Chromatography Skid 3 Automation Integration Layer Upgrade

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Abstract — *This research will focus on upgrading the Chromatography System 3 to reduce time and generate batch reports. In this way, system monitoring is more effective and documentation is more accurate. The system handles an excessive amount of equipment where each one is critical to the process and with the help of the upgrade the operator can be more effective with automation. The process should ensure the quality, safety, and efficiency of the manufactured chromatography system. Revalidation will be used as the only method since it is an upgrade of an existing and validated system.*

Key Terms *— Automation, Chromatography System, Installation Operation Performance Qualification (IOPQ), Validation.*

PROBLEM STATEMENT

Cost reduction, efficiency, and process improvement within biological and pharmaceuticals industries is a very well-known matter in question that business has been facing in today's day. Being competitive and environmentally friendly is a big challenge that manufacturing processes are required to succeed and grow. This research in analyzing and upgrading the **Chromatography System** is focused not only on the reduction of data printing time but also on the lower paper consumption. The validation process in this research is very important because it reduces costs by reducing rejects, reworks, and downtime. The chromatography process is a complex process where flow, pH, conductivity, temperature, among others, are monitored all the time. The system currently has an operator interface terminal, which will be upgraded to a control and data acquisition system. The new system will monitor the process and collect the necessary data (pressure, flow rate, UV, date/time, process steps and other data), date/time, process steps and other information) to generate the necessary reports (pressure, flow, UV, date/time, process steps and other information) to generate the necessary reports including data trends, audit trail and others.

Research Description

In the pharmaceutical industry, documentation management, equipment difficulties and process monitoring are time consuming. The process in the manufacturing area for chromatography is long and extensive. This research seeks the implementation of a SCADA system upgrade which will allow the In-Batch to be managed electronically and generate Real Time (RT) reports.

Research Objectives

The objective of this research is to find a way to mitigate the time-wasting factors in handling reports, data, system verification. With the upgrade of the new software, the manufacturing area can achieve better management of reports, documentation, and monitoring in less time and paper.

Research Contribution

This project contributes to maximum efficiency in the handling of documentation at the industrial level. In a company where one of its objectives is to provide quality products to its patients, it is essential to have an excellent Manufacturing and Quality Control Department. The contribution includes the upgrade of the Skid 3 chromatography systems and the integration to the Automation network. This capability will provide a Wonderware (System Platform) SCADA client along with Wonderware InBatch solution to

manage the Chromatography process using an S-88 Batch Management system. This modification will provide integration to OSI PI System to support batch data storage and electronic report to replace the paper batch record using OSI PI Rt Report. The company that this project will benefit from is a pharmaceutical industry with more than 6 different products used to treat various diseases. Their products treat conditions such as anemia, cancer, among others. With this Project.

- The Chromatography Skid # 3 operator interface terminal (OIT) will be upgraded to a Supervisory Control and Data Acquisition (SCADA) system.
- The SCADA systems will be connected to the Automation Integration Layer network. This capability will provide a Wonderware (System Platform) SCADA client along with Wonderware's InBatch solution to manage the Chromatography process using an S-88 Batch Management system.
- The system will be connected to the OSI PI System to support batch data storage.
- Rt Reports will be used to develop an electronic report to replace the paper.

The following are some of the advantages that the project will have Mitigate time loss: It will be possible to improve the workflow with manufacturing operators and quality experts. Cost reduction in using the same software, lowering the use of paper in the industry, and employee time in printing documentation.

RESEARCH BACKGROUND

For this project, it is necessary to dedicate time to literature research to understand its impact. This project will automate the Chromatography Manufacturing purification process. To achieve the objectives of this project, the SCADA system will be upgraded, and the Automation Integration Layer network will be integrated to the OSI PI system to generate electronic reports.

Chromatography System

This software will be implemented on manufacturing equipment in the purification area in the biopharmaceutical industry, for this reason, it is important that this software complies with the regulations of the pharmaceutical industry. The **Chromatography System** 3 consist of a Semi-purified product tank, pump, filter, liquid control panel, buffer solution supply, solution supply flow control valves, air traps, manual actuator valves, operator interface, pressure sensors, level sensor, flow sensor, pH sensor, conductivity sensor, temperature sensors and Chromatography Column. The system is also assisted by a UV analyzer and UV Inline sensor equipment used to detect product during the purification process. Chromatography System 3 is an anion exchange chromatography step. This column removes the ethanol used as the mobile phase reverse phase chromatography and concentrates the highly dilute product in the prepared buffer solution.

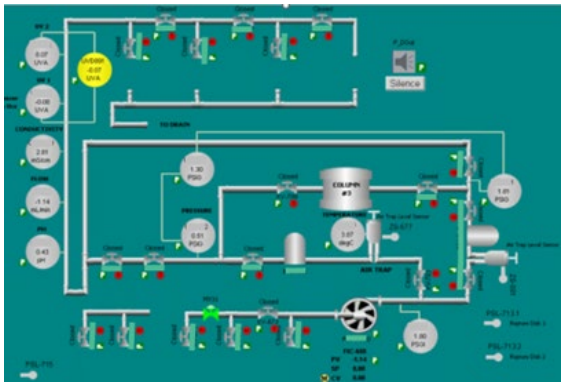

Figure 1
Chromatography System Skid #3

Process Description

The biopharmaceutical industry in which this project will be performed is regulated by the 21 CFR Part 11 code of federal regulations. In the US, the federal Food and Drug Administration (FDA) uses the rules in 21 CFR Part 11 to evaluate and enforce data integrity requirements for electronic records and signatures in drug manufacturing operations. The systems must comply with data integrity. For example, access to the systems must

be limited. Individual accounts must be created with a username and password to control access. Provide an Audit Trail in which the accesses to the software are shown and show us if any type of change has been made in the established parameters [1].

According to the US Food and Drug Administration (FDA) the assurance of product quality is derived from careful and systemic attention to a number of important factors, including selection of quality components and materials, adequate product and process design and statistical control of the process through in-process and end product testing [1]. For this reason, Pharmaceutical Process Validation is important in spite of the problems that may be encountered. Process Validation is established documented evidence which provides a high degree of assurance that a specific process will consistently a product meeting its predetermined specifications and quality characteristics [2].

Figure 2
Stage of Validation

The goal of Process Design is to design a process suitable for commercial manufacturing based on the knowledge gained through development and pilot scale that can consistently produce a product that meets its quality attributes. During the Process Qualification is evaluated to determine if the process is capable of reproducible commercial manufacturing. Continuing Process Verification achieve a system for identifying unplanned deviations from the process as envisaged is required. The data gathered should show that Critical Quality Attributes are being monitored properly throughout the process [3].

Validation is classified into four types. In this case, a revalidation of equipment and processes was carried out. Revalidation helps to ensure that modifications and upgrades to process environments, whether intentionally or unintentionally whether intentionally or unintentionally introduced, do not affect adversely affect the process characteristics of the product.

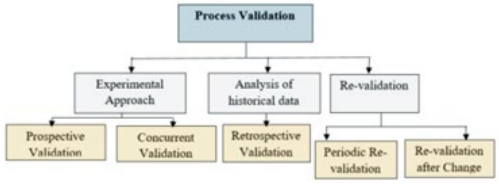

Figure 3
Classification of Validation[4]

The equipment qualification test must be passed before starting the validation. The main stages of qualification include design qualification, Installation Qualification (IQ), Operational Qualification (OQ), and Performance Qualification (PQ). These four major documents are commonly used to validate every piece of manufacturing machinery [4].

To better understand the operation of the system and the automation of the process, a series of literature searches related to the topic of automation and chromatography in computer systems were performed. The System monitors the process, gathering required data (i.e. Pressure, flow, UV, date/time, process steps and other information) to generate the required electronic reports including data trending, audit trail, HETP calculations and others. Process automation manages business processes for uniformity and transparency and typically handled by dedicated software and business software. Automation is desirable if the highest productivity is anticipated and to eliminate most human influence.

METHODOLOGY

To initiate, observations and statistical studies will be performed on the system in the necessary alterations to be made in the project. The Lean methodology "standard work" will be used to identify improvements in the purification process in the system to optimize people, resources, effort, and energy of the company.

With the information obtained, we will be able to analyze if our project will be effective. In

addition, we ensure the fulfillment of one of the objectives, where the RtReports system can be used to generate electronic reports.

Another factor that will be analyzed is human error. Calculations will be made to determine the decrease of discrepancies in the process due to the creation of the electronic reports, the improvements in the procedure and the functioning of the alarms.

Once the proposal has been analyzed and approved, the upgraded system and resources for the project will be acquired. With the acquisition, we proceed to perform qualification exercises. In this process, it is necessary to generate the necessary documentation, such as the System design, Validation Plan, IOQ protocol, Summary Report, SOP. This step will test compliance with 21 CFR Part 11 of the federal regulations. The computerized system will be tested for compliance with data integrity.

The initial plan is to implement this new system on Chromatography Systems 3 at Purification. In this phase of the project, the Chromatography System used is evaluated:

- Installation of the upgraded System
- Activation of the alarms
- Creation of the recipe in InBatch System
- Creation of electronic reports.

The documents are developed to help define the requirements of the business. The User Requirements Specification (URS) defines the business user needs of System. The purpose of the System Design Specification is to provide a description of the Chromatography Skid system in terms of the functions that it will perform, and the facilities required to satisfy the URS. The **Installation and Operational Qualification Protocol** (IOQP) define the objectives, methodology, acceptance criteria, documentation verification and test activities required to provide evidence that the Chromatography Skid #3 was installed per requirements. The methodology according to the requirements of Installation Qualification are:

- Document test case the required information from the implementation.
- Verify the calibration of the instrumentation related to the Control System upgrade project.
- Verify the wiring according to the related approved drawings.
- Verify that the electrical utilizes comply with the manufacturer's and that a licensed electrician.
- Verify that the temperature and humidity are within the acceptable range using a calibrated data logger.
- Using the administrator account to verify that the programmed graphic faceplates for skid.
- The interlock conditions and verify that the system response corresponds to the designed response.
- Trigger the required warnings and alarms conditions by simulating test points (TP) as close as feasible to the set points (SP) and verify that the system response corresponds to the designed response.

The methodology according to the requirements of Operational Qualification are:

- Challenge the new and/or current procedure affected by the System upgrade.
- Verify the functionality of the Pump flow control system.
- Verify that independent Equipment Phase sequences.
- Run the product recipe using a buffer or solution to verify that the programmed recipe sequence for Skid #3 can be executed in automatic mode per specification. Perform test run during this test execution. According to Design Specification, there are 7 recipes programmed in the system; HETP, Sanitization, Equilibration, Purification, Post-Sanitization, Storage, Skid#3. However, Recipe ID: Skid#3 is composed of all Unit Procedures programmed for the other 5 recipes except HETP. Therefore, this protocol will test Recipe Skid #3.

- Verify the displayed data of the Batch Report is accurate and complies with the user requirements. Access the reporting tool from the system and follow the procedure established to generate Batch report. Generate at least one of each of the following events: Actions performed by the operators during, Recipe runs, electronic signatures, electronic reviews, Alarm acknowledge, Recipe Steps aborted actions, Equipment actions, and Operator actions. Perform required recipe runs to obtain the data.
- Verify that the System changes related to the modifications performed to Skid #3 were incorporated in the business program.
- Verify and document that the Electronic Records and Electronic Signatures used by the system are protected from unauthorized alteration or bypass.
- Verify that the system is able to produce a secure, time stamped audit trail that records user entries and actions to create or modify electronic records.

After qualification completion, verify that the Control System InBatch, PLC and SCADA system Applications (Configurations) verify that the final versions were backed up at that the SCADA is included in the plant Back up system. Requirements is acceptable when the associated test steps met with the acceptance criteria. If any test step does not meet with the acceptance criteria (fail), a discrepancy report investigation must be completed and successfully closed to consider the test case acceptable. Discrepancy reports to this approved protocol will be addressed including corrective actions, and will be properly documented.

METHODOLOGY

The intention of this section is to summarize the results for this validation comparing against acceptance criteria. All individuals involved in the Process Qualification execution were trained. The IOPQ was generated and approved prior execution.

RESULTS AND DISCUSSION

As part of the system testing, full sequence of process steps according to the applicable approved operational procedure and recipe was challenged with the following conditions: The buffers solutions currently used for equilibration and purification of the column were used to test flow and volume controls for each step in its approved process sequence. Since the validation is focused on the control system, it was not necessary to perform Clean in Place (CIP) and Steam in Place (SIP) in the buffer tanks during the validation tests. During protocol tests, master batch records and related forms filling were managed according to the test cases content. Test solution volume quantities, used for each step, will be scaled down proportionally from recipe values. Conductivity, pH, and UV parameters were simulated to trigger the necessary step changes.

Information shall include Test, Acceptance Criteria, and Pass/Fail. Actual results must confirm a passing result or acceptable test case.

Upon completion of the qualification, the final releases were backed up to show that the SCADA is included in the plant backup system.

Table 1
Installation Qualification Test Cases

Installation Qualification			
Test Case#1	**Pre-Requisites Verification**	**Acceptance Criteria**	**Pass/Fail**
Change Control		Approved	Pass
User Requirements Specification for Skid #3		Approved	Pass
System Design Specification for Skid #3		Approved	Pass

Test Case #2	Calibration Verification	Acceptance Criteria	Pass/Fail
Instrumentation associated to the Controls System upgrade project.		Not past due	Pass
Test Case #3	**Wiring and Drawings Verification**	**Acceptance Criteria**	**Pass/Fail**
New electrical wring for the Control System upgrade was verified against approved drawings.		Verified	Pass
All monitored system conditions have the correct associated graphic color/icons and all measured variables have the correct associated values.		Verified	Pass
Test Case #4	**Electrical Utilities Verification**	**Acceptance Criteria**	**Pass/Fail**
Voltage (VAC)		115±10%	Pass
Chassis Ground Connected		Yes	Pass
UPS Service		Yes	Pass
Frequency		60 Hz±2%	Pass
Test Case #5	**Environmental Condition Verification**	**Acceptance Criteria**	**Pass/Fail**
Temperature		0°C to 50 °C	Pass
Relative humidity		10% to 80%	Pass
Test Case #6	**Screen Test Verification**	**Acceptance Criteria**	**Pass/Fail**
All phase, Control Modules, Equipment Module, and process trending screen modules function per specifications		Displayed	Pass
Test Case #7	**Interlocks / Manual Operation Verification**	**Acceptance Criteria**	**Pass/Fail**
Local interlocks associated to the Skid Y-1730 control system operate in accordance to design specifications. System components can be operated manually.		Message displayed	Pass
Test Case #8	**Warning and Alarms Verification**	**Acceptance Criteria**	**Pass/Fail**
Warnings and Alarms associated to the Skid Y-1730 control system operate in accordance to design specifications.		Message displayed and verified	Pass

Table 2
Operational Qualification Test Cases

Operational Qualification			
Test Case#9	**Operational Procedures Verification**	**Acceptance Criteria**	**Pass/Fail**
Operational procedure(s) challenged and updated as applicable. Redlined procedures are required to be approved before system release.		Verified	Pass
Test Case #10	**Flow Control System Verification**	**Acceptance Criteria**	**Pass/Fail**
Set flow to 1,000 ml/min		Process value maintained	Pass
Set Flow to 2,000 ml/min		Process value maintained	Pass
Test Case #11	**Phase sequence Test Verification**	**Acceptance Criteria**	**Pass/Fail**

Follow the test procedures during this test execution. The Equipment Phases can be executed independently in semiautomatic mode per specifications.		Displayed	Pass
Test Case #12	**Recipe Sequence/ Automatic Test Verification**	**Acceptance Criteria**	**Pass/Fail**
Follow the test procedures during this test execution. The certified InBatch recipe can be executed in automatic mode per specifications. The system has Unit Procedures and Operational Procedures per S88 standard architecture.		Displayed	Pass
Test Case #13	**Report Data Verification**	**Acceptance Criteria**	**Pass/Fail**
The data storage system stores the batch data as electronic records.		Displayed	Pass
The system produces Batch reports accurately retaining the meaning and content of the electronic records.		Properly generated	Pass
Batch Report data is accurate and complies with user requirements (User ID, Batch, Batch status, Start and End times, Operational Unit, Recipe, Bath Summary [Alarms, CPPs, Duration, Material Addition, Reconciliation, Trends]).		Information is contained	Pass
Verify that the batch report is available in electronic format (e.g PDF).		Exported	Pass
Test Case #14	**Preventive Maintenance Verification**	**Acceptance Criteria**	**Pass/Fail**
Verify SAP Preventive Maintenance related to the project was updated.		Updated	Pass
Test Case #15	**Electronic Record Protection verification**	**Acceptance Criteria**	**Pass/Fail**
Access to the system drive files and folders where Electronic Records and Electronic Signatures are stored was not allowed to Process Operator, Engineer, and Supervisor account levels.		Allowed	Pass
Test Case #16	**Audit Trail Verification**	**Acceptance Criteria**	**Pass/Fail**
Audit trail that records user entries and actions to create or modify electronic records is electronically available for review.		Performed	Pass

CONCLUSION

The objective of this project was to simplify the monitoring of the purification process of System Skid#3 in the Pharmaceutical Industry. All Test Cases included as part of the Process Qualification (IOPQ) have been successfully documented and closed. Based on the comparison of the results presented in this report against the acceptance criteria, it can be concluded that the Skid #3 System Upgrade sequence challenged during the installation and operational validation activities was completed successfully. Reports generated with Batch Data were verified and approved by Quality Personnel. Consequently, by upgrading to the new software, the manufacturing area can achieve better reporting, documentation and monitoring in less time and paper. This system upgrade will allow for more accurate and automated monitoring, where the need for operators per shift can be reduced. In addition, the advantages of implementing this system upgrade are more cost effective which prevents unauthorized access to the system to comply with 21 CFR Part 11 of the Code of Federal Regulations, ensuring a standard of quality and compliance with data integrity (Refer to Tables 1 and 2).

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