



Parenteral Filling Facility

Automation Case Study

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ABSTRACT

This case study will address aspects of MES, Recipe Management, Batch Control, and Data Management in a new aseptic filling facility and illustrate how a unified system approach can lead to a semi-paperless production record.

The case study will look at how the automation system communicates with the ERP system (SAP) to receive production order and material data for use in the “batch” production process all the way from the component preparation areas to formulation and finally to the final filling process. Specifically we will look at how the ERP data “drives” the process and allows components and materials to be tracked throughout the production process using system generated barcodes and mobile computers wirelessly connected to the automation system. We will examine what the term “batch” really means for the various operational areas of the plant and how an automation system can be designed in a rigid, yet flexible manner to facilitate operations.



**Carolina-South
Atlantic Chapter**



**Tarheel Capital Area
Section**

Recipe management means different things to different facilities. We will look at how recipes are managed not just for the batch as a whole, but for each of the individual operations that take place during the making of a product. We will look at the idea and results of using “recipes” for operations like CIP, SIP, integrity tests to allow for controlled, rapid reconfiguration of paths and ending conditions based on product or operation. We will talk about how over 100 recipes are managed and used for over 15 individual pieces of equipment such as fillers, isolators, and lyophilizers. Learn what it takes up front in the design process to allow a single system to interact and manage recipes on what used to be disconnected OEM systems.

By using a unified system approach, data from all parts of the facility including room conditions, environmental monitoring data, clean utilities, electronic log books, cleaning data, batch data, recipe data, historical process data, and ERP data is consolidated and available for use in electronic production reports. We will cover what it takes from the design and implementation perspective to produce and deliver record grade production reports.



Contents

KEY WORDS	1
ABSTRACT	1
1 Introduction	4
1.1 The Unified System Concept	4
1.2 Facility Description	4
1.3 System Description – From a numbers perspective	5
1.4 System Description – From a functional perspective.....	6
2 From Start to Finish.....	7
2.1 Component Prep.....	7
2.2 Compounding	8
2.3 Filling	9
2.4 Other Operations	10
3 Result.....	10

1 Introduction

This case study focuses on a recent installation of a unified automation system in a grass-root Parenteral Aseptic Filling Facility and how a unified system approach enables a single system to perform many of the tasks that used to be performed by separate systems.

Specifically, this paper provides approaches and methods used to address several major technical areas related to manufacturing in a batch production environment including recipe management, batch control, MES, data management and finally batch reporting.

1.1 The Unified System Concept

The unified system concept in terms of automation is one that implies that a theoretical single system is responsible for all aspects of automation in a facility. While this can never truly be the case because a single system is not capable, or in some cases not permitted (e.g. fire alarms, safety systems, etc), to perform all automation functions in a facility, the concept can successfully be applied if the span of control is limited to specific automation functions and areas of the facility. Furthermore, a unified system does not necessarily have to imply a single system, but may instead describe a collection of systems that are acting as one at some higher level, and at that level, all necessary information is available to adequately describe the state of the facility from an operational standpoint.

1.2 Facility Description

The facility in this case study consists of two production lines and supporting areas. Each production line consists of component preparation areas, compounding/formulation area, and a vial filling line. In addition to the production lines, a dedicated lab, inspection/packaging line, and warehousing area are located in the facility.

The component preparation areas consist of staging areas, autoclaves, and partwashers. The compounding area consists of portable compounding vessels, utility panels, scales, and compounding isolators. The filling line is made up of a vial washer, depyrogenation tunnel, vial filler, lyophilizer (for one line only), capper, exterior vial washer, and tray loader. The lab consists of an autoclave, partwasher, ovens, and environmental chambers. The packaging line consists of a cartoner, labeler, and inspection machine.

The facility also consists of the standard major utilities and space conditioning equipment including seven custom air handling units located in a modular penthouse, water pretreatment

system, WFI system, and clean steam system as well as other ancillary utility systems. All other utilities are provided by a separate central utilities building on the campus.

1.3 System Description – From a numbers perspective

The automation system for the facility is a programmable logic controller (PLC) and human machine interface (HMI) based system and consists of two tiers of automation and components. At the lowest tier (OEM tier) are OEM packaged units with dedicated automation systems consisting of dedicated PLC/HMI components. The highest tier (facility tier) consists of PLCs, HMIs, mobile computers, databases, wireless access points, and data historian that together span the remainder of the plant from an automation and visualization perspective. Both automation tiers are connected via a dedicated Ethernet automation network utilizing redundant ring technology. Further network segregation is accomplished by isolating the remote I/O network.

The OEM automation tier is described by the following attributes and characteristics:

- Over 40 PLCs/HMIs
- Various PLC/HMI manufacturers
- Over 30,000 points from the OEM system are part of the unified system
- OEM PLCs perform final control of equipment
- Unified system provides permission/interlock based control of OEM equipment
- OEM systems are access controlled via the upper tier system
- Recipe/cycle data is not stored locally at the OEM PLCs but rather at the unified system level
- Typical OEM equipment includes autoclaves, parts washers, isolators, WFI stills, clean steam generators, filling line equipment, packaging line equipment, waste treatment, etc

The facility automation tier is described by the following attributes and characteristics:

- Over 2000 I/O points
- Eight Programmable Automation Controllers (PAC):
 - 1 PAC dedicated to the lab area of the plant
 - 1 PAC dedicated to performing batch operations
 - 1 PAC dedicated to indirect impact utilities
 - 1 PAC dedicated to direct impact utilities
 - 1 PAC dedicated to indirect HVAC
 - 1 PAC dedicated to direct impact HVAC
 - 1 PAC dedicated to line 1 production equipment
 - 1 PAC dedicated to line 2 production equipment
- 15 thin client HMIs located in various areas of the plant
- 8 mobile HMI computers utilizing thin client technology (combination of tablet computers and ruggedized palm style computers with integral barcode scanner)

- Process and event data historian
- Five data servers (configured in a redundant setup)
- Two HMI terminal servers (configured in a redundant setup)

1.4 System Description – From a functional perspective

At the OEM tier are OEM packaged units with dedicated automation systems that perform control of their connected equipment. These systems are programmed by the OEM, and in this case, programmed with the intent that the equipment would be integrated into a facility system. As result, the OEM systems were specified with several key criteria in mind:

- OEM systems perform final device control of their connected equipment.
- Validated cycle/recipe data is transferred from the facility system to the OEM system when needed for execution.
- The facility system ensures that permissives are met prior to sending recipe data to the OEM systems.
- The facility system provides hard and soft stops to the OEM equipment based on information obtained from other areas of the facility (information outside the scope of the OEM systems)
- Batch information (batch number, product identifiers, etc) are transferred to the OEM systems.
- Access (login) to the OEM system is controlled by the facility domain controller

The facility system is configured to directly control all non-OEM equipment in the facility and to provide monitoring of all attached equipment, including OEM equipment. The facility system directly controls and provides visualization to the following systems:

- Air Handling Units (AHU)
- Room Monitoring (Temperature, Humidity, DP)
- Feedwater Storage and Distribution
- WFI Storage, Distribution, and Use Points
- Nitrogen Storage and Distribution
- Clean Steam Distribution and Sampling
- Chilled Water Distribution and Use Points
- Process Air Distribution
- Compounding Stations
- Particle Monitoring Stations
- CIP/SIP Operations
- Cold Room, Freezer, and Stability Chambers
- Filter Integrity Testing

- Paging/Messaging Systems

In addition to the above equipment control and monitoring, the facility system performs higher level functions as follows:

- Data transfer with SAP
- Electronic Log Books/Cleaning Logs
- Material Tracking and Reconciliation
- Overall Batch and Cycle Coordination
- Recipe and formula management
- Central Security
- Batch Reporting

2 From Start to Finish

Although it is possible to independently describe each major topic covered in the introduction, this case study will attempt to describe the process flow through the facility and to touch on where each topic comes into play and how it is used as a batch goes from start to finish on the production line.

2.1 Component Prep

Activities in the component prep area of the plant consist of preparing materials that will be used in the batch. Preparation includes running materials through parts washers and autoclaves prior to use in the batch.

As items are loaded into the parts washers and autoclaves, they are identified by scanning the barcode of the component (for fixed barcodes on hard-goods), scanning a system generated barcode of the bin or bag, or selecting items from a pick list that are to be loaded. As items are scanned in, quantities are associated with the scanned entry as well as the location and status of the items. The scanned data is entered in the materials database as it is processed.

Prior to running a cycle on the unit, the user selects a validated cycle and is instructed to load the unit per a displayed load diagram. Once a validated cycle is selected for the unit and the cycle is requested to run, all cycle/recipe parameters (times, temperatures, etc) for the selected cycle are downloaded from the facility system to the OEM PLC. Once the download is verified, the facility system verifies all permissives are met (e.g. utilities are available) and allows the cycle to be started locally at the unit. The facility system tracks the cycle from start to finish in order to establish both time and reporting boundaries of the cycle for later use.

When the cycle is completed, items are scanned as they are removed from the unit with updated status information indicating status and location information. A cycle report is generated at the end of the cycle containing critical process data, cycle parameters used, and alarms/events generated during the run.

Cycle runs in component prep are not initially associated with a batch in order to provide flexibility. However, all data and material processed (via the scan process) is associated with a cycle run. As material is used (scanned) later in the process, the material and hence the cycle is then associated with the batch.

2.2 Compounding

Prior to performing compounding operations, order data is transmitted from the SAP system to the facility system in XML format. Order data from SAP includes Process Order information, Bill of Materials, and material data specific to the batch that will be produced. The XML files are transmitted from a SAP to a drop off point and the facility system picks up the XML files and inserts the data via transformation into the facility system material database for use in the batch. When the SAP data is received, the operator may start a compounding procedure from the facility system HMI. As part of the automated procedural process, the operator is required to “check-in” material that has been staged in the compounding area resulting from the SAP order. The check-in process involves verifying that the required material (based on the SAP data) is present and matches the material specified in the material files. The verification process is accomplished by the operator scanning barcoded materials while the system verifies they are the correct materials for the batch. The system requires that all materials are present and correct prior to allowing the procedure to continue. The system also requires that room conditions, vessel status (CIP/SIP), isolator status (VHP), and utility availability criteria are met prior to starting the procedure.

The weigh and dispense process is guided by the facility system using BOM information. As material is dispensed, the facility system interfaces with scales in the area to record and verify weights of materials against targets. Material is scanned for confirmation prior to weighments. The facility system also makes adjustments to targets based on potency of the active ingredient eliminating manual calculations by the operator.

The remainder of the compounding process is controlled procedurally by the facility system included charges to the vessel, temperature control, mixing times, agitator speeds, etc. The procedural execution for compounding is a fixed procedure based on the product being produced.

At the end of the compounding process, material consumption (post reconciliation) data and status information is transmitted from the facility system to SAP.

Data generated during the compounding operation, including operator acknowledgments, confirmations, and comments are used to generate compounding reports. Reports include process data, material data, and alarm/event data.

2.3 Filling

Similar to compounding, prior to beginning filling procedure, the operator is required to “check-in” material that has been staged in the filling area resulting from the SAP order. The check-in process involves verifying that the required material (based on the SAP data) is present and matches the material specified in the material files. The verification process is accomplished again by the operator scanning barcoded materials while the system verifies they are the correct materials for the batch. The system requires that all materials are present and correct prior to allowing the procedure to continue. The system also requires that room conditions are met, cleaning operations (CIP/SIP) have been performed for fill line equipment, isolators have been VHP’d, and utility availability criteria are met prior to starting the procedure.

It should be noted that although cleaning operations such as CIP/SIP are not considered part of the batch procedure for filling or compounding, they are controlled and tracked by the facility system. At all times, the facility system maintains a status and time limit on the status for use as permissives to other operations.

When all general conditions have been met for the filling operation, the facility system interacts with each piece of equipment on the filling line in a similar fashion as in component prep. As the individual pieces of equipment (tunnel, filler, washers, etc) prepare to execute, cycle parameters are requested from the facility system. Once the cycle parameters are transferred, the individual OEM units are permitted to execute their respective tasks. During operation, the facility system acts as the data coordinator for all pieces of equipment on the filling line that need data from another piece of equipment, thereby allowing the facility system to issue holds and stops to the necessary pieces of equipment as conditions arise.

In reality, the procedural execution of the filling line components is much more complex than described above, but the intent is to illustrate the facility system is used as the cycle data repository and is acting as the master coordinator of all activities based on the procedural definition of the system.

At the end of the filling process, material consumption (post reconciliation) data and status information is transmitted from the facility system to SAP.

Data generated during the filling operation, including operator acknowledgments, confirmations, and comments are used to generate filling reports. Reports include process data, material data, and alarm/event data.

2.4 Other Operations

Illustrated above are considered the major procedural operations directly related to producing a batch. However, there are other applicable functions and operations that are not explicitly called out that are worth noting from an automation and data perspective:

- Pre and Post filter integrity tests are performed using a dedicated integrity test unit. The integrity test unit interacts directly with the facility system such a Pass/Fail status is obtained from the tester as well as pertinent test data that is included in a final report.
- The system provides an electronic cleaning log system that is utilized to track room cleaning status.
- The fill line Particle Measuring System (PMS) is controlled by the facility system and is integrated into the filling procedure. Flow calculations, particle counts, accumulated counts, and alarming functions are all directly controlled by the facility system and are used as permissives and interlocks to the filling procedure. The PMS data is also incorporated into the filling line reports.
- As mentioned, CIP/SIP are both controlled and monitored by the facility system and utilize the same recipe based method for parameter and cycle control.
- Although implied, the facility system continuously monitors room conditions and utility conditions that are then correlated to the batch for reporting purposes.

3 Result

One of the major initial goals for the facility was an automation system that could produce batch reports for the major parts of the entire process as opposed to trying to aggregate several different reports in different formats (and varying report definitions) from the various pieces of equipment and areas of the plant. It was understood from the start that in order to accomplish the goal, the automation system had to be integrated into every aspect of the facility, from SAP to scales to a capper. Although not every detail of the integration has been described in this paper, the intent is to illustrate that indeed, the system as a whole acts as unified system enabling consistent data aggregation for reporting purposes as well as material/lot tracking purposes.

So exactly what is the result? The system was designed with the concept of cycles (“operations”) and batches in mind from a reporting perspective. The facility system produces a report for each individual operation (e.g. compounding, filling, CIP/SIP, autoclave, washer, etc) that can act as a standalone cycle report as the production process progresses if needed. However, the system also provides the ability to automatically link and aggregate each cycle report into full report set representing the batch as a whole, which is accomplishes the goal of the facility.