Commissioning and Qualification of Utilities in a new Filling Line Expansion Project

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Abstract *— As part of a project for a Parenteral Filling Line expansion, Commissioning and Qualification activities were performed in new and existing modified systems to provide documented evidence and ensure that all equipment, utilities and facilities were in compliance with all regulations and GMP requirements. During this project, the Define, Measure, Analyze, Improve and Control (DMAIC) methodology were used to shorten the process and execution time of Commissioning and Qualification in two (2) utilities systems. The scope of this project is limited to the Commissioning and Qualification (IQ & OQ) of the Water for Injection (WFI) Generation and Clean Steam Generation utilities. Additionally, the Process Performance (PQ) Qualification is out of the scope of this project. The project consisted on the improvement of the Commissioning and Qualification process by reducing the amount of test cases, and executions during the Operational Qualification (OQ) phase by using a leveraging strategy making the process more efficient. One (1) Commissioning protocol and One (1) combined IOQ (Installation Qualification and Operational Qualification) protocol were executed for each system, which included eighty-two (82) test cases and four (4) summary reports. A total of sixteen (16) deviations were generated including six (6) re-test executions related to protocol errors, error in design documents and equipment failure.*

Key Terms *— Commissioning, Deviation, Leveraging, Qualification.*

INTRODUCTION

Parenteral dosage forms are intended for administration as an injection or infusion which means that the drugs are introduced in a way that evades the body's most protective barriers, the skin and mucous membranes. These drugs, are administrated to patients with chronic diseases and a compromised immune system. Therefore, parenteral drugs must be aseptically manufactured to be free from physical, chemical, and biological contaminants [1].

System Qualification Lifecycle

The lifecycle of a qualification a system consists of the Plan, Build and Test, Operate and Maintain and Decommission Phases. This lifecycle defines the documentation and actions or activities that are required to test, operate and maintain systems in a qualified state. As an example, during the Plan phase, the system requirements, impact, and qualification strategy are defined while on the build and test phase, the system is constructed per the approved design specifications and tested to provide documented evidence that the system is installed, operate and performs according to the design specifications and intended use. After the qualification of the systems is completed, the system must be maintained in a qualified state throughout the system's lifecycle until it becomes decommissioned. Figure 1 shows the Systems Qualification Lifecycle.

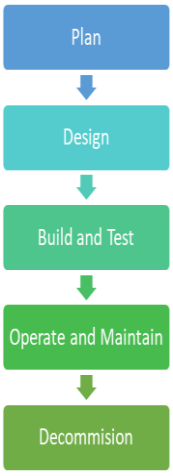

Figure 1
System Qualification Lifecycle

Commissioning and Qualification Phase

Commissioning can be defined as a methodical process that integrates a set of engineering techniques and procedures to inspect and test every operational component of the system, from individual functions, such as instruments and equipment. It verifies that the systems and equipment meet the established requirements established by the design documents (User Requirements, Functional Specification and Software Design Specification) [2].

Qualification can be defined as the documented evidence that a specific equipment, facility or system is fit/ready for intended use. Installation Qualification (IQ) is a documented verification to confirm that the system has been built and installed in accordance to the approved design documents and GMP regulations. On the other hand, Operational Qualification (OQ) is the documented verification that the systems function and operates within its operating ranges, meeting the predetermined acceptance criteria defined on the design documents such as Functional Specification and Software Design Specification [2].

Commissioning and Qualification (C&Q) processes are commonly described by the "V" model (Figure 2). This model demonstrates the relationships between each phase of the development life cycle with its phase of testing. The left side of the "V" describes the User Requirements for the system (what), then the Functional Specification or Requirements (How) finally the Design Specification or Requirements (How to Build) against which the commissioning and qualification will be executed.

The right side of the "V" model describes the steps in the commissioning and qualification processes such as the installation testing, performance and functional testing, that will verify that the system was correctly installed, operates as intended and complies to produce the desired results in accordance to the GMP requirements (if applicable), site requirements and policies and regulations.

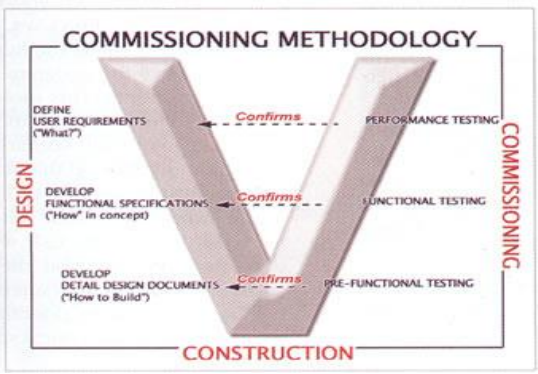

Figure 2
Commissioning & Qualification V Model [2]

Utilities Systems: Water for Injection (WFI) Generation and Clean Steam Generator

Water and steam may be used in the manufacture of products, cleaning operations, and laboratory activities within a biopharmaceutical operation. These systems always come into contact with the product/or process contact surfaces, and testing of the products, therefore, must be qualified.

Commissioning and Startup of a water system is one of the most important phases of any critical utility system since it can be a method of determining major problems with a water system before the qualification phase is executed. The commissioning phase allows major problems to be corrected immediately, therefore minimizing the deviations that would have to be addressed during the execution of the qualification phase.

Leverage Strategy

Operational Qualification (OQ) testing may be leveraged from previous commissioning activities and/or protocols. Prior the start of OQ execution, it is determined which executed commissioning test cases may be leveraged. Then, the executed test plans are evaluated by the Quality department based on the following:

- Test case was executed in accordance to the Good Documentation Practices (GDP).
- Test case was executed without failed acceptance criteria.
- There are no changes to the system that would change the expected result of the test case.

- Instruments used during the test cases (if applicable) remained in a calibrated state during the execution of the test case.

If the test cases, complies with all the criteria for levering, the test case is leveraged and does not have to be executed again during the OQ phase. For each leveraged test case, a copy of the approval for leverage and executed test case is attached to the qualification protocol.

DMAIC Methodology

DMAIC can be defined as a strategy used to improve processes. It is an acronym for the five (5) phases implemented on the process: Define, Measure, Analyze, Improve and Control [3]. During the Define phase, the problem and/or improvement activity is defined as well as the project goals and customer requirements. Then, the process performance is measured to gather data and proceed to the Analyze phase. During this phase, the process is analyzed to determine the root causes of the problems or bad performance. Once the root causes are identified, the process is improved by correcting and eliminating the root causes to the problem. Finally, the process is controlled. During this project, the DMAIC methodology was used by evaluating the Leverage Strategy to reduce the amount of Operational Qualification (OQ) test cases and executions.

PROJECT DESCRIPTION

This project focused on a strategy to shorten amount of Operational Qualification (OQ) documents developed for the Water for Injection (WFI) and Clean Steam Generators by using a leveraging strategy from the commissioning test cases. As a result, a reduction on the document development and execution time will be achieved making the process more efficient. Additionally, "shadowing" and "dry-runs" of the test cases will be performed during the system's Site Acceptance Test (SAT) and Startup to reduce the amount of deviations that may be found during the commissioning phase.

PROJECT OBJECTIVE

The objectives for this project are to:

- Reduce the amount of deviations during the Commissioning and Qualification phases by "shadowing" and dry-running the test cases during the Site Acceptance Test (SAT) and Start-up;
- Reduce the number of Operational Qualification (OQ) test cases by using a leveraging strategy.

DEFINE PHASE

For the Design Phase, a project charter was developed (Table1) to define the project objectives and scope of work. This project charter describes the goals, scope, Start/End project dates and possible risk and constraints.

Table 1
Project Charter: Commissioning and Qualification of Utilities Systems

Background:
As part of the Commissioning and Qualification (C&Q) activities for the expansion of the new filling line, a leveraging strategy will be used to reduce the time of C&Q on the utilities systems. These will include protocol and test cases generation, reduction on deviations and reduction on executions.

Goals

- Reduce the amount of deviations generated during the C&Q of the utilities systems by shadowing and dry-running test cases during the Start-Up and Site Acceptance Test (SAT) activities.
- Reduce the amount of test cases generated for Operational Qualification (OQ) by leveraging test cases successfully executed during the Commissioning phase.

Scope
This project will be limited to the C&Q activities for the Water for Injection (WFI) Generator and the Clean Steam Generator. All other utilities systems being qualified and performance qualification (PQ) activities for the expansion of the new filling line are out of the scope of this project due to schedule constraints.

Key Stakeholders

Project Leader	Francet Rivera
Project Manager	Lou Traglia
Team Members	Utilities C&Q Team Members

Start Date: January 2018 **End Date: March 2018**

Constraints, Assumptions, Risks and Dependencies

Constraints	Predecessors such as Mechanical Completion and Approval of Design Documents.
Assumptions	Mechanical Completion is Completed. Systems Design Documents are approved.
Risks and Dependencies	Construction Delays, Critical Deviations and change of priorities

In addition, a Cross Functional Diagram was developed to delineate the roles and responsibilities of the project members and stakeholders. This

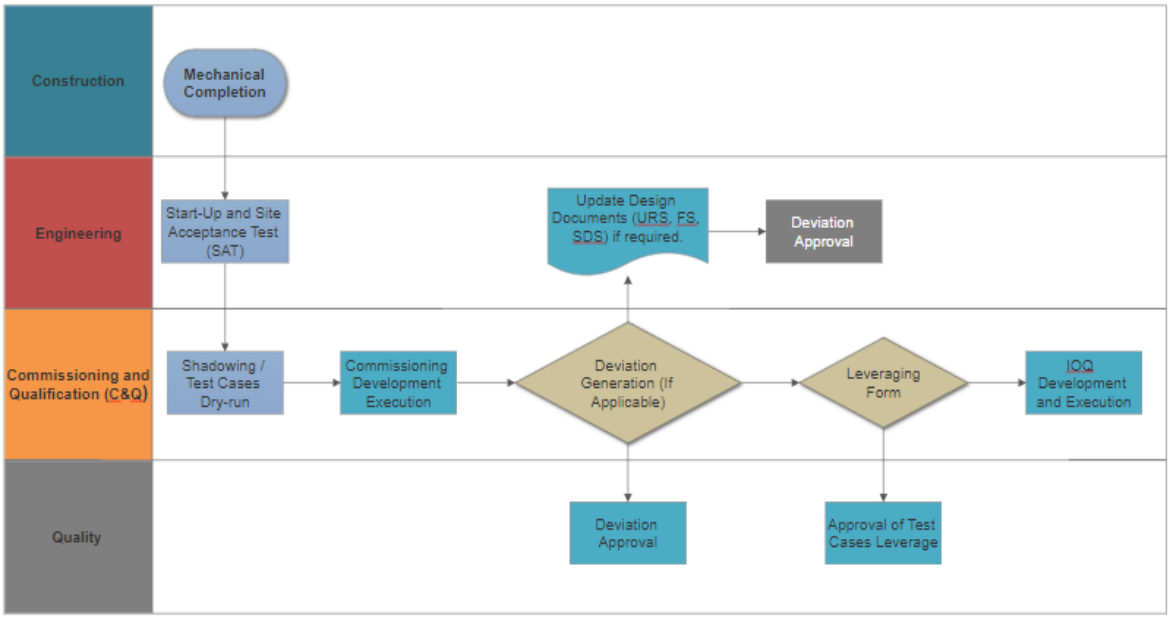

Figure 3
Utilities C&Q Cross-Functional Diagram

diagram provides clarity and accountability by documenting steps or activities of the process flow of the Commissioning and Qualification process. Refer to Figure 3 for the Cross Functional Diagram.

MEASURE PHASE

During the development of Commissioning and Qualification Protocol a test matrix based on the GMP requirements and specification was developed to confirm the testing required for the systems. For the WFI Generator, ten (10) commissioning test cases were identified. For the Installation Qualification (IQ), twenty-two (22) test cases and for Operational Qualification (OQ) a total of nine (9) test cases were identified.

For the Clean Steam Generator ten (10) commissioning test cases were identified. For the Installation Qualification (IQ), twenty-two (22) test cases and for Operational Qualification (OQ) a total of nine (9) test cases were identified.

During the execution of the Site Acceptance Test (SAT) and Start-up of the WFI Generator and Clean Steam Generator, C&Q resources were shadowing the vendors and engineers to identify possible errors on the commissioning test cases or design documents. Dry-runs were performed on the test cases that were more complex such as Alarms and Interlocks and Performance Testing. A total of three (3) test cases were "dry-runned" for the WFI Generator and a total of two (2) test cases for the Clean Steam Generator. Once the SAT and Start-up were completed, the commissioning testing started.

During the commissioning execution, eight (8) deviations were generated for the Water for Injection (WFI) Generator related to: Protocol Generation Errors (2), Equipment Functionality and/or Design Documents updates (6). All deviations were resolved and approved by C&Q Manager, System Owner and Quality.

For the Clean Steam Generator, two (2) deviations were generated and resolved related to: Equipment Functionality and Protocol Generation Error/Design Document Updates. Since multiple test cases were planned to be leveraged, all deviations approved by C&Q Manager, System Owner and Quality.

Installation Qualification (IQ) was performed to provide documented evidence that the system was properly installed and constructed in accordance to the design documents and GMP requirements. For the Water for Injection (WFI)

Generator three (3) deviations were generated, resolved and approved by C&Q Manager, System Owner and Quality.

For the Clean Steam Generator, three (3) deviations were also generated, resolved and approved by C&Q Manager, System Owner and Quality. Refer to Figure 4 for a diagram on the occurred during the C&Q.

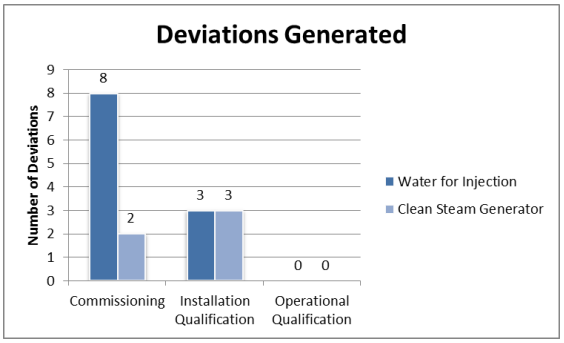

Figure 4
Deviations Generated during the Water for Injection and Clean Steam Generator C&Q

Once Commissioning and Installation Qualification (IQ) were completed, it was determined the commissioning test cases that may be leveraged for the Operational Qualification (OQ) phase. An evaluation of the test cases was performed by Quality based on the leveraging strategy as follows:

- For the Water for Injection (WFI) Generator five (5) commissioning test cases were leveraged.
- For the Clean Steam Generator, at the moment of completion of this project (due to time constraints) IQ was in the process of being completed. However, based on the commissioning results it is expected to have around six (6) commissioning test cases leveraged from Commissioning.

ANALYZE PHASE

From the Measure Phase, it can be seen that five (5) of the nine (9) WFI Generator OQ test cases were approved for leverage. Therefore, these test cases were not re-executed during the Operational Qualification (OQ) of the WFI Generator.

For the Clean Steam Generator, it is expected to leverage six (6) of the nine (9) OQ test plans. Therefore, it can be seen that the Leverage Strategy can reduce significantly the amount of testing performed during the Operational Qualification (Refer to Figure 5 and 6).

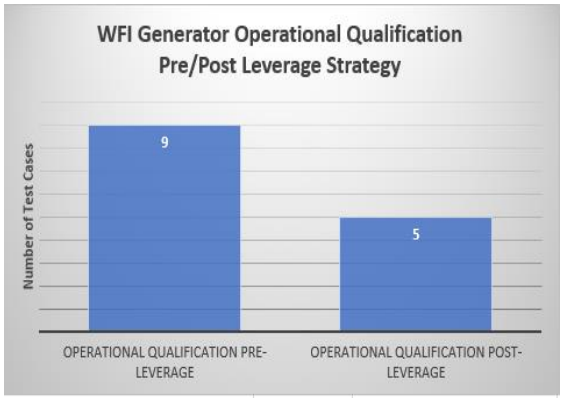

Figure 5
WFI Generator OQ Pre/Post Leverage Strategy

Figure 6
Expected Clean Steam Generator OQ Pre/Post Leverage Strategy

The efficiency equation (See Equation) is a simple comparison of the work output from an operation to the work input to that same operation. For the purposes of this project, the amount of "work" will refer to the amount of time and effort that was reduced by using a Leveraging Strategy based on the amount of test cases developed and executed.

Efficiency = (Work Output ÷ Work Input) x 100 (1)

Where:

- Work Output: Number of Test Cases Leveraged from Commissioning.
- Work Input: Number of Test Cases before the application of the Leverage Strategy.

Therefore,

Efficiency $_{WFI}$ **= (5 ÷ 9) x 100 = 55.5 %**

Efficiency $_{CSG}$ **= (6 ÷ 9) x 100 = 66.6 %**

IMPROVE PHASE

For the Improvement Phase, the Leverage Strategy was implemented on all the Qualification Protocols that were developed as part of the Commissioning and Qualification of the New Filling Line Expansion Project.

In addition, the Quality Department will keep giving oversight and signing Commissioning deviations generated on test cases that may be leveraged for the Operational Qualification (OQ) phase.

It is also suggested to "shadow" or dry-run if possible (budget and schedule) complex test cases during the Site Acceptance Test (SAT) and Start-Up of the equipment to reduce the amount of deviations since it was observed that the majority of the deviations were found on test cases that were not "dry-runned". This would probably reduce even more the amount of test cases executed during OQ making the process even more efficient.

CONTROL PHASE

As part of the Control Phase, a qualification protocol template was created to standardize the protocol requirements on all the impact systems that are new or will be modified as part of the expansion of the new filling line. On this Qualification protocol template, the Leveraging Strategy Section was added. Therefore, all the qualification protocols will have a Leveraging section to allow the leverage from Commissioning test cases.

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