BioProcess™ Modular System

11.1 System description

Table of contents

1 Introduction

Bioprocess is an automated liquid chromatography system built for process scale-up and large-scale biopharmaceutical manufacturing.

1.1 Purpose and scope

The purpose of this document is to describe the system in a general context and can be used as a supportive document to the FS [Ref ID 7].

This document specifies high-level functions included in Bioprocess, based on the P&ID [Ref ID 4].

Physical properties, utilities and environments are specified in the GS [Ref ID 5].

Only specifications with an ID are defined to be testable.

1.2 References

Ref. ID	Document name	Document number(s)
1.	Terminology and Acronyms	29229457
2.	Project guideline document (Internal)	29258591
3.	Test Guideline Procedure	29258590
4.	Piping and instrumentation diagram	29616426
5.	General specification	29616428
6.	Input and Output list	29616011
7.	Functional specification	29623228
8.	Database merge procedure	TBD
9.	Unit design specification	29616019
10.	Phase Shell Design Specification	29257458
11.	Module matrix	TBD

1.3 Terminology and acronyms

See [Ref ID 1].

2 Architecture

The software is developed for real-time control of chromatography separation systems. The system is secured by an alarm management, through failure detections, and by a control of access through passwords, allowing several levels of interaction. The status of the system is displayed in real-time in a graphical display. Figure 1 – System architecture depicts the architecture of the system components.

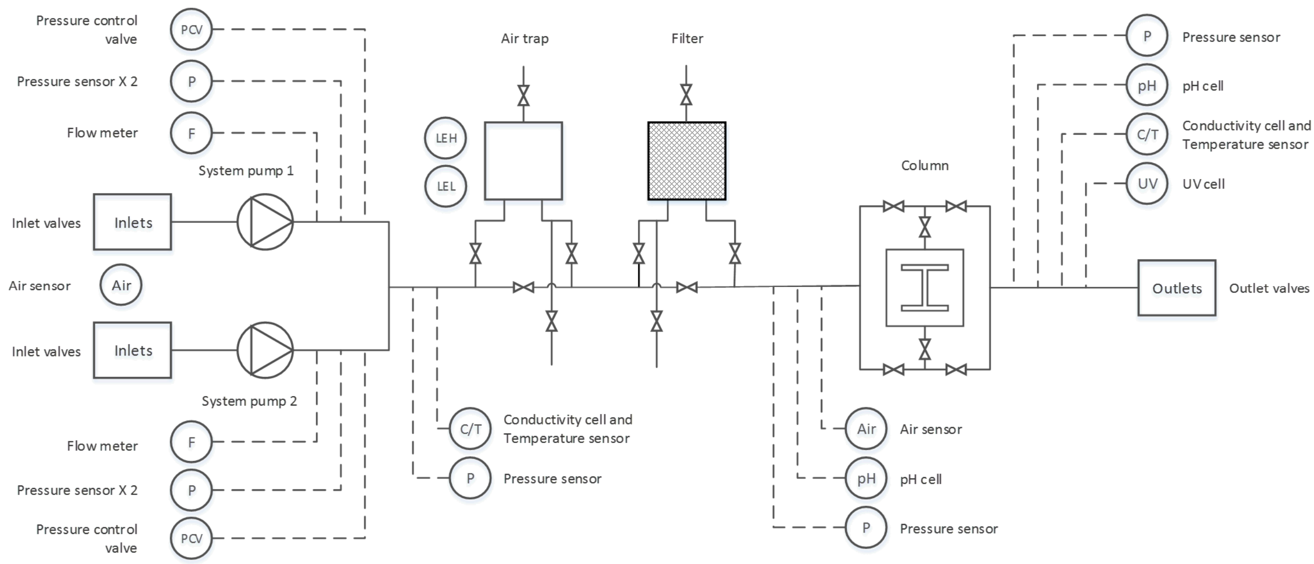

Figure 1 – System architecture

The control system is a distributed system that utilizes an architecture based on ISA-88.01 Batch Standard supporting the FDA's 21 CFR Part 11 requirements.

2.1 Physical model

A physical model can be used to describe the physical assets of an enterprise in terms of enterprises, sites, areas, process cells, units, equipment modules, and control modules enabling setup and runs of automated processes or batches as visualized in Figure 2 – Physical model.

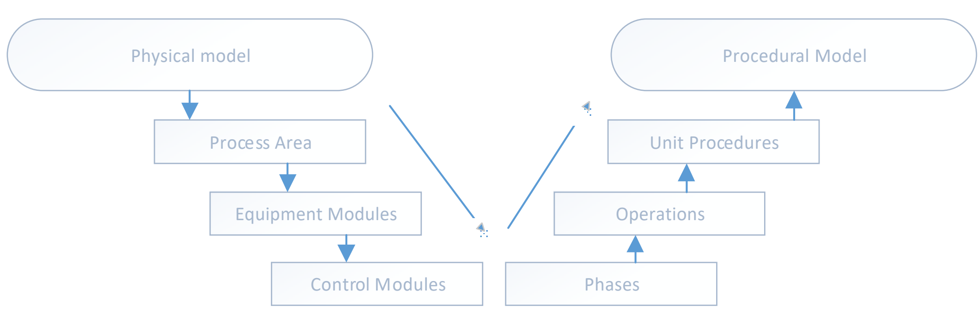

Figure 2 – Physical model

2.1.1 Area

An area is a physical, geographical, or logical grouping determined by the site. It may contain process cells, units, equipment modules, and control modules.

2.1.2 Process cell

A process cell is a logical grouping of unit modules, equipment modules and control modules required for production of a batch.

2.1.3 Unit module

A unit module defines a set of control modules and equipment modules grouped together to perform a specific task such as liquid chromatography.

2.1.4 Equipment module

An equipment module coordinates a group of control modules that work together to perform a specific function and where the associated control modules receive input from the same parameter.

2.1.5 Control module

A control module reflects the characteristics of one physical device with related control logic. This could for example be a valve or a control loop.

2.2 Procedural control

Procedural control is a characteristic of batch processes. It is the control that enables equipment to perform a batch process. Procedural control is made up of procedural elements that are combined in a hierarchical manner to accomplish the task of a complete process as defined by the process model. The hierarchy of identified and named procedural elements is illustrated in Figure 4 and consists of procedures, unit procedures, operations, and phases.

2.2.1 Procedure

A procedure is the highest level in the hierarchy and defines the strategy for carrying out a major processing action such as making a batch. It is defined in terms of an ordered set of unit procedures.

2.2.2 Unit procedure

A unit procedure consists of an ordered set of operations that causes a contiguous production sequence to take place within a unit. Only one operation is presumed to be active in a unit at any time. An operation is carried to completion in a single unit. However, multiple unit procedures of one procedure may run concurrently, each in different units.

2.2.3 Operation

An operation is an ordered set of phases that defines a major processing sequence that takes the material being processed from one state to another, usually involving a chemical or physical change. It is often desirable to locate operation boundaries at points in the procedure where normal processing can safely be suspended.

2.2.4 Phase

The smallest element of procedural control that can accomplish a process-oriented task is a phase. A phase may be subdivided into smaller parts. A phase can issue one or more commands or cause one or more actions.

3 Software

The software is configured with inputs from the design documents GS, FS, UDS, IOL and P&ID as well as the CBS library to build up the functionality.

3.1 Library

The following software library is used for development and control of the system:

- CBS library based on PCSD standard library from Emerson Process Management for DeltaV.

When the CBS library does not fulfill customer requirements, modifications are performed. All items in the Cytiva database are prefixed with CBS_ to enable a later merge with customer database. The configuration of the system devices is grouped together according to Chapter 2 and is visualized in the physical model in Figure 3 – Control system structure.

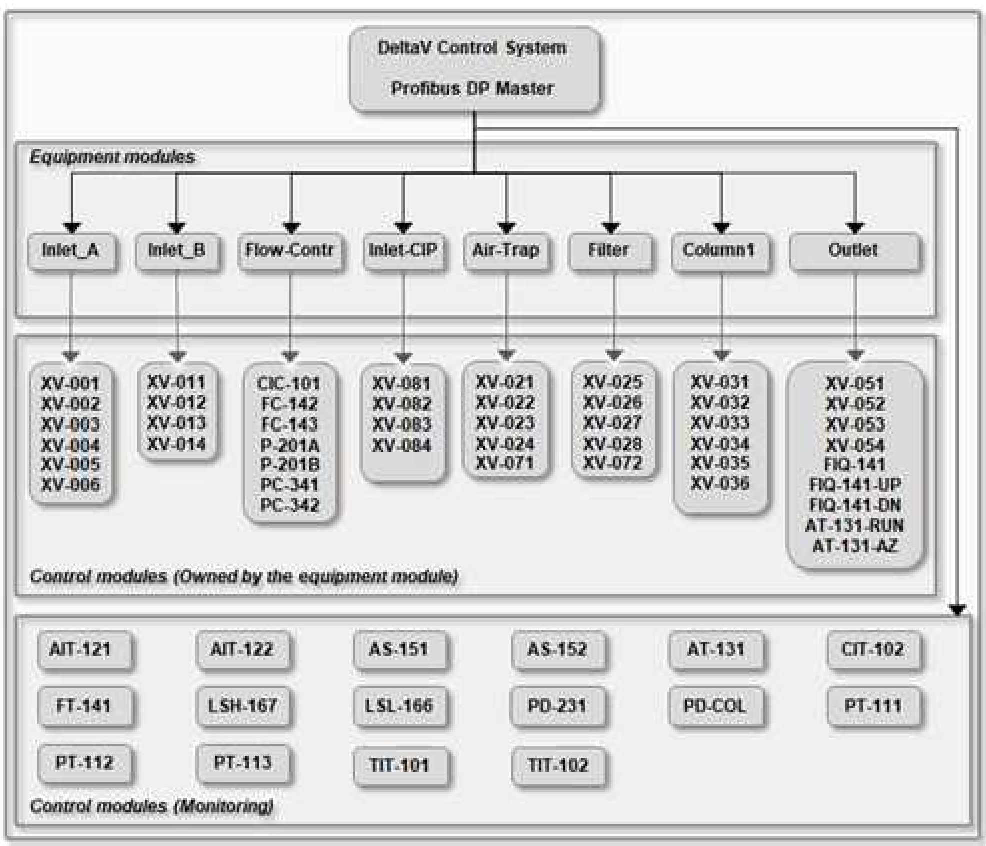

Figure 3 – Control system structure

3.2 User management

The control system supports options for setting different types of security levels, to restrict access to authorized users. It is the customer's responsibility to configure the system access settings.

3.3 Data acquisition

The control system supports the collection of history data. Based on customer licensing of the DeltaV the following historical databases can be enabled:

- Continuous Historian
- Event Chronicle
- Batch Historian

3.3.1 Continuous historian

The Continuous historian is collecting all process data, like transmitter values, set points, modes etc. as defined on each module for history collection. Any parameter defined for history collection on modules will be collected. System parameters, like controller loading, can also be collected.

Each parameter set up for history collection has their own properties, like sampling period, data compression, and maximum time between each sampling.

This information is defined in the control module class documents.

3.3.2 Event chronicle

The Event chronicle collects alarm and event data like user requests (open/close, start/stop, enable disable, etc.) and process-, system- and hardware alarms.

3.3.3 Batch historian

The Batch historian receives batch events generated by Batch Executive (BEX), and campaign related events generated by Campaign manager. Batch historian can also receive process-related alarms and events, including operator changes, system messages, and user-defined events, from the Event chronicle. The Batch historian copies this data into the main database so that process data can be included in batch reports and queries.

BEX creates an event file at run time for each batch. This journal will collect all events like start/stop of batch modules and phases, parameter values used, operator prompt answers, etc. This information can be read by the operator from Batch operator interface (BOI). When the batch is removed from BOI, BEX archives these events to the Batch historian.

3.3.4 Electronic records/Electronic signatures

The system has the capacity to issue each individual user with a unique username. This is used with a password to log on to the system. An extensive audit trail is also required to be maintained, which records the date and time of each operator’s actions, and traceability for file creation and modification.

3.4 Audit trail

The system has functionality to support audit trails. The Audit trail is configurable, examples of content are: user login/logout and process events. It is also possible to add Configuration audit trail that tracks configuration changes and stores the different configuration revisions/versions.

3.5 Graphic display

The operator GUI is designed in accordance with HCD (Human Centered Design) philosophy. All process pictures and faceplates are based on standard templates from the CBS library that can be modified to meet customer requirements.

3.5.1 Main display

The GUI main display is using object-based architecture that is grouped after equipment groups according to the P&ID [Ref ID 4] to provide an overview of the system. An object dynamo is used for all major mechanical components and instrumentation.

3.5.2 Faceplates

Each device has its own dedicated faceplate which is a pop-up picture that contains the graphics and control associated with the control module. The appearance differs depending on the type of module.

3.5.3 Detail display

A detail display is another pop-up picture that shows more module details such as tuning constants or alarm configuration associated with a control module.

3.5.4 Alarm banner window

In the alarm banner the operator is notified of the highest priority alarms that have been activated. The list is sorted dependent on if the alarm is unacknowledged or acknowledged.

3.5.5 Alarm list picture

The alarm list picture displays the active alarms for selected areas. From this display active alarms can be viewed or acknowledged either individually or as a group. Different colors are used to indicate an alarm’s priority.

3.5.6 Live data

Presentation of user-specified parameter field values is supported using process history view.

3.5.7 Historical data

Historical data are provided using Continuous historian which monitors selected parameters for the modules included for the selected area.

4 Functionality

This section is divided into one part describing the functions related to the process of a chromatography system and a second part describing system functionality.

4.1 Unit phase functionality

The Unit process functionality is separated into sections describing each function. Detailed functionality regarding Phases are documented in the UDS [Ref ID 9].

4.2 Process functionality

The process functionality is separated into sections describing each function.

4.2.1 System indication

Other than the GUI indications, the cabinet has green, yellow and red lights indicating the status of the system such as ready, hold and alarm. There is also an integrated audible buzzer sound that is activated when an alarm is triggered.

4.2.2 Inlets

The system consists of one or several inlet valve groups, called Inlet A and Inlet B. This is where liquids enter the system. Valves on each inlet are used to set which inlet is open or closed. Only one valve per inlet may be open at the same time, and they change in an Open First Then Close manner.

4.2.3 Pumps

The system is configured with two pumps with frequency-controlled speed in order to make it possible to run the system in gradient mode.

4.2.4 Pressure control valves

To avoid unintended flow through the system, pressure control valves are available as an option located post inlets to handle liquid received from elevated or pressurized tanks.

4.2.5 Flow control

System flow can be controlled by setting the pump speeds manually or by flow feedback from flow meters post pump A and pre column. The pump B flow is calculated as the difference between the two flow readings.

4.2.6 Gradient

The system pumps can be used simultaneously to produce customized mixtures known as gradient.

It is possible to run a manual gradient without feedback.

It is possible to run a conductivity gradient with control based on feedback from a conductivity meter placed after convergence of the flow path past pumps.

It is possible to run a flow gradient with control based on flow feedback.

4.2.7 Air trap

An air trap is located post pump(s). The purpose of the air trap is to make sure that no air enters the column. The liquid is circulated inside a cylinder and excess air is ventilated via a top valve.

The air trap valve block configuration enables selection of different predefined modes, i.e. whether the liquid should bypass or travel through the air trap.

To maintain a correct liquid level inside the air trap, level sensors are used. These automatically detects if an adjustment of the liquid level is needed.

4.2.8 Air detection

Two discrete air sensors are available to detect the presence of air in the liquid. One is mounted pre column and one is placeable before any Inlet A or B.

4.2.9 Filter

The purpose of this part of the system is to remove impurities before the solution enters the column. Filter supports several flow path settings.

4.2.10 Column

The part of the system denoted as column is a valve block configuration where a column is connected. The liquid may travel either from the top of the column to the bottom (known as downflow) or bottom to top (known as upflow). The valve block can also be set to completely bypass the connected column.

4.2.11 Mixture analysis

Post column, analytical instruments are located to monitor the chromatographic process. UV is used for fractionation commands and conductivity records process values for process validation.

4.2.12 Totalizer

The system is prepared with a software function that can be configured to calculate the accumulated volume pre column. Three settings are available; Column up-flow, Column down-flow and Column bypass and the totalizer function has commands for start, stop and reset.

4.2.13 Outlet

An outlet is the exit point for liquid from the system. A valve on each outlet is used to control which outlet is open or closed. Only one outlet valve is open at the same time, and outlets change in an Open First Then Close manner.

4.2.14 Process safety

Pressure sensors are continuously monitoring the system. They are located on various spots to make sure that the pressure is within safe limits. For example, one pressure sensor is placed directly pre column to monitor the column pressure. The system also has temperature sensors to monitor system and process temperature post pumps and post column.

4.2.15 Air supply

A connection for compressed air is available on the system for the distribution of air to the valves.

4.2.16 Alarms

The system differentiates between several alarm states and could either be of discrete- or analog type. These are categorized as CRITICAL, WARNING and ADVISORY alarms. An alarm text is displayed with information that will help the operator to locate the error. In addition, these are the categorized for logging purposes PROMPT, ALERT and LOG, to call for operator prompt awareness and creating status lists for active bypasses.

4.2.17 Calibration

The system handles calibration of the following devices from HMI interface.

- Air/Level sensor
- ASi Valves

4.2.18 Communication errors

All transmitters will indicate if communication is lost.

4.2.19 Device errors

All discrete valves and pumps indicate if they are electrical disconnected.

4.2.20 Enable/Disable

Alarms & Warning can be Enabled/Disabled and are default disabled at startup. The Init Phase controls the Enable/Disable at startup then later set by process Phases.

4.2.21 Permissive

A permissive is the lowest level of safety and is designed to protect against unwanted operator actions that may harm the system.

4.2.22 Interlocks

The system interlocks are designed to protect the system (from exceeding its design criteria), environment, safety and the product.

Process interlocks:

A process interlock is designed to bring the system into a safe state if one of the process defined interlocks are violated.

Hardware interlocks:

There is a pump hard wire interlock for Emergency stop, system high pressure will shut down the pumps. Violation of a hardware interlock will in turn initiate the DCS to shut down the skid in a controlled manner.

4.2.23 Uninterruptable Power Supply

The system is prepared for an uninterruptable power supply connection fed from customer UPS source.

4.2.24 Valve initiation states

The initial positions of valves will be positioned after the Initial Phase specified in the Unit Design Specification is started.

5 Communication

PROFIBUS and UniNet-1 network technologies are used to send and receive data between devices. The interface to the controller is only PROFIBUS DP. All network devices are monitored and if a device fails an error will be triggered.

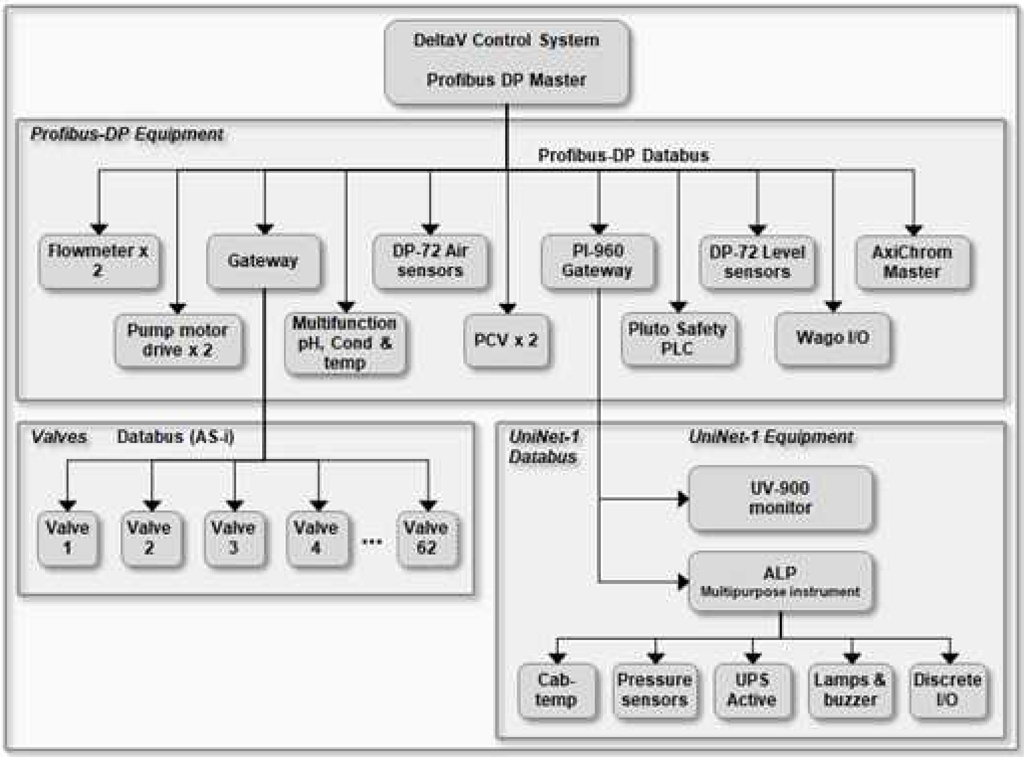

Figure 4 – Typical picture over system network.

5.1 PROFIBUS DP

Main Interface between customers DCS and system. Master network is using PROFIBUS DP.

5.2 CAN UniNet-1

GE proprietary communication bus over CAN to connect with GE instruments. The device PI-960 works as an interface to the ALP and pH/C transmitters, see Section 6.5.

5.3 ASi-interface

Gateway, converting from PROFIBUS DP to ASi for valve communication. Each valve has an Open/Close command, Opened/Closed indication and can be calibrated.

ASI power supply monitoring: ASI PS Failure alarm given in case of failure.

5.4 Redundancy

Primary and secondary ethernet ports on DeltaV PK controller are used to provide network redundancy.

6 Hardware

This section describes the different hardware devices used within the system. For a full device description, see the corresponding instrument manual supplied by the manufacturer.

6.1 Frequency converter

Frequency converter with PROFIBUS DP interface for pump communication. The motor drive is monitoring the health of driver and pump. The built-in protection and settings for the converter is set locally and can be monitored through local panel.

6.2 Flow transmitter

Flow transmitter with PROFIBUS DP interface. The flow is monitored and zero adjustment can be done from GUI.

6.3 DP-72 level sensors

Level Sensors that can indicate High/Low level of Air Trap. Level Sensors handles the air trap level sensor calibration. Calibration are done from an HMI faceplate. Air trap must be calibrated drained (no liquid) and filled. The faceplate shall indicate when the calibration is on-going and inform the operator if the calibration failed.

6.4 DP-72 air sensors

Air sensors that can indicate Wet/Dry. Air sensors are placed pre-column and moveable on any inlet. Calibrations are done from an HMI faceplate. Sensors must be calibrated drained (no liquid) and filled. The faceplate shall indicate when the calibration is on-going and inform the operator if the calibration failed.

6.5 PI-960

The PI-960 is a gateway used as a PROFIBUS interface to selected GE instruments on UniNet.

This module is monitoring the PI-960 in and out data communication and diagnostics for the following instruments:

- pH/C-902
- UV-900
- ALP-900

Communication error / failure generates alarm with alarm message identifying the source of error. After an instrument error has occurred each instrument needs to be restarted.

6.6 AxiChrom Master Interface

The AxiChrom Master is a self-contained operator console featuring interactive guides (wizards) for work procedures such as packing, unpacking and maintenance. The AxiChrom Master can be connected to a Bioprocess system, which enables the column to be controlled by the DeltaV software through AxiChrom Master Interface. Intelligent packing ensures optimally packed beds and decrease dependence on the operator.

DeltaV system will also enable online monitoring of packing progress,

6.7 Pluto Safety PLC

The system is equipped with an autonomous safety PLC with PROFIBUS DP interface, which in case of any issue related to personal safety will initiate a shutdown of the pump motors. The safety PLC is designed to de-energize all its outputs at failure or power loss.

The safety PLC is connected to:

- Two-channel emergency stop buttons
- Redundant pressure transmitters; placed after each pump
- A blue reset button; lit when there is a safety issue, blinking at power on or when a failure has been corrected, and unlit when everything is ok. It must be reset manually.

The safety PLC gateway makes the error information available on PROFIBUS.

6.8 ALP-900 transmitter

The ALP-900 is a multi-purpose monitor to measure and supervise pressure and temperatures in BioProcess modular systems. The ALP-900 is also controlling the cabinet lamps, ASi-gateway power supply failures, the buzzer and sending the remote alarm output.

The ALP-900 can be connected to the pumps and handle the high-pressure safety function by stopping/disabling the pumps. In this project none of these functions will be used. The connected pressure transmitters will be used for pressure monitoring only as the safety is handled by the Pluto Safety PLC.

The ALP-900 also monitors temperature in the electrical cabinet. This temperature is registered by a sensor that is located inside the ALP-900 unit.

- The Air module can monitor signals from two air sensors.
- The Pressure module is used to monitor signals from three pressure sensors: pre air trap, pre column and post column.

6.8.1 ALP Error

The ALP is monitor and storing the 20 latest instrument error codes for this instrument. instrument errors is be available through a faceplate. ALP Error alarm shall be given in case of any instrument error(s). Alarm acknowledgement is to be done from faceplate.

6.9 UV-900 transmitter

Monitor UV-900 is a multi-wavelength UV-Vis monitor that uses fiber optic technology to monitor with high sensitivity at up to three wavelengths simultaneously in the wavelength range 190 to 700 nm.

Three detection channels allow simultaneous measurements of differently absorbing compounds and purity checking.

6.9.1 Auto zero

It is possible to zero the UV signal "UV auto zero". It is possible to activate this signal manually through an operator dialog or from a phase in the operation.

6.9.2 UV lamp

It is possible to turn the UV lamp on and off. It is possible to do this manually through an operator dialog or from a phase in the operation.

6.9.3 UV Error

The UV error monitors and stores the 20 latest instrument error codes for this instrument. Instrument errors are available through a faceplate. ALP error alarm shall be given in case of any instrument error(s). Alarm acknowledgement is to be done from the faceplate.

6.10 pH/C-902 transmitter

The pH/C-902 Monitor is a high precision on-line monitor for measurement of pH and conductivity in high performance liquid chromatography applications. The monitor is suitable for pH and conductivity measurements in pharmaceutical applications where monitoring of running conditions is critical. The pH/C-902 Monitor is a combined monitor with two independent measuring channels for both pH and conductivity.

This module can also be written to by any other module to display relevant operator information.

6.10.1 Temperature measurement

Temperature signal is supplied by the pH/C-902 module, from the temperature sensor in the conductivity cell CE-101. This temperature reading is used for pressure surveillance and to ensure that the liquid temperature does not exceed 80°C.

6.10.2 pH/C-902 error

The pH/C-902 is monitor and storing the 20 latest instrument error codes for this instrument.

6.11 WAGO I/O module

The Wago 750-425 I/O coupler is used to read pump leak detection inputs from P-201A and P-201B then reports to DeltaV via PROFIBUS.

7 Documentation

7.1 Document structure

The documentation package delivered by Cytiva follows a V-model with both descriptive documents and specification documents. A descriptive document of this type provides a deeper understanding of the system as well as general system functionality. Specification documents such as the GS, FS, UDS, EQDS and SMS have a corresponding test record to verify the design/functionality, see Figure 5 – A representation over the document workflow.

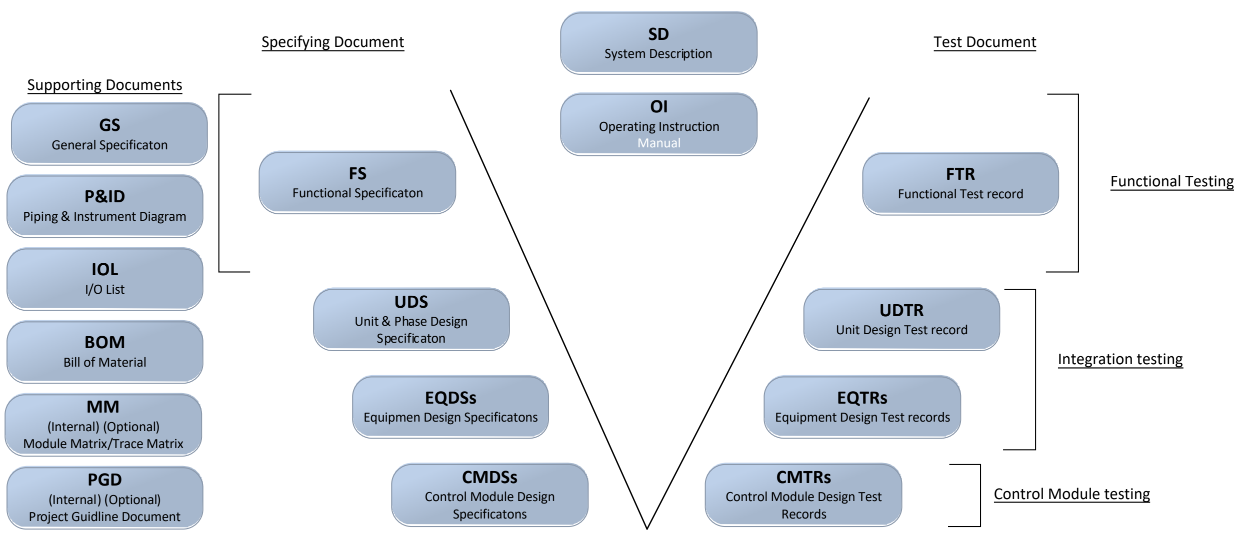

Figure 5 – A representation over the document workflow

- General specification: Outlines main product parameters, technical data, system requirements, system acceptance ranges and codes and standards fulfilled by the system.
- Functional Specification: Defines the functionality that the system provides.
- Unit Design Specification: Specifies the unit design and phases. The defined phase parameters are inputs parameters for constructing Operations. Instances of the equipment modules and control modules are also included.
- Equipment Module Design Specification: Specifies the design of Equipment modules' base template and structure. Instancing and tagging for the unique project will be documented in the UDS.
- Software Module Specification: Specifies the Control modules' design and functionality.
- Project Guideline Document: Contains internal guidelines for DeltaV software development. It is available on request by customer.
- Module Matrix: Presents a traceability matrix from a module's point of view. Requirements and validation of the control modules are mapped to corresponding documentation.

- Cytiva delivers a full setup of the skid configuration developed for customer unique system. The Database Merge Procedure, DMP, [Ref ID 8] describes the revision of the actual configuration package.

The working procedure for a delivery begins from document templates which will be modified according to project specific requirements.

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