

A Quality System Approach to Retrospective Validation of Manufacturing Support Systems

William Lodato, P.E.

Abstract

As manufacturing support systems (HVAC, Electrical, Compressed Air, Nitrogen, WFI, Control/Monitoring Systems) fall under the umbrella of FDA regulated Quality Systems, the need to assess, audit, document, and validate existing infrastructure is getting the attention of both the FDA and the boardroom. Recognition of including the support systems in the quality process often comes about as the result of the improvement process or, in worst cases, as the result of unfavorable FDA inspections.

This article provides a methodology for approaching the task of retrospectively validating existing support systems in pharmaceutical, biopharmaceutical, and medical device facilities. Frameworks for developing the Master Plan as well as the plans for the specific support equipment are presented. Consideration of the computer based control systems that are responsible for the monitoring and control of the systems is discussed.

A synopsis section outlines several "tips" on various aspects of developing and executing a retrospective validation effort.

Introduction

Support systems that have operated outside of corporate quality systems are often saddled with outdated documentation and a series of upgrades/expansions/maintenance changes.

Continuously improving Quality Systems in the life sciences industry are recognizing the need to include facility infrastructure systems (HVAC, Electrical, Compressed Air, Nitrogen, WFI, Control/Monitoring Systems) in the quality process. These systems can have direct impact on maintaining the production environment in a state of control. Applying appropriate quality system controls is a good business practice that increases production output while lowering operating expenses. Good practices also help to mitigate any health and safety issues surrounding the manufacturing support systems.

Although many of these systems have indirect bearing on the manufacturing process, good business practice and health/safety concerns dictate that exercising a reasonable level of quality control is prudent. Other support systems, such as those maintaining the environmental conditions in the manufacturing spaces, have can have direct impact on the product quality. A retrospective validation of these systems poses unique challenges that can be overcome with well designed planning and exhaustive testing.

Definitions

Validation - Establishing documented evidence which provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality attributed.

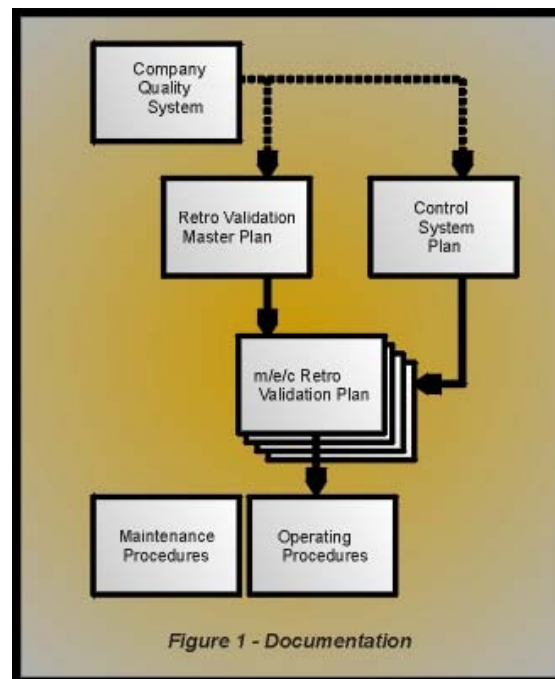
Retrospective Validation - Validation of a process for a product which has been marketed based upon accumulated manufacturing, testing and control batch data.

Project Master Plan

The Project Master Plan is a high level document aimed at defining the purpose of the project, it's overall scope, the approach and methodology to be used, and the resources required. This high-level plan will be used as the "parent" document for the "sibling" plans that will be written for each of the mechanical/electrical/control (m/e/c) systems under consideration.

Evaluate the mission by writing a clear purpose and "Statement of Objectives". State these objectives in terms of business, safety, and regulatory issues. Include references to all sections of your company safety and quality policies as well as the appropriate FDA documents. Develop an initial m/e/c systems list and perform an initial system assessment to determine the various system classifications. Determine the relationships between the m/e/c systems and use this information as an aid in prioritizing and grouping m/e/c systems for a "parent-child" approach. (Fig 1)

Computer based control systems may present additional concerns with regard to 21 CFR Part 11. Consult your quality processes and assess the implications. Often, a network approach can address the computer validation. A network approach involves a separate retrospective validation for the global aspects of the control system (i.e. Database, SCADA system, communication network, etc.) as an independent effort and a "sibling" to the "parent" Master Plan. Individual control system



Retrospective Validation Master Plan

Project Description

Purpose
Project Overview

Objectives

Business
Safety
Regulatory

Definitions

Reference Standards

Approach/Methodology

Project Team - Roles & Responsibilities

Resource Requirements

Constraints

Appendices (as applicable)

Equipment/Systems List
References
Project Schedule/Staging
Vendor Selection
Resource Requirements List

Table 1 - Master Plan Outline

nodes that control the mechanical and electrical systems can then be included in the m/e/c efforts.

Consult your corporate quality system to determine the expected documentation for each system and write this into the Project Master Plan. One of the major challenges to retrospective situations is the lack of original requirements and design documentation. Include descriptions on dealing with this eventuality.

Describe the approach of utilizing "child" plans for each m/e/c system. Write this section such that the documentation for each "child" will

stand on it's own, utilizing the Master Plan as a reference document. Confirm that adequate document controls are in place for this effort. Confirm that numbering systems for the m/e/c equipment and their components are valid. Make note, in both the master and child plans to review children upon revision of the Master Plan.

Describe, in terms of title and/or skills, the personnel that will be involved in the process. Make note of required qualifications of outside vendors. The asset, time, and financial resource requirements of this effort can be outlined in broad terms.

Use the last section of the Master Plan to discuss constraints that may be placed on this project and contingencies for handling those situations. Examples might include plant production schedules and/or resource constraints. Consider the time-worthiness of your quality process (i.e. How often has the quality system been used with consistent effectiveness.) and note how this project will deal with changes or gaps in the higher level documents. Be aware that seasonal temperatures may delay or prohibit a portion of the operational tests and explain how the project will deal with these issues. Lastly, a pharmaceutical plant is an evolving institution, and provision will need to be made for additions and alterations to the plant while this project is underway.

An appendix can be created to attach lists of equipment, resource lists, reference lists, etc. (*Table 1*)

Involve all stakeholders in the planning effort, making certain that they understand appropriate sections of the initiative, agree with the scope, and have a sense of their required involvement. Use the opportunity to build your team.

m/e/c System Plan

The m/e/c System Plan is an equipment specific document for retrospective validation of a m/e/c system or group of systems. Develop a solid, workable "child" template that can be used for the m/e/c systems described in the "parent" Master Plan and the control system global effort. This document will follow the guidelines and format of the parent documents (Master Plan and Control System Global elements) and contain the elements of a typical validation. (*Table 2*)

Authoring the m/e/c system plan will require gathering and reviewing the existing documentation. Refer to the Master Plan for a list of the requirements, design, testing, traceability, and summary documents. It is not unusual for the requirements and/or design documents to be either non-existent or lacking in substance. When requirement and/or design documentation are insufficient, they will need to be retrospectively created from existing documents, field survey, testing and balancing data, and empirical data.

For retrospective situations, an author-test-revise-test approach (*Fig 2*) will streamline the process and minimize deviations. If an audit has not been conducted in the past five years, or if the existing documentation is questionable, pre-test the IQ and OQ before any of the m/e/c validation documents are signed. Use a checklist approach for this testing. The results of the pre-test may necessitate a challenge to the requirement specifications, design modifications, updating of the design documents, and/or defective component replacement.

Conducting a pre-test utilizing the IQ / OQ protocols will examine both the m/e/c system and the validation testing protocols. Once discrepancies are discovered and corrected, modify the appropriate documents and determine what re-testing is prudent. Recognize, in this determination, that the goal is to minimize deviations during validation testing.

Before seeking approval signatures, verify that the required SOP's for system operation and maintenance are current. Confirm that personnel have been adequately trained, and that the proper security and safety measures are in place.

With the above steps completed solicit approval signatures for the m/e/c plan. If the plan is amended due to signatories'

m/e/c System Plan
<i>Purpose and Objectives</i>
<i>System Description</i>
<i>Definitions</i>
<i>Reference Standards</i>
<i>Approach/Methodology</i>
<i>Project Team - Roles & Responsibilities</i>
<i>Resource Requirements</i>
<i>Constraints</i>
<i>Appendices (as applicable)</i>
User/Functional Requirements
Design Documents
Traceability Matrix
Component List
References
Project Schedule/Staging
Vendor Selection
Resource Requirements List
Validation Summary
<i>Table 2 - m/e/c Plan Outline</i>

request, determine the appropriate level of pre-testing the changes prior to resubmitting for signature. Upon completion of these steps, the remaining retrospective validation activities (i.e. validation testing and activity summaries) will yield the expected results efficiently and without setbacks.

Synopsis

Retrospective validation presents several unique challenges, chief among these are the plant production schedule, and the interdependence of the existing systems. As an example, consider the case of multiple production rooms that share a common corridor, where each of the production rooms are maintained at a lower pressure than the corridor. In this case, the corridor HVAC system has an effect not only on all of the adjoining manufacturing rooms, but also on other areas adjacent to the corridor. Conversely, each production room will impact the corridor and potentially other production rooms. Central chiller systems, hot water systems, emergency power distribution, compressed air, water and gas systems are also typically global in nature. Survey and testing these systems may have substantial impact on production.

Information gathering can be an arduous task that is difficult to schedule. Start this process early using a filing and numbering system. A checklist will aid in determining the outstanding items.

While developing the first m/e/c plans, select a relatively complex and a relatively simple mechanical or electrical system as prototypes. For these prototypes, expect that the validation efforts will be onerous, with multiple revisions and deviations. Complete the retrospective validation on these systems in their entirety before embarking on other m/e/c systems. The prototypes will help to identify areas of weakness and allow the project team to work through any difficult or conflicting situations while establishing the foundation for the remaining systems..

Computer control systems are prevalent in many mechanical and control systems. Determine that the tools, training, and experience are available for testing these systems. Implement GAMP guidelines and substantiate the vendors understanding of quality

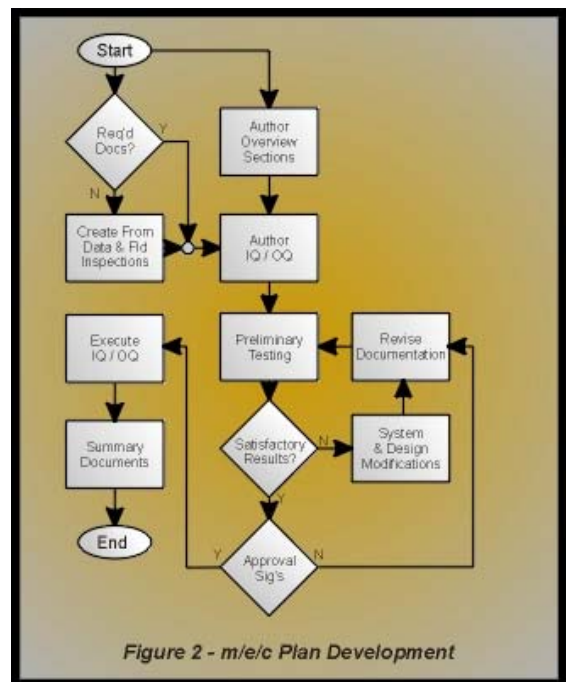


Figure 2 - m/e/c Plan Development

procedures and corporate quality systems. Enforce appropriate security measures, version/document controls, and software development (and testing) methods. It is not unusual to have a variety of computer control systems that require at least a corresponding number of development/programming tools. Consider developing an in-house level of expertise on the most critical systems and a long range plan to consolidate systems.

Planning and pre-testing are the keys to success in any validation effort. Pre-testing is an extremely important tool that cannot be over emphasized. When schedules begin to slip and resources become scarce, the tendency will be to relax pre-testing requirements. Failure to diligently and thoroughly test any changes to either the systems and the documents prior to validation testing will have negative consequences. Extensive deviations during the validation testing can quickly multiply the time and resources that would have been spent in pre-testing. Just as any professional craftsman or sportsman executes their trade with apparent ease, the validation testing phase is where the amateurs and professionals parse.

Negative consequences can also result from replacing or adding project team members as the project evolves. New members bring different influences on the project and it's requirements. Decisions that have been authored into the validation plans can be reversed while new requirements can be imposed. Similarly, alterations to the corporate quality system may strain the project by changing the requirements of the retrospective validation effort. . These, and other challenges, will place additional strain on the schedule and resource requirements. Resist the pressures to relieve this strain by eliminating or curtailing pre-testing.

Conclusions

The business advantages of any quality system apply to the infrastructure that supports pharmaceutical manufacturing processes. Systems that operate in a state of control lead to increased production output, lower maintenance/operating costs, and improved employee satisfaction.

The process of documenting and testing the m/e/c support systems is, in and of itself, a continuously improving process. Future audits will improve upon the methods and documentation produced in an initial effort. Plant upgrades and expansion can take advantage of this work product and incorporate inspection and testing into their project deliverables.