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.

PROBLEM STATEMENT

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**. This validation will challenge the capacity of the CIP Skid, using current validated cleaning parameters, to remove media residues from the line. This cleaning validation, using CIP100 as cleaning agent, will be executed after the filing process of media in the flow paths to filling line. Three (3) cleaning validation runs with satisfactory results should be obtained to validate the cleaning agent CIP100 for use in the Media tanks delivering products to Filling Line. The current approved cleaning procedures will be used in this validation. The intention is to guarantee that the cleaning process is standardized and reliable to reduce media product residues carryover from a previous production batch to subsequent batches to acceptable limits.

Research Description

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. To comply with the FDA requirements and appropriate sampling method shall be performed for example, rinse sampling or swabbing sampling to guarantee that the manufactured product do not represent a quality risk. 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].

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.

RESEARCH BACKGROUND

The cleaning process for a manufacturing line must be design for effective and consistent to guarantee the product integrity and effectiveness.

Cleaning Validation

The cleaning validation process importance at the pharmaceutical industry nowadays had increase due to the FDA requirements and economic factor to the pharmaceutical production. Cleaning validation has two major objectives; the first one is to ensure safety efficiency and quality of the manufactured product. The second one is to minimize the equipment downtime considering an impact to the economics for the company. Standard cleaning procedures and disinfectants for each equipment the manufacturing process minimizes the opportunity for microorganisms to proliferate and preventing cross contamination [5].

Clean in place Skid System (CIP) and CIP-100 Detergent

Clean-In-Place Skid System is technique used for the interior product contact surfaces such as process pipes, vessels and equipment, without disassembly. This cleaning process important factors applied to this system are the **T**ime, **A**ction, **C**hemical and **T**emperature (**TACT)**, establishing that for effective cleaning, decreasing one factor automatically implies strengthening one or more of the others (Figure 1). For this system the time of exposure, the mechanical action of the water, the temperature and the chemical agent parameters must be optimized to guarantee the successful for the cleaning process. The CIP100 is an alkaline liquid used as process and research cleaning detergent and is specially formulated for the industries and it effectively removes a wide range of process residues. The special surfactant selected for CIP100 cleaner is active across the full pH range (from pH 2.0 to pH 13.5) and across the full temperature range from 5ºC to 85ºC. CIP100 is free of perfumes and dyes and is designed to be extremely free rinsing. The composition of CIP100 is: 10% to 30% of potassium hydroxide and 1% to 5% of Tetrasodium EDTA.

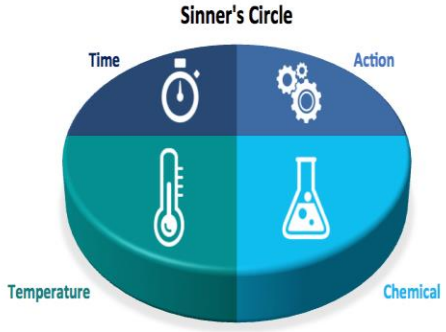

Figure 1
Factors in Sinner's Circle of a Clean in place Skid System

Process Description

The CIP skid perform the cleaning of the mix tanks, hold tanks and filling line using automated recipes (Figure 2). The CIP skid programming will allow the cleaning process to run independently for a mix tank, hold tanks and filling line. The cleaning procedure will consist of a deionized water (DI) flush at ambient temperature followed by a caustic wash with CIP detergent and a two-rinse cycles. The DI water flush will remove any remaining media in the tanks/filler path and prepare the system for the chemical cleaning. The chemical cleaning cycle will cover the media paths to remove media residues and provide sanitization of the system, if required. The rinse cycle will flush any remnants of CIP/sanitization agent solution using DI water at the

temperature, flow rate and time required. The CIP skid System functions will be accessed via Human Machine Interface (HMI). The CIP Skid programming can perform the following operations: (1) Clean and Sanitize, (2) Clean only. The operator selects the cleaning operation to be performed, the tank or filling line to be cleaned and monitor the cleanliness status of the tanks. The system also provides a timer to monitor the Clean Expire Time. The valves configuration will allow the cleaning of the mix tanks, hold tanks and filler transfer lines (including the filler) without compromising the CIP solution, the media or the product being filled.

The mix tank is used to mix product at an elevated temperature to dissolve raw materials. Upon completion of the mixing cycle, the product is transferred to one of the hold tanks for completion of the batch and then transfer to the filler. After the first batch/portion has been transferred out to the Hold tank, the mix tank is to be cleaned with a CIP process. System (HMI) shall indicate that the Mix Tank is dirty. Once the mix tank is cleaned, a second batch/portion of product can be started.

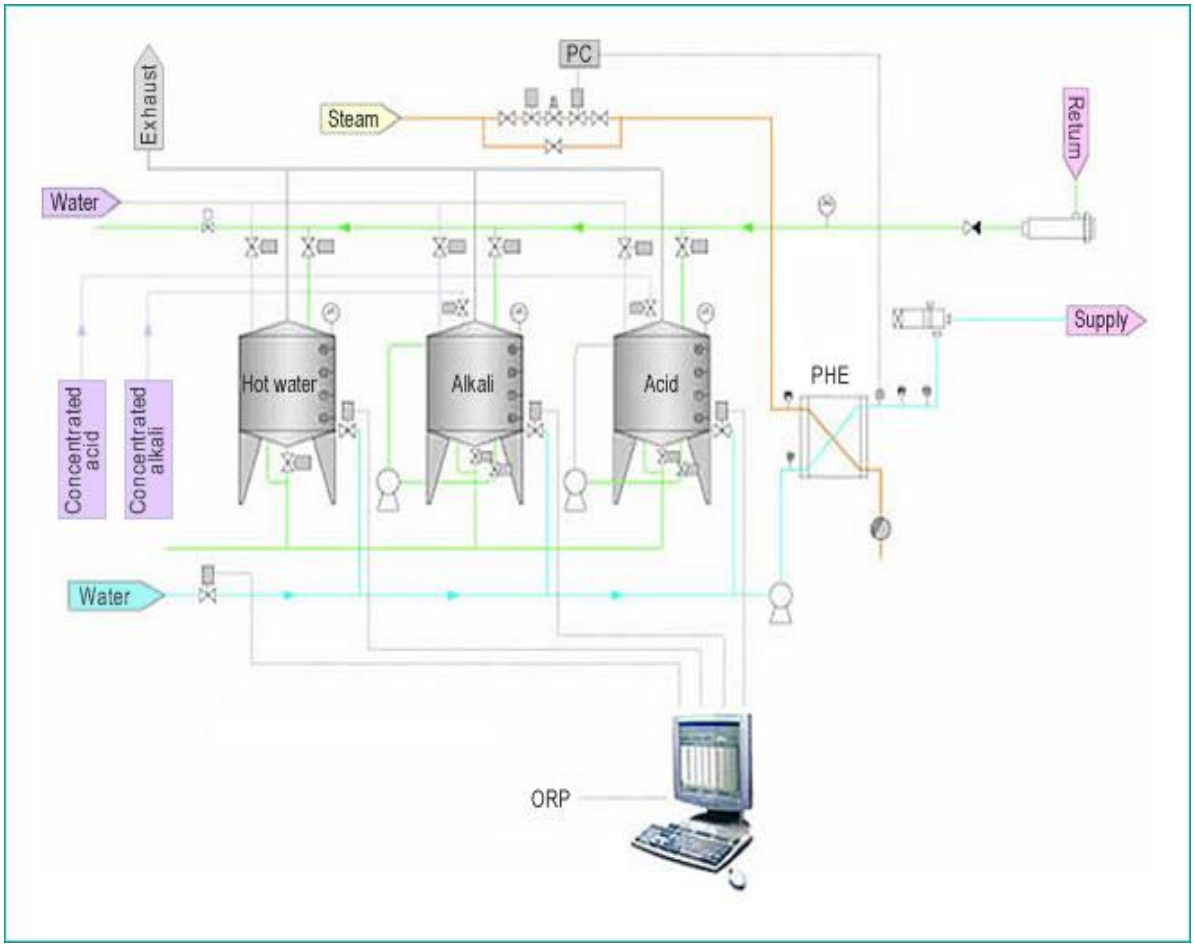

Figure 2
Clean In Place Process General Operation using the CIP Skid System

Upon completion of the second batch/portion in the mix tank, it will be transferred to the second hold tank and the mix tank cleaned again. The media preparation process will continue in this manner until the manufacturing run(s) have been completed. Media that has been transferred to the hold tanks is heated to the product's required temperature. Heated product is held at that temperature for several hours during discharge. It is held at product required temperature for several hours during discharge/transfer to filling line. The mix tank and hold tank side wall jackets are zoned so that as the tank empties over time, a zone's hot water or steam supply can be shut down independently to improve

temperature control and reduce product baking onto the side of the tank. The cleaning agent CIP100 will be used in Media and Filling Line.

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).

Table 1
Filling Line Sampling Points

Sample Location	Plate Count (35°C and 55°C)	TOC Sample Type
Nozzle #1	Liquid	Liquid
Nozzle #2	Liquid	Liquid
Nozzle #3	Liquid	Liquid
Nozzle #4	Liquid	Liquid
Nozzle #5	Liquid	Liquid
Nozzle #6	Liquid	Liquid
Nozzle #7	Liquid	Liquid
Nozzle #8	Liquid	Liquid
Nozzle #9	Liquid	Liquid
Nozzle #10	Liquid	Liquid
Nozzle #11	Liquid	Liquid
Nozzle #12	Liquid	Liquid
Nozzle #13	Liquid	Liquid
Nozzle #14	Liquid	Liquid
Nozzle #15	Liquid	Liquid
Nozzle #16	Liquid	Liquid

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.

Table 2
Rational Method

Run	Rationale
1	Indirect method will be used as the only method because all sampling points are rinse samples (liquid). After completing the cleaning process, a rinse water will be sampled for the cleaning material. Negative controls will be included with all sampling events to determine background contribution to results. Positive controls will be included to confirm analytical method detection at levels approximately equal to acceptance criteria.
2	
3	

Table 3
Cleaning Methodology Criteria

KPOV / CTQ	Sample point	Number of samples	Acceptance Criteria
Microbial Testing	16 nozzles filling line	A minimum of 17 samples (Including control)	≤ 150 CFU/mL (Liquid)
Analytical Chemical Test (TOC)	16 nozzles filling line	A minimum of 17 samples (Including control)	≤ 13 ppm (Liquid)
Visual Residues	16 nozzles filling line	N/A	No visual signs of residue in product contact surfaces

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.

Table 4
Cleaning Acceptance Criteria

<table>
<tr><th>Criteria</th><th>Cleaning Validation</th></tr>
<tr><td>Safety</td><td>1) All safety procedures are followed as defined in the equipment operation procedures.</td></tr>
<tr><td>Quality</td><td>1) The Key Process Input Variables (KPIV) for the cleaning cycles are agitation, flow, time and temperature to produce reliable and consistent cleaning cycles for the process equipment after run that meets pre-determined specification at normal operating conditions.</td></tr>
<tr><td>Production</td><td>1) All the samples collected must meet the specified acceptance criteria.
<table>
<tr><th>Testing Type</th><th>Agent</th><th>Testing Method</th><th>Acceptance Criteria</th></tr>
<tr><td>Visual Inspection</td><td>N/A</td><td>N/A</td><td>Visually Clean</td></tr>
<tr><td>Analytical/ Chemical Testing</td><td>CIP100</td><td>TOC (liquid & swab)</td><td>≤13ppm (Liquid samples)</td></tr>
<tr><td>Microbial Testing</td><td>CIP100</td><td>Plate Count (liquid sample)</td><td>≤150 CFU's/mL [1]</td></tr>
<tr><td>Conductivity</td><td>CIP100</td><td>In-Line conductivity meters</td><td>Set point: ≤ 1 miliSiemens/cm</td></tr>
</table></td></tr>
<tr><td>Documentation</td><td>1) All referenced and supporting documentation required for this qualification must be available.
2) The Signature and Training Log will be completed by all personnel involved in the protocol execution.</td></tr>
</table>

Table 5
RUN #1

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 ºC	55 ºC	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 6
RUN #2

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 ºC	55 ºC	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 7
RUN #3

KPOV/CTQ	Acceptance Criteria	Nozzle #	35 ºC	55 ºC	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

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. The acceptance criteria of less than ≤150 CFU's/mL for microbiological results (liquid samples) was achieved after the 3 runs were completed.

The acceptance criteria of less than ≤13ppm for the total organic carbon results (liquid samples) was achieved for all the 3 runs. The visual results obtained for all three runs (Refer to Tables 5, 6 and 7).

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