Optimizing Automated Clean-In-Place Operations to Increase Productivity in a Biotechnology Manufacturing Plant

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Abstract *— Automated Clean-In-Place Operations are an essential part of the manufacturing operations by ensuring a clean state of the equipment and/or transfer lines. However, during a voice of the customer (VOC) and value-added activities assessment, it was determined that some equipment surfaces were only exposed to salts solutions that were easy to remove. During these observations, it was evident that the clean-in-place operations needed to be optimized to increase productivity. Cleaning cycle optimization was performed under a characterization study that confirmed the effectiveness of the optimized cleaning cycle for non-product contact equipment and/or transfer lines. The optimization consisted of several rinses with purified water and a final rinse with hot water for injection (WFI). Automated recipes were modified to prevent the use of aggressive cleaning agents and/or recirculation's in the cleaning operation. The optimization of the cleaning operations increased productivity by hard savings in detergents and a significant cycle time reduction.*

Key Terms *— Automation, Cleaning, Clean-in-Place, Cycle Time, Productivity, Savings, Water for Injection (WFI).*

INTRODUCTION

Clean-in-place (CIP) is an essential part of the bio-pharmaceutical manufacturing [1]. CIP usually refers to an automated method of cleaning an equipment too large to be cleaned manually. The cleaning procedure works by circulating solutions composed of water and cleaning agents (i.e. citric acid, caustic soda) through the transfer lines and vessel to be cleaned. The mechanical force caused by the: 1) *turbulent flow rate*, 2) *heat used* and 3) *chemical interaction* of the cleaning agents ensures a thorough and reproducible cleaning as required per regulatory agencies all over the world. In terms of timing, the cleaning operations may be carried out prior to processing or between batches to ensure process sanitization and prevent carryover of product and/or unwanted impurities [2]. Failure to appropriately clean and sanitize the equipment could lead to unwanted soilants and/or contamination resulting in the loss of the batch [1]. A loss of a batch impacts the supply chain and could affect the supply of medicines to patients.

It is important to distinguish between product contact or non-product contact surface. When a surface makes any contact with the active ingredient is considered a product contact surface. Product contact surfaces have tighter acceptable residue limits that must be defined prior to any cleaning validation and development work [3].

BACKGROUND

The term "Clean-in-Place" generally refers to an automated system that consists of a recirculation system which uses various tanks and a return system such as an educator or return pumps. A system of piping delivers the cleaning solution to the equipment and returns it to a motive or recirculation tank. There is usually a pre-rinse tank and a final rinse or purified water rinse tank. The equipment utilizes spraying devices to provide coverage and physical impingement of the cleaning solution of the equipment surfaces. The spray-balls may be stationary or moving (e.g. rotating, oscillating). These systems are commonly used to clean large pieces of equipment such as manufacturing tanks, blenders, fluid bed dryers, reactors and fermentation tanks. It is important to note that the CIP system does not need to have a recirculation system, i.e., it may be single pass system where appropriate. Bulk pharmaceuticals are typically manufactured within

closed systems increasingly equipped with automated CIP equipment. The mechanical qualification of flow rates, pressures and spray balls must be established [4]. Figure 1 shows a typical clean-in-place system [5].

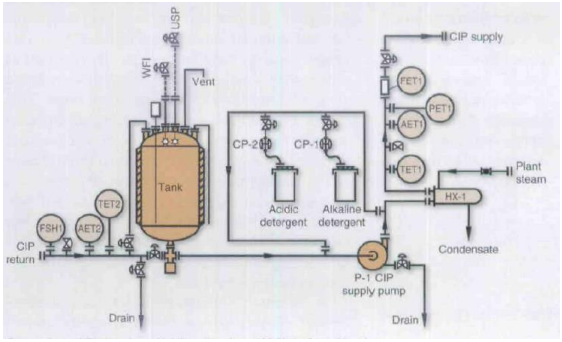

Figure 1
Typical Clean-In-Place System [5]

Critical Parameters

The critical control parameters for pharmaceutical process equipment cleaning include temperature, concentration, contact time and energy input. Control of these factors within scientifically determined boundaries provides the basis for the operation of cleaning cycles that are effective, repeatable, and reliable [5]. Laboratory-scale process residue cleaning studies can provide an excellent starting point for CIP cycle parameters [6].

- **Water/Detergent Contact Time -** Parameter is essential to ensure removal of components. The longer the contact time, the more effective the cleaning cycle, but this is not without cost because time spent cleaning is time not spent in production. Because of these factors the control and monitoring of contact time is critical for optimal cleaning cycle performance [5]. The contact time can be established by the rinses times.
- **Energy Input** – Cleaning solution turbulence and impingement are functions of the external energy put into the cleaning solution in the form of turbulence and impingement. These actions are critical for post-production residue removal. The transport phenomenon employed is mass transfer, and since the rate of mass transfer is directly proportional to turbulence (typically reported as a Reynolds Number) higher levels of turbulence generally result in higher cleaning rates. This makes the control and monitoring of cleaning solution turbulence a critical factor [5].
- **Temperature** – Cleaning solution temperature is critical because the cleaning rate is directly proportional to it for many pharmaceutical residues. As cleaning solution temperature increases, phenomena which are directly proportional to the cleaning rate increase, including reaction rates and residue solubility. With increased cleaning solution temperature, phenomena that are inversely proportional to cleaning rate decline, including chemical bond strength and solution viscosity. All this makes temperature control and monitoring a critical factor in the cleaning cycle performance [5].
- **Final Conductivity** - The parameter should be at the same level as the source water; this will indicate that there are no residual chemicals on equipment surfaces. Typically a 0-100 micro-Siemens sensor ensures that the purity of the final rinsing water is in accordance with established limits for clean equipment. A conductivity sensor is used for this task because conductivity is a criterion established in the U.S. Pharmacopeia (USP) for evaluating water purity and because many cleaning agents and some post-production residues are conductive and easily detected by this instrument. The conductivity sensor is installed on the return side of the cleaning system as this is the point of maximum surface area contact, making it a worst-case location [5].

Cleaning Frequency [4]

The frequency and rigor of cleaning is usually determined by the nature of the changeover process. For example, the frequency will depend upon whether the manufacturing involves many different products or several batches of the same product.

- **Between batches of different products -** When equipment is changed over from one product to another, cleaning must take place to prevent product cross-contamination.

- **Between batches of the same product (campaign)** - Validation should be accomplished to determine the number of lots of the same product that may be consecutively manufactured before a more rigorous cleaning necessary.

Cleaning Agent Selection

The development of a scientific rationale should apply to cleaning agent selection and limit determination in much the same way as it applies to product cleaning program development. Cleaning agents should be selected for their suitability to remove the product residues and for low toxicity. Detergents, rinsing fluids and cleaning agents should be acceptable to the process and for use with pharmaceutical products. The acceptable limits for cleaning agent residues should be established using scientific rationale in much the same way as the limits for product residues are established. The established cleaning agents should be reviewed against the vendor's current specification [4]. Methods of storage, expiration dating, inventory control, and change control of the cleaning agents will help establish and maintain a reproducible process.

It is important to note that laboratory testing must show that the chemical chosen is effective, but not corrosive or harmful to the system being cleaned. An industry standard is the use of a caustic solution with a high pH, such as CIP-100® alkaline detergent [7]. CIP-100® is a proprietary blend of potassium hydroxide, surfactants, chelants, and other performance-enhancing ingredients that provide multiple cleaning mechanisms. It has low foaming product that removes a wide range of process residues, from fermentation-by-products to silicone-based emulsions and lubricants that is ideal for clean-in-place (CIP) applications [7].

In addition, Citric Acid, i.e., such as a Micro® A-07 Citric Acid Cleaner is used for removal of oxide, scale, mineral deposits, milkstone, and inorganic soils. With a typical pH of 2.5, Micro A-07 is milder than most acids, yet powerful enough to replace more aggressive acid cleaners [8].

Water Quality

Water used to prepare cleaning agents and for equipment rinse should be of suitable quality. Generally, water used for final rinse should be the same grade used for the manufactured product, e.g., parenteral products should utilize WFI, oral products would employ purified water [4]. Table 1 presents the temperature and conductivity requirements for Water for Injection that meets the acceptance criteria of quality [6].

Table 1
Temperature and Conductivity Requirements [9]

Temperature (°C)	Conductivity (µs/cm)
0	0.6
5	0.8
10	0.9
15	1.0
25	1.3
30	1.4
35	1.5
40	1.7
50	1.9
55	2.1
60	2.2
65	2.4
70	2.5
75	2.7
80	2.7
85	2.7
90	2.7

Automated Process

Automated process allows the cleaning process to occur without involving personnel intervention ensuring consistency and minimizing safety hazards. In an automated cleaning system the cleaning may be controlled through a PLC (Programmable Logic Controller) and other platform, such as *FactoryTalk® Batch* to support reuse of code in multiple tanks and transfer lines. The control system is an integral and critical part of the overall cleaning process it regulates the: cleaning cycles, addition of cleaning agents, temperature, time and other critical cleaning parameters [4]. A consistency can be achieved by programming the code to obtain a

passing cycle only when the acceptance criteria is met, i.e., such as a value of conductivity.

Transition Criteria

Defining step transition criteria provides a way to control the critical cleaning-cycle parameters. For example, the chemical-wash duration, minimum temperature set point, and concentration target can all be set as requirements before the wash step transitions to the next step [6].

Steps Sequence

Typically, a cleaning cycle, should start with water rinses followed by detergent cleaning and post-detergent rinses. In between any rinse or detergent wash, the system should be drained completely to prevent dilution or chemical reaction with the next cycle step. An air-blow step, placed before the drain, can greatly decrease the gravity drain time and thus decrease the gravity drain time and thus decrease the overall cycle time [6].

METHODOLOGY

The goal of the project is to optimize the cleaning cycles of non-product contact equipment to achieve a reduction of cycle time of 40%. In order to optimize the cycle while maintaining the cleaning quality, several methodologies were followed including Lean Six Sigma methods:

- **Voice of the Customer** - Direct discussion to engineering/manufacturing staff confirmed that the cleaning cycle was excessive. Feedback received confirmed that the cleaning cycle was required in order to increase productivity and meet the requirements of the customer.
- **Value Adding Activities** - Current steps of the cleaning cycle were evaluated to identify if they added value to the process. It was noted that for the series of equipment in the scope of the project, the steps did not add value to the process. Optimization of the cleaning cycle was seen as a top priority to only execute steps that add value, as long as, the cycle meets the established parameters the first time.

A thorough analysis of the cleaning strategies was performed to understand which part of the overall cleaning process needed the optimization to further increase productivity and reduce equipment downtime. Table 2 and Figure 2 presents the steps in the current cleaning cycle.

Table 2
Typical Steps in a CIP Cycle [10]

Step/Description	Description
1/ Pre-Rinses	Purpose: Dislodges any gross soil particles from surfaces. Recirculation: No Cleaning Agent: No Water Quality: Purified Water Temperature: Ambient
2/Caustic Wash	Purpose: Provide mechanical removal, and degradation to remove organic soils. Recirculation: Yes Cleaning Agent: Alkaline Cleaning Agent Water Quality: Purified Water Temperature: Higher than Ambient
3/Rinse	Purpose: Remove residual alkaline detergent. Recirculation: No Cleaning Agent: No Water Quality: Purified Water Temperature: Ambient
4/Acid Wash	Purpose: Neutralizes alkaline detergent and remove inorganic soils. Recirculation: Yes Cleaning Agent: Acidic Cleaning Agent Water Quality: Purified Water Temperature: Higher than Ambient
5/Rinse	Purpose: Remove residual alkaline detergent. Recirculation: No Cleaning Agent: No Water Quality: Purified Water Temperature: Ambient
6/Acid Wash	Purpose: Neutralizes alkaline detergent and remove inorganic soils. Recirculation: Yes Cleaning Agent: Acidic Cleaning Agent Water Quality: Purified Water Temperature: Higher than Ambient
7/Final Purified Rinse	Purpose: Remove residual acid. Recirculation: No Cleaning Agent: No Water Quality: Purified Water

	Temperature: Ambient
8/Final WFI Rinse	Purpose: Remove residual acid and ensures all cleaning solutions have been rinsed from the system. Recirculation: No Cleaning Agent: No Water Quality: Water For Injection Temperature: Higher than Ambient

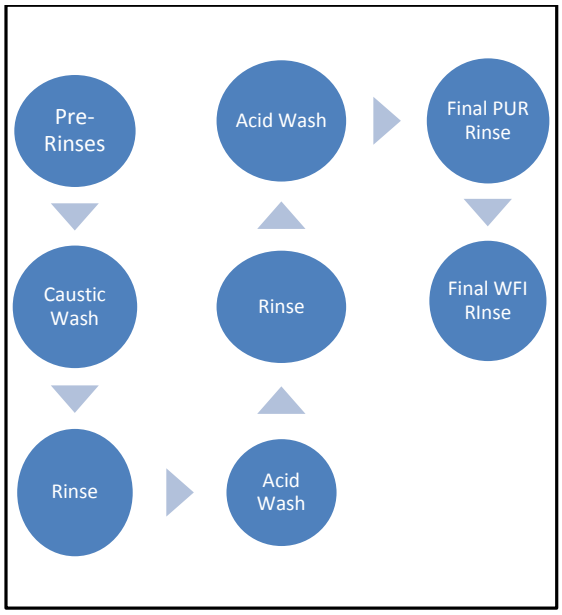

Figure 2
Typical Steps in Clean-In-Place System

DISCUSSION & ANALYSIS

In-depth study revealed that the water and cleaning agents current contact time was more than enough to remove the common soilants the equipment surface area were exposed. The process was optimized by removing steps that did not added value to the cleaning process such as the steps that involved solution recirculation and cleaning agents. As shown in Table 3 and Figure 3, the optimized cleaning cycle consisted of two (2) steps: Series of Pre-Rinses with Purified Water and a Final Rinse with Water for Injection. The remaining rinses, acid wash and caustic wash were removed from the cleaning cycle.

A minimum contact time with purified water was established in a residue removal study to ensure that the equipment's were equally clean as the previous cleaning cycle. This minimum contact time is the activity that will add value to the process by ensuring equipment meet the cleaning parameters the first time.

This optimization needs a validation to ensure a thorough cleaning before implementing it. The benefits of optimizing the cleaning cycle will bring a significant cycle time reduction of up to 40% and considerable hard savings in cleaning agents. As specified in the Pharmaceutical Technology Article [6], a cleaning circuit optimization yields both time and cost savings.

Table 3
Steps in the Optimized CIP Cycle

Step/ID	Description
1/ Pre-Rinse	Purpose: Dislodges any gross soil particles from surfaces. Recirculation: No Cleaning Agent: No Water Quality: Purified Water Temperature: Ambient
2/Final WFI Rinse	Purpose: Remove residual acid and ensures all cleaning solutions have been rinsed from the system. Recirculation: No Cleaning Agent: No Water Quality: Water For Injection Temperature: Higher than Ambient

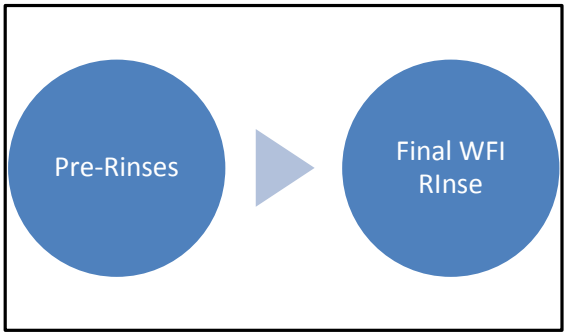

Figure 3
Steps in Optimized Clean-In-Place System

CONCLUSION

The implementation of the proposed optimization will result in a 40% reduction in the cleaning cycle time, this will have a positive direct impact in productivity. Increased productivity will be achieved with an improved equipment uptime and a considerable amount in hard savings due to water

usage reduction, reduction of cleaning agents and their treatment in the water treatment facility. This optimization is aligned with lean culture and will reduce waste in the manufacturing plant.

REFERENCES

[1] K. Roy, C. Undey, T. Mistretta, G. Naugle and M. Sodhi, "Multivariate statistical monitoring as applied to clean-in-place (CIP) and steam-in-place (SIP) operations in biopharmaceutical manufacturing", *Biotechnol Progress*, vol. 30, no. 2, pp. 505-515, 2014.

[2] A. Mollah, Cleaning validation for biopharmaceutical manufacturing at Genentech, Part 1", *BioPharm Int*, vol. 21, no. 2, 2008.

[3] R. Forsyth, "Rethinking Limits in Cleaning Validation", *Pharmaceutical Technology*, vol. 39, no. 10, pp. 52-61, 2015.

[4] D. LeBlanc, "Points to Consider for Cleaning Validation", *PDA Technical Report*, vol. 29, no. 1, pp. 1-23, 2012.

[5] Hyde, P. Watler and K. Bader, "PAT for Pharmaceutical Cleaning", *Control Engineering*, vol. 54, no. 4, pp. RX1-RX4, 2007.

[6] A. Wong and C. Shrader, "A Lifecycle Approach to Optimizing Cleaning Systems", *Pharmaceutical Technology*, vol. 36, no. 12, pp. 42-44, 2012.

[7] CIP-100® Alkaline Detergent Sell Sheet", *Sterislifesciences.com*, 2011. [Online]. Available: http://www.sterislifesciences.com/~/media/Files/LifeSciences_com/PDF/Pharmaceutical Detergents/CIP 100/CIP 100 Sell Sheet EN new.ashx. [Accessed: 01-Apr-2016].

[8] "Keeping Clean", *Industrial Maintenance & Plant Operation*, vol. 69, no. 7, p. 23, 2008.

[9] "General Chapters: Water Conductivity (USP 29 - NF 24)", *Pharmacopeia.cn*, 2016. [Online]. Available: http://www.pharmacopeia.cn/v29240/usp29nf24s0_c645.html. [Accessed: 01-Apr-2016].

[10] R. Hayward, M. Shulim and B. Watts, "Expanding CIP System Functionality to Meet FDA Requirements", *Control Engineering*, vol. 47, no. 6, p. 60, 2000.