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Risk-Based Engineering Assessment and Qualification – A Case Study

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ABSTRACT

Recent spate of life saving drug discoveries is requiring drug manufacturers to bring these drugs to market with a reduced time-to-market as well as at a lower cost. These challenges need to be met while maintaining a high level of drug manufacturing safety. Besides the challenge of reduced time-to-market, there is also an increasing realization that drug costs can be lowered through an environment conducive to innovation and continuous process improvement in order to realize process optimization and elimination of wasted efforts in production. To support this environment, a flexible regulatory system which focuses on risk-based approaches to critical areas of the manufacturing process is gaining industry wide acceptance.

This paper outlines a risk based approach to validation of a plant utilities and facility management automation system in a bulk manufacturing biotech facility. This is one of the four key subsystems which regulatory agencies consider as representing the largest risk and, if in control, the manufacturing process is considered to be in compliant. This paper describes how existing techniques such as FMEA and FTA were tailored and applied to engineering principles in order to develop an integrated approach to good engineering practice and validation testing without compromising production safety. Business process benefits derived from adopting such a risk based strategy are also addressed.

INTRODUCTION

The past few years have witnessed a spate of new life saving drug discoveries. These drugs are required to be manufactured at a lower cost so as to make them more affordable for all. Lower manufacturing costs may be realized through efficiency improvements obtained through a scientific understanding of how formulation and process factors affect product quality. Additionally, a mechanistic understanding of the process, results in a reduced downtime caused by process and equipment failures.

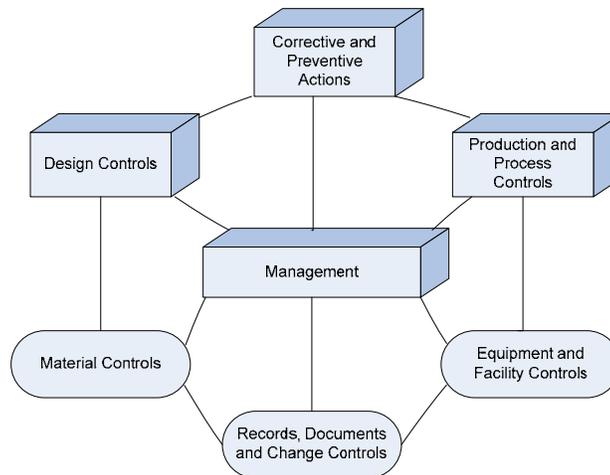
The drive to lower manufacturing costs through a better understanding of the drug manufacturing process presents Quality and Validation groups an opportunity to develop qualification strategies which are not only cost effective but also regulatory compliant. Developing such strategies provides industry the added benefit of being less rigid and more conducive to scientific innovation.

The effort to better understand the process provides insight into the technical aspects of the manufacturing process including the stratification of process risk factors. For factors which present a higher process risk, a detailed functional/area risk assessment is conducted to determine where to focus validation activities. The others are subjected to good engineering practice testing. This risk based approach to validation provides for a safe and affordable drug product. It also provides a level of assurance that validation strategies developed from an approach based on a level of process understanding will survive regulatory scrutiny.

REENGINEERING INSPECTION

Risk can be defined in many ways. Before establishing a risk based validation strategy, it is important to look at the Food and Drug Administration's (FDA) risk-based systems approach to inspection of facilities. This provides insight into one of FDA's inspectional strategies which could be helpful in evaluations of risk assessment when looking at validation strategies.

Of interest is the FDA's Quality System Inspection Technique (QSIT) which focuses on key manufacturing and quality areas during inspections. The QSIT approach is illustrated in the diagram below.

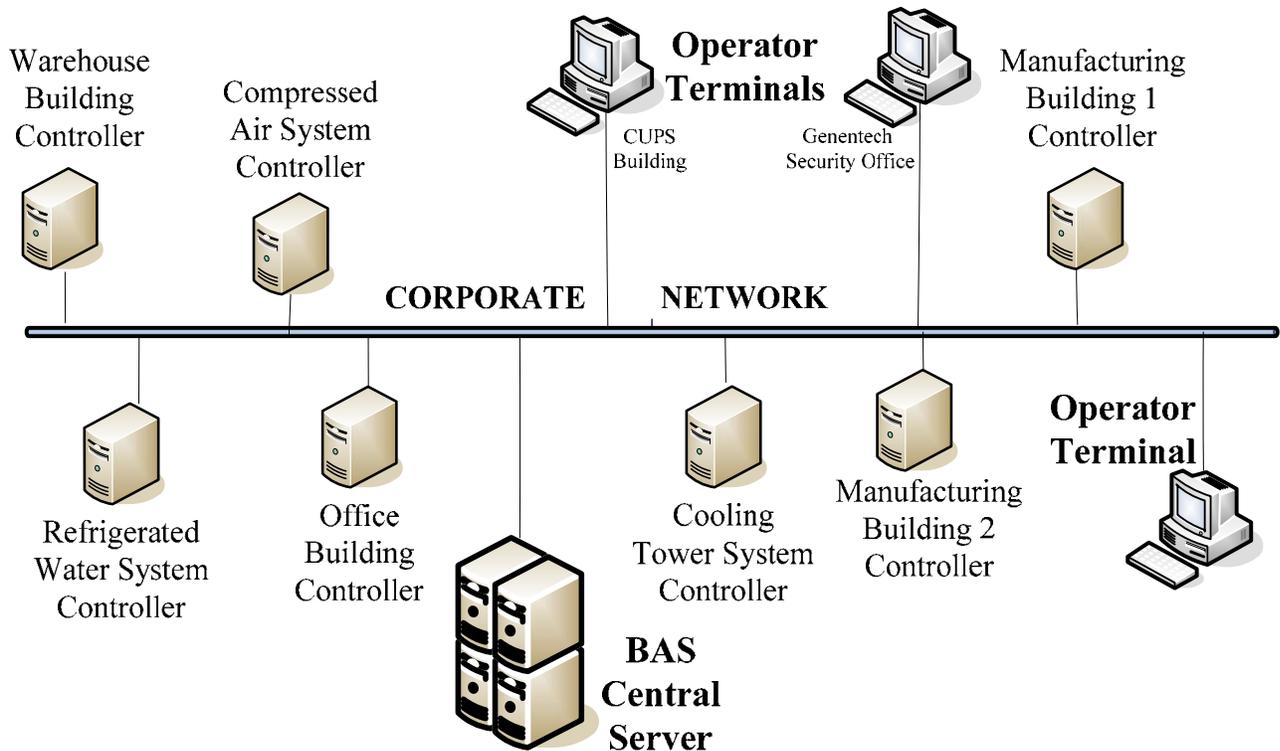


Under this approach, the inspection focuses on four primary areas. These include Management Controls, Design Controls, Corrective and Preventive Actions (CAPA) and Production and Process Controls. There are three other subsystems, sometimes referred to as secondary systems, which the FDA, at its discretion, may opt to inspect. These subsystems include Material Controls, Records, Documents and Change Control and Equipment and Facility Controls.

While assuming product quality is significantly dependent on the four primary areas mentioned above, it is also recognized that the three other subsystems play a major role in ensuring product quality as well. The inter link between the systems provides the forwards/backwards traceability perspective, which could produce an audit trail across the primary and secondary systems. Hence the validation of all subsystems is equally important. With new FDA guidance that validation decisions can be based on risk assessment, the risk based validation decision making process for the seven subsystems is subject to scrutiny during the FDA inspection process.

AUTOMATION SYSTEM OVERVIEW

Plant utilities and Air Handling units at Genentech's bulk manufacturing site in Vacaville, CA are controlled by a Building Automation System (BAS). The BAS is a centralized client server system. A central server communicates with multiple field based controllers over the corporate network. Operator terminals communicate with the central server to interact with and monitor the process. The BAS also provides the monitoring infrastructure to monitor and alarm cold room temperatures where product is stored. Depicted below is a representative architectural block diagram of the BAS:



The BAS monitors and controls the following systems:

1. Plant Refrigerated Water system
2. Cooling Tower system
3. Process Refrigerated Water system
4. Compressed Air system
5. Plant Steam system
6. Air Handling Units
7. Heating Hot Water units
8. Facility Alarm Monitoring system

RISK ASSESSMENT APPROACH

The engineering assessment's objective is to understand BAS controlled processes and systems and focus qualification efforts on only those factors which can affect the quality of the product. The assessment is done in three steps which are:

1. Identification
2. Impact assessment
3. Criticality assessment

During identification, a team of subject matter experts identify all BAS controlled systems along with their primary function. For each system the component sub-systems are also identified. Examples include Refrigerated Water system, Plant Steam, Compressed Air system, Facility Monitoring system etc.

The impact assessment follows after systems and their functions are defined. During this step, the team assesses each system's impact on overall product quality. Based on their expertise, they provide YES/NO answers to a series of questions pertaining to each system's impact on product quality. The answers form the basis for each system's categorization as direct impact, indirect impact or no impact system.

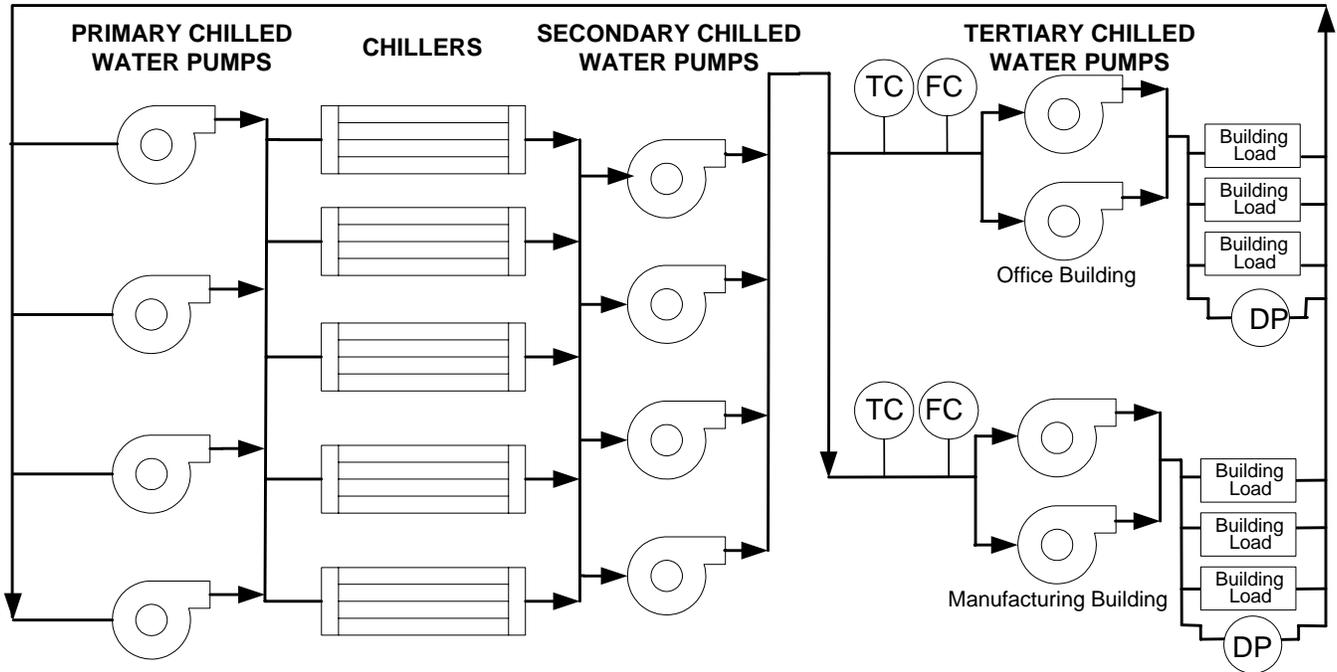
During criticality assessment, sub-system components and sub components of direct and indirect impact systems are ranked to reflect the magnitude of their failure consequence. The ranking provides the basis for identifying the critical sub-systems.

The criticality assessment adopts a top down and a bottoms up approach. The top down approach is a functional or equipment level assessment in which the system function is viewed as a collective function of its sub-systems. The critical effects of each sub-system's failure to product quality are assessed. Typically each sub-system's failure consequence is examined, by assessing its severity along with the likelihood that they can occur. Based upon the probability of their occurrence their effect on product quality, the sub-system is given a criticality rating. Those with the highest criticality rating or with the highest impact to process are identified for validation testing. The remainder of the sub-systems are tested using Good Engineering Practices.

Process control assessment constitutes the bottoms up approach. Process parameters whose control and/or monitoring ensure proper operation of other (subordinate) process parameters are identified as critical process parameters. Control elements which directly impact the measurement, control and excursion detection of these parameters are identified as requiring validated level testing. The remainder of the components is tested using Good Engineering Practices.

CASE STUDY OF A PLANT REFRIGERATED WATER SYSTEM

The Refrigerated Water (RW) system is one of the BAS controlled plant utility systems. Its key function is to produce and supply refrigerated water to all the buildings at site. The following is a representative block diagram of a typical RW system.



Typical Plant Refrigerated Water System Distribution System

The identification step identified the RW system’s primary function to be the production and supply of refrigerated water at a fixed temperature and pressure differential for varying loads in all the buildings at site. The sub-systems were also identified and their results tabulated as follows:

| System | Sub-systems | Operational Function |
|---------------------------|---|--|
| Refrigerated Water | Chillers Primary Refrigerated Water Pumps Secondary Refrigerated Water Pumps Tertiary Refrigerated Water Pumps | Produce and provide refrigerated water at a preset temperature differential, flow rate and differential pressure |

During impact assessment, the RW system was deemed to be an indirect impact system based on the following analysis.

| | RW System |
|---|------------------|
| System has direct product contact? | No |
| System provides an excipient or produces an ingredient of solvent (e.g. WFI)? | No |
| System is used for cleaning and sterilizing? | No |
| System preserves or monitors product status? | No |
| | RW System |

| | |
|---|----|
| System produces data which is used to accept or reject product? | No |
|---|----|

Since chilled water does not contact the product, it does not have a direct impact on product quality. However, systems that receive chilled water, do impact product quality. Examples include Air Handling units, jacket coolers etc. Consequently, chilled water quality is somewhat critical. Based on this conclusion, subsequent assessment efforts shifted focus from the RW system's impact on the plant product's quality to the impact of RW sub-systems on the RW system's product which is the production and supply of refrigerated water to the plant.

Functional criticality was determined using Failure Modes and Effects Analysis (FMEA) techniques. The team of experts identified various sub-systems. For each sub-system, failure modes, failure impact severity and likelihood of their occurrence was assessed. The FMEA analytical technique addressed the following questions:

1. How can each sub-system fail?
2. What might cause these modes of failure?
3. What could the effects be if the failures did occur?
4. How serious are these failure modes?
5. How is each failure mode detected?

A chiller failure was deemed as having the highest impact to refrigerated water quality. Consequently, chiller failure detection and alarming along with failure recovery were validated. Components such as primary chilled water pumps, secondary chilled water pumps etc. were not deemed that critical and were tested as per General Engineering Practice testing.

Operational criticality was assessed through a review and analysis of the systems control modules, control sequence or procedure and alarms. Control modules and procedures which directly impacted the control of the system's primary function were validated. Since the RW system's primary function is to produce refrigerated water at a desired temperature and supply it at a desired pressure, the following control entities are validation tested.

1. PID temperature control
2. PID flow control
3. PID control of Pump Speed with VFD (secondary pumps only)

CONCLUSION

The conceptual understanding and perception of risk is expected to differ depending on an individual's pertinent training, prior beliefs about the risk and other factors such as the vulnerability of the human mind to fallacies in human reasoning. These vulnerabilities may be partially overcome through an open-ended brainstorming approach to identify hazards which will generate an abundance of factors believed by individuals or groups of individuals to contribute to risk. Some factors are likely to be objective and qualitatively supported while others are likely to be subjective and value-based.

While cognizant of these vulnerabilities, regulatory agencies are cautiously embracing risk assessment and mitigation initiatives by the industry. They recognize that such initiatives are based on a better process understanding leading to built-in quality by design. They also lead to the development of better qualification efforts which are cost-effective and simultaneously regulatory-compliant.

Significant challenges lie ahead for the pharmaceutical community to move to the "desired state" for pharmaceutical manufacturing in the 21st century. Nevertheless, important steps have already been taken. Industry efforts to develop a structured regulatory format for risk assessment and management is currently in progress. Risk management principles and tools will be necessary to describe and communicate the level of risk-mitigation achieved through quality by design and process understanding. Current efforts through a framework of initiatives such as Process Analytical Technologies (PAT) and International Conference on Harmonization (ICH) and committees such as American Society of Testing and Materials' (ASTM) E55.03 will provide a basis for risk mitigation through the development tools and risk management principles.

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