QbD Approach for Successful Initial Sterile Aseptic Filling Facility Validation

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Abstract

The world's pharmaceutical regulatory agencies strongly suggest pharma-industries to implement QbD (Quality by Design) approach for pharmaceutical product robust design. In the Pharmaceutical Engineering knowledge perspective, the QbD approach is defined as a part of the Pharmaceutical Quality System for product life cycle that has to be validated. Process design should not only cover the scope of product design. Especially in the sterile production, facility and manufacturability design has a huge impact on a sterility product attribute. Sterile facilities that choose the aseptic filling process as a process decision have to strive for a successful Sterile Aseptic Filling Validation (Media fill) before this facility becomes available for commercial sterile drugs production.
Media Fill is the simulation mimicking a real production. It consumes similar real production resource-cost but only to provide evidence that the system has a capability to produce sterile products. Once complete setup of all sterile manufacturing systems is done, the initial media fill will become an important proof of the system design effectiveness.
This paper proposes a QbD approach for designing a facility and process manufacturability in sterile products with aseptic filling process. In this paper, a literature review conducted for QbD in the pharmaceutical industry application in sterile aseptic process facilities to build a system model approach for step by step process design. And a case study on QbD for the HVAC (Heating, Ventilation and Air Conditioning) operational for conducting a control strategy with the objective to fulfill the acceptance criteria and cost minimizing at initial validation.

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Keywords
Quality by design, Pharmaceutical industry, Aseptic filling, Media fill, Design of experiment

1. Introduction
Pharmaceutical Industries are having a more and more stringent challenge these days. Delivering the product that fulfills the quality, efficacy and patient safety target will bring the industries to always step ahead on having clear understanding where is the base line to achieve that objective. On the other hand, competitive situations also make the industries find the way to do that efficiently.

Some pharmaceutical industries produce sterile products, which the product sterility must become one of their critical quality attributes. There are two most common strategies to achieve that product sterility, one is the process called terminal-sterilization, with various sterilization methods such as moist-heat, dry-heat, irradiation, and chemicals. Two is the process called aseptic filling process that uses sterilizing grade filters for end product filling. The objective of aseptic processing is to produce a sterile product and to minimize or eliminate potential sources of contamination in the product (International Society of Pharmaceutical Engineering [ISPE] 2018). Ideally, products should be designed from the outset to be terminally sterilized. Where this is not feasible without detriment to the product, alternative processes, such as aseptic processing, can be employed (ISPE 2018). That is why most practitioners suggest terminal sterilization as a main choice, and shift to aseptic process ideas when this becomes the one and only solution.

Once an aseptic process becomes the industry's decision to produce their sterile product, they will have an obligation to do an aseptic filling process validation that in pharmaceutical regulation is known with a terminology called media fill. Validation of aseptic processing should include a process simulation test using nutrient medium (media fill) and the process simulation test should be performed as initial validation with three consecutive subsequent manufacturing steps (PICS 2021). The ultimate goal is zero microbial growth in every container of media fill product. This acceptance criteria has to be provided even when the sterile product that will be processed in this aseptic filling facility can be still in the early design stage. It becomes obvious that the success factor for media fill process simulation mostly depends on facility, procedure and human resource involved knowledge and skill.

ICH (International Conference on Harmonisation of Technical Requirements for Registrations for Registration of Pharmaceuticals for Human Use) published a guideline initially in 2004 that adopt a QbD (Quality by Design) terminology that define as a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. (ICH 2009). It brought a systematic guideline in pharmaceutical product life cycle and continual improvement in Pharmaceutical quality system. The step will involve quality risk management of product and process development, design space and the drug product control strategy. This includes the design of manufacturing process and process control, and the control of critical steps.

However, since the aseptic process validation can be done simultaneously with the design of the product, the success factor of the validation will have everything to do with the facility design, installation, its operational condition, and the media fill challenge as its performance qualification. QbD of the manufacturability and manufacturing process can be defined as a process design of a facility and its operation that also covers method development and human resource management for every person involved in that sterile facility.

In pharmaceutical industries, typically, 90% energy goes to manufacturing equipment power and HVAC systems (Hassan and Ahmed 2021). The HVAC system is considered as the most critical utility in the aseptic process which required a highest ISO room class standard in pharmaceutical manufacturing. Aseptic process validation (media fill) has exactly the same scenario with the production situation. It will consume approximately the same amount of energy but there will be no commercial product to produce. It is defined as operating cost as one category of a quality cost (Phadke 1997). Successful media fill also depends on a highly skilled worker that is well trained in aseptic GMP knowledge. Utilizing a delicate sophisticated expensive machine that is not only required for pharma machinery but also categorized as for sterile production purposes. It is the important element of manufacturing cost that is also one category of quality cost (Phadke 1997).

In the simple word, it is important, after complete set up of the system and ready for producing a commercial product, inisial media fill with 3 run consecutive media batches (PICS 2021) must succeed. QbD concept approach hypothetically can apply to achieve those objectives. It pulls the robust design understanding before designing the process and product. Robust design has to apply for a new or renovated sterile facility to assure the sterility attribute of the coming product.

1.1 Objectives

This study aims to propose a method with a QbD approach using systems thinking tools to improve an operational design of sterile aseptic filling facilities so that they can be used as part of a control strategy to increase the likelihood of successful initial media fills. The results of the proposed method are also applied in a case study on the scope of HVAC operational design to achieve robust quality standards according to room grade classification minimal requirements. The case studies that will be discussed in this article are only limited to the room grade performance requirements for temperature and relative humidity (RH) parameters as a one of operation control strategy.

2. Literature Review

The pharmaceutical industry is one of the highly regulated industries, with many rules and regulations enforced by the government to protect the health and well-being of the public (Handoo et al, 2012). Regulatory bodies in their country's jurisdiction have an obligation to always closely watch every pharmaceutical (including biopharmaceutical) industry to assure drug quality products and protect patients for their safety as a drug consumer. To build a better understanding among regulators, several countries have legalized a world organization forum in the form of The Pharmaceutical Inspection Co-operation Scheme (PIC/S) that was established in 1995 as an extension to the Pharmaceutical Inspection Convention (PIC) of 1970. They harmonized guidelines which can then be adopted by each member country to become a regulation in their jurisdiction that binds on how the pharmaceutical industry should be operated.

PIC/S published a Guide to Good Manufacturing Practice (GMP) for Medicinal Products. This guide's first chapter explains the Pharmaceutical Quality System (PQS) with the key principle is to ensure that they are fit for their intended use, comply with the requirements and do not place patients at risk due to inadequate safety, quality or efficacy (PIC/S 2021). GMP applies to the lifecycle stages from the process design, technology transfer, commercial manufacturing through to product discontinuation, and can extend to the pharmaceutical development lifecycle stage (PIC/S 2021).

The concept was initially published in ICH Q10, as a guideline to assist pharmaceutical manufacturers achieving an effective pharmaceutical industry quality management system (ICH 2009). It has to be understood side by side with the ICH Q8 Pharmaceutical Development and ICH Q9 Quality Risk Management, that recommend building a product quality through the whole product life cycle and adopt the principle of QbD (Quality by Design) concept. Built Quality since the product design and development (ICH 2009) and apply a risk based thinking concept approach to maintain a high quality medicine product and keep assure on patient safety.

The QbD based thinking approach as an elaboration of the concept of robust design (Phadke 1989; Belavendram 1995). It is a new concept which later became the foundation of the industry so that it can implement its manufacturing activities with its design and operations using scientific studies to ensure the quality of its products. QbD which was then applied consisted of steps to determine Quality Target Product Profile (QTPP), Critical Quality Attribute (CQA) and Critical Process Parameter (CPP) (Rantanen and Khinast 2015) with scientific steps Design of Experiment (DoE) to determine design space and identify science and risk based control strategy (Gapp and Holzknecht 2011; Gandhi and Roy 2016; Politis et al, 2017).

Numerous research about QbD implementation in the pharmaceutical industries that focus on product design has published (Baert et al, 1993; Merkku et al, 1994; Lundstedt et al 1998; Bro and Jakobsen 2002; Naelapa et al, 2009; Sugiyama and Schmidt 2012; Cui et al, 2012; Sauhi et al, 2013; Stocker et al 2014; Yu et al, 2014; Rantanen and Kinash 2015; Grangeia 2019; Kovacs et al, 2021), but there are limited source of research of QbD in pharmaceutical industry that focus on design and operation of facility. As mentioned before, sterile facilities have a direct impact on the sterility of the product. Beside the product chemical compound property as a quality attribute, sterility will always be a critical quality attribute of the product (Mesut et al, 2015).

In the pharmaceutical industry, sterile products are a group of products that have a high critical level. Sterile products require strict control of potential contamination which can be in the form of particulates, microorganisms, and endotoxins (ISPE 2018). Types of sterile products including parenteral and ophthalmic products have special needs for sterile facilities that must be maintained and monitored very closely. Design issues related to hygiene are well defined in terms of equipment and facility design, such as HVAC system design and operational (Odum 2004).

To produce sterile products, there are two main strategies: 1) Terminal sterilization, where the sterilization process is carried out with a choice of various sterilization methods (i.e dry heat, moist heat, irradiation, chemical) at the final stage after the product is completely packaged. 2) Aseptic filling, by carrying out the filling process using a sterilizing grade filter (Joseph et al, 2010; Gorsky and Baseman 2020). The choice of process using the aseptic filling method has the consequence of carrying out the obligation to periodically conduct aseptic filling validation. This process is known as 'media fill' (PIC/S 2021).

Media fill is a regulatory requirement for aseptic product manufacturers. Media trials using microbiological growth media as product substitutes to simulate the product filling process; the media is processed in an identical way to that of the processed product. The media simulation provides information on whether the process compromises the sterility of each component and the finished product. Thus, media filling is designed to evaluate the aseptic assembly and operation of critical equipment, qualify operators and assess their technique, and demonstrate that environmental controls (by HVAC system) are adequate to meet the basic requirements necessary to produce sterile drugs by aseptic processing (Joseph et al 2010; Agalloco and Carleton 2016; Sandle 2021).

Media fill is a validation activity that simulates actual production conditions, using the same resources when the production process is carried out, the only difference is that the manufacturing process and filling do not use products but with microbial growth media. Failure of the media fill not only results in non-compliance with the requirements to be accepted as a facility that is allowed to carry out aseptic production processes for commercially sterile products, but also has an impact on the unit cost of resources that have been spent which is equivalent to the unit cost of production. There are numerous factors for successful initial aseptic filling validation (media fill) (Beaney 2016; ISPE 2018; Sandle et al, 2021). A system thinking approach (Daellenbach 2005) can be used to see the whole situation to minimize or even avoid the unacceptable possibility of media fill result (Joseph et al, 2010). Unacceptable media fill will result in lost costs equivalent to production costs. Hassan and Ahmed (2021) have studied that the most of the pharmaceutical manufacturing costs are the energy costs of operating the HVAC. So it is important that the HVAC system that serves the sterile process can be ensured to be a factor that supports the success of the media fill.

The HVAC system for the most critical area in an aseptic filling process is in grade A room in a grade B room as a surrounding. Grade A room classification has more stringent environmental attributes than grade B room. Exceptions can be applied to the manufacturer which uses a Blow-Fill-Seal (BFS) machine for the aseptic filling system while using grade A in a grade C room as a surrounding. Every room grade classifications (A, B, C and D for pharmaceutical sterile production) are having a certain quality attribute to achieve (ISPE 2011; PIC/S 2021).

3. Methods

The method used in this research is to perform the following steps:

1. Preceded by a discussion about system thinking using an influence diagram to see as a whole all factors (boundary of the system, component and subsystem, transformation process, input, output, and accept performance criteria for every subsystem) that have the possibility of influencing the success of media fills, to conduct a study with a QbD approach to each component and subsystem. This research is limited to a case study of operational design using the Design of Experiment (DoE) for multiresponse optimization using Taguchi and PCR-TOPSIS (Process Capability Ratio and Technique for Order Performance by Similarity to Ideal Solution) method (Damayanti et al, 2016; Lim et al 2020) of HVAC system operation in grade C room as a surrounding of grade A where aseptic filling process is done. Further research needs to be done in the future for another component and subsystem in the influence diagram built. Optimized design, installation and operation of all things that give direct impact on product sterility in the sterile facility must be considered for successful aseptic filling validation (media fill). Subsystems on system thinking models include every method developed for the activity inside sterile area, and all personnel competency that involve in sterile production.
2. Method steps for multiresponse optimization using Taguchi and PCR TOPSIS:
    a. Measuring every attribute (Temperature and RH) with 3 data samples for every run as a response value.
    b. Transformation from response value to SNR (Signal to Noise Ratio).
    c. Calculating PCR-SNR.
    d. Calculating TOPSIS from PCR-SNR
    e. Determining the optimum level for every factor.
3. Validate the DoE method on the HVAC operational design by comparing the performance on HVAC system attributes studied between before and after the optimization process as one thing to increase the likelihood of media fill success.

4. Data Collection

System thinking using an influence diagram was developed to give a better understanding about what can impact the likelihood of media fill success factor. It shows at figure 1. It uses diagrammatic convention (Daellenbach 2005), starting at the end the oval shape as the objective to make a successful media fill. The circle can be a system variable, component attribute, or state variable value. The cloud shape is an uncontrollable input data or constraints, and the

rectangular shape is control input or decision rule. The dotted line can be seen as a boundary system. There are many factors that can influence media fill acceptance criteria and for successful initialization, every component and subsystem path must assure to fulfill every component accept criteria. The scope of this study shows in the figure 1 yellow path, media fill success factor preceded by passed facility, that is HVAC system design, installation, operation and performance (D, I, O, P). It will run in accordance with process parameter setting, while the decision of number of people working in the area become a controllable influencing input, and outdoor air quality is considered as an uncontrollable input.

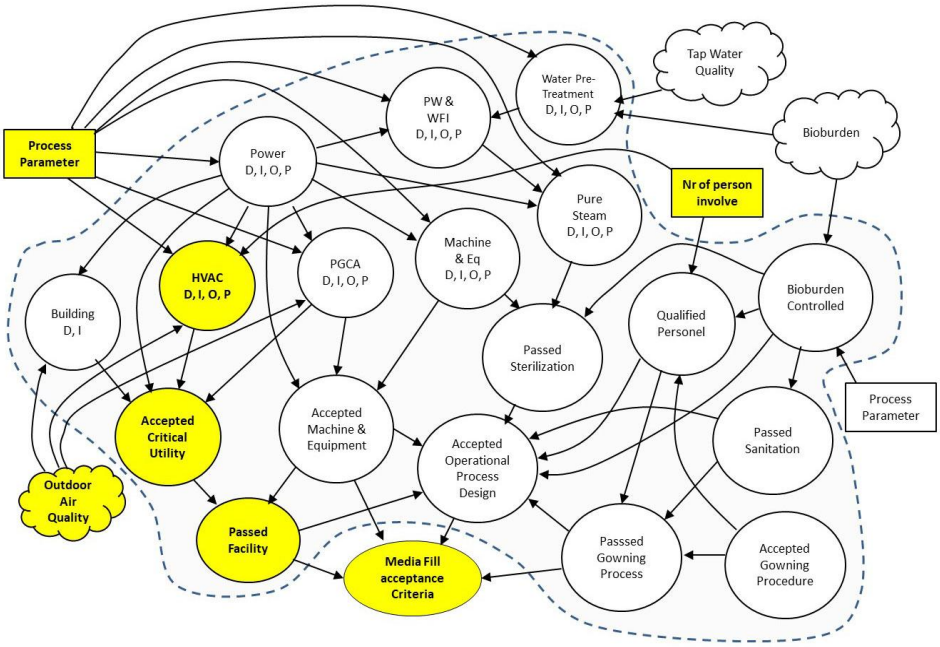

Figure 1. System thinking using influence diagram to see the big picture for successful media fill

This research conducted a case study of HVAC operational design at PT. XYZ, a well-known pharmaceutical company in Indonesia, after renovations were done on a sterile facility by updating the HVAC system. Engineering design as required specification is carried out, in HVAC at-rest performance qualification conditions are justified as having met the acceptance criteria, while in operational conditions, large variations are obtained on the attributes of Temperature and RH. Improvements must be made before conducting the media fill. Improvements with the QbD approach were carried out on grade C coverage as a grade A surrounding in the aseptic filling system using a Blow-Fill-Seal machine. Figure 2 shows the schematic diagram on the HVAC system in this scope at about 10 m^2 grade C area. The DoE with multiresponse using the Taguchi approach and PCR-TOPSIS was carried out to optimize the HVAC system in the coverage of the system. In this study, 4 factors with 2 levels each were determined, with the temperature and RH as responses. The specification for temperature and RH attributes are shown at table 1 (Haycocks et al, 2021):

Table 1. Temperature and RH required specification for grade C room classification

Room Classification	Lower Limit	Operating Range	Upper Limit
Grade C Temperature	15 °C	18 – 22 °C	30 °C
Grade C RH	25 %	30 - 60 %	65 %

Temperature and RH setting has been justified as a fixed parameter with the value on target mean that is 20 °C and 45%. The factors and its levels are determined as figure 2 shown and table 2 details.

Table 2. Factors and levels of the experiment

Factors	Description	Level 1	Level 2
CCV	Cooling Control Valve, auto-regulate set level for Chilled Water Opening.	60	100
STMV	Steam Valve, auto-regulate set level for Steam Valve Opening	95	100
VSD	Variable Speed Drive, auto-regulate set level for AHU Blower rpm	98	100
People	Number of people assigned inside grade C area	1	2

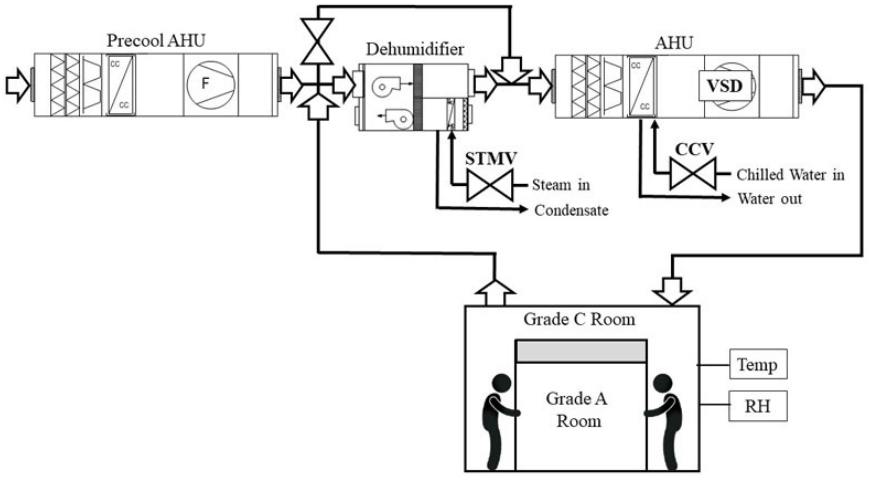

Figure 2. Schematic diagram of HVAC system scope for operational improvement

The scope of HVAC system studied limited on one particular grade C room area as a surrounding of one particular grade A filling area that served by Precool AHU (Air Handling Unit), Dehumidifier (Dehumidification Unit) and particular AHU (Air Handling Unit) for that room zone.

5. Results and Discussion

5.1 Numerical Results

A. Measuring every attribute (Temperature and RH) with 3 data samples for every run as a response value.
Data collection on temperature and RH with a standard Taguchi orthogonal array using Minitab 18 software, from the results of measurements using a calibrated temperature-RH logger that put in the most critical area, the data obtained are as follows in the table 3:

Table 3. Data collection

Run	Factors and Levels				Temperature (°C)			RH (%)		
	CCV	STMV	VSD	People	R-1	R-2	R-3	R-1	R-2	R-3
1	60	95	98	1	21,4	20,4	20,4	48,4	48,4	44,4
2	60	95	100	2	19,6	19,7	19,6	57,3	57,2	57,3
3	60	100	98	2	22,2	19,0	20,2	50,3	40,6	66,2
4	60	100	100	1	18,9	22,3	20,2	40,6	66,3	49,1
5	100	95	98	2	21,6	21,5	21,6	50,1	50,2	50,1
6	100	95	100	1	20,4	21,1	21,8	44,4	48,4	46,3
7	100	100	98	1	18,9	21,6	20,1	53,9	68,5	44,9
8	100	100	100	2	20,2	26,8	17,5	49,1	75,3	34,8

B. Transformation from response value to SNR (Signal to Noise Ratio).

SNR results from the response value shown at table 4. Both temperature and RH are using a quality characteristic as Nominal the Best.

Table 4. Result of SNR calculation

Run	SNR	
	Temperature	RH
1	31,1046	26,1843
2	50,6311	59,9293
3	22,0490	12,1528
4	21,5325	11,9792
5	51,4469	58,7737
6	29,5837	27,2999
7	23,4825	13,4091
8	13,0523	8,2447

C. Calculating PCR-SNR.

The next stage was SNR calculated from the PCR shows at table 5.

Table 5. Result of PCR-SNR calculation

Run	PCR-SNR	
	Temperature	RH
1	-0,0818	-69,0765
2	0,3627	-35,3316
3	-0,2879	-83,1080
4	-0,2997	-83,2816
5	0,3813	-36,4871
6	-0,1164	-67,9609
7	-0,2553	-81,8517
8	-0,4927	-87,0161

D. Calculating TOPSIS from PCR-SNR

The result of calculating TOPSIS from PCR-SNR is stated at table 6.

Table 6. Result of TOPSIS calculation

Run	PCR-SNR		di^+	di^-	PCR-TOPSIS
	Temperature	RH			
1	-0,0818	-69,0765	33,7481	17,9443	0,3471
2	0,3627	-35,3316	0,0186	51,6916	0,9996
3	-0,2879	-83,1080	47,7811	3,9135	0,0757
4	-0,2997	-83,2816	47,9549	3,7395	0,0723
5	0,3813	-36,4871	1,1555	50,5366	0,9776
6	-0,1164	-67,9609	32,6331	19,0589	0,3687
7	-0,2553	-81,8517	46,5245	5,1698	0,1000
8	-0,4927	-87,0161	51,6919	0,0000	0,0000

E. Determining the optimum level for every factor

Level factor chosen is the level that gives the largest average value of PCR-TOPSIS that shows at table 7.

Table 7. Optimum Condition

Level	CCV	STMV	VSD	People
1	0,37370	0,67328	0,37512	0,22205
2	0,36159	0,06201	0,36017	0,51325
Delta	0,01212	0,61127	0,01495	0,29120
Rank	4	1	3	2
Optimum Level	60	95	98	2

5.2 Graphical Results

Graphical result for optimization shows main effect for mean of the TOPSIS value in every run states at figure 3.

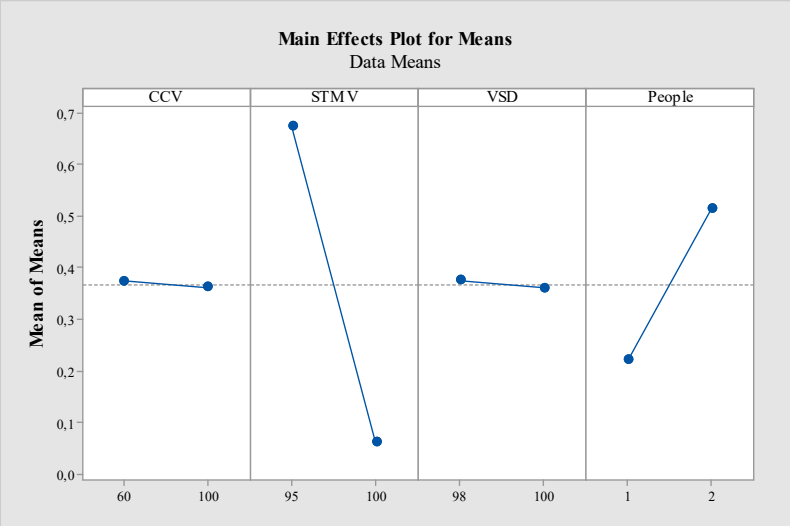

Figure 3. Main effect for mean of the TOPSIS

5.3 Proposed Improvements

Optimum level for the studied HVAC scope shows the rank factor for temperature and RH optimum response on that AHU scope is STMV at set level 95; determining 2 people working on the area as an optimize operational recommendation; CCV that set at a level 60 and VSD that set on level 98.

Number of people working in the area, practically, should be considered as minimum as possible to achieve the grade C room in-operation acceptance criteria for an airborne particle attribute (viable and non-viable) inside the area. Normal production running must be determined with only 1 person (machine operator) inside the area. Next 1 person who comes into the area only happens at a machine breakdown situation that needs the technician's intervention, or when the inspection person does the environmental monitoring inside the area. The DoE result is understood that in a scientific base analysis, maximum allowable 2 persons inside this room area will make a better influence of robustness for temperature and RH room attributes.

The graph shows on figure 3 states CCV and VSD only give a small contribution for the optimum condition to achieve a robust temperature and RH result, however, the optimum level of CCV and VSD can be considered as a low level adjustment that consumes less energy in HVAC system operation. Further verification needs to be justified for energy consumption improvement at optimum level condition.

This optimum level improvement can be considered as a part of control strategy to increase the likelihood of successful initial media fill.

5.4 Validation

Figure 4 is a temperature monitoring and figure 5 shows RH monitoring, both are using a calibrated logger in 30 min interval for 5 days observation before and after the optimization. Default setting before optimization during the functionality test is CCV at 100; STMV at 100; and VSD at 100. Day-1 and day-2 with no activity in the area, Day-3

and day-4 with 2 people's activity and dry-running machine operation. Day-5 is an activity shut down condition inside the room area.
Similar scenario also applied after optimization. Day-1 and day-2 with the full activity situation, 2 persons and dry-running machine operation, day-3 and day-4 with no activity in the area (during weekend) and day-5 is a set-up situation for a full activity the next day.
Optimization shows a better result for robustness of temperature and RH attributes. Both measurements were conducting during rainy season outdoor ambient condition, further experiment still need to run to verify the robustness during hot season.

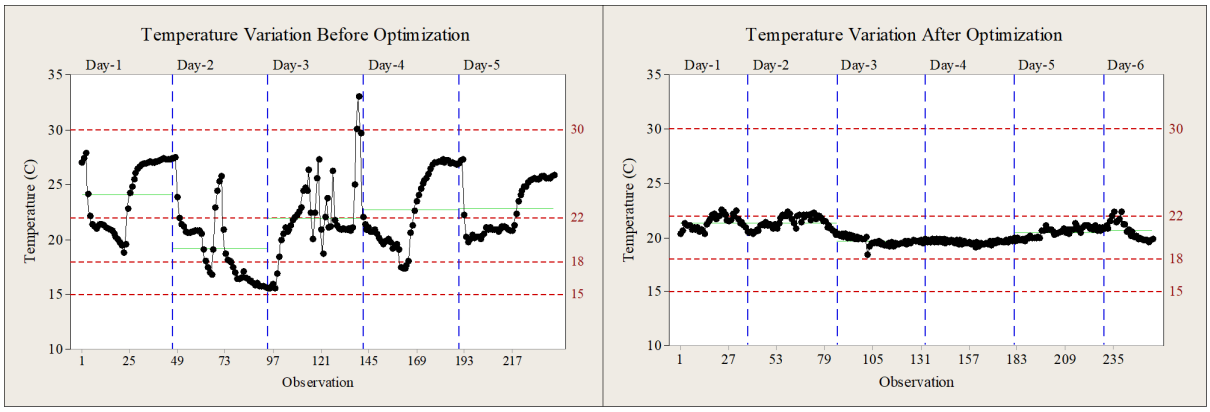

Figure 4. Temperature monitoring before and after optimization

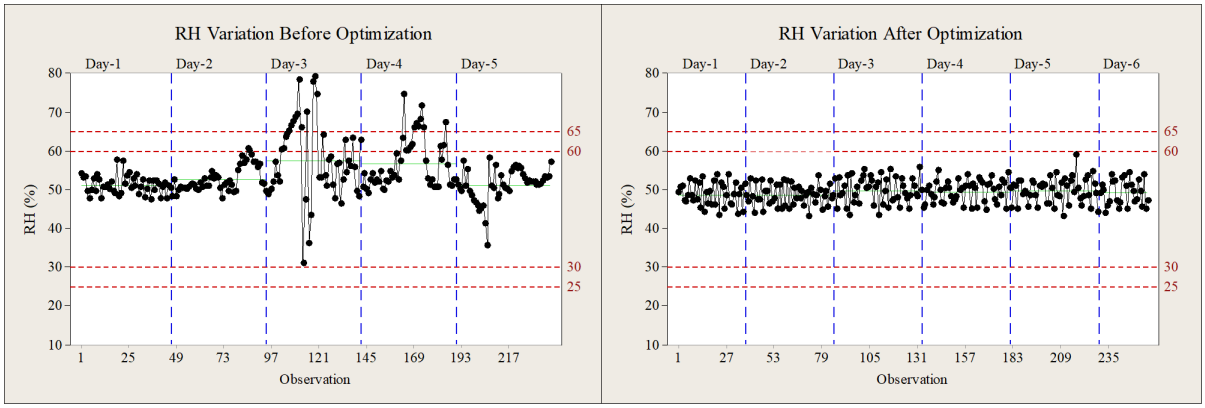

Figure 5. RH monitoring before and after optimization

6. Conclusion

This research shows that QbD approach for robust facility operation design can be applied to improve the sterile aseptic filling facilities operation so that they can be used as part of control strategy to increase the likelihood of successful initial media fill. The optimum result above can increase the confidence level that media fill will run without deviation.
The study that is limited only in HVAC systems is one subsystem that its robustness can give a contribution for media fill success run. Further study with the similar QbD approach can be applied to other subsystems for achieving the successful of initial media fill as a main objective (see influence diagram figure 1). Even at the HVAC subsystem scope, there is still any further research needed to achieve the robustness for other attributes requirements, such as an airborne particle (viable and non-viable) as a response with several control factors that can be studied (temperature, RH, airchange, and persons activities).
Other subsystems that do not influence each other can be studied independently, such as compendial water supplied to the aseptic filling production system, persons bioburden controlled, pharma-grade compressed air supply, and the sterilization process used.

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