Changeover Reduction Time by Adjusting the Cleaning Critical Parameters in Automated CIP Systems

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Abstract *— Clean-In-Place (CIP) is a widely use process to clean biotechnology vessels contact surfaces. CIP is an automated cleaning method that involve minimum to no equipment disassembling thereby reducing labor and time expense. CIP provides higher level of repeatability and safety when the process is optimized. The objective of this project was to reduce the changeover time by determining where are the wastes in the cleaning process and campaign changeovers in the pharmaceutical manufacturing that are reflected as effective design of the automated CIP systems, avoid build up overtime, and manual cleaning of small parts. In field-testing were performed under combination critical parameters to clean the manufacturing vessels to acceptable limits. Different combinations were tested and samples once the cleaning process where completed. Data was statistically analyzed to visualize the reduction time based on the critical parameter adjustment. The goal was to not rework the equipment with the optimal CIP condition, which will lead to the changeover reduction time and compliance satisfaction.*

Key Terms *— Automated CIP, CIP skids, Critical parameters, TACT.*

PROBLEM STATEMENT

Pharmaceutical processes face some challenges in the cleaning processes when changing between products campaign. Cleaning process generally involve the demonstration of the removal of the product been manufactured, microbiological control levels, and cleaning agent removal. Therefore, the challenges that most of the pharmaceutical manufacturing faces are effective design of the automated CIP systems, build-up overtime, and reproducibility of the manual cleaning of small parts that are not clean in place (CIP). These challenges can lead to extensive cleanings and sampling that result in downtime of the equipment for more than 12 hours. This laborious process, combined with the idle time of the manufacturing equipment, is a very expensive part of manufacturing cost. Appropriate assessment of the waste in the cleaning process ensure to the pharmaceutical companies that the cleaning activities performed will reduce the changeover time between manufacturing campaigns while maintaining the critical parameters of the process and complying with the acceptance criteria defined.

Research Description

This project is about the cleaning process of automated processes in the biotechnology field. The investigation allows the industry to understand how to develop the cleaning processes to be prepared for future challenges.

Research Objective

To reduce the changeover time by determining where are the wastes in the cleaning process and campaign changeovers in the pharmaceutical manufacturing that are reflected as effective design of the automated CIP systems, avoid build up overtime, and manual cleaning of small parts.

Research Contribution

Assessment of the recommendations will help pharmaceutical manufacturing to identify changeover wastes between manufacturing

campaigns that can reduce the time to change from product A to product B and vice versa causing the equipment downtime. All wastes elimination will not impact the cleaning critical parameters and remains in compliance with the acceptance criteria defined.

LITERATURE REVIEW

A key component of a biopharmaceutical industry is to reach and stay at its optimum capacity. This competiveness has force the biopharmaceutical industry to become multiproduct biopharmaceutical facilities. In this process, minimization of the risk of cross-contamination is becoming increasingly important [1]. The strategy works by using shared equipment in campaign basis. This shared equipment reduces the cost of duplicated equipment and maintenance activities [2]. The ability of a company to use the same piece of equipment for multiple products is turns in less storage space, centrate raw material contracts, increasing the technical knowledge and understanding of the process that is translated in a design of more effective processes and equipment.

On the other hand, one of the mayor concerns with the use of shared equipment is cross-contamination between products used in the same equipment. Therefore, the cleaning design and process is a critical component of the strategy to minimize risk to the patient. Numerous guidance document currently exists to address appropriate risk evaluation and establish control of the multiproduct facilities cleaning such as ICH Q7 to Q10, 21 CFR 211.182 FDA Expectation, FDA 21st Century–Risk-Based Approach, FDA: Guide to Inspections Validation of Cleaning Processes, EMA Guidance on Shared Facility, ISPE Risk-MaPP. These brings a set of unique challenges to implement complex and time and cost consuming changeover procedures.

Optimization of a changeover procedures is needed to stay competitive and to minimize the slowdowns in the manufacturing waiting for availability of equipment. This changeover cleaning optimization is the process of determining the most efficient and effective cleaning process design to achieve lesser time and cost to change from Product A to product B, without adversely affect the quality of the products manufactured and the safety of the patients [3]. Figure 1 shows how the risk of cross contamination occurs within a shared vessel caused by poor cleaning design.

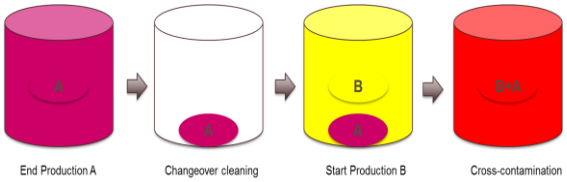

Figure 1
Risk-of-Cross Contamination caused by Poor Cleaning Design

The cross-contamination residues that could affect a patient is mathematically and toxicologically calculated in milligrams between the residual product that could be left in the equipment surfaces and are in contact with the next product campaign. This scenario encompass that a patient of product B can receive an active ingredient from product A that is not prescribed for.

Appropriate cleaning design involve the distribution of the TACT (Temperature, Action, Concentration of chemical, Time) parameters to fit an effective cleaning process. Following is a summary of each critical parameter:

- **Temperature:** Cleaning efficiency increases as the temperature increases. Heat makes molecules move faster, and therefore clean or solubilized faster.
- **Mechanical Action (i.e. Agitation, turbulence, flow):** Mechanical action can be obtained in several ways, depending on the cleaning process for the specific type of equipment. Commonly known as scrubbing is achieved through a brush and physical action, water pressure or mechanically assisted brushes. This action helps distribute cleaning agents for maximum soil suspension and removal. In complex system, where extended

piping is installed, it is achieved by turbulence and flooding inside the line.

- **Chemical Action/Concentration:** In general, the higher the concentration of an aqueous cleaning agent could increase reaction rates and increase solubilization. Cleaning agents are selected based on their effectiveness in solubilizing and removing the known residues of product.
- **Contact Time:** A measure of seconds, minutes, or hours for the other three cleaning parameters to interact for optimum efficiently. This contact time can be minimized with the proper use and understanding of the other three parameters.

Surface properties (porosity and roughness of surface), water quality, environmental conditions, and hold times (including dirty and clean hold times) can also influence the cleaning procedure effectiveness [4]. These elements must be included and requires to be considered as part of the cleaning process.

All cleaning process have some combination of the critical parameters. Depending on the individual requirements, the parameters can be increased or reduced but followed by a balance of the rest of the parameters to achieve an effective cleaning. For example, to use a cold cleaning solution would require an increase in mechanical action, chemical action and/or time. In cases where a cleaning solution is used without any mechanical action, it would require an increase of cleaning solution temperature, a stronger cleaning chemical and or more time. To use a water only cleaning, it would require an increase in temperature, more mechanical action, and or more time to remove soil. To minimize contact time to perform a cleaning procedure would require an increase in cleaning solution temperature, more agitation, and or a stronger cleaning product.

Cleaning method directly influences the level of action on the surface when combining the four cleaning control parameters. In a manual cleaning method, the operator can apply a lot of force in scrubbing the surface, but operator safety considerations may limit time, chemical concentrations, and temperature options. On the other hand, automated CIP systems provide less action on the surface compared to manual cleaning but time, temperature, and chemical interaction/concentrations can be increased to enhance chemical effectiveness.

Available cleaning methodologies are Clean-In-Place (CIP), Clean-Out-of-Place (COP) like part washers, and Manual cleaning. These methodologies can be implemented by automated the cleaning systems or by extensive and detailed procedure instructions. When choosing the appropriate methodology is important to consider that automated recirculation system operation costs are substantially higher when compared to a manual cleaning. Most companies hurriedly the next product introduction by choosing manual cleaning process as they tend to be easily implemented. In the long range, this decision is where the highest cost arise.

Manual cleaning depends on three main factors: well explained procedures, personnel training, and operator commitment. Applicability of these factor result in satisfactory removal of soil to acceptable levels. When analyzing the changeover downtime, it will be observed that manual cleaning requires a greater number of operators assigned to execute the task, space to perform the cleaning, drying, and storage. Also, extensive instructions must be provided to the person that will perform the task in order to maintain the process as consistent as possible. Automated systems offer greater flexibility to adjust parameters such as chemical concentrations and temperature of the cleaning solutions for demanding cleaning procedures.

Capacity of facility will be dictated to their ability to conduct changeovers in a reduced time. The flexibility of an automated CIP system will provide alternatives to adjust the cleaning as appropriate to the soil needed to be clean without the disassembling of the equipment, which affect the reliability and the involvement of multiple people to perform the cleaning. Some equipment

cannot be connected to a CIP Skid due to its design, such as small parts including fitting, clamps, utensils, tank vent and casing. In this cases, manual cleaning is the only option available. New technology provides COP equipment such as part washers and ultrasonic sinks to assist with these tasks. COP provides an advantage above manual cleaning procedures as saving cost, time, chemical, and water usage and minimizes operator exposure to high temperatures and strong chemical concentration limited in manual cleaning. This part is important as looking into the future of new product small adjustment will be required to clean different combinations of soils with low resources.

METHODOLOGY

The study was conducted applying different variables to the automated recirculated cleaning cycles. The tested variables were adjusted accordingly to the cleaning critical parameters of temperature, mechanical action, cleaning agent concentration, and contact time. These variables will lead to the effective cleaning of the equipment and are easy to adjust in the automated code parameters in the cleaning recipe when designed with this type of flexibility.

The experimental runs consisted of soiling the manufacturing vessels ranged from 60,000 L to 15,000 L with the normal production material. Then, a cleaning run is applied according to Table 1: "Cleaning Parameters Adjustment Matrix". Once completion, the surfaces must be inspected for cleanliness and surface sampling were collected. A vessel location was evaluated in term of hard to clean location in order to collect the samples. Hard to clean location are the internal location that are clean by a CIP and that are difficult to clean. Most cases, the location are difficult to clean due to the geometry of the vessel or difficult to reach by the cleaning process. The representative locations within a vessel are walls, bottom of the vessel, dome, inlet product pipe, and agitator. More locations can be added depending on the complexity of the internal parts of the vessel.

Evaluation of the cleanliness of the surfaces required the applicability of the acceptance criteria of NMT 100 ppm for change over. The acceptance criteria are based on the carryover limits between the Product A to Product B change over limit.

Sample results were considered in the statistical analysis even if the acceptance criteria were exceeded, which means that the equipment needed to be re-clean in order to be release for manufacturing purposed. Those repetition runs final results were not considered as the equipment was rework. These data were used to understand that an adjustment to one of the four cleaning parameters in the cleaning cycle was required. The table below described the cleaning parameters challenged:

Table 1
Cleaning Parameters Adjusting Matrix

Run No.	Temperature	Cleaning Agent Concentration	Mechanical Action	Contact Time
1	No adjustment	No adjustment	No adjustment	No adjustment
2	No adjustment	No adjustment	Manually clean the locations	No adjustment
3	Increase from 65°C to 75°C	Increase 3X molarity	No adjustment	Extend 3X recirculation time
4	Increase from 65°C to 75°C	Increase 3X molarity	Change to rotation head jet	Extend 3X recirculation time

RESULTS AND DISCUSSION

Experimental data shows significant results when adjusting the cleaning critical parameters. The set of data points were average for the population of vessels assessed during each experimental run. This means, that if five different vessels that are similar were tested, then the data was an average of all the results obtained. Run 1 showed most of the results above the acceptance criteria of 100 ppm. This run represents the experimental control as the original cleaning process was applied with no adjustment performed to the TACT parameters. This run served as a baseline to understand the starting point of the

experiment. Run 2 adjusted the mechanical action as a testing mechanism to understand the variability of the manual cleaning procedures. This run applies the technique of manual cleaning to the inlet product, which was the only location small enough to apply the technique. It was observed inconsistency between operators when applying the mechanical force pattern. Operators were shadowed during the manual cleaning by a technical expert. The technical expert observed that the same operator performed the cleaning pattern different between days. Also, that a group of operators performed the technique in different manners. This led to discard this technique during automated processing. Run 3, that adjusted the cleaning agent concentration, increased the temperature and extended the contact time of the higher parameters demonstrated significant results for vessels range 15,000 L to 30,000 L. Vessels larger than 30,000 L did showed failures in the upper side of the walls. This confirms that the mechanical force applied by a static sprayball can be optimized for larger vessels. This led to the next run. Run 4 demonstrated satisfactory results with larger vessels. Rotation spray head provide an increase of the system pressure to 10X psi. Even that this showed a better cleaning process, it is not recommended to routinely applied this pressure to the surfaces of the equipment. Constant high pressure could lead to a surface reliability issue in the lifetime of the vessel. Figure 2 summarized the results obtained during each experimental run.

Cleaning a larger vessel can take up to three working days operating at 24/7. More than one operator is required to intervene the equipment along with mechanics if disassembling is required. Not counting the safety potential situation that implies every intervention to the equipment. Reduction time observed in the optimization process of the automated CIP will saved additional repetitions runs. These repetitions are translated as three additional working days [5] each time a result does not complies with the acceptance criteria. Meaning that instead of cleaning one large vessel in three days, it can take approximately six to nine days. Saving cost are reflected in the startup of the next manufacturing process because if the process of changeover is performed in the minimum time, the next manufacturing campaign can start on time.

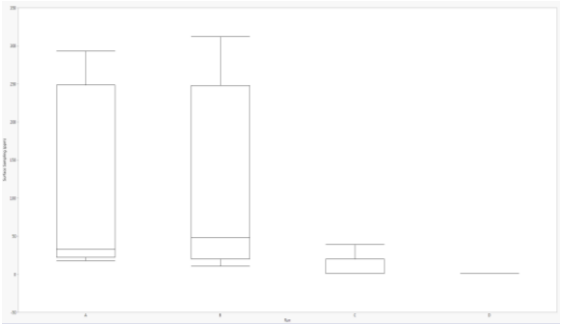

Figure 2
Surface Contact Protein Sampling Results by Experimental Run

Designing the CIP systems with the capacity to adapt the parameters and avoid manual interventions resulted in an optimization of the TACT parameters during changeover. These times are reduced by adjusting these parameters, and satisfactory cleaned the equipment without rework, meaning that the change over time is reduced. In addition, rework avoid cleaning until clean which is a phrase recognized to be avoided by the industry. Therefore, having the equipment cleaned the first time guarantee to maintain the equipment within compliance.

CONCLUSION

The results of the investigation confirm the feasibility of optimizing the CIP critical parameters by automated changing the CIP recipe. The investigation was based on vessel equipment connected to pipping and to a CIP Skid that is automated controlled. It was possible to test different combination of TACT to reach the final proposal of clean the equipment to acceptable limits without rework.

Based on the results of the study, adjusting concentration of the cleaning agent, temperature, and contact time provides a viable approach to reduce the rework of equipment and to optimize the cleaning process. Not only helps the change over

time, but also, the waste of materials such as water, energy and cleaning agents used during the rework. Changeover time studied for larger vessels was reduced from six to nine days approximately because of the repetition runs to the minimum time of three days. The minimum time is defined as the time that last one optimized cleaning run. The same concept applies for any pieces of equipment. Changeover time is reduced by the amount of times that requires to re-clean the equipment. Miscellaneous equipment or loose part must be cleaned within a cabinet washer to also apply the concepts proven within this investigation. Equipment that is cleaned manually should be evaluated to be included into the automated systems and provides the flexibility to adjust to future projects.

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