Are cleaning faults, really, quality or administrative issues?: Cleaning Validation Program optimization for a Pharmaceutical plant

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Abstract *— The cleaning procedure process validation has generated considerable discussion when executing a US Food and Drug Administration (FDA) inspection at Pharmaceutical Plants. In general, the FDA requires the equipment to be clean prior to its use for manufacturing, processing, packing, holding of a drug product and/ or when sampling a raw material. Currently, some pharmaceutical plants have failed to design a good manual cleaning process. In regards to this, the Management Theory is crucial to manage effectively a cleaning procedure with the optimization of the Cleaning Process Validation. The application of the management functions contributed on the development of a guide to correct these faults and/or prevent further occurrence. By implementing the Administrative Management Theory a cleaning validation program is without a doubt optimized.*

Key Terms *— Administrative Management Theory, Cleaning validation, crucial, optimization*

INTRODUCTION

Reference [1] states that accurate cleaning of manufacturing equipment and facilities have always been a mandatory requirement for the pharmaceutical industry. By means of a designed guide the US Food and Drug Administration (FDA) establishes the expectation for cleaning procedure processes and also addresses the acceptable or unacceptable practices for consistency and uniformity. The FDA expects firms to have written standards operating procedures (SOP's) detailing the cleaning processes used for various pieces of equipment. If firms have one process for cleaning between different batches of the same product and use a different process for cleaning between product changes, they expect the written procedures to address this different scenario. One major concern of the FDA regulation is "clean manually pieces of equipment" for which many Plants are committed to optimize their Cleaning Process Validation. The worst case scenario is based on the difficulty of equipment cleaning for extremely small internal surface areas and systems that cannot be routinely disassembled for cleaning and sampling. Another important variable to take into consideration is the equipment complexity in terms of design and shape. The first step is to focus on the objective of the validation process in the role abilities of a pharmaceutical plant to manufacture a drug product and remain in compliance with the FDA regulations. Finally, the FDA's Guide to the Inspection of Cleaning Validation Process [2] states the following: "It is not unusual to see manufacturers using an extensive sampling and testing programs when following the cleaning process without ever really evaluating the effectiveness of the steps used to clean the equipment". However, the responsibility for the removal of product residues relies primarily on the operator who performs the cleaning tasks manually.

Cleaning tasks performed without adequate planning often falls short of the desired goals or misses them entirely. In the long run, the required rework at the end of the process takes much more time than it would have taken to plan adequately – a living proof of the variation on Murphy's Law: "There's never time to do it right, but always time to do it over".

BACKGROUND

The Pharmaceutical Plant's constraint is to manufacture their drug product and remain in compliance with the established FDA regulations. In order to accomplish the FDA acknowledge the manufacturing practices they consider correct. These practices, known as current good manufacturing practices (cGMP's) are used by the manufacturer as a guide to develop and establish their operating procedures. The cGMP's related to cleaning process include the control of microbiological contamination; equipment and utensils cleaning and maintenance; avoidance of adulterated drugs and devices; and guides to assure that product drug meets the characteristics of quality and purity it purports or is represented to possess. A cleaning verification is performed to assure the equipment is suitable prior to the next use, nevertheless manual cleaning is considered the worst – case scenario. Any production area and equipment used for the manufacturing of a drug product shall be visually examined prior to use to ensure that all production materials and documents not required for the subsequent operation have been removed and both the equipment and area are visually clean. Understanding each aspect of the process, the relationships among these activities, and the sequence in which they should take place will facilitate the development of a robust cleaning validation program and a successful FDA inspection experience. Multiple publications and guidelines from regulatory agencies that make this critical process of equipment cleaning easier exist.

The question is: whether to take risk in quality with an easier process or make it easier without affecting quality. Because of industrial globalization and fast tract advances in technology, today's manufacturing environment is increasingly competitive.

Manufacturers need to stay focused on finding new ways to design, produce, sell and deliver quality products. They should identify opportunities for improvement and reduce the risk of not conformance. Although there will be unforeseeable circumstances that remain out of management control, in many cases they can anticipate and be prepared for potential problems.

Throughout the years, the significance of managing has changed. Some would define management as an art, while others would define it as a science. Whether management is an art or a science isn't what is most important. Management is a process that is used to accomplish organizational goals; that is, a process that is used to achieve what an organization wants to achieve.

The role of a manager has changed; years ago, managers were thought of as people who were "the boss." While that might still be true today, many managers view themselves as leaders rather than as people who tell subordinates what to do.

Managers are the people to whom this management task is assigned, and it is generally thought that they achieve the desired goals through the key functions of (1) planning, (2) organizing, (3) directing, and (4) controlling. Some would include leading as a managing function, but for the purposes of this discussion, leading is included as a part of directing. The four key functions of management could be applied throughout the Manufacturers organization. Manufacturers have different needs dictated by the product they produce, following regulations guidelines and the product quality level they sustain, for example: Pharmaceuticals - use quality to comply with regulations while keeping low costs. The point is how the operator who performs the cleaning tasks manually applies the key functions of management during the cleaning and manages effectively this process in order to obtain satisfactory results.

Planning in any organization occurs in different ways and at all levels. A top-level manager plans for different events than does a manager who supervises. The plant manager must be concerned with the overall operations of the plant, while the assembly-line manager or supervisor is only responsible for the line that he or she oversees.

Planning could include setting organizational goals. This is usually done by higher-level managers in an organization. As a part of the planning process, the manager then develops strategies for achieving the goals of the organization. In order to implement the strategies, resources will be needed and must be acquired. The planners must also then determine the standards, or levels of quality, that need to be met in completing the tasks.

In general, planning can be strategic planning, tactical planning, or contingency planning. Strategic planning is long-range planning that is normally completed by top-level managers in an organization. Examples of strategic decisions managers make are: who the customer or clientele should be, what products or services should be sold, and where the products and services should be sold. Short-range or tactical planning is done for the benefit of lower-level managers, since it is the process of developing very detailed strategies about what needs to be done, who should do it, and how it should be done. Plans must be made for the best way to move it through the plant so that each worker can complete assigned tasks in the most efficient manner. These plans can best be developed and implemented by the line managers who oversee the cleaning process rather than managers who sit in an office and plan for the overall operation. The tactical plans fit into the strategic plans and are necessary to implement the strategic plans.

Contingency planning allows for alternative courses of action when the primary plans that have been developed don't achieve the goals of the organization.

Organizing refers to the way the organization allocates resources, assigns tasks, and goes about accomplishing its goals. In the process of organizing, managers arrange a framework that links all workers, tasks, and resources together so the organizational goals can be achieved. The framework is called organizational structure. Organizational structure is shown by an organizational chart that depicts the structure of the organization showing positions in the organization, usually beginning with the top-level manager (normally the president) at the top of the chart.

Directing is the process that many people would most relate to managing. It is supervising, or leading workers to accomplish the goals of the organization. In many organizations, directing involves making assignments, assisting workers to carry out assignments, interpreting organizational policies, and informing workers of how well they are performing. To effectively carry out this function, managers must have leadership skills in order to get workers to perform effectively. Some managers direct by empowering workers. This means that the manager doesn't stand like a taskmaster over the workers barking out orders and correcting mistakes. Empowered workers usually work in teams and are given the authority to make decisions about what plans will be carried out and how. Empowered workers have the support of managers who will assist them to make sure the goals of the organization are being met. It is generally thought that workers who are involved with the decision-making process feel more of a sense of ownership in their work, take more pride in their work, and are better performers on the job. By the very nature of directing, it should be obvious that the manager must find a way to get workers to perform their jobs. There are many different ways managers can do this in addition to empowerment, and there are many theories about the best way to get workers to perform effectively and efficiently.

The controlling function involves the evaluation activities that managers must perform. It is the process of determining if the company's goals and objectives are being met. This process also includes correcting situations in which the goals and objectives are not being met. There are several activities that are a part of the controlling function. Managers must first set standards of performance for workers. These standards are levels of performance that should be met. For example, in a cleaning process, the standard might be the completion of a process in twenty hours without deviations. This is a standard that must then be

communicated to managers who are supervising workers, and then to the workers so they know what is expected of them.

After the standards have been set and communicated, it is the manager's responsibility to monitor performance to see that the standards are being met. Once the problems are analyzed and compared to expectations, then something must be done to correct the results. Normally, the managers would take corrective action by working with the employees who were causing the delays. There could be many reasons for the delays. Perhaps it isn't the fault of the workers but instead is due to inadequate equipment or an insufficient number of workers. Whatever the problem, corrective action should be taken.

METHODOLOGY

The Cleaning Validation Process program of two Pharmaceutical Plants were studied and evaluated with a Value Stream Mapping technique. Of these two plants, one is developing and the other already has a validated cleaning process. The study case was performed on the plant with the validated cleaning process. Non-value – adding activities were identified from a Coater machine cleaning process flowchart.

Throughout a survey, current procedures of Cleaning Validation Process were analyzed to determine if management functions are being applied. The total sample used in the study is ten manufacturing Coater machine operators from a pharmaceutical company of a specific product. These operators are distributed in three shifts seven days a week. All ten operators are fully trained on coater cleaning procedure with technical knowledge required to perform such duty. The surveyed completed the auto submitted questionnaire without the intervention of the interviewer. The questionnaire was returned completely answered confidentially. The questionnaire was submitted on the month of August 2008.

The effectiveness of the steps used to clean equipment in contact mistake - proof challenge was measured due to failures or discrepancies of the procedure execution in a period of three consecutive months (July-September 2008).

The utilization level of management functions during the execution of cleaning procedure was established and its impact for success was recommended. A methodology guideline was designed for an effective management process. This provided recommendations, remedial and corrective actions to achieve an effective cleaning validation management.

RESULTS

The following table shows the results obtained in the survey. According to the survey results, 100 percent of the surveyed agreed that the operational cleaning procedure is considered as critic.

This means that procedure can impact the product quality. For which employee is completely convinced of the importance of such procedure and committed to execute correctly, as per standard operating procedure.

An 80 percent of the surveyed people indicate that the procedure’s instructions are not clearly delineated. This result shows that the managerial function of the organization was not effectively applied. Therefore, causing possible delay on the task realization due to confusion and leading to further negative consequences.

Significantly, 60 percent of the participants point out that ten percent of the required time for task completion they have to wait for an administrative decision. In this manner, deficient planning from the management is demonstrated. The directing function should be more effective; this is obtained with more accessibility from the supervisor to the employees. The recommendation is a more diligent supervisor that dedicate more time on the floor with the employee.

An 80 percent of the surveyed employees are classified on subject matter expert (SME) according to training curriculum requirements.

Table 1

Survey Questionnaire and Answers

Questions	Answers	
1. Do you consider the cleaning operational process as?	critic	10
	non-critic	0
2. Does the current standard cleaning operational process clearly delineate all the steps to be executed?	yes	2
	no	8
3. What is the percentage of times, in general terms, you wait for an administrative decision to continue with the cleaning operational process?	5%	3
	10%	6
	25%	1
	50%	0
4. In a scale of 1 through 10 in which 10 means that you are an expert operator and in addition, certified in the cleaning procedure and 1 that you have absolutely no experience in this matter, indicate how would you describe yourself?	seven	2
	eight	6
	ten	2
5. How many interruptions do you have during the cleaning operational process from start to end?	one	0
	two	2
	three	0
	more than three	8
6. Which one of these options describe best your point of view:	The cleaning operational process is not aligned with the practice and way of operating.	8
	I can follow each of the steps of the cleaning operational process, one by one, without difficulty and gain satisfactory results.	2
7. Are you involved since the beginning of the cleaning operational process stratification or making of plans?	yes	0
	no	10
8. Has the supervisor asked you to help improve a current cleaning operational process?	yes	10
	no	0
9. Are you convinced with the personnel assigned to accomplish the cleaning operational process to be fully trained with the technical knowledge required to perform such duties?	yes	10
	no	0
10. Are you convinced that the manufacturing operator assigned to accomplish the cleaning operational process is a capable expertise in that matter?	yes	3
	no	7
11. Can you determine the critical steps while performing a cleaning operational process?	yes	8
	no	2
12. When a cleaning operational process needs to be re-evaluated, are the plans to strive improvement, established by the administration, workable and easy to implement solutions?	yes	0
	no	10

The 80 percent of the surveyed indicate interruption in more than three times during the task realization. This reflects a lack of control in the moment of the job's accomplishment. Controllable interruptions should be diminished or possibly eliminated.

The whole part surveyed are convinced that training and technical knowledge is necessary for performing cleaning duties. Furthermore, only 30 percent believe that this training and knowledge is interrelated that can be applied to different products. 70 percent agree that employees should be fully trained, including cleaning procedures, for particular areas or products. Employees are not 100 percent dedicated to a particular product.

An 80 percent indicates that operational Cleaning procedure is not aligned to reality. The operator presents difficulty on the persistent consultation seeking for direction. The provided procedure instructions do not guarantee wanted results.

All of the surveyed agree in not forming part of the cleaning process planning. This demonstrates that executers, principal job resource, are not considered in planning.

According to the survey, 80 percent of the surveyed employees indicate capability of determining critical steps on cleaning operational procedures.

The total sample indicates the consult in some moment for the improvement of the procedure. This demonstrates a good direction focusing on employee contribution, although noticing difficulty on implementation from the management because of bureaucratic means. Finally, employees' idea is undervalued and not implemented.

Using the process flowchart technique, cleaning process steps were identified as value adders or non-value. Value adders are identified by questioning if the costumer is willing to pay for the time required to perform each specific cleaning step or task in order to guarantee the product's quality. On the other hand, if the task is done to confirm that the work was correctly done, it is considered as non-value. Most of the time, non-value adders

increase costs to the company. Non-value adders and their total cost are shown in the Tables below (2-4). The cleaning process from start to finish at optimum conditions takes 17.5 hours. The cleaning process is realized once a week (five labor days) per machine. Fifty two (52) weeks make up a year; two weeks are subtracted for shut down purposes yearly. This analysis considers one machine with a crew of three (3) certified operators whose working fee is $20/hour on any shift.

Table 2

Cost Analysis per non-value delaying Tasks

Step #	Tasks identified as non-value	Task time in minutes	Total cost daily and weekly/task	Total cost monthly /task	**Total cost yearly/task**
13	Fill tank with purified water and discharge tank.	190	190.00	760.00	9500.00
17	Request authorization for confined spaces	30	30.00	120.00	1500.00
20	Document starting time to clean the eight (8) teflon defectors.	01	1.00	4.00	50.00
24	Document time and date finished.	01	1.00	4.00	50.00
25	Document starting time to clean the six (6) twigs.	01	1.00	4.00	50.00
29	Document time and date finished.	01	1.00	4.00	50.00
30	Document starting time to clean the four (4) stainless steel defectors.	01	1.00	4.00	50.00
34	Document time and date finished.	01	1.00	4.00	50.00
35	Document starting time to clean the by-pass.	01	1.00	4.00	50.00
46	Document finished time and date when clean the by-pass.	01	1.00	4.00	50.00
47	Document starting time for pre- wash of equipment inside walls.	01	1.00	4.00	50.00
49	Document time and date finished.	01	1.00	4.00	50.00
52	Document starting time and date for spray balls cleaning.	01	1.00	4.00	50.00
58	Document time and date finished.	01	1.00	4.00	50.00
59	Document starting time for Coating Pan cleaning.	01	1.00	4.00	50.00
62	Document time and date finished	01	1.00	4.00	50.00
64	Document starting time and date for Coater cleaning.	01	1.00	4.00	50.00
69	Follow instructions for drying process.	02	2.00	8.00	100.00
74	Notify the Manufacturing Leader after cleaning completion.	15	15.00	60.00	750.00
	Total	252	252.00	1,008.00	12,600.00

Table 3

Cost Analysis per non-value movement of Material or Service from one location to another Tasks

Step #	Tasks identified as non-value	Task time in minutes	Total cost daily and weekly/task	Total cost monthly /task	**Total cost yearly/task**
5	Get cleaning utensils at storage cabinet outside the room	15	15.00	60.00	750.00
19	Remove internal parts of coating pan and take to sink.	60	60.00	240.00	3000.00
36	Clear inlet air side opening trap doors.	05	5.00	20.00	250.00
40	Close trap doors.	05	5.00	20.00	250.00
41	Open trap doors exhaust air side of the by-pass.	05	5.00	20.00	250.00
45	Close trap doors.	05	5.00	20.00	250.00
50	Remove manifold and disassemble parts	30	30.00	120.00	1500.00
51	Locate parts and manifold in washer sink.	02	2.00	8.00	100.00
53	Remove all spray balls.	15	15.00	60.00	750.00
57	Re- installs all spray balls.	15	15.00	60.00	750.00
63	Re- installs interior parts of Coating Pan.	60	60.00	240.00	3000.00
	Total	202	202.00	808.00	10,100.00

Table 4
Cost Analysis per non-value work or service for Completeness, Irregularities or Quality Tasks

Step #	Tasks identified as non-value	Task time in minutes	Total cost daily and weekly/task	Total cost monthly /task	**Total cost yearly/task**
11	Equipment visual inspection (report any malfunction, worn piece, assure equipment is product free)	05	5.00	20.00	250.00
72	Verify and assure that all equipment is clean and dry.	30	30.00	120.00	1500.00
75	Cleaning verification/inspection from manufacturing leader	30	30.00	120.00	1500.00
	Total	65	65.00	260.00	3,250.00

A result of process flowchart analysis shown on the graph (Figure 1) indicates that there is an excellent opportunity for optimizing cleaning process. It allows one to focus effort in the non value activities that in this case limits a system from achieving higher performance versus goal. It shows ineffective time management, inefficient resource utilization, excessive cleaning material use and repetitive steps to perform work. If management theory were applied in this case, the first step should be establishing a goal. Achieving a goal depends on the classification of each step in terms of its contribution to the realization of the principal objective.

The principal objective is to perform an effective and cost efficient clean. For that reason, it is important to determine if each step drives, deviates, or maintains on reaching the objective. Throughout this research, although the cleaning procedure was validated, noticeably the lack of Administrative Management Theory application is perceived.

When establishing a procedure for cleaning equipment, the management needs to clearly demonstrate that planning was taken into consideration by establishing a clear objective in terms of time and quantity of work done. This procedure should show organization in sequence of steps followed.

After several times of repetitiveness with the expected results written procedures should be established with a description in sufficient details of the steps, instructions and the directions to be followed. Focusing on an effective process monitoring the standardization of the tasks reduce variability obtaining a sustainable performance. The person who is assigned to clean the equipment should demonstrate confidence in using the established procedure and guidelines to perform it efficiently and cost-effectively. The number one goal for optimization is to maximize the time utilized to perform effective equipment cleaning with less time spent. Repeating steps, waiting for permission and or making decisions delay the process.

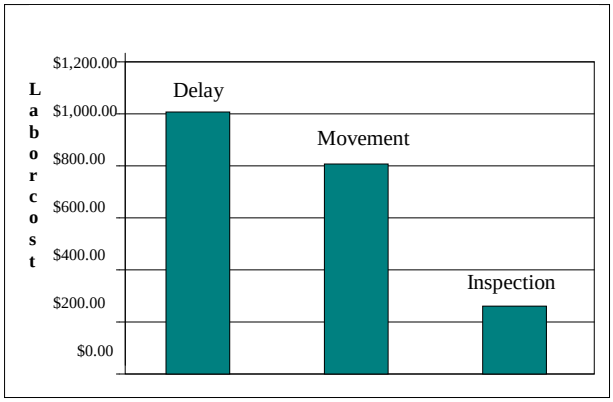

Figure 1
Histogram on non-value Tasks Cost Analysis on a Monthly Basis

These steps should be ordered in a way that the person assigned to execute them can realize the job without deviation and continuously directing to achieving the principal goal. Nevertheless, in a period of three months using the established procedure several incidents of deviation and discrepancies were reported. The following graph (Figure 2) shows a tendency of observed faults.

After revising the procedure from beginning to end we can observe a deficiency of the supervisor's assistance. This lack of direction can contribute to error or deviation in the process. This type of fault

can interrupt the flow of continuous work. When not counting with the immediate support of the supervisor or facilitator, the cleaning process can run wild. An uncontrolled cleaning process may be due to the time the assigned operator remains unauthorized or waits for an administrative decision. Also, if the person assigned needs to clarify any doubt regarding the steps to follow the process is delayed or possible errors can occur.

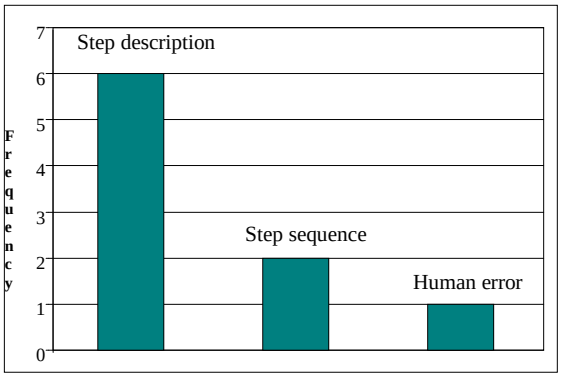

Figure 2
Histogram on the Frequency of Faults occurred in a Period of three months which required Investigation

Deviations were due to human error, step description and step sequence. When referring to human error, we focus on operator's distraction. Step description regards various interpretations because of incongruence in the description. The sequence of steps refers to the lack of organization in logical sequence.

We can observe from the graph that the top fault tendency is caused by step description. This indicates that specific step instructions and directions in sufficient detail are not established.

CONCLUSION

According to these results, the answer for the primary question is that cleaning faults are mostly due to administrative issues. In this case, the findings during incident investigations do not show that cross contamination nor residue limits were the problem's cause. For which, product quality and/or procedure effectiveness is not questionable. Furthermore, the company establishes as a corrective action to retrain operators and reform standard operating procedures to include special additional instructions. However, it is my concern that the real root cause was not identified according to tendency results shown. The root cause was not, indeed, eradicated. During root cause analysis, if a corrective plan is not established to attend these faults, issues with regulatory agencies could appear. As a result, an open door is left for further deep investigation of these tendencies. Based on the study and evaluation of the cleaning validation program of two pharmaceutical plants I observed that the Administrative Management Theory needs to be applied in the revision of the standard operating procedure.

The Administrative Management Theory has a crucial role to achieve goals and sustain results. A smart delegation has to be chosen for careful planning and the implementation of this theory. Possible candidates include: administrators, accountants and planners. This delegation will, then, be part of a cross-functional interaction focal group. This way, people with administrative skills will be responsible of assuring cost- effective prioritization of projects, efficient time management, and effective organization on steps to be followed with effective supervision and operation control.

Value stream mapping is a basic planning tool for identifying wastes, designing solutions and communicating the utilization of resources through the visualization of materials and information flows. This technique was applied to establish guidelines for an optimized cleaning process. With the value stream map, refer to Figures 3-7, the operators will accomplish a fault-free procedure. In conclusion, the Administrative Management Theory should be embedded on the cleaning process development to guarantee optimized procedures. The optimization would resemble on a 40% reduction of cycle time and $15,600 on yearly labor costs.

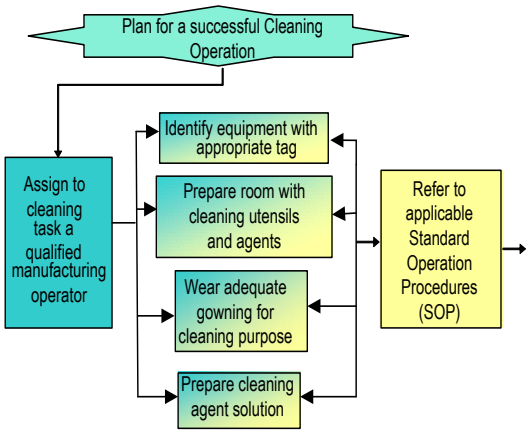

Figure 3
Cleaning Process Validation Flowchart addressed to optimization by means of the Administrative Management Theory

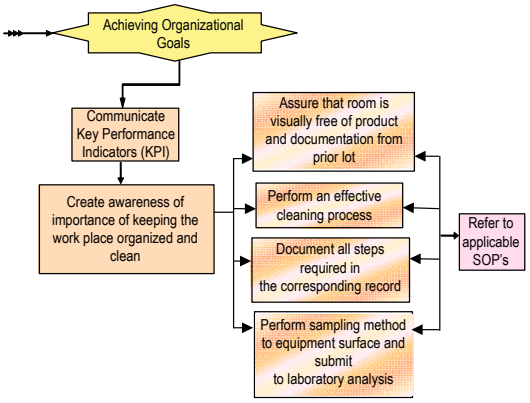

Figure 4
Cleaning Process Validation Flowchart

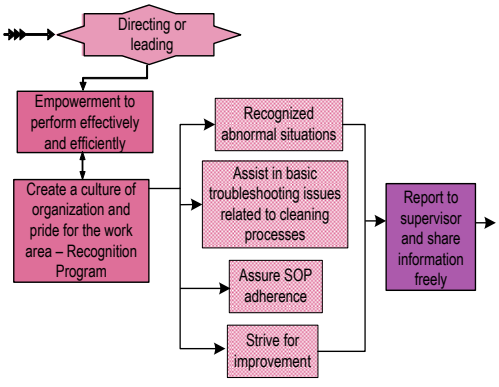

Figure 5
(Cleaning Process Validation Flowchart

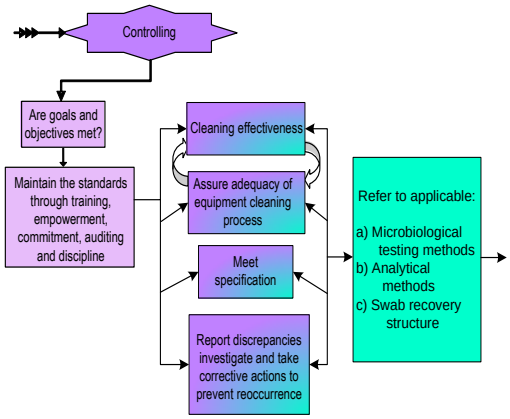

Figure 6
Cleaning Process Validation Flowchart

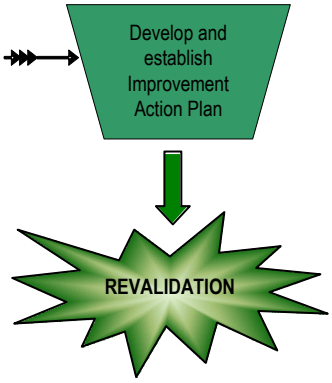

Figure 7
Cleaning Process Validation Flowchart

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