Buffer Formulation Vent Filter Re-Use at Manufacturing Plant

Author: Jorge Figueroa-Rodríguez
Advisor: Jose A. Morales, PhD
Master in Manufacturing Competitiveness

Abstract

For sterilization-in-place cycles that used vent filters as a redundant non-contact product, the filter membranes could be re-used several times without impacting their integrity neither compromising the sterilization cycle. At a parenteral manufacturing plant in Puerto Rico, the vent filter is discarded after exposed to a one-single sterilization-in-place cycle. With the implementation of this project, the vent filter used during the sterilization-in-place as part of the buffer formulation at Manufacturing Plant can be re-used up to 50 times. With DMAIC (Define, Measure, Analysis, Improve and Control) quality strategy, the use of vent filters during buffer formulation at Manufacturing Plant was improved. Under DMAIC, the sterilization conditions of the filter's manufacturers was identified as the worst-case sterilization scenario. Also, validation activities were executed to confirm no moisture residual particles were found in the vent filter membrane after multiples consecutives sterilization cycles. At the end, this project implementation will provide better manufacturing flexibility and cost-savings for up to USD 105,000 yearly.

Introduction

Currently, the plant buffer vent filters are one time use only. Buffer vent filters are used as part of the buffer fixed tanks. The primary function of the vent filters (hydrophobic membranes) is to protect the tanks' internal volume from the environment while exchanging air from the manufacturing room. Vent filters protect the tanks internal volume when air moves toward the tank's interior, but also protect the environment when air is expelled out of the tank's head space. These filter membranes and housings are not direct product contact elements. The purpose of this research is to provide substantial evidence that the vent filter used during the SIP cycle as part of the buffer preparation can be re-used up to 50 times.

Background

Sterilization describes the process that eliminates all forms of microbial life. Steam under pressure, dry heat, hydrogen peroxide gas plasma, ethylene oxide (EtO) gas and liquid chemicals are the principal sterilizing agents used in the industry. To ensure sterility of product contact surfaces from the start of each operation, the entire path of the sterile processing stream should be sterilized.

For manufacturing industries, mainly for parenteral pharmaceuticals, high sterility level is vital. Parenteral products are mostly administered to patients via injections. The parenteral route allows medications to be directly absorbed into the body in a quickly manner.

Problem

As part of manufacturing process improvements, it was identified an opportunity that could provide more flexibility in the manufacturing process and cost savings. Currently, the use of vent filters during the manufacturing process is one time only and is a non-product contact part. Vent filters are used in buffer preparation fixed tanks during Steam-In-Place (SIP) cycle after the preparation of buffer solutions. When finished, vent filters are discarded. This practice provide high costs to the manufacturing process.

Methodology

Define

Vent filters used during the SIP cycle as part of the buffer formulation completion activities in Manufacturing Plant are discarded after one-time usage generating high costs and lack of flexibility during manufacturing process.

Measure

Currently, the vent filters used during the SIP cycle after the buffer formulation process in Manufacturing Plant is discarded after one-time usage.

Analysis

As part of the analysis of this project, three main activities were identified:

1. SIP Cycle Comparison:
   - ❖ SIP cycle conditions were evaluated between vent filter's manufacturer and Manufacturing Plan.
2. Vent Filter New Lifetime Calculation at Manufacturing Plant:
   - ❖ A Safety Factor of one-third (1/3) and 150 SIP cycles as the validated vent filter lifetime, the Equation #1 was used to calculate the new lifetime of the vent filters at Manufacturing Plant.

Equation #1:
New Lifetime = (Maximum SIP Cycles) x (Safety Factor)

3. Manufacturing Plant Validation Activities:
   - ❖ As part of the vent filters reuse activities, a Test Run protocol was generated to confirm that no moisture residual particles are not present in the vent filter after consecutives SIP cycles.

Improve

During this project implementation, the following were established:

- ❖ SIP cycle conditions from the vent filter's manufacturers are considered as the worst-case sterilization scenario.
- ❖ Vent filter reuse for up to 50 times can be met maintaining the vent filter integrity.
- ❖ Validation activities established that no moisture residual particles were found in the vent filter after consecutives SIP cycles maintaining the SIP cycle integrity.

Control

After calculate the new vent filter lifetime of up to 50 times, Manufacturing Plant established manufacturing controls following quality practices and federal regulations. Manufacturing procedures related to the buffer formulation and SIP cycles found impacted as part of the vent filter reuse activities were revised to include the following:

- ❖ Vent filter handling after the SIP cycle completion by manufacturing operators.
- ❖ Determine the vent filter spaced to be stored between SIP cycles.
- ❖ Instructions to request a new vent filter after the completion of the 50th SIP cycle of the previous vent filter.

Also, systematic controls were developed to maintain the cycle counting of the vent filter through the SIP cycles and to systematically block the vent filter in the electronic batch record after completed the 50th SIP cycle.

Results and Discussion

Table 1
SIP Cycle – Filter Manufacturer vs. Manufacturing Plant

Parameter	Vent Filter Manufacturer	Manufacturing Plant
Cycles	150	1
Temperature, (°C)	100	80
Differential Pressure, (psid)	6	3
Time, (min)	100	50
Steam Flow Direction	A	A

Note: Table 1 results were modified to protect confidentiality from both companies, vent filter manufacturer and Manufacturing Plant.

Using the Equation #1, 150 SIP cycles as the maximum lifetime validated at vent filter's manufacturer and a safety factor of one-third, the new lifetime determined for the vent filters at Manufacturing Plant is 50 SIP cycles.

New Lifetime = (150 SIP Cycles) x (1/3) = 50 SIP cycles

Two Hypothesis Tests were performed: "2-Sample T Test" and "2-Sample Standard Deviation" were used using Minitab V18.0.

Figure 1

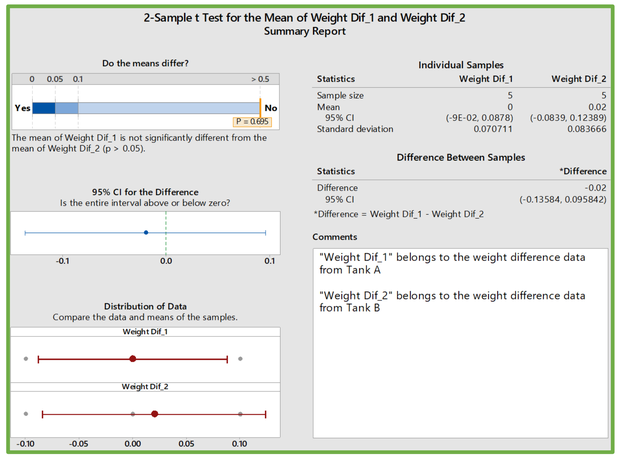
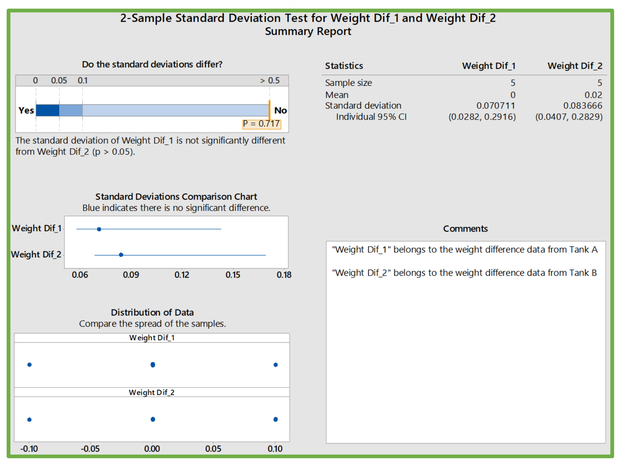


Figure 2



Conclusions

The activities required to the implementation of this project has demonstrated:

- ❖ The re-use of the vent filters up to 50 SIP cycles without compromising the filter and SIP cycle integrities, as part of the buffer formulation process at Manufacturing Plant.

The implementation of this project allows the Manufacturing Plant to have greater flexibility in manufacturing areas. Also, it is a cost-saving project that provides savings related to the vent filter re-use for up to $105,000 yearly.

Future Work

Based on these benefits, new proposals have been generated to expand the scope of this project to a different manufacturing area. Using the validated sterilization cycle at the Manufacturing Plant, any manufacturing process that uses the vent filter as a redundant non-product contact filter can consider implementing this project.

Also, after one year of project implementation, a greater safety factor, such as 50%, will be used to upgrade the project to re-use the vent filters for up to 75 times. This would generated greater cost savings and manufacturing flexibility.

Acknowledgements

I wish to extend my special thanks to my management and my functional team that help me to implement this project successfully.
Also, I would like to thank to my advisor, Jose A. Morales, PhD, for the effort and time dedicated to help me finalize this article.

References

[1] W. A. Rutala, D. J. Weber, and HICPAC, "Guideline for disinfection and sterilization in healthcare facilities," CDC, Chapel Hill, NC, May 2019. [Online]. Available: https://www.cdc.gov/infectioncontrol/pdf/guidelines/disinfection-guidelines-H.pdf
[2] "Guidance for industry sterile drug products produced by aseptic processing — Current good manufacturing practice," FDA, Rockville, MD, Sept. 2004. [Online]. Available: https://www.fda.gov/media/71026/download.
[3] J. Doornmalen and K. Kopinga, "Review of surface steam sterilization for validation purposes," *American Journal of Infection Control*, vol. 36, no. 2, pp. 495-526, Feb. 2007. [Online]. doi: 10.1016/j.ajic.2007.02.002
[4] J. J. Perkins, "Prevacuum high temperature steam sterilization," in *Principles and Methods of Sterilization in Health Sciences*, 2nd ed. Springfield, IL: Charles C. Thomas, 1983, p. 137.
[5] M. Dion and W. Parker, "Steam sterilization principles," *Pharmaceutical Engineering*, vol. 33, no. 6, pp 1-8, Nov. 2013. [Online]. Available: https://www.ispe.gr.jp/ISPE/02_katsudou/pdf/201504_en.pdf
[6] M. Kawai, "Sterilization and cleaning in place," *PDA Journal of GMP and Validation in Japan*, vol. 4, no. 2, pp. 107-113, Jul. 2002. doi: https://doi.org/10.11347/pda.4.107
[7] P. F. Stanbury, A. Whitaker, and S. J. Hall, "Sterilization," in *Principles of Fermentation Technology*, 3rd ed. Oxford, UK: Butterworth-Heinemann, 2017, pp. 273-333.
[8] R. T. Wood, "Fundamentals of thermal sterilization processes", in *Development and Manufacture of Protein Pharmaceuticals*, 1st ed. Medford, MA: Springer, 2002, pp. 191-212.
[9] S. Kovary, J. Agalloco, and B. Gordon, "Validation of the steam-In-place sterilization of disc filter housings and membranes," *PDA Journal of Pharmaceutical Science and Technology*, vol. 37, no. 2, pp. 55-64, Mar. 1983. [Online]. Available: https://journal.pda.org/content/37/2/55
[10] S. Killen and M. McCourt, "Decontamination and Sterilization," *Surgery*, vol. 30, no. 12, pp. 687-692, Dec. 2012. doi: https://doi.org/10.1016/j.mpsur.2012.10.008
[11] J. Seibert and R. Rahimi, "Vent filter assembly," U.S. Patent 5,353,949, Oct. 11, 1994. [Online]. Available: https://patents.justia.com/patent/5353949
[12] D. A. Gray, G. E. Harrison, and S. T. McCoy, "Pipeline branch arrangement," U. S. Patent 5,857,715, Jan. 12, 1999. [Online]. Available: http://www.freepatentsonline.com/5857715.html
[13] M. W. Jornitz, "Integrity testing," *Sterile Filtration*, vol. 98, pp. 143-180, Jan. 2006. doi: https://doi.org/10.1007/b104248
[14] *Sterilization of Health Care Products — Microbiological Methods — Part 1: Determination of a Population of Microorganisms on Products*, ISO 11737-1:2018, Jan. 2018. [Online]. Available: https://www.iso.org/standard/66451.html
[15] J. Charvat, "Understanding project methodologies," in *Project Management Methodologies: Selecting, Implementing, and Supporting Methodologies and Processes for Projects*, 1st ed. Somerset, NJ: Wiley, 2003, pp. 1-30.