Design a Predictive Control Model for a CIP System

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Abstract — *This document describes the analitical method to define control parameters during a clean in place (CIP) cicle in the pharamaceutical/food industry. The new models of CIP systems comes with many automatic controls and are monitored in live with a monitoring and data historian like PI. This system give us the oportunity to analize deeper the process parameters in order to identify posible failures factors during the CIP runs like the supply pressure, supply flow and return flow. For example: We can analyze the relation with supply flow and return flow with the supply pressure in order to identify and define the safest process targets and if required the alarms addition to the recipes if the cycle is found exceeding the recommended limits. Be aware prior events occurred is a challenge for the industry of this century because at most events of safety, process fails occurs, it can finish in profit looses or OSHA observations depend the case. Using data analysis on every aspect in the industry could results in more benefits for the company and also for the workers more than expected. Once establish the required process parameters based in the analyzed data we can also implement mistake proofing (Poka Jokes), additional visual aids, continuous improvement tools as required.*

Key Terms *– Acid, Biotechnology, Caustic, Rupture disc.*

INTRODUCTION

The biotechnology are compounded by many different process used in the production environment. Process like formulation, bulk manufacturing, filling process, filtration are some of the process utilized to manufacture the protein that will be injected in the blood current of a human that require to improve his quality of life. After finish all the mentioned process the equipment utilized becomes dirty and needs to be cleaned. This cleaning process is known in the industry as Clean in Place (CIP). Cleaning-In-Place (CIP) is a system designed for automatic cleaning and disinfecting without major disassembly and assembly work.

In this project, a CIP system will be analyzed to predict possible failures using process data (Supply Pressure, Flow Supply, Flow return) in order to reduce the probability of equipment failure that could result in a rupture disc broken/or safety relieve valve use and/or equipment damage caused by an exceeds in pressure.

BACKGROUND-THEORY-LITERATURE REVIEW

The Cleaning Process [1]

Cleaning is a complex process based on both chemical and physical principles. The primary task of cleaning is the detachment of soil from a surface. Soil can be attached to surfaces by a combination of three physical effects as illustrated in Figure 1, including van der Waal's forces, electrostatic effects, and mechanical adhesion. The sum of these effects can be termed as soil adhesion. In the cleaning process, soil adhesion has to be subdued by providing forces counteracting the adhesion. These forces can be reduced to the four basic parameters of any cleaning process.

1. The cleaning temperature
2. The cleaning time
3. The cleaning kinetics (mechanical effects)
4. The chemical activity of the used cleaner

The chemical activity depends primarily on the efficacy of a specific cleaner regarding a specific type of soil. It is a very complex phenomenon based on direct chemical reactions as well as the physical principles of desorption, dispersion, emulsification, and dissolution. The detergent concentration, as often stated, is only a factor of secondary importance. The higher the chemical activity, the lower the concentration required!

The four basic parameters of the cleaning process are all dependent on each other. Reducing or increasing any of these components will alter the balance of the other three; however, all four segments are required. If only one of them is omitted, then no cleaning occurs.

Cleaning is the net to make (a place or object) removing any dirt or anything detrimental to the cleanliness.

Disinfection is the elimination or the inhibition of microorganisms in a place, an object or on the external surface of the human body. In food industry (food), cleaning and disinfection are designed to remove dirt and destroy the microorganisms present in the appliances and packaging. In some cases, these operations must be conducted on the products themselves contaminated by for earth, microbes, or residues of pesticides.

The results of these two operations are not exclusive of each other because if the cleaning operation will remove a number of waste, it will also achieve a certain level of elimination of microorganisms. This elimination can then be supplemented if necessary by a proper disinfection implementing a specific product. Commonly a detergent (alkaline) will be used simultaneously with a disinfectant (chlorine and derivative) in the form of alkaline chlorine. Some formulations include even a quaternary ammonium or other product to increase the disinfecting power in a single operation for cleaning / disinfection.

Cleaning and disinfection operations are among the most important of the IAA and this for various reasons: The quality of the finished product is often influenced by the tastes of foreigners due to microbial development. These developments are dependent on the residues of this product in the device or in a container after use, or from deposits that are formed during the processing of certain products such as beer, milk.

The ability to heat treatment is highly dependent on the initial population. Indeed, when sterilizes pasteurizes or on a product by heat, time of treatment depends on the initial microbial load. It is much longer if this burden is not reduced by a preliminary cleaning. This increases the cost of treatment and may diminish the quality of the product.

The dirt may contain pathogenic microorganisms and, thus, constitute a source of contamination is extremely harmful to the food.

The presence of residues such as dried crusts or altered insects or their larvae, rodents or even in the packaged products can have a catastrophic influence on the opinion of the consumer.

Nature of Contamination

Denotes dirt (or dirt) products are totally different. These products are components of food more or less degraded, or modified by heat, cold, humidity, light, oxygen and / or microorganisms.

These components may be more or less mixed with others: filter, yeasts or molds, plant debris or minerals, seeds of the atmosphere or made by staff.

In theory, a stain is characterized by the ratio of its water solubility and lipid solubility, and it is this characteristic that should be taken into account when choosing chemical decontamination agents. The stain is a complex organic matter, mineral matter and microbial germs. Each of these three families of compounds must be known in detail.

Organic compounds are: lipids, proteins and carbohydrates. The inorganic compounds can be divided into several categories which are based on their nature and power of elimination: The alkaline earth salts, silicates, oxalates and aluminates.

Microbial germs are classified into two categories: useful germs and harmful germs. When present simultaneously in the environment of the food product or the product itself, it is not possible in current practice, to make selective treatment, to control bacterial life in a product, we start by destroying everything and layers useful decimated.

Kinetics of the Contamination Removal

Between certain limits, often at the beginning of the elimination of dirt, the elimination of dirt behaves as a first order reaction. If m represents the mass of soil per unit area, we have:

$$Ln\ (mA / mA0) = - K*t \quad (1)$$

The rate constant k is determined by several factors:

The nature of the support of the dirt: We know, for example a surface of polished stainless steel is easier to clean a rough surface or plastic. Wooden surfaces are extremely difficult to clean.

The nature and concentration of detergent: When using a dilute solution of caustic soda, the reaction of removing dirt becomes second order. However, this finding can be extended to other surfactants.

Temperature: Between broad intervals of temperatures, the rate constant follows the Arrhenius law, in that we obtain a linear relationship on log (K) against T-1.

The Mechanics: The mechanical action during the passage of a fluid in a conduit, only becomes significant when the Reynolds number (Re) is greater than 25 000; beyond this value, the rate constant varies roughly as log (Re).

The mechanical action can be influenced by the presence of foam in which the action may be detrimental by preventing contact between the surface and the solution. The action of the foam may also be beneficial when the air is dispersed in the solution in motion, which improves the abrasive action, the latter can be improved by making advantage of suspended solids as elastic or rubber bullets, which are driven in the circuit.

This theoretical approach to the kinetics of cleaning is widely criticized because it does not reflect the experimental results and the methods used for measuring the speed of cleaning is inaccurate.

Regarding the chemical destruction of microorganisms, it is generally considered that the reaction is first order. If Nm is the number of cells in a given microorganism per Kg of product, we have:

$$Ln\ (Nm/Nm0) = -K*t \quad (2)$$

In this case, the rate constant k is a function of the strain of microorganisms, the nature and concentration bactericidal agent, it is also strongly influenced by temperature and the composition of the environment in which the destruction takes place.

In practice, the problem is not chemically sterilize a suspension of microorganisms, but a surface that is possibly a deposit containing living microorganisms. In this situation, several interactions may exist: support, trust, solid, suspended matter, microorganisms, cleaning and disinfection. These interactions are extremely complex and it is very difficult to model.

Disinfection in depth of deposition, materials porous interstices of various joints, valves, etc., is generally not possible by use of highly reactive body as halogens which the concentration drops sharply and fell to values at a depth very low. On the other hand when using products such as formaldehyde, protein deposits can be hardened on the surface and make their removal more difficult than ever without the formaldehyde concentration in the deposits is less than a truly bactericidal.

Finally, it should be noted that in general the nature of the cleaning agents and disinfecting that can be used depends mainly on the materials constituting the apparatus, the phenomena of corrosion still playing a decisive role.

Selection of the Product Worst Case:

The Worst case related to products is the most insoluble active ingredient. As defines in the cleaning validation policy, cleaning validation is performed after cleaning the equipment from the product containing the most insoluble active ingredient in witch case the analytical method is developed for this ingredient. [2]

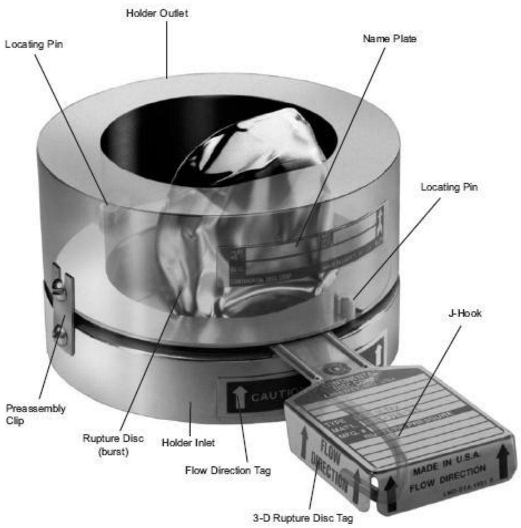


Figure 1
Rupture Disk

Figure 2
Pressure Transmiter

Figure 3
Temperature Transmitter

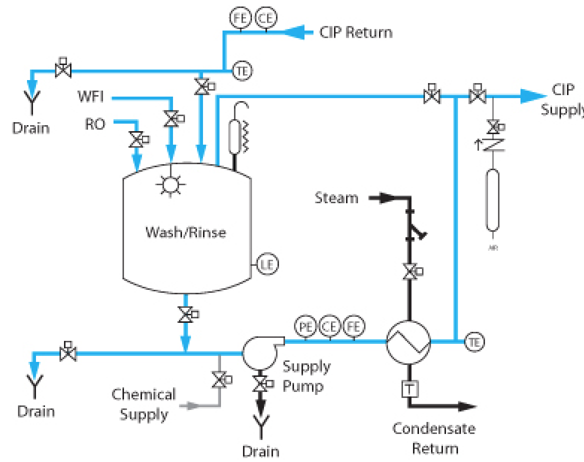


Figure 4
CIP Diagram

Figure 5
Flow indicator

Figure 6
CIP Unit

Problem Statement

The CIP unit analyzed in this project includes the following parameters:

1. Pressure (psi)
2. Time (2 minutes intervals)
3. Supply Volumetric flow (LPM)
4. Return Volumetric flow (LPM)

The case study three (3) CIP runs comparing the same cycle in the process in order to establish operational limits using the upper control limits and lower control limits when possible.

Methodology

Project process information was gathered from SOP's, data historian (PI) and the technical experience of the automation team. To define the CIP actual situation it was decided to use a fish bone diagram as a start point.

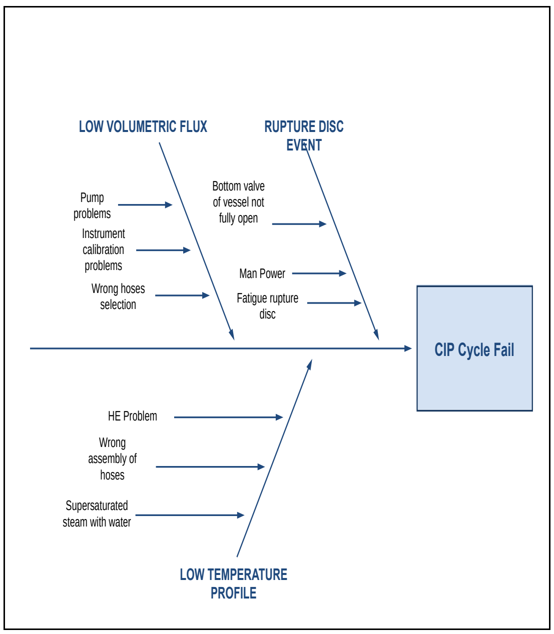


Figure 7
Fish Bone Diagram

The data historian (PI) data was normalized in order to have a clear point of view to analyze the data. The following data shows the volumetric flow rate of the supply line, return line and the supply pressure. (The average value of the three runs will be used for the calculations).

Table 1
Volumetric Flow Rate –Supply (WFI) Line

Volumetric flow 2 (Supply)	Volumetric flow 2 (Supply)	Volumetric flow 2 (Supply)
66.91562653	67.59249878	64.84937286
68.81562042	69.13624573	70.32374573
69.82499695	70.27624512	69.95561981
70.08625031	70.91749573	70.65625
69.48062134	69.74187469	69.65874481
69.69437408	69.99124908	69.56375122
70.0625	69.84874725	70.12187195
70.00312042	69.84874725	70.31187439
70.01499939	70.0625	69.40937042
69.86062622	69.70624542	69.89624786
70.32374573	69.72999573	70.27624512
69.96749878	70.33562469	70.33562469
70.14562225	69.46875	70.09812164
70.16343689	70.05062103	70.09812164
69.32624817	70.06843567	70.5078125
69.65874481	69.91999817	69.99124908
70.0625	70.38312531	69.89624786
69.51625061	70.14562225	70.19312286
70.0625	70.19312286	70.33562469
70.38312531	70.18717957	70.39499664
70.15750122	70.0625	69.91999817
69.74187469	70.08625031	69.67062378
70.19906616	70.03874969	69.97937012
70.34749603	70.33562469	69.65874481
69.65874481	70.28812408	69.89624786
70.40687561	69.37374878	69.89624786
70.15750122	70.18125153	69.65874481
70.12187195	69.61125183	70.47812653

70.18125153	70.0625	70.08625031
70.02687073	69.63500214	69.90812683
69.21937561	70.33562469	70.21687317
69.57562256	69.65874481	70.29999542
70.45437622	70.24062347	69.74187469
69.43312073	70.58499908	70.28812408
69.30249786	70.43062592	69.80124664
69.45687103	69.40937042	70.01499939
69.93187714	69.67062378	69.75374603
70.92937469	70.01499939	69.86062622
69.77749634	69.56375122	70.00312042
70.26437378	70.73937225	70.21687317
70.02687073	70.53749847	69.70625305
69.70624542	70.14562225	70.43062592
70.16937256	69.77749634	70.05062103
69.71812439	69.78937531	70.24062347
69.68249512	69.70624542	69.61125183
70.08625031	70.359375	70.28812408
70.09812164	70.62656403	70.0625
69.88437653	70.52562714	69.93187714
70.08625031	70.14562225	70.19312286
69.87249756	70.28812408	70.33562469
69.95561981	70.14562225	69.87249756
70.00312042	69.82499695	69.765625
116.2324982	117.7168732	119.5931244
113.5368805	118.7381287	118.6549988
112.9193726	118.5481262	118.2987518
112.6581268	118.0731201	117.9721832
112.1356201	117.7525024	117.7168732
106.6374969	117.5743713	92.00749207
2.570936203	0.005089351	0.001187515

Table 2
Volumetric Flow Rate – Return Line

Volumetric flow 1 (Return)	Volumetric flow 1 (Return)	Volumetric flow 1 (Return)
195.5337524	195.5337524	40.97171783
84.68061829	195.5456238	195.5574951
69.32624817	88.71812439	38.64125061
69.90812683	85.26249695	45.567543
69.91999817	73.73187256	60.74062347
71.10749817	70.47812653	68.77999878
68.24562073	70.44249725	70.32374573
68.79187012	70.96499634	70.13375092
70.38312531	70.01499939	69.97937012
78.18499756	69.87249756	71.41625214
74.42062378	69.07687378	69.67062378
121.9681244	69.26687622	71.11937714
144.2099915	68.92250061	72.61562347
42.13249969	70.27624512	68.32875061
55.01687622	70.98874664	69.29062653
91.09312439	69.18374634	82.99436951
73.82687378	69.40937042	51.26437378
29.31937408	69.77749634	138.6287537
46.3125	77.22312164	68.79187012
28.46437073	67.79437256	70.20500183
49.77999878	69.78937531	69.82499695
80.09687042	68.60187531	69.78937531
27.38375092	69.46875	69.65874481
99.82124329	70.14562225	70.24062347
113.40625	69.36186981	69.97937012
9.678123474	70.27624512	69.89624786
18.86937714	69.81312561	69.72999573
113.7149963	69.97937012	70.43062592

48.390625	69.69437408	69.57562256
25.623556	70.71562195	69.40937042
16.89812469	69.83687592	70.00312042
0.534374237	73.56562042	71.19062042
69.10062408	69.40937042	44.09187317
71.19062042	69.56375122	68.79187012
71.05999756	70.43062592	69.81312561
70.29999542	69.765625	69.75374603
70.50187683	69.59937286	69.62312317
69.87249756	69.84874725	68.69687653
68.50687408	70.21687317	70.00312805
69.19562531	70.51374817	69.26687622

Table 3
Pressure – Supply (WFI) Line

1-Pressure (Supply)	2-Pressure (Supply)	3-Pressure (Supply)
13.02187729	12.98906326	12.16875076
13.15312576	12.75000381	13.15312576
12.85312653	12.43125153	12.54375076
12.67500305	12.40312576	12.26250076
12.31875229	11.89687729	12.00937653
12.35625076	11.94375229	12.11250305
12.50625229	11.97187805	12.22500229
12.47812653	12.04375362	12.15937805
12.45000076	12.02812576	12.00937653
12.44062805	12.15937805	12.10312653
12.56250381	12.08437729	12.24375153
12.55312729	12.27187729	12.23437881
12.60000229	11.97187805	12.05625153
12.55312729	12.09375381	12.13125229
12.30937576	12.08437729	12.19687653
12.43125153	11.89687729	12.03281403
12.57187843	12.03750229	11.93750381
12.45937729	12.11250305	12.09375381
12.49687576	11.97187805	12.08437729
12.60000229	12.10312653	12.17812729
12.64687729	12.07500362	12.06562805
12.43125153	12.01875305	11.93906593
12.57187653	11.98594093	11.99062729
12.61875153	12.12187576	12.04375172
12.51562881	12.08437729	12.07969093
12.86250305	11.85937881	12.03750229
12.55312729	12.00000381	11.91562653
12.33750153	11.86875153	12.13125229
12.19375324	11.83125305	12.00000381
12.09375381	11.79375076	11.86875153
11.93437576	12.00937653	12.01875305
12.11250305	11.74687576	12.01875305
12.34687805	11.85937881	11.84062576
12.16875076	11.86875153	11.97187805
12.20625305	12.13125229	11.87812805
12.39375305	11.70937729	11.91562653
12.45937729	11.77500153	11.84062576
12.79687881	11.84531403	11.85000229
12.41250229	11.80312729	11.88750076
12.48750305	12.08437729	11.93437576
12.54375076	11.98125076	11.8546896
12.37500381	11.80312729	12.03750229
12.50625229	11.75000095	11.78437805
12.35625076	11.80781364	11.87812805
12.38437653	11.71875381	11.73750114
12.44062805	11.97187805	11.88750076
12.42187881	11.94375229	11.77500343

12.33750153	11.97187805	11.69062805
12.39375305	11.82187653	11.85000229
12.43125153	11.86875153	11.74687576
12.44062805	11.70000076	11.84062576
12.42187881	11.65312576	11.63437653
36.45000458	35.97187805	36
36.57187653	35.92500305	35.87812424
36.48750305	35.83594131	35.81719208
36.4125061	35.76562881	35.71406555
36.34687805	35.6625061	35.61187744
26.50312805	34.21875	15.25312805
2.331250429	2.184375763	2.176341534

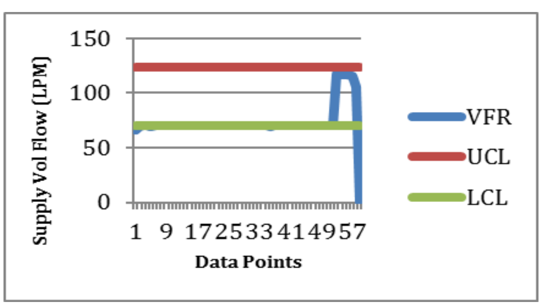
This data was used to complete the analysis and it will be discussed in the results and discussion section.

RESULTS AND DISCUSSIONS

The calculations were performed for the three data inputs (SP, SFR, RFR) with the following results:

Table 4
Volumetric Flow Rate (Supply)

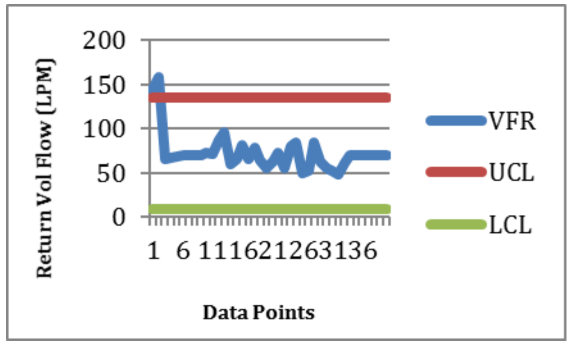
Average	73.04563939
Std. Deviation	16.76616052
UCL	123.6253657
LCL	70.32688419



Graph 1
Volumetric Flow Rate (Supply)

Table 5
Volumetric Flow Rate (Return)

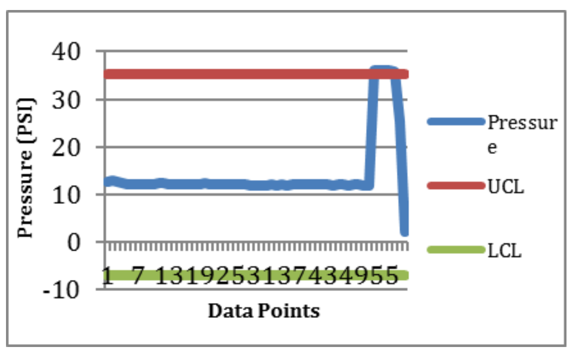
Average	67.9192904
Std. Deviation	21.07646722
UCL	135.5180954
LCL	9.059292023



Graph 2
Volumetric Flow Rate (Return)

Table 6
Pressure (Supply)

Average	14.57102993
Std. Deviation	7.031810693
UCL	35.33439495
LCL	-6.856469211



Graph 3
Pressure Supply

CONCLUSIONS

In general, all CIP units show variations in their physical parameter (example: flow rate) because of the validated recipe. But also you can define a limit point during the complete recipe in order to protect the equipment involves in the CIP run like the CIP unit and the pressure vessel. Is recommended to evaluate characteristic parameters during the validation process in order to protect the respected equipments. For the process described in this project a pressure limit can reach 39 psig or 40 psig for example, because the Maximum allowed working pressure (MAWP) of the vessel is 45 psig and we don't want to use the rupture disk or a pressure safety relieve valve whichever the case. If the supply pressure exceed 37 psig is highly possible that something is wrong with the CIP run and we can react in time to avoid safety incidents and possible equipment damage.

References

[1] Saiberling, D. A., *Clean in place for Biopharmaceutical Processess*, Volume 173, 2007, pp. 32-74.

[2] Bismuth, G. and Neumann, S., *Cleaning Validation: A Practical Approach*, 2000, pp. 65-94.