Implementation of a Change Control Process in a Pharmaceutical Industry

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Graduate Project EXPO, October 2024

Abstract *— The pharmaceutical industry is monitored by the highest regulatory bodies such as the Food and Drug Administration (FDA) and other agencies to ensure compliance with Good Manufacturing Practices (GMP) and Good Documentation Practices (GDP). The quality of the product is demonstrated through data generated within the process and supporting documentation. The data should demonstrate consistency, accuracy and completeness for data integrity. At the same time the equipment, process and systems should be validated for the intended use. This project focuses on the implementation of a change control in a validated system emphasizing in the required documentation to demonstrate the system has the capacity to function as it is intended and continues to meet regulatory standards. Additionally, the project provides a solution to a problem that has the potential to have data integrity issues.*

Key Terms *— Change Control, Computer System Validation, Pharmaceutical Industry.*

INTRODUCTION

A Process Team in the pharmaceutical industry was facing instances of power failures on the site. Power failures do not occur every day on site, but it is an unexpected event that may happen even when there is production in the process. A power failure during the encapsulation process was causing additional documentation such as deviation and incidents, data gathering and reconciliation since a counter of samples was reset to zero and did not store the last value before the power failure. The counter started from zero when the power came back. The ideal strategy is to store the last value before the power failure and once the power is back and the process continues, keep counting from that last value. Since this is a validated system, the changes implemented to correct the problem need to be documented accordingly to the regulatory requirements. Based on this information, there are several steps to document this improvement.

RESEARCH DESCRIPTION

The pharmaceutical industries are highly regulatory industries that require documentation for most improvements. Since the improvement to target the problem involves a qualified and validated system, documentation and analysis is required. This research focuses on the regulatory requirements and documentation required to successfully complete the improvements.

RESEARCH OBJECTIVES

- Identify the solution for the reset of counters during a power failure.
- Analyze the impact the improvement will have during its implementation.
- Investigate the industry requirements for control systems.
- Develop the required documentation to meet the regulatory requirements during changes performed to a validated system.

RESEARCH CONTRIBUTIONS

As part of the research contributions, the facilitation of the regulatory requirements that are present for validated control systems in the pharmaceutical industry is presented. This research will facilitate the implementation process by offering an approach to implement improvements to a validated system that includes documentation requirements, such as Validation Protocols and

Assessments. Finally, this research will successfully achieve the goal of correcting the problem and offer exposition to the regulatory requirements for the validation of control systems that contribute to the operations of a pharmaceutical industry.

LITERATURE REVIEW

This literature review will explain the pharmaceutical industry and the importance of data integrity. In addition, the qualification and validation process, and the change control process are discussed.

Pharmaceutical Industry and Data Integrity

The pharmaceutical industry is a highly regulated industry. The quality of the product is a priority for the industry. Product quality is demonstrated through the process and is supported by the documentation and data that is generated. The data and documentation are as important as the product since it ensures the quality of the product that will be delivered to the patients. Data Integrity in the pharmaceutical industry is defined as consistency, accuracy, and completeness of data documentation [1]. Data integrity is important since it demonstrates the quality of products and safety of patients. The principles of ALCOA, attributable, legible, contemporaneous, original, and accurate should be applied to the data [1]. This is an important requirement for the regulatory agencies since it impacts the Good Manufacturing Practices (GMP). The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) set minimum conditions and limitations, both in general and in the field of computer-aided systems in the pharmaceutical industry [2].

Qualification and Validation Process

In the pharmaceutical industries, equipment is qualified and validated. Process validation includes the collection of data from the design stage to commercial production that offers scientific evidence that a process is capable of functioning as designed [3]. The computer systems as well as the equipment go through the process of validation, and it is categorized as Computer System Validation (CSV). The CSV ensures the computer system will produce data and meets the regulatory requirements [4]. The stages of validation include process design, process qualification and continued process verification [3]. The process design stage expectation is to design a process that can produce a product with quality attributes and meets all the regulatory requirements [3]. The process qualification evaluates and demonstrates the process design expectations [3]. Finally, the continued process verification targets improvements or issues on a validated process [3].

The validation documents ensure the process performs what it is intended to do. The validation includes a validation master plan that describes all the activities required to complete the validation project. The validation should meet the user requirement specification expectations for the equipment and process. This is the acceptance criteria to successfully qualify and validate an equipment and process. The validation process includes the execution of protocols. These protocols should have clear objectives and measurable criteria. The protocol will describe the purpose, equipment, documentation required, safety measures and personnel executing the protocol. The protocol should include the acceptance criteria for the tests to pass or fail during the execution of the protocol. The qualification process includes design qualification, installation qualification, operational qualification, and process qualification. The installation qualification ensures the equipment is installed in the facility with all the components necessary to function as expected. It includes the equipment's design features, installation conditions, environmental conditions, safety features and supplier documentation. The operational qualification ensures the equipment operates as expected during normal and unexpected events. The operational qualification includes the process control limits, software parameters and operating procedures. The process qualification ensures the process occurs as normal operations. As established

in the operational qualification, it evaluates the process parameters, process capabilities and repeatability.

Change Control Process

The equipment and process are meant to be used in their qualified and validated state. Any modification made to the equipment or process should be documented. The modifications implemented are documented in a change control. The change control includes the current state of the equipment or process and the proposed state of the equipment or process. The change control includes a risk assessment and the impact the change will have. There are various categories the change control will evaluate such as quality, safety, and environmental impact. The change control will include the implementation plan and the timeline for the change will be implemented. The completion of the change control will include all the required documentation.

During the execution of change control, some protocols will have to be developed. There are verification protocols that will challenge the validated state or the new improvements to the equipment or system. The verification protocols will target specific user requirements. Through the protocols, the new acceptance criteria will be documented. The change control process includes a final report related to the results of the verification protocols. The report must be approved by the required personnel before the equipment is released for operations. This report is included in the return to service requirements. The change control also includes an evaluation after the change is implemented. It is usually a period after the change is implemented to ensure it is effective.

METHODOLOGY

The strategy to solve the problem and implement the improvement starts with identifying the root cause of the problem. Once the root cause of the problem is identified, the necessary modifications to correct the root cause need to be analyzed. After establishing the complete solution to target the problem, the solution is presented to document a change control.

The solution to the problem will be documented through a change control. The change control will document all the change control requirements to implement the fix. Table 1 demonstrates the change control requirements that will be documented for the approval of the change control. The description will detail the objective of change control, the justification for completing the change, and the risks present when completing the change control. Additionally, the change control will be classified in the various categories of quality, environmental, and health and safety. Also, the implementation steps needed to be established and have the corresponding information to successfully complete the change control. Once the change control is discussed and has the approval to continue, the records will be opened and documented. After the change control has all the required information, the execution of the implementation of the change will be completed.

Table 1
Change Control Requirements

Change Control Requirements	
Description	Current State
	Proposed State
	Justification
	Change Control Discussion Meetings
	Risks
Classification	Quality
	Environmental
	Health and Safety
Implementation Steps	Actions
	Action Owner
	Action Completion Criteria
	Due Date

RESULTS AND DISCUSSION

An analysis of the problem was performed to determine the root cause of the problem. The root cause of the problem was due to a Design Verification Issue since the Programmable Logic

Controller (PLC) Software source code did not have a countermeasure to backup the last value of the counter samples in case an unexpected power outage occurred.

The permanent solution to this problem was to make a software modification on the PLC. For the software fix to work as expected, it was required to replace the existing Uninterruptible Power Supply (UPS) and do a wire modification of the UPS with the PLC.

Once the root cause and solution of the problem were identified, the change control was generated, and the required documentation was identified.

Change Control Requirements

The change control requirements were explained in the different sections that include the change control document.

Description

The current state of the situation was part of the description. The current state of the situation was that the Capsule Filling Machine resets the counter values to zero in the occurrence of a power outage. Once the power was back, the counter started to count from zero instead of resuming on the last value before the power outage.

Then, the proposed state was stated in the description. The proposed state was to perform a software fix modification along with the replacement of the existing UPS and do a wire modification of UPS with the PLC.

Additionally, the justification was presented also in the description. The justification for the change control was to permanently fix the root cause of the deviation generated by the event and avoid additional documentation of incidents in the occurrence of a power outage during a batch in progress.

The discussion of the change control was also included in the description. A change control Discussion was held with:

- Computer System Quality Representative (CSQ)
- Quality Assurance Representative (QA)
- Automation Engineer
- Safety Representative
- Environmental Representative
- Process Engineer
- Technical Services Representative

Finally, the risks of implementing the change control were included. One of the risks identified was that once the change was implemented the counter values reset to zero after the occurrence of a power outage. The mitigation to ensure the counter values do not reset was to test the fix with an Installation Verification (IV) and an Operational Verification (OV). The probability of the risk was low since the fixed targets the risk and it was going to be tested.

Classification

The quality change classification was “Change” since the change control has the potential to impact the control strategy.

The safety change classification was “Not Applicable” since it did not impact any safety measures of the Capsule Filling Machine.

The environmental change classification was “Not Applicable” since it did not impact the environmental controls of the Capsule Filling Machine.

Implementation Steps

There were general activities completed during the execution of the change control. Table 2 demonstrates the activities completed for the change control. Each of the activities had a prerequisite completed before the next activity was worked. The first activity completed was the change control generation and approval. The approval was crucial for the implementation of the change control, and it was approved by the Organizational Unit Approver, the Quality Assurance representative, the Health and Safety representative and the Environmental representative. Once the change control was approved, the change was implemented. The

implementation of the change control required the replacement of equipment, electrical wiring of the new equipment and installation of the software update.

Table 2
Activities for Change Control

Step	Activity	Prerequisite	Activity Owner
1	Change Control generation and approval	Discussion of Change Control with the team	Automation Engineer
2	Implementation of Change	Change Control Approval	Automation Engineer
3	Execution of required protocols	Change implemented and protocols approved	Automation Engineer
4	Generation of required documentation	Protocols executed and reviewed	Automation Engineer
5	Return to Service of the Capsule Filler machine to production	Approval of Qualification Review Summary	Quality Assurance Representative

The implementation steps were generated based on the requirements of documentation. Table 3 demonstrates the implementation steps generated in change control, the completion criteria, and the timing to execute the implementation steps.

While the change was implemented, documentation was generated. The first document generated was the Installation Verification (IV) Protocol. The IV Protocol was generated with the objective of confirming that each of the devices installed was compliant with the requirements. The IV Protocol included the Test Summary with the scope, the test case execution summary, the test case completion review, and the signature log. The scope of execution was the new device installation. The test case execution was the overall status of the test case that included if there were any discrepancies. The test case completion review was a post-execution review. The signature log included the executor of the test script. Additionally, the IV Protocol included the execution instructions and the test script. The tests were field verified to ensure the manufacturer, model specifications and quantity met the expected results.

Table 3
Implementation Steps

Implementation Step Description	Implementation Step Completion Criteria	Implementation Steps Timing
Generation and execution of Protocols	Protocols executed and complete	Execution
Approve and Effective Qualification Review Summary (QRS) Report	QRS Effective	
Update Traceability Matrix (TMX)	TMX effective	
Return to Service of the Capsule Filler machine to production	QRS and TMX effective	
Update Capsule Filler Machine software revision history	Software Revision History effective	Post-Execution
Update Master Document List (MDL)	MDL effective	
Add equipment as spare parts	Equipment registered on the Maintenance System	

The second document generated was the Operational Verification (OV) Protocol. The OV Protocol was generated with the objective that the UPS supplies power to the computer for enough time for a correct shutdown to occur and the counter samples values were retained. The OV Protocol included the Test Summary with the scope, the test case execution summary, the test case completion review, and the signature log. The scope of execution was the retention of the counter values after a power failure occurs. The test case execution was the overall status of the test case that included if there were any discrepancies. The test case completion review was a post-execution review. The signature log included the executor of

the test script. Additionally, the IV Protocol included the execution instructions and the test script. The tests included several steps to properly challenge the implementation of the change. Figure 1 demonstrates the test instructions to execute the operational verification protocol.

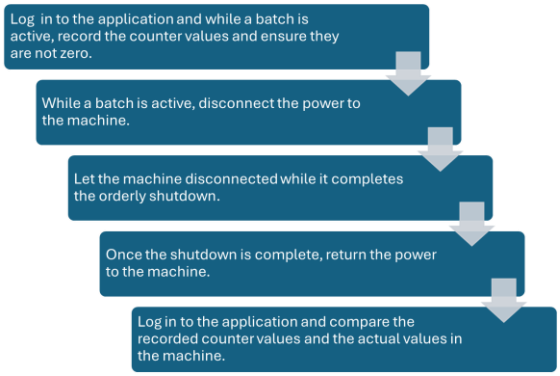

Figure 1
Test Instructions

Once the protocols generation was completed, the protocols were approved. The execution of the IV and OV Protocols was completed once the change was implemented. The overall status of the IV and OV protocols was pass and no discrepancies were identified. Once the protocols were executed, the test case completion review was completed. The implementation step was closed after the review was completed.

After the protocols were executed and reviewed, additional documentation was required. The Qualification Review Summary Report (QRS) was generated. The QRS had the purpose of summarizing the review of the verification activities performed with the IV and OV protocols. The QRS listed the executed test cases, the status of the test cases, and the discrepancies identified. The QRS included the IV Protocol number and title and the OV Protocol number and title. Since no discrepancies were identified in either of these Protocols, no actions were created as a result. Once the QRS was generated, it was approved by the Organizational Unit Approver, the Quality Assurance Representative, and the Automation Engineer. Once approved, the QRS was effective.

Along with the QRS Report, the Traceability Matrix (TMX) for the Capsule Filler machine was updated. The TMX lists the Process User Requirements (PUR), and the General User Requirements (GUR) based on the company requirements for the Capsule Filler machine. The TMX contains the requirement statement and the design summary. Based on the requirement statement and the design summary, the verification strategy was established. For the GUR impacted by the change, the verification strategy was an IV- Device Installation Verification and an OV- UPS Verification. The TMX was updated with the approved QRS on both the IV Device Installation Verification and OV- UPS Verification. After the TMX was updated, it was approved by the Organizational Unit approver, the Quality Assurance representative, the Automation Engineer, and the Automation Manager. Once approved, the TMX was effective. After the QRS Report and the TMX

The Capsule Filler Machine could not be used by operation for production until it had the Return to Service from Quality Assurance. Once the execution of the protocols was complete, a “Hold” was placed on the Capsule Filler machine to indicate it cannot be used. The “Hold” was placed to give an indication while the documents required to complete the Return to Service were approved. Once the QRS Report and the TMX were approved, the Quality Assurance representative reviewed the documentation. The implementation step for the Return to Service was completed.

Additional documentation and activities were completed after the execution steps. The software revision history document was updated. The purpose of the document was to have a history of all the changes related to the codes. This document was updated to include the latest version of the impacted PLC program version. Once the document was updated, it was approved by the Automation Engineer and the Automation Manager. After the software revision history document was approved, it was made effective, and the implementation step was completed.

At the same time, the Master Document List (MDL) was updated. The purpose of the MDL was to ensure that the Computer System validation documents were easily retrievable and facilitate maintenance of all documents related to the validation package. The MDL was updated to include the QRS Report for future reference. Once the MDL was updated, it was approved by the Automation Engineer. After the MDL was approved, it was made effective, and the implementation step was completed.

The last implementation step to close was related to the devices installed. The devices/ equipment installed as part of the change control were added to the maintenance system as spare parts. Having them listed as spare parts ensures there is at least one available on-site in case the equipment needs to be replaced. Once the devices were added to the maintenance system as spare parts, the implementation step was closed.

After all the implementation steps were closed, the governing change control document was reviewed. The related documents were attached to the change control and the change control was completed.

CONCLUSION

The benefits after implementation of the change control process were aligned with the objectives of the research. The first benefit of implementing this change control was that the solution to the problem targets the root cause of a deviation. This eliminates the reoccurrence of deviations related to this problem. Additionally, the implementation of this change control reduces the effort required to document through incidents the correct counter sample values when there were unexpected power failures during a batch. As part of the benefits of this implementation, exposure to regulatory requirements that are present for validated control systems in the pharmaceutical industry. The requirements for a change control were presented and described during the implementation. From the initial presentation of the change control to the documentation and required approvals.

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