Integrated Automation of Filling Line for Parenteral Products

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ABSTRACT
Integration of batch process and pharmaceutical production equipment (OEM) towards MES and Business System in a sterile manufacturing

About 40 Filling, Inspection and Packaging machines from 20 different suppliers and a formulation batch process have to be controlled from a central control room with a limited amount of operators in such a way that the operator interface is similar for every machine.

Data communication from and to the equipment PLC’s over SCADA and MES towards Business System in order to have electronic tickets with data storage.

An identical hard and software platform for each control unit creates a structural and uniform communication platform between different equipment.

SCADA gives the operator a HMI with the same look and feel. MES offers the operator an interactive production ticket.

Use of client server technology in order to have the same information on different places. Use of a common data base as storage and communication medium.

Results and Conclusions:
- Identical PLC-SCADA interface
- Similar HMI for batch processes and machinery
- Reduce PLC code complexity
- Reduce validation time
- Easy recipe building

INTRODUCTION

Pharmacia & Upjohn stands among the top-tier pharmaceutical companies and produces sterile and non-sterile products and active pharmaceutical ingredients. The Company employs worldwide around 30 000 people. The Puurs plant in Belgium – Europe, is a strategic pharmaceutical plant for sterile manufacturing with a current annual production of 200 Mio units. The plant employs around 1 000 people.

According to the Company’s new strategy to create highly efficient plants, fully compliant with the recent technology developments in the pharmaceutical industry, a new plant has been erected. It produces one vial size for sterile injectable products with high volume output.

In comparison with the existing facility, this plant had to produce from start to finish without any intermediate storage. This makes it one of the first plants where sterile products will be produced in a fully automatic mode, starting from active pharmaceutical ingredients to finished goods ready for distribution.

The major targets for the project were defined as follows:
- Increase production capacity with 50 million of vials/year by continuous operations, 24 hours/day and 7 days a week with 6 operators in each shift.
- Increase the production quality by applying isolator technology with fully automated VHP sterilization, clean in place systems and NIRA (near infrared analyses) for content uniformity verification.
- Include process and computer validation.
- Reduce manufacturing cost and production lead-time by in-line production. All machines to be supervised and controlled from a central Control Room.
- Increase flexibility by implementing a high degree of automation: electronic tickets, AGV (automatic guided vehicles) and robots for material handling.

The full sterile production line is composed out of different sub units: formulation, filling, inspection and packaging. The different machines are supplied with pharmaceutical and industrial utilities and the goods are brought to and carried away from the line by automated material handling systems. The complete line consists out of more than 40 machines from different vendors and a formulation area of 8 units. Around 40 monitors (pc’s) control and supervise the totally integrated line.
The 3 level design is based on following principles:

**Upper level** with weighing systems, formulation and stopper sterilization unit. The formulation with the clean in place installation produces different batches according to their proper recipes. The sterilized stoppers and the solutions or suspensions are fed into the filling machines.

**Intermittent level** with units for washing and dry heat sterilization before filling. Once the filling and weight control is accomplished and the filled vials are stoppered and capped, they are inspected in several inspection machines.

**Ground floor level** with packaging operations were the vials are labeled and put in cartons together with their proper inserts. Afterwards the cartons are shrinked in cellophane, put in hardboard cartons and palletized.

The materials and goods are brought to the line and carried away by automatic guided vehicles (AGV) and robots.

Clean steam and WFI installations supply the different machines with their pharmaceutical utilities. The technical area for HVAC is situated on a fourth level.

Consequently, a high amount of automation is needed to reduce manual operations.

With fewer people to operate the same amount of machines, uniform operating panels help to make the equipment easier to operate and to avoid errors.

To assure electronic batch records a higher degree of automation is needed to make the step into paperless manufacturing.

Compared to a conventional line we had to design for larger electrical cabinets, industrial PC’s hanging on the ceiling instead of the usual operator panels and electronic SOP instead of instructions on paper.

The challenge of the project was driven by the fact we had to deal with a hybrid process that has both batch (formulation) and discrete and continuous elements (machinery) in the manufacturing process. The batch standard S88 helped us in the design methodology of the process.

For the equipment / machinery the S88 physical model can be seen as:

- Enterprise: PNU
- Site: Puurs Plant Belgium
- Area: FC1 installation
- Process Cell: Filling and Inspection, Packaging, Utilities
- Unit: Filling machine, Isolator, Capper, Washing machine, Sterilization tunnel
- Equipment module: Machine constructors’ responsibility
- Control module: Machine constructors’ responsibility

Here MES determines the different recipes by controlling the production flow through the different machines / units.
For the formulation the S88 physical model can be seen as:

- Enterprise: PNU
- Site: Puurs Plant Belgium
- Area: FC1 installation
- Process Cell: Formulation
- Unit: Solution tank, Holding tank, Suspension tank, Filter testing unit
- Equipment module or automation function: Agitating-, Heating-, Cooling-, Circulating- equipment.
- Control module or object: Pump-, Valve- assembly.

Here a batch engine controls the different recipes.

Our major question was: “How to design and engineer a hybrid plant like this, dealing with more than 20 different machine constructors and suppliers?”
- Our basic option was to control all the machines by PLC’s of the same type, which gives us the opportunity to standardize communication and protocols.
- A SCADA system was selected to supervise the different machines and to control the workflow whereby we excluded, in close cooperation with the different vendors, the local operator panels
- MES (Manufacturing Executing System) has to guide the operators in their actions to be performed and to log the different steps taken.
- Connections to other systems, like the Business System must be possible.

In MES each machine is seen as a unit controlled, by an Intelligent Form, say a unit procedure:
- MES launches the recipes, organizes the batch / lot sequence, gives an overview of the different product lots and offers traceability.
- Formulation is seen from MES point of view as one big unit where the batch engine organizes the different (sub)units.

More in detail the functionality on MES can be defined as follows:
- controls the process flow.
- provides the operator with an interactive ticket.
- manages the electronic batch record, which means:
  - management of pharmaceutical parameters to be downloaded to the equipment.
  - data logging of production runs.
- supports the manufacturing process with order scheduling and material handling and requisition.

All MES PC’s are connected to the industrial LAN.
MES can not be seen as a real time system.
SCADA visualizes the machines with their equipment and control modules:
- gives an overview of the line, each machine and the process.
- determines the HMI (human machine interface) for all the machines and gives the opportunity to adjust the process within one batch /lot.
- can be seen as a real time system.

SCADA is set up as a client server system where:
- SINEC H1 (TCP/IP) connects all the PLC’s (50).
- Industrial LAN (TCP/IP) connects all the SCADA Clients (35) to the SCADA Servers (4).

Logical the project is organized in 4 projects where each project has a server and several clients. In that way there’s a server for each process cell: one for formulation, filling and inspection, packaging and utilities.
Each server has a client in the Production Control Room from where everything can be operated and supervised in the same way as in the field.

A machine can be visualized on all clients within one server configuration:
- each picture gives a detailed view of the machine showing whether the machine is running or not, alarms are present, parameters like set points being used and indications of measuring devices.
- different SCADA pictures have the same look and feel on all the machines, including the pictures of the formulation. This means e.g. that the way of starting or stopping a machine, reset of alarms or the adaptations of parameters on each machine can be executed in an identical way.
- the upper part of the screen visualizes the different machines in one server configuration or process cell. Here you have the possibility to switch over from one picture (machine) to another and to overview all alarms in that process cell.
- colored pictures (green, red, purple, …) are giving you an indication of the machine and alarm situation. Green e.g. means running perfect, red is a technical alarm that stops the machine and purple is a pharmaceutical alarm.
- a status window shows the batch / lot number, mode and phase the machine is working with.
- at the bottom of the screen, using command buttons, machines can be started and stopped, alarms can be reset. Other control functions as pop up of alarm loggers and indications of measurements can be shown.
In this way the different machines and installations are keyboard driven, which means there are no recorders, no push buttons and no indicators.

Each Process Cell is visualized in a picture in order to overview process and alarm situations, together with batch / lot numbers that are running at that moment.
In the overview of the complete line, driven by exceptions and not by actions, the operators are told where to interfere when something is going wrong.
Measurements and controllers have a faceplate where parameters like set points, limits and controller settings can be viewed and adapted for trouble shooting. There’s a general alarm logger and a pharmaceutical alarm logger where you see pharmaceutical alarms only. The alarm text in the alarm logger has the same color as the color in the pictures of the proper machine.

SCADA is used as the communication tool between MES and equipment PLC’s by means of tables in the Common Database. It performs the up- and download from MES and SCADA to the machines. On the parameter screens you find both the original or downloaded parameters and the actual parameters. When parameters are changed after they are downloaded, it’s indicated by an orange field and exported to MES for additional comments.

To fulfill all these objectives, major efforts were needed on organization and communication between the different machine suppliers, engineering and software companies. An identical HMI philosophy, has been written and installed in each PLC in order to have common protocols and functions for each machine. Documents like P&Id’s, alarm lists, data up- and download lists, command, recorder and display functions had to be discussed thoroughly. Each separate machine-interlock had to be verified regarding the common HMI.

The following strategic decisions guided us to our software selection:
- Since the machines were supplied by different constructors from different European country’s, the equipment had to be controlled by one brand and type of PLC, with an important market share in Europe, a standard for the future.
- The SCADA system, developed in 32-bit application, must have perfect connection possibilities to the selected PLC type.
- The selected DCS system for the formulation should have good integration and connectivity possibilities towards both PLC and SCADA.
- The engineering company to realize the project, needed to have former experience in pharmaceutical industry and computer validation.

A conventional production line has for each machine a typical and own HMI with own operator panel. The new line has a common HMI and communication layer in each machine that makes it possible to have for all the connected machines an identical HMI.

Given that this production line has more than 10 000 alarms and data items, it is impossible to consider every item. We therefore need to categorize alarms and data types, modes, phases and states.
Alarms are categorized in messages, starting conditions, operator alarms and defects. Each of them has some sub categories. For the defects the most important are the pharma alarms since they influence the pharmaceutical quality of the product. The requirements for pharma alarms were defined as follows:
- to be reset one by one,
- to change the quality state of a unit,
- to create a deviation report for explanation.

For data we defined 6 main categories: parameters to be downloaded one data generated during production:

- Shop order related data is typical for a certain batch or lot. They are managed by MES e.g. operator name, date and equipment selection and by the Management System for the item description and number.
- Pharmaceutical parameters, managed by MES cannot be changed in the SCADA screens. These parameters contain all the pharmaceutical limits.
- Critical parameters are parameters controlled by SCADA but only adjustable with a proper password. These parameters are setpoints for good functionality of the equipment.
- Technical parameters can be changed by every operator and are not critical for the good functionality of the machines. Examples of these are speed of conveyer belts and hoppers.
- Machine restrictions are parameters fixed in the PLC program to protect the machine from damage and are the responsibility of the machine constructor.

- In process data is produced during a batch or lot cycle. We deal with two types: discrete data as there is quantities of good and rejected products and bulk data as graphs of pressure and temperature that witnesses the process.

Those parameters can only be downloaded if the proper machine has a quality state and an availability state that are both OK:
- The quality state indicates the pharmaceutical condition of a unit.
- The availability state indicates if the machine is mechanically ready to receive a download.

During production, alarms and data are generated and sent to MES. When the batch is finished we have the opportunity to save the adjusted SCADA parameters if it is relevant.

A mode, defined as a certain way to produce on a machine, is initiated by MES, which means that the sequence of different modes within a recipe is a MES responsibility. Phases are defined as steps within a mode. The sequence of the different phases within a mode is the responsibility of SCADA / PLC. For the different machines it means it’s the responsibility of the machine vendor.
Due to the high complexity of the project, the most difficult parts to manage can be summarized as follows:
- Coordination between different teams and constructors in the different country’s.
- Difference in automation knowledge for everyone involved in the project, certainly at the beginning of the project.
- Managing the enormous amount of details as there are alarms, interlocks, data items, commands.
- Combination of automation skills, IT and process knowledge.