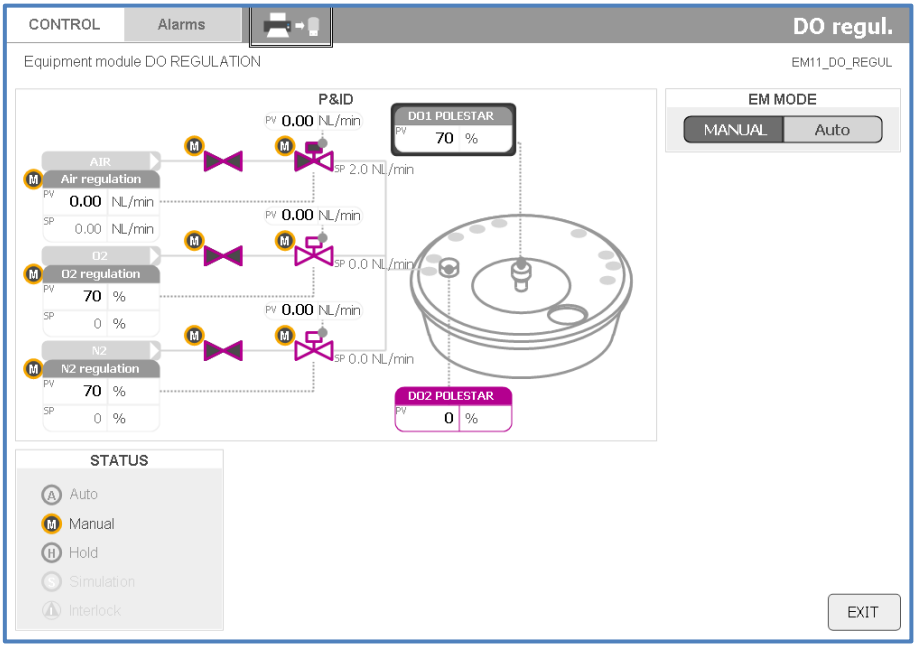


Figure 19: DO regulation EM in manual mode

After the EM has been set to MANUAL, each actuator's set-point must be set and activated one by one. To access the actuator command settings, select the actuator in the EM dialog box or from the P&ID screen to open the ACTUATOR CONFIGURATION tab (Figure 16).

Each actuator type has specific manual commands detailed in Table 5.

Table 5: Manual commands of all actuators sorted by EM

EM	Actuators	Manual Command
AGITATION	Agitation motor	START/STOP Speed set-point (rpm)
pH	Base pump Base pinch valve CO_2 valve CO_2 MFC	START/STOP Speed set-point (rpm) Pump direction (CW/CCW) OPEN/CLOSE OPEN/CLOSE Flow-rate (NL/min)
TEMPERATURE	TCU heater	START/STOP Temperature (°C)
INOCULATION	Inoculation pump	START/STOP Speed set-point (rpm) Pump direction (CW/CCW)
FEED IN	Feed IN pump	START/STOP Speed set-point (rpm)

	Media Preheater	Pump direction (CW/CCW) START/STOP Temperature (°C)
FILL	Fill pump	START/STOP Speed set-point (rpm) Pump direction (CW/CCW)
FEED OUT	Feed Out pump	START/STOP Speed set-point (rpm) Pump direction (CW/CCW)
DRAIN	Drain pump	START/STOP Speed set-point (rpm) Pump direction (CW/CCW)
SAMPLING	Sampling pump	START/STOP Speed set-point (rpm) Pump direction (CW/CCW)
GAS OUT	Filter heater	START/STOP
DO	AIR ,O_2,N_2 valves AIR, O_2,N_2 MFCs	OPEN/CLOSE Flow-rate (NL/min)

7.4 EM01 – AGITATION

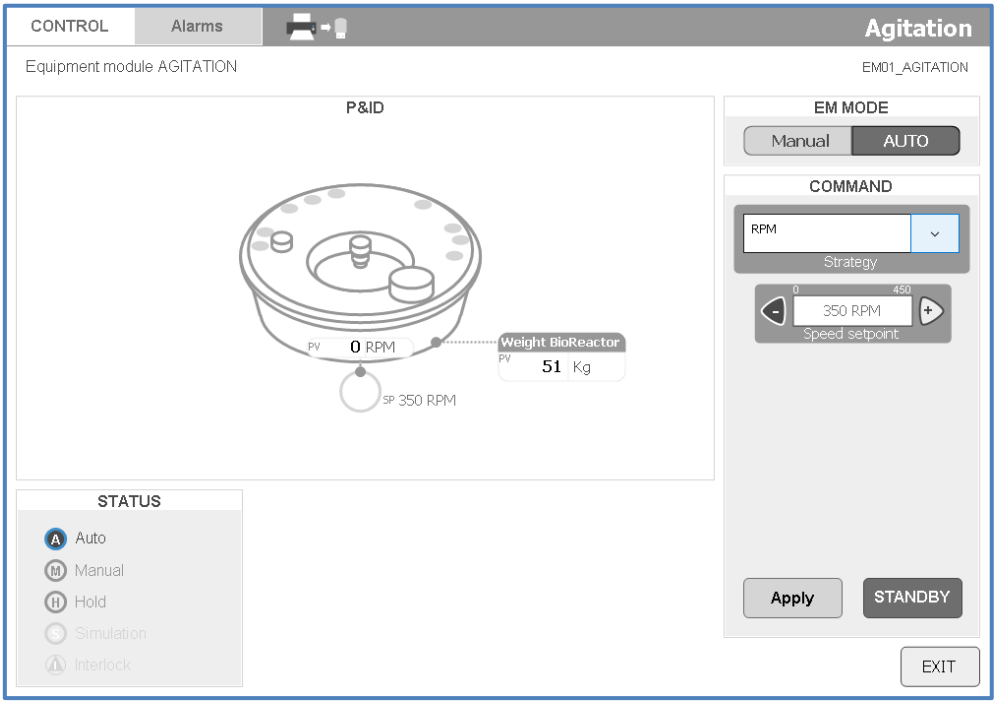


Figure 20: Agitation EM dialog box

The AGITATION EM is dedicated to the management of the Agitation motor. It controls only one actuator, the Agitation motor, and relies on the feedback of the motor speed to control the output. It is enslaved to the Bioreactor low filling level (minimum weight) interlock which stops the motor if activated. The main purpose of this interlock is to prevent the agitation motor from running when there is not enough media present inside the bioreactor.

Table 6: AGITATION EM AUTO control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
rpm	Speed set-point (rpm)	Motor feedback Speed agitation	Agitation motor	Sets the motor speed to a fixed-speed set-point

7.5 EM02 – pH

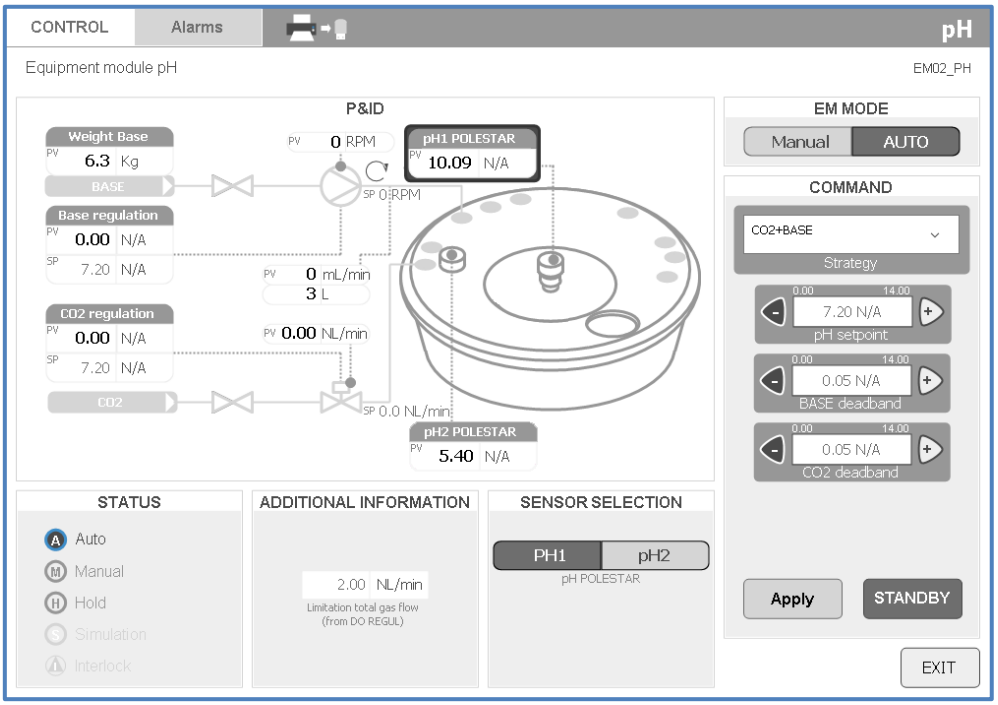


Figure 21: pH EM dialog box

The pH EM is dedicated to the control of the culture medium pH in the bioreactor. The pH is managed by two independent Control Systems: Base control loop (to increase the pH) and CO_2 control loop (to lower the pH). Actuators for each control loop share the same reference pH sensor. There are three strategies available to control the pH: controlling only above, only below or both above and below the target pH set-point. For each control loop a deadband setting is available to define a no-action zone. The pH EM is enslaved to the following interlocks:

- High bioreactor pressure interlock will shut down CO_2 and base flows;
- Low gas exhaust temperature interlock will shut down the CO_2 flow.
- High pressure in the middle assembly interlock will shut down the CO_2 flow.
- High high weight of the bioreactor will stop the base pump.

pH regulation can be based on either of the two sensors: pH before the fixed-bed (pH 1) or pH after the fixed-bed (pH 2). A slight difference can appear between the two sensors depending on process kinetics (cell concentration and metabolism) and agitation speed.

Table 7: pH EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
BASE	pH (N/A) Base DB (N/A)	pH1 or pH2 sensor	Pinch Valve Base pump	Regulates pH upwards when pH goes below SP-DB
CO_2	pH (N/A) CO_2 DB (N/A)	pH1 or pH2 sensor	CO_2 valve CO_2 MFC	Regulates pH downwards when pH goes above SP+DB
CO_2+BASE	pH (N/A) Base DB (N/A) CO_2 DB (N/A)	pH1 or pH2 sensor	Pinch Valve Base pump CO_2 valve CO_2 MFC	Regulates pH at set-point when pH drifts above or below SP+/-DBs

7.6 EM03 – TEMPERATURE

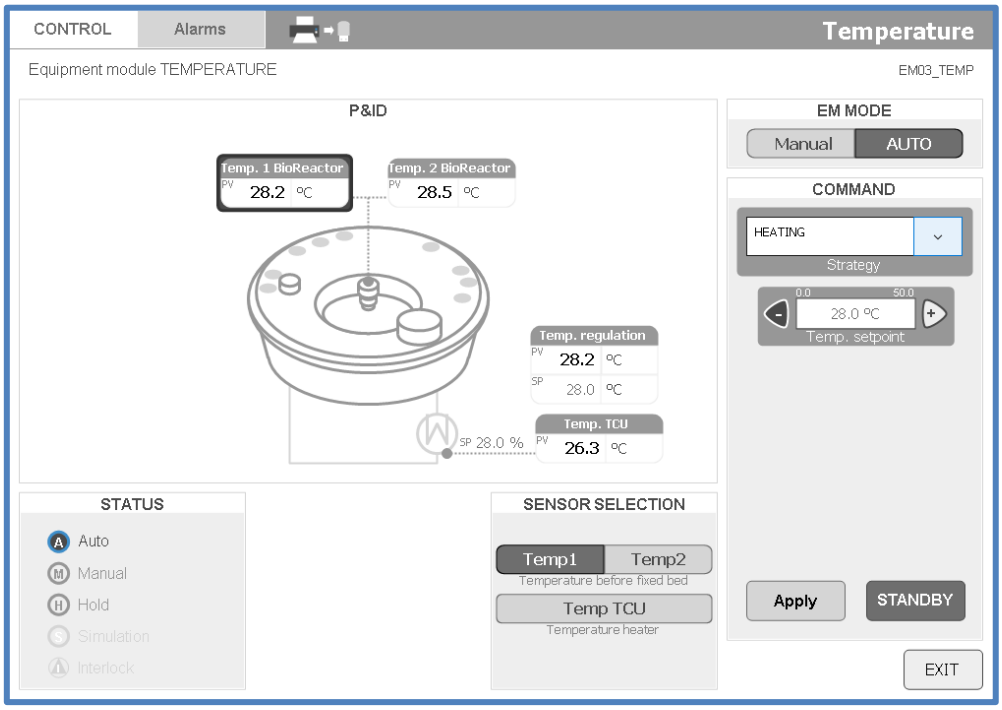


Figure 22: Temperature EM dialog box

ALERT!
Heating the bioreactor with Temp. 1 or Temp. 2 for reference sensor, in empty and/or non-agitated bioreactor will result in local overheating of the bioreactor shell and/or media and cells.
Temp. TCU should be used to preheat the Double-Jacket when the bioreactor is empty or when the agitation is stopped.
Starting heating without agitation in bioreactor will trigger a warning message.

The TEMPERATURE EM is dedicated to the management of fluid circulation and temperature in the bioreactor double-jacket. There is only one Control System and one actuator (the TCU) for temperature control, but three reference sensors are available: Temperature 1 Bioreactor (Temp. 1), Temperature 2 bioreactor (Temp. 2) and Temperature TCU (Temp. TCU). Temp. 1 and Temp. 2 are equivalent and measure the temperature of the media in the bioreactor. Temp. TCU measures

temperature of the heating/cooling fluid inside the TCU. Controlling the temperature with the Temp. TCU will likely result in a lower media temperature in the bioreactor.

The TEMPERATURE EM is enslaved to the following interlocks:

- High pressure in the double-jacket interlock will shut down the TCU;
- High temperature in the bioreactor interlock will shut-down the TCU and the pre-heater;
- High temperature in the TCU interlock will shut-down the TCU.

Table 8: Temperature EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
HEATING	Temperature (°C)	Temp. 1 BioReactor or Temp. 2 BioReactor or Temp. TCU	TCU	Controls temperature in bioreactor double-jacket based on SP and reference sensor selected.

7.7 EM04 – INOCULUM

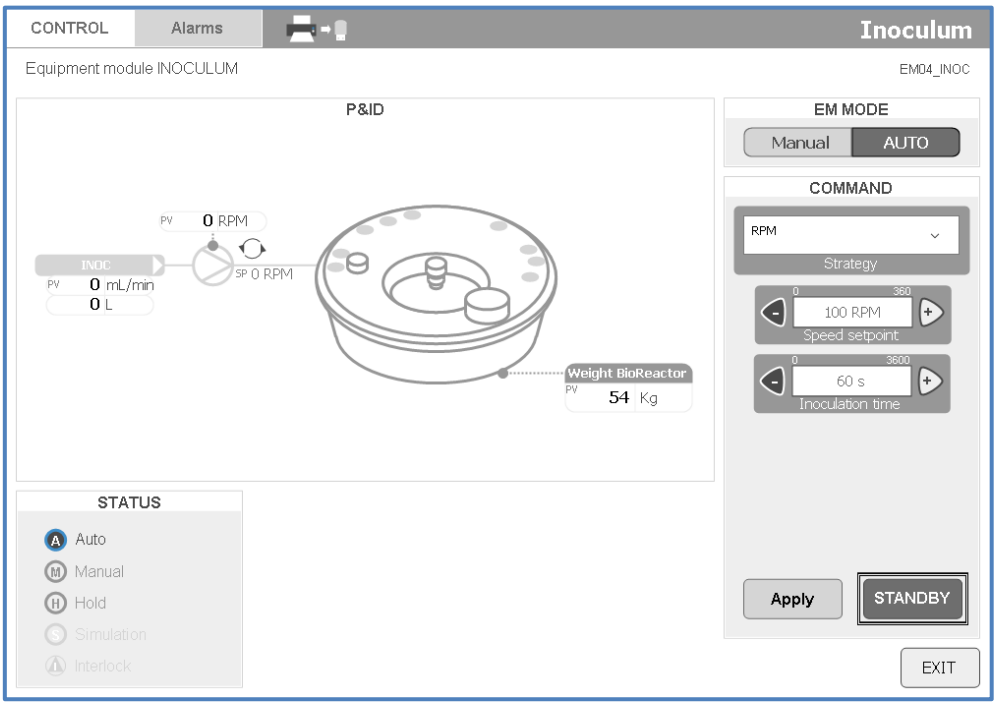


Figure 23: Inoculum EM dialog box

The INOCULATION EM is dedicated to the addition of small volumes to the bioreactor, for example cell inoculum or virus addition. It controls a small peristaltic pump combined with a potentiometer, which when selected can quickly be used to adjust the pump speed and is located directly on the skid next to the inoculation pump. The INOCULUM EM is enslaved to the high bioreactor weight and high pressure in the bioreactor interlock.

Inoculum pump potentiometer is linear and allows controlling pump speed between 0 rpm and 360 rpm.

Table 9: Inoculum EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
rpm	Pump Speed (rpm) Inoc. Time (s)	Pump feedback Timer	Inoculum pump	Runs pump at fixed SP for required time regardless of potentiometer position.
POT_rpm + Potentiometer	Time out delay (s)	Timer	Inoculum pump and potentiometer	Allows manual control of pump with external potentiometer during time-frame defined by time-out SP. At the end of the delay the EM goes back to STANDBY.

7.8 EM05 – FEED IN

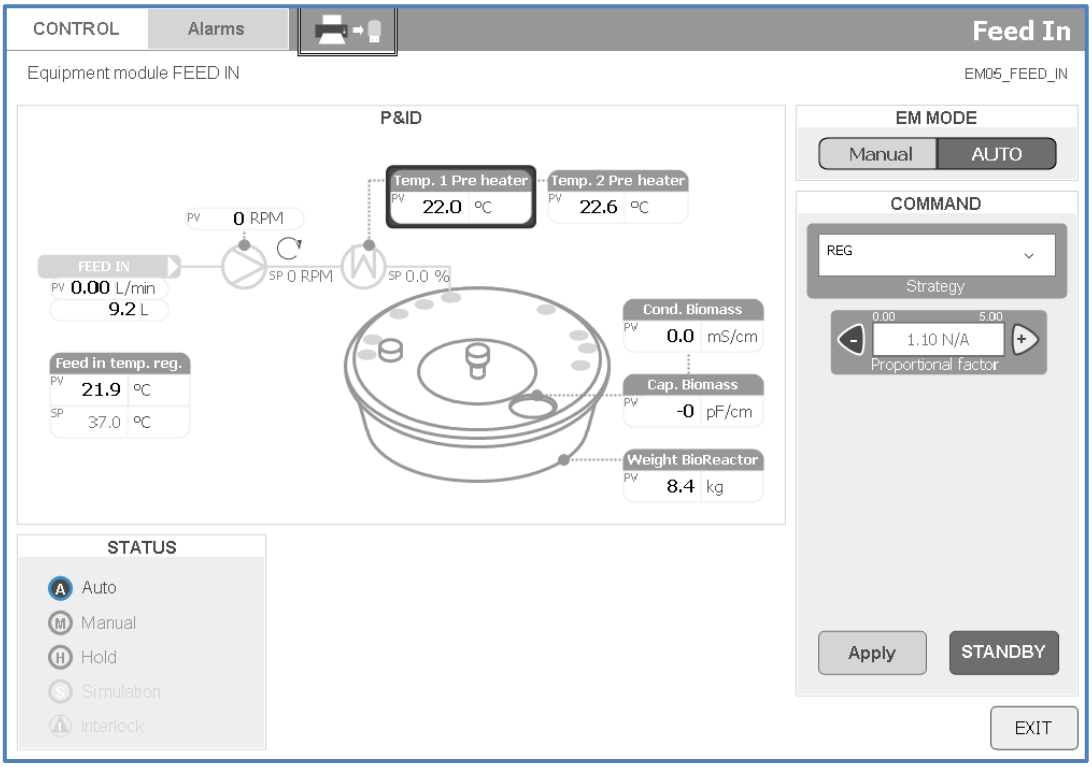


Figure 24: Feed IN EM dialog box

The FEED IN EM is dedicated to media addition to the bioreactor during recirculation or perfusion operations. It controls a peristaltic pump and a media bag preheater. The process value sensors are pump speed feedback, and preheater temperature probes (1&2). The FEED IN EM will modulate flow-rate and heating power based on the selected strategy. It is enslaved to the following interlocks:

- High and high high bioreactor weight will stop the FEED IN EM;
- High bioreactor pressure will stop the FEED IN EM;

- Low Low bioreactor weight will stop the FEED IN EM, if the EM is running in one of the strategy other than rpm or rpm_HEAT. The reason of this interlock is to prevent drain of bioreactor due to reverse tubing placed on FEED IN pump.

Note that two temperature sensors in the media preheater are available as reference for temperature in HEAT strategies. These two sensors are for redundancy and should be considered identical.

The FEED IN EM allows various control strategies to answer to the different process modes possible in the iCELLis 500 bioreactor:

- rpm strategies have a fixed pump speed for constant flow over time, adapted to recirculation processes;
- CURVE strategies allow variable pumping speeds based on time periods, adapted to intermittent feed cycles or perfusion processes;
- REG strategies allow variable pumping speeds based on biomass concentration measured by the capacitance Biomass probe, adapted to a well characterized perfusion process.

Each Feed strategy can be coupled with the bag preheating (HEAT) or not. HEAT strategies will control the temperature of the media in the media preheater bag to the temperature setpoint. The strategies' parameters are detailed in Table 10.

Table 10: Feed IN EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
rpm	Speed (rpm)	Pump Feedback	Feed IN pump	Runs the Feed IN pump at a fixed set-point.
rpm_HEAT	Speed (rpm) Temp. (°C)	Pump Feedback Temp. 1 and 2 Bag preheater	Feed IN pump Bag preheater	Runs the Feed IN pump at a fixed SP and bag preheater to maintain temperature SP.
CURVE	Curve points (rpm/time)	Pump Feedback	Feed IN pump	Runs the Feed IN pump at variable speeds depending on programmed Curve points.
REG	Proportional factor	Pump Feedback Biomass (Capacitance)	Feed IN pump	Runs the Feed IN pump at variable speeds depending on Biomass sensor evolution.
REG_HEAT	Proportional factor Temp. (°C)	Pump Feedback Biomass (Capacitance) Temp. 1 and 2 Bag preheater	Feed IN pump Bag preheater	Runs the Feed IN pump at variable speeds depending on Biomass sensor evolution and bag preheater to maintain temperature SP.

Rpm strategy should be applied during the first fill of bioreactor

CURVE strategies are based on the user's input in a speed curve profile accessible using the CURVE SETPOINTS button in the EM COMMAND box. The CURVE SETPOINTS dialog box allows the creation of a curve profile with up to 5 different stages (Figure 25).

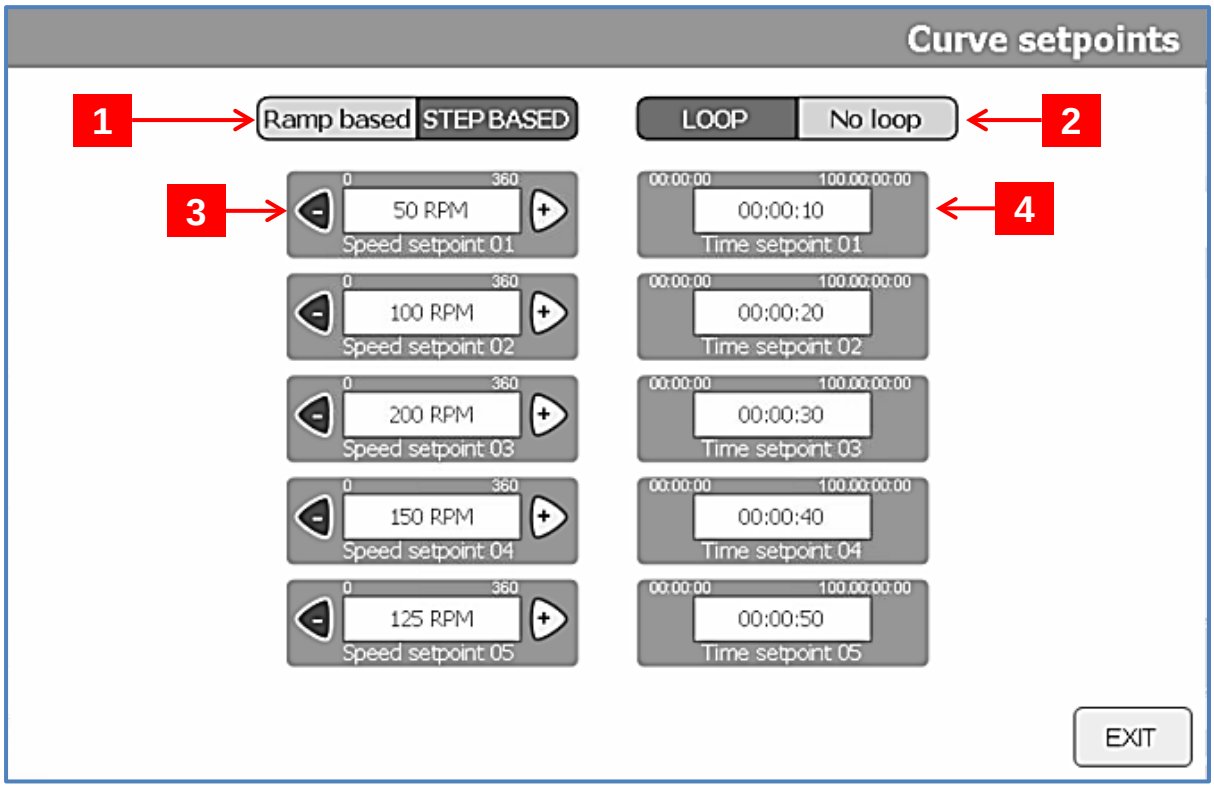


Figure 25: Curve set-points dialog box – 1) RAMP/STEP based switch, 2) LOOP/NO LOOP switch, 3) Pump speed SP, 4) Stage duration.

For each stage the user must define a pump speed in rpm and a duration in hh:mm:ss (Figure 25-3/4). The user also has 2 transition possibilities (Figure 25-1):

- Ramp based gradually increases pump speed to SP over the stage's duration;
- Step based directly changes pump speed to the new SP at the beginning of the stage.

It is also possible to loop (repeat) the Curve profile or not (Figure 25-2):

- LOOP restarts curve profile at stage 1 at the end of stage 5;
- NO LOOP brings pump to standby at the end of stage 5.

7.9 EM06 – FILL (Optional)

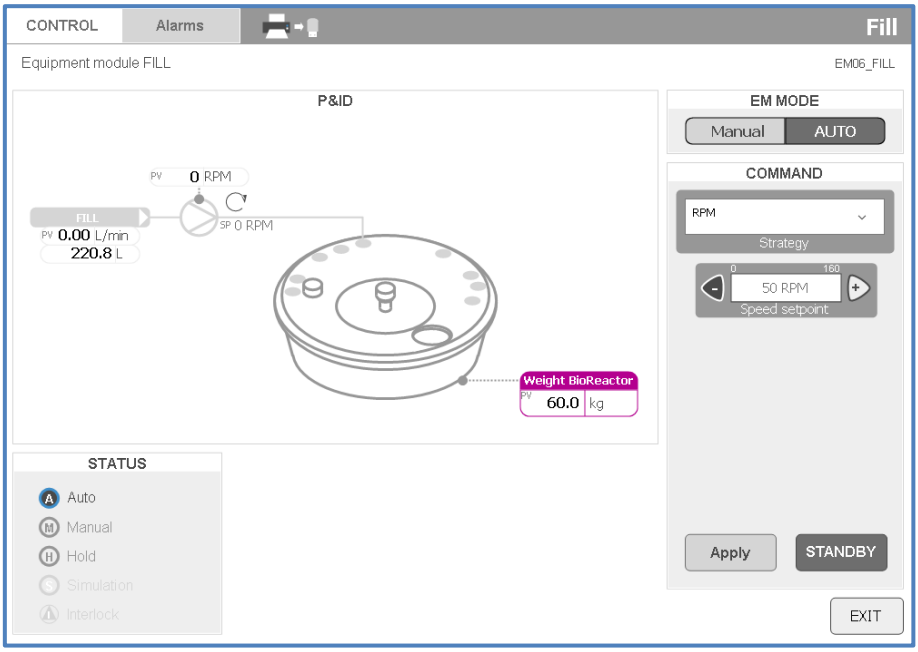


Figure 26: Fill EM dialog box

The FILL EM controls a high speed peristaltic pump and is dedicated to fast bioreactor filling operations. It is dependent on the bioreactor High and High High weight interlock that will stop the EM if activated. Also, a High bioreactor pressure interlock will stop the FILL pump.

FILL and DRAIN pumps are optional on the iCELLis 500+ bioreactor control system. Customers have the possibility to get this option. If not selected, then all actuators and control loops linked to these pumps will not be shown on HMI.

Table 11: Fill EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
rpm	Pump Speed (rpm)	Pump feedback	Fill pump	Runs Fill pump at fixed SP

7.10 EM07 – FEED OUT

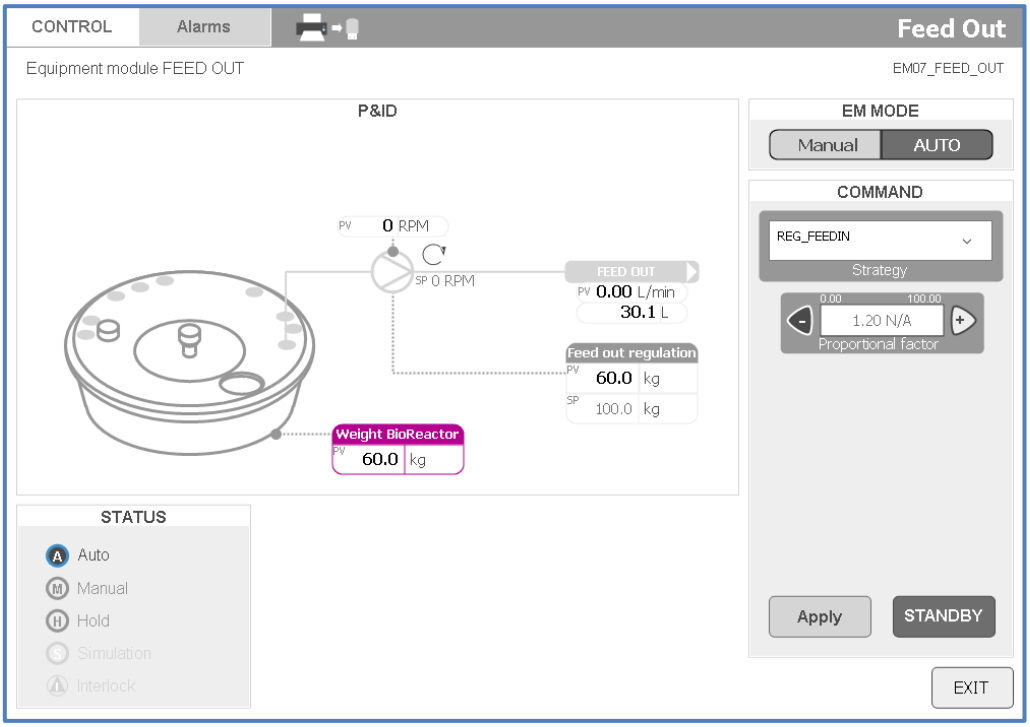


Figure 27: FEED OUT EM dialog box

The FEED OUT EM is dedicated to media removal from the bioreactor and is used in combination with the FEED IN EM to control the media perfusion or recirculation strategy. The FEED OUT pump can modulate flow-rate based on input from the bioreactor weight or pump speed of the FEED IN EM or a fixed speed. The FEED OUT EM is enslaved to the following interlocks:

- Low and Low Low bioreactor weight turns off the FEED OUT pump, if EM is running in one of the strategies other than rpm. The reason is when user wants to drain the bioreactor, these interlocks will not be applicable if the pump is running in rpm strategy or in manual mode, which will allow a user to drain the bioreactor.
- High high bioreactor weight will stop the FEED OUT EM. The reason of this interlock is to prevent overfilling of the bioreactor due to reverse tubing placed on the FEED OUT pump.
- High pressure interlock.

The FEED OUT EM allows different control strategies detailed in Table 12.

Table 12: Feed Out EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
REG_VOL	Weight bioreactor (kg)	Bioreactor load cells	Feed Out pump	Maintains a constant weight (and volume) in bioreactor. Allows working at defined falling film height.
REG_FEEDIN	K feed in (proportional factor)	Feed In pump feedback	Feed Out pump	Maintains a Feed Out pump speed proportional to Feed In pump speed (Out = K*In). Used to maintain maximum falling

				film height when K>1 with same size tubing on In and Out pumps.
rpm	Pump speed (rpm)	Feed Out pump feedback	Feed Out pump	Runs Feed Out pump at fixed speed.

When using the REG_VOL strategy, the FEED OUT Control System will aim at maintaining a fixed volume in the bioreactor based on the weight from the bioreactor load cells. The Control System, based on a fixed weight set point, will control the bioreactor weight using a PID Control System, increasing the FEED OUT pump speed for higher weights and reducing it for lower weights. This allows working with defined falling film heights, based on volume.

7.11 EM08 – DRAIN (Optional)

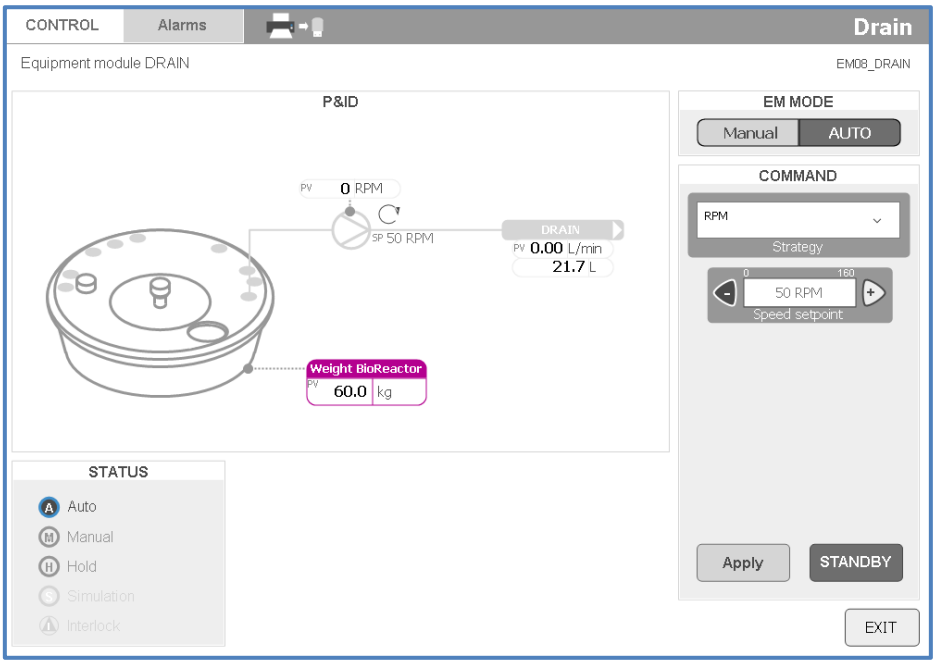


Figure 28: DRAIN EM dialog box

The DRAIN EM controls a high flow-rates peristaltic pump and is dedicated to fast bioreactor draining operations. It is used in combination with bioreactor weight load cells. The DRAIN EM is enslaved to the following interlocks:

- High high bioreactor weight will stop the DRAIN pump.
- High pressure interlock will stop the DRAIN pump.

FILL and DRAIN pumps are optional on the iCELLis 500+ bioreactor control system. Customer have the possibility to get this option. If not selected, then all actuators and control loops linked to these pumps will not be shown on HMI.

Table 13: Drain EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
rpm	Pump Speed (rpm)	Pump feedback	Drain pump	Runs Drain pump at fixed SP.

7.12 EM09 – SAMPLE

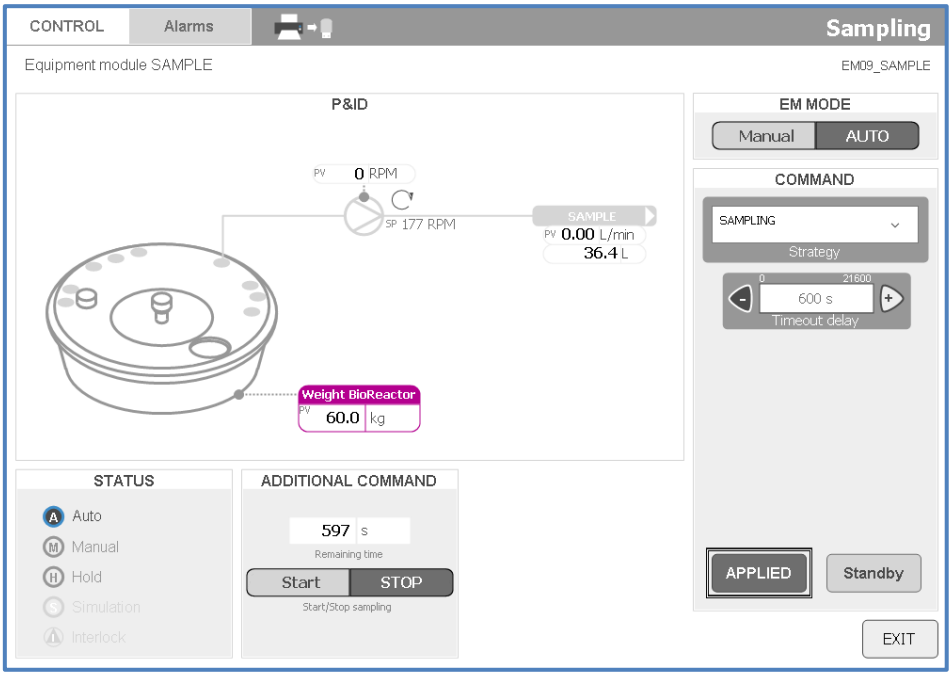


Figure 29: Sample EM dialog box

The SAMPLE EM is dedicated to the sampling of small volumes from the bioreactor. It controls a peristaltic pump combined with a potentiometer located directly on the skid next to the Sampling pump. It is enslaved to the Low Low bioreactor weight interlock.

The Sampling pump potentiometer is linear and allows controlling the pump speed between 0 RPM and 360 RPM.

Table 14: Sampling EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
SAMPLING	Time out delay(s)	Timer	Inoculum pump Potentiometer	Allows manual control of the pump with external potentiometer during the time-frame defined by user. At the end of the delay the EM goes back to STANDBY.

7.13 EM10 – GAS OUT

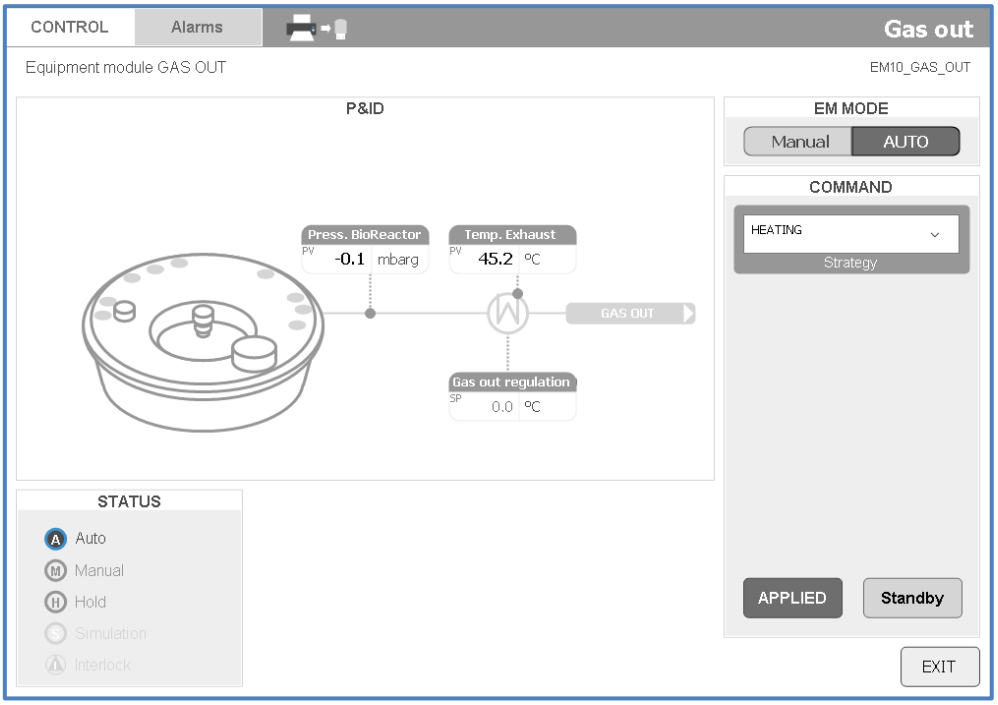


Figure 30: GAS OUT EM dialog box

The GAS OUT EM is dedicated to the heating of the gas exhausts filter to prevent the Gas Out filter from clogging by condensate. The GAS OUT EM controls a filter heater which when activated regulates its temperature based on a single integrated temperature sensor in the filter heater. An interlock turns the filter heater off if a high filter heater temperature threshold is reached (Configured to 75 ºC in factory default).

Table 15: Gas Out EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
HEATING	N/A	Temp. Exhaust	Filter heater	Turns on filter heater

7.14 EM11 – DO REGULATION

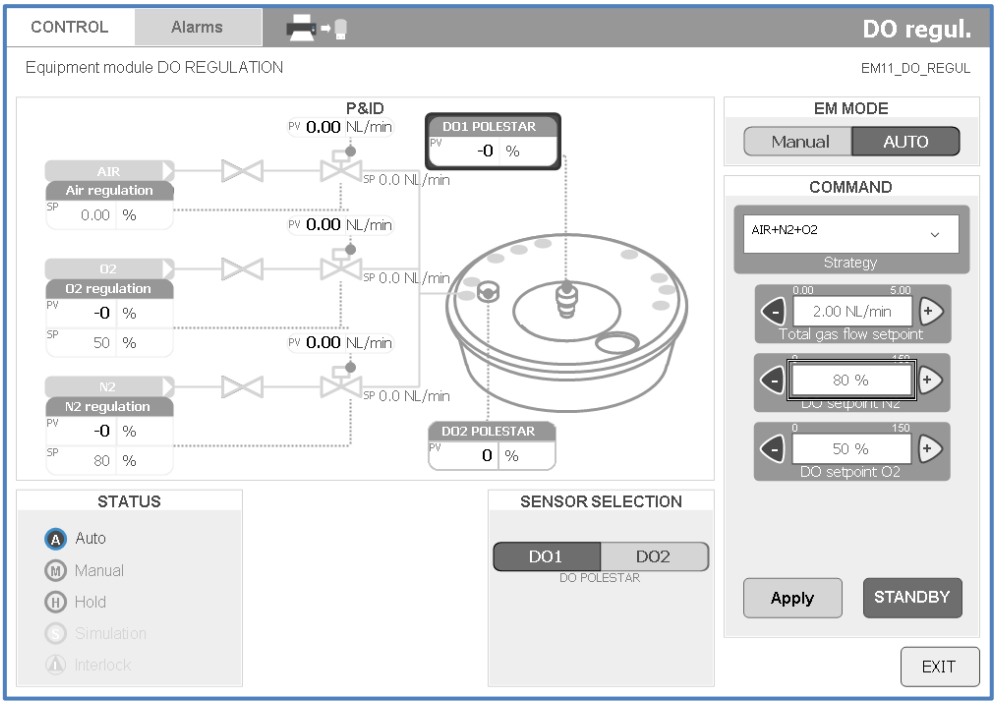


Figure 31: DO regulation EM dialog box

The DO REGULATION EM is dedicated to gas flow management into the bioreactor through the overlay for the regulation of the dissolved oxygen in the media. It includes three Control Systems ($AIR/O_2/N_2$), each one managing a gas valve and a gas MFC, which are regulated based on DO measurements coming from a DO sensor located before or after the fixed bed (DO1 and DO2 respectively). It is enslaved to the following interlocks:

- High bioreactor pressure interlock will shut down gas flows;
- Low gas filter heater temperature interlock will shut down gas flows;
- High pressure in the middle assembly will shut down the gas flows.

DO regulation is based on a total gas flow and one of the DO probes. Due to O_2 consumption by cells, DO1 (before FB) and DO2 (after FB) can show a difference depending on cell concentration and media agitation speed.

There are different strategies available to control the DO in the iCELLis bioreactor (Table 16). For each strategy a total gas flow set-point must be defined. The makeup (mixture) of this total gas flow will be based on the strategy selected and the demand created by the DO and pH (for CO_2).

Total gas flow also takes CO_2 gas flow into account.

Table 16: DO regulation EM control strategies

Strategy or Command	Set-Points (Unit)	Reference Sensors	Actuators	Description
AIR	Total gas flow (NL/min)	Total gas flows	Air valve/MFC	Applies a constant Air flow on overlay.
AIR+N_2	Total gas flow (NL/min) DO setpoint N_2 (% AS)	Total gas flows DO1 or DO2	Air valve/MFC N_2 valve/MFC	Sends N_2 gas when DO PV is above DO set-point and completes the total flow with Air.
AIR+O_2	Total gas flow (NL/min) DO setpoint O_2 (% AS)	Total gas flows DO1 or DO2	Air valve/MFC O_2 valve/MFC	Sends O_2 gas when DO PV is below DO set-point and completes the total flow with Air.
AIR+N_2+O_2	Total gas flow (NL/min) DO setpoint N_2 (% AS) DO setpoint O_2 (% AS)	Total gas flows DO1 or DO2	Air valve/MFC O_2 valve/MFC N_2 valve/MFC	Sends O_2 or N_2 gas to maintain DO between the 2 DO set-points, and completes the total flow with Air.

7.15 EM SIMULATION Mode

ALERT! Risk of damage to data!
SIMULATION mode allows the user to change the state of sensors and actuators or simulate process values. This mode must never be used during a GMP batch in order to guarantee data authenticity.
It is the responsibility of the user to ensure the appropriate access level to SIMULATION mode is granted.

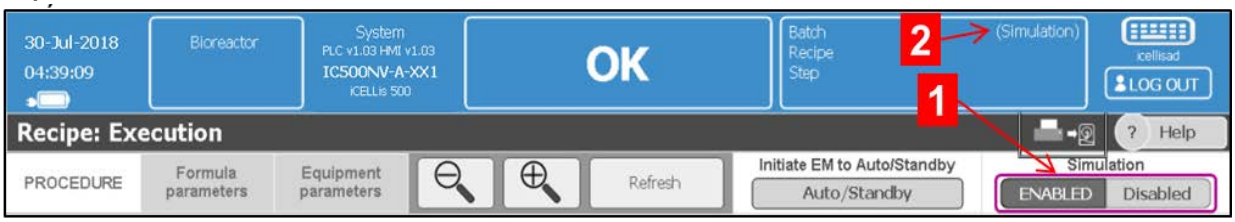
WARNING! Risk of injury to personnel!
In SIMULATION mode the iCELLis 500+ bioreactor control system will still activate actuators placed under AUTO or MANUAL control based on control settings and process values. Make sure your simulation settings are compatible with the equipment use (no operator interacting with the equipment, no tubing in peristaltic pumps…).

SIMULATION mode is dedicated to equipment testing in non-operating conditions. It is particularly useful to test the sequence from a recipe and check that transitions of the recipe have been properly programmed. SIMULATION mode allows simulating Feedback to the PLC of all actuators and sensors and hence testing response of regulation loops, alarms or recipe transitions.

User access level to activate SIMULATION mode can be defined in the SECURITY settings.

To start SIMULATION mode, navigate to RECIPE: EXECUTION and set the SIMULATION switch to ENABLED (Figure 32-a1). Then select the sensors or actuators to simulate the response in SIMULATION settings of the Sensor/Actuator configuration tab (see Figure 16 and Figure 18). When an actuator is in simulation mode, the simulation will only simulate a feedback of the command. If this actuator is set in SIMULATION, the real actuator will be also commanded. The user will not be able to see the real feedback of the actuator, as it will be in SIMULATION mode.

A)



B)

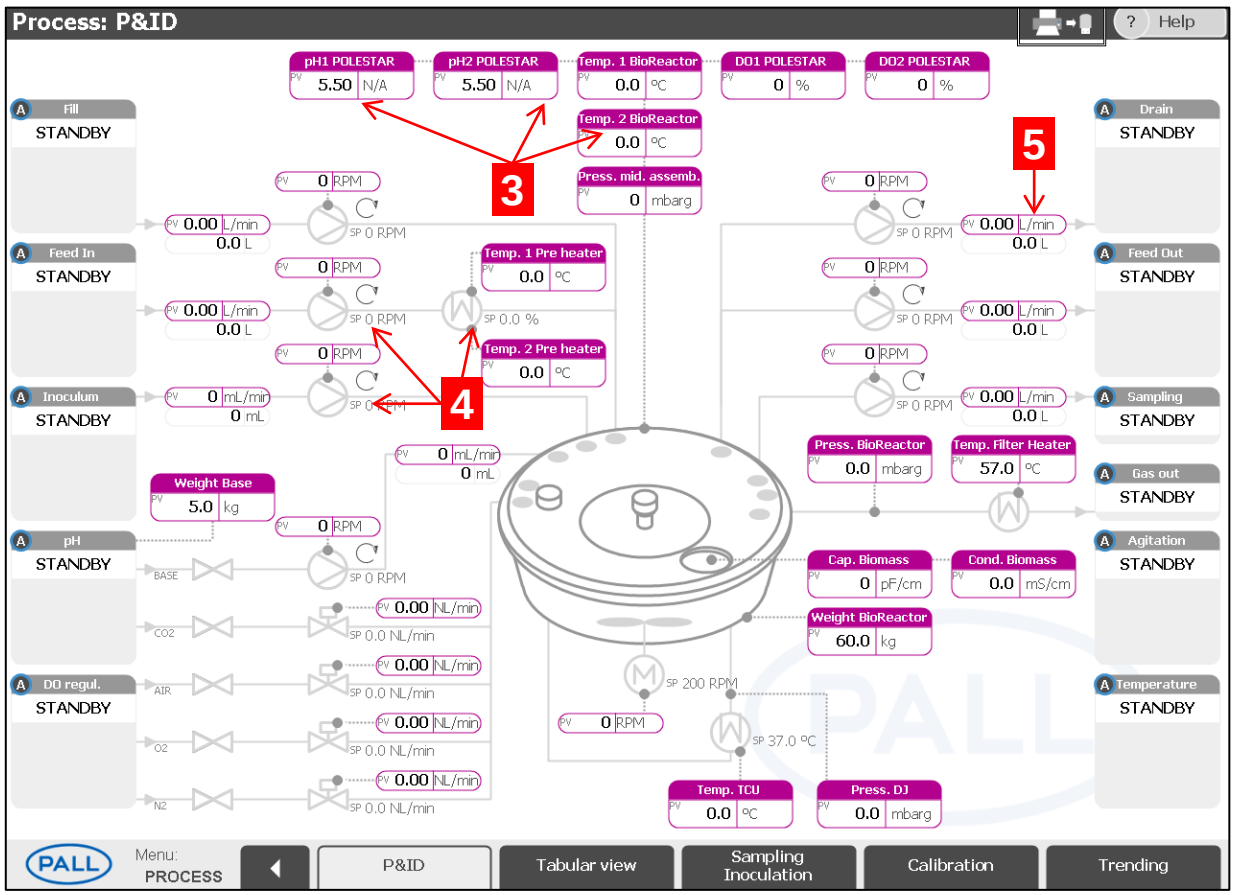


Figure 32: Activation and visualization of Simulation mode – A) RECIPE: EXECUTION screen cut view, B) P&ID screen, 1) Simulation switch, 2) Simulation inscription in HEADER, 3) Simulated sensors, 4) Simulated actuators, 5) Simulated flow rates.

When enabled, SIMULATION mode is constantly visible in the HEADER with the (Simulation) inscription in the Recipe shortcut. When a response of an actuator or a sensor is simulated the element is displayed in purple on the process visualization screens (HOME, P&ID, EM dialog boxes) (Figure 32-b).

Simulation of actuator includes the POWER status (ON/OFF) and a FEEDBACK status. To simulate an actuator, start by simulating POWER to ON. Other simulation options depend upon actuator type (Table 17).

Table 17: Simulated elements options (actuators/sensors configuration tabs)

Element	Simulation Options When Enabled
Valve	FEEDBACK OPEN: send OPEN feedback to PLC POWER ON: send power ON/OFF feedback to PLC
MFC	POWER ON: send power ON/OFF feedback to PLC
Pump	FEEDBACK RETURN: activate pump feedback to PLC POWER ON: send power ON/OFF feedback to PLC
Heater	FEEDBACK RETURN: activate pump feedback to PLC POWER ON: send power ON/OFF feedback to PLC
Sensor	SIMULATION VALUE: send simulated measure value to PLC
Totalizer	SIMULATION VALUE: send simulated total value to PLC

8. Calibration of Sensors

8.1 General Information

Calibration actions required for routine operation can be performed from the PROCESS: CALIBRATION menu and navigating through tabs and pages to access a specific sensor. Note that apart from the DO calibration only 1-point calibrations are accessible in the Calibration menu.

It is not possible to perform the calibration of any sensor if it is in simulation mode. All sensors that are going to be calibrated must be out of simulation mode before starting the calibration.

8.2 Bioreactor Pressure Sensors Calibration

The iCELLis 500+ bioreactor includes three pressure sensors: bioreactor overlay pressure sensor (pressure inside the vessel or pressure of the bioreactor), double-jacket (DJ) pressure sensor and pressure of the hardware middle assembly sensor. The bioreactor pressure is linked to all 'flowing' EM of the bioreactor, either liquid or gas. The DJ pressure is linked to the TEMPERATURE EM (TCU) only. The pressure sensor for the middle assembly is present to detect any leakage of the gases before the safety valves inside the hardware cabinet.

Pressure sensors should be zeroed when the bioreactor is in place and empty and before any flow is applied, gas or liquid, to the bioreactor overlay or double-jacket. All EM should be OFF during calibration of the pressure sensors.

To zero a pressure sensor, access the corresponding tab/page in the CALIBRATION menu. Both sensors present the same calibration procedure (Figure 33):

- Reset the offset (RESET button);
- Review the Actual value, it should be close to zero;
- Enter zero in offline measurement to define zero point;
- Confirm the entry with the CONFIRM button.

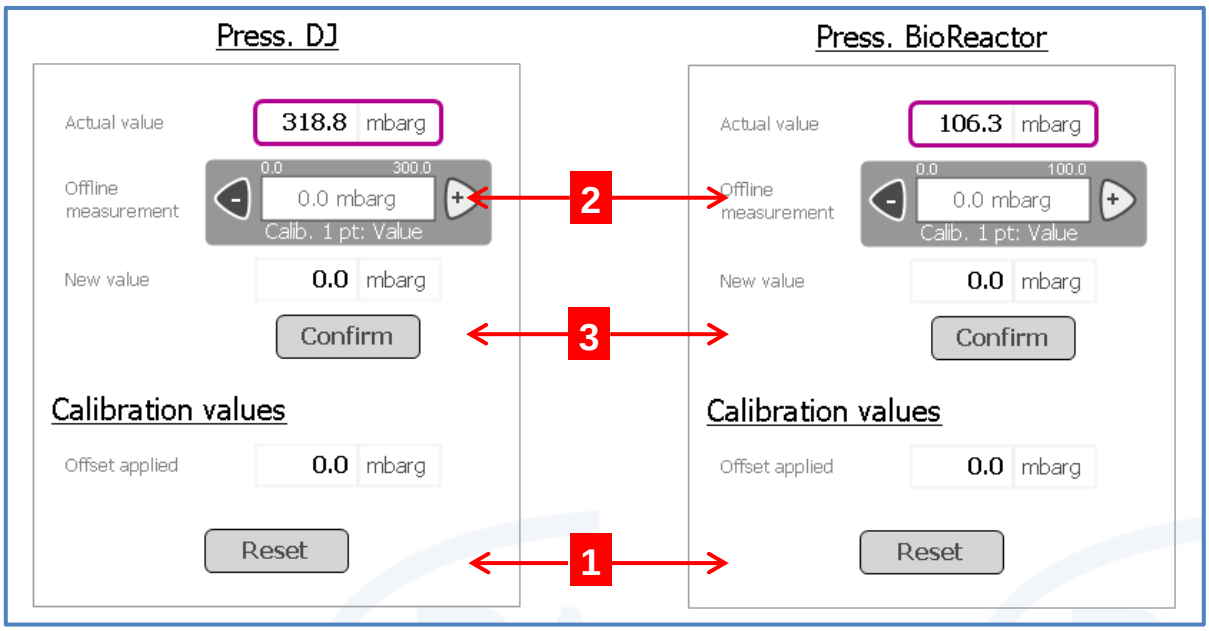


Figure 33: Pressure sensors calibration box – 1) RESET button, 2) CALIBRATION offline measurement input, 3) CONFIRM button.

8.3 Weight Scales Calibration

The iCELLis 500+ bioreactor system has a base weight and bioreactor weight scale. The base scale is linked to the pH EM. The bioreactor weight scale is linked to the Fill/Drain/Feed IN/Feed OUT/Inoculum/Sampling/Agitation EM.

Taring of the base weight scale should occur before putting the base bag and manifold on the scale. Base addition during a process can be followed by subtracting the current weight from the initial weight.
Taring of the bioreactor weight should occur after positioning the bioreactor on load cells, connecting all manifolds and completely filling the double-jacket of the bioreactor with heat transfer fluid. This way the process will record only the weight of media going IN/OUT of the bioreactor.
Due to the agitation at higher speeds there are fluctuations in the weight measurement reading of the Bioreactor due to the interactions between the magnets (The fluctuation is +-3% of the total weight). Hence in the PLC, a weight compensation formula is programmed. This weight compensation formula takes speed feedbacks to calculate the loss of weight due to misalignment of magnets and adds this value to the measured weight from the load cells.
The result of the weight compensation formula on the measured weight is as below,
Corrected Weight (when, agitation speed < 300 rpm) = +- 1% of real weight of media at 0 rpm
Corrected Weight (when, 350 rpm < agitation speed < 450 rpm) = +- 3% of real weight of media at 0 rpm.
All related EM should be OFF during the calibration procedure.

Taring (zero) of weight scale is accessible from the CALIBRATION menu and corresponding tab/page. Both weight scales present the same dialog box (Figure 34).

Figure 34: Weight base Calibration dialog box – 1) RESET TARE button, 2) Initial weight = raw data without Tare offset, 3) TARING button, 4) Currently applied Offset, 5) Live weight with Tare offset applied.

If necessary, use the RESET TARE button to clear the previous taring offset. Then use the TARING button to initiate the scale tare and wait for the button to come back to the initial state (lower case on light grey background).

8.4 Capacitance Calibration

ALERT! Risk of damage to the process!
Do not use the CLEAN PULSE button during a process as this would damage cells below the Biomass probe. The CLEAN PULSE button refers to the electrical cleaning of the probe electrode surface. The CLEAN PULSE should be used before the first use of the probe, or if it has been handled. The electrical cleaning is best done in water with Sodium Chloride or Potassium Chloride in as high a concentration as possible. It is recommended by Aber to use 30 mS/cm Sodium

Chloride solution but it might not be possible to use such a high conductivity solution in some applications.

The integrated Biomass probe in the iCELLis 500+ bioreactor is based on radio-frequency impedance, related to the permittivity and capacitance. By misuse of language the name has been simplified to Capacitance probe or Biomass probe. The measurement is expressed in pF/cm. Capacitance depends upon the measuring frequency settings and those can vary based on application. Biomass probe settings can be modified in the Calibration: Cap: Biomass menu. Capacitance's absolute value is dependent on the environment background measurements, cell concentration and cell morphology.

IMPORTANT!
The Biomass probe should be zeroed just before inoculation of cells when the media has equilibrated at culture temperature.

IMPORTANT!
The Biomass measurement is only valid when the probe is submerged which is the case only if the volume in the bioreactor exceeds probe level or if agitation is high enough to create a falling film. Always check that the probe is immersed before zeroing.

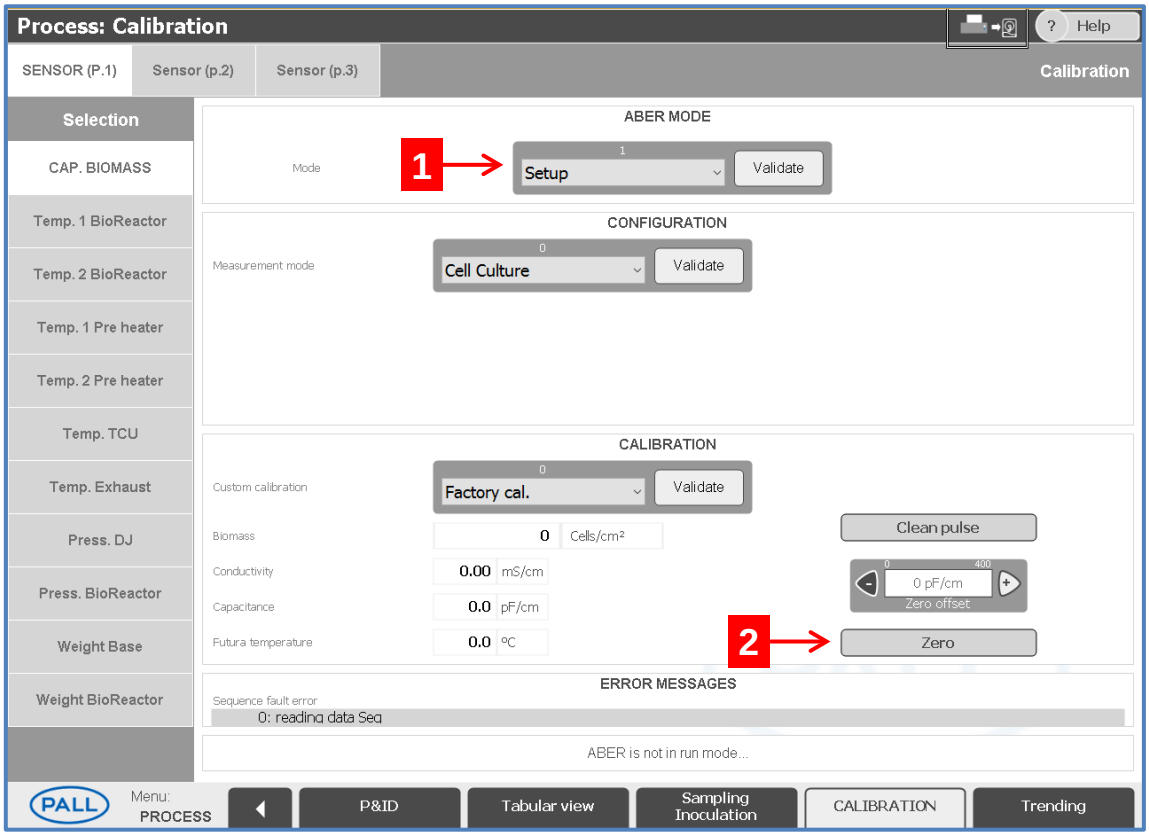


Figure 35: Capacitance calibration screen – 1) Probe mode selector, 2) ZERO button.

To Zero Biomass probe:

- Go to the Calibration page of Biomass;
- Set the probe to Setup (ABER MODE => Setup => Validate);
- Select the ZERO button to zero the measure.

8.5 pH and DO Sensors Pre Calibration

The pH and DO sensors are single use sensors integrated into the bioreactor vessel that transmit measurements through optical fibers to a dedicated sensor module named the Polestar module. Calibration data specific to the sensor lot in the bioreactor vessel must be loaded on to the Polestar sensor module prior to starting a run.

The iCELLis 500+ bioreactor Control System hosts the DSP-4000 Polestar technology which provides pH and DO measurements using single-use sensors. The signals received by this module are used to monitor and control cell culture processes in the iCELLis 500+ bioreactor. Before starting a culture, users should assure the bioreactor is delivered with a USB key (Figure 36) which contain the calibration files of the single-use pH and DO probes.

Figure 36: Polestar USB Key for iCELLis 500+ bioreactor

ALERT! Risk of damage to the process!
Never remove the USB key from the Polestar module when in running mode. Carefully follow instructions described in this User Manual. Any other intervention than the ones specified in this manual are under the responsibility of the user.
To remove or replace the USB follow the guide described below.

- Go to Configuration: Pre-process: Polestar Parameters View on HMI.
- Select any of the 4 channels, select shut down mode from drop down menu, and hit apply.
- Click on the 'Eject' button, and wait for the message 'you can now safely remove the USB key' Once the message is displayed you can replace or reinsert the USB key.
- Once the USB is replaced or reinserted, click on the 'Start' button. The message 'Polestar is starting up wait for minimum 1 minutes' will be displayed. After successful 'power on' the user will have the option to put the polestar back to Run or setup mode.

ALERT! Risk of damage to the process!
Do not leave the current channel's calibration screen while the calibration of any Polestar sensor is ongoing. There is a risk that the calibration could not be finished. Wait until the success message of the Polestar appears.
If the screen is changed while the calibration is ongoing, the calibration must be performed again.

IMPORTANT!
Each iCELLis 500+ bioreactor is supplied with a USB key. This key is specific for each bioreactor and its labeling should match the labeling of the iCELLis 500+ bioreactor's lot number. In case this key is missing, please directly contact your Pall sales representative.
The calibration files supplied on the USB key can be checked using the DSP Config Utility software directly accessible on the Polestar website (http://polestartech.com/support/) for end-users. For more details, please contact your dedicated bioprocess application specialist.
The firmware installed on the DSP-4000 should be version 4.785. In case the firmware version is not correct, please contact your dedicated bioprocess application specialist.

IMPORTANT!
Two different USB keys come with the iCELLis 500+ bioreactor. One for the old iCELLis 500 Control System and the other for the iCELLis 500+ bioreactor. Make sure that the USB key marked with 500+ bioreactor is plugged in the iCELLis 500+ bioreactor (Figure 36).

IMPORTANT!
The lot numbers should correspond to the numbers on the documentation delivered with the iCELLis 500+ bioreactor vessel. If the DSP Config Utility software or calibration screen display a lot

number value of 123-456-789, then the calibration files are corrupted and default values for pH and DO are being read. In this case, the correct patch calibration files should be downloaded from the Polestar website and loaded into a new USB key using the DSP Config Utility software from Polestar. For more details, please contact your bioprocess application specialist.

IMPORTANT!

For pH measurements user must enter the PV high and low limit to scale the 4 – 20 mA signals. This can be done by following the guide described below.

- using the DSP Config Utility software (http://polestartech.com/support) from Polestar to obtain the high and low limits for the pH sensors. These values should match the values on the USB label.
- Go to Process: Calibration: Sensor (P.3) and select pH1 Polestar
- Select the 'Setup' mode from drop down list and apply.
- Enter the PV low and High limit (the smaller value for low and the larger value for high).

Follow the same procedure mentioned above for pH2 as well.

8.6 pH Sensors Calibration

ALERT! Risk of damage to process!

Note that setting the Polestar module to SETUP mode interrupts all channels measurements (pH1, pH2, DO1 and DO2) which will result in the last measured value to be displayed continuously until the Polestar module is changed back to run mode. Any on-going regulation will continue with the last received value.

IMPORTANT!

The pH measurement is only valid when the probe is submerged which is only the case when the volume in the bioreactor exceeds the probe level or if agitation is strong enough to create a falling film. Always check that the probe is submerged before calibrating.

There are two pH sensors: one sensor measures the pH of the media before the fixed-bed and the other one measures the pH after the media passes through the fixed-bed. Initially the calibration data needs to be downloaded directly onto the Polestar module. After which a 1-point calibration is performed based on the off-line pH readings of the culture media.

Figure 37: pH 1 Calibration page – 1) Transmitter mode selection list and button, 2) RESTORE DEFAULT CALIBRATION button, 3) pH Off-line calibration value setting, 4) CALIBRATE button, 5) Sensor calibration lot information, 6) Polestar module calibration messages.

With the pH probes submerged in media and an off-line reference measurement, navigate to PROCESS: CALIBRATION and apply the following procedure for calibration:

- Select the page of the sensor to be calibrated (Figure 37);
- Set the Polestar module to SETUP mode and validate (Figure 37-1);
- Enter the offline pH value (Figure 37-3)**;**
- Select CALIBRATE (1 POINT) button (Figure 37-4) and wait for the calibration to be complete; The Polestar module must display the message ‘CAL_SUCCES’ (Figure 37-6);
- Turn the sensor module back to RUN mode and validate (Figure 37-1).

IMPORTANT!
The pH drift during process is a normal behavior observed with any type of pH probe (single-use or re-usable). It is thus necessary to check off-line pH daily and recalibrate if necessary. If the offline pH value is greater than 0.1 during the process, it is recommended the offline pH is retested to confirm the reading is accurate. Also confirm the fiberoptic cables are fully inserted.

In the pH calibration menu, it is also possible to check the patch lot number corresponding to the loaded calibration data (Figure 37-5) and reload the factory calibration if required (Figure 37-2).

8.7 DO Sensors Calibration

ALERT! Risk of damage to process!
Note that setting the module to SETUP mode interrupts all channels measurement (pH1, pH2, DO1 and DO2) and this will display the last measured values.
Any on-going regulation will continue with last received value.

ALERT! Risk of damage to the process!

It is recommended to calibrate DO prior to pH to get the most accurate DO reading.
It is particularly the case for 2-points calibration procedure.

There are two DO sensors: one sensor measures the DO of the media before the fixed-bed and the other one measures the DO after the passage of the media through the fixed-bed but before its equilibration in the overlay. After loading the initial calibration data in the Polestar sensor module, it is possible to proceed to 1-point or 2-point calibration of the DO sensors.

IMPORTANT!
DO measurements are only valid when the probe is submerged which is the case only if the volume in the bioreactor exceeds the probe level or if the agitation is strong enough to create a falling film. Always check that the probe is immersed before calibrating.

To calibrate DO sensors, navigate to PROCESS: CALIBRATION (Figure 38).

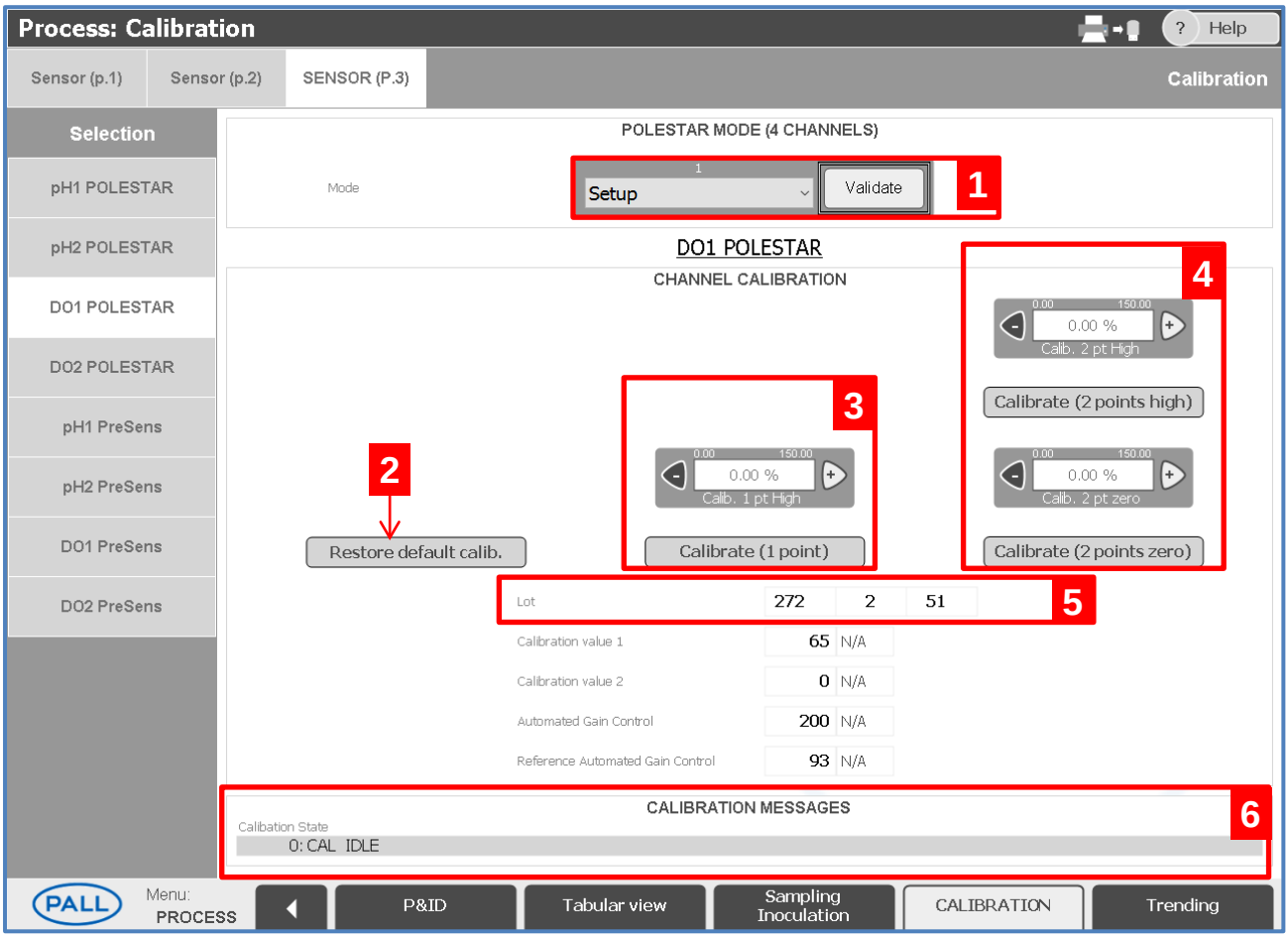


Figure 38: DO 1 & 2 Calibration screens – 1) Transmitter mode selection list and button, 2) RESTORE DEFAULT CALIBRATION button, 3) 1-point calibration value and CALIBRATE button, 4) 2-points calibration values and CALIBRATE buttons, 5) Sensor calibration lot information, 6) Polestar module calibration messages.

8.7.1 1-Point Calibration

It is recommended to use a DO 1-point calibration when the observed/controlled dissolved oxygen values in the process are not in a low range (DO below 20 % Air saturation). To be accurate, 1-point calibration should be done on media equilibrated at process temperature, with Air flush in the overlay. In these conditions, at stable DO measurement, DO can be calibrated to 100 % AS.

For 1-point calibration, apply the following procedure:

- Select the page of corresponding sensor (Figure 38);
- Set Polestar module to SETUP mode and validate (Figure 38-1);
- Set DO conditions in the bioreactor (100 % AS) and wait for stabilization of the DO measurement, then enter DO calibration absolute value (100 %) (Figure 38-3);
- Select CALIBRATE (1 POINT) button (Figure 38-3) and wait for the calibration to be completed. The Polestar module must display the message ‘CAL_SUCCES’ (Figure 38-6);
- Turn the sensor module back to RUN mode and validate (Figure 38-1).

8.7.2 2-point Calibration

It is recommended to proceed to perform a DO 2-points calibration when the observed/controlled dissolved oxygen values in the process are in low DO range (DO below 20 % Air saturation) to have more precise measurements/control. Set the bioreactor conditions for the High calibration point as described for the 1-point calibration. For the Low calibration point, flow N_2 through the overlay until reaching a stable DO reading and calibrate to 0 % AS.

For 2-points calibration apply the following procedure:

- Select the page for the corresponding sensor (Figure 38);
- Set the Polestar module to SETUP mode and validate (Figure 38-1);
- Set the high DO conditions in bioreactor (100 % AS) and wait for the stabilization of the DO measurement, then enter the DO calibration absolute value in CALIB. 2 pt HIGH field (Figure 38-4);
- Select the CALIBRATE (2 POINTS HIGH) button and wait for the first point calibration to be complete. The Polestar module must display the message ‘CAL_SUCCES’ (Figure 38-6);
- Set the low DO conditions in bioreactor (0 % AS, see below) and wait for stabilization of the DO measurement, then enter DO calibration absolute value in CALIB. 2 pt zero field (Figure 38-4);
- Select the CALIBRATE (2 POINTS ZERO) button and wait for the second point calibration to be complete. The Polestar module must display the message ‘CAL_SUCCES’ (Figure 38-6);
- Turn the sensor module back to RUN mode and validate (Figure 38-1).

8.8 Pumps Flow Rate and Totalizer Calibration

For each peristaltic pump of the iCELLis 500+ bioreactor control system, it is possible to establish the correlation between pump speed in rpm and flow rate in L/min or mL/min. This correlation depends upon the tubing ID, OD, material, back pressure, age, media viscosity. To establish this correlation, the user must measure the flow-rate based on the mass transferred versus time of operation at two pump speeds. This data can then be entered in the iCELLis 500+ bioreactor control system and is used to display flow-rate on the P&ID screen and to totalize flow through a pump.

All pumps must be calibrated before the totalizer displays an accurate value.

To enter the correlation data into the iCELLis 500+ bioreactor control system, navigate to PROCESS: CALIBRATION and select the page of the corresponding pump. The following dialog box is displayed (Figure 39).

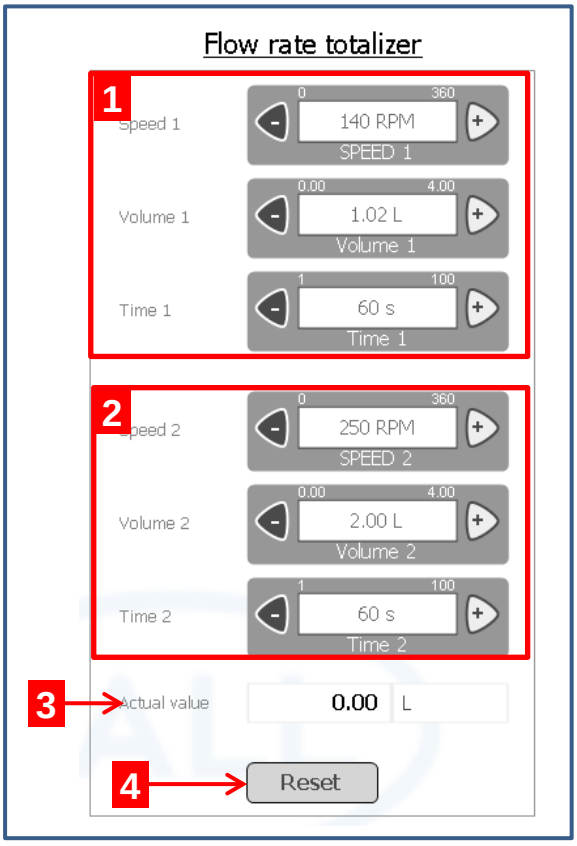


Figure 39: Pump flow rate calibration and flow rate totalizer calibration box – 1) Correlation data set 1, 2) Correlation data set 2, 3) Current value of pump totalizer, 4) RESET TOTALIZER button.

Enter the correlation data set 1 and 2 in the corresponding rows (Figure 39-1&2):

- Speed: pump speeds chosen to establish correlation
- Volume (kg): Mass transferred to establish correlation
- Time (s): time required for mass transfer

The calculated flow rate is automatically updated when values the are changed.

The flow rate totalizer calibration box also displays the Total volume which has gone through the pump since its last reset (Figure 39-3). To zero the totalizer, select the RESET button (Figure 39-4).

9. Control Loop Tuning

ALERT! Risk of damage to the process!
Incorrect settings of control loops can result in inconsistent behavior of regulations and can impact process parameters.
Factory settings of PID in the iCELLis 500+ bioreactor have been defined to cover standard applications. PID settings can be optimized for a specific application however it will require strong theoretical knowledge of control loop regulation and time-consuming experimental testing with the iCELLis 500+ bioreactor system before finding stable and optimized parameters. Control loops settings modification is the user's responsibility.

9.1 Control Loop Tuning Principles

Control loops in the iCELLis 500+ bioreactor control system rely on classical regulation strategies using Proportional-Integral-Derivative (PID) parameters that can be modified by the user.
In order to clarify the terms used in the iCELLis 500+ bioreactor software a general description of control loop parameters is given in Table 18.

Table 18: General description of control loop parameters

Parameter	Description
P	Proportional term. Amplification of control output proportional to present delta between PV and SP. Output increases with P.
I	Integral term. Modulation of control output based on time of integration of delta between PV and SP. The higher I, the slower the Control System response.
D	Derivative term. Modulation of control output based on the rate of change between SP and PV.
Dead-band width	Zone around the SP where Control System output is stable. For base and CO_2 regulation there is a special deadband that must be defined via the EM dialog box of pH (Figure 21.) This deadband is created to have a dead zone where Base and CO_2 regulation are not active thus meaning no flow of Base or CO_2. The reason to create this deadzone is to avoid 'ping pong effect' of continuous addition of Base or CO_2.
PWM	Pulse-Width Modulation is a regulation mode in which the actuator output is binary (ON/OFF), or pulsed-delivered, with a pulse duration modulated by the control loop. In other terms, the control loop controls ON/OFF time rather than output level.
Cycle time	Cycle time of Pulse-Width Modulation (PWM). This is the period of time required for PWM to complete an ON-and-OFF cycle.
PWM threshold	Under this actuator output threshold, the regulation switches to PWM.
Output Low Limit	Minimum Control System output to start the actuator.
Output High Limit	Maximum Control System output sent to actuator. This allows restriction of the control loops impact on the process.

9.2 Control Loop Parameters Tuning

To access the control loop parameters, navigate to CONFIGURATION: LOOP TUNING. From this menu parameters of the following control loops are accessible:

- pH regulation
- DO regulation
- Feed IN Preheater regulation
- Feed Out regulation (when based on bioreactor weight)
- Bioreactor temperature regulation
- Gas Out heater regulation

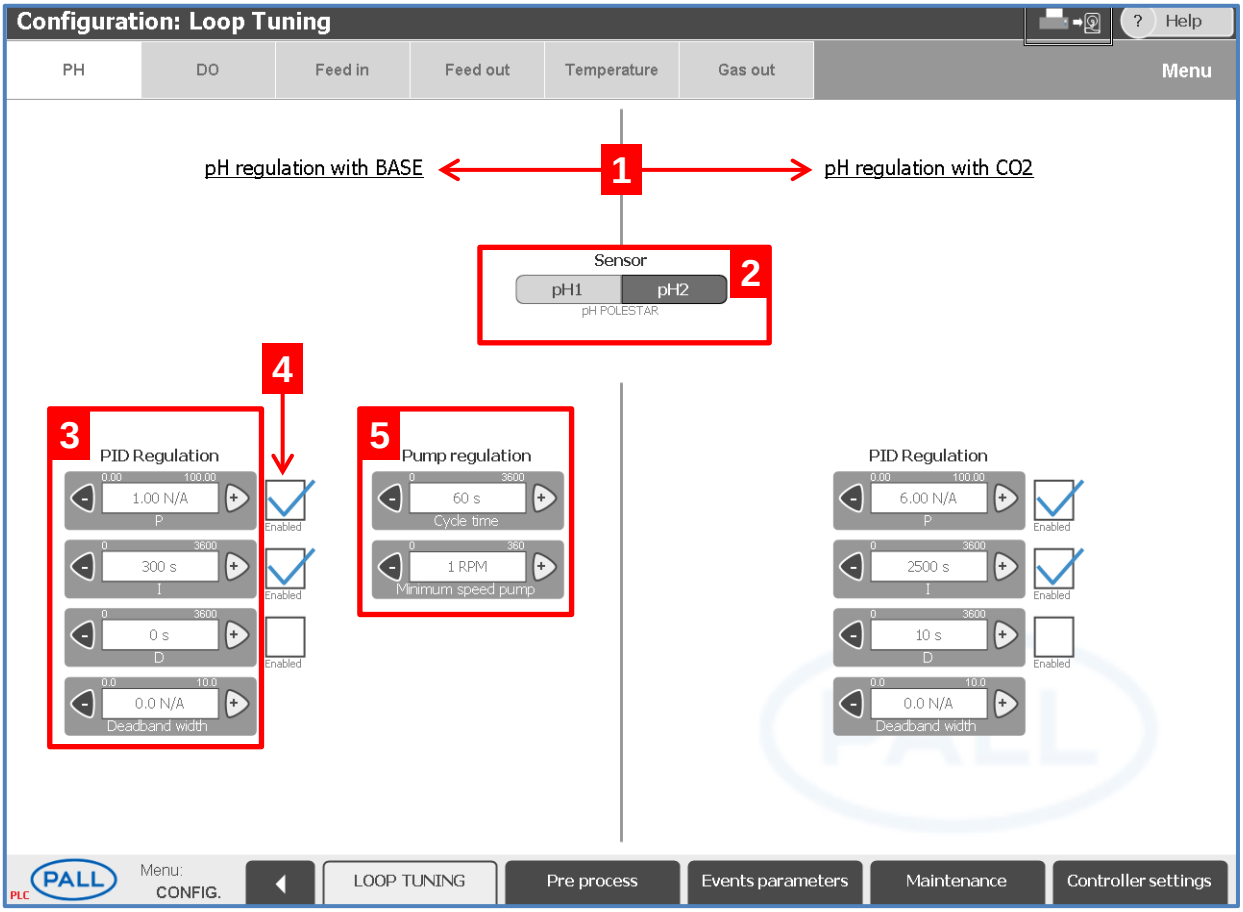


Figure 40: LOOP TUNING menu – 1) Control loop name, 2) Control loop sensor selector, 3) Control loop PID settings, 4) PID settings enabling checkbox, 5) PWM regulation parameters.

Depending on control loop structure, accessible parameters are:

- Sensor selection (Figure 40-2);
- PID settings value (Figure 40-3) and enabling/disabling checkbox (Figure 40-4);
- PWM parameters (Figure 40-5).

9.3 Output Limits

The Output Low limit of a control loops is the minimum required output of the actuator. By default, this is usually 0.
If the output lower limit is set to a value higher than 0, when the actuator is activated, it will not be able to operate at any values lower than the output lower limit value. The actuators will only be turned off if they are set to off (as explained in the chapter 7).

The Output High limit allows the restriction of an actuator output and decreases the risk of overshooting in regulation. However, if the value for the High limit is too low, it will make the regulation less dynamic and could even make it inefficient. High limits for CO_2 and Base pump should be set at 66.6% and 54 rpm respectively, to match with previous system version: iCELLis 500 bioreactor.

Output limits for the control loops can be found in CONFIGURATION: PREPROCESS (Figure 41).

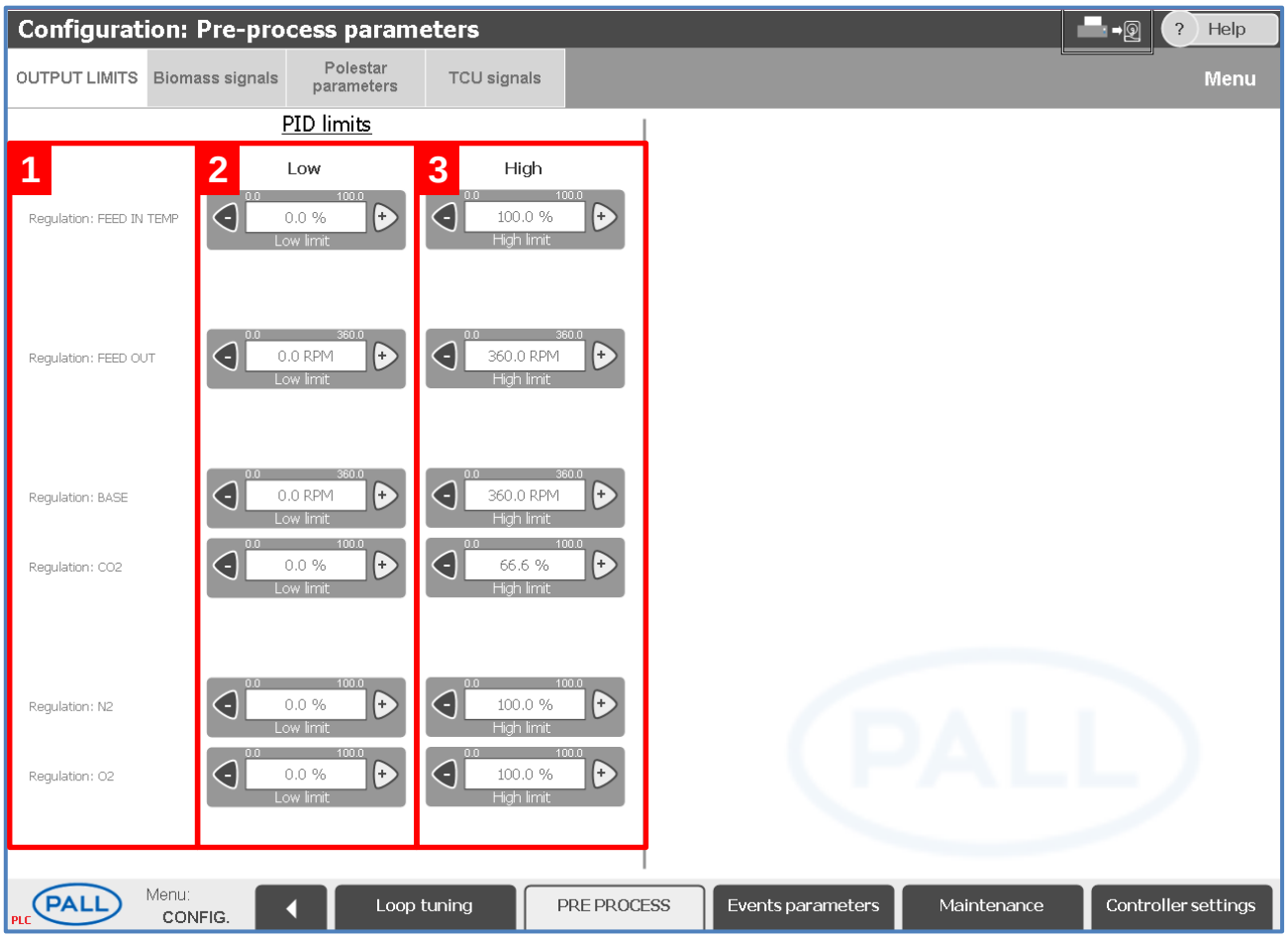


Figure 41: Output limits of control loops – 1) Control loop name,2) Output Low limits, 3) Output High limits.

Output limits are available for the following actuators:

- FEED IN preheater bag;
- FEED OUT pump speed based on REG_VOL strategy;
- BASE pump speed;
- CO_2 MFC flow;
- N_2 MFC flow;
- O_2 MFC flow.

9.4 Temperature Control Unit Settings

The Temperature Control Unit (TCU) is part of the TEMPERATURE EM and the TCU settings are accessible in CONFIGURATION: PREPROCESS: TCU SIGNALS (Figure 42).

All TCU parameters are displayed on this screen however only a few parameters can be modified through iCELLis 500+ bioreactor software. Particularly, PID settings of the TCU (Figure 42-5) can only be modified directly on the TCU touch panel after unlocking it through iCELLis 500+ bioreactor software.

ALERT! Risk of damage to the process!
Incorrect settings of control loops can result in inconsistent behavior of regulations and can impact process parameters.
Factory PID settings for the TCU have been defined to cover standard applications. PID optimization for a specific application will require strong theoretical knowledge of control loop

regulation and time-consuming experimental testing with the iCELLis 500+ bioreactor system before finding stable and optimized parameters.
The control loop's settings modification is the user's responsibility.

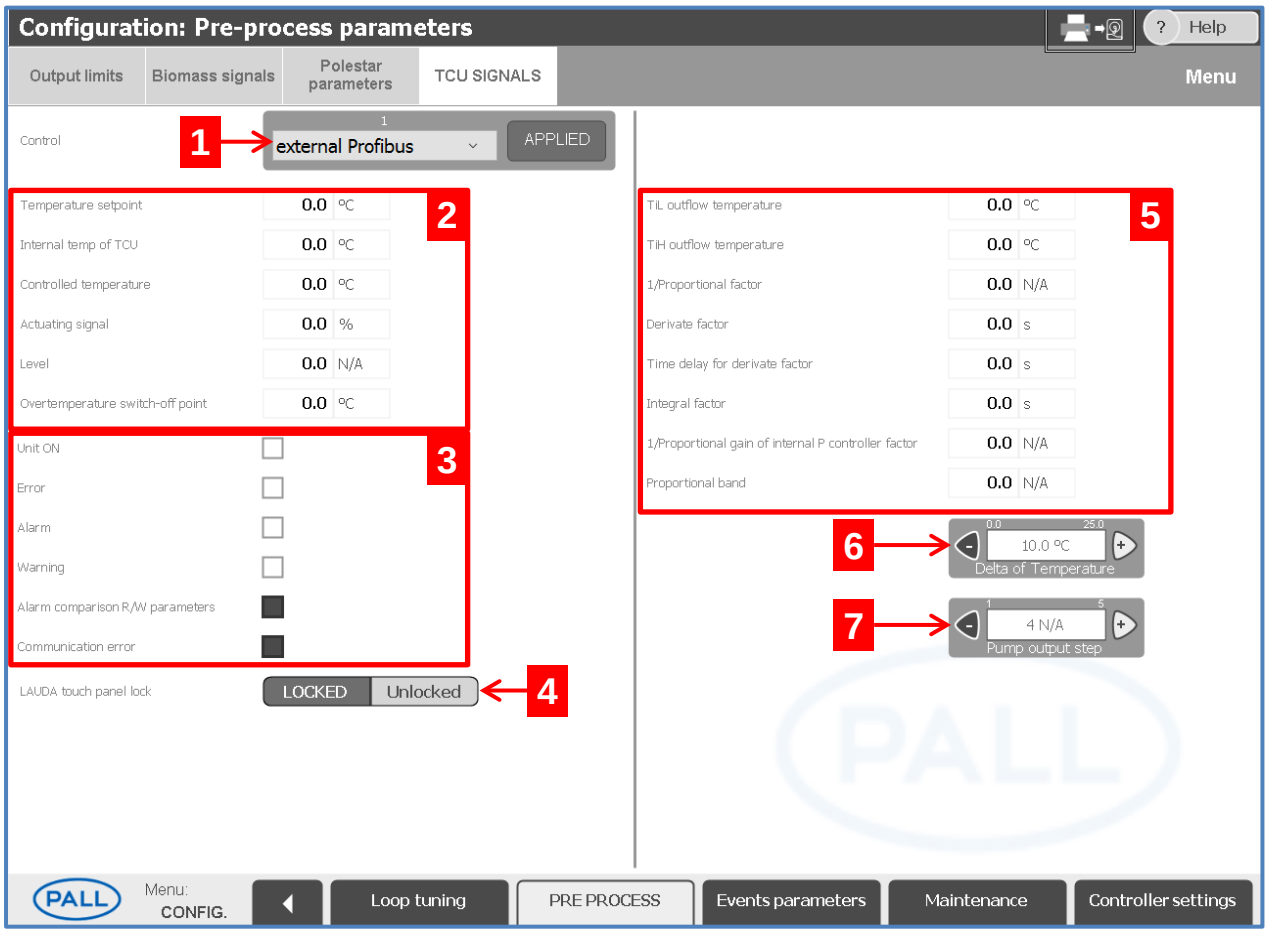


Figure 42: TCU signals page – 1) TCU Control setting, 2) TCU live signals value, 3) TCU status, 4) TCU touch panel Locking/Unlocking button, 5) TCU PID parameters value, 6) Delta of Temperature, 7) Pump Output step.

The following parameters can be modified through iCELLis 500+ software:

- TCU Control (Figure 42-1): regulation can be controlled by the iCELLis500+ PLC value (external Profibus) (Recommended), or by the TCU internal probe as a standalone device (internal). The first option allows regulation control by bioreactor temperature probes or the internal probe of the TCU (see Section 7: EM03 – TEMPERATURE);
- TCU touch Panel lock (Figure 42-4): allows locking or unlocking the TCU touch panel to modify the local settings of the TCU;
- Delta of Temperature (Figure 42-6): A parameter that limits the temperature of the water in the TCU, based on the measurement of the temperature in the bioreactor. This feature can prevent the difference between the bioreactor temperature and TCU water from being too large. The Output High limit will supersede this control function. This parameter is used to optimize temperature regulation stability in a steady-state situation.

Delta of Temperature parameter depends upon process conditions (culture temperature set-point, agitation, feed-in and feed-out flow-rates) but also environmental conditions (room temperature, feed-in media temperature).
This value must be determined in process conditions by users for optimal performances of temperature regulation. The value for Delta of Temperature is limited in a maximum of 25 ºC for process safety reasons.

- Pump Output step (Figure 42-7): This parameter defines the speed of the pump circulating fluid between the TCU and the bioreactor's double-jacket. Its value is fixed by steps between 1 and 5. To avoid overflowing the TCU, it is recommended to use a fixed step of 4.

WARNING! Risk of injury to personnel and/or damage to equipment!
TCU pump stage has a direct impact on pressure in the double-jacket. Special care must be taken when modifying this parameter.

The following parameters can only be observed by iCELLis 500+ bioreactor software:

- TCU live signals value (Figure 42-2): Presents the actual setpoint used by the TCU, the internal temperature of the TCU, the controlled temperature (can be the internal TCU temperature, or any of the temperature sensors of the bioreactor, depending on the configuration), the actual control signal, the level of liquid in the TCU and the temperature that switches off the TCU in case of overheating;
- TCU status (Figure 42-3): Presents binary notifications of the TCU, if it is powered On, if there is an internal error, alarm or a warning, if there is a difference between writing and reading the parameters or if there is a communication failure;
- TCU PID parameters value (Figure 42-5): Displays the control parameters of the TCU: High and low temperature limits, the proportional, integral, and derivative factors, the delay for the derivative factors. It also shows the proportional factor if the TCU is operated using its internal control instead of external Profibus (Figure 42-1) and the current proportional band of the control.

10. Hardware Tuning in Maintenance

ALERT! Risk of damage to process!
Incorrect settings in MAINTENANCE menu will lead to inconsistent behavior of hardware elements and could impact process.
Hardware settings must be changed only by trained persons using reliable reference sensors.

MAINTENANCE menu is mainly dedicated to tuning of hardware feedback precision and status. It is accessed in CONFIGURATION: MAINTENANCE.
Hardware tuning is done through different approaches depending on its type (Figure 43):

- Motors feedback (pumps and agitation), temperature probes, pressure sensors and MFCs are tuned through 1 or 2-points calibration of a standard communication protocol between the actuator (or its transmitter) and the PLC. It occurs at PLC level;
- Weighing scales are tuned through calibration of the signal between the scale and its transmitter. This occurs at the transmitter level (hardware) and calibration can be made through zeroing and 1-point calibration;
- Polestar probes (pH and DO) and Capacitance Biomass probe being single-use sensors, tuning is done through configuration of the transmitter to consider process or environment variables.

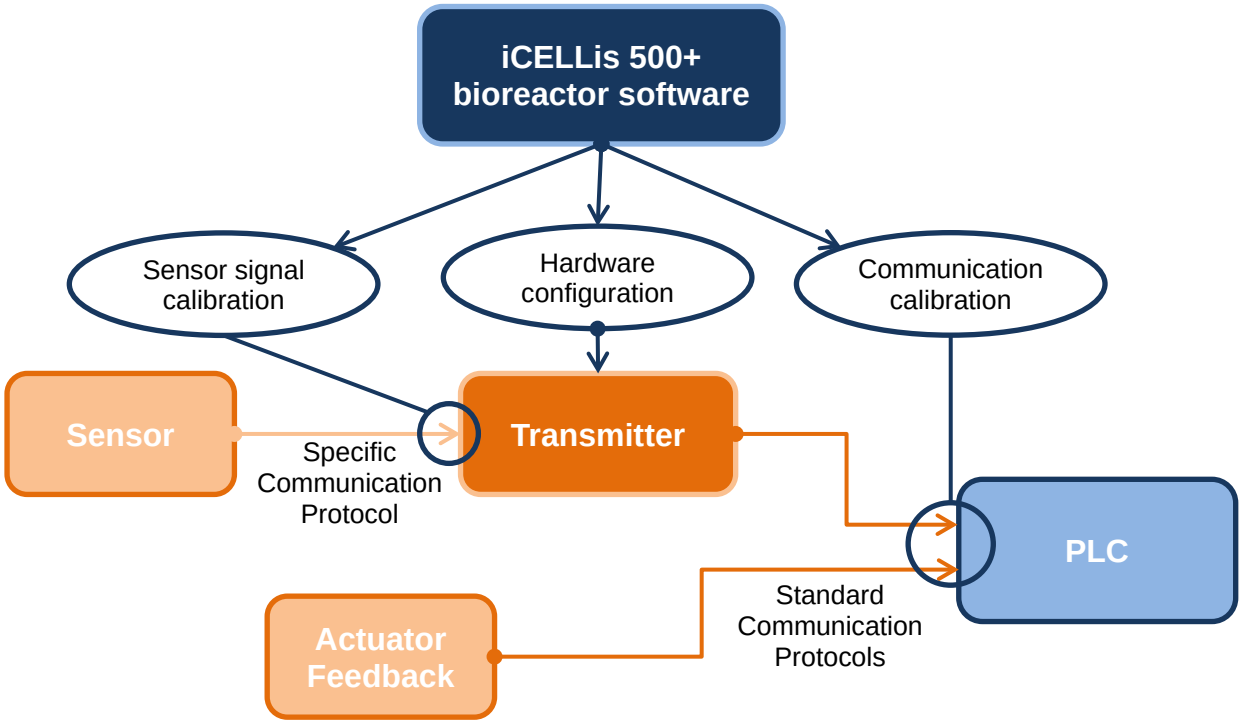


Figure 43: Illustration of the different hardware tuning methods

10.1 2-Points Calibration of Transmitters/PLC Communication

Transmitter/PLC communication of following sensors can be calibrated:

- Conductivity and Capacitance probe;
- All 6 temperature probes of the system;
- Double-jacket and bioreactor pressure sensors;
- MFCs gas flow;
- All pumps speed feedback;
- Agitation speed motor feedback.

For each item to calibrate, navigate to corresponding page; The 2-points calibration dialog box will be displayed (Figure 44).

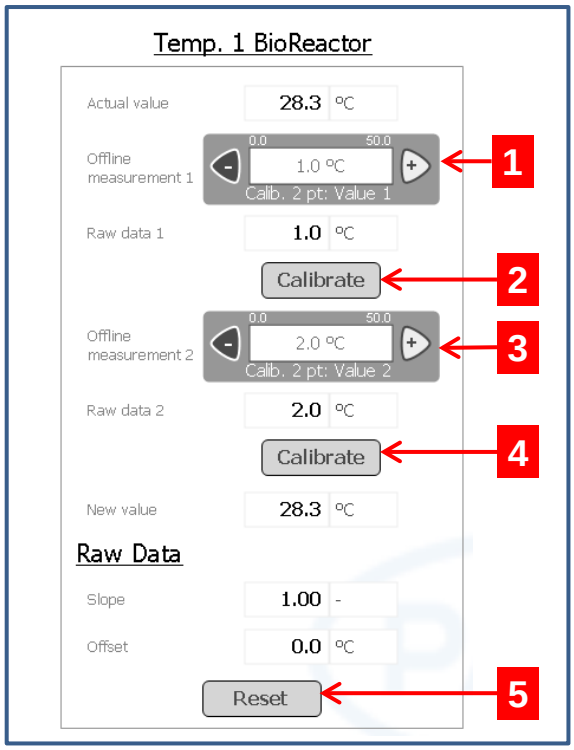


Figure 44: 2-points calibration dialog box in MAINTENANCE menu (Temp. 1 bioreactor as example) – 1) Calibration value 1 entry field, 2) CALIBRATE confirmation button for value 1, 3) Calibration value 2 entry field, 4) CALIBRATE confirmation button for value 2, 5) RESET to factory calibration button.

To calibrate follow this procedure:

- Place the item in state number 1 (e.g. submerge temperature probe in cold fluid; start the pump at a low speed…);
- Wait for the measure to stabilize on the iCELLis bioreactor system and measure the state with a reference probe;
- Enter reference probe value in Calib. 2pt: Value 1 field and confirm entry with CALIBRATE button just below;
- Place the item in state 2 (e.g. submerge temperature probe in hot fluid, set pump to high speed…);
- Wait for the measure to stabilize on iCELLis system and measure the state with a reference probe;
- Enter reference probe value in Calib. 2pt: Value 2 field and confirm entry with CALIBRATE button just below.

- Note the final Slope and Offset obtained (raw data at bottom of the box) and check they are in within accepted range of your quality assurance policy.

Use RESET button to come back to factory calibration. In this case slope of 1 and offset of 0 is applied.

10.2 Weighing Scale Hardware Calibration

Weighing scale calibration in CALIBRATION menu consists in a simple software Offset and is not written in Hardware settings. MAINTENANCE menu allows real calibration of weighing scale transmitter. For each weight scale to calibrate, navigate to corresponding page in HARDWARE PARAMETERS tab; the calibration dialog box will be displayed (Figure 38).

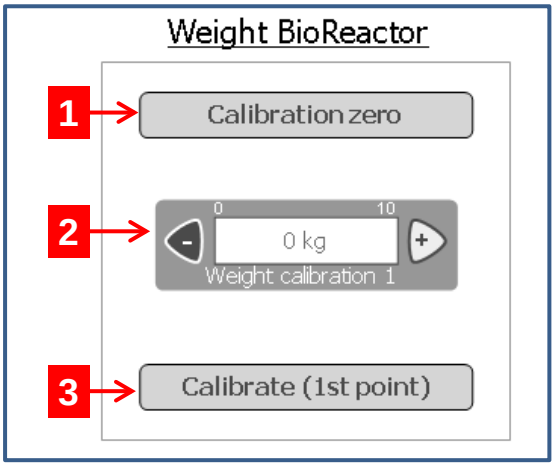


Figure 45: Weighing scale calibration dialog box – 1) CALIBRATION ZERO button, 2) Weight calibration value, 3) CALIBRATE button

To calibrate weighing scale Hardware, follow this procedure:

- Check the scale or load cells are properly installed, with tray in correct position;
- Select CALIBRATION ZERO button to set the system net weight to zero;
- Place the standardized mass on the scale and wait for measure to stabilize;
- Enter standardized mass in Weight Calibration 1 field;
- Select CALIBRATE (1st point) button and wait for the calibration to be done. The button returns to initial state when the calibration is finished.

10.3 pH and DO Hardware configuration

Maintenance menu allows changing settings of pH and DO sensor channel by channel. To do so navigate to corresponding page in HARDWARE PARAMETERS tab and set sensor module state to Setup mode (Figure 46-1).

ALERT! Risk of damage to process!
Note that setting the module to Set-up mode interrupts all channels measurement (pH1, pH2, DO1 and DO2) and this will display the last measured values.

All the suggested parameters that can be used in this section can be found on the hardware Design Specification (HDS).

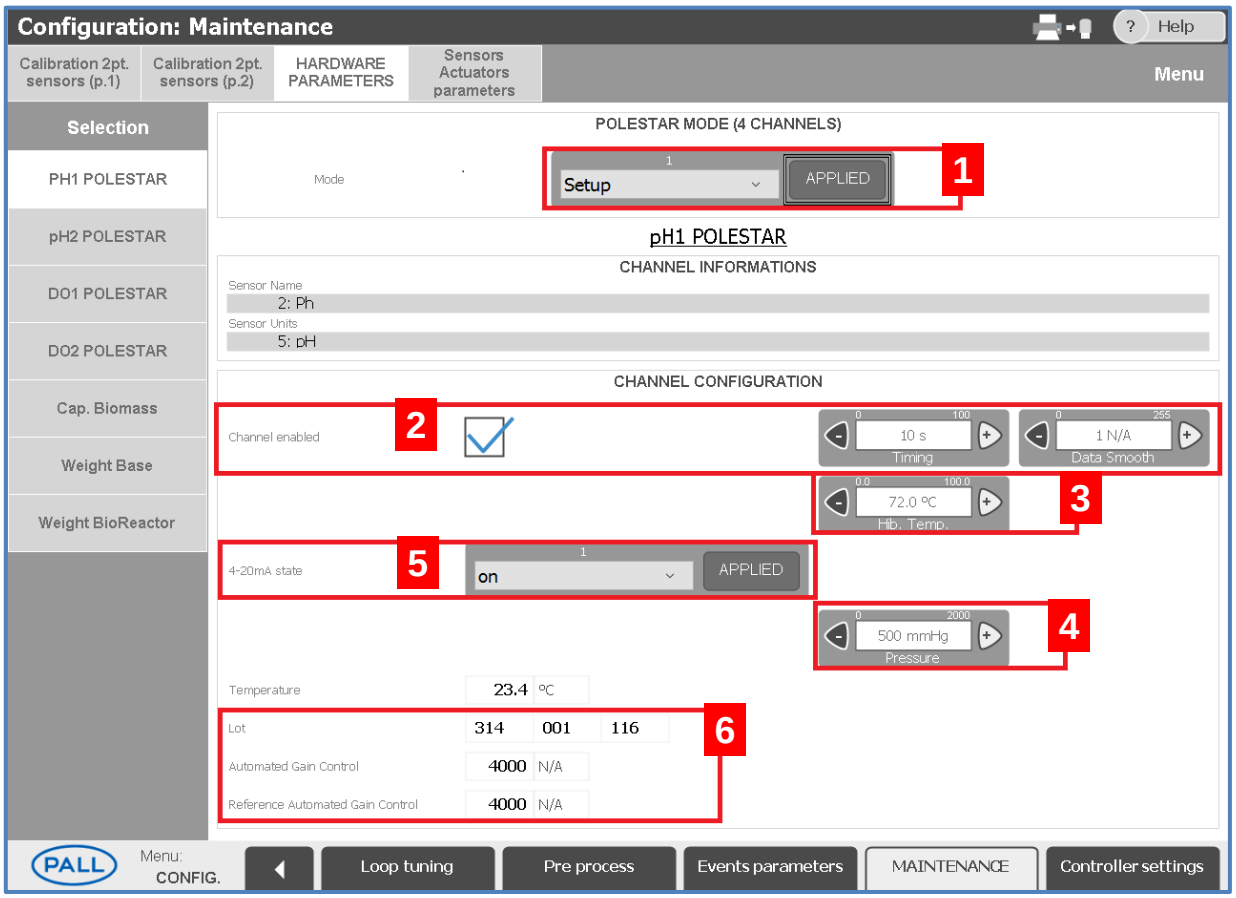


Figure 46: pH & DO transmitter settings maintenance page – 1) Transmitter mode settings, 2) Channel settings, 3) Temperature settings, 4) Pressure settings, 5) Communication to PLC state, 6) General calibration information.

The following parameters are accessible:

- Channel settings (Figure 46-2) allows enabling/disabling the channel, setting the sampling frequency and choosing the interval of data smoothing;
- Temperature settings (Figure 46-3) allow choosing working temperature source and setting manually working temperature and Hibernate temperature;
- Pressure settings (Figure 46-4) allow choosing working pressure source and setting manually working pressure;
- 4-20 mA state (Figure 46-5) represent the state of signal and it should be kept always ON. By switching it off user will lose the data for that channel.

10.4 Biomass Probe Hardware Configuration

Capacitance measurement depends upon measuring frequency settings and those can vary based on application.

If cells are growing at a very high cell density frequency should be increased from 580 kHz to 1000 kHz. This lowers the sensitivity of the probe but avoids saturating biomass probe signal. This should be considered if the signal exceeds 350 pF/cm with standard settings.

Access Capacitance Hardware settings and set ABER Hardware to Setup mode (Figure 47-1) for modification of measurement configuration.

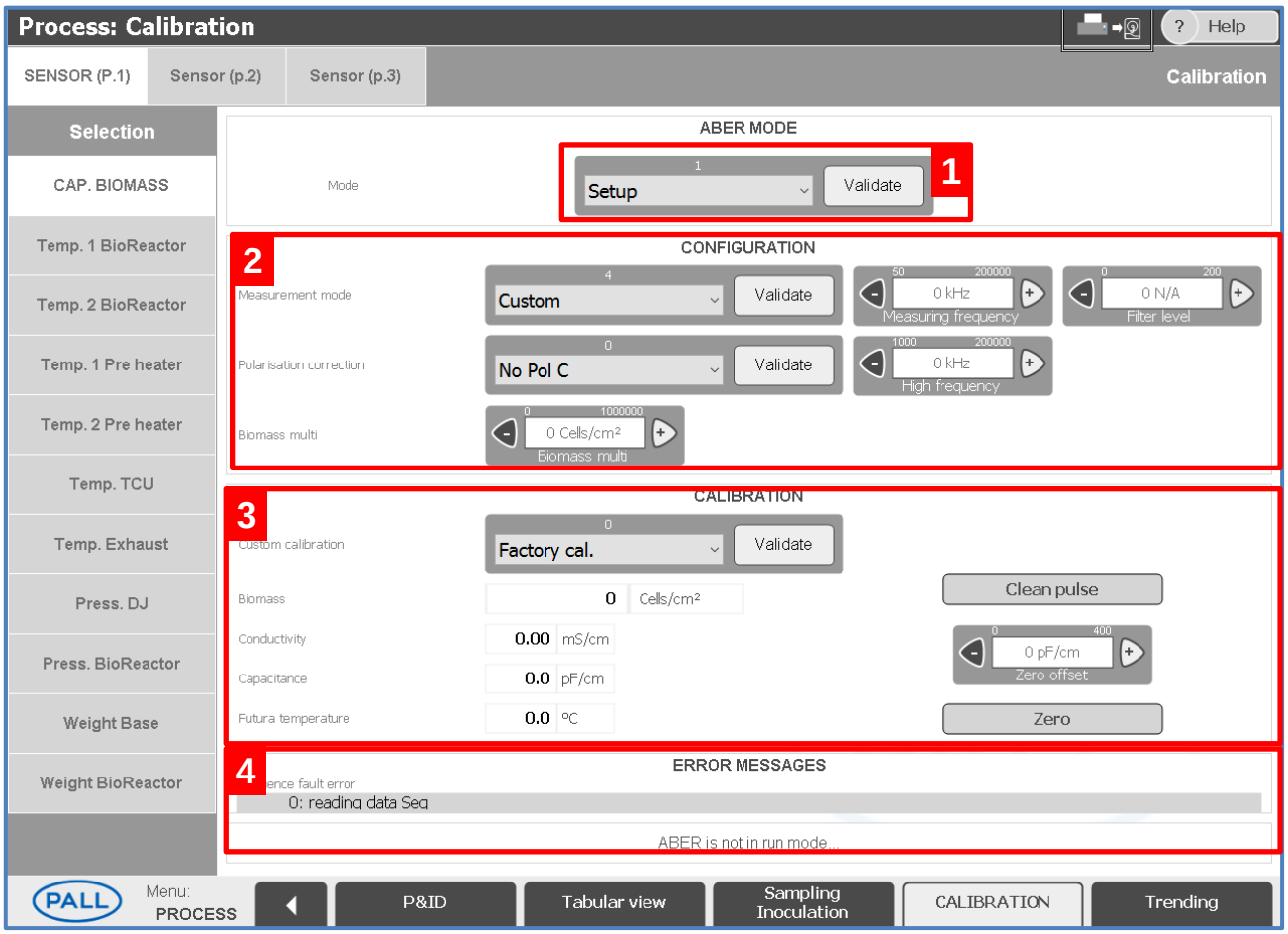


Figure 47: Biomass probe hardware configuration screen – 1) Hardware mode selector, 2) Measurement settings, 3) Calibration settings, 4) Error messages from ABER module.

The following measurement modes are available (Figure 47-2):

- Signal simulator mode: only used to check system response with calibrated simulators
- Custom mode: measurement with customer-defined parameters for:
    - Measuring frequency: generally, from 500 kHz to 1000 kHz for cell culture;
    - Filter level: data smoothing, should be between 1 and 100 points;
    - Polarization correction: eliminates artifacts from probe, should be left ON in cell culture;
    - High Frequency: dual frequency for background capacitance elimination. Set it to 0 kHz (OFF) or 20000 kHz.
- Cell culture mode: standard mode for cell culture processes with following parameters:
    - Measuring frequency: 580 kHz
    - Filter level (= data smoothing): 30
    - Polarization correction: ON
    - High Frequency correction OFF

Other measurement modes are not applicable in cell culture process and are not discussed here.

Note that Calibration options are also accessible from this screen (Figure 47-3).

10.5 Sensors Actuators Parameters

The SENSORS ACTUATORS PARAMETERS tab is mainly a diagnosis tool to quickly access the status of hardware components during maintenance of the equipment.

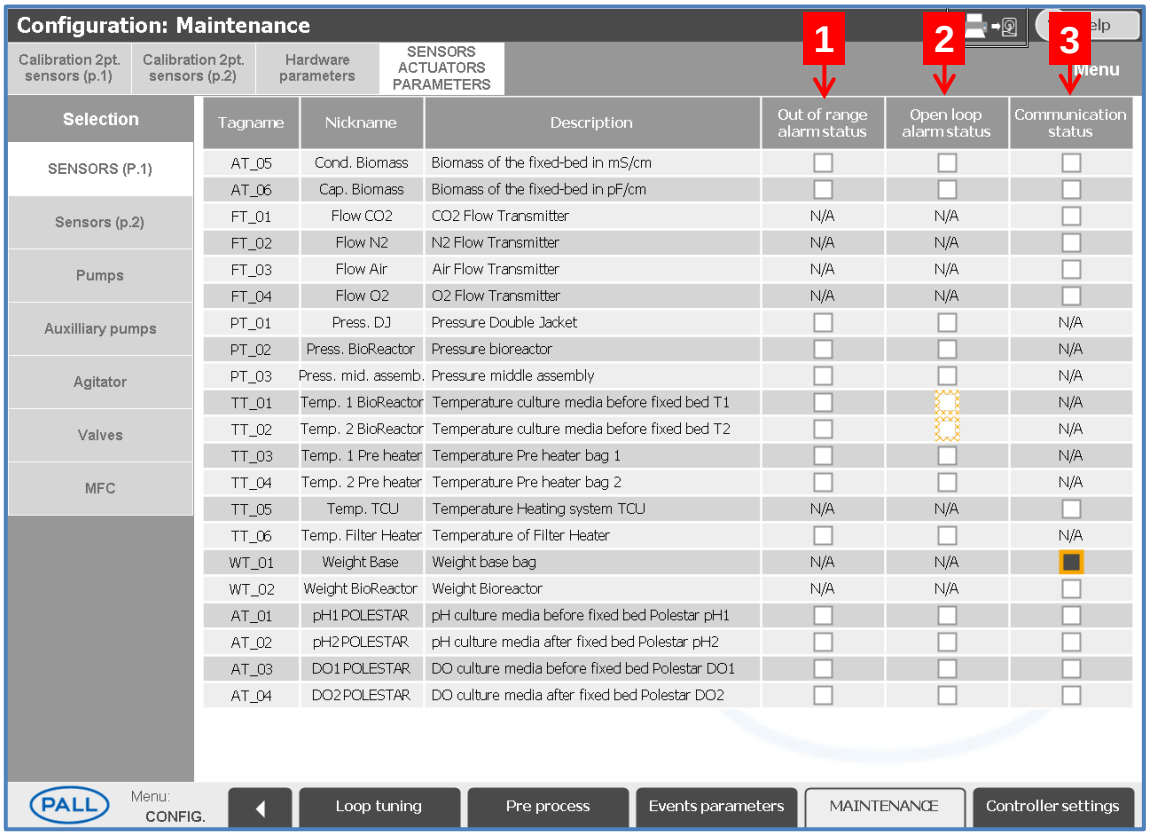


Figure 48: Sensors parameters page in MAINTENANCE menu –
1) Out of range alarms, 2) Open loop alarms, 3) Communication status.

In SENSORS pages' live status of different hardware errors is displayed (Figure 48):

- Out of range error is displayed when sensor reads value out of the normal range of operation, the reason being the sensor is faulty;
- Open loop error represents wire break between transmitter and IO card of PLC.
- Communication error is dedicated to those sensors where signal is not transmitted over 4 – 20 mA but over standard communication protocol like profibus ot profinet. This error also represents the communication failure between PLC and transmitter.

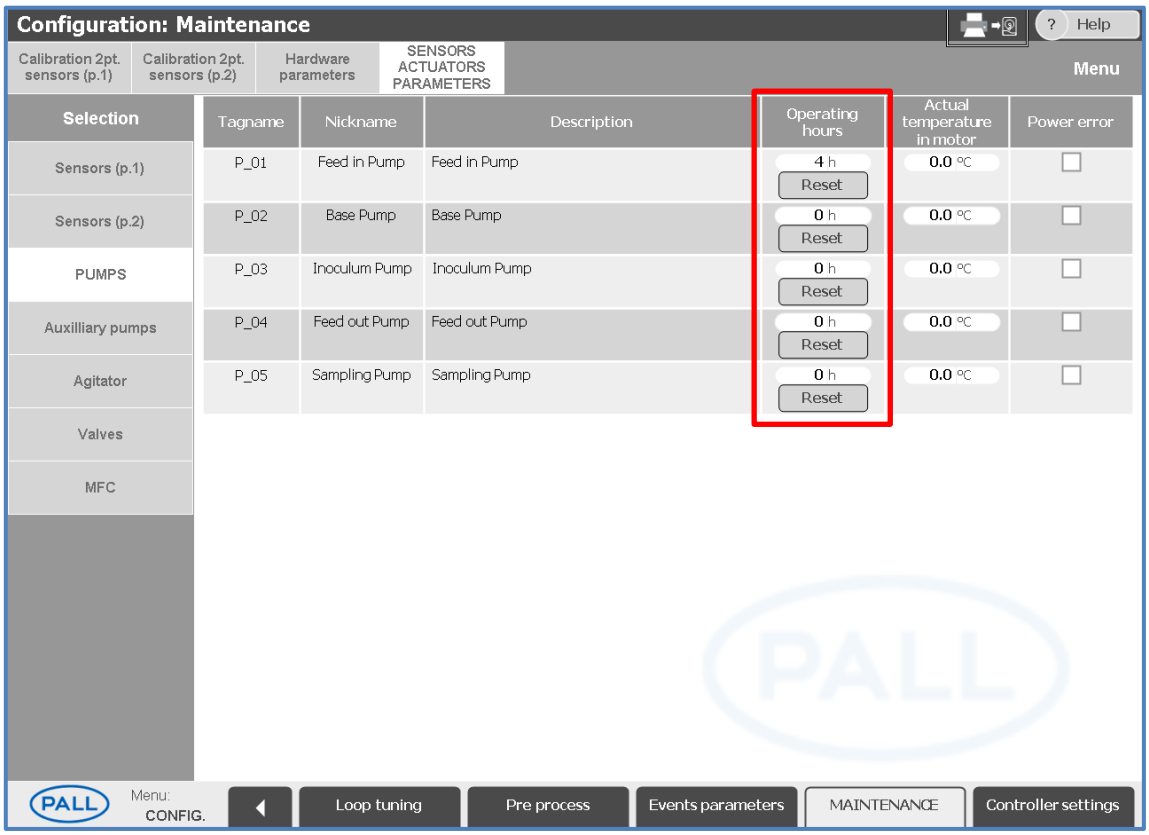


Figure 49: Actuators parameters page with operating counter (red box)

For some actuators (pumps, Agitation motor and valves) the MAINTENANCE menu displays operating counters (Figure 49) and allows resetting this counter, for example after a preventive maintenance.

11. Recipe Manager

11.1 Introduction to Recipes

When the iCELLis 500+ bioreactor process can be lead in a reproducible manner from batch to batch, it is interesting to go further in automation of workflow by defining all steps and actions and accomplish them through a controlled program. Ideally this program should contain all information on tools (or actuators), actions (or output), desired state (or set-point) and final result (or process value) sorted by ‘parameters’ (or ingredients) and method. This program is hence called a Recipe.

In the frame of process control in the iCELLis 500+ bioreactor software, the Recipe will contain:

- Parameters:
    - On-line parameter information, retrieved automatically through system sensors;
    - Off-line information, supplied manually by the user;
    - Calculations and variables based on available information;
    - Equipment modules strategies and set-points;
    - Alarms settings;
    - Operator messages, counters, timers;
- Phases or steps of the recipe, linked to each other and accomplished sequentially;
- Transitions between phases, based on time (fixed phase duration) or on defined conditions.

The list of parameters and their target value necessary to accomplish a process is called Formula. Distribution (or mapping) of the Formula across phases together with conditions to make transition between phases constitute the Recipe.

Recipe management in the iCELLis 500+ bioreactor software is done through a special module called Recipe Manager Plus (RMP).

11.2 Recipe Creation

To create a new recipe or modify an existing one go to RECIPE: CREATION.

11.2.1 Recipe Creation Environment

Recipe creation and editing is made through a semi-graphical environment that makes visualization of phases and transitions user-friendly.

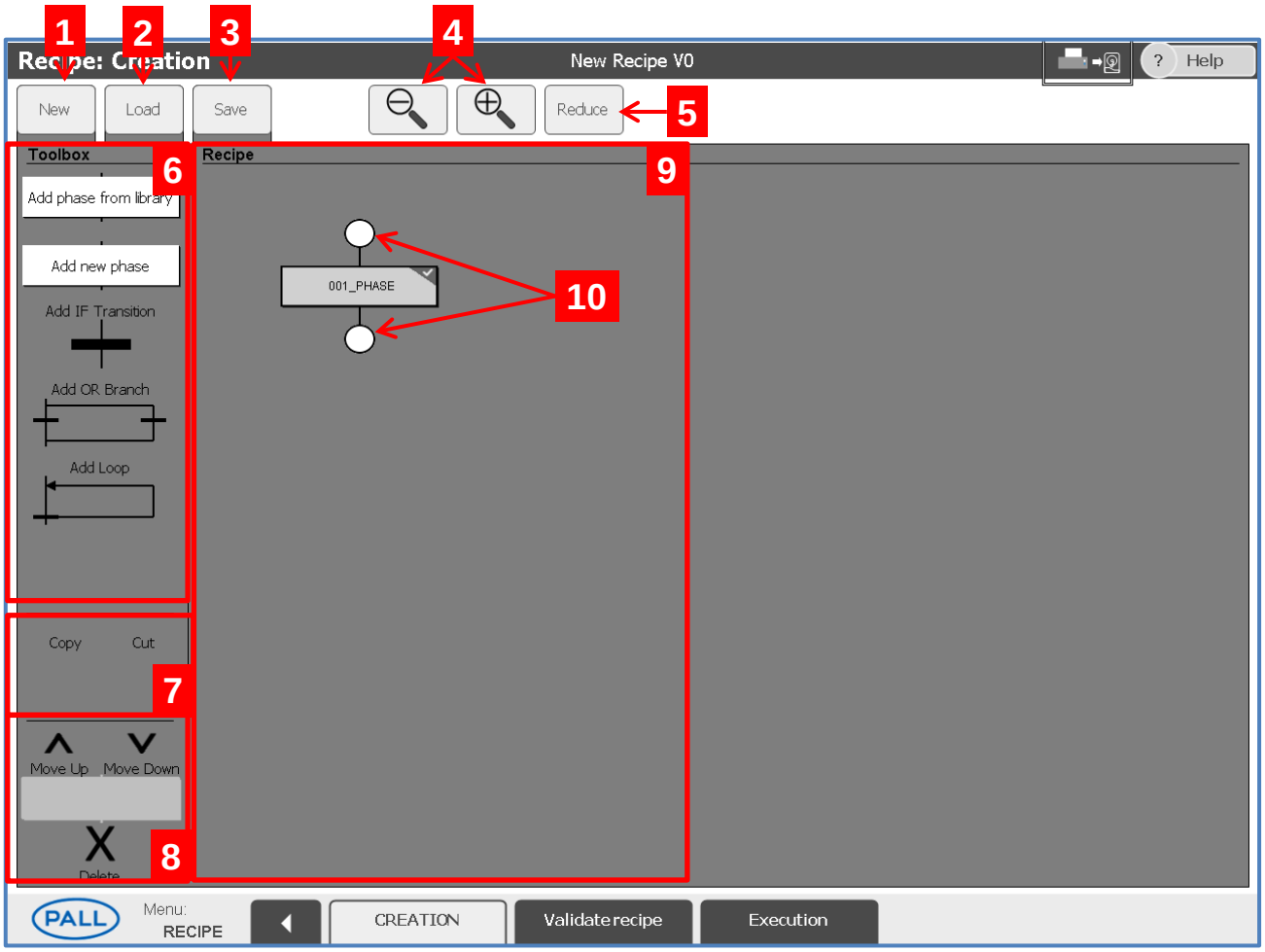


Figure 50: Recipe creation screen – 1) Create NEW recipe button, 2) LOAD existing recipe button, 3) SAVE recipe button, 4) ZOOM IN/OUT Recipe display window buttons, 5) EXPAND/REDUCE Recipe display window button, 6) INSERTION toolbox frame, 7) COPY/CUT/PASTE toolbox frame, 8) MOVE UP/DOWN and DELETE selected item toolbox frame – Note: selected element type is displayed in the middle of the toolbox, 9) Recipe display window, 10) Recipe START/END points.

Use buttons on top of WORKING AREA to create a recipe from scratch (NEW) or load an existing recipe (LOAD) (Figure 50-1/2).

The recipe will appear in Recipe Display window (Figure 50-9) with Start and End points. Recipe display window can be expanded or reduced and zoomed in/out with buttons above (Figure 50-4/5).

User can position the cursor on one element in recipe display window and add new elements to the recipe chart with Insertion toolbox (Figure 50-6):

- Add phase from library;
- Add new blank phase;
- Add IF/OR/LOOP transition;
- Add branch to OR transition (when selected).

Each element is described in following sections. When elements have been introduced in recipe chart it is possible to:

- Copy/cut/paste existing elements (Figure 50-7),
- Move selected element in the recipe with MOVE UP/DOWN buttons (Figure 503-8),
- Remove selected element from chart with DELETE button (Figure 50-8).

By selecting an element and pushing REDUCE button (Figure 50-5), the Element information dialog box will appear to allow configuration of the phase or transition (see corresponding sections).

11.2.2 Saving and Loading Recipes

To save a recipe, use SAVE button (Figure 50-3). This will open the SAVE dialog box with two tabs (Figure 51):

- 'SAVE TO SQL DATABASE' allows making a centralized recipe saving with follow-up of modifications through recipe versions.
- 'SAVE TO FILE' creates 2 files necessary for recipe validation or export to external storage device:
    - .csv file contains all parameters and values used in the recipe
    - xml file contains the operations made with these parameters (method)

User must make sure the file used for validation is the latest version.

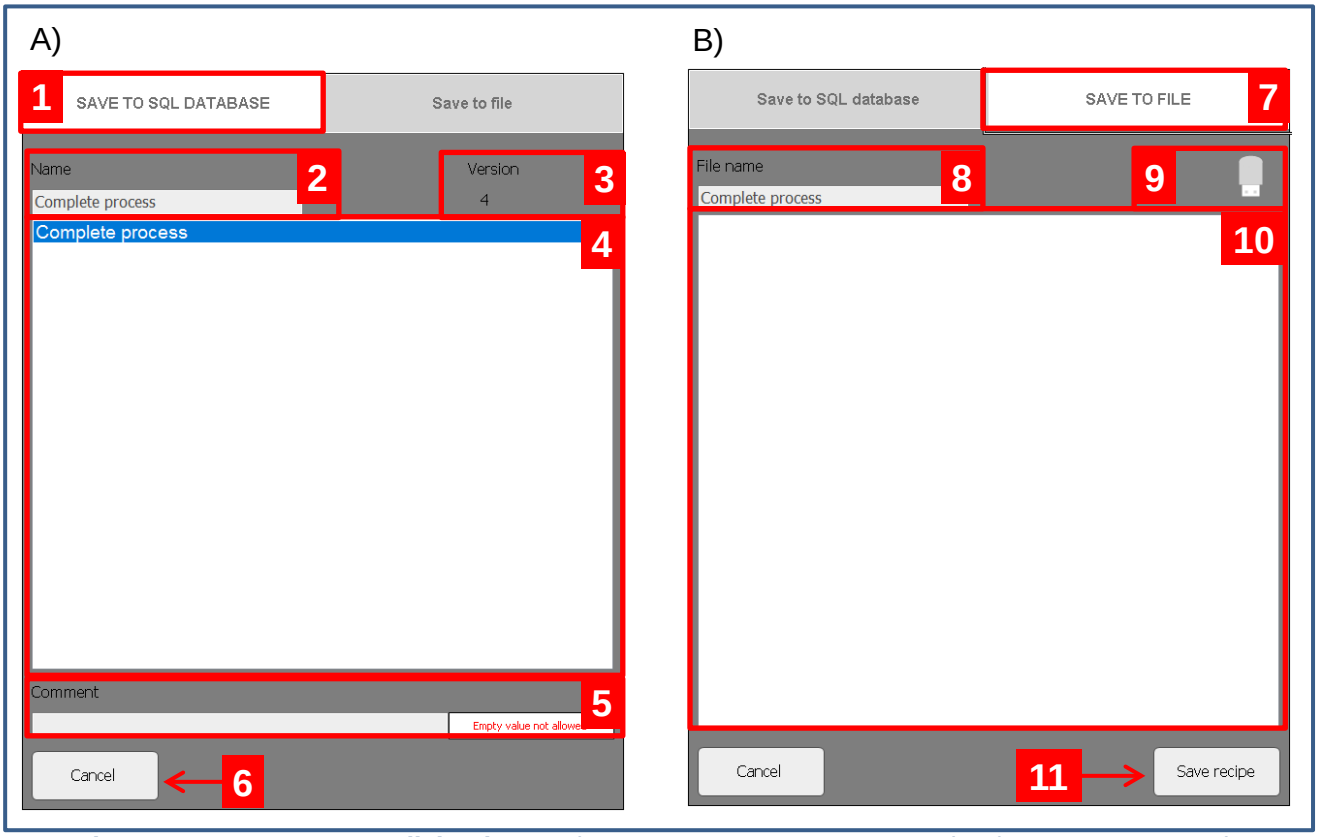


Figure 51: SAVE RECIPE dialog box – A) SAVE TO SQL DATABASE tab, B) SAVE TO FILE tab, 1) SAVE TO SQL DATABASE tabs, 2) Recipe name, 3) Recipe version, 4) Recipes stored in SQL database, 5) Reason for new version edition (mandatory), 6) CANCEL button, 7) SAVE TO FILE tabs, 8) File name 9) Storage drive (hard drive or USB), 10) Existing recipes on drive, 11) Save button.

Once created, recipes can be saved and modified multiple times. Recipe manager keeps a history of each recipe created in SQL database. Saving a modified recipe under the same name will create a new version of the recipe (Figure 51-3) and will require commenting the reason of change (Figure 51-5).

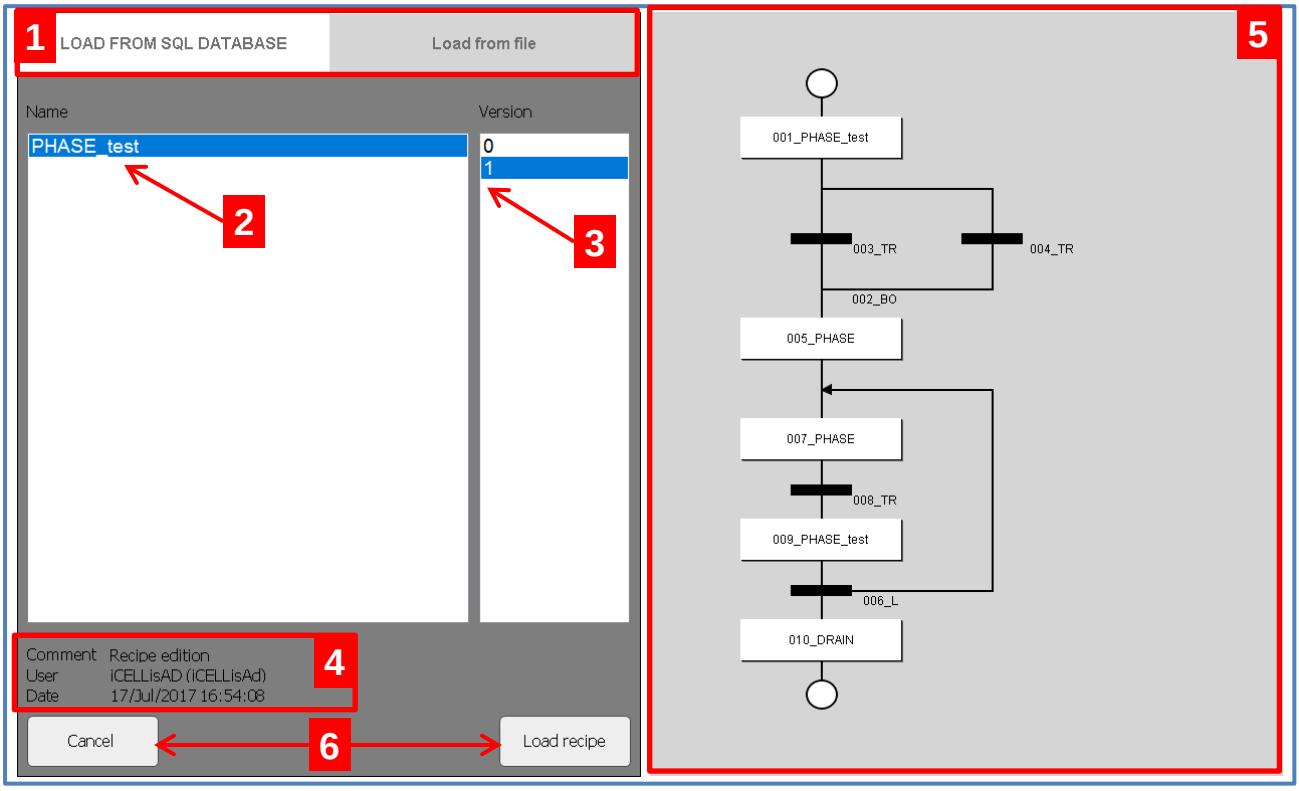


Figure 52: Recipe Loading dialog box – 1) Load from SQL/from file tabs, 2) Available recipes list and selected recipe highlighted in blue, 3) Available versions of the recipe and selected version highlighted in blue, 4) Recipe version save information, 5) Recipe overview, 6) CANCEL/LOAD buttons.

When a recipe has been saved into SQL database it is possible to load any version of it as starting point for new edition. Press LOAD button (Figure 50-2) to open the Recipe Loading dialog box (Figure 52-5).

Select LOAD FROM SQL DATABASE tab to access locally saved recipes and their different versions.

Select LOAD FROM FILE if the recipe will be imported from Hard drive or USB. If a USB storage device is connected to Control System USB port, LOAD button will allow you to browse it and import a recipe. Otherwise, it will display the list of locally stored recipes.

11.2.3 Equipment Parameters Accessible in Recipe Creation

As explained in introduction the Recipe requires a Formula, that is a set of parameters and values that will be used during the process. A very large number of parameters are available and they have been sorted by family for easier selection through nested dropdown lists. These parameters are detailed in the next table (Table 19).

Table 19: Recipe parameters list and description

Family	Sub-Family	Parameters	Value Type or Available Commands	Description
Equipment modules	Agitation pH Temperature	For all EM (when applicable)		This family of parameters allows setting all parameters and commands

	Inoculum Feed IN Fill Feed Out Drain Sampling Gas Out DO regulation	Strategy Reference sensor Set-points	*Text* *Equipment tag* *Decimal*	of EM as available in AUTO mode. Refer to Section 0 Process Control: Equipment Modules for more details.
Alarms	pH sensors DO sensors Biomass sensors MFC sensors Pressure sens Pump sensors Temp. sensors Weight sensors	For all sensors: Low Low Low High High High Alarm Enabling/ Disabling (for every alarm)	 *Decimal* *Decimal* *Decimal* *Decimal*	This family of parameters allows setting through the Recipe the different Alarms parameters for all sensors (Alarm thresholds and enabling/disabling.
Interlocks	Process	Temp exhaust Weight Bioreactor Low Weight Bioreactor High	*Decimal* *Decimal* *Decimal*	Process interlocks set-points.
Timers	N/A	Timer 1 to Timer 5	*All are timers* Start timer Set duration in Days/Hours/Min/s/ms Description Stop timer	Timers can be either started or stopped in a phase. Starting a timer requires input of duration and a description. Up to five timers can be set simultaneously.
Counters	N/A	Counter 1 to Counter 5	*All are integers* Initialize counter + initial value Increment (+1) Decrement (-1) Increment (+X) Decrement (-X)+ value Reset counter	Counter are integer values used to keep track of repeated actions.
Totalizers	N/A	Base tot. Feed In tot. Feed Out tot. Fill tot. Inoc. tot. Drain tot. Sample tot.	*All are decimals* Reset totalizer	Totalizers can be set to zero from the recipe.
Memory Calculations	N/A	Memory 01 to Memory 10	*Decimal* Expression editor	Memory registers are parameters defined by a mathematical expression.
Operator message	N/A	Message content	*Text* *Text*	Operator message is composed of a content which will be displayed and a selection tool that will

		Message type (Info/Ack. OK/ YES/NO) Message response	*Text* No sign/Single sign/Dual Sign	define message response value: ‘‘ (blank value)/ ‘Ok’/ ‘Yes’/ ‘No’. Note that Message response value is not set in phase creation but during phase execution.

11.2.4 Phase Edition

Introducing a Phase in the recipe diagram is done by choosing a position in the recipe and selecting ADD NEW PHASE or ADD PHASE FROM LIBRARY insertion buttons. This operation or the selection of an existing phase will open the Phase information dialog box used to configure the phase. Select EDIT button on top to start editing the phase (Figure 53).

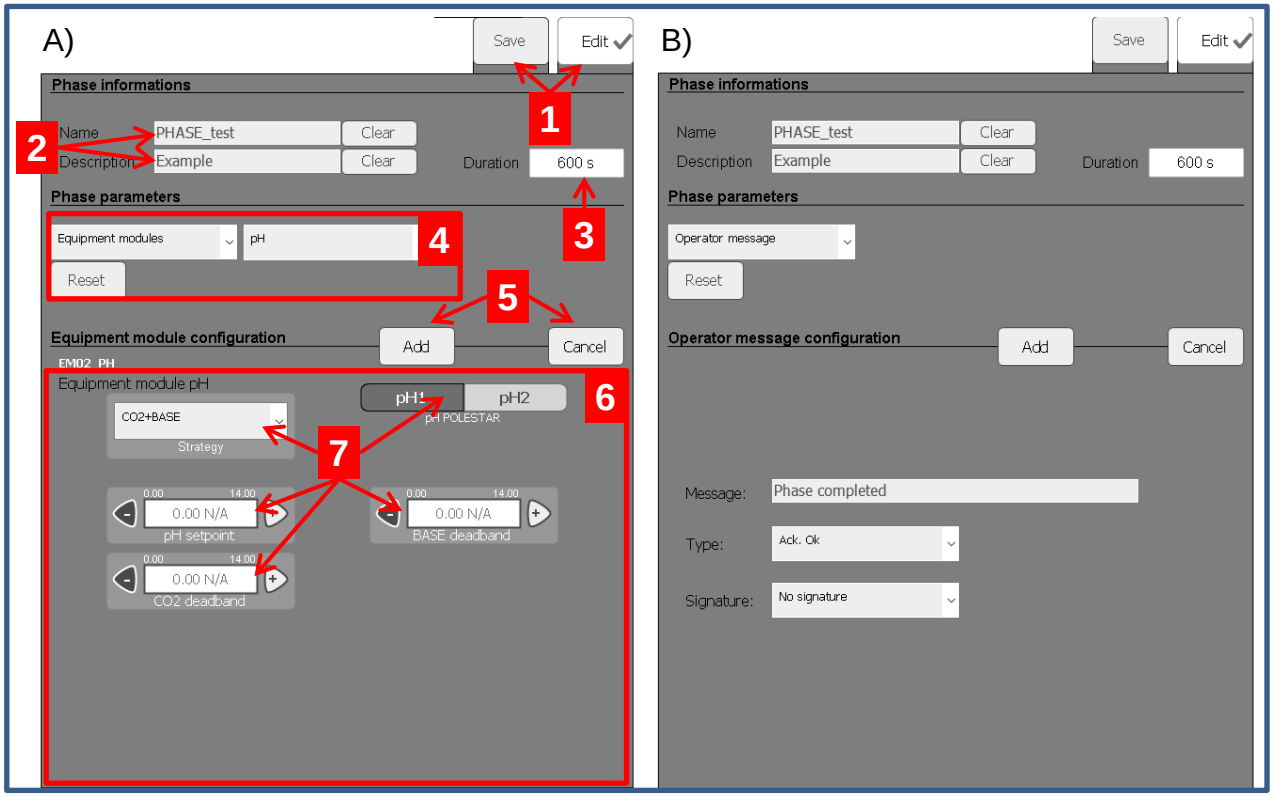


Figure 53: Phase information dialog box – A) Edition of Equipment module parameters (detailed), B) Edition of Operator message parameters, 1) SAVE and EDIT buttons, 2) Phase Name and Description fields, 3) Phase duration (s), 4) Parameter family and sub-family selection lists, 5) ADD configured parameters to phase button, 6) Parameter configuration box, 7) Parameters configured.

Phase edition should go through following steps:

- Define phase Name and Description (mandatory). Phase Name must be unique to the recipe;
- Define phase duration in seconds (Figure 53-3). If the duration is set to 0s, the recipe will directly jump to next step (phase or transition) as soon as all actions of the phase are performed. Otherwise it will let the countdown go to zero before proceeding to next step or transition;
- Select parameter(s) with dropdown list (Figure 53-4);
- Configure parameters and commands in Parameters configuration box (Figure 53-6/7);
- Add configured parameters with ADD button (Figure 53-5);

- Repeat these operations as much as necessary to configure all parameters modified in the phase;
- Save the phase with SAVE button on top of the dialog box (Figure 53-1).

Once saved, the Phase information dialog box becomes inactive (light grey background) and the SAVE PHASE TO LIBRARY button is displayed next to EDIT button. Saving phases to the library will allow loading it for creation or modification of any recipe by using the insertion toolbox. The main advantage to save the phases in the library is to build a library of all predefined phases that can be use frequently in future recipes.

To delete any existing parameters or commands in the phase, open first the detail of the phase and select the parameters/commands to be deleted, ‘delete’ button will be available in the section (Figure 53-5).

If any parameters or commands in the phase are changed, ‘Modify’ button will appear automatically to apply the change.

All parameters that are not explicitly modified in a phase will remain the same. For example, if Fill EM is started to fill the bioreactor in phase 1, it will continue running unless set to STANDBY in a following phase.

11.2.5 Transitions Expression Edition

Common to all Transitions is the logical expression that will define the recipe’s next step. Expression is a single logic statement that will be evaluated during runtime to TRUE or FALSE value. Depending on the expression value, effects of the transition will be applied:

- IF transitions will pause the recipe until the expression is found TRUE
- OR transitions evaluate the Expression of each branch until finding one TRUE
- LOOP transitions will repeat the steps within the loop if the Expression is TRUE

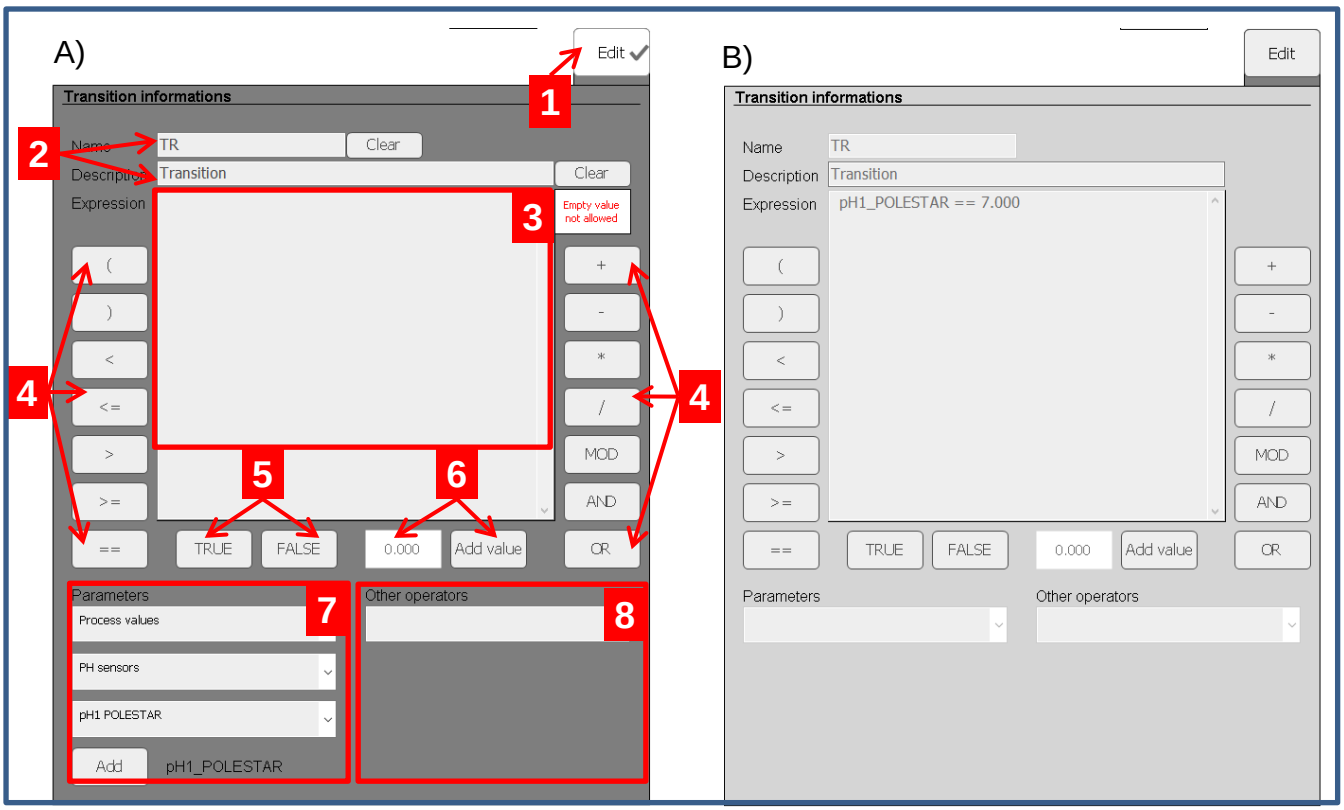


Figure 54: Transition information dialog box – A) Transition information box under edition, B) Edited Transition information dialog box, 1) EDIT button – Note: SAVE button is only visible when a valid expression is present, 2) Transition Name and Description fields, 3) Transition Expression edition window, 4) Mathematical and Logical operators, 5) TRUE and FALSE value addition buttons, 6) Numerical value addition defining field and button, 7) Recipe parameter dropdown lists and ADD button, 8) Advanced Operators addition list.

When a transition is inserted, it can be edited by selecting in the recipe schematic the black bar of the desired transition and pushing the EDIT button on top of the displayed Transition information dialog box (Figure 54-1). Transition edition should follow the steps below (all mandatory):

- Define transition Name (32 characters max.) (Figure 54-2). Transition Name must be unique in the Recipe;
- Define Description (120 characters max.) (Figure 54-2);
- Define Expression (Figure 54-3).

Expression is built with logic operands and operators. Operands are either equipment parameters or static values (Numeral, e.g. 37.5; Logical value, e.g. TRUE; Text, e.g. 'OK'…).
All the parameters defined in Phases are accessible in Transition expression through a dropdown list (Figure 54-7), except for Equipment modules set-points; select the desired parameter and click ADD button to insert it in the Expression edition window. Similarly, use TRUE/FALSE buttons or ADD VALUE and attached input field (Figure 47-5/6) to insert logical and numerical operands.
The field (Figure 54-6) is only for help when creating an expression. Due to the precision of floating point value, some values cannot be added by using this field (for e.g; 0.0001). In this case, the numerical value can be written directly in the expression (Figure 54-3) by using the keyboard.

IMPORTANT!
Use of process values in transitions should rely on =>, =< operator types, as reaching an exact value is not very likely and the expression could be never found TRUE.
In the example above, (Figure 54-b) the expression of the IF transition will be found TRUE when the pH process value measured by probe pH 1 will be strictly equal to 7.000.

Logic and Mathematical operators (Table 20) are added using corresponding buttons around the EXPRESSION EDITOR. The buttons will add spacing before operator insertion. Other operators can be selected using the Advanced Operator list (Figure 54-8) below the Expression edition window.

Table 20: Standard expression edition operators

Operator	Description
AND	Logical AND. Groups two sub-expressions into one. Both sub-expressions must be TRUE for AND to be true. Otherwise it is FALSE
OR	Logical OR. Groups two sub-expressions into one. Any of the sub-expressions must be TRUE for OR to be true. Both have to be FALSE for OR to be FALSE
NOT	Logical NOT; negates the result of a Boolean expression within parenthesis placed after
==	Strictly equal
<>	Not equal to
> =>	Strictly greater than Greater than or equal to
< =<	Strictly less than Less than or equal to
*, /, +, -	Mathematical operators
()	Parenthesis. Use it to create a logical sub-expression and control operators' precedence

Specific syntax rules are to be followed to establish a correct expression:

- Only one space before expression start
- One space between each expression element

When the edition of the expression is complete, use the SAVE button on top of the Transition information box to save your entry. If the SAVE button is not used, the entry will be lost.

11.2.6 IF Transitions Insertion

IF transition will maintain all control parameters of the equipment in the same state until the expression is evaluated TRUE. The state of the recipe until the expression is TRUE during recipe execution is like a Pause state. To insert an IF transition in the recipe, place the cursor on a step and select the IF transition insertion button. Then complete the Transition information as explained in the previous section.

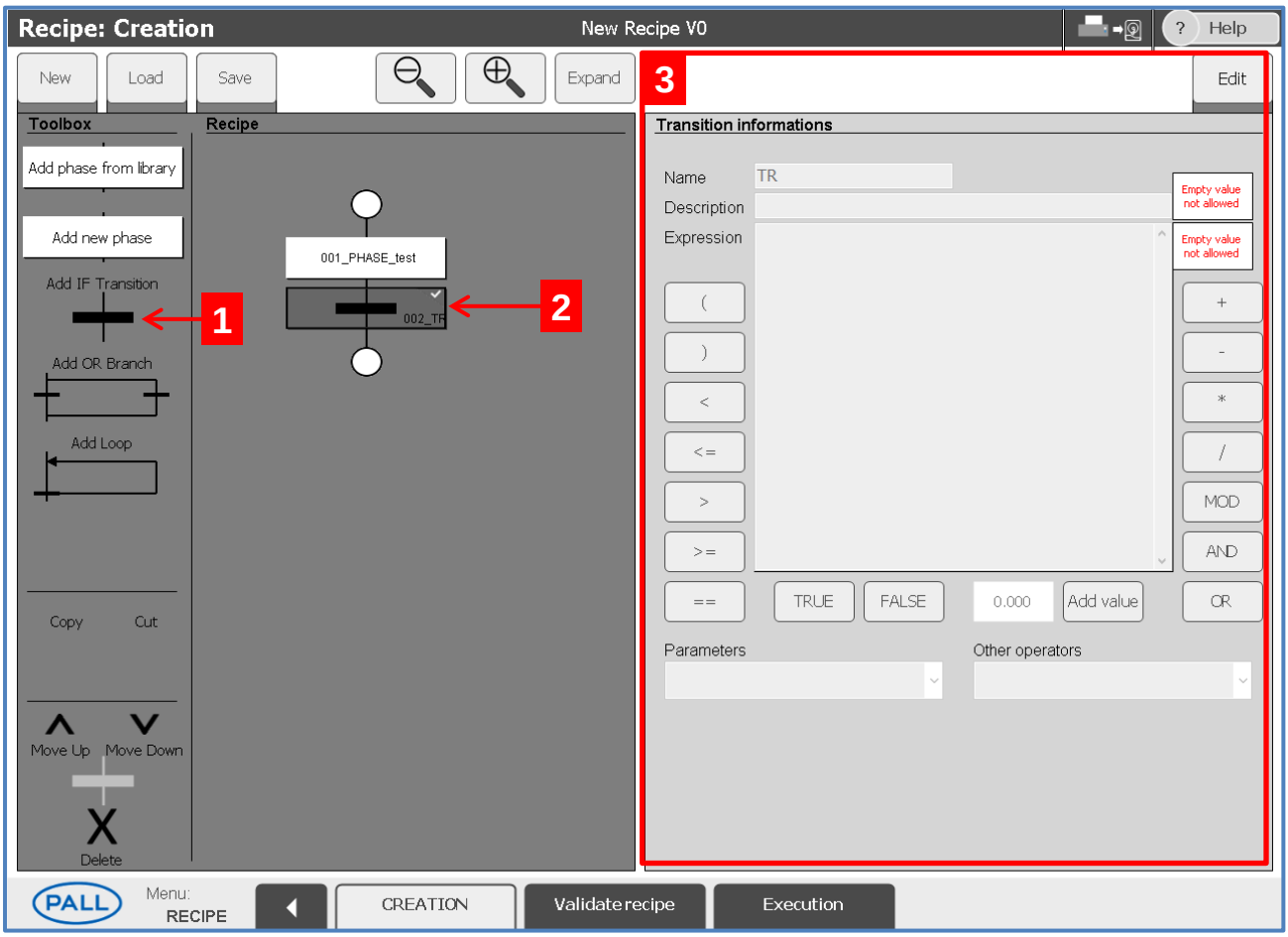


Figure 55: IF transition insertion in recipe – 1) IF transition insertion button, 2) Newly inserted IF transition, selected, 3) Transition information dialog box of selected IF transition.

11.2.7 OR BRANCH Transition Insertion

OR BRANCH transition will execute only one branch of the transition. For each branch it is necessary to define a transition expression that will be evaluated during runtime. The evaluation will start with the left-most branch. If the expression logic is true, or there is no expression defined, the branch will be processed and all other branches aborted; otherwise the evaluation will pass to the next branch expression. If all branches have expression logic that is FALSE, the procedure will repeat the evaluation until one of the branches is TRUE.

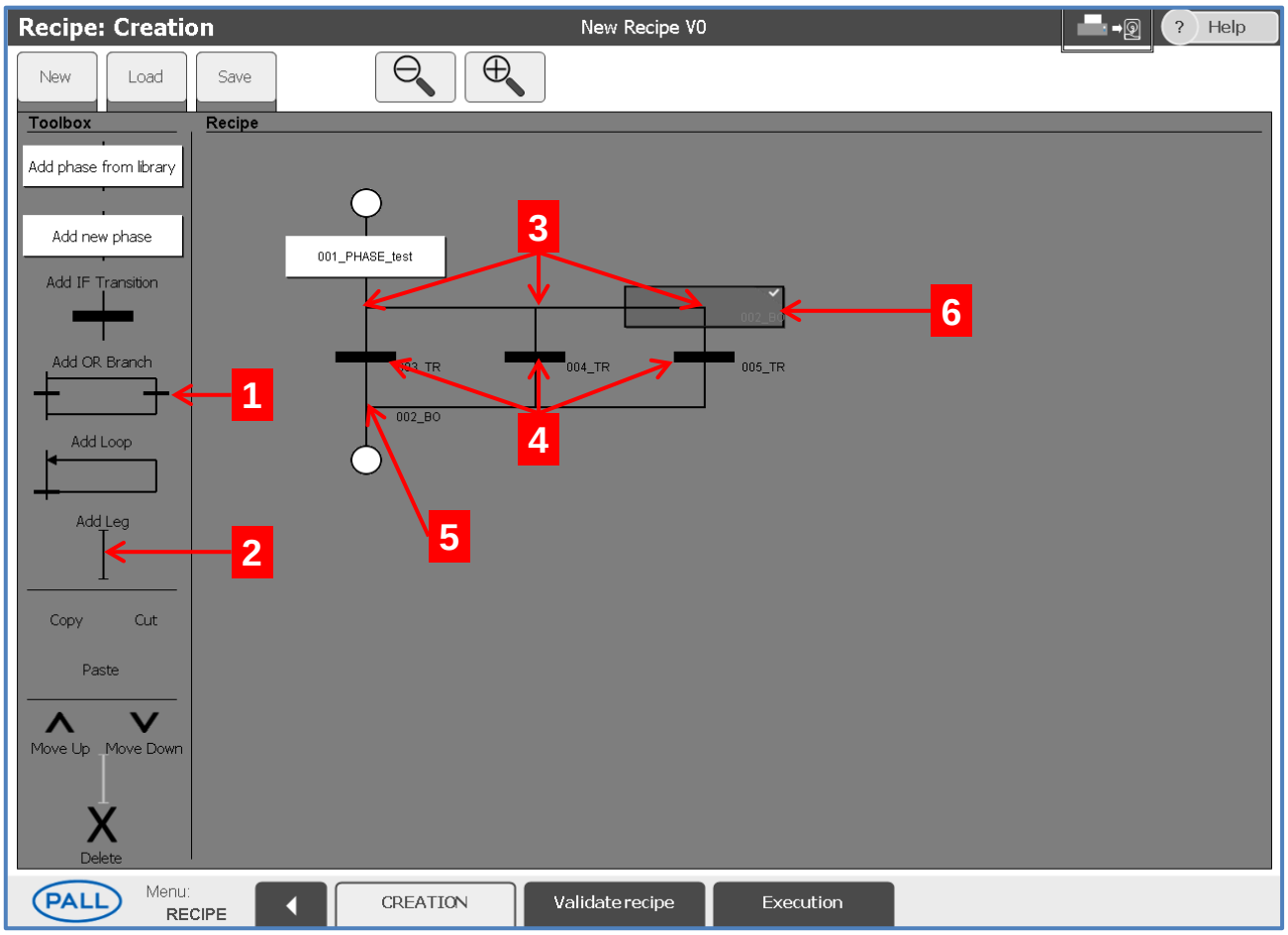


Figure 56: OR Branch transition insertion in recipe – 1) OR Branch transition insertion button, 2) ADD LEG button, 3) OR Branch nods, 4) Branch transition expression bars, 5) OR Branch transition end point, 6) Cursor position.

To insert an OR Branch transition, set the cursor to the desired position in the recipe and use the ADD OR BRANCH insertion button (Figure 56-1). Branches can be added to the transition by selecting a node and using the ADD LEG insertion button (Figure 56-2/3). Branches can then be rearranged by dragging them to a new position. Deletion of a branch can be done by selecting the unwanted element and using the Delete button in the Toolbox. Use the Select Expression bars (Figure 56-4) to define the expression of each branch with the Transition information dialog box (see Section 11.2.5 for details). With the cursor on the expression bars, you can add steps (phases and transitions) to the branch. To insert steps after the transition, select the end point of the transition (Figure 56-5) and insert new steps.

11.2.8 LOOP WHILE Transition Insertion

Loop transitions enable re-running a phase or a group of steps based on recurring evaluation of the Loop transition expression value.
Loop steps will always be executed at least once as the loop condition is at the bottom of the loop. Loops will be repeated if evaluation of the loop's expression leads to TRUE value of logical statement. If the value is FALSE, the loop will break and the process will continue. This is hence the structure of a LOOP WHILE programming.

IMPORTANT!
If the expression of a LOOP is never evaluated FALSE the loop will repeat endlessly.

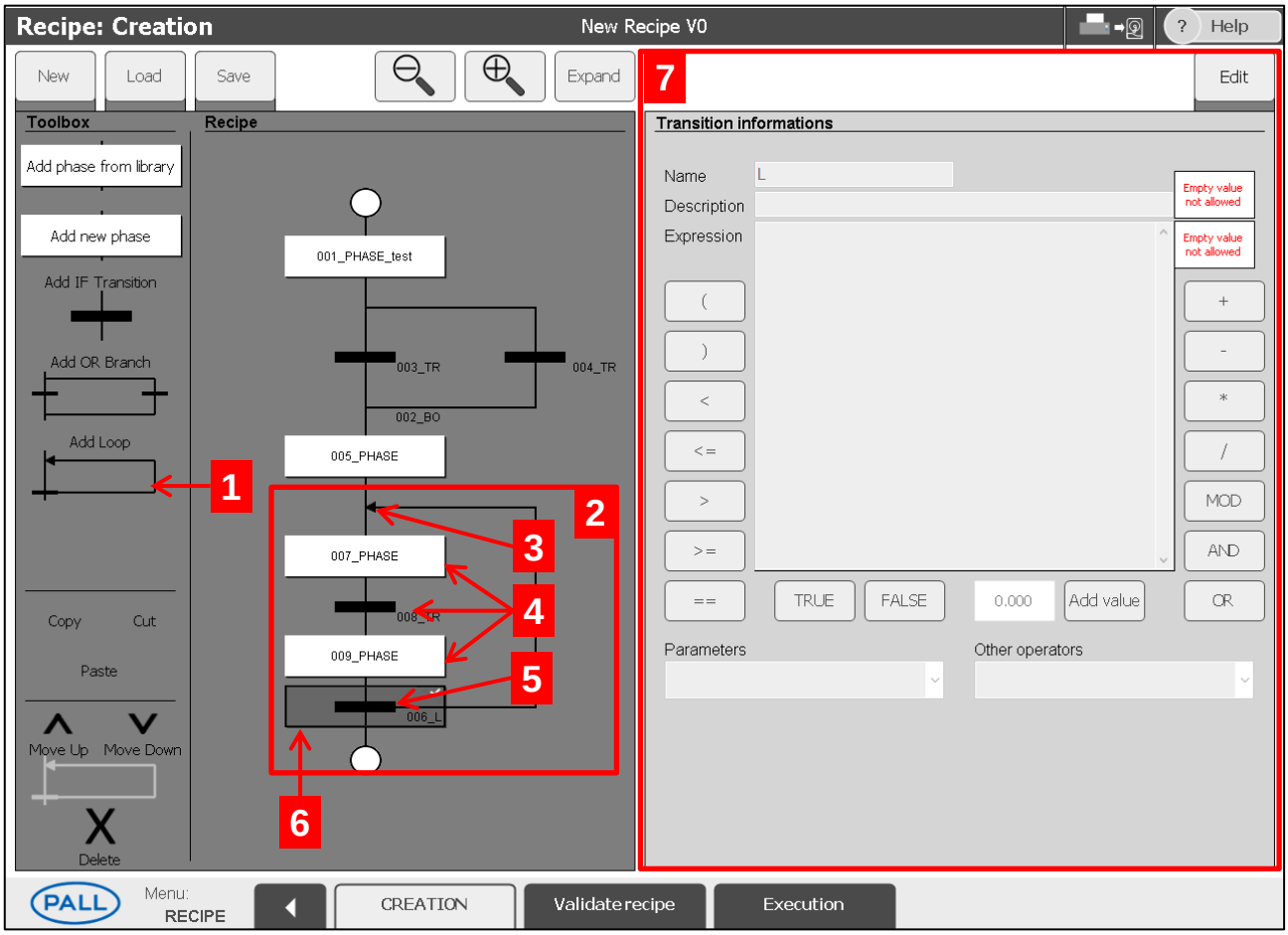


Figure 57: LOOP transition insertion in recipe – 1) LOOP transition insertion button, 2) LOOP sequence, 3) LOOP start point, 4) LOOP repeated step, 5) LOOP end point with Transition expression evaluation, 6) Cursor position, 7) LOOP transition information dialog box.

To insert a LOOP transition, set the cursor to the desired position in the recipe and use the ADD LOOP insertion button (Figure 57-1). Then select the loop start point (Figure 57-3) and insert the desired phase or transition. Any recipe element, including Loops, can be included inside a loop structure.

It is not possible to move elements in and out of loops with MOVE UP/DOWN buttons. All steps of a loop must be created in the loop, copied/pasted or imported from the library.

To define Loop transition conditions, select the LOOP end point (Figure 57-5) and complete the Transition Information dialog box (Figure 57-7). Refer to Section 11 for details on expression edition. To insert steps after the transition, select the end point of the loop and insert new steps.

If a phase got executed multiple times in a loop, then all the instances are displayed in the history ordered by time. Execution instance count starts from zero (0).

IMPORTANT!
The maximum number of steps in recipe manager is dependent of the number of parameters used in the recipe. The maximum number of parameters per recipe tested by Wonderware with success is 5500. Using 382 parameters in each step of the recipe, the user can use 14 steps per recipe.

11.3 Recipe Validation

Recipe validation is necessary to validate the existence of all parameters in the equipment, the coherence of the method and to transform the files generated during the creation in a RECIPE file that can be assigned to the equipment and executed.

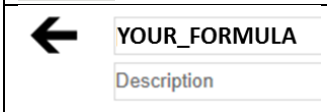
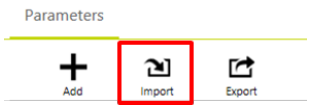
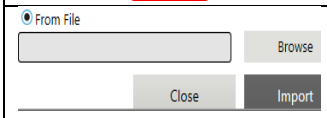
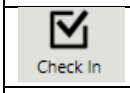
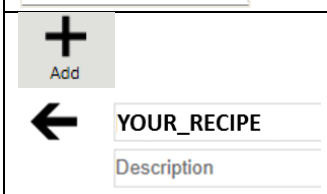
Recipe validation must be done every time a recipe is modified or imported to a new equipment.

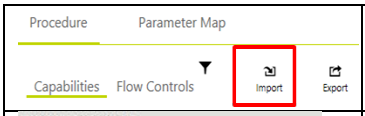
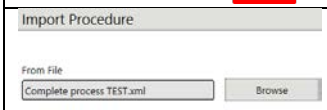
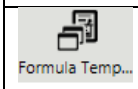
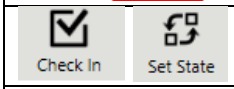
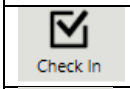
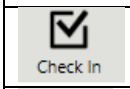
The process of recipe validation requires several steps necessary for the Recipe Manager to finalize RECIPE file. These steps include the generation of a FORMULA file from a FORMULA TEMPLATE and the generation of a RECIPE file from a RECIPE TEMPLATE and FORMULA file.

11.3.1 Recipe Validation Procedure

To start the recipe validation, navigate to HOME: RECIPE: VALIDATE RECIPE and follow the procedure bellow (recipe is named here '*Your_Recipe'* as example).

Table 21: Recipe validation step by step procedure

Item	Description
	1. Select FORMULA TEMPLATE page.
	a. Select ADD button.
	b. In Formula template give the Formula template a name (e.g. '*Your_Formula*') and a description.
	c. Select IMPORT button.
	d. In IMPORT PARAMETERS dialog box select 'From file' – 'Browse' and select Your_Recipe_Name.csv file in the list. Press ENTER. Press 'Import' then Parameters are imported in the Formula template.
	e. Select CHECK IN button.
	f. Verify that the State is 'Current' or set it to 'Current' with SET STATE button.
	2. Select RECIPE TEMPLATE page.
	a. Select ADD button and give the Recipe template a name (e.g. '*Your_Recipe'*) and a description.

	b. Select IMPORT button under the PROCEDURE tab.
	c. Browse to Your_Recipe_Name.xml file and select IMPORT. Confirm your selection with YES button on the confirmation message and acknowledge the Notification with OK button.
	d. Select FORMULA TEMPLATE button (RMP HEADER) and choose *Your_Formula* created in step 1. Confirm with ADD button. **CAUTION!** Ensure you select the right Formula template from the list.
	e. Select PARAMETER MAP tab and select AUTO MAP button. Acknowledge Notification.
	f. Select CHECK IN button and verify that state is ‘Current’. Otherwise set it to ‘Current’ using SET STATE button.
	3. Select FORMULAS page.
	a. Select ADD button. A dialog opens to propose formula templates. Choose *Your_Formula* created in step 1.
	b. Give to the Formula a name (e.g. ‘*Formula1*’) and a description.
	c. Select CHECK IN button.
	d. Select SET STATE and modify the state to ‘Approved’.
	4. Select RECIPES page.
	a. Select ADD button. A dialog opens to propose Recipe templates and Formulas. Choose Your_Recipe created in step 2 and Your_Formula created in step 3 (Note that the list of proposed formula contains only 1 proposal). Select ADD to confirm.
	b. Give the Recipe a name (e.g. ‘*Recipe1*’) and a description. The description will be the title displayed on the main scren
	c. Select CHECK IN button.
	d. Select SET STATE and modify state to ‘Approved’.
	Recipe validation is complete.

11.3.2 Deleting Formulas or Recipes from Lists

For traceability reasons, it is not possible to delete Formulas and Recipes files from the system, however if they are not used anymore it is possible to set their state to ‘Obsolete’. This will delete the file from the displayed list and could ease further selection. Follow the indications given in Figure 58 to set the state to ‘Obsolete’.

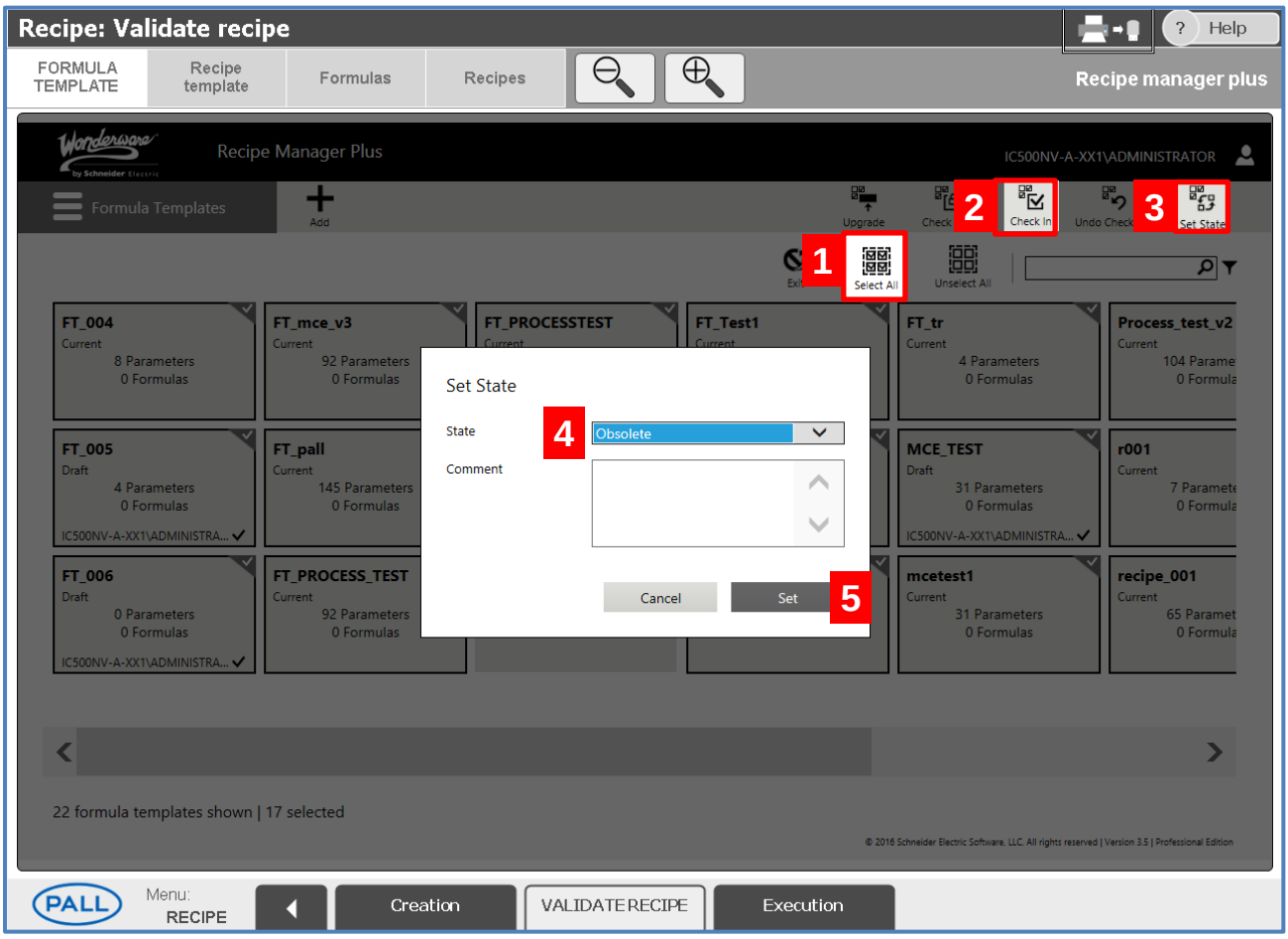


Figure 58: Setting state to obsolete in RMP – 1) Multiple selections keys, 2) Check IN button, 3) Set state button, 4) State list, 5) SET button.

Recipe template, formula template, formula and recipe can be deleted individually by setting their state to Obsolete. A Formula Template cannot be set to Obsolete unless all the Formulas derived from it have been set to Obsolete. And a Recipe Template cannot be made Obsolete unless all the Recipes derived from it have been made Obsolete.

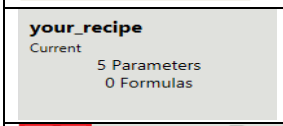
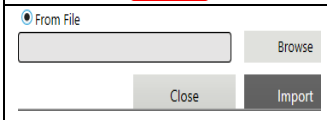
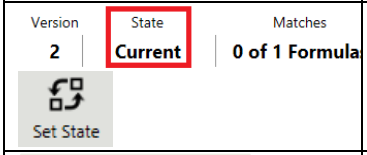
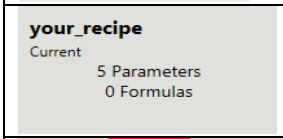
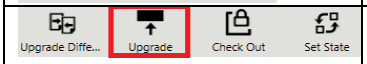
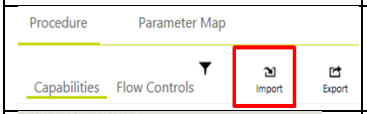
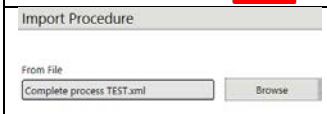
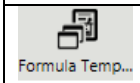
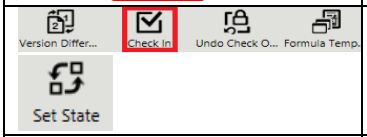
Once its state is changed to obsolete, the Item will no longer appear on the summary page unless filtered by Obsolete.

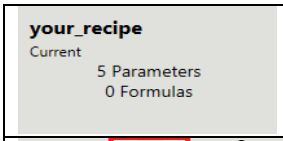
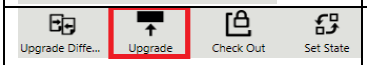
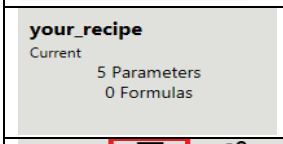
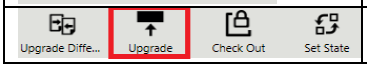
11.4 Modifying a Recipe

To modify a recipe, load the desired recipe (as per Section 11.2.2) and implement the changes required. Once finished, the user needs to save the modified recipe (as per Section 11.2.2).
If the recipe wasn't validated before modification, the user must validate it (as per Section 11.3) to be able to execute it.

If the recipe had been validated before the modification, simpler steps can be followed. Navigate to HOME: RECIPE: VALIDATE RECIPE and follow the procedure below (recipe is named here '*Your_Recipe'* as example).

Table 22: Recipe validation step by step procedure

Item	Description
	1. Select FORMULA TEMPLATE page.
	a. Select the formula template that was created (e.g. '*Your_Formula*').
	b. Select CHECK OUT button
	c. Select IMPORT button.
	d. In IMPORT PARAMETERS dialog box select 'From file' – 'Browse' and select Your_Recipe_Name.csv file in the list. Press ENTER. Press 'Import' then Parameters are imported in the Formula template.
	e. Select CHECK IN button.
	f. Verify that the State is 'Current' or set it to 'Current' with SET STATE button. Note also that the VERSION number has increased
	2. Select RECIPE TEMPLATE page.
	a. Select Recipe template that was created (e.g. '*Your_Recipe*').
	b. Note that there is an UPGRADE option available now. Select UPGRADE button.
	c. Select IMPORT button under the PROCEDURE tab.
	d. Browse to Your_Recipe_Name.xml file and select IMPORT. Confirm your selection with YES button on the confirmation message and acknowledge the Notification with OK button.
	e. Select FORMULA TEMPLATE button (RMP HEADER) and choose *Your_Formula* created in step 1. Confirm with ADD button. CAUTION! Make sure you select the right Formula template from the list.
	f. Select PARAMETER MAP tab and select AUTO MAP button. Acknowledge Notification.
	g. Select CHECK IN button and verify that state is 'Current'. Otherwise set it to 'Current' using SET STATE button. Note that the version has also incremented.
	3. Select FORMULAS page.

	a. Select the formula that was created (e.g. '*Your_Formula*').
	b. Note that there is also an UPGRADE option available now. Select UPGRADE button.
	c. Select CHECK IN button.
	d. Select SET STATE and modify the state to 'Approved'.
	4. Select RECIPES page.
	a. Select the recipe that was created (e.g. '*Your_Formula*').
	b. Select UPGRADE button.
	c. Select CHECK IN button.
	d. Select SET STATE and modify the state to 'Approved'.
	Recipe validation is complete with the version incremented.

11.5 Recipe Execution

Once the Formula and Recipe are properly configured and 'Approved' they become available for execution.

Recipe execution is the loading and realization of a validated recipe on the equipment. To execute a recipe, navigate to HOME: RECIPE: EXECUTION menu (Figure 59).

11.5.1 Recipe Execution Screen Overview

Recipe Execution menu contains several important information and selection keys.

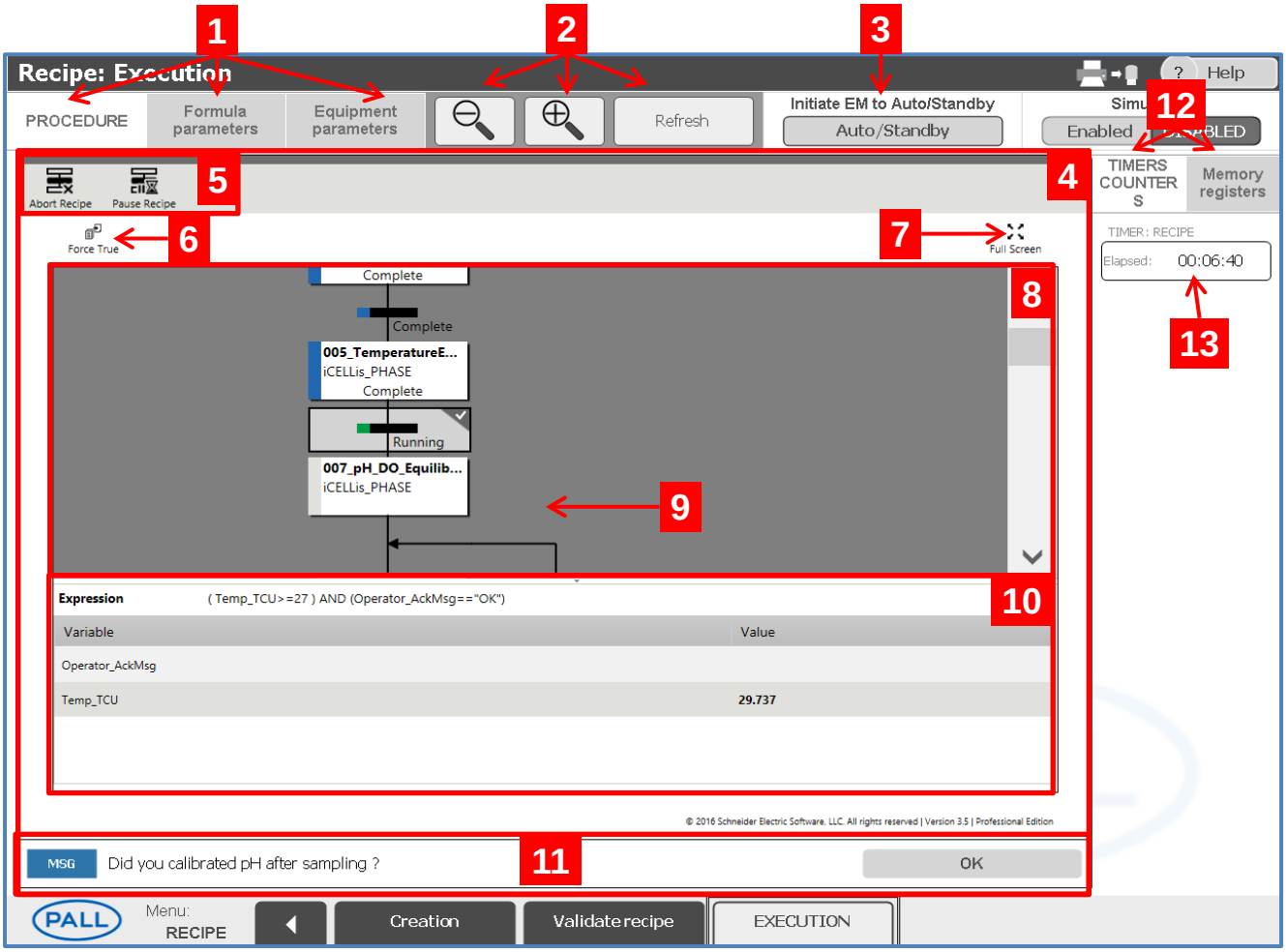


Figure 59: Recipe Execution screen – 1) Execution tabs (Recipe visualization modes), 2) Zoom IN/OUT Refresh buttons for Recipe Execution box, 3) EM AUTO/STANDBY button, 4) Recipe Execution Box, 5) Playing recipe buttons (ASSIGN/START or ABORT/PAUSE /HOLD), 6) Step forcing buttons area (FORCE TRUE button for IF transition; ABORT/RESTART for phases), 7) FULL SCREEN button displays the whole recipe in Recipe Execution box (adjust zoom to recipe length), 8) Recipe Visualization window, 9) Step selected, 10) Selected step details, 11) Operator Message zone with OK/YES/NO/ACK buttons (depending on message type), 12) Timers and counters or Memory registers live visualization, 13) Timer elapsed time (example recipe elapsed time)Tabs selection buttons (Figure 49-1/2/12) allow different visualization modes of the main information displayed in the Recipe Execution Box (Figure 49-4).

Recipe Execution buttons allow loading and executing a recipe (Figure 59-5).

The Recipe Visualization window displays a live state of steps (Figure 59-8) as well as the details of a selected step (Figure 59-9/10).

If an operator message is programmed, it will be displayed in the OPERATOR MESSAGE ZONE (Figure 59-11) and the MSG icon will appear in the RECIPE SUMMARY area of the HEADER as long as the message is active and the user is in different screen than the execution view.

If starting a new batch, it is highly recommended inserting an Operator message at the beginning of the recipe to check that everything is setup correctly.

11.5.2 Assigning and Starting a Recipe

User access level of Operator or Supervisor is necessary to execute a recipe (according to the defaults setting of RMP security).

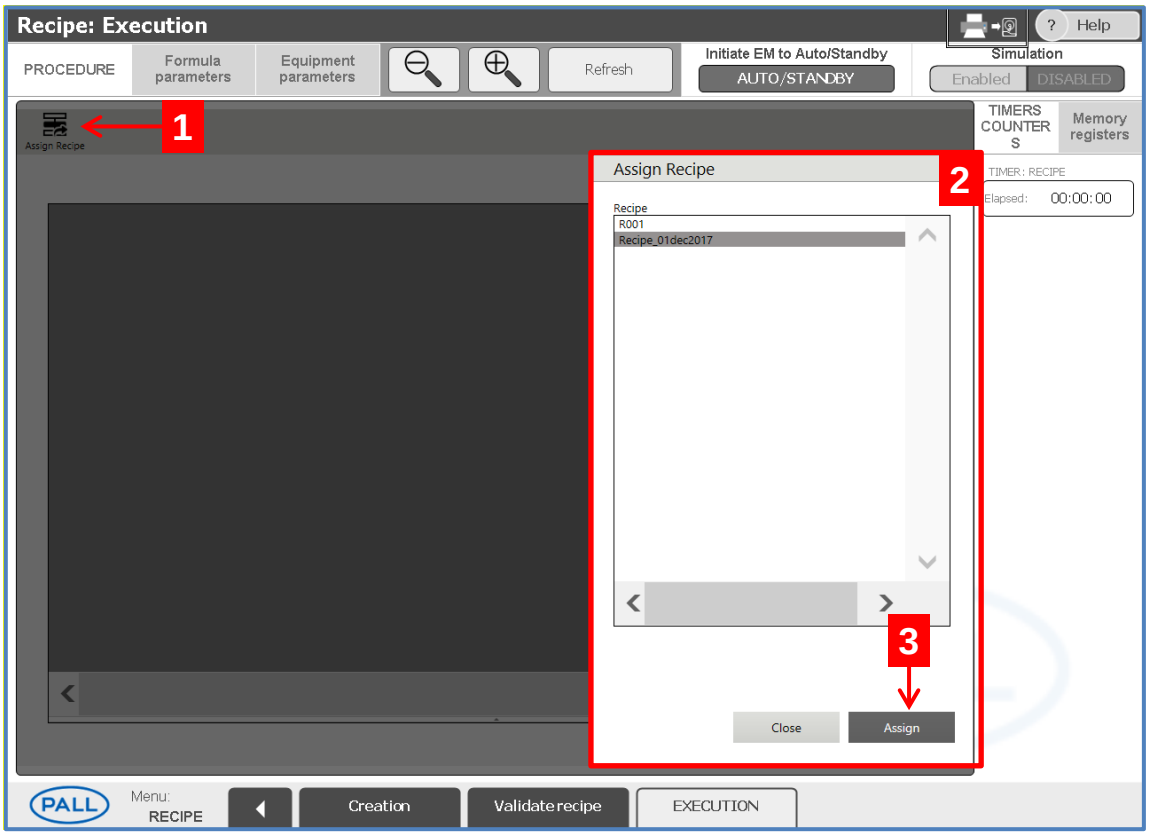


Figure 60: Assigning recipe in Recipe execution menu –
1) ASSIGN RECIPE button, 2) Recipe list, 3) ASSIGN button.

To load a recipe, use the ASSIGN RECIPE button on top of Recipe Execution box (Figure 60-1). Available validated Recipes list is summoned for recipe selection and confirmation (Figure 60-2/3). The recipe is loaded in RMP Execution Box and becomes visible in the Recipe visualization window (Figure 61); loading can take a few minutes.

Once assigned the recipe and on-going step appears in HEADER Recipe summary field with recipe state between brackets (Assigned/Running/Paused/Held/Aborted/Complete).

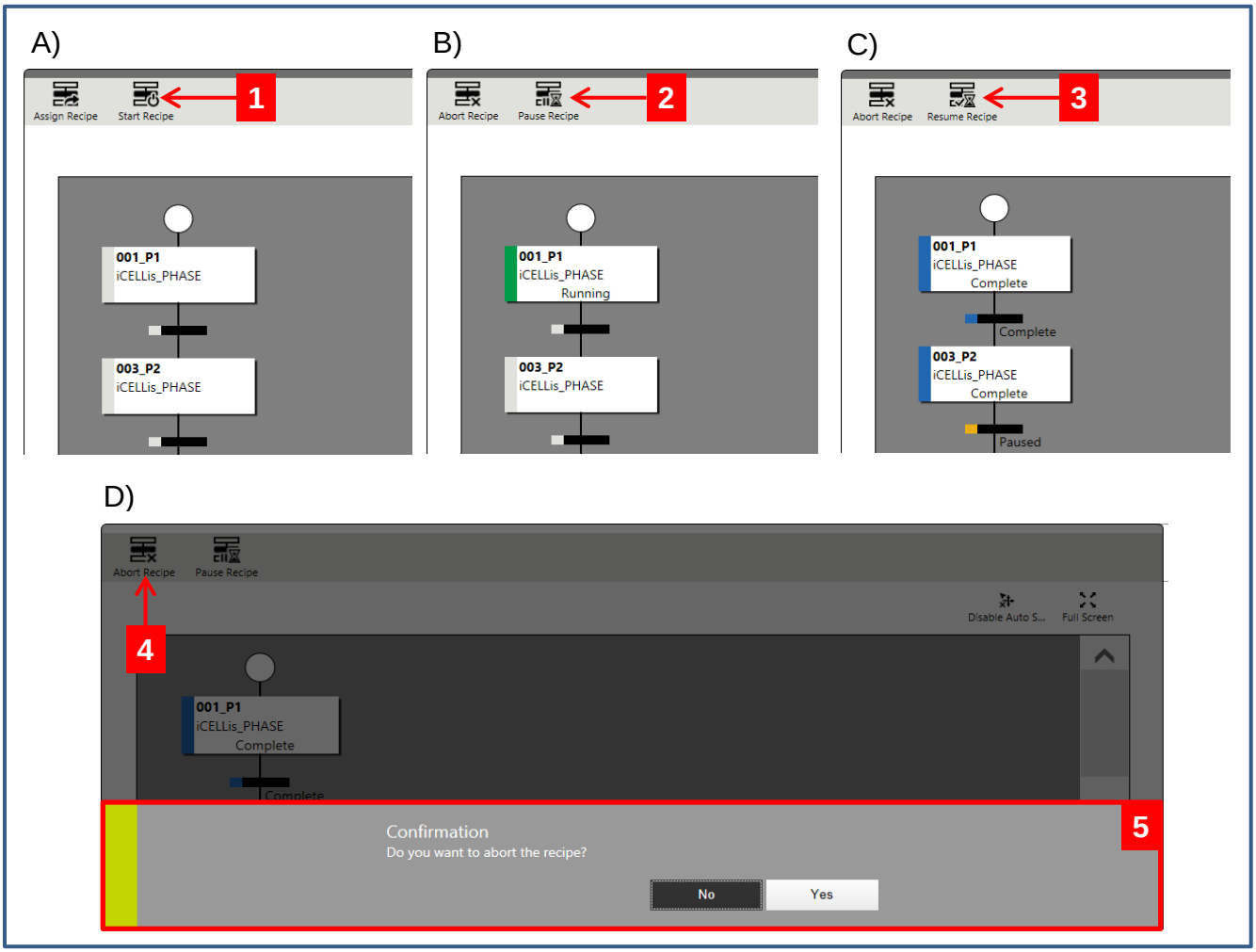


Figure 61: Recipe visualization window details for recipe starting, pausing, resuming and aborting – A) Assigned recipe not started, B) Started recipe running, C) Running recipe paused, D) Confirmation of running recipe abortion, 1) START RECIPE button, 2) PAUSE RECIPE button, 3) RESUME RECIPE button, 4) ABORT RECIPE button, 5) ABORT RECIPE Confirmation box.

An assigned recipe can be initiated using the START RECIPE button (Figure 61-a1). The recipe then follows sequence of phases and transitions programmed. Displayed buttons are changed to ABORT RECIPE and PAUSE RECIPE.

IMPORTANT!
Before starting a recipe, it is recommended to initiate all EM to AUTO mode in STANDBY state. This can be done manually, one EM at a time, from P&ID screen or in one single step with INITIATE EM AUTO/STANDBY button on RMP Execution pages (Figure 49-3).

11.5.3 Pausing Recipe, Holding Recipe, Forcing Transitions & Aborting Recipe

In the absence of user's request, each recipe step sequentially goes through 4 stages: Assigned, Requesting Start, Running, Complete. Stages are graphically displayed on recipe execution box for an easier visualization (Figure 62 a to d).

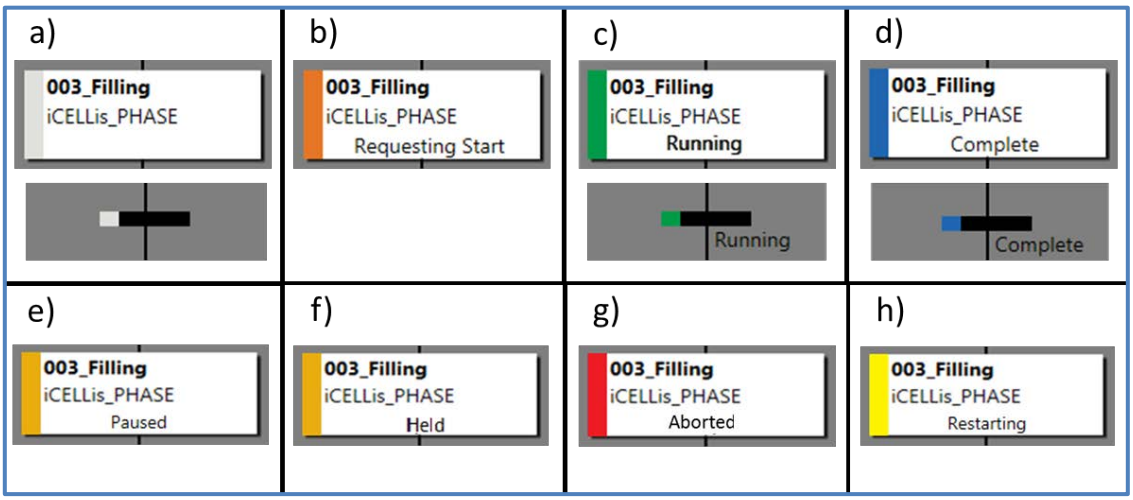


Figure 62: Phases and transitions states during execution – A) Assigned stage, B) Requesting Start stage: conditions for start are checked, C) Running stage, D) Complete stage, E) Paused, F) Held, G) Aborted, H) Restarted.

It is possible to modify the course of a step by different manners:

- Recipe can be paused at any time with PAUSE RECIPE button (Figure 61-b2); In Pause mode the equipment will continue running with latest settings but the recipe will not go to the next step until the RESUME RECIPE button (Figure 61-c3) is used.
- In case of Emergency Shutdown, the recipe will switch automatically to HOLD mode, all EM will go to STANDBY mode and Control Systems/actuators will stop, when the Emergency Shutdown is reset and the acknowledgment is done the recipe can be restarted by using RESTART RECIPE button.

In Hold mode, it is not possible to override EM and actuator controls in auto mode, Recipe has to be restarted or aborted to be able to restart EM, but it is still possible to change to manual mode and control the actuators.

- Recipe can be aborted at any time with ABORT RECIPE button and confirming entry (Figure 61-d4/5). Aborting the recipe will end the recipe and all EM will go to standby mode.
- It is possible to force the logic state of IF transition by selecting IF transition and using FORCE TRUE button then displayed in Step Forcing Buttons Area, dual signature with comments are required in this case:
    - First level signature needs to be signed by an engineer user.
    - Second level signature needs to be signed by an administrator user.

Transitions (IF/OR/LOOP) require their expression (logic statement) to meet a specific value at runtime (TRUE or FALSE) to continue to next step. If the value for going forward is not met (error in programing or too long time) it could result in an endless recipe.
IF transitions have FORCE TRUE option that can be used also in OR BRANCH. LOOP transitions do not have FORCE BREAK option.

All those states are graphically displayed in the recipe execution box (Figure 62E - H).

If the recipe is executed until the Finish point, all steps will be marked ‘Complete’ and the Recipe will end however all EMs will remain in the last programmed state.

12. Batch Data

12.1 Editing Run Information

This section will present how to edit the name of the Batch, the name of the Bioreactor and the information of the Batch. These three names will be registered and appear in a Batch Report.
By selecting the BATCH INFORMATION button in the HEADER (Table 1), a dialog box opens that allows introducing any run-related information.

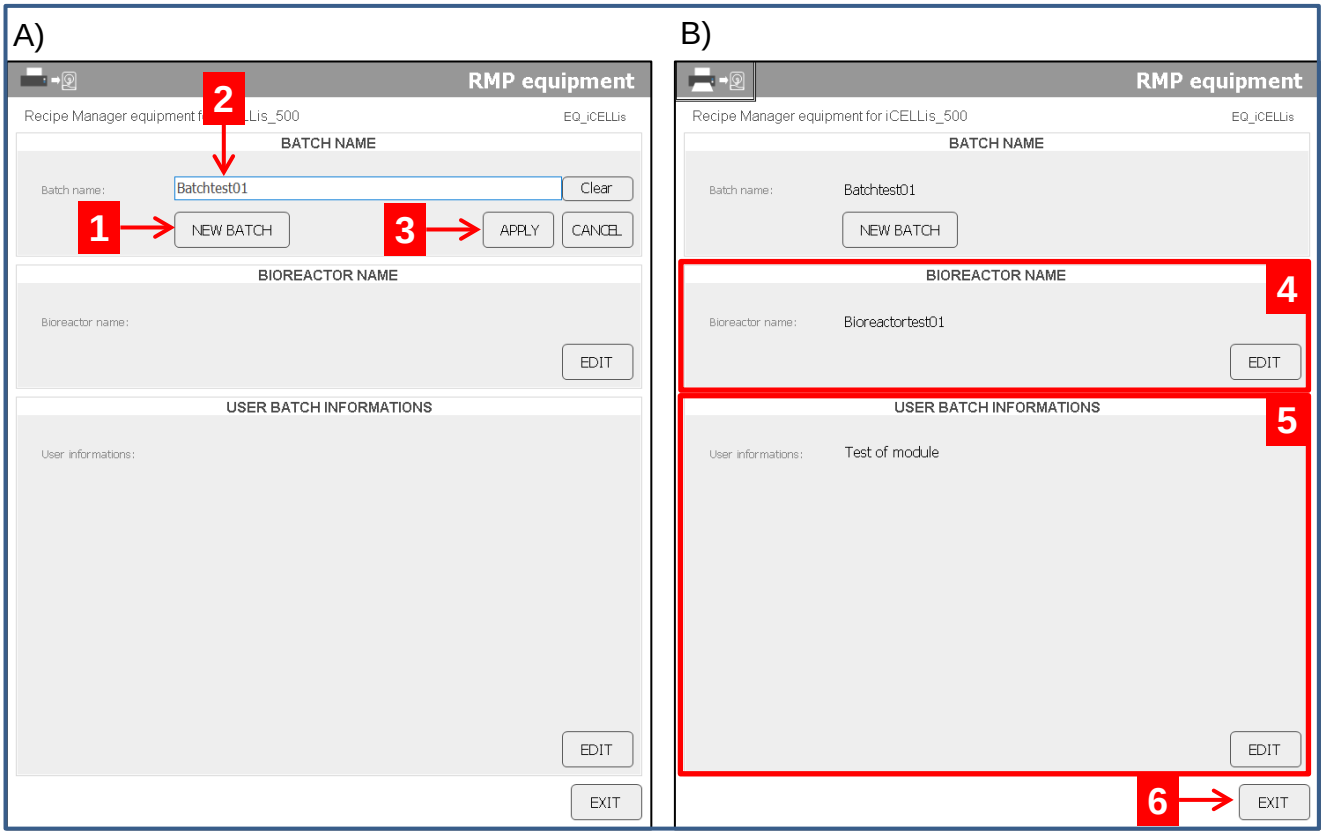


Figure 63: BATCH INFORMATION dialog box – A) New batch edition, B) Bioreactor name and user information introduction, 1) NEW BATCH button, 2) Batch name introduction field, 3) Batch name APPLY button, 4) BIOREACTOR NAME field, 5) USER INFORMATION field, 6) EXIT button.

User can define the following run data:

- Batch Name: this name is chosen by the user and must be written without blanks. Use the NEW BATCH button (Figure 63-A1) to enter batch name and apply entry (Figure 63-A2/3);
- Bioreactor Name: edit bioreactor name or ID (serial number) in the dedicated field (Figure 63-B4);
- User batch information: edit additional information in the dedicated field (Figure 63-B5).

When all Batch information is filled, selection of NEW BATCH button clears all fields.

The data entered in BATCH INFORMATION is stored in the database and included in the Batch report. However, there is no protection to prevent introducing several times the same information. Updating and certifying the data is the user's responsibility.

12.2 Report Generation

The iCELLis 500+ bioreactor software stores all run data in a secured database and this database can be accessed to generate electronic reports.

IMPORTANT!
Electronic reports are exclusively based on the completion of an existing recipe. It is thus not possible to generate a report for a period that was not under a recipe execution.

To generate a report go to HOME:BATCHDATA (Figure 64).

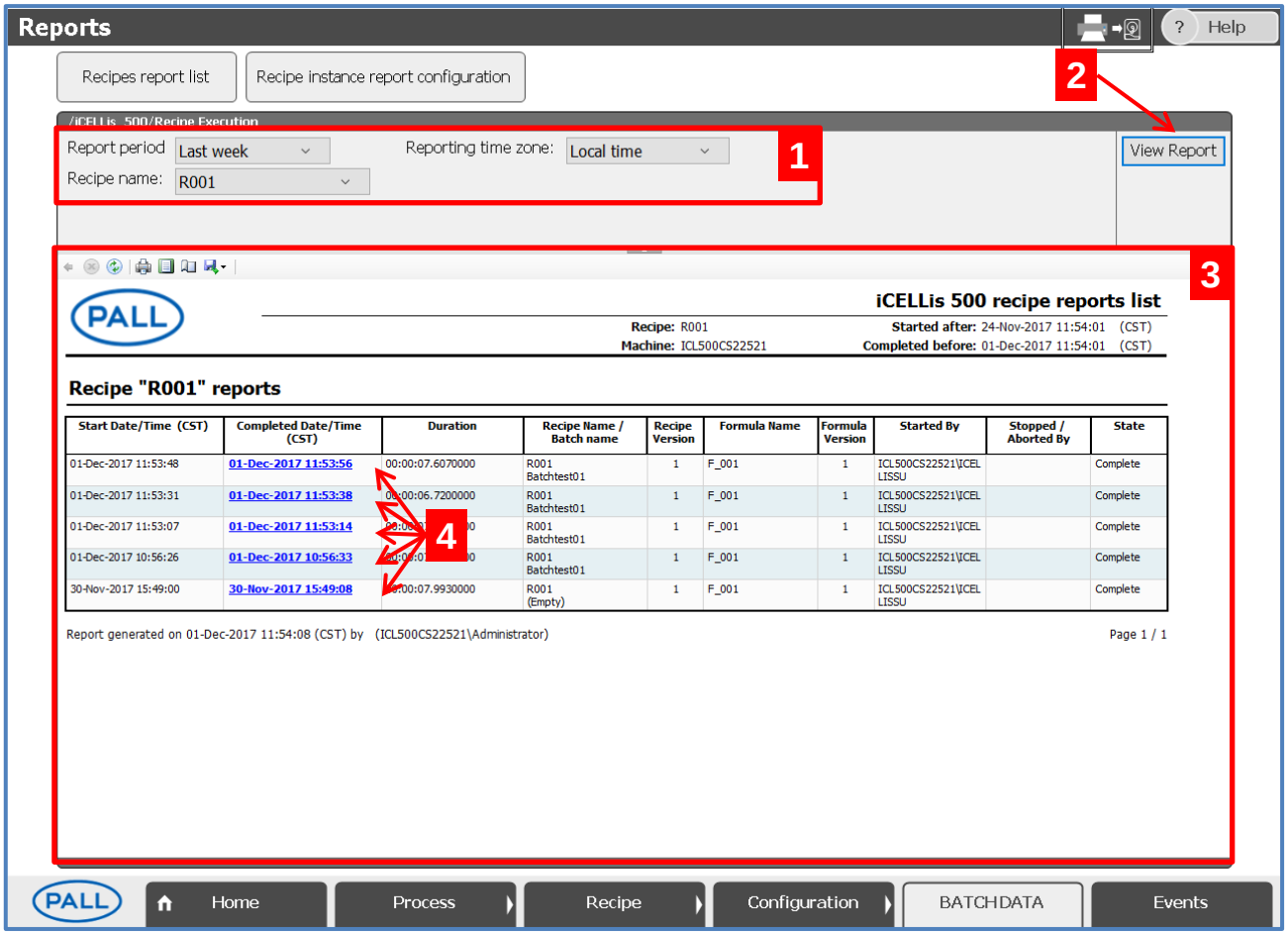


Figure 64: Batch report generation page – 1) Report display settings, 2) VIEW REPORT button, 3) Available reports list, 4) Report opening link.

Available report list can be displayed after definition of report display settings (Figure 64-1) and validation with VIEW REPORT button (Figure 64-2). The list of corresponding reports is displayed by completion date/Time and a report can be open by selecting the link in Completed Date/Time column (Figure 64-3/4).

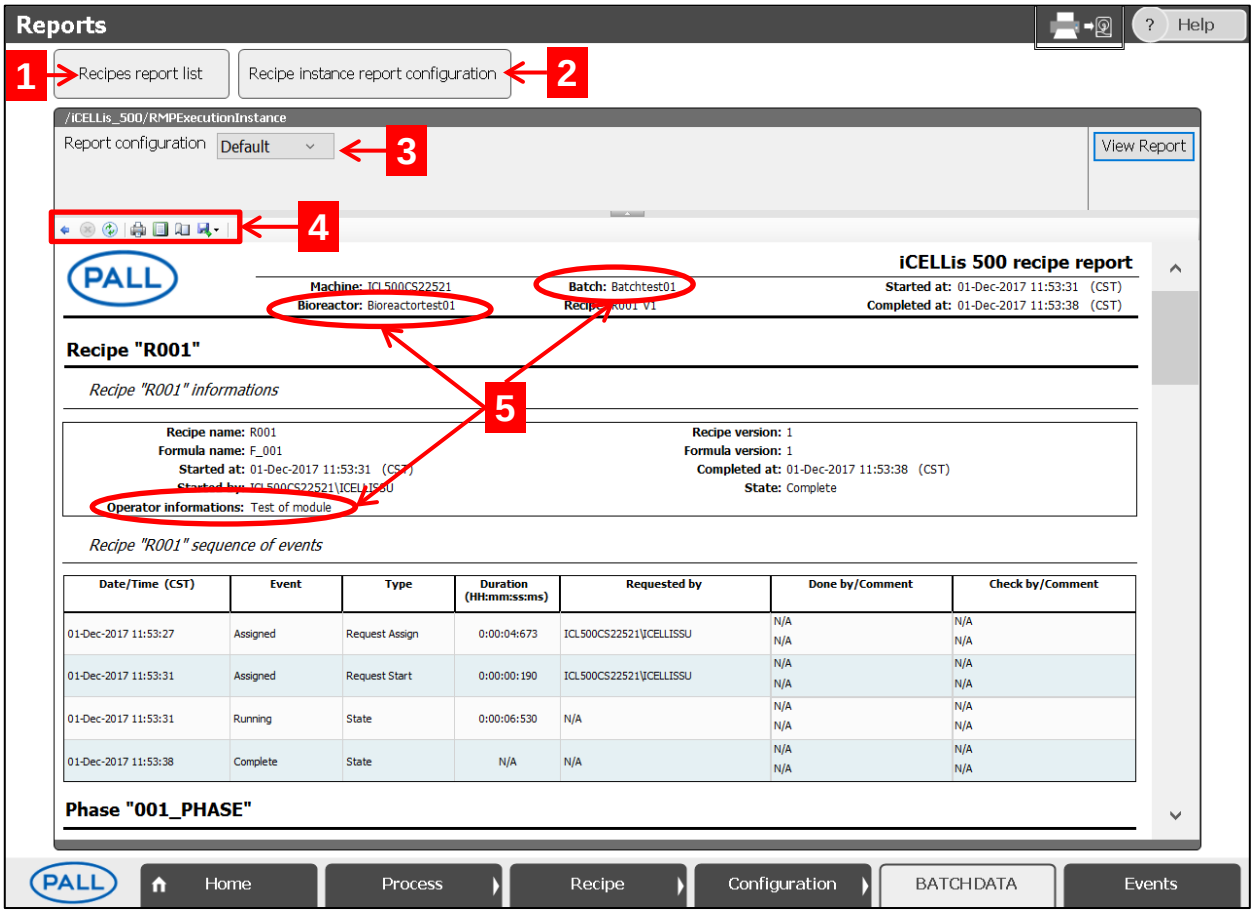


Figure 65: Visualization and modification of a report – 1) RECIPES REPORT LIST button, 2) RECIPE REPORT CONFIGURATION button, 3) REPORT CONFIGURATION drop-down list, 4) Report File Management buttons, 5) User's Batch information.

When selected, the report opens in the main window. Using File Management buttons, it is possible to print the report (Figure 65-4), and to export as PDF file the button EXPORT TO PDF is available, the file will be saved in the Hard drive or in the external USB if it's connected. The content and presentation of the report can also be changed using an existing Report Template from the drop-down list (Figure 65-3), the template should be selected during the configuration of the report (refer to the next section).

Batch information entered by user in BATCH INFORMATION dialog box is displayed in the report header (Figure 65-5).

As described in the next chapter the configuration of the report can be modified.

12.3 Report Configuration Tool

It is possible to configure the content of batch reports used in iCELLis 500+ bioreactor software with the RECIPE REPORT CONFIGURATION button (Figure 65-2). This button toggles to a new page where the user can start a new report model or modify an existing model (Figure 66).

Figure 66: Report edition frame – 1) NEW report button, 2) Existing report selection lists.

Report models are compulsorily attached to a recipe name and it is not possible to select a report template from another recipe when generating a report. That is why the report selection list is refined first by Recipe Name. However, it is possible to create a report by copying an existing one.

12.3.1 Report Model Creation

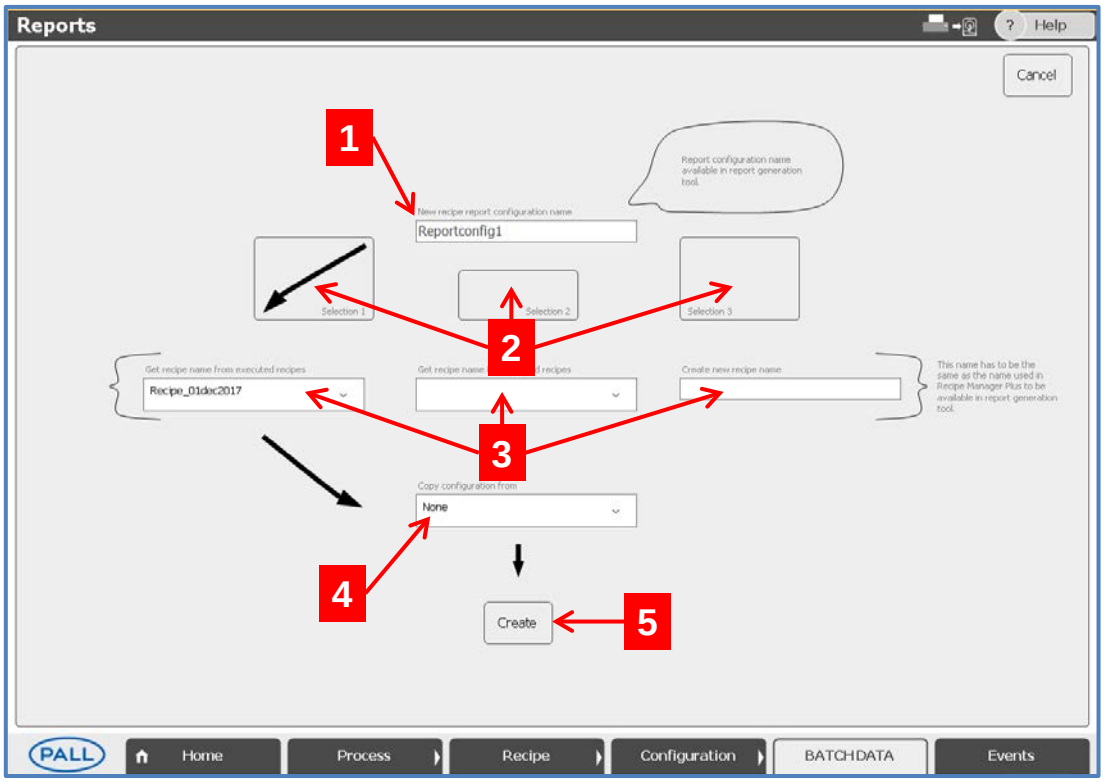


Figure 67: Report model creation dialog box – 1) Report name, 2) Recipe status selection (new recipe, created recipe, executed recipe), 3) Associated Recipe Name, 4) Copy configuration from existing Template, 5) CREATE report model button.

When selecting NEW button in the RECIPE REPORT CONFIGURATION page, the user must first define the name of the new report (Figure 67-1) and then associate the model to a recipe. There are three possibilities:

- The recipe exists and has been executed once (3- Left branch);
- The recipe exists but has never been executed (3- middle branch);
- The recipe does not exist yet (3- right branch).

User must select one of these possibilities and select or define a recipe name in accordance (Figure 67-2/3). Only the first option (3- Left branch) leads to the immediate generation of a report.

It is then possible to select an existing Report template as basis of the new report model (Figure 67-4) and validate selection with CREATE button (Figure 67-5).

12.3.2 Report Model Edition

The data displayed in the Batch reports can be customized. To do this, report models need to be created/modified. To create a new model, click on New. To update an existing one, change the Recipe report configuration name to the one to be updated and click on Update (Figure 68-1).

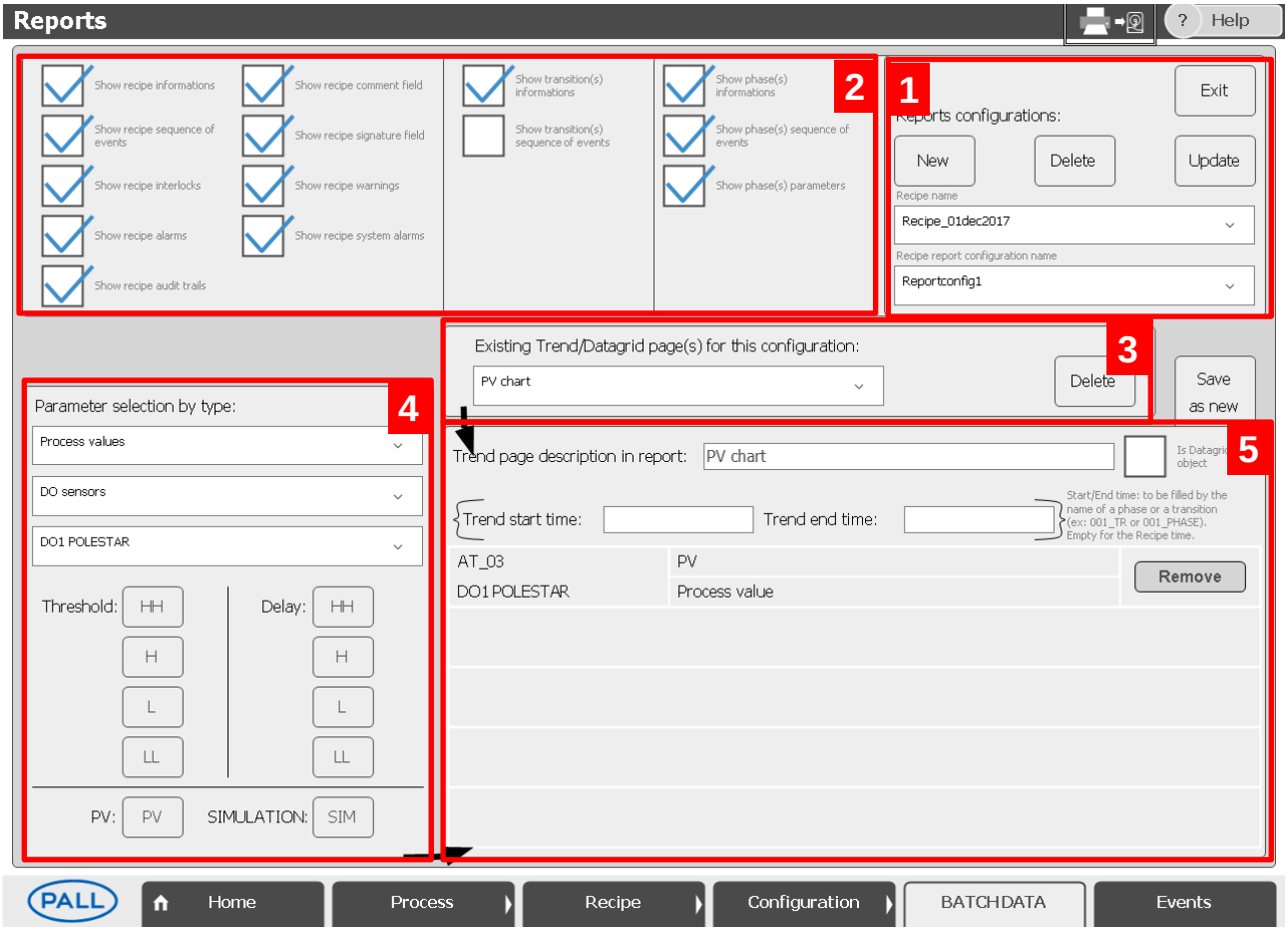


Figure 68: Batch report configuration tool – 1) Report edition frame, 2) Report content categories, 3) Trend groups list, 4) Trend parameter selection, 5) Selected parameters in trend & trends name/time edition.

The content of the report is sorted in categories. User can select which categories are to be included in the report (Figure 68-2).

Trends can be added to the report template as an object. The configuration of this object (Parameters selected) must be saved under a description name and can then be re-used (Figure 68-3/5). Parameters can be added to the Trend using the Trend Parameter Selection (Figure 68-4), and just clicking on the desired parameter. The parameter will appear on Figure 68-5. A maximum of 5 parameters can be plotted together on one Trend page. If more parameters need to be plotted, a new group of parameters (page) needs to be created by changing the name of the description and saving as new.

12.4 Change Logo on the Reports

The iCELLis 500+ bioreactor software allow the customer to use its own logo in the generated reports in a very simple way. Figure 69 presents a batch report list with the default Pall logo.

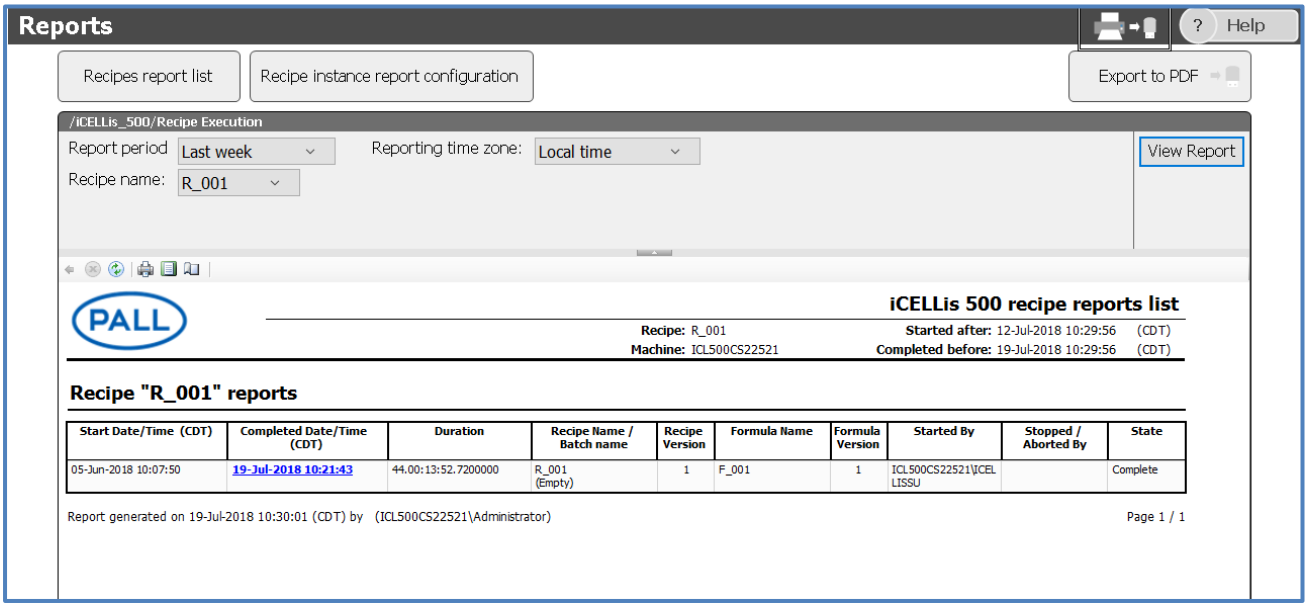


Figure 69: Batch report list with the default Pall logo

To change the logo, it is required to first log in with the windows administrator user account, to have access to the windows features. Go to the folder '*D:\Reports logo*' and paste in this folder the new logo with the name 'REPORT-LOGO.png' in png format, as shown in Figure 70.

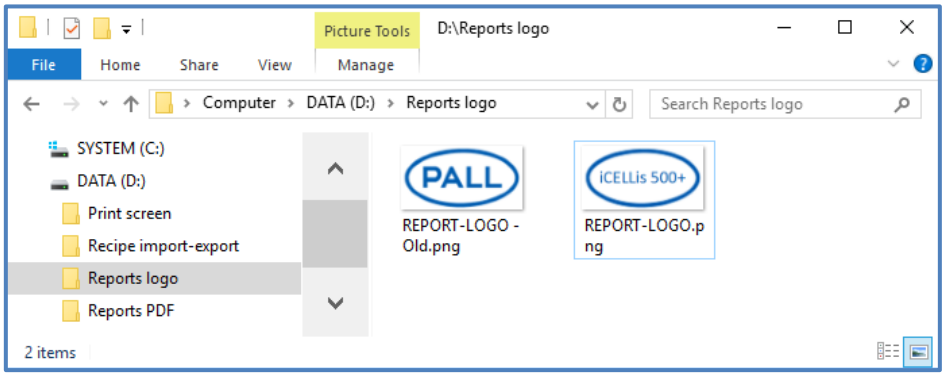


Figure 70: New logo to be placed in the Batch reports

Now, as can be observed in Figure 71, the logo from Pall is replaced by the chosen logo in the Batch report and will be present in all the report pages.

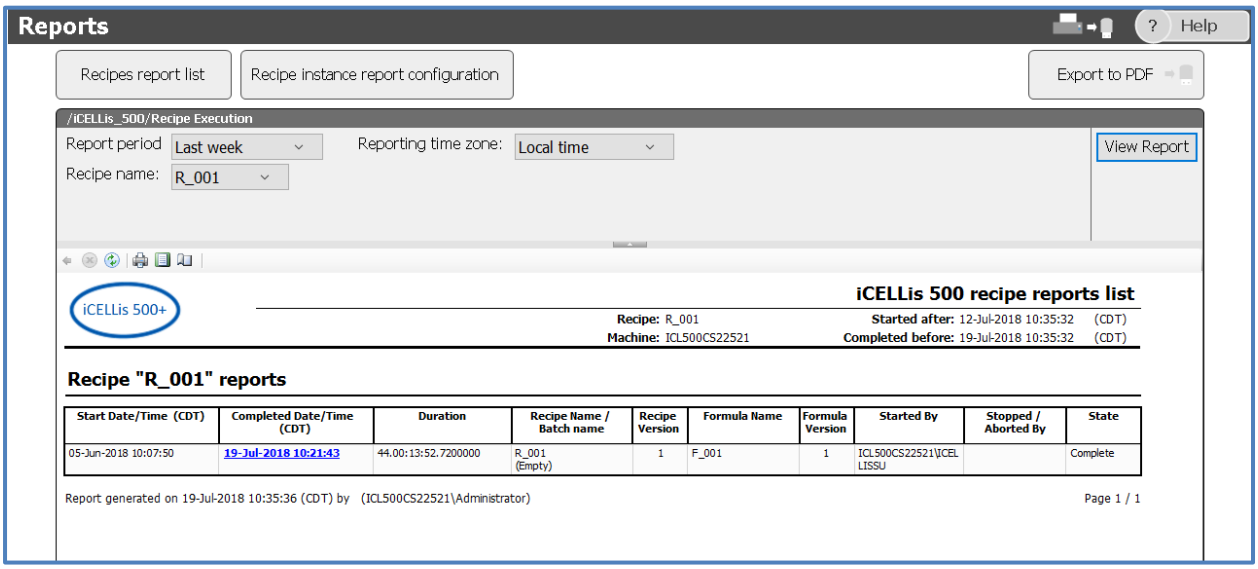


Figure 71: Batch report list with a different logo (iCELLis 500+ bioreactor)

12.5 Simple Recipe for Batch Data Report

If a recipe execution is not desired by the end-user, in case of a manual use of the equipment modules, or other application, and it is needed to create a report, it is recommended to use a very simple recipe.

In this section, a very simple recipe example, with no actions on the equipment modules, is given in order to obtain Batch reports.

The following example (Figure 72) consist in a recipe with 1 phase and 1 transition, that makes the system run a recipe that has no actions in the equipment modules, running indefinitely, until the operator acknowledges a message in Recipe Manager Plus (HOME: RECIPE: EXECUTION menu – Figure 73).

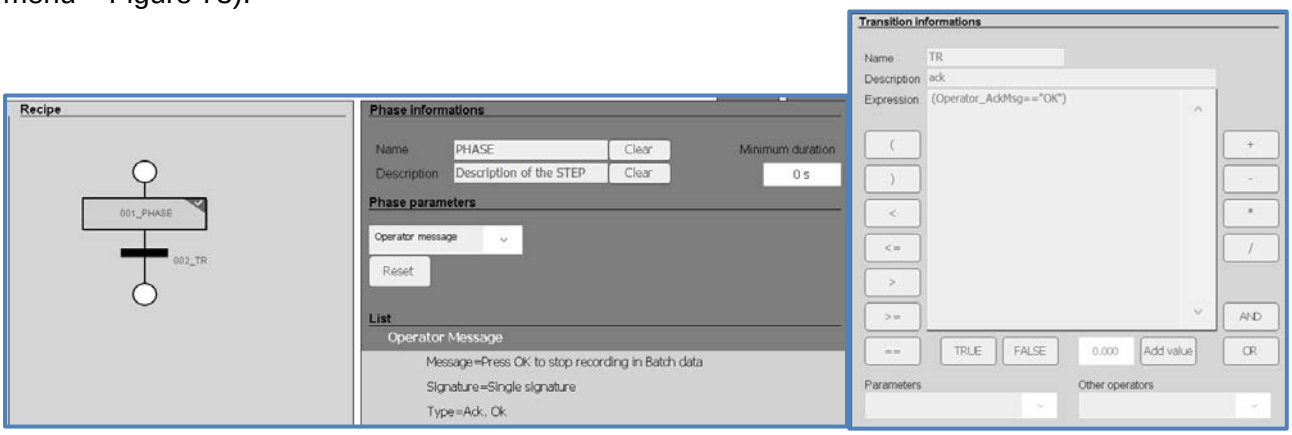


Figure 72: Simple recipe for Batch data report

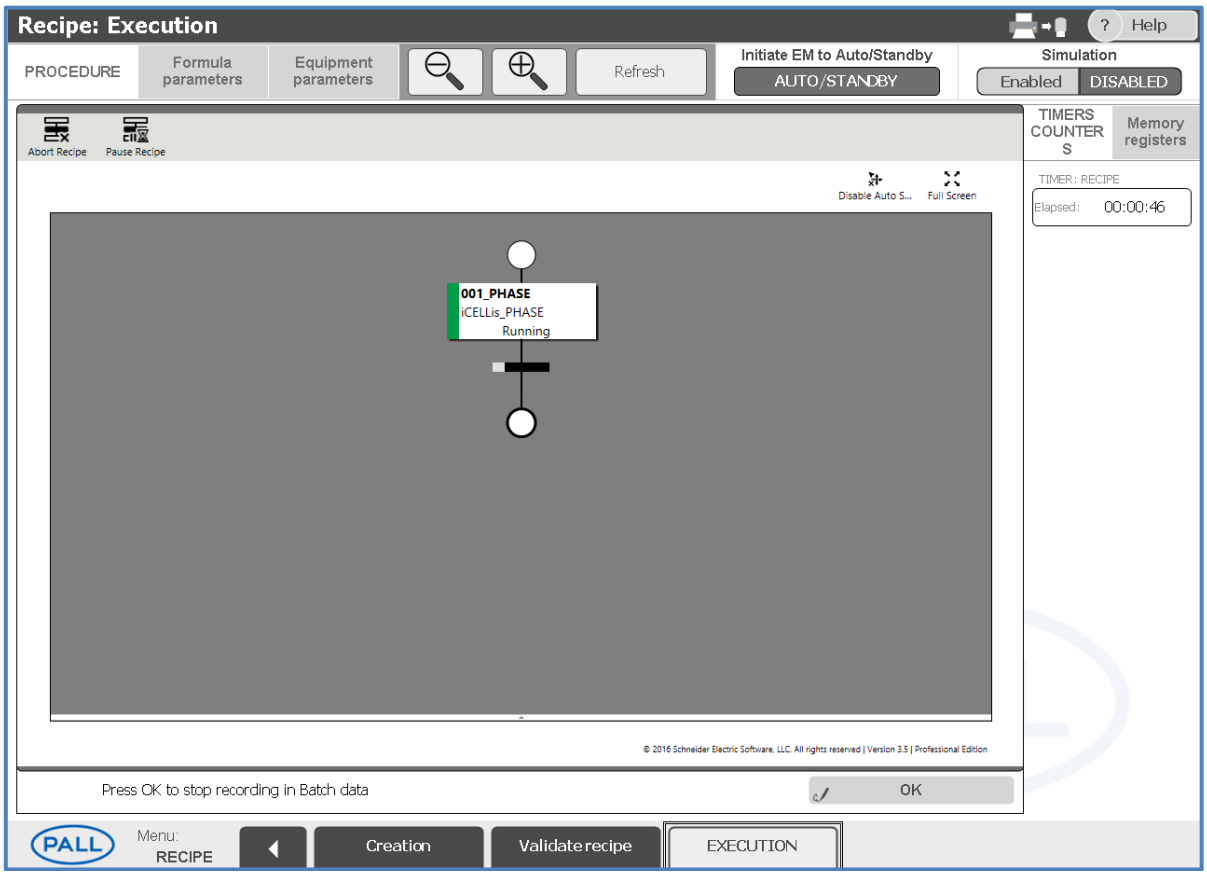


Figure 73: Acknowledge for stopping the simple recipe for Batch data.

13. EVENTS: Alarms and Journal

ALERT! Risk of damage to the equipment/process!
Even if Actions can override Alarms, failure to observe an alarm message could result in damage to the device.

13.1 EVENTS Definitions

The term EVENT in the iCELLis 500+ bioreactor software designates a data set generated by a User action or a deviation from normal state. Deviations encompass process deviations (between PV and SP) and equipment's hardware faults due to electro-mechanical issues. All EVENTS are recorded by the Data Acquisition module and can constitute the proof that a run or a batch has been completed following an accepted procedure (the sequence of operator actions), with or without deviations of process and of equipment from accepted states.

Events in the iCELLis 500+ bioreactor system are sorted into 7 categories:

- INTERLOCKS: automated safety actions triggered by deviations of a process value or a hardware failure. They are divided between Critical Interlocks and Process Interlocks:
    - Critical Interlocks: safety interlocks aiming at protecting iCELLis bioreactor, Control System and process from immediate danger.
    - Process Interlocks: safety interlocks aiming at protecting iCELLis bioreactor, Control System and process from non-immediate danger.
- SENSOR ALARMS: highlight a deviation of a process value from accepted operating range.
- SENSOR WARNINGS: highlight a deviation of a process value from accepted operating range. The two-stage event thresholds (Warning -> Alarms) allows user to take action at Warning stage before reaching the Alarm stage.
- REGULATOR ALARMS: highlight a persistent deviation between a process value and its target value regulated by set-point of an active regulation loop.
- HARDWARE FAULTS ALARMS: will go off if hardware component undergoes power failure, or in case of loss of communication.
- ACTUATOR FEEDBACK ALARMS: will go off if PLC receives no more feedback from active actuator.
- EVENTS: all commands sent by the iCELLis software HMI to the PLC, resulting from user action in software or recipe execution.

EVENT categories have different impact on process or equipment. They can be hierarchized by priority over PLC commands:

INTERLOCKS > HARDWARE > OPERATOR ACTION > ALARMS > WARNING

Alarms and Warning activation is done from Sensors and Control System configuration tabs, by enabling the alarm with check box (see Figure 12 for example).

13.2 Events Visualization

Events and generated alarms can have a critical impact on the good proceedings of a process. Hence, special efforts have been made to emphasize events visualization and impacted elements.

13.2.1 HEADER Event Display

Constantly visible on iCELLis 500+ bioreactor screen, the HEADER is used to display real-time system status associated with a color code: OK (blue), INTERLOCK (Red), ALARM (Red), HARDWARE (Orange) and WARNING (Orange). The priority of status displayed (Figure 74) is as follows:

INTERLOCK > ALARM > HARDWARE > WARNING > OK

When the system status is different than OK, the STATUS button becomes a shortcut for the corresponding Event journal page.

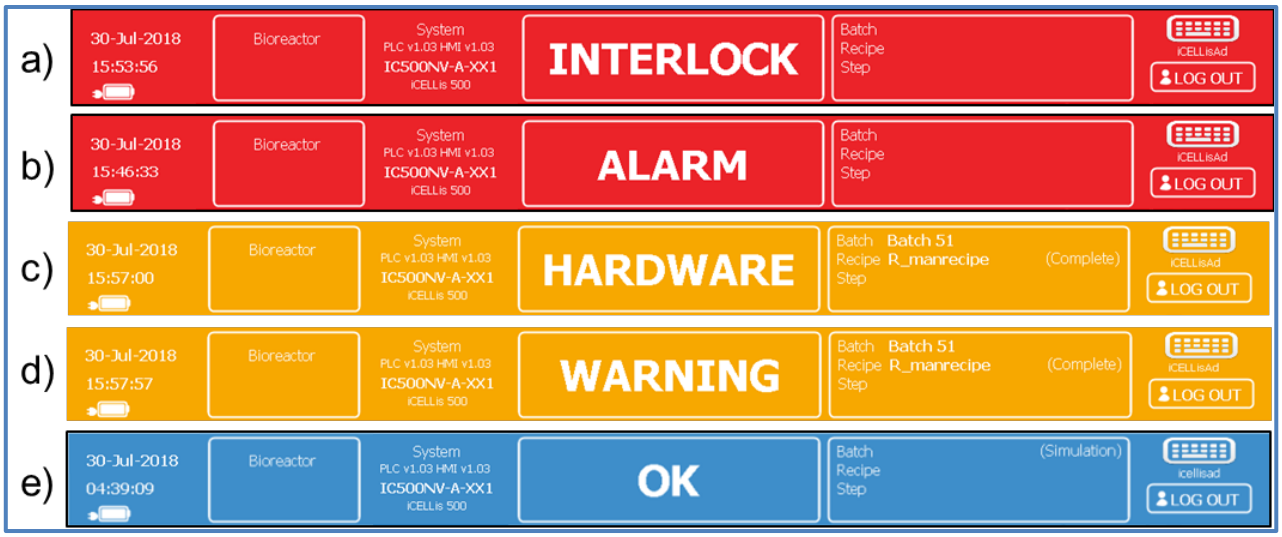
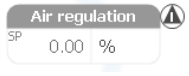
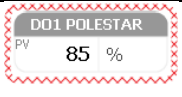


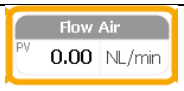
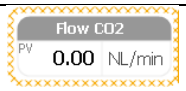
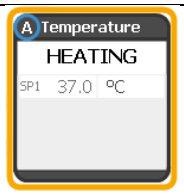
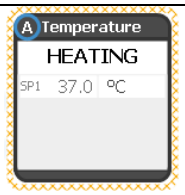
Figure 74: System status display in HEADER by order of priority (top to bottom) – A) Interlock state, B) Alarm state, C) Hardware fault state, D) Warning state, E) OK state.

13.2.2 HOME and P&ID Screens Events Display

In addition to the HEADER status display, HOME and P&ID screens will display more detailed information about alarms/warnings by circling items generating the event and displaying a small icon ⚠ next to the elements affected by Interlocks (Table 23 & Figure 75). Note that these signals will also be displayed in the reduced P&ID exhibited in EM dialog boxes and in the Actuator/Sensor configuration dialog boxes.

Table 23: Visualization of interlocks, alarms and warnings on single elements

Item	Description
1.  2. 	1. Control System locked by interlocked 2. Actuator locked by interlocked
1.  2. 	1 – Blinking. Sensor Alarm active and not acknowledged 1 – Not blinking. Sensor Alarm active and acknowledged 2 – Not blinking. Sensor Alarm inactive and unacknowledged
1.  2. 	1 – Blinking. Regulation Alarm active and not acknowledged 1 – Not blinking. Regulation Alarm active and acknowledged 2 – Not blinking. Regulation Alarm inactive and unacknowledged

1.  2. 	1 – Blinking. Actuator Feedback Alarm active and not acknowledged 1 – Not blinking. Actuator Feedback Alarm active and acknowledged 2 – Not blinking. Actuator Feedback Alarm inactive and unacknowledged
1.  2. 	1 – Blinking. Hardware Fault Alarm active and not acknowledged 1 – Not blinking. Hardware Fault Alarm active and acknowledged 2 – Not blinking. Hardware Fault Alarm inactive and unacknowledged
1.  2. 	1 – Blinking. Sensor Warning active and not acknowledged 1 – Not blinking. Sensor Warning active and acknowledged 2 – Not blinking. Sensor Warning inactive and unacknowledged
1.  2. 	EM boxes reflects alarms of related regulation loops to allow Alarms/Warnings visualization on P&ID screen. 1 – Blinking. Regulation Alarm active and not acknowledged 1 – Not blinking. Regulation Alarm active and acknowledged 2 – Not blinking. Regulation Alarm inactive and unacknowledged

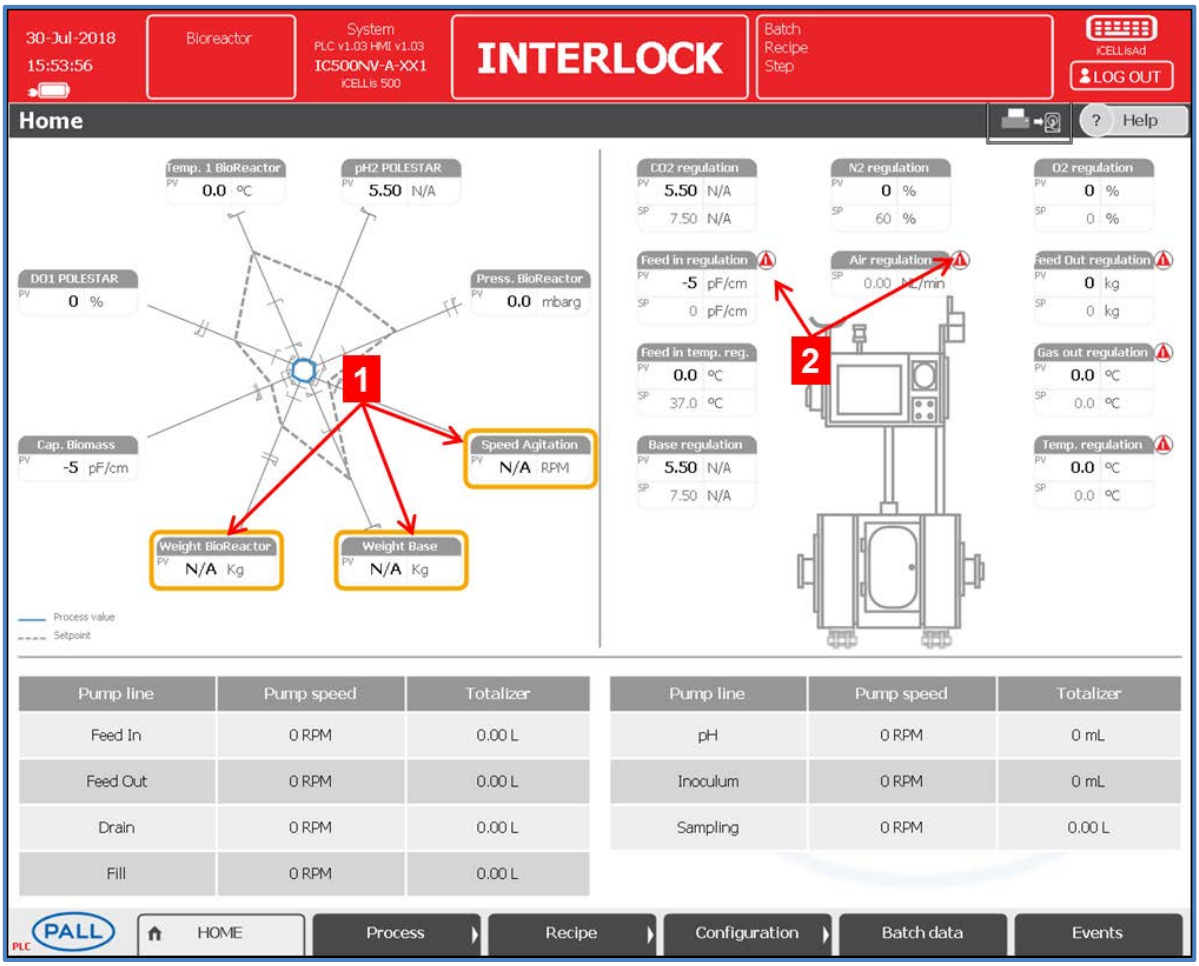


Figure 75: Visualization of events on HOME screen – 1) Active Sensor Warning, 2) Active Interlock.

13.2.3 Sensor Alarms and Warnings in Auto-Trend Window

Auto-trend window displays sensor trends over the last 5 hours in Sensor configuration tab in EM dialog box. If the PV is going beyond alarms limits and alarms are enabled, it will be highlighted by orange (warning) and red (alarm) flags on the graph (Figure 76).

Figure 76: Warning and Alarm levels highlighted in pH auto-trend window

13.2.4 PLC Connection and ESD Status Boxes

The FOOTER of the iCELLis 500+ bioreactor software displays in the bottom left corner the error status of two important components:

- PLC connection status box (Figure 77-a) indicating the state of the communication between Control System's PLC and the computer;
- Emergency Shutdown (ESD) status (Figure 77-b) indicating the state of ESD interlock.

When neither error nor interlock is active, there is no signal on the FOOTER. Otherwise the faulty component causes a red text blinking next to Pall logo in FOOTER (see Table 2).

PLC connection status box is a maintenance tool used by Pall Service only. In case the status is not OK (red cross instead of blue check in upper frame) contact Pall Service.

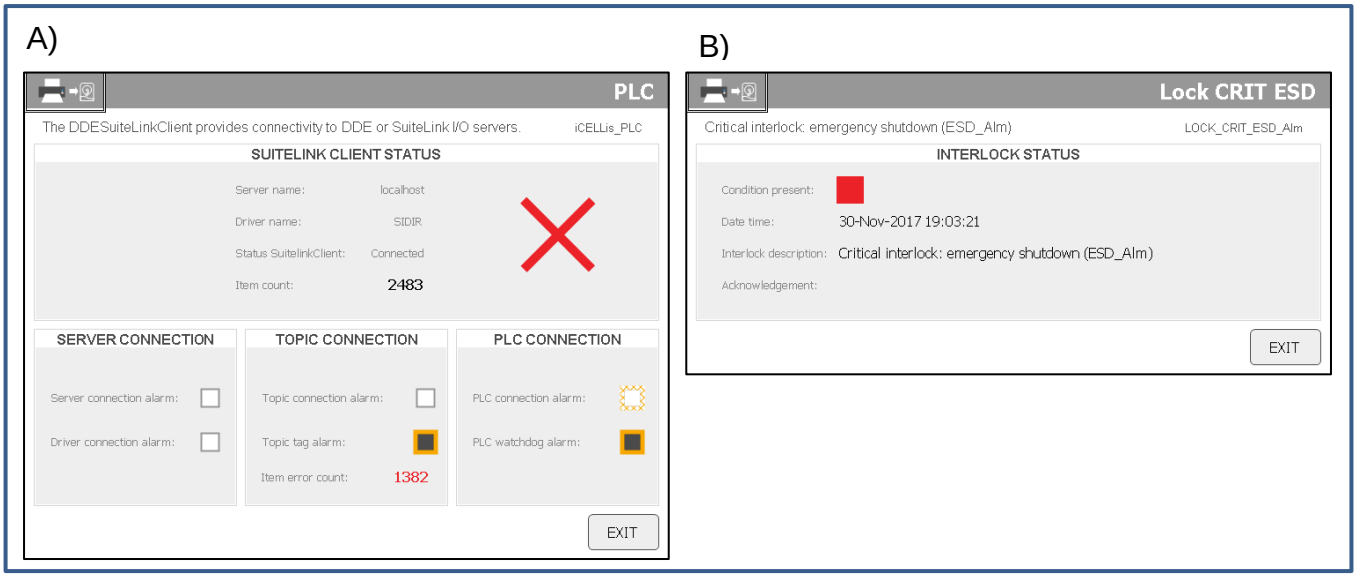


Figure 77: PLC connection and ESD status boxes – A) PLC connection in error status (red cross) with active alarms on Topic and PLC connection, B) ESD status with ESD critical interlock active (red square).

13.3 EVENTS Resolution

13.3.1 EVENTS Journals

Events are logged into a journal accessible through HOME: EVENTS menu. The Journal is divided in 6 Events sub-categories sorted as follow:

- INTERLOCKS category: Critical & Process interlocks are listed here
- ALARMS category: this journal groups three categories of events:
  - Sensor Alarms
  - Regulator Alarms
  - Actuators Feedback Alarms
- WARNING category: displays Sensors, regulations and actuators Warnings
- HARDWARE category: two events categories are listed here:
  - Hardware Faults Alarms
  - Actuators Feedback Alarms
- ALL: groups ALARMS, WARNINGS and HARDWARE categories in a single view
- EVENTS journal: logs ACTIONS.

An additional event category appears in the journal called LOGVIEWER. These events are related to background software operations and are of no use for iCELLis 500+ bioreactor user but can be useful for maintenance or IT services. It will not be discussed in this User Manual.

13.3.2 Critical Interlocks

Critical interlocks events having some specificity, they are treated differently than other events in iCELLis 500+ bioreactor software. There are 11 critical interlocks, listed in the HOME: EVENTS: INTERLOCKS page. Each critical interlock can override the control of actuators and control loops to shut them down (Table 24).

Table 24: Critical Interlocks description

Interlock name	Reference sensor	Description	Affected EM
Emergency shutdown (ESD_Alm)	N/A	Triggered by emergency shutdown buttons. Stops all EMs	All EMs
High pressure in Double Jacket	DJ pressure sensor	Prevents damage of Double-Jacket by overpressure. Stops TCU heating and fluid circulation	TEMPERATURE
High pressure in Bioreactor	Bioreactor pressure sensor	Prevents damage of bioreactor due to overpressure. Stops all incoming flows	FILL FEED IN INOCULATION pH / DO REGUL.
High pressure in middle assembly	Middle assembly pressure sensor	Prevents damage of gas circuit in the iCELLis 500+ bioreactor control system. Stops incoming gases	DO REGUL. pH with CO_2 (Control of pH using the Base pump will continue).
High temperature in bioreactor 1	Temperature bioreactor probe 1 (Only if sensor probe is selected for regulation or TCU temperature probe is selected)	Prevents media and bioreactor overheating. Stops TCU & media preheater	TEMPERATURE FEED IN
High temperature in bioreactor 2	Temperature bioreactor probe 2 (Only if sensor probe is selected for regulation or TCU temperature probe is selected)	Prevents media and bioreactor overheating. Stops TCU & media preheater	TEMPERATURE FEED IN
High temperature in pre-heater bag 1	Temperature pre-heater bag probe 1 (Only if sensor probe is selected for regulation)	Prevents media overheating in preheater bag. Stops media preheater	Heater FEED IN
High temperature in pre-heater bag 2	Temperature pre-heater bag probe 2 (Only if sensor probe is selected for regulation)	Prevents media overheating in preheater bag. Stops media preheater	Heater FEED IN
High temperature TCU	TCU temperature probe	Prevents internal overheating of TCU. Stops TCU.	TEMPERATURE with TCU
Low temperature exhaust	Filter heater temperature probe	Prevents condensation in venting filter in case of filter heater failure. Stops incoming gases.	DO REGUL. pH with CO_2 (Control of pH using the Base pump will continue).
Low low weight bioreactor	Bioreactor weight scale	Prevents damage of vessel in case of low volume. Stops FEED IN, FEED OUT, SAMPLING & AGITATION. (For Feed in & Feed out: Except if rpm strategy is applied or EM is in manual mode)	AGITATION FEED IN/OUT SAMPLING

High High weight bioreactor	Bioreactor weight scale	Prevents from overfilling the bioreactor. Stops all pumps except Sampling.	FILL/Drain FEED IN/OUT INOCULUM pH with Base pump (Control of pH using the CO_2 will continue)

When a Critical Interlock is activated, equipment status shifts to INTERLOCK in HEADER and will stay in this state (Figure 63A) until the Interlock is not active anymore AND the interlock event has been acknowledged by user. Once the interlock returns to normal state, navigate to interlock journal or use the STATE button shortcut in the HEADER. The page displays the critical interlocks list, live condition (Figure 67-1) and highlights in red interlocks that are active or have been activated (Figure 67-3/4). Only when the interlock is not active anymore an ACKNOWLEDGE button will be displayed to get rid of interlock effects (Figure 67-5).

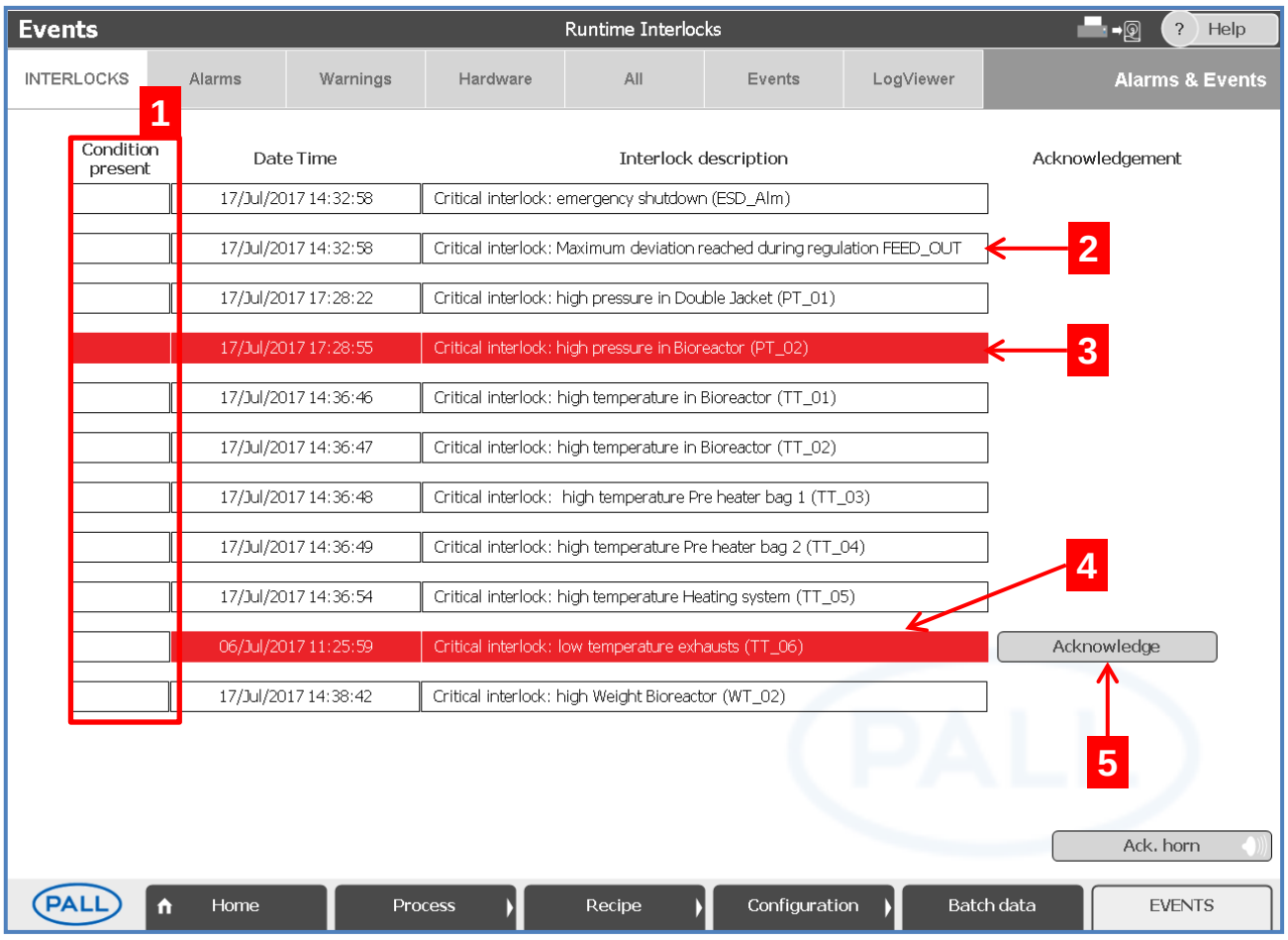


Figure 78: Interlock Journal page in Events menu – 1) Interlock Live condition (White: inactive; Red: active), 2) Non-activated interlock, 3) Activated and still active interlock, 4) Activated then inactivated interlock not acknowledged, 5) ACKNOWLEDGE interlock button.

13.3.3 Process Interlocks

Process Interlocks are set to prevent non-critical damage to the system or to prevent the system to trigger a critical Interlock. Process Interlock and their effect are described in next table.

Table 25: Process interlocks description

Interlock Name	Reference Sensor	Description	Affected EM
Temperature Filter heater High	Filter heater temperature probe	Prevents from damaging GAS OUT vent. Stops heating	GAS OUT
Weight Bioreactor Low	Bioreactor weight scale	Prevents damage of vessel in case of low volume. Stops Feed Out pump (Except in Manual mode or rpm strategy)	FEED OUT
Weight Bioreactor High	Bioreactor weight scale	Prevents from overfilling the bioreactor. Stops Feed In, Inoculation and Fill pumps	FEED IN FILL INOCULUM

13.3.4 Interlocks Matrix

Table 26 presents the interlock matrix. This matrix resumes all the critical and process interlocks mentioned in Sections 13.3.2 & 13.3.3:

Table 26: Process interlocks description

Action	Interlock Conditions => / Device Locked	emergency shutdown (ESD_Alm)	high pressure in Bioreactor or sensor failure (PT_02)	high pressure in Double Jacket or sensor failure (PT_01)	high temperature in Bioreactor (TT_01)	high temperature in Bioreactor (TT_02)	high temperature Pre heater bag 1(TT_03)	high temperature Pre heater bag 2(TT_04)	high temperature TCU or communication error (TT_05)	high temperature filter heater or sensor failure (TT_06)	low temperature filter heater or sensor failure (TT_06)	High High Weight Bioreactor or communication error (WT_02) (*5)	High Weight Bioreactor or communication error (WT_02)	low Weight Bioreactor or communication error (WT_02)	Low low Weight Bioreactor or communication error (WT_02)	High pressure middle assembly or sensor failure (PT_03)	CO2 safety valve not open (XV_01)	N2 safety valve not open (XV_02)	Air safety valve not open (XV_03)	O2 safety valve not open (XV_04)	Base valve not open (XV_05)
Close	XV_01: Safety Valve CO2	CI	CI								CI					CI					
Close	XV_02: Safety Valve N2	CI	CI								CI					CI					
Close	XV_03: Safety Valve Air	CI	CI								CI					CI					
Close	XV_04: Safety Valve O2	CI	CI								CI					CI					
Close	XV_05: Base Pinch Valve	CI	CI									CI									
Stop	P_01: Feed-in Pump	CI	CI									CI	I		CI (*6)						
Stop	P_02: Base Pump	CI	CI									CI									I (*8)
Stop	P_03: Inoculum Pump	CI	CI									CI	I								
Stop	P_04: Feed-out Pump	CI										CI		I (*7)	CI (*6)						
Stop	P_05: Sampling Pump	CI													CI						
Stop	M_06: Agitation System	CI													CI						
Stop	P_07: Fill Pump	CI	CI									CI	I								
Stop	P_08: Drain Pump	CI										CI									
Stop	HX_01: Heater Feed-in	CI			CI(*9)	CI(*9)	CI(*10)	CI(*10)													
Stop	HX_02: Heater TCU	CI		CI	CI(*9)	CI(*9)			CI												
Stop	HX_03: Heater Gas Out line	CI								I											
Close	FCV_01: CO2 flow Control Valve	CI	CI								CI					CI	I (*1)				
Close	FCV_02: N2 flow Control Valve	CI	CI								CI					CI		I (*2)			
Close	FCV_03: Air flow Control Valve	CI	CI								CI					CI			I (*3)		
Close	FCV_0 4: O2 flow Control Valve	CI	CI								CI					CI				I (*4)	

CI: Critical interlock and **I**: Process interlock

Table 26 Note:

TT_01 / TT_02 and TT_03 / TT_04 probes are redundant. Locking is active only when both sensors are defects.
(*1): Only if EM02_PH is in strategy CO_2 or CO_2+BASE
(*2): Only if EM11_DO_REGUL is in strategy AIR+N_2+O_2 or AIR+N_2
(*3): Only if EM11_DO_REGUL is in strategy AIR+N_2+O_2 or AIR+N_2 or AIR+O^2 or AIR
(*4): Only if EM11_DO_REGUL is in strategy AIR+N_2+O_2 or AIR+O_2
(*5): Critical high high interlock is calculated on total weight after zero (value not tared).
(*6): Bypass Critical low low interlock if rpm strategy is applied or in EM is in manual mode
(*7): Bypass low interlock if rpm strategy is applied or in EM is in manual mode
(*8): Only if EM02_PH is in strategy BASE or CO_2+BASE
(*9): Only if sensor probe is selected for regulation or TT_05 selected
(*10): Only if sensor probe is selected for regulation

13.3.5 Alarms and Warnings

Sensors Alarms and Warnings, Actuator Feedback Alarms and Hardware Faults Alarms are treated similarly. They can be visualized in the dedicated journal or in ALL EVENT journal. They follow the same rules for display in this view (Figure 79):

- White fonts on colored (Red or Orange) background for active/un-acknowledged messages
- Colored fonts (Red or Orange) on white background for active/acknowledged messages
- Blue fonts on white background for inactive/un-acknowledged messages

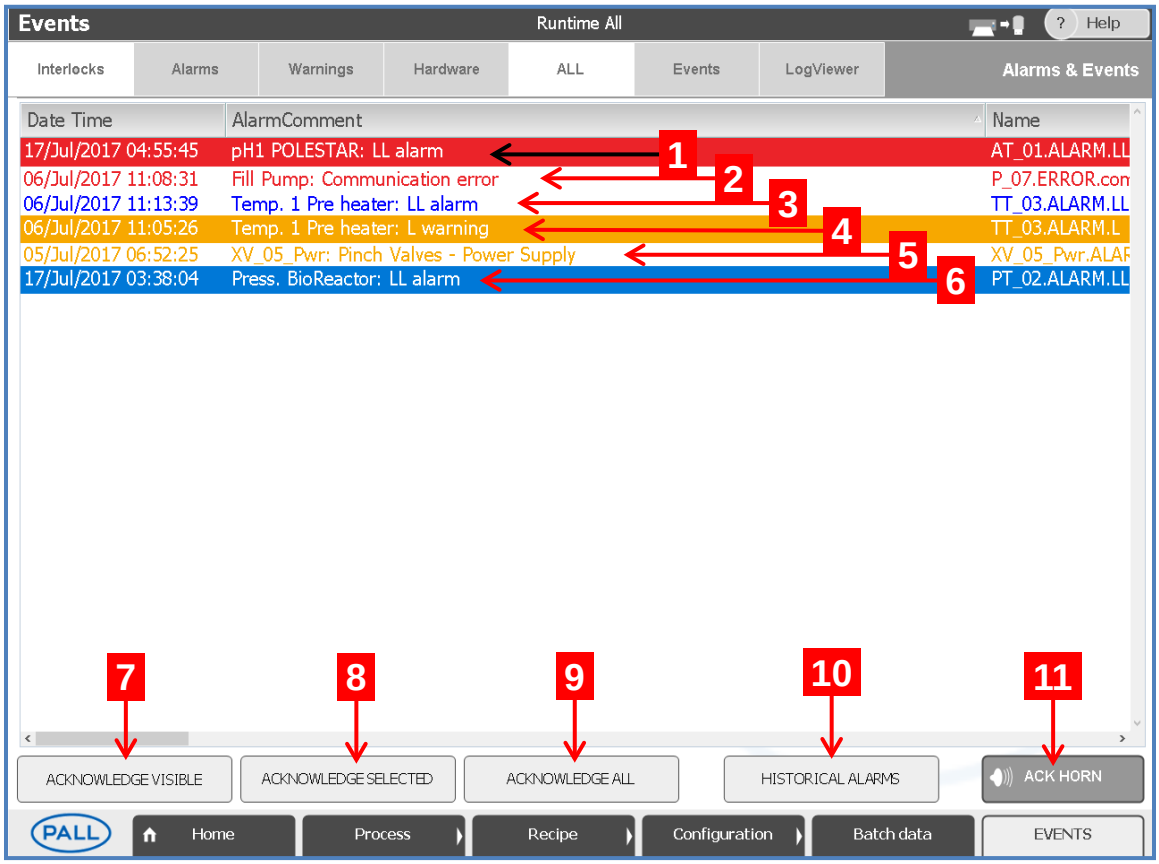


Figure 79: Alarms and Warnings displayed in ALL EVENT journal page – 1) Active Alarm message, 2) Active, Acknowledged Alarm message, 3) Inactive, non-acknowledged Alarm (or Warning) message, 4) Active, non-acknowledged Warning message, 5) Active, Acknowledged Warning message,

6) Selected Alarm message, 7) ACKNOWLEDGE VISIBLE message button, 8) ACKNOWLEDGE SELECTED message button, 9) ACKNOWLEDGE ALL message button, 10) Shift button between HISTORICAL ALARMS and RUNTIME ALARMS – Note: in Historical view user can choose time span, 11) ACKNOWLEDGE HORN button.

From Events journal pages, Alarms and Warnings can be acknowledged one by one or in groups (Figure 79-7/8/9). Inactive, acknowledge messages will disappear from runtime view. It is possible to find these messages by shifting between runtime view and historical view (Figure 79-10).
Note that alarms related to a specific EM can be visualized directly in the EM dialog box by selecting the ALARM tab in the EM dialog box. In this view, it is also possible to acknowledge alarms (Figure 80).

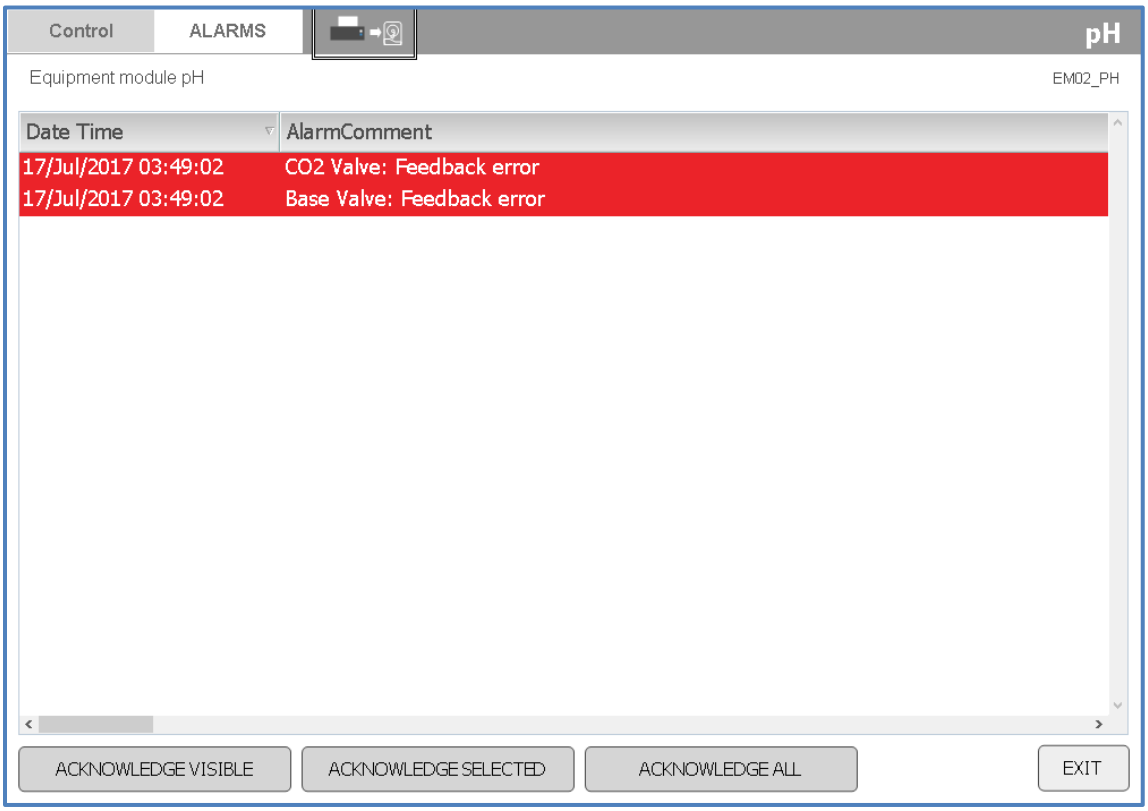


Figure 80: Alarm summary in EM dialog box

13.4 EVENTS Parameters

The Events Parameters menu allows modification of events limits. Events are sorted by event type on different menu pages (Figure 81). Navigate to CONFIGURATION: EVENT PARAMETERS.

Events Parameters pages allows setting Events thresholds but do not allow enabling or disabling specific Alarms. For enabling alarms select related sensor/Control System and enable alarms with the check box in configuration tab.

Depending on the event type, different parameters are available. For example, Sensor Alarms can be set both alarm threshold value and alarm delay (Figure 81), while Hardware Faults Alarms can be set only alarm delay. Available parameters for each Event type are summarized in the next table.

Table 27: Available parameters for each event type

Event Type (Tabs)	Available Parameters
Critical Interlocks	Low or High Alarm thresholds Safety Offset for reset
Process Interlocks	Low or High Alarm thresholds
Sensors Alarms	Low and High = Warning thresholds Low-Low and High-High = Alarm thresholds Delay for each event (in seconds)
Hardware Faults Alarms	Delay (in seconds)
Motor / Heater Pump / Valve Alarms	Delay (in seconds)
Regulator Alarms	Max. deviation |PV-SP| (PV unit) Delay (in seconds)

Figure 81: Sensors Alarms parameters page

Temperature 1&2 Preheater Bag Critical Interlocks have a parameter called ‘Safety offset for reset’ (Figure 82). This is the minimum temperature delta below interlock value to be able to acknowledge the Interlock when it has been triggered.

Figure 82: Critical Interlocks parameters page

14. Security, Users and Groups Management

ALERT! Risk of damage to equipment and/or data!
Incompatibility between user's knowledge and granted access level may lead to incorrect use of the equipment and potential corruption of equipment settings or recorded data.
It is the responsibility of the users' administrator to grant access levels to users in accordance with their training and role.

14.1 Users and Groups Management Policy

Users management in iCELLis 500+ bioreactor software has been built to comply with guidance on electronic signature for GMP environment. In this view, each user must have unique credentials (login and password) to guarantee both user identification and his electronic signature.

The Windows OS account policy supports assignment of user Accounts and Password in iCELLis 500+ bioreactor software. Hence, login is not specific to the application but is effective on entire OS. For the same reason, Password must be renewed at a frequency defined in Windows OS.

Furthermore, equipment and process integrity is protected by defining adapted access level to each user in function of his role through Security settings.

Security menu is dedicated to the creation of user and management of his rights on the equipment through different access levels definitions. After User creation, User must be assigned to a Group. It is at the Group level that access levels are granted or not. This is done through Navigation access level and Certificates access level.

This section describes Security settings step by step.

14.2 Local Users Management

Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: LOCAL USER MANAGEMENT

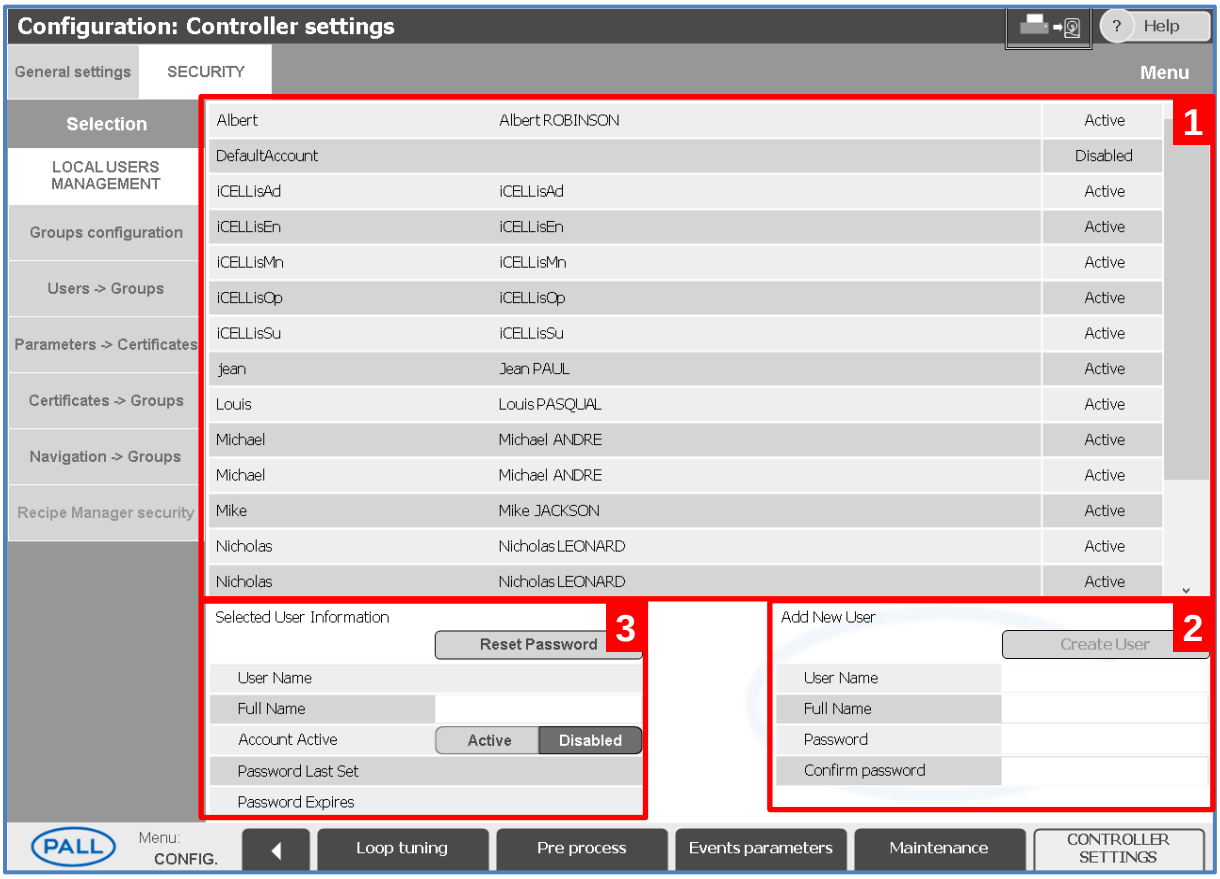


Figure 83: Local User Management screen – 1) Users list, 2) User creation box, 3) User information box.

LOCAL USERS MANAGEMENT page displays the complete list of local users existing on the equipment (Figure 83-1).

Addition of a new user can be done using the USER CREATION box (Figure 83-2). The following data must be provided for user creation:

- User Name: this name will be used for login on the equipment
- Full Name: allows full identification linked to login name
- Password: for login and signatures. It's recommended to contain:
  - Minimum 8 characters
  - At least 1 upper case and 1 lower case letter
  - At least 1 numeral
  - Special characters allowed in Windows 10 password policy
- Confirm password: re-enter password defined above
- Select CREATE USER button to complete new user creation

Refer to WINDOWS 10 OS password creation policy for more details about password creation on iCELLis 500+ bioreactor system.

Selecting a user in the list displays user information in the USER INFORMATION box (Figure 83-3). This dialog box allows modifying user password with RESET PASSWORD button. When the password is reset, a pop message will appear asking the user to type-in the new password. When the user that has changed his password tries to log on the system for the first time, the system will ask the user to change the password for a new one.

It also allows changing user status on the equipment between ACTIVE status and DISABLED status. Once disabled, the user remains in Users list but its status is changed to 'Disabled'. Disabled users can be shifted back to 'Active' status.

Once created, it is not possible to delete a user from users list. Users can be disabled but the name will remain in equipment Users list for compliancy with electronic records and signatures authorities' guidelines.

During the first Login of a new user, it's mandatory to change the password by using the safe mode otherwise the login to the system is denied. The user should be also assigned to an iCELLis 500+ bioreactor group.

14.3 Groups Management

Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: GROUPS CONFIGURATION (Figure 84). This page allows management of Users Groups on the iCELLis 500+ local system.

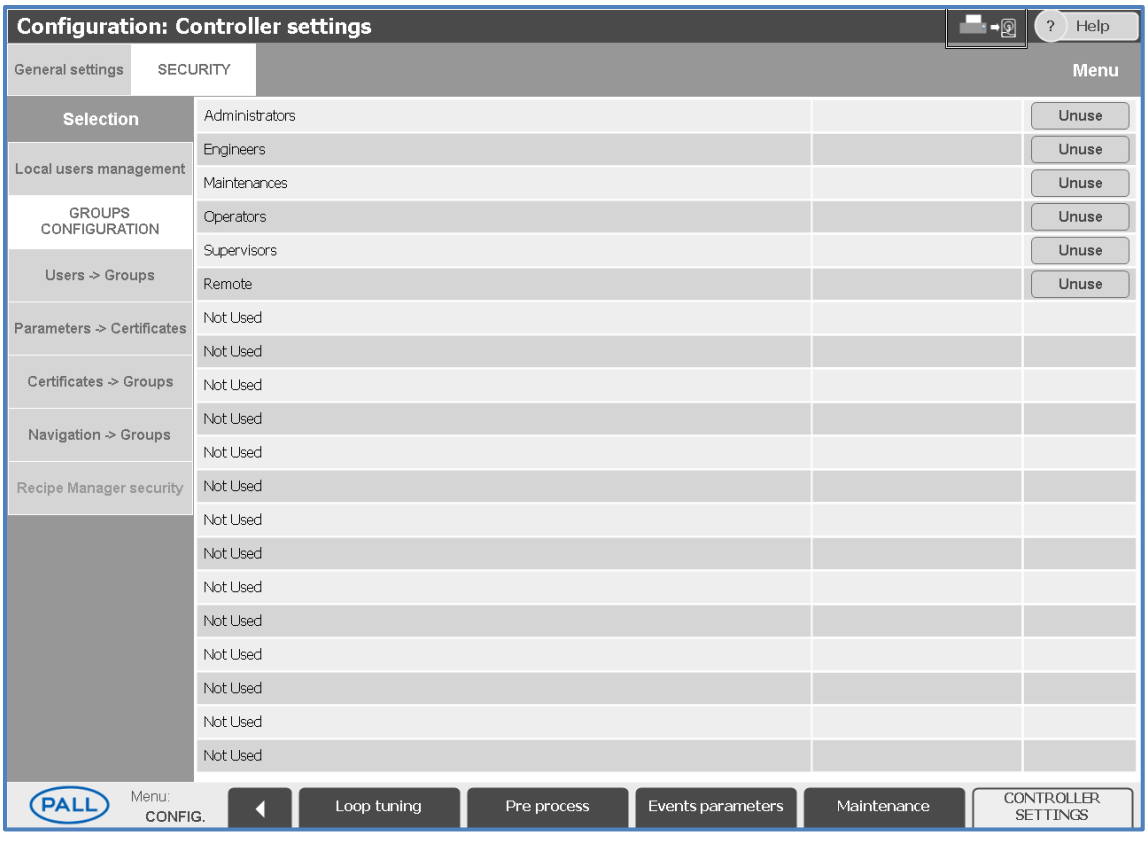


Figure 84: Group configuration screen

To create a new group, select one of the ‘Not Used’ row and type the desired name of the group, press ENTER and confirm the entry by pressing VALIDATE button. The new group is displayed in the Group List with UNUSE button in front. To rename a group, select the desired group and proceed the same way than for group creation.

To remove a group, select the UNUSE button in front of the group and confirm by pressing the VALIDATE button.

14.4 Users – Groups Assignment

Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: USERS: GROUPS (Figure 85).

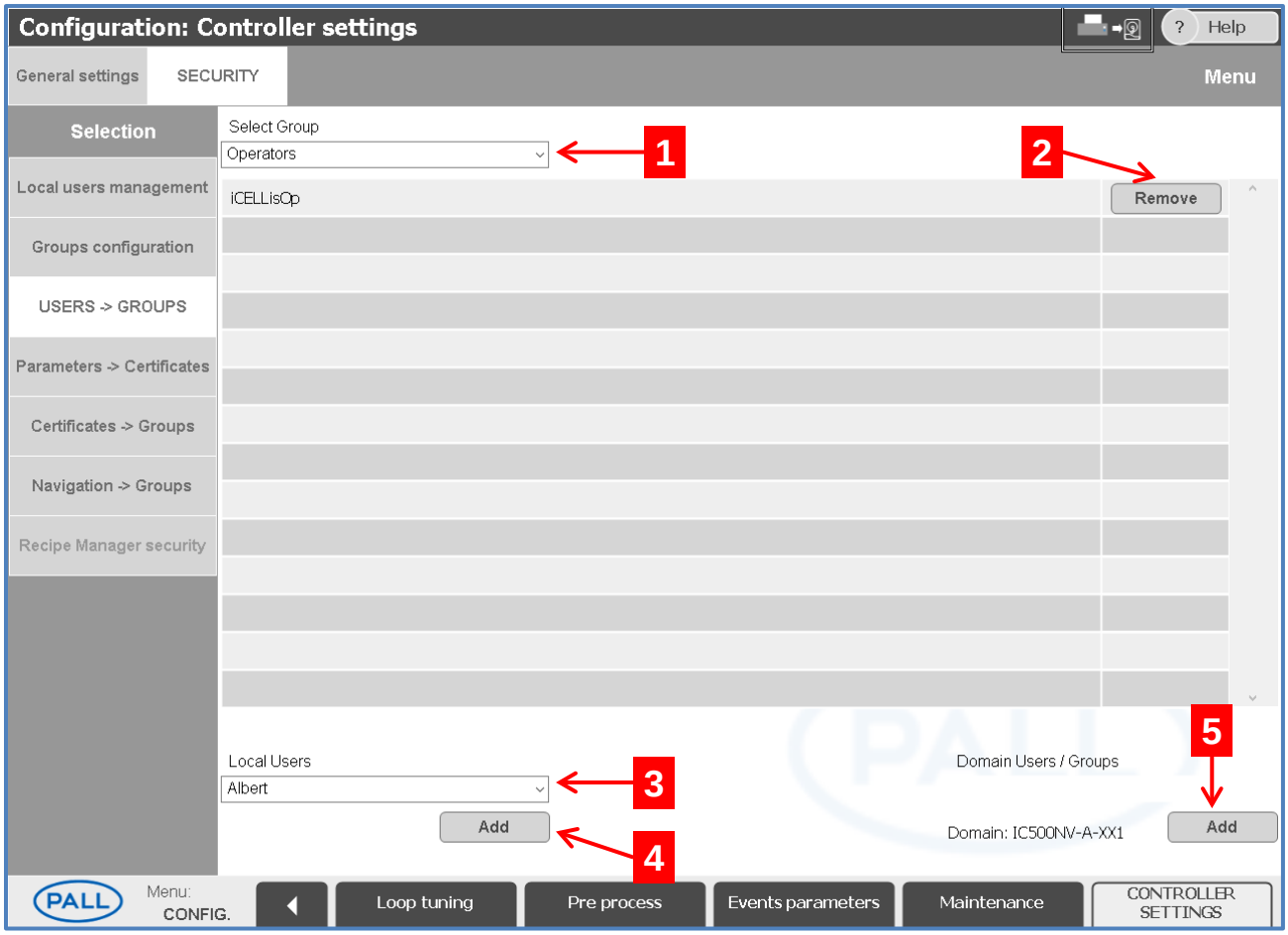


Figure 85: Users to Groups Assignment screen – 1) Groups list, 2) REMOVE button, 3) Local Users list, 4) ADD button, 5) ADD DOMAIN button.

Use the ‘Select Group’ dropdown list (Figure 85-1) to select a Group. The table below displays all Users assigned to this Group.

To remove a User from a Group, use REMOVE button (Figure 85-2) in front of the User name. To add a new User to a selected group, use the 'Local Users' dropdown list to select the User and click ADD (Figure 85-3/4). User is added to the Group.

If the iCELLis equipment is connected to a central server, Users can be added from another domain by using the Domain/Users field and selecting ADD button (Figure 85-5).

14.5 Parameters – Certificates Assignment

Certificates are sets of parameters allowing easier User's rights management. By default, parameters are sorted into pre-defined certificates, however it is possible to move a parameter from a certificate to another one.

Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: PARAMETERS: CERTIFICATES (Figure 86).

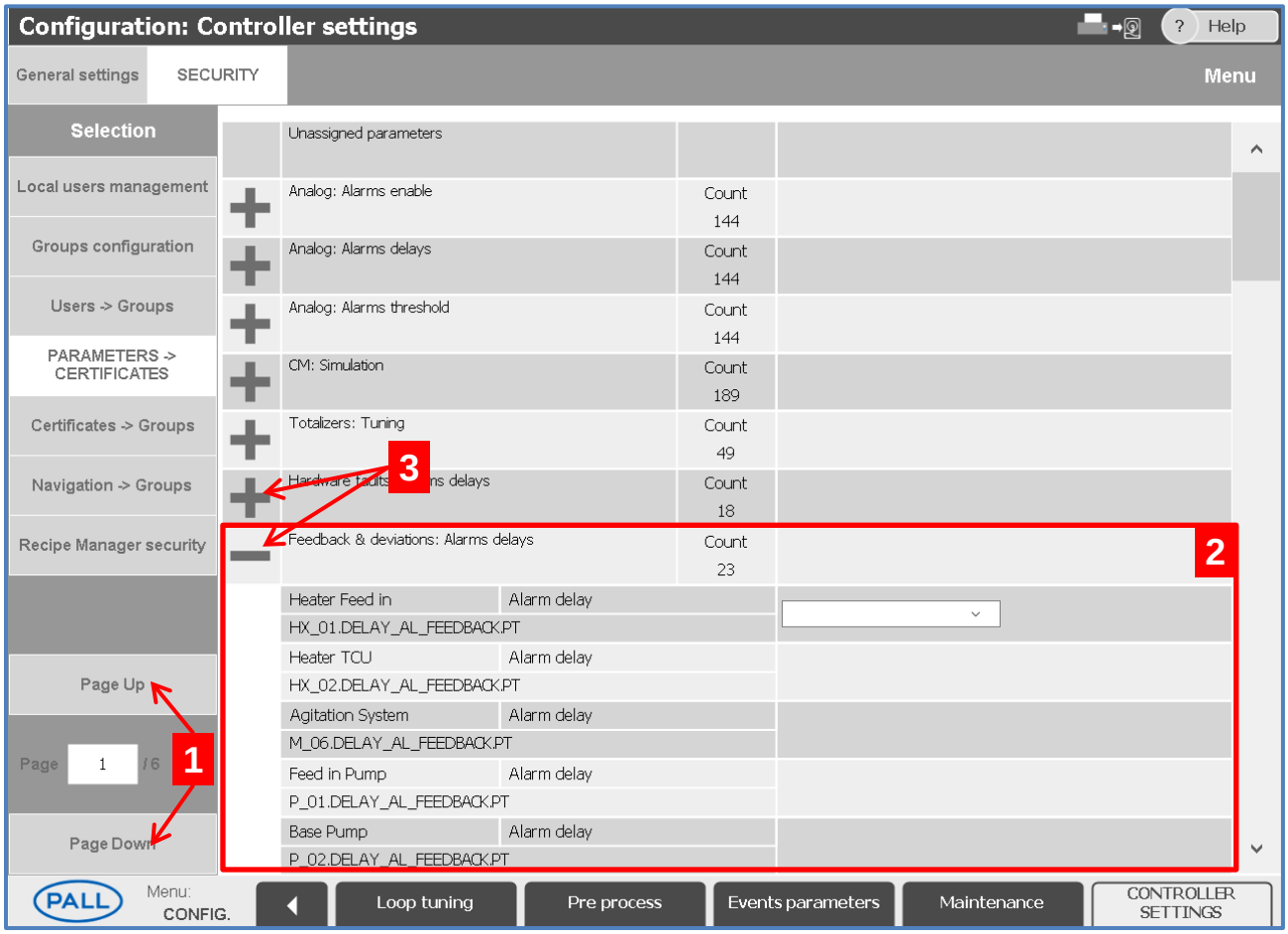


Figure 86: Parameters to certificates page – 1) Scroll page UP/DOWN buttons, 2) Certificate and contained parameters, 3) EXPAND/MINIMIZE buttons.

To move a parameter, navigate to the current containing-certificate and select the desired parameter. A drop-down list appears that allows selecting a new certificate for the parameter.

14.6 Navigation Groups: Menu Access Level Settings

To configure the Navigation access levels of a Group, navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: NAVIGATION->GROUPS (Figure 87).

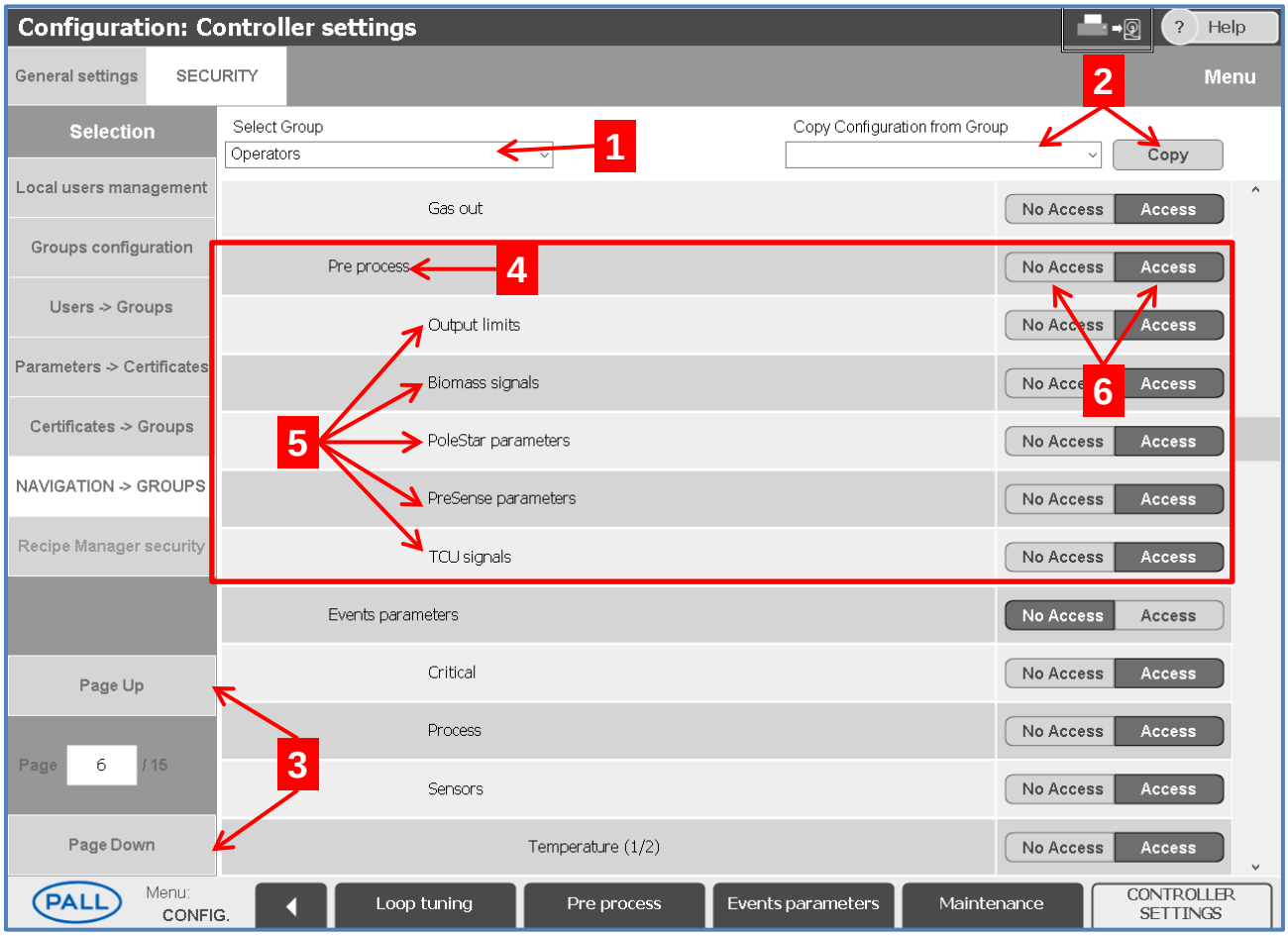


Figure 87: Navigation Groups page, allowing Navigation access level settings – 1) Group selection list, 2) Group template selection and COPY button, 3) Scroll page UP/DOWN buttons, 4) Menu name, 5) Submenu or screen or button, 6) Access level configuration.

Select a Group for Navigation access modification in SELECT GROUP list (Figure 87-1).

It is possible to directly copy navigation access levels configuration from another existing group with COPY CONFIGURATION FROM GROUP drop-down list and COPY button (Figure 87-2). Otherwise, browse Menu list through pages (Figure 88-3) and set navigation access level for a complete menu branch (Figure 88-4) or individually for submenu/screen/Button (Figure 88-5).

Access level can have 2 different values (Figure 88-6):

- NO ACCESS: group's users cannot access related menu branch;
- ACCESS: Group's users can access and visualize menu branch.

14.7 Certificates Groups: Parameter Access Level Settings

To configure Parameters access levels of a group, navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: CERTIFICATES->GROUPS (Figure 88).

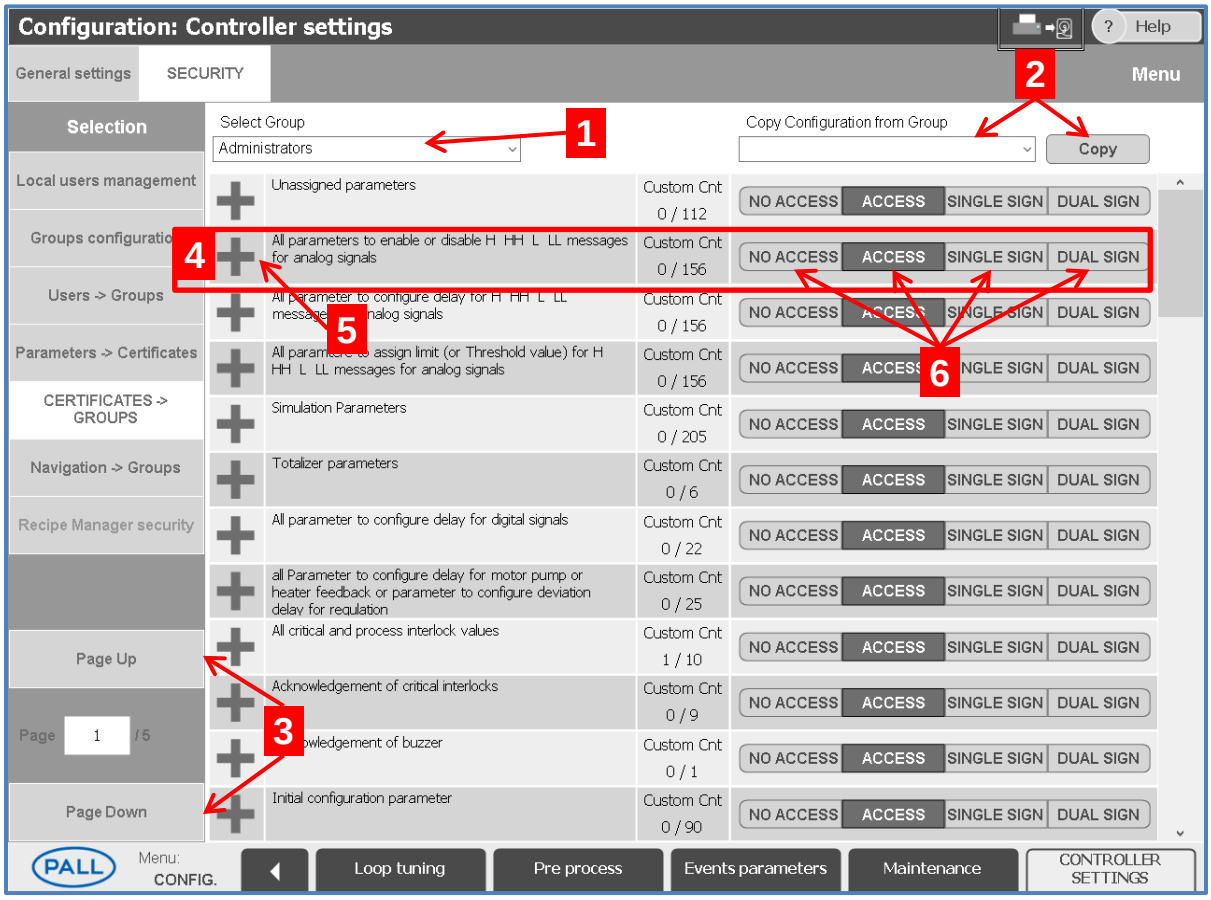


Figure 88: Certificates Groups page, allowing parameters access level settings – 1) Group selection list 2) Group template selection and COPY button, 3) Scroll page UP/DOWN buttons, 4) Certificate, 5) EXPAND Certificate button, 6) Access level configuration.

Select a group to modify in SELECT GROUP list (Figure 88-1).

It is possible to directly copy access levels configuration from another existing group with COPY CONFIGURATION FROM GROUP drop-down list and COPY button (Figure 88-2). Otherwise, browse certificates (Figure 88-4) through pages (Figure 88-3) and set access level for the whole certificate or expand certificate to set access level individually for each parameter (Figure 88-5).

Access level can have 4 different values (Figure 88-6):

- NO ACCESS: group's users cannot modify related parameter;
- ACCESS: group's users can modify related parameter without signature;
- SINGLE SIGN: group's users can modify related parameter after secured write (digital signature from one user);
- DUAL SIGN: group's users can modify related parameter after verified write (digital signatures from two users).

14.8 Sign Types and Signatures

When Navigation and Certificates access levels have been defined, Users must confirm an action through single or dual signature. When a signature is necessary to perform an action, the sign type is displayed next to the button in WORKING AREA (Table 28).

Table 28: Sign types and visualization next to button and switch

Sign Type	Visualization	Description
ACCESS	Apply / Manual AUTO	No signature is necessary
SINGLE SIGN	Apply / Manual AUTO	Signature from 1 user required to acknowledge
DUAL SIGN	Apply / Manual AUTO	Signatures from 2 different users required to acknowledge

When Sign type is set to ACCESS, no signature is necessary to perform a command or action on the Control System. When single or dual sign is activated for a command, selecting this command calls a dialog box for confirmation: Secured Write and Verified Write respectively Figure 89-a/b). Users must fill a COMMENT field and complete the credentials of one or two users. First user must have adequate access level to activate the command. When Dual Sign is activated the second user must have a Verifier role.

A User can have a Verifier role by being included in dedicated Verifier Group.
In case of Dual signature, Operator and Verifier cannot be the same user, even if the user is assigned to Verifier Group (an error message is generated in this case).
In the iCELLis 500+ bioreactor software default settings, only Administrator is part of the Verifier group.

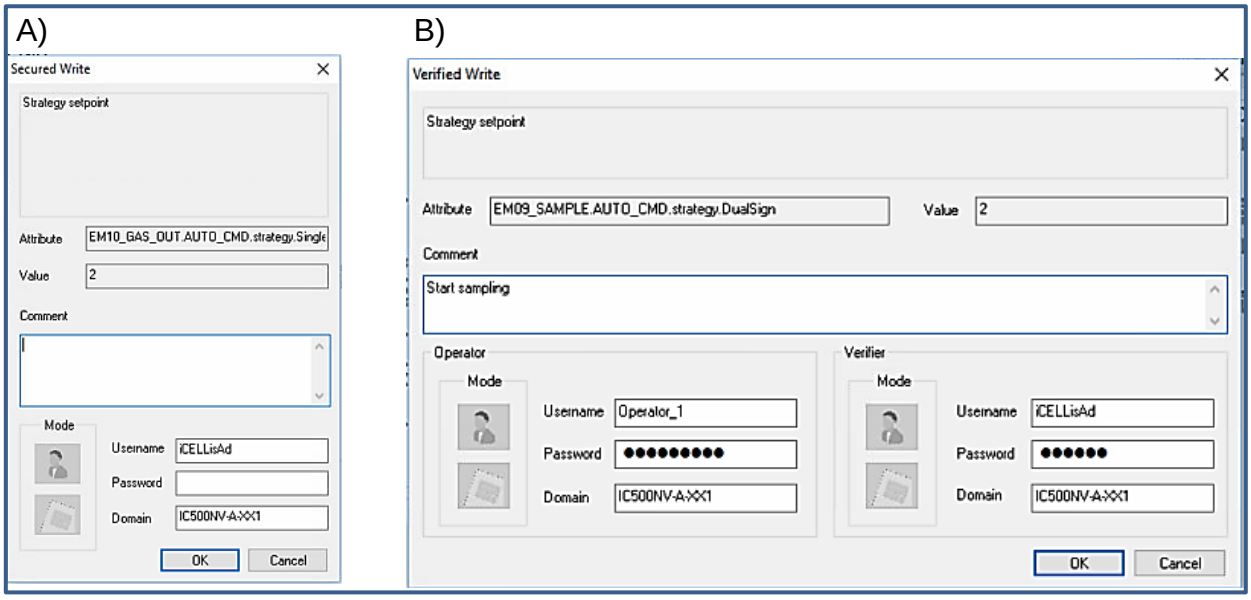


Figure 89: Signature dialog boxes – A) Secured Write (single signature), B) Verified Write (dual signature).

14.9 Recipe Manager Security Settings

Recipe Manager Plus is a separated software of Wonderware, that is integrated in the HMI of the iCELLis 500+ bioreactor software. Therefore, the access to Recipe Manager (RM) modules (Recipe Creation, Validation and Execution) is managed separately from other access levels. To configure the RM's access levels navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: RECIPE MANAGER SECURITY (Figure 90).

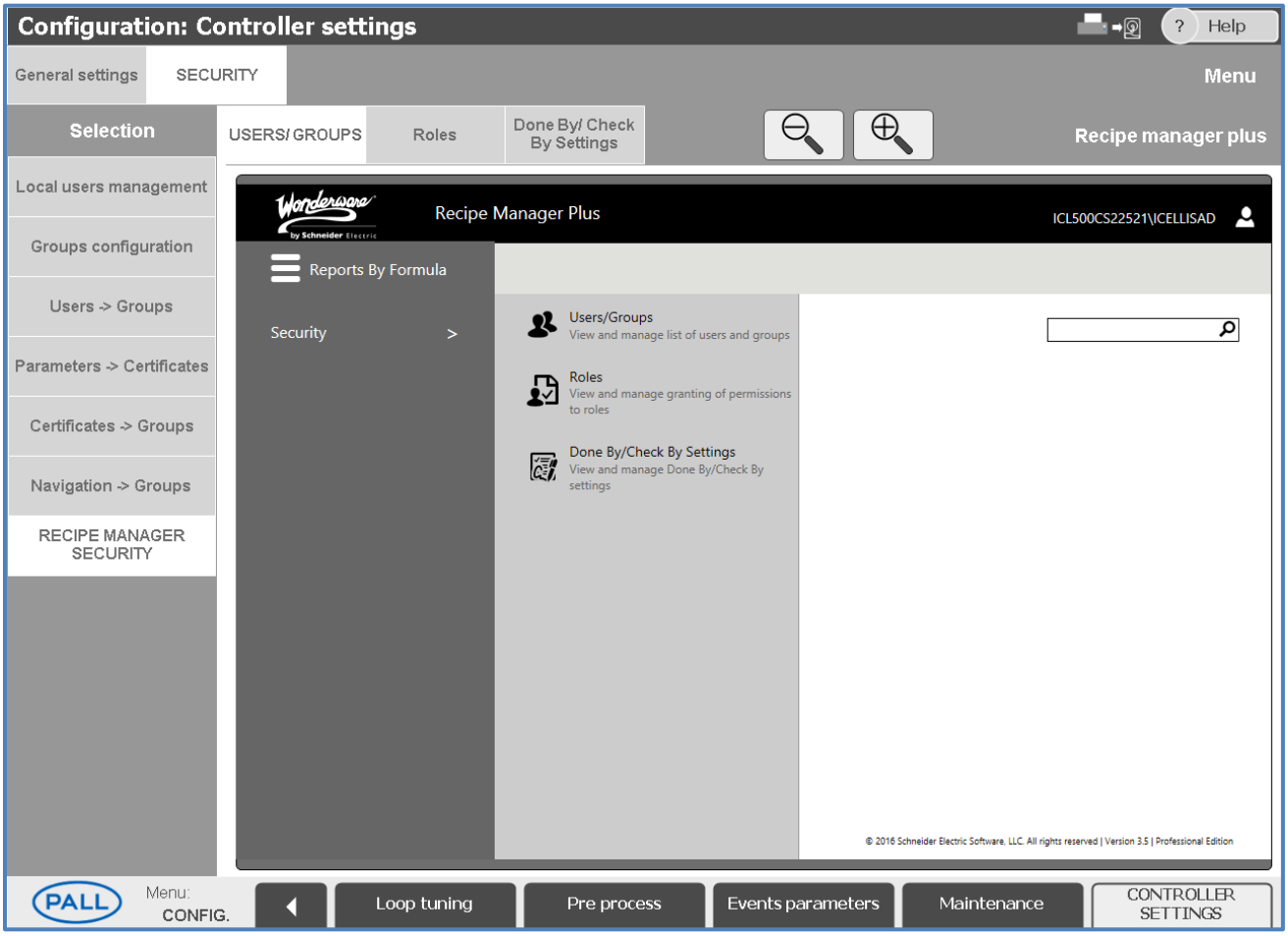


Figure 90: Certificates Groups page, allowing parameters access level settings

Users, Groups and permissions are managed similarly to iCELLis 500+ bioreactor software Security. The user must be assigned to a group and all the permissions are configured for these groups. When creating new groups in the iCELLis 500+ bioreactor software, if it is needed that their assigned users have access to Recipe Manager Plus, it is required to assign the Recipe Manager Plus permission in the CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: RECIPE MANAGER SECURITY page.

For example, creating the group 'test' with the Section 14.3 procedure, as indicated in Figure 91. It is important to note that 'test' is the 12th group in the list.

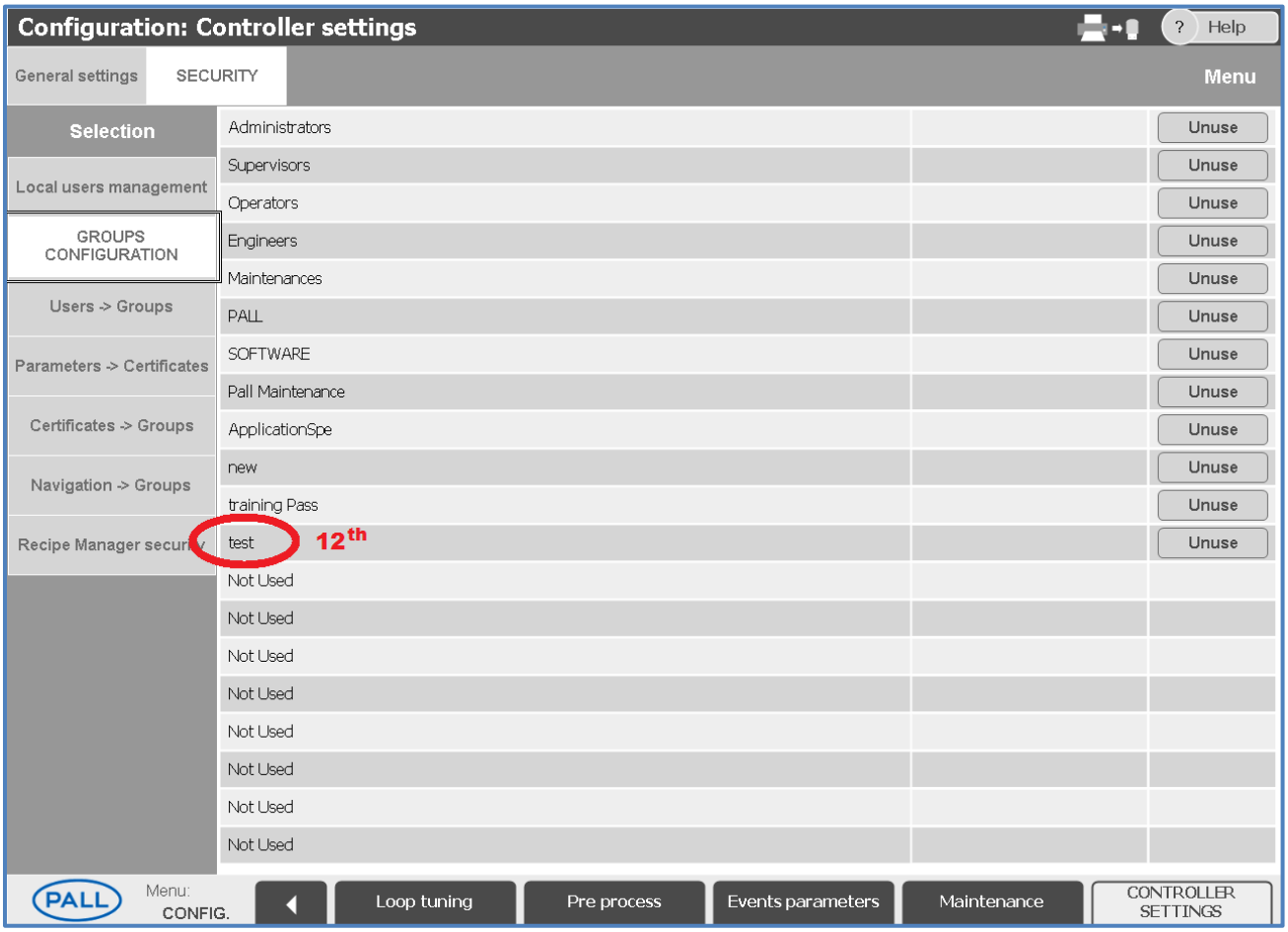


Figure 91: Creating a new group combined with Recipe Manager Plus

To assign this group in Recipe Manager Plus it is required to navigate to CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: RECIPE MANAGER SECURITY: USER/GROUP.

It is possible to note that all the groups in CONFIGURATION: CONTROL SYSTEM SETTINGS: SECURITY: GROUPS CONFIGURATION, even the groups assigned as 'not used', are already created in the RECIPE MANAGER SECURITY.

The order of the groups in the GROUPS CONFIGURATION page is the number of the group in RECIPE MANAGER SECURITY. This way, as the group 'test' is the 12th group of the list, the group 'test' is the group 'iCELLis_12' in RECIPE MANAGER SECURITY (Figure 92). Click in the desired group to enter its configuration.

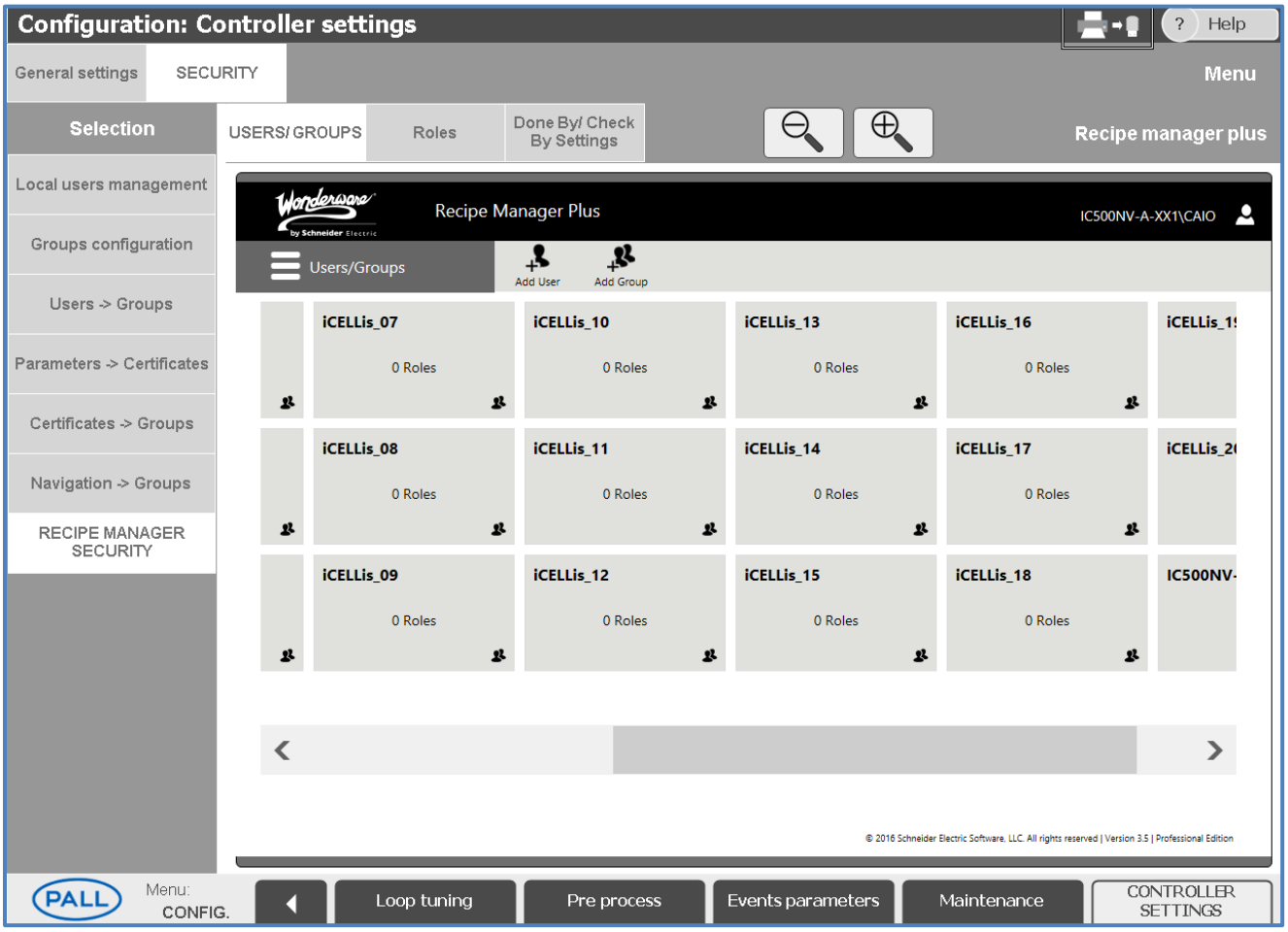


Figure 92: Groups in Recipe Manager Security

The page of the desired group will open as shown in Figure 93. In this page, it is possible to check that there are four fields. It is necessary only configure the first one, the roles. Here it is possible to assign to this group the required role. In this example, we chose to assign the role Supervisor to the ‘test’ group. So, it is required to click on the check box in left side of the role and then to click on ‘Update’. It is possible to check the permissions of the assigned rule by clicking on permissions. After the role is assigned, click on the left arrow to go back to RECIPE MANAGER SECURITY: USER/GROUP page. Now it is possible to note that the desired group has 1 role assigned (Figure 94).

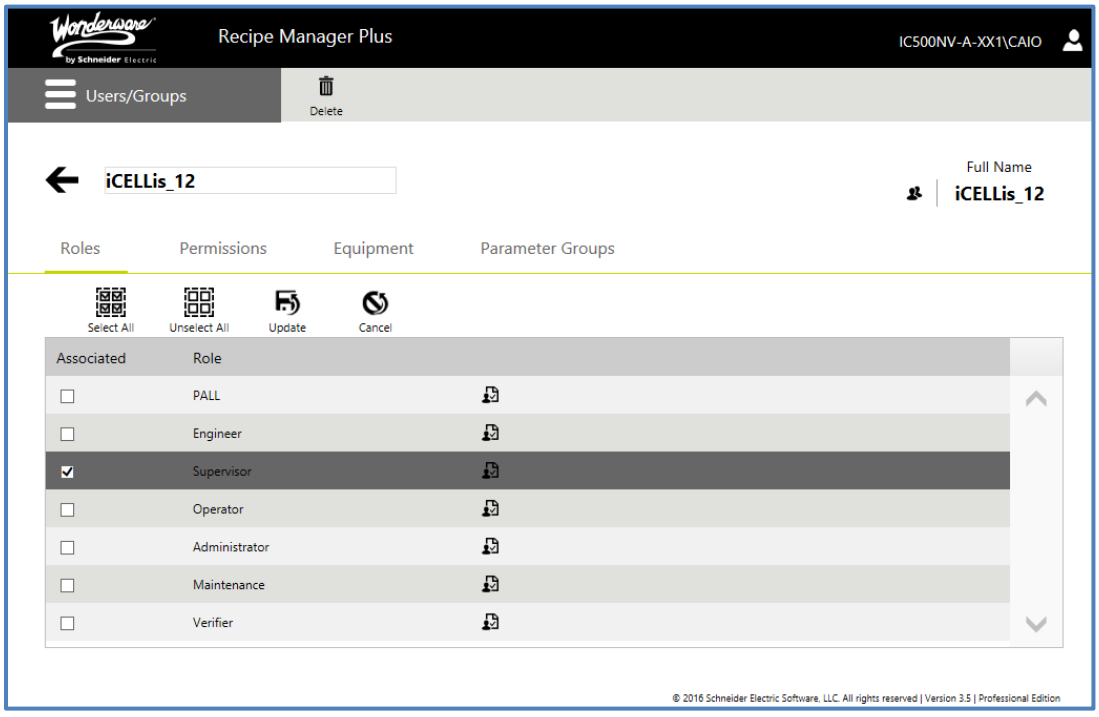


Figure 93: 'Test' Group configuration in Recipe Manager Security

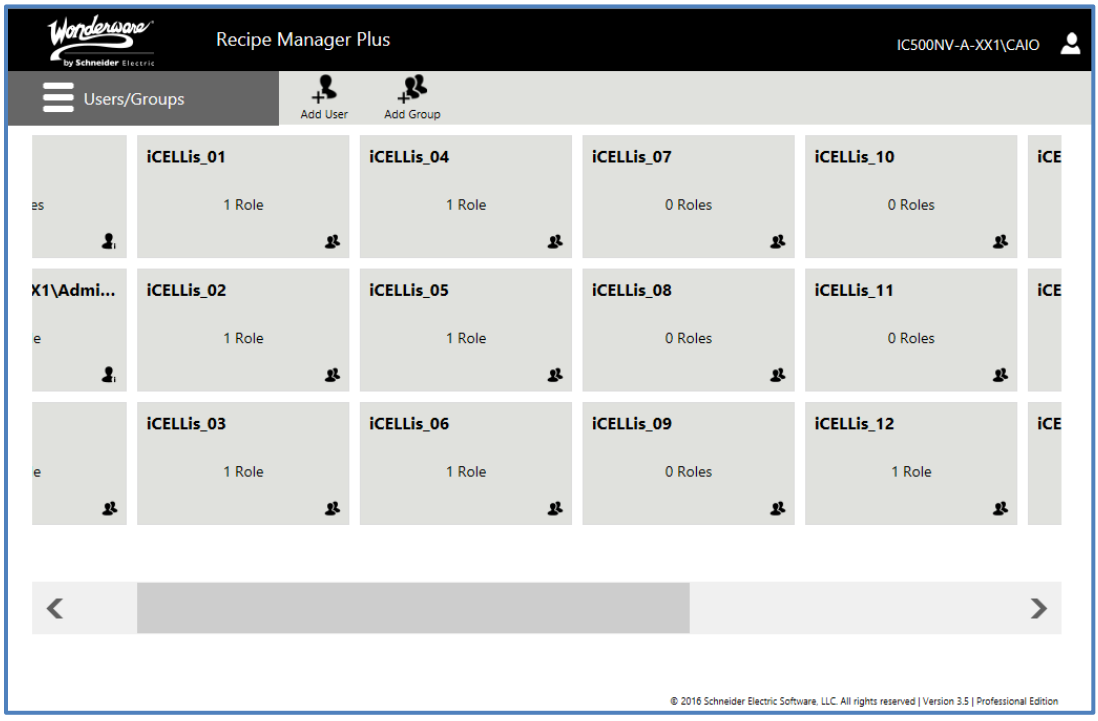


Figure 94: Groups in Recipe Manager Security with the 'test' group with 1 role assigned

15. Control System General Settings

General Settings menu gives access to HMI configuration and to Windows commands.

15.1 Control System Default Settings

DEFAULT SETTINGS pages allow saving and loading values of all parameters of iCELLis 500+ bioreactor control system. This can be used to shift equipment configuration between different processes.

Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: GENERAL SETTINGS: DEFAULT SETTINGS (Figure 95).

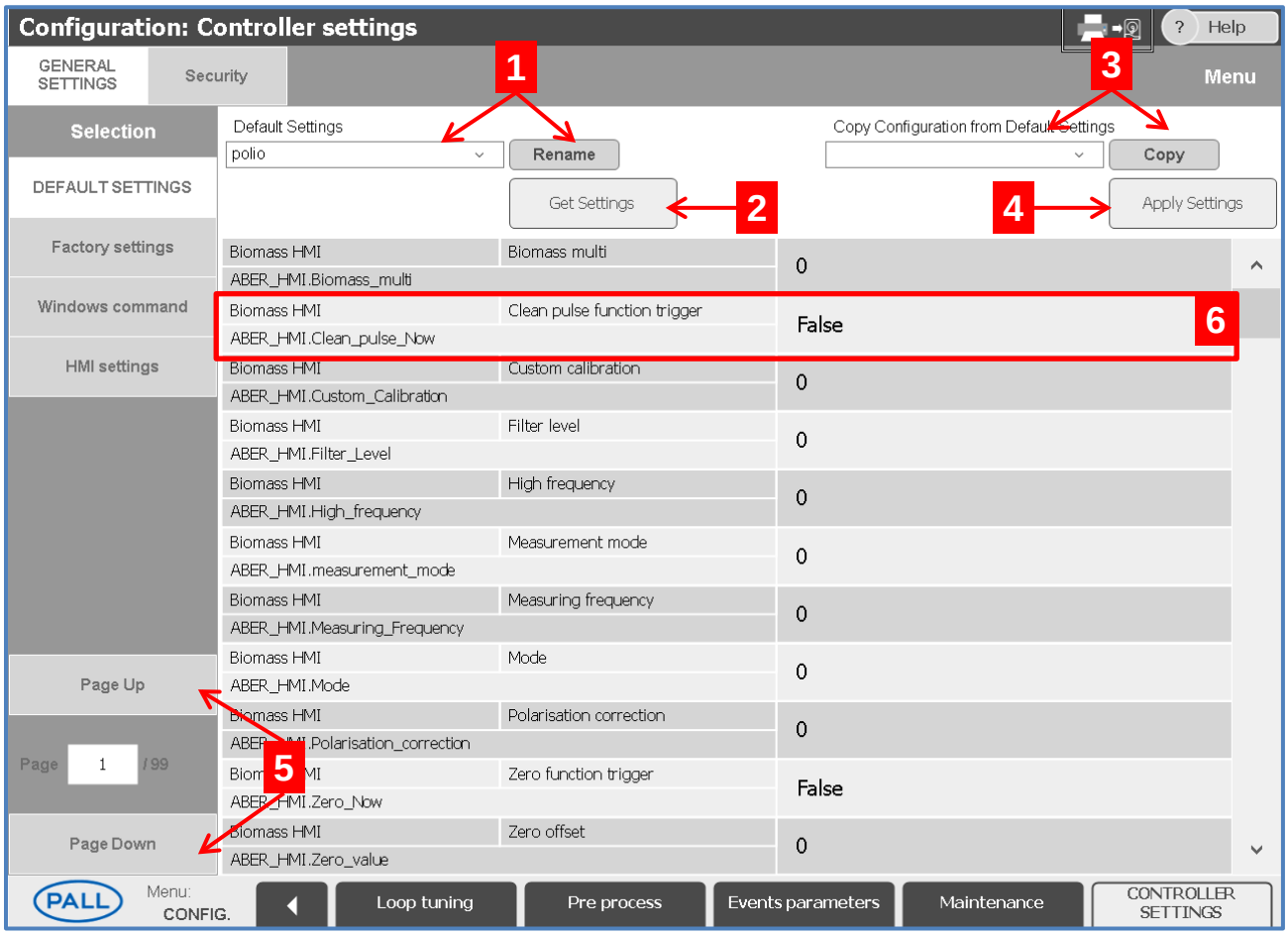


Figure 95: Control System Default settings page – 1) Default Settings set, 2) GET SETTINGS button, 3) Default Settings template list and COPY button, 4) APPLY SETTINGS button, 5) Parameters pages UP/DOWN browsing buttons, 6) Parameter setting visualization (Name, description, tag name, value).

Store current settings in a default set by selecting GET SETTINGS button and renaming the set with RENAME button (Figure 95-1/2). Use Copy configuration from existing defaults settings and COPY button to copy settings from selected Default set (Figure 95-3). Use APPLY SETTINGS button to load settings from selected Default settings.

A maximum of 5 default settings can be saved. Therefore, each process produced on the iCELLis 500+ bioreactor can have its default settings stored.

Loading of default settings set will change the calibration settings of the corresponding actuators. The calibration of the sensors should be done after loading the choses default setting set (if applicable).

15.2 Control System Factory Settings

Factory Settings page allows the re-loading of factory settings of the iCELLis 500+ bioreactor control system. Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: GENERAL SETTINGS: FACTORY SETTINGS (Figure 96) and use FACTORY SETTINGS button to reset the Control System settings. A Manual reset of the PLC will be required to apply the factory settings.

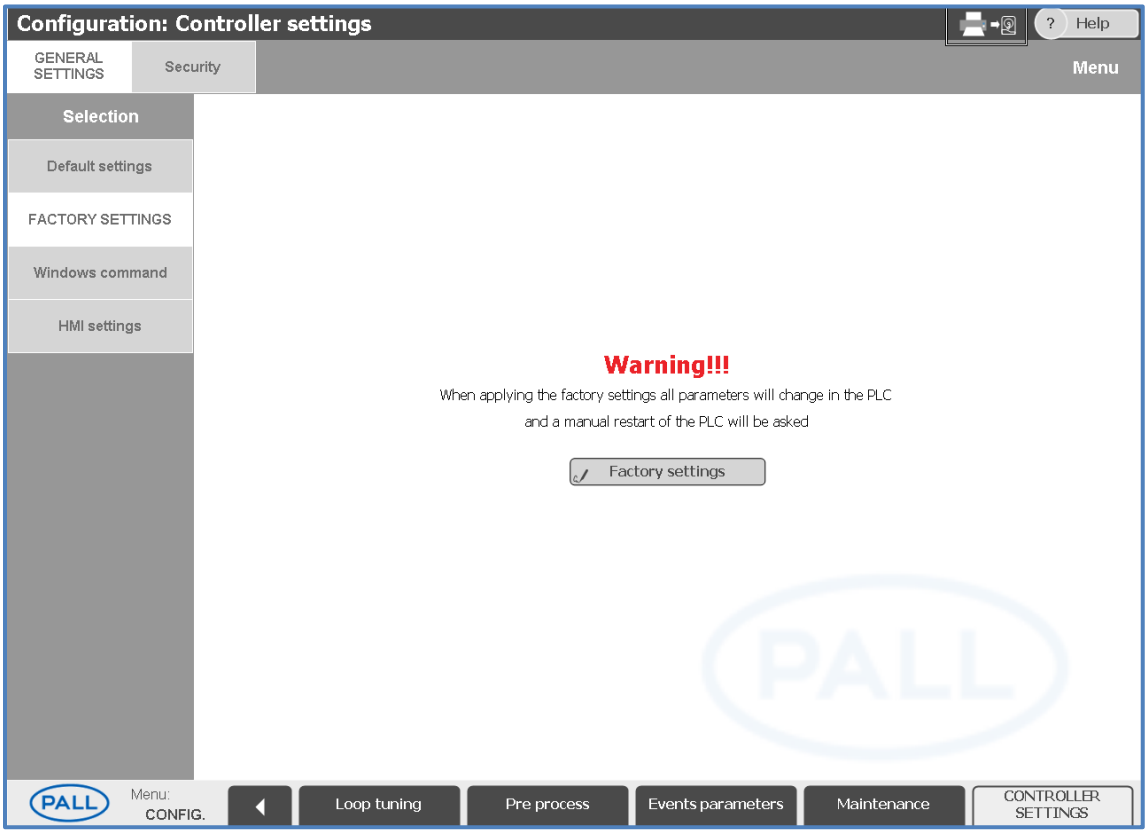


Figure 96: Factory Settings loading page

15.3 Windows Commands

ALERT! Risk of damage to data!
SHUTDOWN PC and RESTART PC commands will interrupt data recording by iCELLis 500+ bioreactor Control System and could affect data authenticity in the frame of GMP batch record.

ALERT! Risk of damage to equipment/data!
Polestar USB drive should be in shutdown mode and ejected before shutting down the PC. Shutting down the PC without ejecting Polestar USB drive may cause corruption of the USB drive.

The Windows Command page allows direct interaction with the computer hosting the iCELLis 500+ bioreactor software. Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: GENERAL SETTINGS: WINDOWS COMMAND (Figure 97).

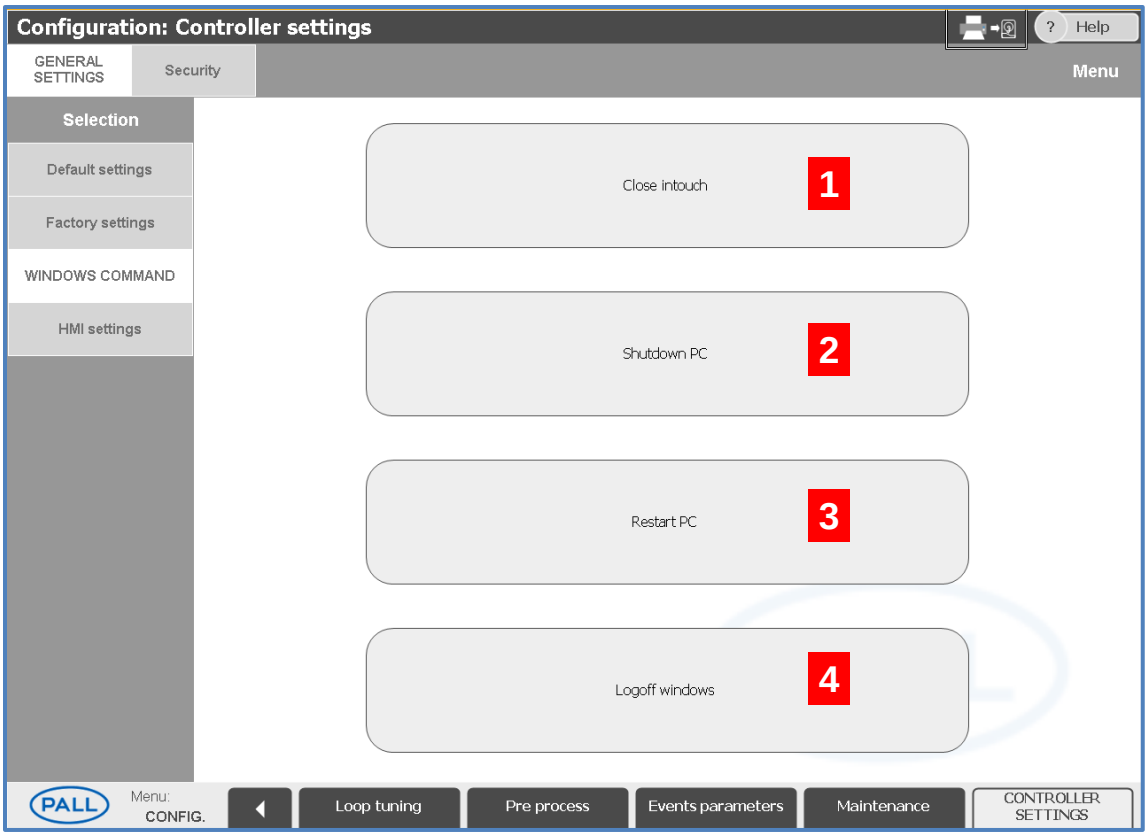


Figure 97: Windows command page – 1) CLOSE HMI button, 2) SHUTDOWN PC button, 3) RESTART PC button, 4) LOGOFF FROM WINDOWS button.

Since the iCELLis 500+ bioreactor Windows user has no access to Windows, this page allows interaction with Windows command (shutdown/restart of the computer hosting iCELLis 500+ software or Logoff Windows user) and the closure and restart of HMI (Intouch) by using Close Intouch button.

It is recommended to use:

- CLOSE HMI button to Restart Intouch HMI
- SHUTDOWN PC button when shutting down the system.

Closure of HMI alone does not affect data recording by iCELLis 500+ bioreactor data recording module. In the event of HMI closure or PC shutdown/restart, PLC configuration is not affected and process control will continue with last recorded settings.

15.4 HMI Settings

HMI settings page allows defining automatic log out time. Navigate to HOME: CONFIGURATION: CONTROL SYSTEM SETTINGS: GENERAL SETTINGS: HMI SETTINGS (Figure 98).

Inactivity time out can take a value between 1 and 1440 min. Select 0 to deactivate the time-out function.

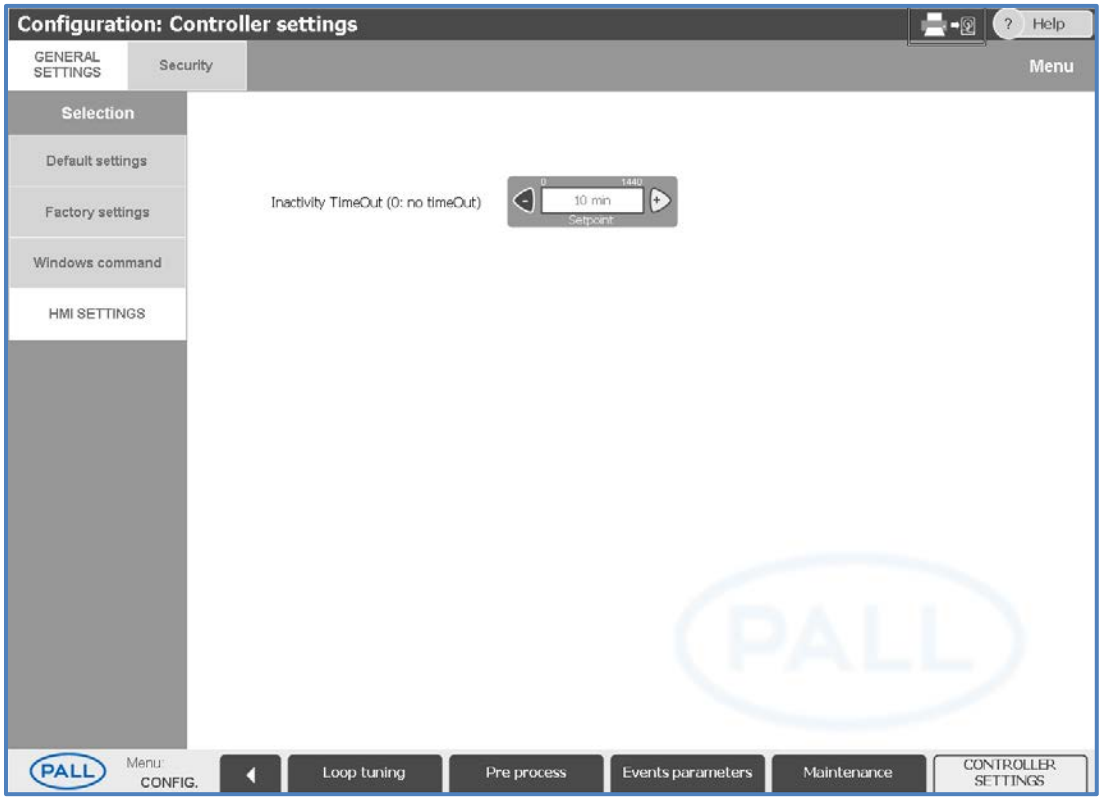


Figure 98: HMI settings page

16. Accessing the iCELLis 500+ Bioreactor Control System in a Network Environment:

The iCELLis 500+ bioreactor Control System was specifically designed to control and monitor the iCELLis 500+ bioreactors via a touch screen located on the top front panel of the equipment. In its standard configuration, the system supports a standalone and network configuration.

In both configurations a monitoring of process data, alarms, warnings, interlocks, recipe information has been stored in the local historian of the system. Following information can be accessed through different protocols. In the picture (Figure 99) below, a short schematic overview is given when the control system is connected to a network.

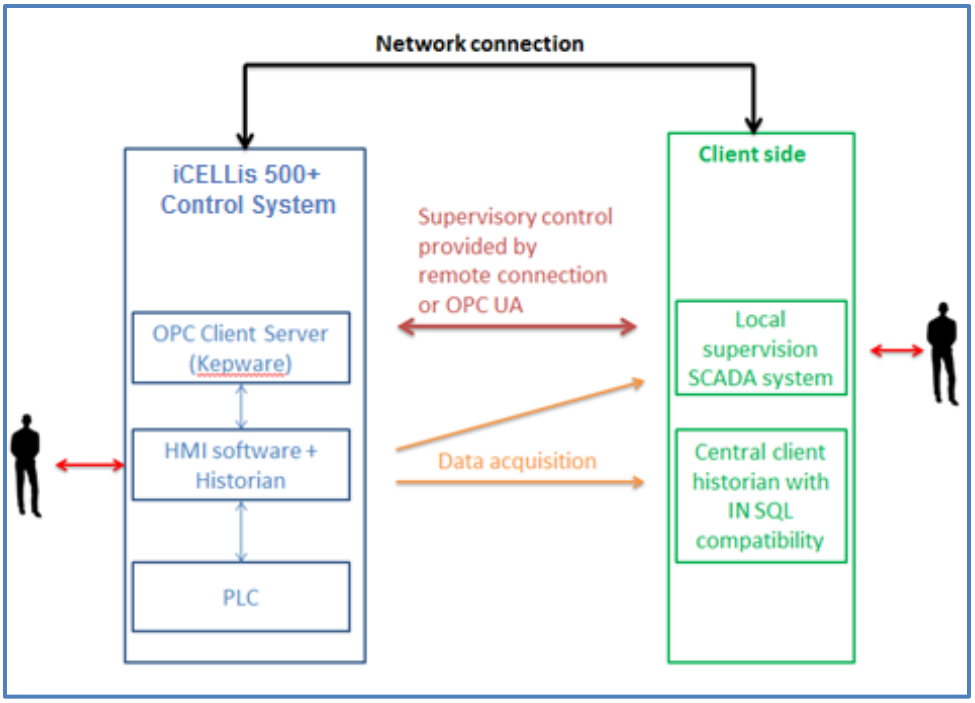


Figure 99: Network connection diagram

In case of network configuration, the following methods are available to communicate with the control system:

- Remote desktop connection
- Reading historical data
- Real-time data through OPC UA client

By default, the machine is setup in dynamic addressing. The network integration of the control system falls under the responsibility of the customers IT.

Integration of the iCELLis 500+ bioreactor control system in customer network is possible by an Ethernet port which is available on the back side of the machine (Figure 100.).

Figure 100: Available connection on the back of machine

To ensure the IP-rating of the control system an Ethernet cable must be selected compatible with the connector. (for e.g. Bulgin connector). If the Ethernet cable is connected after turning on the machine, the PC needs to be restarted.

16.1 Remote Desktop Client

The iCELLis 500+ bioreactor control system is a Microsoft♦ Windows based system which allows users to access remotely the system via RDP protocol. The remote desktop connection application is a standard application developed by Microsoft, that only requires to be configured properly by the user. The machine and the remote desktop should be connected to the same network, and when the customer's network infrastructure is properly setup, a remote connection can be setup with the following windows accounts available in the machine:

- Administrator
- iCELLis 500+

These 2 accounts are Windows accounts where administrator has full access while the iCELLis 500+ user is restricted as this user is dedicated only to access runtime of the system (HMI). The main purpose of the administrator account is to maintain the system by a customer IT person or Pall service personnel. The 'iCELLis 500+' account allows operators to monitor and control remotely the iCELLis 500+ bioreactor control system via the HMI interface. Administrator account also has the possibility to launch the HMI program but it's recommended to use it for IT settings or maintenance.

16.1.1 How to Access the iCELLis 500+ Bioreactor via Remote Desktop:

To monitor or to take control through remote desktop client make sure that the windows application is installed on your computer. If the remote desktop connection software is not installed or no access is given, verify with your internal IT department to install the Microsoft remote desktop connection software. The program can be launched via Windows start button, search for remote desktop connection (Figure 101) in Windows 7 or Windows 10.

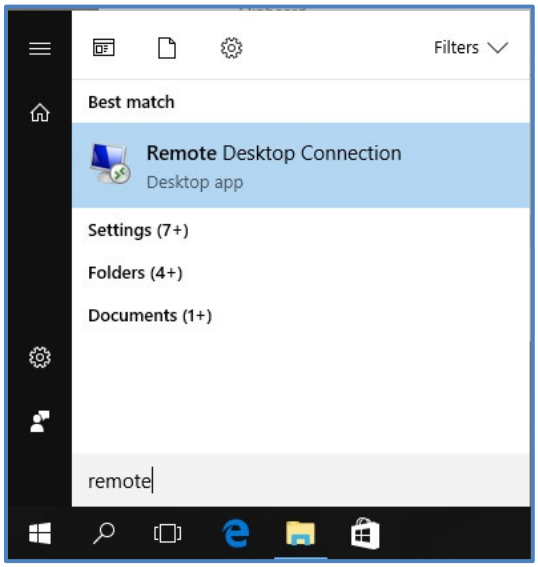


Figure 101: Remote desktop connection

IMPORTANT!
Use of other operating system platforms than Windows 7, Windows server 2016, and Windows 10 cannot be guaranteed and may affect the system performance.

When opening the Remote Desktop Connection program, some logon settings need to be entered to make the communication with the computer. Additional settings can be setup like display, sound, keyboard, mouse, printers and quality of connection settings. If a remote desktop gateway is used, please contact your IT department to verify the restrictions which are setup via the server.
To be able to connect remotely, the following information is needed:

- Name or IP address of machine
- Windows user name and password

In the pictures below, examples are given to log in into the remote session.

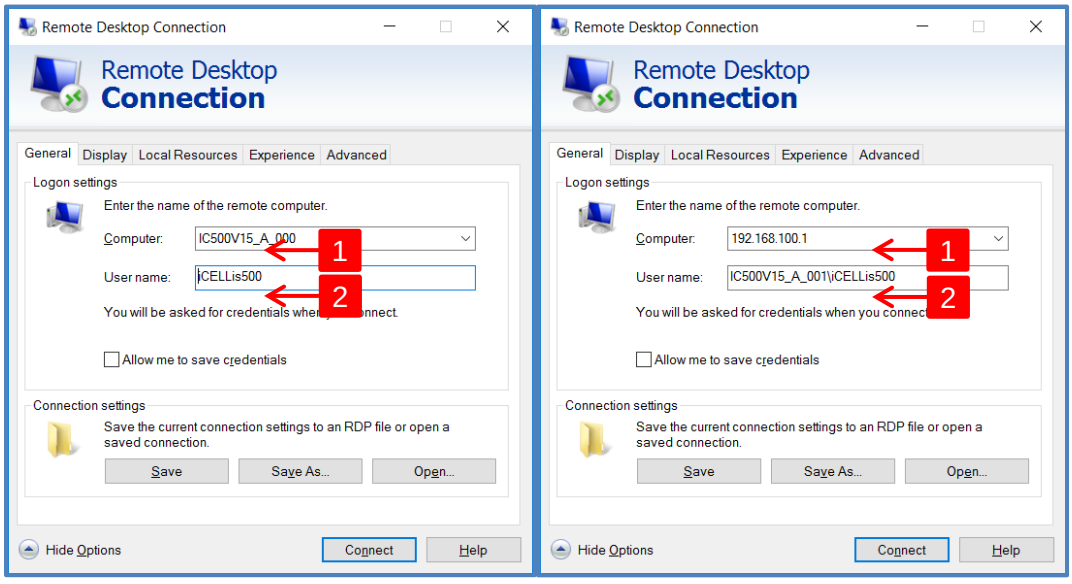


Figure 102: Remote desktop connection – 1) Computer name, 2) Windows user.

Once all preferred settings are properly set, click on connect. Before the remote connection is established, the corresponding windows account password must be filled in to gain connection and a certificate needs to be acknowledged.

IMPORTANT!
If the control system is setup in a domain server with remote desktop gateway services, contact your local company IT department to verify, if all required settings are properly setup for the remote desktop gateway.

16.1.2 Behavior When Using Remote Connection:

In the following section the equipment's behavior will be explained when using windows remote desktop in its default setting. When a desktop gateway server is used, the behavior may vary. In the following section, local computer means the computer located inside the iCELLis 500+ bioreactor and local user means the person who is logging in the local computer and remote computer means any other computer in the same domain and remote user means the person who is logging into the remote computer.

In the following table (Table 29), an overview is given of what the control system will do when switching between remote and local with the same windows user.

Table 29: Switching between the same windows accounts

Computer Affected	Software Affected	Effect of Going from Remote to Local	Effect of Going from Local to Remote
Status on Remote computer	Windows account	Windows account is locked	Windows account logs in directly (no need of user confirmation)
	HMI program	Internal HMI login will automatically logout the current HMI user and the HMI application will stay running	Internal HMI login is available to login by any HMI user
Status on Local computer	Windows account	Windows account logs in directly (no need of user confirmation)	Windows account is locked
	HMI program	Internal HMI login is available to login by any HMI user	Internal HMI login will automatically logout the current HMI user and the HMI application will stay running

In the following table (Table 30.), an overview is given of what the control system will do when switching between remote and local with a different windows user.

Logging in from Remote to Local or from Local to Remote with the same windows account will connect directly to this account locking the windows account for the Local/Remote user that was logged before.

Table 30: Switching between the different windows accounts

Computer Affected	Software Affected	Effect of Going from Remote to Local	Effect of Going from Local to Remote
Computer affected	Software affected	Effect of going from Remote to Local	Effect of going from Local to Remote
Status on Remote computer	Windows account	Popup appears to ask for confirmation to release the control to local user account. If no answer is given, after 30 seconds the connection is given automatically to local user. Windows account will be locked	Windows account logs in if remote user grants access. If remote user doesn't reply in 30 seconds Local user will automatically get the access to windows account
	HMI program	Internal HMI login will automatically logout the current HMI user. If local user is logging with 'iCELLis500' user, the HMI application in the remote computer will be closed. If local user is logging with 'Administrator' user, user will have possibility to launch the HMI runtime application	If remote user is logging with 'iCELLis500+' user, the HMI application in local computer will be closed, and HMI runtime application will be launched in Remote computer. If remote user is logging with 'Administrator', user will have possibility to launch the HMI runtime application, by opening 'WindowViewer' application, located in the desktop
Status on Local computer	Windows account	Windows account logs in if remote user grants access. If remote user doesn't reply in 30 seconds, Local user will automatically get the access to windows account	Popup appears to ask for confirmation to release the control to remote user account. If no answer is given, after 30 seconds the connection is given automatically to remote user. Windows account will be locked
	HMI program	If local user is logging with 'iCELLis500' user, the HMI application in remote computer will be closed, and HMI runtime application will be launched in local computer. If local user is logging with 'Administrator', user will have possibility to launch the HMI runtime application	Internal HMI login will automatically logout the current HMI user. If remote user is logging with 'iCELLis500' user, the HMI application in local computer will be closed. If remote user is logging with 'Administrator' user, user will have possibility to launch the HMI runtime application

16.2 Real-Time Data Through OPC

When setting up an external system e.g. Plant overview SCADA system, Alarm system, the OPC (OLE for Process Control) protocol can be used to collect real-time data like: Process data, Alarm, warnings, system inputs, PID settings, etc. No storage of data is done here.

A detailed list of tags (Accessible via OPC UA Client) can be found in the Appendix 8 of the software Design Specification document. All the TAGs are read only through OPC server due to data security, except only two TAGs, EQ_iCELLis_BATCHNAME and EQ_iCELLis_BIOREACTORNAME that are available for reading and writing.

The external system can communicate with the iCELLis 500+ bioreactor control system based on OPC Client Server principle. Once the communication between the corporate network(s) and the Control System are established, OPC UA client can be utilized to communicate with the control system.

Therefore, the external system must have the following minimum specifications:

- OPC Unified Architecture (OPC UA): version 1.01
- Windows platform starting from Windows 7 or greater
- 2.0 GHz Processor
- 1 GB installed RAM
- 180 MB available disk space
- Ethernet card

Further detailed information regarding the specification can be found on the Kepware♦ website (https://www.kepware.com/getattachment/5759d980-7641-42e8-b4fb-7293c835a2f9/kepserverex-manual.pdf).

16.2.1 What is OPC UA?

OPC Unified Architecture (UA) is a part of OPC technology. OPC UA is a more secure, reliable mechanism for transferring information between servers and clients. It provides easier transports, better security options and a more complete information model than the original OPC DA. This means that the tags or data points can be grouped and be given context which make governance and maintenance much easier. Another advantage is that it doesn't rely on OLE or DCOM technology from Microsoft that makes it possible to implement it on any platform if that being Apple, Linux (JAVA) or Windows. In our examples we will explain further by using a Kepserver, but a different UA client could be used instead.

16.2.2 How to Set-Up the Communication Between Server and Client

When setting up first time an OPC UA client, it is important to make sure that the proper dedicated ports are open to communicate between client and server. Depending on the OPC Client, a search tool can be used to search for the Server. It is also possible to make the communication by the OPC address.

A typical example of such a OPC address is dependent on the setup of the Control System. The address to access OPC server is linked to an IP address (or computer name) and port.

Here is the address format: opc.tcp://xxx.xxx.xxx.xxxx:49320 OR opc.tcp://‘computer name’:49320

where, ‘xxx.xxxx.xxx.xxx’ indicates IP address or computer name and ‘49320’ is the port assigned in our default configuration.

Additional security policies can be setup at server level. Following security settings are available:

- None
- Basic128Rsa15
- Basic256

Within the Basic128Rsa15 and Basic256 Sign and/or Sign & Encrypt can be setup.

For further details regarding the Security policies can be found in the Kepware user guide of the OPC communication Suite.

This is an example of how to configure the communication, using the Kepware OPC Client (KEPServerEX 6).

Open the software KEPServerEX 6 Configurator. Add a new connection by clicking on ‘File’ and choose ‘New’ (Figure 103).

Figure 103: KEPServer 6 new connection

A popup will appear. Click on ‘Yes, Update’.
On the left column, click on ‘Click to add a channel’ (Figure 104-A).
A pop up will appear (Figure 104-B), choose ‘OPC UA Client’.

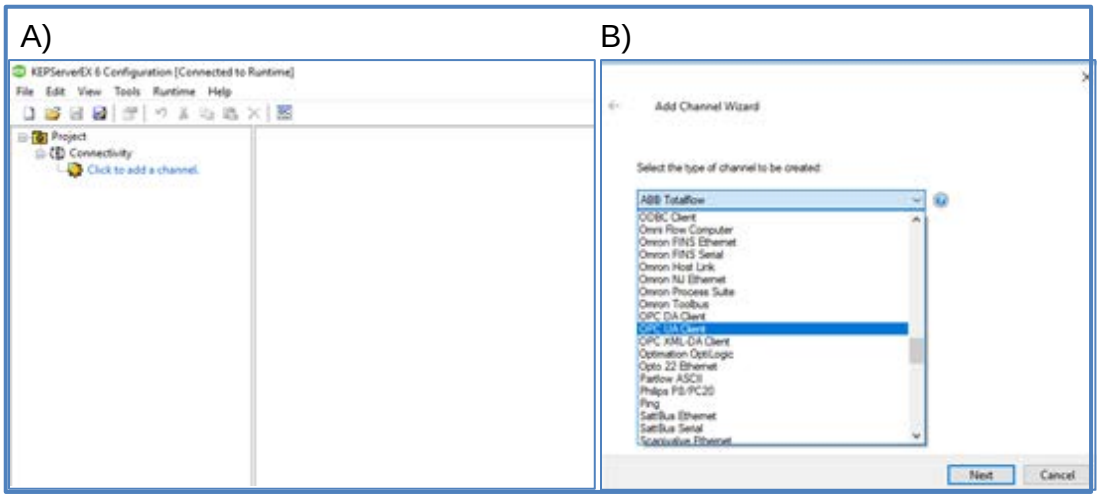


Figure 104: KEPServer 6 new connection – A) Add a new Channel, B) Choosing OPC UA Client

Click on ‘next’ three times, until Figure 105 appears. In ‘Endpoint URL’, replace ‘localhost’ by the computer name of the control system. (If no specific computer name is defined by the customer the serial number of the control system is the computer name). Set the ‘Security Policy’ and the ‘Message Mode’ to ‘None’ and click on ‘Next’.

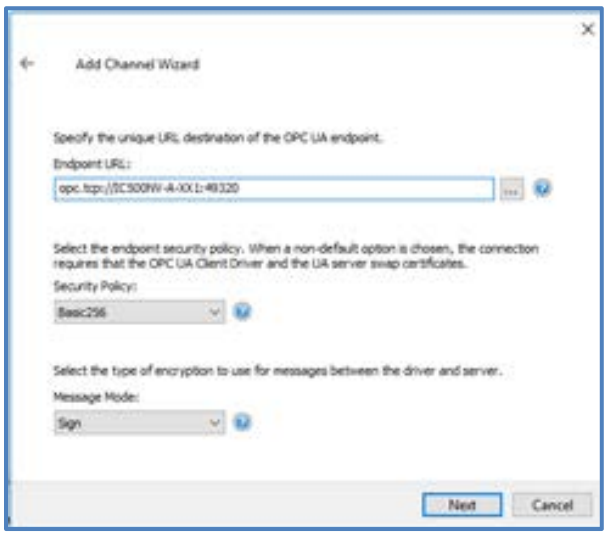


Figure 105: Setting the name of computer in OPC Client

Click on ‘Next’ again and Figure 106 will appear. Enter the ‘Username’ and ‘Password’ of the local windows account of the machine and click on ‘Next’. After that, click on ‘Finish’. A new Channel was created on the OPC Client.

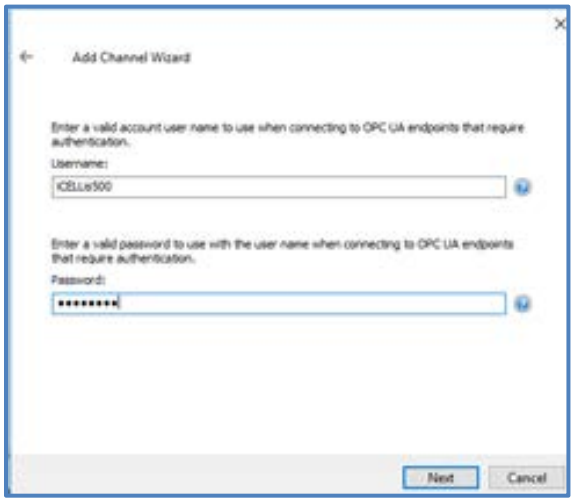


Figure 106: Username and password of the iCELLis bioreactor windows account in OPC Client

Add a new device by clicking on ‘Add a device’ (Figure 107A). A pop up will appear, click on ‘Next’ 7 times, until Figure 107B appears. Click on ‘Select import items…’

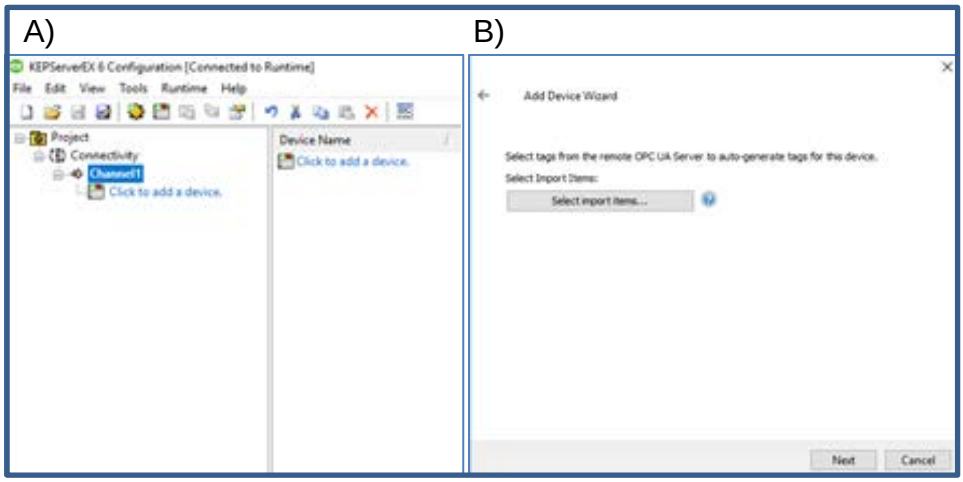


Figure 107: Add a device – A) Select import items, B) In OPC Client

A new pop up will appear (Figure 107-A). Click in the left column to expand the folder. Expand also ‘iCELLis’ folder and select ‘iCELLis500+’. Click on ‘Add branches >>’. All the tags will be imported in the right column (Figure 107-B). Click on ‘OK’. This pop up will be closed. In the previous pop up, click on ‘Next’ and them on ‘Finish’.

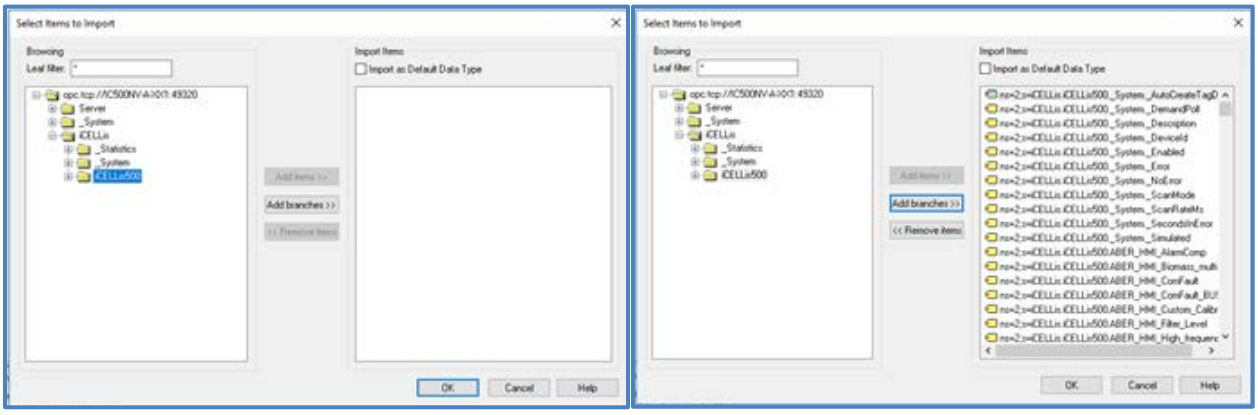


Figure 108: Importing Tags in OPC Client

Now it is possible to check that all the tags can be displayed by expanding the folder ‘Device1’ > ‘iCELLis’ > ‘iCELLis500+’. Now that the channel and the device are configured and the tags are imported, click now on ‘Quick Client’ icon on the top menu to open the OPC Client. A pop up with the OPC Client will appear (Figure 109). At selecting the folder ‘Channel1.Device1.iCELLis’ it is possible to see the values of the tags. The connection of the OPC Client is settled.

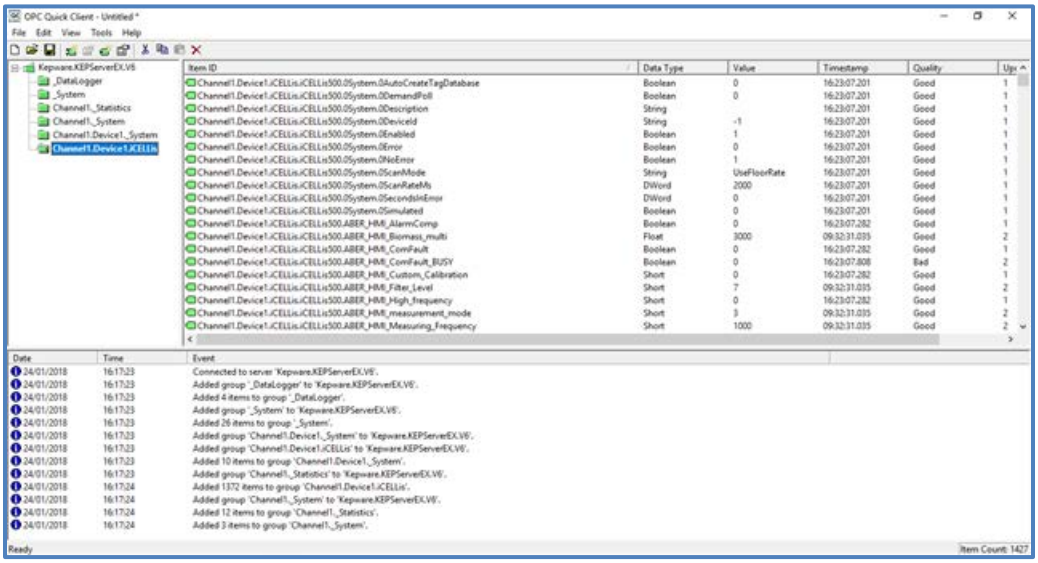


Figure 109: Tag Values in OPC Client

A list containing all the tags is provided in the design documents. All the available tags are listed in the Appendix 8 of the software design specification.

16.3 Historical Data

The iCELLis 500+ bioreactor control system allows users to read historical data via a standalone or a network environment. To be able to archive all the data in a secured and organized way, the local SCADA platform utilizes an SQL server to store historical data.

16.3.1 What is an SQL Server

Microsoft SQL Server, part of the Windows Server Systems, is a relational database management package for data management. SQL stands for Structured Query language. This is the basis where the HMI software is relining on for data storage of the recorded data from the PLC and recorded HMI actions. It is based on a Client-server topology.

SQL was developed with the idea that people would be able to request information from a database by means of simple command instructions. The HMI software installed on our iCELLis 500+ bioreactor control system sends SQL commands to utilize the data into a database. The SQL server is the bridge between the HMI software and historian block which are stored on the local hard drive.
Therefore, a relational database stores the data in tables that have a relationship, rather than in one long list. The big advantage is the speed and flexibility which it provides. To be able to collect the data, the Query language needs to be used. Therefore, SQL statements are used to perform certain tasks such as storing, backup, retrieving, transferring data from and to a database. Microsoft SQL Server also supports Transact-SQL (T-SQL), which is an addition to SQL. By using a scripting language like T-SQL, or SQL commands it allows to call up the specified data point from the dedicated database(s). Within these databases data points are organized in tables which can be called up based on the scripting.

An SQL server provides following beneficial aspects like:

- Security
- Scalability
- Integration features

Security
An SQL Server provides security models which are benefiting of Windows Authentication to provide robust security platform for managing your organization informations like process data or batch data. Security is managed across the database objects, tables, views. To access data from SQL server of iCELLis 500+ bioreactor control system, a dedicated account has been created called ‘wwUser’.

Scalability
The storage capability is depending on the size of the hard drive. The control system also allows storing data locally or in a network environment by using other additional SQL servers.

Integration
SQL Server provides a variety of high availability features including fail over clustering, database mirroring, log shipping, and database snapshots to meet your organizations' needs.

16.3.2 Database Structure

The database structure of the iCELLis 500+ bioreactor is build up out of multiple databases. For the collection of process data in a network or standalone environment the following databases will provide most of the required data for batch generation:

- Pall Configuration (PallConfig)
- Recipe Manager PLUS History database (RecMngrPlusDB)
- Runtime

Each database has a unique set of tables. Some of these tables are dedicated to the Wonderware platform and are setup by default.

In the overview below a set of useful tables can be found to pull data from.

- Pall (PallConfig)
  - Dbo.Capabilities
  - Dbo.Recipe
  - Dbo.Report
  - Dbo.ReportTrends

- Recipe Manager PLUS History database (RecMngrPlusDB)
  - Dbo.ExecutionInsctance
  - Dbo. ExecutionSequenceOfEvents
  - Dbo.ParameterDetails
  - Dbo.TransitionDetails
  - Dbo.CapabilityDetails

- Runtime
  - Dbo.Events
  - Dbo.v_history
  - Dbo.v_live
  - Dbo.Alarmhistory

Within each table multiple columns are created that represent the objects or parameter of a recorded or live value. Figure 110 presents a graphical representation for the following historical parameter TT_01.

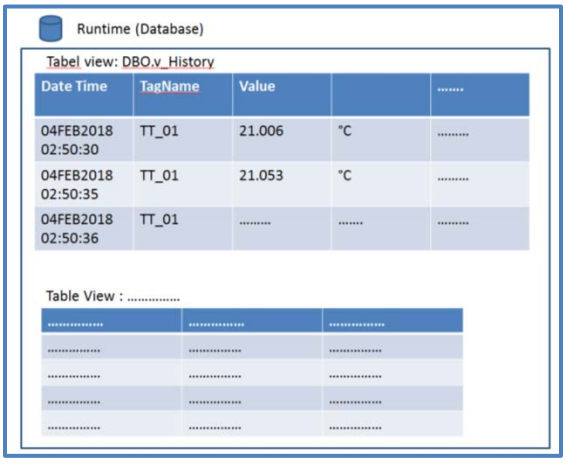


Figure 110: Graphical representation for TT_01

Some of the parameters or objects are internal information form the Wonderware platform. The data in these extension tables can be manipulated by using normal Transact-SQL code, as well as the specialized SQL time domain extensions provided by the IndustrialSQL Server historian. The IndustrialSQL extensions provide an easy way to query time-based data from the history tables. They also provide additional functionality not supported by Transact-SQL.

In the list below some examples are given of internal information like:

- wwTagKey
- wwRowCount
- wwTimezone
- wwParameters
- wwCycleCount
- wwFilter
- wwRetreive
- wwVersion

Further information about these parameters can be found in the datasheet of IndustrialSQL Server Historian Concepts Guide of Wonderware.

16.3.3 How to Write Queries to Read Data

To be able to read data from an SQL server, a supported reporting tool needs to be used within the SQL server: a module called SQL Server Reporting Services (SSRS). On the market there are many tools that can provide solutions. Like:

- SQL server data tools
- Visual studio
- Dream report
- Wonderware query tool
- Microsoft Excel
- SQL server management studio

To ensure that the proper tool is selected for reading data from the SQL server, make sure your preferred tool complies with the data integrity rules. This responsibility falls under the responsibility of the customers' IT.

IMPORTANT!
Once a specific report generation tool is selected, make sure that the persons which are creating reports are trained on using the software. This responsibility falls under the responsibility of the customers.

Once the preferred tool is selected, a communication with the server needs to be setup and Queries must be written to be able to get the data from the server. A query command is used to extract data from the database in a readable format according to the user's request. A standard set of commands to interact with relational databases are 'select', 'or', 'and' and 'declare'.

16.3.4 Overview of Query COMMANDS

In the following section a short overview is given of query commands which will help retrieving the data from the SQL server. This overview can be used as a guidance to access the raw SQL data.

IMPORTANT!
Make sure that the persons who will be coding the queries are trained or qualified personnel. This responsibility falls under the responsibility of the customers.

AND
The ‘AND’ function is an operation that combines two conditions. Both conditions must be true for the row to be included in the result set.

Code:
```
SELECT column_name(s)
FROM table_name
WHERE column_1 = value_1
AND column_2 = value_2;
```

AS
The ‘As’ is a keyword in SQL that allows you to rename a column or table using an ‘alias name’.

Code:
```
SELECT column_name AS 'Alias'
FROM table_name
```

BETWEEN
The ‘Between’ operation is used to filter the result set within a certain range. The values can be numbers, text or dates.

Code:
```
SELECT column_name (s)
FROM table_name
WHERE column_name BETWEEN value_1
AND value_2
```

Declare
Variable(s) are declared in the body of a procedure with the DECLARE statement. These are assigned values by using either a SELECT or SET statements. It is important to add the data type after the named Variable.

Code:
```
DECLARE @StartDate DateTime
DECLARE @EndDate DateTime
SELECT column_name (s)
FROM table_name
WHERE column_name IN Variable(s)
AND StartDateTime >= @StartDate
AND EndDateTime <= @EndDate
```

IN
The IN operator allows you to specify multiple variable(s) in a WHERE condition.

Code:
```
SELECT column_name (s)
FROM table_name
```

WHERE column_name IN Variable(s)

OR
The ‘OR’ statement is an operation that filters the result set to only include rows where either condition is true.

Code:
SELECT column_name (s)
FROM table_name
WHERE column_name = values_1
OR column_name = value_2;

SELECT
SELECT statements are used to fetch data from a database. Every query will begin with SELECT.

Code:
SELECT column_name (s)
FROM table_name

WHERE
WHERE statement condition used to extract only those records that fulfil a specified condition.

Code:
SELECT column_name (s)
FROM table_name
WHERE column_name operation value:

16.3.5 SQL Clients

SQL client is any system that can read the data of a SQL server and make this data available for the user. It was tested some different SQL clients. The tested SQL clients will be shown in the following examples.

16.3.5.1 Wonderware Historian Client

Wonderware Historian Client is an analysis and reporting software that communicate with your Wonderware Historian. This is the recommended solution, as it is provided by Wonderware.

The software is divided in two different applications, the ‘Query’ to obtain the data and the ‘Trend’ to generate graphs. The advantage of using this software is that it is very easy to configure and obtain the data and the graphs, not being necessary to create SQL queries.

The first step when using Wonderware Historian Client is to open the Wonderware ‘Query’ application installed in the designed computer.

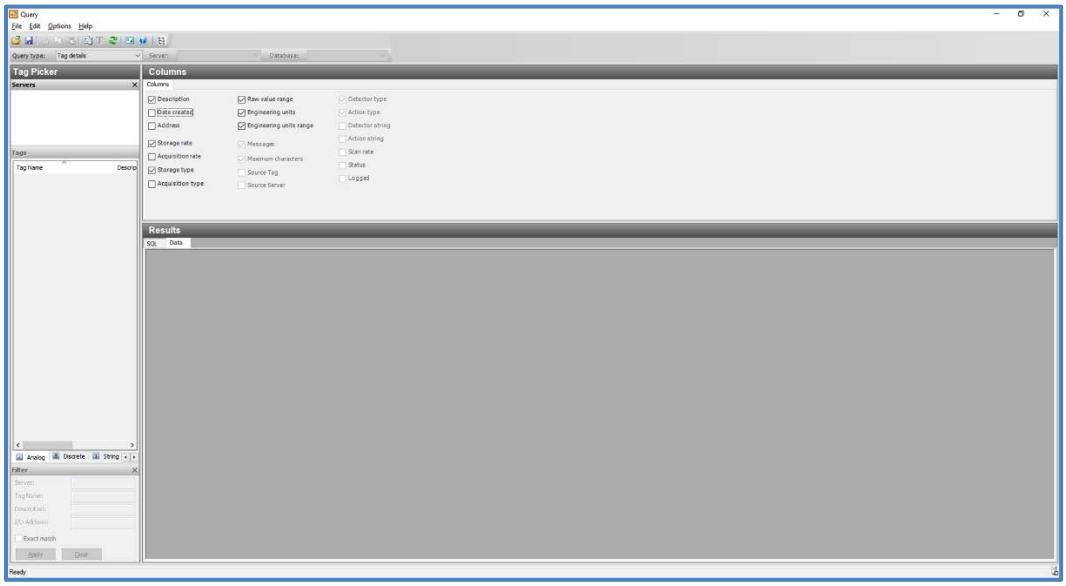


Figure 111: Historian Client example – Opening the Query application

Then click on ‘Option’ and click on ‘Servers…’ to configure the access to the SQL server. On ‘Server’ type the name of the server, or its IP address. Choose the ‘Database (SQL Server)’and ‘SQL Login’, and fill the SQL login and the password. Click on ‘Add’ and then on ‘Close’.

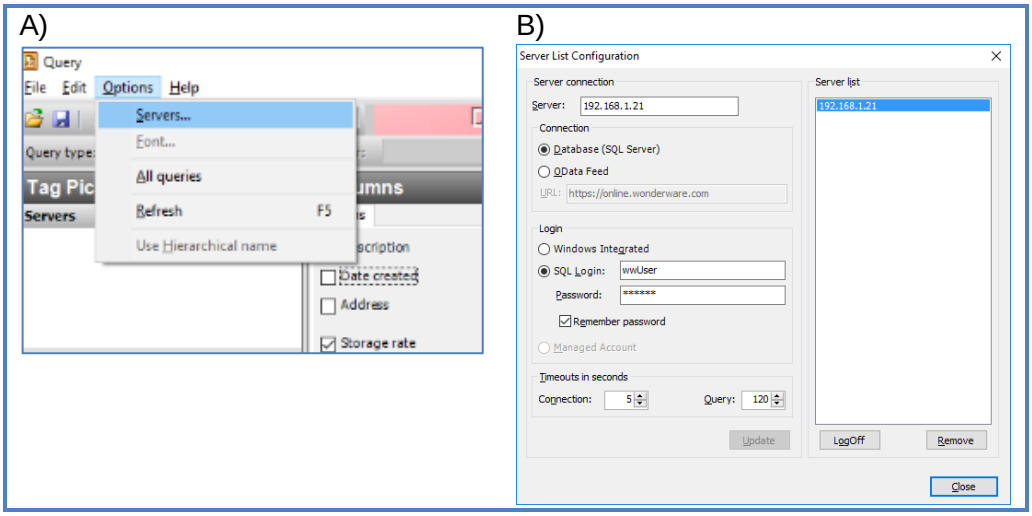


Figure 112: Historian Client example – Configuring the server –
A) Options Servers, B) Server List Configuration.

The default view is o of the ‘Tag Detail’. To see the History data, click on ‘Query type:’, and choose ‘History Values’. Click on the desirable variable to show the history values. If it is desired to show more than one variable, click on the other variable while pressing ‘Crtl’ key on the keyboard.

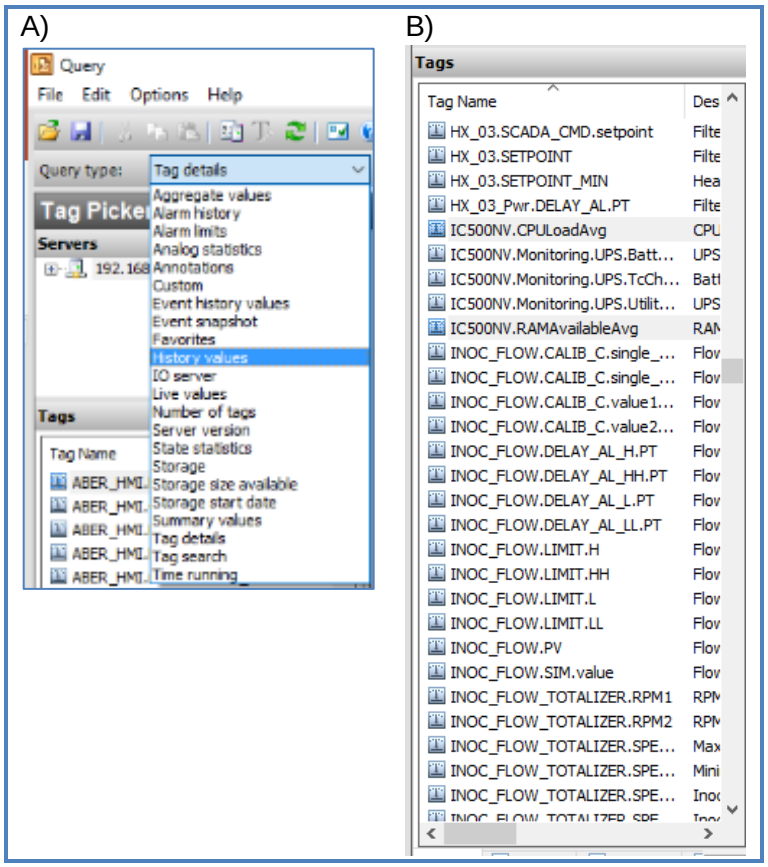


Figure 113: Historian Client example – Choosing TAGS – A) Tag details, B) Tags.

To configure the displayed variables, some configuration needs to be done in the ‘Columns’ workspace. In the ‘time’ tab, choose the data and time to display the variables. In the ‘Format’ tab, choose ‘Wide query format’ to make the variables separated by columns. In the ‘Retrieval’ tab, choose ‘Interpolated’ in the ‘Retrieval Mode’ and choose the number of lines of the data in ‘Values over equal time intervals’. The data will be displayed in the ‘Results’ workspace.

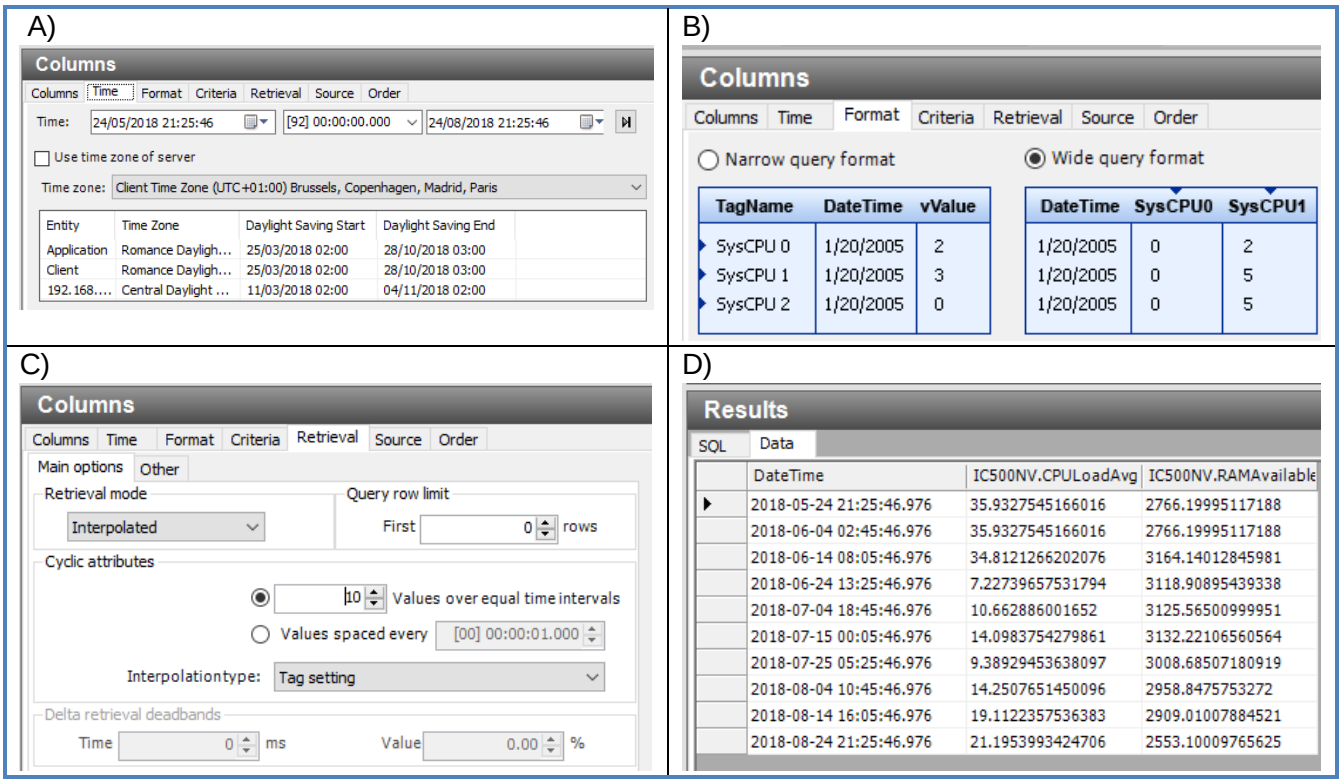


Figure 114: Historian Client example – Configuring the columns and showing the result data – A) Columns Time, B) Columns Format, C) Columns Retrieval, D) Results data.

To create a graph, it is necessary to open another application, the Wonderware 'Trend' application installed in the designed computer. As the server was already configured in the 'Query' application, it is not necessary to configure it again in 'Trend'. Click on the configured server and then click twice on the desired variables to the graph be automatically displayed. In the upper part of the page, choose the desired date and time and the interval of the graph.

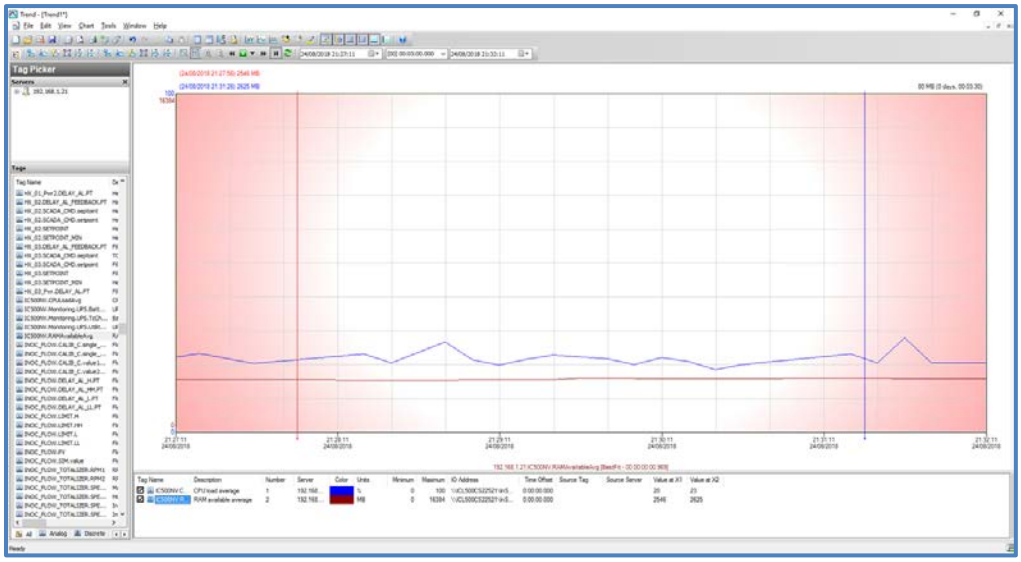


Figure 115: Historian Client example – Trend example

16.3.5.2 Dream Report

Dream Report, from Ocean Data Systems, is a reporting software that can communicate with a wide range of SQL servers and with OPC servers. Like the Wonderware Historian Client, it is very to configure and obtain the data and graphs, not being necessary to create SQL queries.

When installing the Dream Report, make sure to install the 'Wonderware Drivers'. This way will the configuration will be very simple.

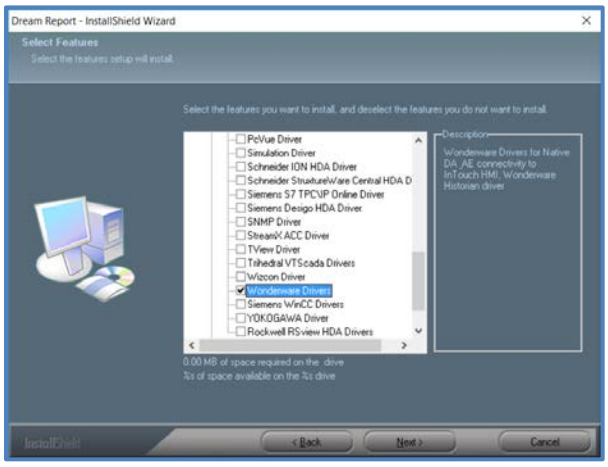


Figure 116: Dream Report Example – Additional Wonderware drivers installation

When opening the Dream Report, choose 'Run Project Wizard', and click on 'OK'. Type a name for the project and click on 'Next'.

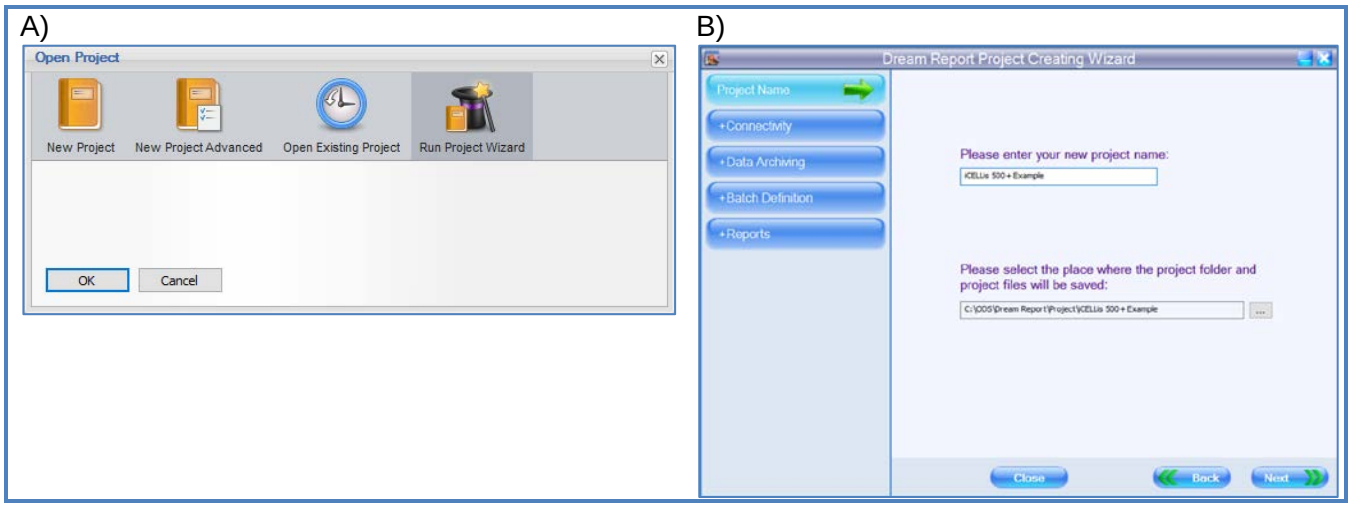


Figure 117: Dream Report Example – Run project wizard –
A) Open project, B) Dream Report Creating Wizard.

In Connectivity, click on ‘Configure Driver(s)’. Open the ‘Wonderware’ folder and choose ‘WW Historian’. Type a name for the Server connection on ‘Driver Logical Name’, and click on ‘Configure’. Click on ‘…’ button to choose a computer in the network, or type its name or IP address. Type on the ‘User name’ the SQL user details, and then click on ‘Test Connection’. If the connection is succeeded, click on ‘OK’ to close the message and in ‘OK’ again to close the server configuration. Click then on ‘Add’ button to add this configured server on the ‘Defined Drivers List’.

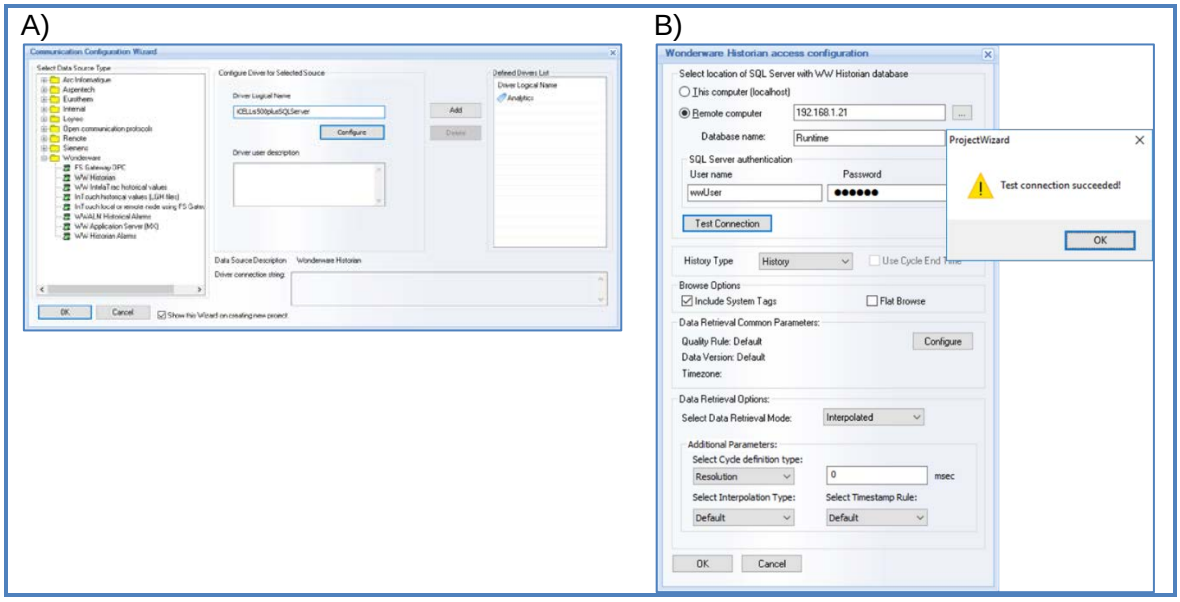


Figure 118: Dream Report Example – Server configuration – A) Communication Configuration Wizard, B) Wonderware Historian access configuration.

For a quick view of the reports, click on ‘No’ and then ‘Next’ for the next two pages. In the Reports tab, give a name to the Report. Click on ‘Next’. Choose then ‘Never’, and click on ‘Next’ again. Choose then ‘No’ and click on ‘Next’ again, and then ‘Next’ another time. Choose then the desired time period. In the Page Design page, choose ‘I will design report myself’. And fill the information needed.

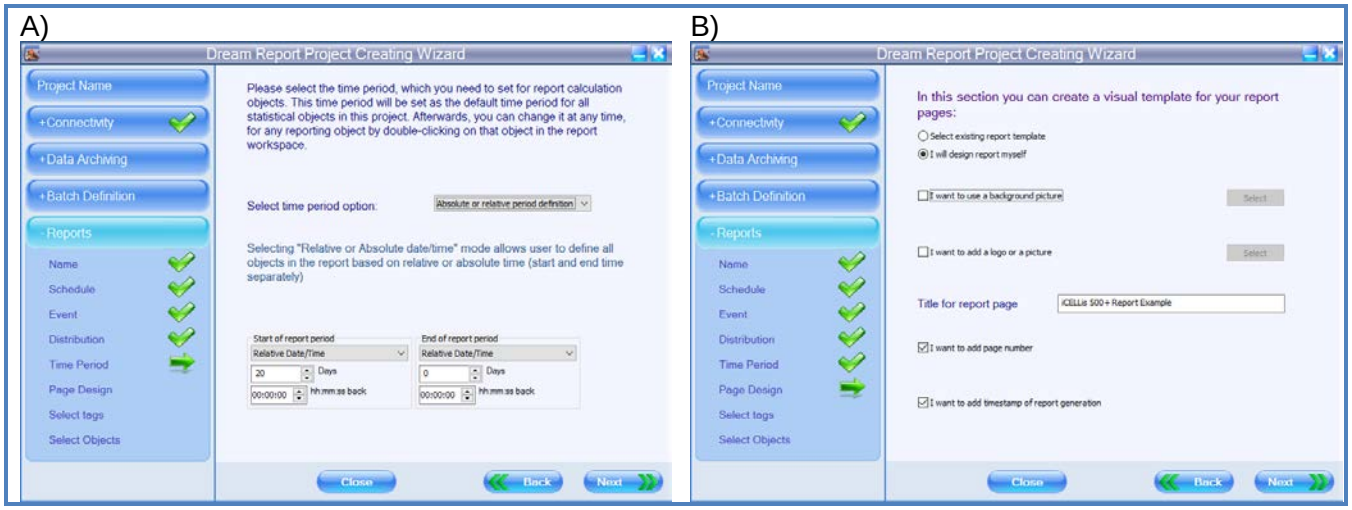


Figure 119: Dream Report Example – Report design and data period – A) Reports Time Period, B) Report Page Design.

Choose ‘External History Server’ and click on ‘Select Tags’. Choose the configured server in the ‘Select Data Source’. Choose the Tags desired and click on ‘Add >>’ to add these Tags into the report.

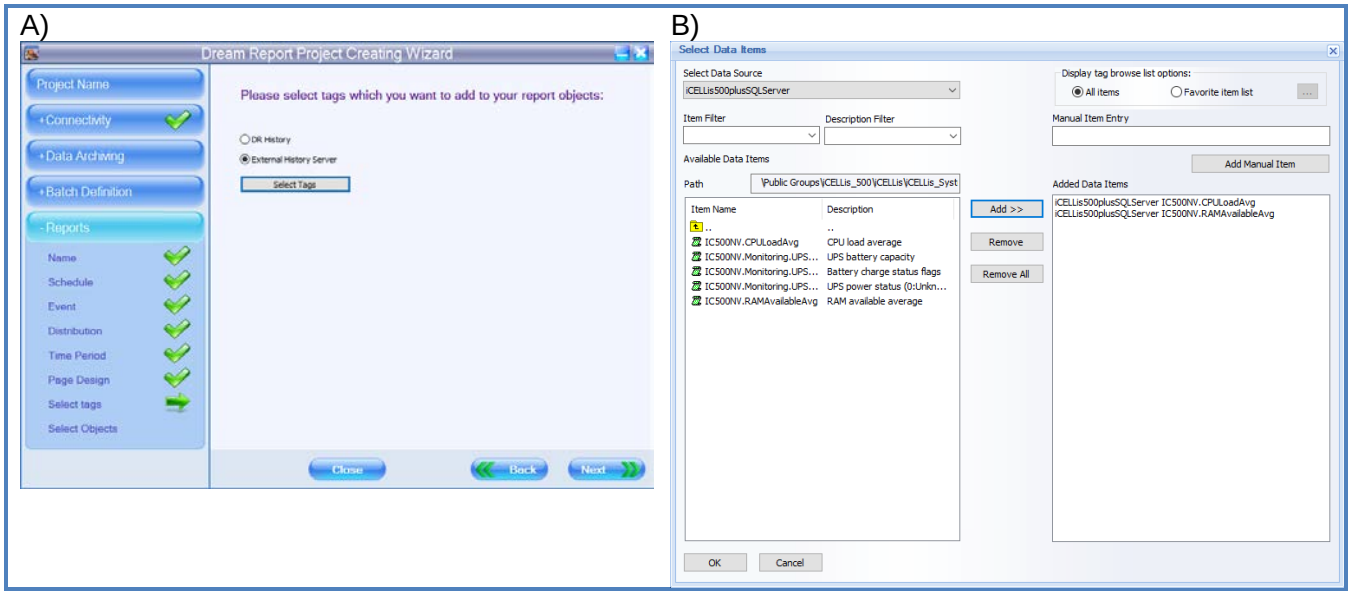


Figure 120: Dream Report Example – Selecting Tags – A) Report Select tags, B) Select Data Items.

Choose the desired basic items to be shown in the report. In this example, it was chosen a chart and a table with the values. Click on ‘Next’ twice, to generate the report template. Use the right workspace to add more tables or charts. To edit an existing table or chart, just click on it twice. It is possible to add more Tags, change the time period, or just to change their appearance.

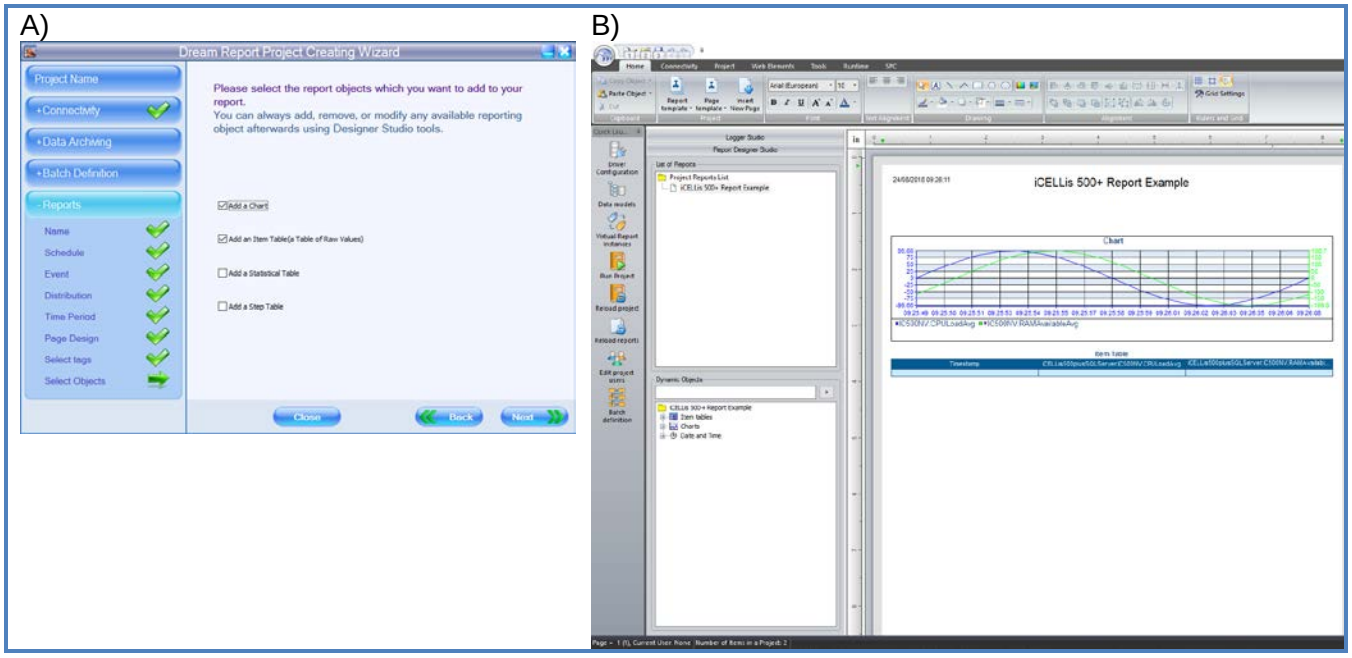


Figure 121: Dream Report Example – Creating the report template –
A) Report Select Objects, B) Report example.

Click on ‘Run Project’ in the ‘Quick Launch Bar’, to run the Runtime Management Console. Choose the created report on the Available Reports workspace. On the reports workspace, in the Generate field, choose to generate PDF/XLS file, or just PDF file. And then click on the respective option on Open field. The PDF of the report will open, showing the chats and the table with the data of the TAGS.

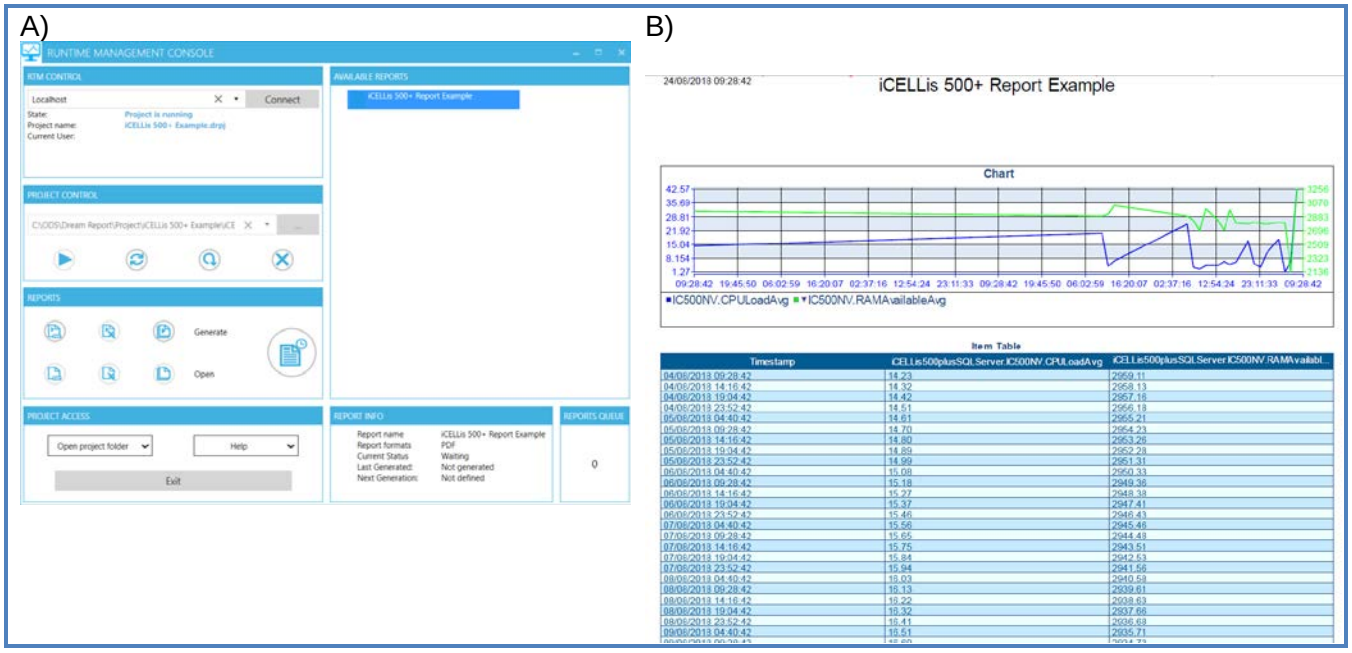


Figure 122: Dream Report Example – Report generation –
A) Runtime management console, B) Report example.

IMPORTANT!
The following examples are more dedicated for IT and Engineering personnel.
Make sure that the persons who will be coding the queries are trained or qualified person. This falls under the responsibility of the customers.

16.3.5.3 SQL Server Management Studio

SQL Server Management Studio (S.S.M.S.) is a free software of Microsoft, used for configuring, managing, and administering all components within Microsoft SQL Server. The tool includes both script editors and graphical tools which work with objects and features of the server. The version tested was Microsoft SQL Server Management Studio 17.

In this example we will make a combination of multiple PV’s with a time interval of 1 second. Following PV’s will be shown:

- Temperature 1 of bioreactor (TT_01)
- pH 1 of the bioreactor (AT_01)
- DO1 of the Bioreactor (AT_03)
- Agitation speed of the bioreactor (ST_06)
- Feed in pump speed (ST_01)
- Feed out pump speed (ST_04)

All this data will be created in a table by using the SQL server Management studio.

To ensure the following section will work, SQL server Management studio must be installed on the dedicated computer. The SQL server management is also accessible in the iCELLis 500+ bioreactor, logging in with the administrator account.

Navigate to the SQL server management studio. Open the program. Go to File and select ‘Connect Object Explorer…’.

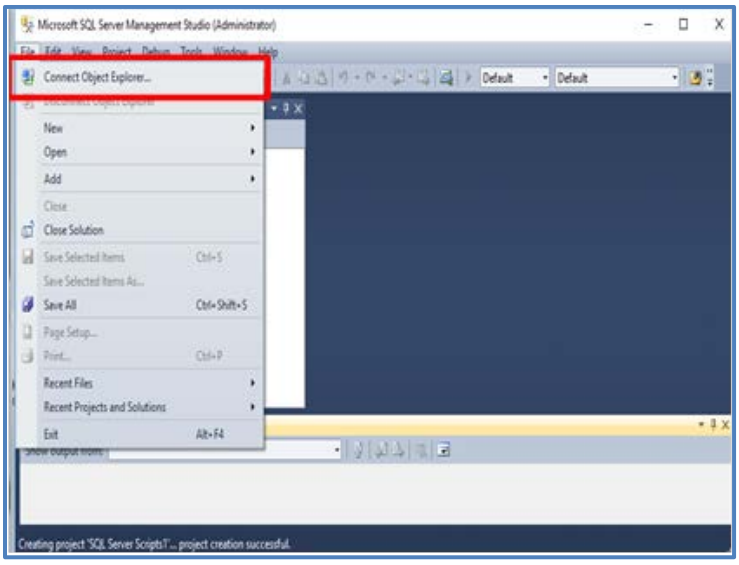


Figure 123: Microsoft SQL server management studio

A new window will open to connect to the server. Select in the drop down menu ‘<Browse for more…>’ the purpose is to search the iCELLis 500+ bioreactor control system from a network server.

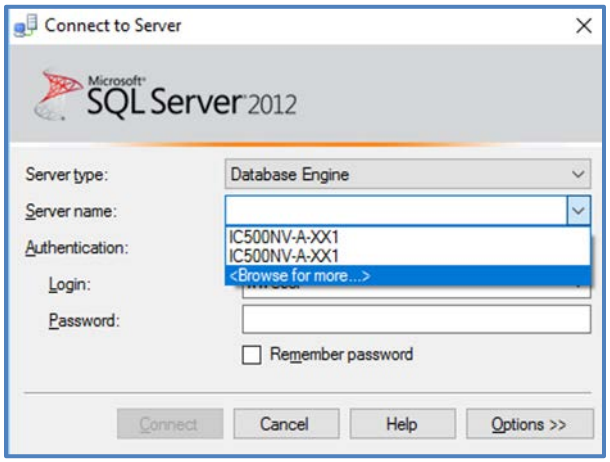


Figure 124: Browse for more option in SQL server

A new window will open and select Network server. All available network servers will be displayed. In this example IC500NV-A-XX1 is used.

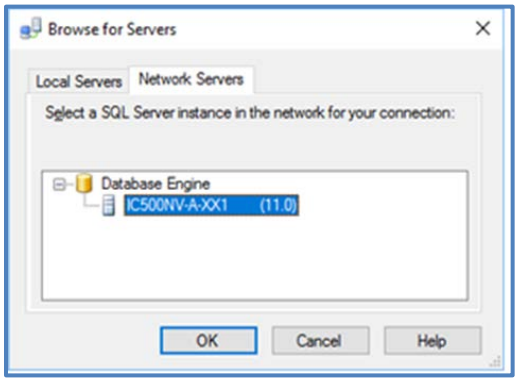


Figure 125: Network server in SQL Server

Make sure that the Authentication is set to SQL server Authentication. And Login with 'wwUser' with its dedicated password and click on connect.

Figure 126: Authentication set in SQL Server

After the connection with the server is established, select New Query.

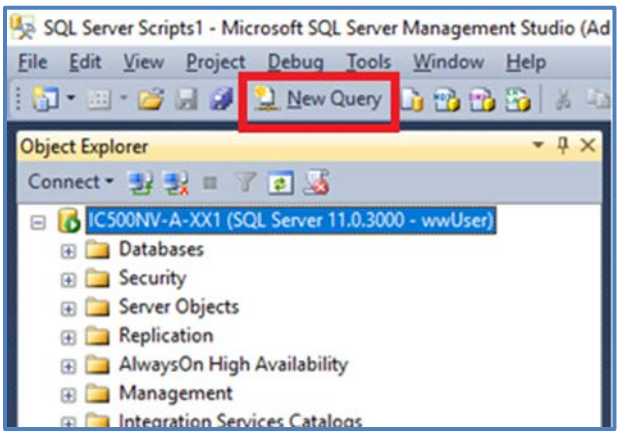


Figure 127: Selecting 'New Query' in SQL Server

Enter the following query to get the data.

```
SET QUOTED_IDENTIFIER OFF
SELECT * FROM OPENQUERY(INSQL, 'SELECT DateTime = DateAdd(mi,-420,DateTime), [TT_01.PV], [AT_01.PV], [AT_03.PV],
[ST_01.PV], [ST_04.PV], [ST_06.PV]
 FROM WideHistory
 WHERE wwRetrievalMode = 'Interpolated'
 AND wwResolution = 1000
 AND wwVersion = 'Latest'
 AND DateTime >= DateAdd(mi,-5,GetDate())
 AND DateTime <= GetDate()')
```

In the middle of the program the response is shown in Figure 128.

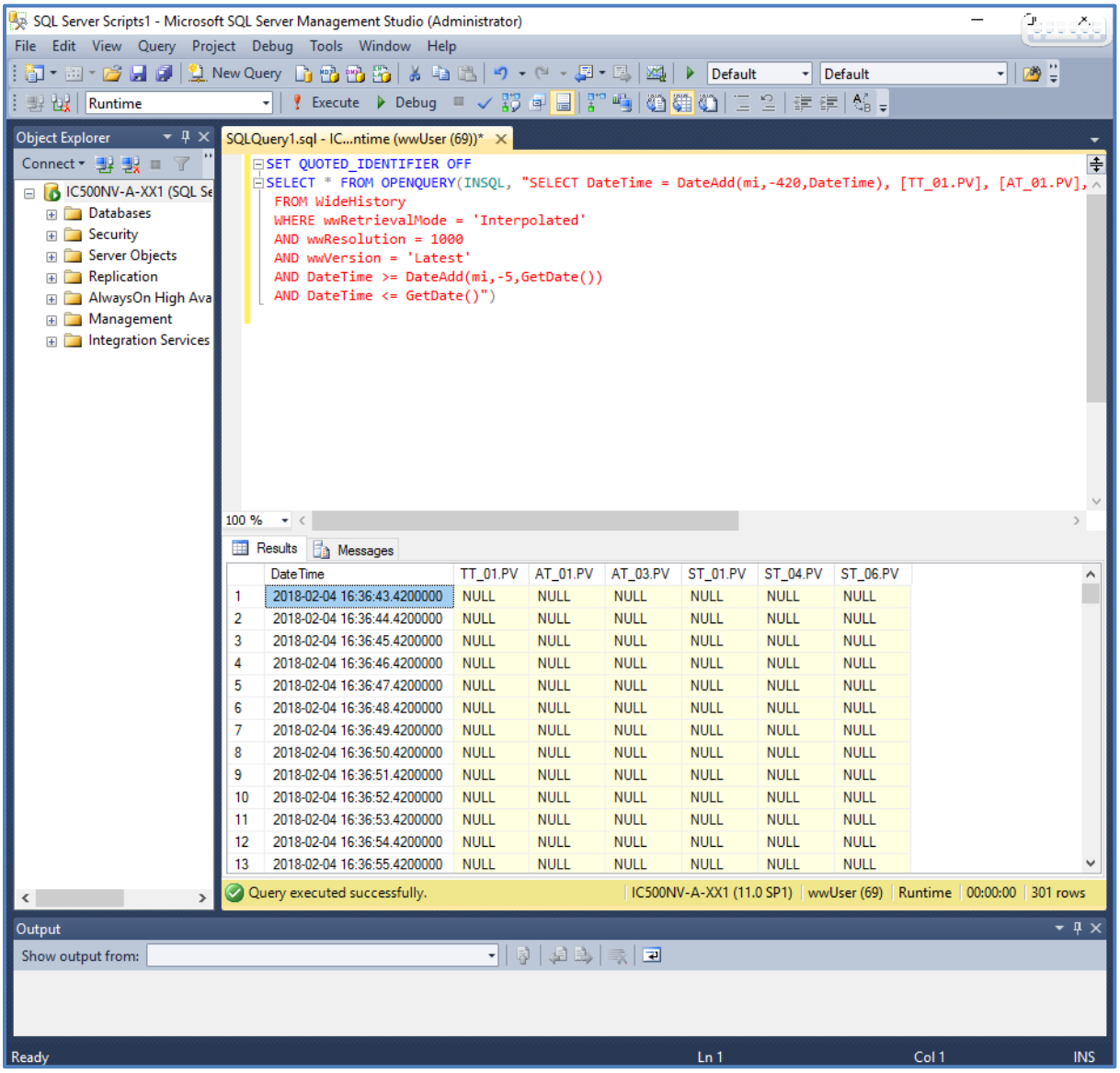


Figure 128: E.g. Query in Microsoft SQL server management studio

16.3.5.4 DBeaver SQL Client

DBeaver is a free and open source SQL client and database administration tool. It has a desktop application written in Java and based on Eclipse platform. The version used for the example was the 5.1.3

In this example, a combination of multiple PV's will be made, with pre-determinate date/time, with a time interval of 1 hour. The following PV's will be shown:

- Temperature 1 of bioreactor (TT_01)
- pH 1 of the bioreactor (AT_01)
- DO1 of the Bioreactor (AT_03)
- Agitation speed of the bioreactor (ST_06)
- Feed in pump speed (ST_01)
- Feed out pump speed (ST_04)

Open the installed DBeaver. Go to File and select 'New' .

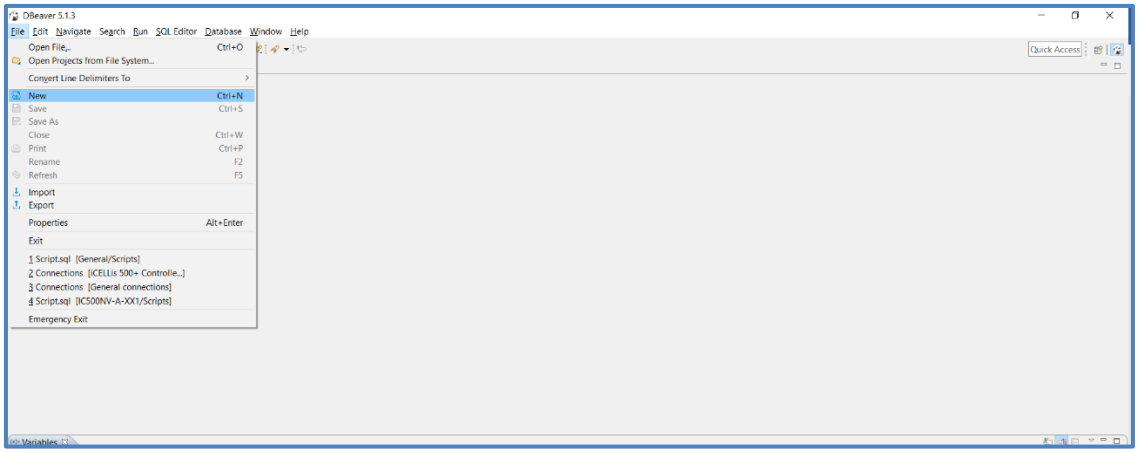


Figure 129: DBeaver example – Creating a new project

In the new window, choose 'Project' (under the 'General' folder) and click on 'Next'. Choose a name for your project and click on 'Finish'.

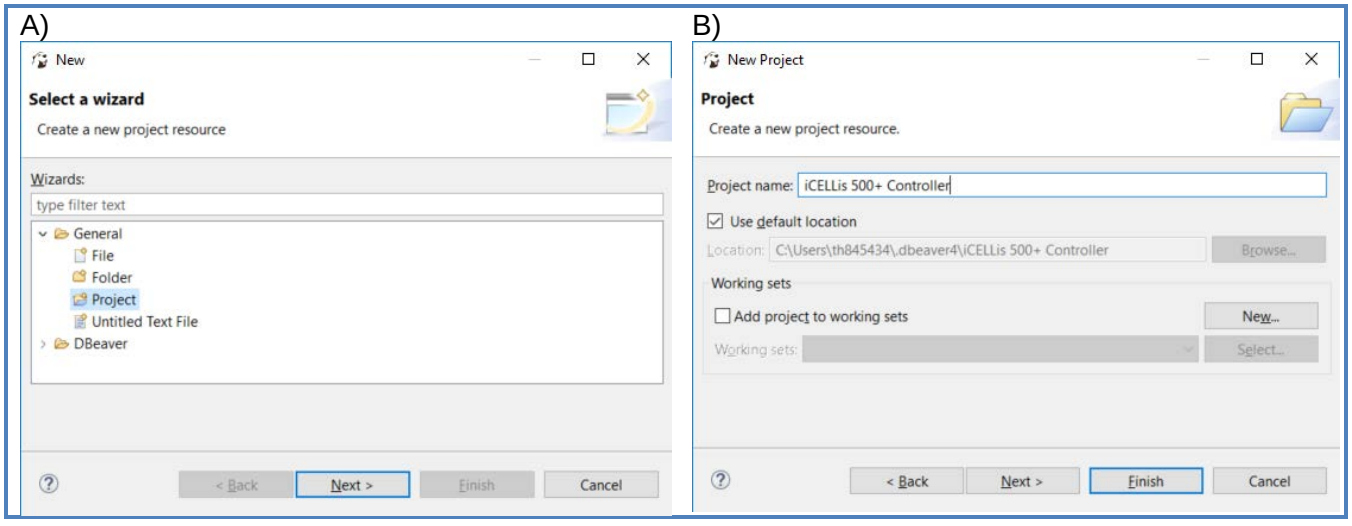


Figure 130: DBeaver example – New project – A) Select a Wizard, B) New project.

Click with the right button of the mouse on ‘Connection’ and choose ‘Create New Connection’. Find ‘MS SQL Server’ in the list, choose ‘jTDS driver’, and click on ‘Next’.

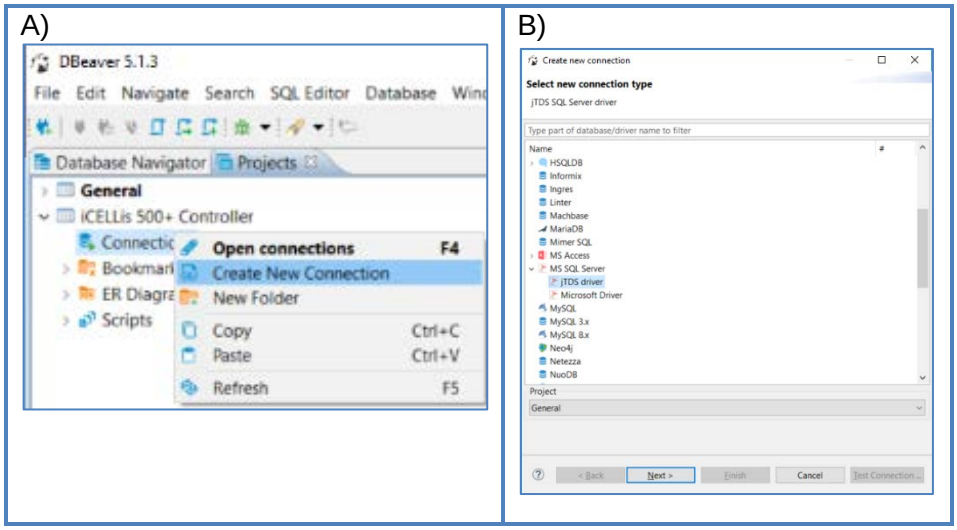


Figure 131: DBeaver example – Creating a new connection.

Fill the ‘Host’ field with the name of the iCELLis 500+ bioreactor or its IP address. Fill ‘User name’ and ‘Password’ field with SQL Queries password. Click then on ‘Test Connection’. When the ‘Success’ message appear, click on ‘OK’ to close the window and then click on ‘Next’.

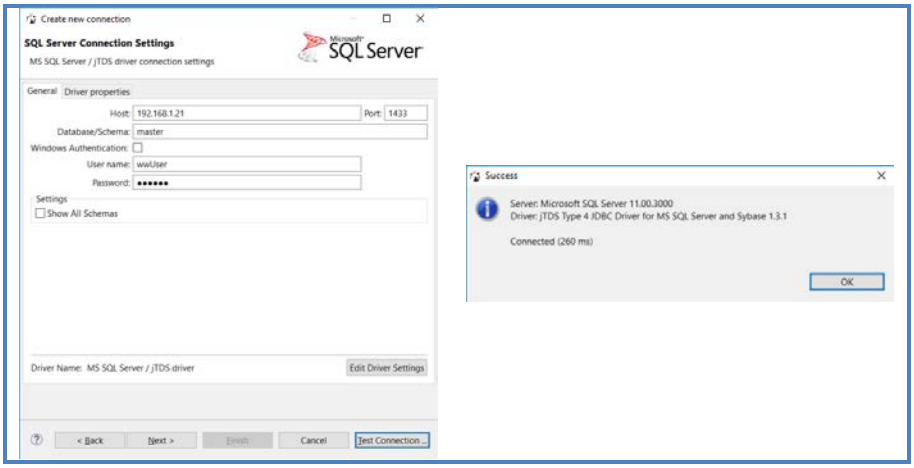


Figure 132: DBeaver example – Configuring the remote PC

Click on Next again. Choose a ‘Connection name’ and click on ‘Finish’.

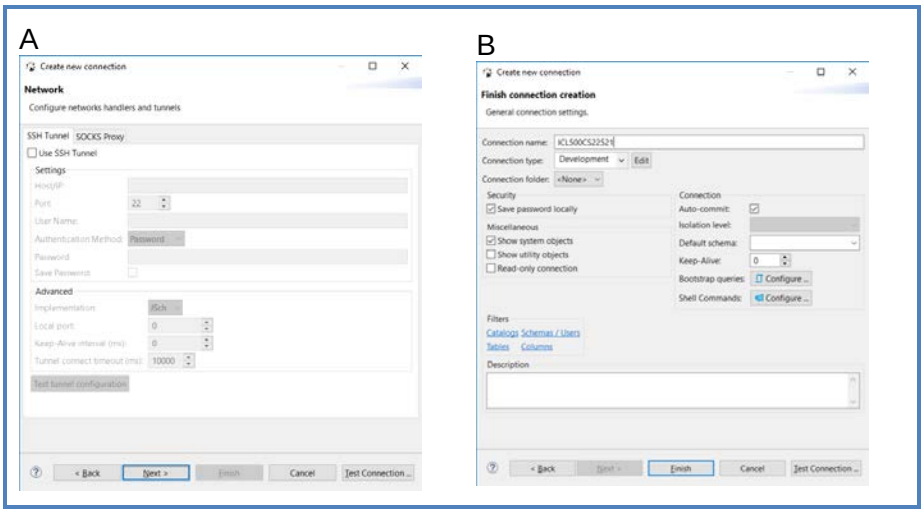


Figure 133: DBeaver example – Finishing the configuration

Click with the right button on the Connection created, under the ‘General’ sheet, and click on ‘SQL Editor’.

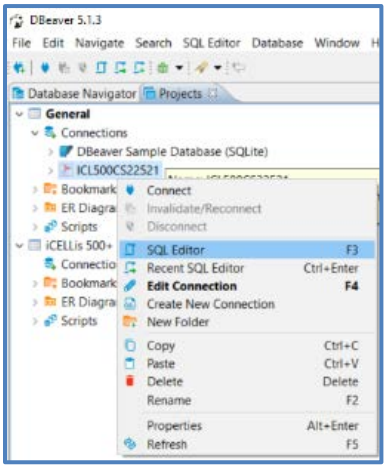


Figure 134: DBeaver example – Opening the query editor

Enter the following query to get the data:

```
SET QUOTED_IDENTIFIER OFF
SELECT * FROM OPENQUERY(INSQL, 'SELECT DateTime = DateAdd(mi,-420,DateTime), [TT_01.PV], [AT_01.PV], [AT_03.PV],
[ST_01.PV], [ST_04.PV], [ST_06.PV]
FROM WideHistory
WHERE wwRetrievalMode = 'Interpolated'
AND wwResolution = 3600000
AND wwVersion = 'Latest'
AND DateTime >= DateAdd(mi,-5,'20180701 00:00:00.000')
AND DateTime <= '20180723 00:00:00.000'')
```

Click on the ‘play’ button (indicated in Figure) to run the query. The data will be displayed on the middle part of the page.

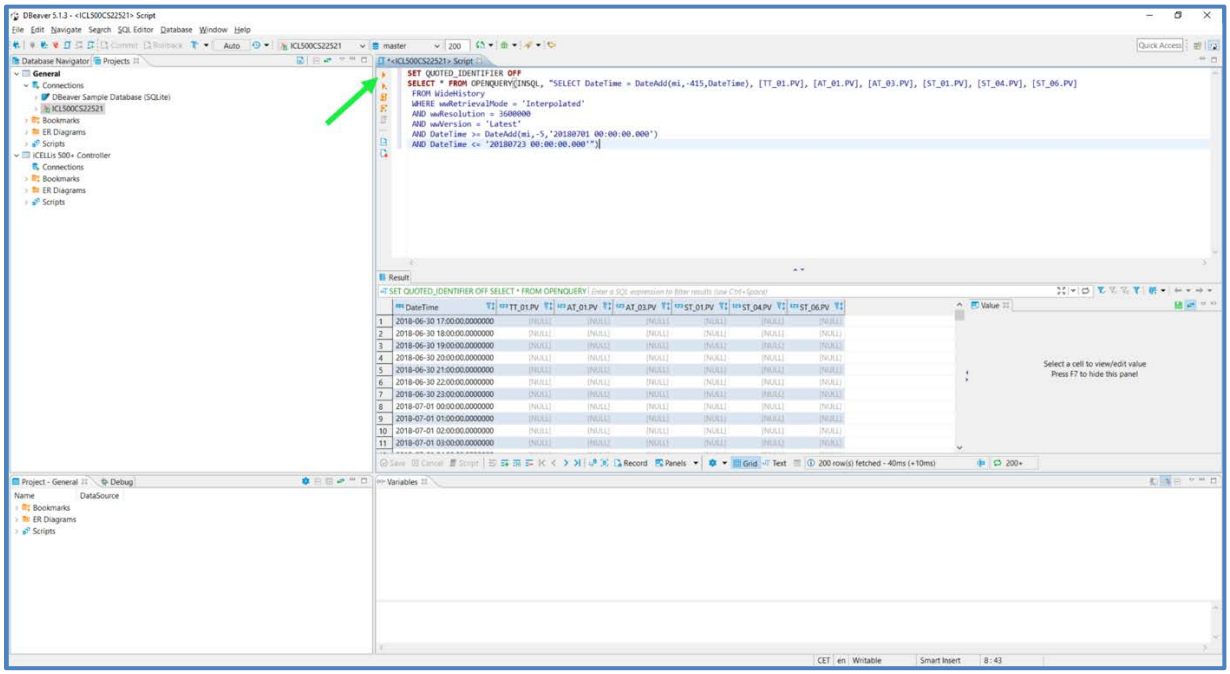


Figure 135: DBeaver example – Run the query

16.3.5.5 Excel 2016

It is also possible to use Excel as a SQL Client. In this example, Excel 2016 will be used to collect data from the SQL server.

Figure 110 shows graphical representation for the parameter TT_01.

When using excel it is recommended that the data module from Excel is available.

Open a new workbook go to the ‘DATA’ tab and select ‘From Other Sources’ and click on ‘From SQL Server’. The purpose now is to make the connection with the SQL database.

Fill in server name, see figure below (Figure 136). Enter the computer name of the iCELLis 500+ bioreactor Control system. Enter the user name and password of the user created in control system to put queries.

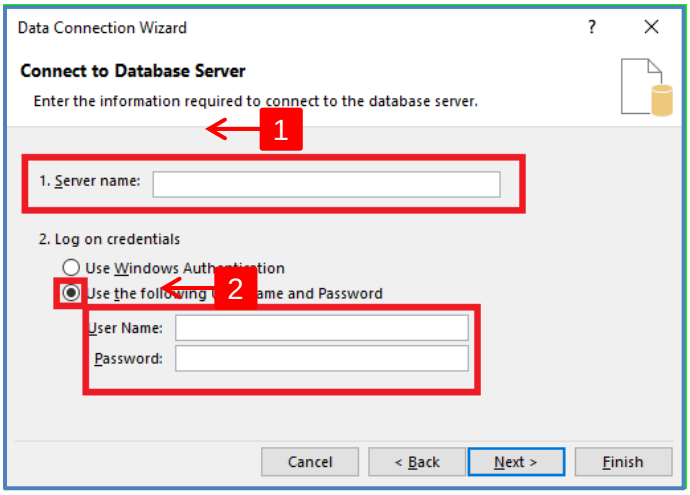


Figure 136: Connection to SQL Database server using Excel

Click next to continue and finish the process of connection to the database server.
Now select the Database which is required to get the data for our example ‘Runtime’ and select the History table and click on Finish (Load). A new window appears; an error is displayed ‘History queries must contain at least one valid tagname’

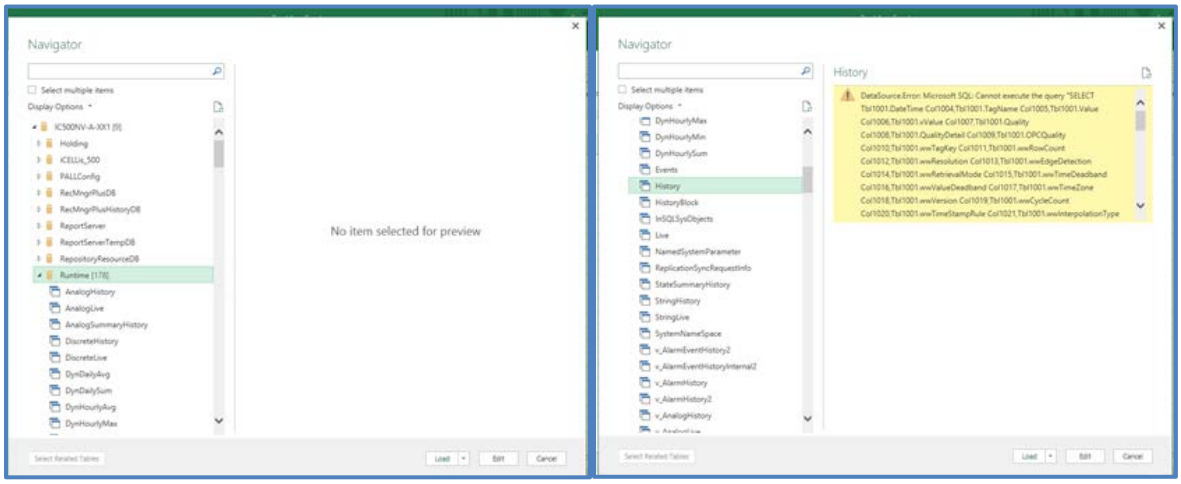


Figure 137: Error while accessing the history table from Runtime in SQL server database

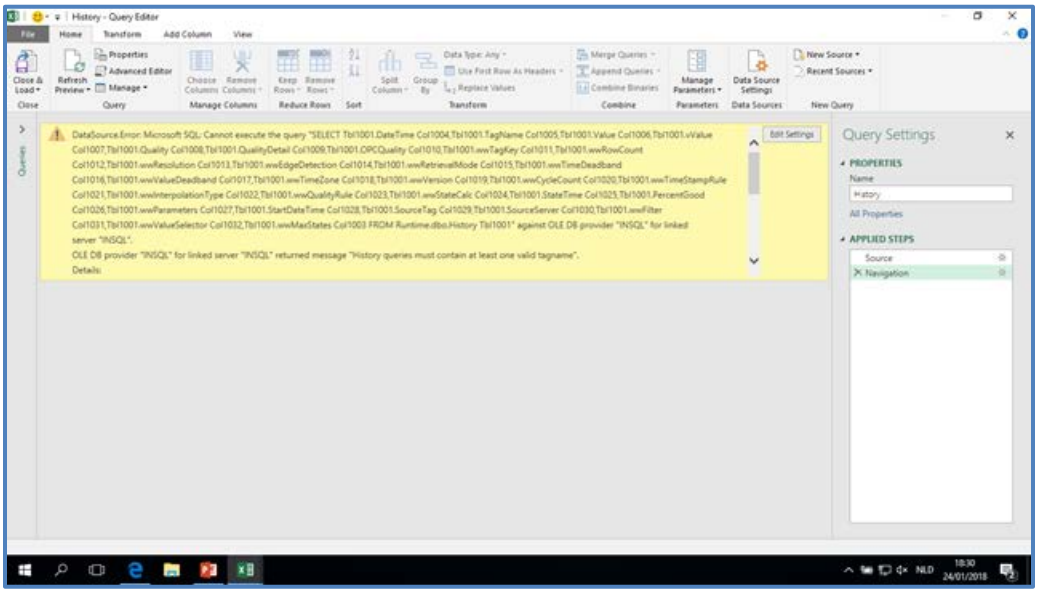


Figure 138: Error while accessing the history table from Runtime in SQL server database

Go to ‘Advanced Editor’ and write this query to get specific tag value. Once the query is free from any syntax error, click on Done and afterwards Excel will populate the requested data in new sheet.

```
let
        Source = Sql.Databases('IC500NV-A-XX1'),
        Runtime = Source([Name=Runtime'])[Data],
        Dbo_History = Runtime([Schema='dbo',Item='History'])[Data],
        Filter = Table.SelectRows(dbo_History, each[TagName] = 'TT_01.PV')
in
        Filter
```

Figure 139: E.g. Query to get the data for TT_01 Tag (temperature of the bioreactor)

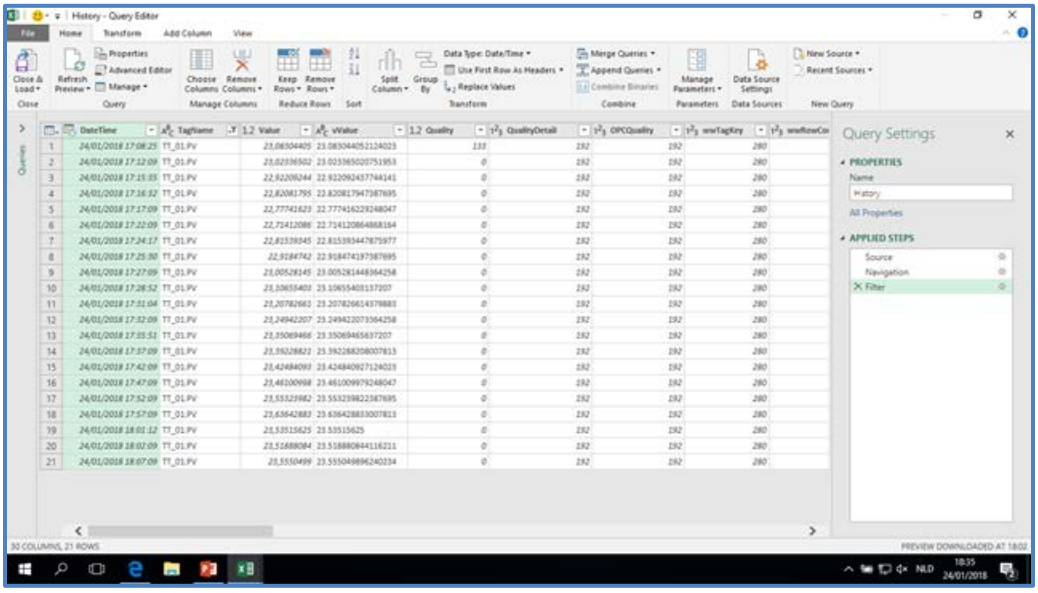


Figure 140: Result of a query

16.4 Domain Integration

The iCELLis 500+ bioreactor control system allows the system to be integrated in the client site domain.

When the iCELLis 500+ bioreactor is integrated with the client domain the log in dialog box shown in Figure 7 will be changed, allowing the user to log in using a local windows account (disabling the domain integration check box in Figure 141), or using a client domain account. All the other functionalities of iCELLis 500+ bioreactor will remain the same.

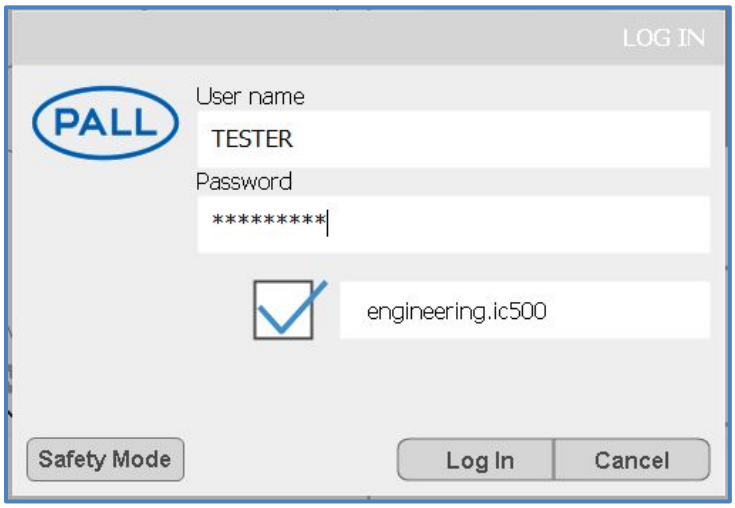


Figure 141: Login with domain account

For requesting domain integration, please contact your Pall Representative.

The integration at the client server site falls under the responsibility of the customer that is maintaining the IT network.

Appendix 1: Abbreviations and Symbols

Abbreviation, symbol	Signification
A, mA	Ampere, milliamp
Barg, mbarg	Bar, millibar, gauge pressure
CE	Declaration of European conformity
DO	Dissolved Oxygen
EM	Equipment Module
GMP	Good Manufacturing Practice
HMI	Human Machine Interface
Hz	Hertz
IPA	Isopropyl Alcohol
m, mm	Meter, millimeter
MFC	Mass Flow Control System
OD	Outer Diameter
OS	Operating system
P&ID	Piping and Instrumentation Diagram
PET	Polyethylene terephthalate
PETG	Polyethylene Terephthalate Glycol
PLC	Programmable Logic Control System
PV	Process Value
RMP	Recipe Manager Plus
rpm	Revolution per minute
SAT	Site Acceptance Test
SCADA	Supervisory Control and Data Acquisition Software
SP	Set-point
TCU	Temperature Control Unit
V, mV	Volt, millivolt
W	Watt
CFR	Code of Federal Regulations

Biotech

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