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An Overview of Validation and Comparison of HVAC System at Rest and in Operation in Pharmaceutical Industry

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ABSTRACT
The main goals of this research work it to carry out the validation on HVAC (Heating Ventilation and Air Conditioning). We are well known that the prime idea of any pharmaceutical organization is to produce the product that meets the quality standard where HVAC system plays a vital role to eliminate contamination or cross contamination. Validation in simple term that can be explained as the process of attaining and documenting the sufficient confirmation which gives a prominent step of assurance that the products are of quality standard and are safe to practice. In this present study, validation of HVAC system was executed once which is probably done once in six months. Various tests including Air change per hour, Differential pressure, airborne particle count, temperature and relative humidity were performed for the functional test of components like Air handling unit, duct, and interlocks. The validation of HVAC was conducted at Simca Laboratories Pvt. Ltd. Located in Nepal (a pharmaceutical company) which has 13 AHU where all 13 AHU at different condition (at rest and in operation) were validated. Various parameters were observed for every AHU that was allocated for the various rooms.

Keywords*: HVAC system, validation, Equipment Validation, Parameters to validate HVAC system, Qualification.*

INTRODUCTION
HVAC system simply stands for Heating, Ventilation and Air Conditioning System. In order to remain or stick to basic regulatory requirements and to manufacture the quality pharmaceutical products, HVAC plays an important role. So as to prevent contamination and cross contamination, air is passed through **HEPA** filter which filters the air and gives 99.995% efficiency.

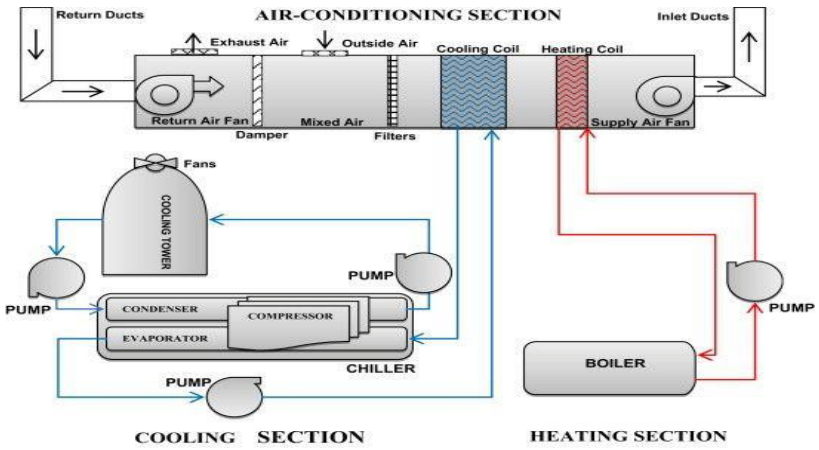

Fig. 1: Diagram of HVAC System in Pharmaceutical Industry.

The core functions of an HVAC system includes: [6]

1) **Controls airborne particles, dust and micro-organisms:** Airborne particles, dust and micro-organisms directly affects the quality of the product which is controlled by HVAC system where air is filtered and unwanted particles are removed.
2) **Maintain room temperature:** Uncontrolled room temperature leads to the degradation of the quality of product and microbial growth. Hence, HVAC system controls the room temperature.
3) **Maintain room humidity/ moisture (RH):** In order to stabilize the drugs while it is being manufactured, proper humidity is maintained.
4) **Maintain room pressure (ΔP):** Prevention of cross contamination can be possible when the pressure of clean rooms is maintained positive than the black area. HVAC system assures positive pressure at rooms by keeping the air flow higher than black areas.

COMPONENTS OF HVAC SYSTEM

Figure 1 shows the basic components of HVAC system. HVAC boxes and AHU that are placed in a pharmaceutical industry is made up of Stainless-steel supporting frames, galvanized iron, and mild steel. The components that are present in HVAC system are described below: [1]

Filters: Dust particles that directly degrade the quality of air as it may contaminate or cross contaminate the drug product is removed with the help of filters in HVAC system. At the very starting of AHU, filters are kept which helps to keep all the following components of the AHU clean. There are various types of filters placed in AHU. They are as follows: [31] [32]

- ✓ Coarse filter
- ✓ Pre filters
- ✓ Intermediate filter
- ✓ Fine filter

Heating and cooling coil: Air handling unit provides heating, cooling or give both in order to change the air temperature and maintain the humidity as required in particular area. Heating and cooling effect in the supply air is possible only because of heating and cooling coil. [31] [32]

Blower fan: A blower in the air handling unit is run by variable frequency drive which provides a wide range of air flow rates [31] [32].

VCD (Volume Control Dumper): Pressure must be maintained in the adjacent rooms which are possible due to VCD which is made up of aluminum and Galvanized iron. The air flow volume is measured in CFM.

Distribution system: HEPA is fitted at the terminal side in the ceiling with a cover plate screen, through which air is supplied in the room [31] [32].

Return Air: These are boxes with filters fitted in the wall at the bottom side to collect the air from the room, and are connected to the return air duct.

VALIDATION

The main motto of the pharmaceutical industry is to provide or deliver a quality, safe and effective product consistently at a minimum price. Good manufacturing practice in pharmaceutical industry plays a vital role to reduce the hazards and risks to the operators, patients and economical losses. While validating, each and every step is monitored constantly

which ensures lesser rejects and reworks hence it leads to effective cost reduction. So as to follow the guidelines and to stick to good manufacturing practice, validation becomes the primary step to ensure GMP. [19][23].

As per WHO, validation can be defined as "The documented act of proving that any procedure, process, equipment, material, activity or system actually leads to the expected results." [17]
According to ICH, Validation can be defined as "Process Validation is the means of ensuring and providing documentary evidence that processes within their specified design parameters are capable of repeatedly and reliably producing a finished product of the required quality." [17][20-22]

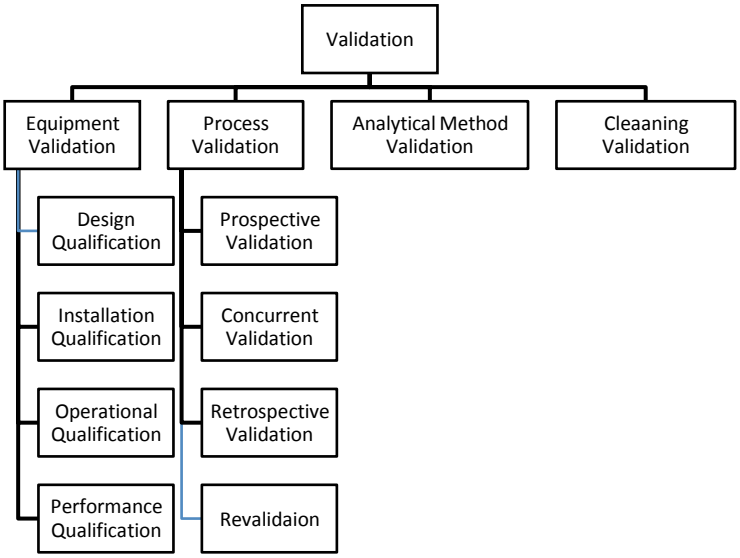

Fig. 2: Types of Validation [24]

TYPES OF PROCESS VALIDATION

a) **Prospective Validation:** It is defined as the establishing documented evidence that a process does what it intends to do based on a pre-planned protocol. This validation is usually carried out before the distribution of a new product and the manufacturing process performed on at least three consecutive production batches [18] [24-25].

b) **Concurrent Validation:** It is similar to the prospective, except the operating firm will sell the product during the qualification runs, to the public as its market price. This validation involves in process monitoring of critical processing steps and product testing. This helps to generate and documented evidence to show that the process is in a good state of control with quality characteristics [18] [24-25].

c) **Retrospective Validation:** Retrospective validation is defined as the establishment of documented evidence that a system does what it intends to do on review and analysis of previous historical data. This validation is based on the historical or past data which includes the changes in the procedure, equipments, protocols, specifications etc. Retrospective validation is for processes that are well established and this will be unsuitable for the processes where there have been recent changes in composition of the product, equipment or operating procedures [18] [24-25].

d) **Revalidation:** It is the repetition of a validation process or a part of it. This is carried out when there is any change or replacement in formulation, batch size and in the case of sequential batches that do not meet its product specifications, equipment plans or site location, and is also carried out at specific time intervals in case of no changes. [18] [24-25].

TYPE OF DOCUMENTATION IN VALIDATION PROCESS

Validation master plan

Validation master plan also referred to as "VMP" is an approved written plan of principles, objectives and actions for maintaining a qualified facility by achieving compliance with the GMP requirements regarding validation. Master plan outlines the methods to be used to establish the performance capability. It even holds the calibration and qualification of equipment's summary and conditions of Validation Protocol [12][26-27].

Process validation protocol

A documented plan which is written in order to perform a specific procedure for manufacturing the pharmaceutical product and also assures whether the procedure followed is as specified or not [12] [25].

Validation Reports

After doing any work, it should be always written so, a validation report should be available after completion of the validation. It should be approved and signed by authorized person with date. The report must consist of at least the following titles: [12] [17]

- Title and objective of study
- Reference to protocol
- Details of Equipment
- Details of procedures and methods
- Results (compared with acceptance criteria)

SOP (Standard Operating Procedure)

Standard Operating Procedures (SOPs) are issued to instruct and help employees in areas of responsibility, appropriate specifications, work instructions and carry out routine operations. These outline procedures which includes step by step instructions must be followed to claim the compliance with GMP principles or other legal rules and regulations. [12]

VALIDATION OF EQUIPMENTS

There are generally 5 steps of equipments validation, which includes: [3] [5]

a) User Requirement Specification:

Some general requirements that might be stated are:

- Equipment's size
- Equipment's speed
- Equipment's effectiveness
- Low sound and dust generation
- Easy operation, dismantling and cleaning
- Easy availability of spare parts

b) **Design Qualification:** This provides the documented evidence that the design

specifications were met.

c) **Installation Qualification:** This provides the documented evidence that theinstallation was complete and satisfactory.
d) **Operational Qualification:** This provides the documented evidence that systems, equipments operate in accordance with operational specifications.
e) **Performance Qualification:** This provides the documented evidence that systems, equipments can consistently perform under routine use.

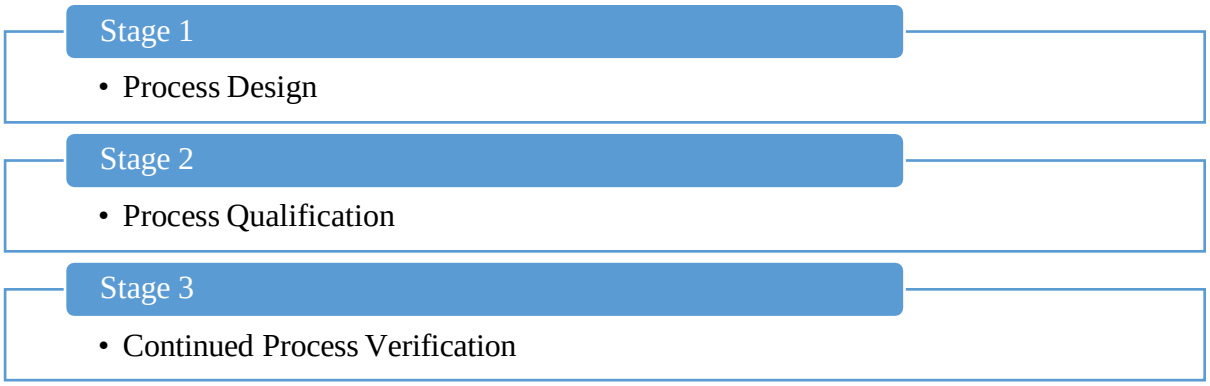

Fig. 3: Approaches to Process Validation [17] [29]

PARAMETERS TO BE VALIDATED

Air Flow Pattern

Titanium tetrachloride stick is burned and placed in front of running AHU. The flow of air is observed with the help of smoke distribution in room. Then, the flow of the smoke is drawn in the sheet of paper and the smoke distribution is tracked [3][6].

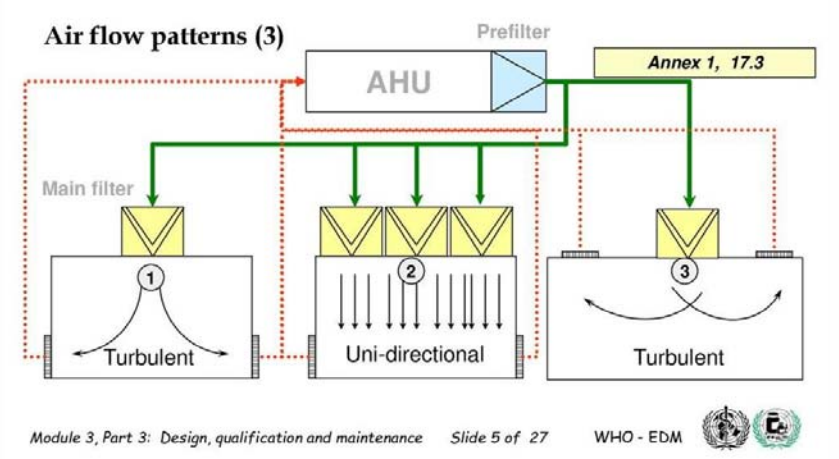

Fig. 3: Air flow Patterns

1. **Air Flow Velocity and changes per hour**

a) The area of HVAC is divided into four hypothetical grids and the air velocity is measured at each grid *i.e.* V1, V2, V3, V4 and then the average air velocity (V) is calculated. [3]

Average of air velocity is given by: $\mathbf{V = \frac{(V1 + V2 + V3 + V4)}{4}}$

The area of the HEPA filter inlet (A) is calculated in feet, A= l x w,

Where, l= length of inlet, w= width of inlet

The total air volume (T) is then calculated, $T = A \times V$

After this, the volume of the room is calculated:

V= Length x Breadth x Height
Then air changes per hour are obtained by dividing the total air change by the volume of the room.

2. **Differential Pressure Monitoring**
   The manometer is attached at the walls of the area that is to be validated. As per EU Guidelines & WHO (TRS No. 961) 10-15 Pascal can be the approximate pressure differentials of rooms of various grades [3][6].

3. **Temperature and Humidity Uniformity Test**
   Temperature and humidity were monitored by using a calibrated thermometer and hygrometer where thermometer is used for measuring temperature and hygrometer is used for measuring humidity of the area [3][6].

4. **Recovery test (Temperature & Humidity)**
   HVAC system was turned off and temperature & humidity of room was checked using hygrometer. The temperature was increased to 40°C using hot air blower. HVAC system is then operated and waits to stabilize the temperature in the area within specification limit and then Record the time. [3][6]. Recovery time limit is 15 – 20 minutes.

5. **Particle count**
   A particle counter is used to conduct the particle count test. There are two different conditions for particle count *i.e.* at rest condition and in operation condition. The particle count should be within the specified range. [3][6].

Table 1: Acceptance Criteria as per EU Guideline & WHO (TRS No. 961)

Grade	At Rest		In Operation	
	0.5µ	5.0µ	0.5µ	5.0µ
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	Not defined	

RESULT & DISCUSSION

1. **AIR FLOW PATTERN**
   The nature of air flow pattern was seen to be turbulent in all the rooms. In case of LaminarAir Flow the pattern was seen to be unidirectional.

2. **AIR VELOCITY TEST**

Table 2: The obtained results for average air velocity test performed in 2019

S. No.	AHU	Avg. Velocity	Supply Grill Size	Total Supply Vol.	Room Volume	Air Change/ hr	
		FPM	Sq. ft.	CFM	Cu. Ft.	Design	Actual
At Rest							
1	AHU 1	194	2	349	1089.62	20	21

2	AHU 2	225	8	1620	3649.50	25	27
3	AHU 3	212	2	382	1195.04	25	27
4	AHU 4	164	4	608	1380.00	25	25
5	AHU 5	119.5	4	498	1196.00	25	28
6	AHU 6	285	8	1447	4026.94	22	21
7	AHU 7	201	8	1233	3912.49	22	21
8	AHU 8	265	2	649	960.00	22	22
9	AHU 9	284	8	1342	3660.00	22	23
10	AHU 10	239	24	3942	11826.78	20	23
11	AHU 11	182	6	1038	3115.13	20	23
12	AHU 12	337	4	812	2437.24	20	23
13	AHU 13	119	4	450	1213.68	22	23
In Operation							
1	AHU 1	184	2	363	1089.62	20	20
2	AHU 2	221	8	1521	3649.50	25	22
3	AHU 3	230	2	567	1195.04	25	22
4	AHU 4	173.10	4	607	1380.00	25	25
5	AHU 5	161	4	498	1196.00	25	22
6	AHU 6	274	8	1389	4026.94	22	21
7	AHU 7	298	8	1306	3912.49	22	20
8	AHU 8	303.24	2	694	960.00	22	21
9	AHU 9	249	8	1396	3660.00	22	19
10	AHU 10	206	24	3743	11826.78	20	19
11	AHU 11	173	6	947	3115.13	20	20
12	AHU 12	285	4	812	2437.24	20	20
13	AHU 13	135	4	455	1213.68	22	22

Table 3: The obtained Results for Average Air Velocity Test performed in 2020

S. No.	AHU	Avg. Velocity	Supply Grill Size	Total Supply Vol.	Room Volume	Air Change/ hr	
		FPM	Sq. ft.	CFM	Cu. Ft.	Design	Actual
At Rest							
1	AHU 1	197	2	363	1089.62	20	19
2	AHU 2	223	8	1521	3649.50	25	21
3	AHU 3	235	2	565	1195.04	25	24
4	AHU 4	163.24	4	575	1380.00	25	23
5	AHU 5	159	4	460	1196.00	25	22
6	AHU 6	286	8	1477	4026.94	22	19
7	AHU 7	309	8	1435	3912.49	22	21
8	AHU 8	303.08	2	676	960.00	22	20
9	AHU 9	242	8	1342	3660.00	22	20
10	AHU 10	210	24	3942	11826.78	20	18
11	AHU 11	175	6	1038	3115.13	20	18
12	AHU 12	285	4	812	2437.24	20	21
13	AHU 13	128	4	445	1213.68	22	23
In Operation							

1	AHU 1	227	2	363	1089.62	20	19
2	AHU 2	223	8	1521	3649.50	25	22
3	AHU 3	237	2	567	1195.04	25	22
4	AHU 4	163.01	4	575	1380.00	25	23
5	AHU 5	164	4	498	1196.00	25	24
6	AHU 6	286	8	1477	4026.94	20	20
7	AHU 7	309	8	2803	3912.49	22	21
8	AHU 8	303.45	2	670	960.00	22	20
9	AHU 9	242	8	1342	3660.00	22	21
10	AHU 10	213	24	3942	11826.78	20	18
11	AHU 11	175	6	1038	3115.13	20	18
12	AHU 12	285	4	1098	2437.24	20	21
13	AHU 13	140	4	445	1213.68	22	21

Table 4: The obtained results for average air velocity test performed in 2021

S. No.	AHU	Avg. Velocity	Supply Grill Size	Total Supply Vol.	Room Volume	Air Change/ hr	
		FPM	Sq. ft.	CFM	Cu. Ft.	Design	Actual
At Rest							
1	AHU 1	227	2	441	1083.17	> 20	21.56
2	AHU 2	223	8	1716	3635.64	> 20	28.33
3	AHU 3	239	2	464	1187.98	> 20	23.40
4	AHU 4	165.35	4	640	1372.68	> 20	24.98
5	AHU 5	165	4	639.90	1189.39	>20	32.23
6	AHU 6	299	8	2322	3643.06	≥ 20	38.26
7	AHU 7	311	8	2415	3912.51	≥ 20	36.91
8	AHU 8	303.14	2	586	959.85	≥ 20	36.71
9	AHU 9	242	8	1881.56	3660.01	≥ 20	30.86
10	AHU 10	213	24	4956	11826.88	≥ 20	25.14
11	AHU 11	179	6	1044.60	3115.10	≥ 20	20.13
12	AHU 12	285	4	1106.05	2437.06	≥ 20	27.23
13	AHU 13	140	4	545	1213.76	≥ 20	26.93
In Operation							
1	AHU 1	220	2	440	1089.62	22	24
2	AHU 2	210	8	1460	3649.50	22	24
3	AHU 3	195	2	1460	1195.04	22	25
4	AHU 4	250	4	920	1380.00	22	24
5	AHU 5	163.33	4	612.67	1196.00	22	26
6	AHU 6	424	2	2632	4026.94	22	29
7	AHU 7	282	8	1480	3912.49	22	22
8	AHU 8	290	2	580	960	22	36
9	AHU 9	250	8	2256	3660.00	22	27
10	AHU 10	164.00	24	2776.4	11826.78	22	24
11	AHU 11	222	6	1870.66	3115.13	22	26
12	AHU 12	297	4	1159.85	2437.89	22	31
13	AHU 13	172	4	896	1213.68	22	24

3. DIFFERENTIAL PRESSURE

Table 5: The obtained results for Differential Pressure

S. No.	AHU	Δ, Pascal 2019		Δ, Pascal 2020		Δ, Pascal 2021	
		At rest	Operation	At rest	Operation	At rest	Operation
1	AHU 1	10	10	10	12	10	8
2	AHU 2	8	10	10	10	8	8
3	AHU 3	12	12	10	12	10	12
4	AHU 4	8	10	10	12	10	6
5	AHU 5	10	10	12	12	12	12
6	AHU 6	8	8	10	10	10	10
7	AHU 7	10	10	10	12	10	10
8	AHU 8	10	10	10	10	8	8
9	AHU 9	10	8	8	8	10	8
10	AHU 10	8	8	10	10	12	12
11	AHU 11	10	10	10	10	10	10
12	AHU 12	10	10	10	12	10	10
13	AHU 13	8	10	10	9	10	10

4. TEMPERATURE AND HUMIDITY TEST

Table 6: The obtained result for Temperature and humidity test

S. No.	AHU	2019			2020			2021		
		Temperature		RH	Temperature		RH	Temperature		RH
		Dry	Wet		Dry	Wet		Dry	Wet	
At Rest										
1	AHU 1	21	15	49	22	16	50	22	15	50
2	AHU 2	23	16	45	22	16	50	21	15	49
3	AHU 3	24	17	46	23	16	45	22	15	50
4	AHU 4	22	15	43	23	16	45	22	16	54
5	AHU 5	23	16	45	22	15	45	22	16	54
6	AHU 6	24	18	53	22	16	50	22	15	50
7	AHU 7	25	17.5	44	23	16	45	22	16	54
8	AHU 8	23	16	45	23	16	45	23	16	45
9	AHU 9	24	19	60	22	16	54	22	15	50
10	AHU 10	24	17	46	24	17	46	24	17	46
11	AHU 11	23	16.5	48	24	17	47	22	15	50
12	AHU 12	25	19	54	24	17	47	22	15	50
13	AHU 13	24	17	46	22	16	50	22	16	50
In Operation										
1	AHU 1	23	16	45	21	15	49	22	16	53
2	AHU 2	22	16	50	22	16	50	24	17	50
3	AHU 3	23	16	45	22	16	50	23	16	49
4	AHU 4	23	16	45	22	15	45	22	16	54
5	AHU 5	23	16	45	22	15	45	22	16	54

6	AHU 6	22	16	50	24	18	53	22	15	50
7	AHU 7	23	16	45	23	16	45	22	16	54
8	AHU 8	23	16	45	23	16	45	23	16	45
9	AHU 9	22	16	54	22	16	54	22	16	54
10	AHU 10	24	17	46	24	17	46	24	17	46
11	AHU 11	24	17	47	22	16	54	23	17	56
12	AHU 12	23	17	56	23	17	56	22	16	54
13	AHU 13	22	16	50	22	16	50	22	16	50

5. RECOVERY TEST

Table 7: Recovery test was performed in random rooms of every AHU

S. No.	AHU	Recovery Time (minutes)	Result
1	AHU 1	17	Within Range
2	AHU 2	15	Within Range
3	AHU 3	18	Within Range
4	AHU 4	20	Within Range
5	AHU 5	18	Within Range
6	AHU 6	18	Within Range
7	AHU 7	20	Within Range
8	AHU 8	20	Within Range
9	AHU 9	15	Within Range
10	AHU 10	15	Within Range
11	AHU 11	20	Within Range
12	AHU 12	16	Within Range
13	AHU 13	17	Within Range

PARTICLE COUNT TEST

Table 8: Particle Count Test result performed in 3 consecutive years

S.No.	AHU	Particles							
		2019				2020			
		At rest		Operation		At rest		Operation	
1	AHU 1	985562	25564	19845621	200365	172159	3532	710025	7651
2	AHU 2	889562	21326	25413698	236584	215794	4789	109123	2239
3	AHU 3	1253262	28955	24587946	203658	627259	547	755963	406
4	AHU 4	2658491	23658	29845612	236584	468505	2394	2033206	11760
5	AHU 5	1569874	29658	24870136	286549	163754	3108	2472000	4049
6	AHU 6	1691354	12654	18002368	196540	736417	583	575367	2472
7	AHU 7	1832015	26584	28564123	254013	764651	3123	2521220	1077
8	AHU 8	1321478	21036	21547836	236581	824256	1342	2472064	5421
9	AHU 9	1000659	14659	21360894	198546	307195	657	1522796	883
10	AHU 10	1802365	18654	13698751	214785	1197785	4900	2383863	3258
11	AHU 11	1897432	17562	19685473	178954	103910	1208	356943	1263
12	AHU 12	1984562	14652	18695470	233341	188792	1077	963792	1554
13	AHU 13	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

S. No.	AHU	Particles			
		2021			
		At rest		Operation	
1	AHU 1	1850	310	26500	2120
2	AHU 2	1070	310	124000	14800
3	AHU 3	1130	210	125000	6360
4	AHU 4	1890	530	17000	1060
5	AHU 5	2770	250	156000	18000
6	AHU 6	1720	510	889000	13800
7	AHU 7	20420	430	481000	17000
8	AHU 8	12330	310	588000	20100
9	AHU 9	380	50	797000	3180
10	AHU 10	13690	430	150000	9530
11	AHU 11	800	190	75200	5300
12	AHU 12	2070	370	211000	8480
13	AHU 13	0.00	0.00	0.00	0.00

CONCLUSION

This paper described an approach to development and performance validation of HVAC system at rest and in operation for pharmaceutical industry using various parameters as described above used to validate the HVAC system. The main objective of this paper was to validate the HVAC system in pharmaceutical industry at two different conditions *i.e.* at rest and in operation. As mentioned, if the data collected while validating the in operation is in between the acceptance criteria, further industry does not need to stop the work so as to validate the HVAC system.

While we produce the pharmaceutical products, its utmost motto is the production of quality products within the minimal cost so that we can provide the medical facilities to the people in lower cost without compromising the quality. HVAC system plays an important role in the quality control by minimizing cross contamination which is a critical parameter for quality of products. While we stopped the production (*i.e.* at rest) for the validation of HVAC system, it would cost not only the validation charge also the time, labor charge, delay in production etc in between validation.

Data collection was performed from three consecutive years for two different conditions in order to demonstrate the performance validation of HVAC system in pharmaceutical industry. The industry in which the performance validation was performed is SIMCA LABORATORIES PVT. LTD., located at Bhaktapur, Nepal. There are all together 13 AHUs in the pharmaceutical industry and all of them were validated as per the guidelines.

The paper is evidence for the result that it does not make any difference to validate the HVAC system in operation condition. The paper illustrated data for all the parameters used to validate the HVAC system clearly. Under the guidelines of WHO GMP the validation was performed.

On the contrary, the paper demonstrated that the validation procedure can be performed without any doubt while in operation condition. Further this assures the high percentage of

validation of HVAC system despite the continuous work being performed, material and personnel flow. Thus, this can lead to a proper validation that is cost effective increasing profits without compromising the quality of products and safety of personnel.

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