Cleaning Validation of a Manufacturing Line using CIP-100 Detergent and a Clean-in-place Skid System

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Abstract

Cleaning Validation is a prime element of control to the cross contamination and potential carryover topic at the manufacturing industry. This process must assure the quality, safety and efficiency of cleaning process for residual materials from previous batches manufactured in the same manufacturing line. The cleaning effectiveness will be determined by using critical quality attributes verification methods such as: Visual inspection, Analytical residues determination for total organic carbon (TOC), Microbial testing and Conductivity readings (in-line instruments for CIP100). Indirect method will be used as the only method because all sampling points are rinse samples (liquid). Providing documented evidence that the method employed at the facility consistently controls impurities that can be hazard to the human health.

Key Terms — Clean-In-Place (CIP) Skid System, Contamination, Cleaning Validation, Validation.

Introduction

The Validation concept was introduced by the United State Food and Drug Administration (U.S.F.D.A) officials at the 1970s due to problems that affect the quality of manufactured products [1]. At the year 1976, FDA develop the first Good Manufacturing Practices (GMP) regulations that nowadays are followed as a good management and business practices. The pioneer concept of validation or process validation is defined by the U.S.F.D.A, as a tool of documented evidence that proves a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specification and quality characteristics [2].

Cleaning validation is part of the FDA requirements to prove that the equipment involved prevent cross contamination and adulteration of the product [3]. This includes written procedures, sampling methods detailing the cleaning process for each equipment involved between different batches of the same product or different product. Practical standardized microbial acceptance limits are used as a measurement of effectiveness and are determined through the guide used to inspect Validation Cleaning Process at the pharmaceutical industry [4]. The refurbished filling line has been installed at the manufacturing facilities. Therefore, a cleaning validation process is required using its dedicated **Clean-In-Place (CIP) Skid System**.

Research Objectives

This validation will establish documented evidence that the cleaning process of the Clean-In-Place (CIP) Skid System, is capable to remove media products residues, CIP100 cleaning agent residues, and reduce the microbial bioburden from Media into acceptable levels in order to prevent carryover contamination to the next product manufactured in Filling Line. .

Research Contribution

The FDA considers cleaning validation necessary for product development, establishing controls and guidance for the manufacturing department. Involving multidisciplinary departments as; Engineering, Quality, Compliance for accurate results in products with the desired quality attributes. Also cleaning validation reduce product recalls and troubleshooting helping economical operations at the company. A robust process validation process facilitates the FDA pre-approval inspection program, sustained by empirical data collection and ensures public health.

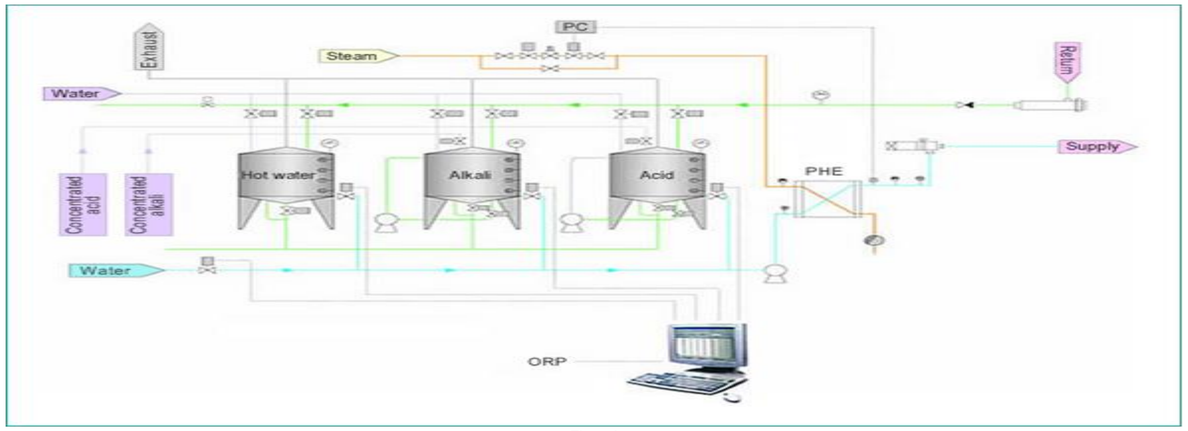

Figure 1
Clean In Place Process General Operation using the CIP Skid System

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 °C	55 °C	TOC Results [ppm]	Pass/Fail
Microbiological Test (CFU's/mL) for CIP-100 cleaning agent	Microbiological Test ≤150 CFU's/mL (liquid samples)	1	8	0	0.122	Pass
		2	1	0	0.129	Pass
		3	0	0	0.141	Pass
		4	3	0	0.142	Pass
		5	0	0	0.156	Pass
		6	0	0	0.148	Pass
		7	0	0	0.147	Pass
		8	1	0	0.126	Pass
TOC Results	Total Organic Carbon Test ≤13 ppm (liquid samples)	9	2	0	0.139	Pass
		10	0	0	0.147	Pass
		11	0	0	0.023	Pass
		12	6	0	0.139	Pass
		13	0	0	0.161	Pass
		14	0	0	0.150	Pass
		15	1	0	0.143	Pass
		16	0	0	0.135	Pass

Table 5: Run 1

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 °C	55 °C	TOC Results [ppm]	Pass/Fail
Microbiological Test (CFU's/mL) for CIP-100 cleaning agent	Microbiological Test ≤150 CFU's/mL (liquid samples)	1	0	0	0.519	Pass
		2	0	0	0.426	Pass
		3	0	0	0.501	Pass
		4	0	0	0.440	Pass
		5	0	0	0.050	Pass
		6	0	0	0.652	Pass
		7	0	0	0.319	Pass
		8	0	0	0.414	Pass
TOC Results	Total Organic Carbon Test ≤13 ppm (liquid samples)	9	0	0	1.454	Pass
		10	0	0	2.198	Pass
		11	0	0	0.241	Pass
		12	0	0	0.589	Pass
		13	0	0	0.236	Pass
		14	0	0	0.389	Pass
		15	0	0	0.231	Pass
		16	0	0	0.516	Pass

Table 6: Run 2

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 °C	55 °C	TOC Results [ppm]	Pass/Fail
Microbiological Test (CFU's/mL) for CIP-100 cleaning agent	Microbiological Test ≤150 CFU's/mL (liquid samples)	1	0	0	0.087	Pass
		2	0	0	0.093	Pass
		3	0	0	0.095	Pass
		4	0	0	0.096	Pass
		5	0	0	0.107	Pass
		6	0	0	0.134	Pass
		7	0	0	0.168	Pass
		8	0	0	0.105	Pass
TOC Results	Total Organic Carbon Test ≤13 ppm (liquid samples)	9	0	0	0.248	Pass
		10	0	0	0.275	Pass
		11	0	0	0.228	Pass
		12	0	0	0.212	Pass
		13	0	0	0.121	Pass
		14	0	0	0.109	Pass
		15	0	0	0.107	Pass

Table 7: Run 3

Methodology

A total of three (3) cleaning runs will be performed as part of this Cleaning Validation. The three (3) cleaning runs will be performed after dispensing Media product to Filling Line. The product sampling locations included in this validation are the 16 nozzles locations that will be sampled by collecting liquid samples from each one and one control sample from the DI system water (Refer to Table 1).

Runs definitions associated with the validation – Three (3) runs were selected to comply with minimum requirements of run replications of current manufacturing operations. The three (3) runs will be performed after Media formulation and transfer to filling line.

The cleaning effectiveness will be determined by using critical quality attributes verification methods such as: Visual inspection, Analytical residues determination for total organic carbon (TOC), Microbial testing and Conductivity readings (in-line instruments for CIP100).

The Rationale Method contain the methods to be used to assess the results against the acceptance criteria and number of samples selected (Refer to Table 2). Visual inspection will be performed as a first-tier evaluation prior to location sampling. No visual signs of residue in product. If signs of residue are visible, test will fail and there is no need for performing the sample test. Deviations to this approved protocol will be addressed including corrective actions, will be properly documented.

Results and Discussion

The intention of this section is to summarize the results for this validation comparing against acceptance criteria. Information shall include KPOV, Acceptance Criteria, Result and Pass/Fail. All individuals involved in the cleaning validation execution were trained. The prerequisite steps specified in the CV protocol were completed prior to execution of the CV. The Cleaning validation was approved prior execution and training on execution of the CV protocol was completed prior execution. The cleaning process failure mode and effect analysis (pFMEA) was approved. No high-volume items (RPN >125) were identified during risk analysis for the KPIV's included in this CV. The CIP-100 cleaning agent capacity for media residuals was tested, and all samples for the microbiological test results met the acceptance criteria of ≤150 CFU's/mL (liquid samples) for the three (3) runs (Refer to Tables 3 and 4). The CIP-100 cleaning agent capacity for media residuals was tested, and all samples for the Total Organic Carbon (TOC) results met the acceptance criteria of ≤13 ppm (liquid samples) for the three (3) runs. Also, the visual results obtained met the acceptance criteria, no residual material was observed (liquid samples) for the three (3) runs. All deviations from the cleaning validation were documented, analyzed, corrected and approved.

Conclusion

The cleaning process using the CIP-100 as a cleaning a agent performed under, was successfully executed. The CV activities provided documented evidence that the cleaning process with CIP-100 cleaning agent and Filling was validated in accordance with the requirements established. Based on the comparison of the results presented in this report against the acceptance criteria, it can be concluded that the cleaning agent sequence challenged during the cleaning validation activities using CIP-100 as cleaning agent was completed successfully (Refer to Tables 5, 6 and 7).

References

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