VALIDATION AND QUALIFICATION OF HEATING ,VENTILATION, AIR CONDITIONING SYSTEM

Alka N Choudhary, Jyoti Rawat*
Associate professor M.pharm Ph.d, Student M .pharm
Department of Pharmaceutical Chemistry
School of Pharmaceutical Science, Shri Guru Ram Rai University patel nagar, Dehradun,uttarakhand

ABSTRACT
This paper present a validation of Heating Ventilation and Air Conditioning System(HVAC). The validation study provides the accuracy, sensitivity, specificity and reproducibility of test methods employed which must be documented. Validation studies are conducted in accordance with predefined protocol. Written reports, results and conclusion are prepared and evaluated, approved and maintained properly. Validation is the art of designing and practicing the designed steps alongside with documentation. HVAC system is needed for maintenance for suitable temperature, proper and continuous flow of air which prevents any contamination in process, hence providing optimum condition in premises. Qualification of HVAC system include DQ, IQ, OQ and PQ. Validation with proper procedure and acceptance criteria are mentioned according to ISO guidelines. Various parameters to be evaluated for validation of HVAC system include air flow pattern, air flow velocity, air change per hour, filter leak test, particle count, viable monitoring, filter integrity test, pressure differential, recovery test for temperature and humidity uniformity and fresh air determination.

Key Words: HVAC, validation, qualification, documentation, RH.

1. INTRODUCTION

Validation is the process of establishing documentary evidence that provides a high degree of assurance demonstrating that a specific procedure, process and activity carried out in testing and production will systematically produce a product meeting its pre-determined specifications and quality attributes[1]. In pharmaceutical industry it is very important that at every step of a procedure result in quality product and should show accurate results. This is done to maintain and assure higher degree of quality of food and drug product. It results in written operating and maintenance procedures for personnel to follow, which in turn helps ensure consistent system performance. it is highly required by food, drug and pharmaceutical agencies such as US FDA and their manufacturing practices guidelines Qualification of system and equipment is therefore part of validation[2]. The purpose of the validation is to demonstrate the capability of the manufacturing process and other utilities to continuous supply of air , water and to maintain proper environment with specified quality attributes. A properly designed HVAC system will provide high degree of assurance that every step, process and change has been properly evaluated before its implementation[3].

Heating, ventilation and air conditioning (HVAC)[4] performs heating or cooling for residential, commercial or industrial buildings. It ensure that an indoor air should have enough oxygen and be free from noxious gases. HVAC systems provide occupants thermal comfort, dehumidification, and good air quality. Improved HVAC control may reduce its energy consumption without additional costs[5,6]. The goal of the HVAC is to provide comfort to the occupants for varying heating and cooling loads with the time of the day and of the year. A quality pharmaceutical product depends on Heating, Ventilation and Air-conditioning (HVAC). Heating system increases the temperature in a space to compensate for heat losses between the internal space and outside[7]. Ventilation systems supply air to space and extract polluted air from it. Cooling is needed to bring the temperature down in spaces where heat gains have arisen from people, equipment or the sun and are causing discomfort[8]. A well designed HVAC system is the every operator demand so that he can feel comfort in operating it. HVAC system design also influence architectural layouts with regard to items such as airlock positions, doorways and lobbies. Hence, Temperature, relative humidity and ventilation must be appropriate. It vary widely in terms of size and the functions they perform[9].

HVAC system performs four basic functions

- Control air borne particles, dust, and microorganism by air filtration using high efficiency particulate air (HEPA) filters.
- Maintain room pressure which is achieved by providing more air into the cleaner space than is mechanically removed from that same space.

- Maintain space moisture controlled by cooling air to dew point temperature or by using desiccant dehumidifiers[10]. As it can affect the efficacy and stability of drugs and is sometimes important to effectively mould the tablets.
- Maintain space temperature as it can effect production directly or indirectly by fostering the growth of microbial contaminants on workers[11].

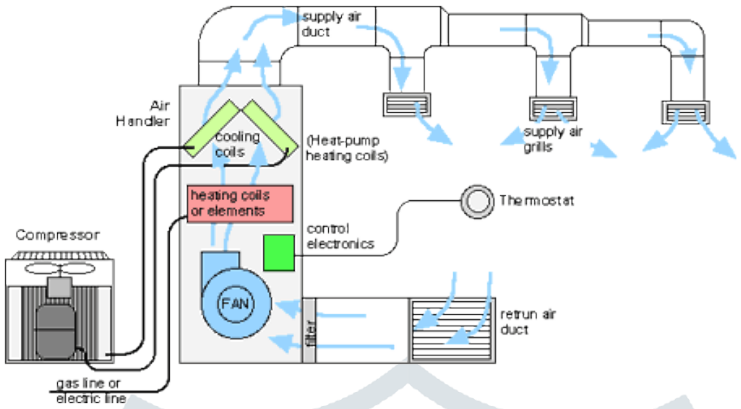

Fig 1: HVAC SYSTEM

2. QUALIFICATION OF HVAC SYSTEM

2.1 DESIGN QUALIFICATION – It is the process of completing and documenting design reviews to illustrate that all quality aspects have been fully considered at the design stage. Purpose is to ensure that all requirements for the final system have been clearly defined at the start[10,11]. It defines the functional and operational specification of the instrument and detailed made in the selection of supplier and ensures that instrument have all necessary functions and performance criteria that will enable them to be successfully implemented for the intended application and to meet user requirements[12] . Based on the URS supplier, design of the equipment is first step in the qualification of new HVAC systems. It documents the design of the system and include functional specification, technical specifications, detailed air flow schematics and detailed layout drawing of the system. DQ should compliance with GMPs and other regulatory requirements.

Ensures that design :

1. Meets the user requirements
2. Details facility airflow and pressure
3. Detail materials of construction
4. Detail safety requirements
5. Full details of the intended construction prior to implementation

2.2 INSTALLATION QUALIFICATION – The objective of installation qualification is to demonstrate that the HVAC system is in conformance to the URS and manufacture literature. The information must be documented that the equipment meets specification[13,14]. Installation qualification protocol no. shall be generated. The proper installation of the system components must be in accordance to the URS and manufacturers recommendation and the workmanship standards that are set in engineering specification[14].

To provide the elements that will affirm the following for all novel components of the HVAC system that have been installed.

- Components are included with their approved design and engineering specification, proper utility requirement are served such as electric power, chilled water, pure steam plant and compressed air[15,16].
- All critical measuring instruments and gauges are calibrated against traceable primary instrument[17]. Operational manual and spare parts list must be available to assure the proper and continuous operations systems.Documents must be provided for purchase orders for major components, factory acceptance test and copy of URS.

2.3 OPERATIONAL QUALIFICATION- The OQ is to verify that the specified components of HVAC system operates as specified and are in agreement with the acceptance criteria and critical systems[18]. The HVAC system, components described in the final design or specification needs to be qualified to demonstrate their adequate operation[19]. In general the operational qualification scope is to test the individual components of the system such as air-handling unit, ductwork, blowers checks ability to provide air of sufficient quality and quantity in clean room. Ability to maintain temperature, relative humidity, pressure set points and any critical parameter stated in DQ[20]. It also include the tests that have been developed from knowledge of processes, systems and equipments. The final

performance of the system in terms of environmental quality can be assessed only under dynamic conditions whether real or simulated and when the other components of the environmental control system are in place.

Qualification activities for the OQ must be performed are[20]:

- **Verification of critical instrument calibration**: Instrument which provide data that is recorded as part of production or maintenance records, are considered to be as critical instruments. They should be verified to be in current state of calibration. critical instrument included are pressure gauges, pressure sensor, thermometers, temperature sensor, RH display system, flow meters, and data loggers/recorders.
- **Operational procedure compliance test**: A final draft or higher standard operating procedure for the operation of the equipment comprising the HVAC system should be verified to be available. Personal operating the system or its individual components during OQ[20.21]. Execution should be verified and to have been trained to the referenced SOP. Operational procedure ensures that the outcome of the individual OQ tests are not disorted by operating the system.
- **HVAC start-up and shutdown operation test**: Sequence of the air handling unit are as controlled by the controlled system. The protocol should outline the sequence to be followed and the device that intervene in system[22].
- **Loss of utility test**: Responses to the loss of electrical power must be tested in all cases, which should include retention of critical data as well as equipment/ system response[22]. Equipment behavior upon loss or resumption of a given utility must be in accordance with available documentation. Support utilities for HVAC systems include electrical power, clean steam, compressed air, hot/ cold water and chilled water and glycol.

2.4 PERFORMANCE QUALIFICATION – The purpose is to verify and document that an HVAC systems provide acceptable control under "full operation" condition. After successful completion of IQ and OQ, PQ should follow[23]. Various test should be conducted under "in use", condition either or simulated as close as possible to the actual process. Any changes to the HVAC systems should be revalidated before proceeding to the PQ phase. The test frequency is much higher than for OQ also it should always be performed under conditions that are similar to routine sample analysis[24]. The final and real challenge for the environmental control system and HVAC system is represented by the process that must be executed within the areas it is serving. Upon determination of new approved conditions, if needed, changes to the system are to be executed and revalidated before proceeding to the performance qualification[25].

- It must be performed on the facility in three different stages that are
  i. As – built (No equipment, no personnel).
  ii. At – rest (equipment but no operations and no personnel)
  iii. Operational (with personnel, equipment operations)
- The success of the system to control the levels of viable and non viable particulate levels as well as its ability to regulate temperature and relative humidity conditions depends not only on the system performance but on outside factors such as personnel training, room sanitization and system maintenance
- Method of sanitization procedures, supporting utilities and personnel should be qualified before the initiation of the PQ as well as procedure for sampling, operation and maintenance should be place[26]. The success for PQ is greatly extended and it is much easier to isolate attributes causes in the event of PQ failure
- SOPs and training documentation for equipment operation, room sanitization, gowning and environment monitoring. Training in maintenance machines are completed and documented from all concern departments and persons. Standard operating system must be developed and approved before performance qualification tests are executed for
  i. Environmental monitoring
  ii. System operation
  iii. System maintenance

2.5 REQUALIFICATION : It is performed as the result of an event –based or time based assessment as defined in the validation master plan in both cases of time or event based circumstances the system owner quality assurance, engineering and validation departments will be responsible for assessing the level of the revalidation requirement[27]. Normally the requirement for IQ, OQ and PQ can be summarized below:

- IQ- Requalification
  Modification in the HVAC system
  Requalification of major component
  Relocation of any component of the HVAC system
- OQ & PQ Requalification
  Modification in the HVAC system
  Replacement of major component
  Annual requalification and any contamination problem

3. VALIDATION PARAMETERS

1. Non viable particle count
2. Pressure differentials
3. Air flow pattern
4. Air flow measurement
5. Filter integrity testing (HEPA leak test)
6. particle count
7. Temperature and relative humidity
8. Sound level test
9. Microbial count

3.1 NON VIABLE PARTICLE COUNTS

Non viable particle is a particle that acts as transportation for viable particles but does not contain living microorganism . The particles are sampled using a selected volume of air.Non-viable particles are monitored using particle counter[28]. It consist of a dark chamber, or sensor, containing a discrete laser which uses mirror and optics to view the particles and a pump to pull the required sample through the sensor. Principle behind detection and sizing of particle is simple, the vacuum pump sucks the particle through the sensor and laser beam then deflects the light from the laser onto mirrors which are focused onto a photo detector, reflected light is then converted into an electrical impulse by the photo detector the pulse are counted and seized by the electronics within the particles counter[29]. Bigger the particle the more light it reflects and therefore the .Bigger electrical pulse converted by the photo detector if the particle is bigger so it will reflects more light.

PROCEDURE: The particles are sampled using a selected volume of air and the concentration of particles per volume is displayed on the screen of particle counter. It display particle counts at different size ranges. Testing is done in Minimum 3 location for 1 min. frequency should be of 6 months

ACCEPTANCE CRITERIA

GRADES	AT REST		AT OPERATION	
	≥0.5µg	≥5.0µg	≥0.5µg	≥5.0µg
A	3520	20	3520	20
B	3520	29	352000	2900
C	352000	2900	3520000	29000
D	3520000	29000	NA	NA

3.2 PRESSURE DIFFERENTIALS

Pressure that is measured relative to the pressure in the atmosphere around it is called differential pressure. This increased pressure is created by HVAC system[30]. It is usually, measured in pascals This pressure difference is important as it helps to prevent cross-contamination. Dust particles that are produced during the manufacturing process may enter the air and could contaminate other products. Positive airlocks must be activated to maintain the positive pressure before entering such corridors to prevent loss of higher pressure ,as well as maintaining the pressure differences, these airlocks also help prevents contaminated air from reaching sterile areas[31]. In the adjacent areas of lower classification correct degree of overpressure are maintained to ensure that air moves from clean areas to less clean areas[30,31].

PROCEDURE: Electronic manometer is used which is portable and easy to use. Location of testing is between adjacent areas.

ACCEPTANCE CRITERIA

>10 Pa between classified area and adjacent area of lower concentration.

>15Pa between classified area and unclassified area

3.3 AIR FLOW PATTERN

There are mainly three types of Air flow pattern available for clean rooms design and these are Unidirectional (laminar), Non-unidirectional flow (turbulent) and Mixed flow. Air flow from AHU to each individual supply air location within the area must be adjusted to with specified tolerance of design flow[35]. This is necessary to achieve proper airflow patterns within the area. Air change in the room must be not less than 20air changes per hour[32]

Air flow velocity be determined for each HEPA filters, as the average of multiple measures taken at various locations across a plane parallel to and not more than 6inches from filters face[35,36].

It is important that air flows through critical area in a smooth pattern without any disturbance which would prevent particulate matter from being swept out of the area by the airflow or cause less clean air to be brought into cleaner area[38]. Air pattern testing shall be designed to verify airflows from high pressure areas towards lower pressure areas

PROCEDURE[40] : All air patterns shall be verified by visually observing air flow with smoke stick, vapour generators by burning titanium tetra chloride stick and by placing it in front of AHU flow of air and smoke distribution is observed which should be uniform. It should be done in both static and dynamic conditions.

ACCEPTANCE CRITERIA

ROOM CLASSIFICATION	AIR CHANGE PER HOUR
Class 100	NLT 250
Class 10,000	60±10%
Class 1,00,000	40±10%

Relative pressurization standards is 0.05 of water relative to adjacent les clean areas[42,44]

3.4 AIR FLOW MEASUREMENT

Air flow velocity (distance travelled per unit time) is most often expressed in feet per minute. It is the movement of air from one area to another[43]. Airflow exist because of pressure gradients. Air behaves in a fluid manner, meaning particles naturally flow from areas of higher pressure to the area of low pressure.

PROCEDURE: For this test, the area of HVAC is divided into four hypothetical grids and the air velocity is measured at each grid and then the average air velocity (V) is calculated. Record the velocity readings taken at the center of the grids, and at the junction of dividing lines (center of HEPA filters). Calculate the Average Velocity as[45]

$V = (V1+V2+V3+V4)/4$

V = Velocity observed at each point

Calculate the area of the filter by multiplying the width and length of the filter in feet.

$A = l \times w$

l = length of HEPA filter

w = width of HEPA filter

The total air volume per minute supplied in the clean room is calculated by the following formula:

$T = A \times V$

A = area of HEPA filters in square feet

V = average velocity of air in feet per minute

The total air in the room multiplying the length, width and height of the room in feet.

$Volume = L \times W \times H$

Now we can calculate the air changes per hour using the following formula:

Air changes per hour = $T \times 60 / VOLUME$

ACCEPTANCE CRITERIA

20 ir change per hour and average velocity should be 90 ft/min±20%[48]

3.5 FILTER INTEGRITY TESTING

Filters prevent dust from entering HVAC system while trapping airborne particles and allergens such as dust mites. Fiberglass air filters are normally used in both furnace and air conditioners unit. HEPA filters should be replaced after five or ten years[49]. Filters system are designed and installed so the system can be quantitatively leak tested.

Types of filters used are

1. Coarse filter
2. Fine filters
   HEPA, ULPA
3. Carbon Air Filters
4. UV Light air filters

PROCEDURE : Velometer is placed at the front of AHU unit then the velocity is checked in all corner of AHU. Velocity of air should be within the higher limits of HEPA filters[50]. If limits are found to exceed the upper limit, then silicon is used to decrease leakage. Filter leak test should be performed according to the test procedure as per ISO which will confirm the filter media and filter seal integrity[53] .

ACCEPTANCE CRIETRIA

The leakage rate of all the terminal HEPA filters should NMT 0.01%

3.6 PARTICLE COUNT MEASUREMENT

It is useful in detecting significant deviations in air cleanliness from qualified processing classification. Immediate results are obtained and useful tool for qualification and monitoring before/during and after operations[56,55].

PROCEDURE: Suitable particle counter is taken and operated to check the particles in the room at non working operations. Information is collected from particles counter and filled in the format[57,58]. Then again the particle

counter is taken and operated when the work is in progress and data is recorded. Operate the particle counter for all the room maintaining grade A, grade B, grade C and grade D.

ACCEPTANCE CRITERIA

ROOM CLASSIFICATION	PARTICLES/FT3	Cfu/ft3
100	100	<0.1
10000	10000	<0.5
100000	100000	<2.5

Less then the indicated number of particles of diameter <0.5 micron/ft[60]

3.7 TEMPERATURE AND RELATIVE HUMIDITY TEST

Percentage of water vapor in the air that changes when the air temperature changes is represented by relative humidity [62,61]. As air temperature increases, air can hold more water molecules and its relative humidity decreases and when temperature drop, relative humidity increases. Test is performed to check the ability of the HVAC system to provide temperature and relative humidity within the specified range. Temperature and relative humidity sensor display unit is used for testing[64,63].

PROCEDURE: Temperature and relative humidity is observed through respective display unit wherever installed and hygrometer is used to check the readings of other rooms for 2 hours (5 readings per day) consecutively for 3 days. Observation is done and recorded in both the condition, static and dynamic. Observed results should meet the requirements as specified in system specification[66].

ACCEPTANCE CRITERIA

Temperature : should be within 23^0 C ± 2 and NMT 27^0 C

Humidity : should be within 45 ± 5% and NMT 55%

3.8 SOUND LEVEL TEST

Sound level test is done verify that the sound level is in limit in the clean room area. Test equipment used to measure sound is sound level meter[65]. It should be duly calibrated with the traceability to national/ international standards.

PROCEDURE[68,69] : Readings at 5 locations in the room are taken and average of the sound in the unit of decibels is calculated

ACCEPTENCE CRITERIA:

The clean room or clean zone shall meet the acceptance criteria[69] for sound level as mentioned in the table below:

S.no	Cleanliness class	Sound level limit (db)
1	Class 100/ ISO 5	NMT 60
2	Class 10,000/ISO 7	NMT 80
3	Class1,00,000/ ISO 8	NMT 80

3.9 MICROBIAL COUNT

Solid growth media (settle & contact plate) Soyabean Casein Digest Agar Medium can be used for both Bacteria and Fungi tested. Recommended size of solid media is 90 mm in diameter(for settle plate) and 55mm for contact plates. Air borne microbial contamination level is checked in critical area[70,71].

PROCEDURE : Air borne microbial count by settling plate exposure method:

Pre incubated SCDA Media plates shall be exposed in locations mentioned for 4 hours and incubated for 48 hours at 30 C to 35 C followed by next 72 hours at 20 C to 25 C[71]. Record the results in respective format. PDA plates shall be exposed weekly to monitor the fungal counts and SCDA plates shall be incubated once in fifteen days to monitor the anaerobic microorganisms[72].

ACCEPTANCE CRITERIA

TESTS	ALERT LIMIT	ACTION LIMIT
1.Settle plate exposure(CFU/90mmplate/4 Hrs)		
• Under dispensing and sampling booth	NMT 1	NMT 1
• Other locations	NMT 75	NMT 100
2. Active air sampling(CFU/Cubic meter of air)		

• Under dispensing and sampling booth • Other locations	NMT 3 NMT 100	NMT 5 NMT 200
3. Surface monitoring (CFU/55mmplate)		
• Surface of dispensing and sampling booth • Other locations	NMT 10 NMT 25	NMT 25 NMT 50

Conclusion:

This article present the validation and qualification of HVAC system which is very important for pharmaceutical industry for maintaining the quality of product. HVAC system are of great importance as it provide specific set of environment condition required to make quality product so therefore it must be validated. The Article discuss the different validation parameters and qualification of HVAC system with proper procedure with acceptance criteria according to guidelines. Proper HVAC system renders reduction in the cost linked with process monitoring, sampling and testing and it is the most important and recognized parameters of cGMP.

REFERENCES

[1] Choudhary N and Sekhon BS. 2011. An overview of advances in the standardization of herbal drugs. Journal of Pharmaceutical Education and Research. 1;2(2):55.

[2] WHO. Annex 4. 2006. Supplementary Guidelines on Good Manufacturing Practices: Validation, World Health Organization. Technical Report Series, No.937, 116–121. Sugarman Samuel C. HVAC Fundamentals. The Fairmont press, Inc; 2005, 1–3

[3] World Health Organization. Quality assurance of pharmaceuticals 2016: WHO guidelines, good practices, related regulatory guidance and GXPs training materials. Quality assurance of pharmaceuticals 2016: WHO guidelines, good practices, related regulatory guidance and GXPs training materials.. 2017.

[4] Kohli R. 2017 . Gas-Phase Cleaning for Removal of Surface Contaminants. InDevelopments in Surface Contamination and Cleaning: Methods for Surface Cleaning (pp. 27-82). William Andrew Publishing.

[5] Guideline IH. 2005. Quality risk management Q9. In International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use.

[6] Breuer D and Bower J. editors. 1999. Monitoring ambient air quality for health impact assessment. WHO Regional Office Europe.

[7] Suriyaprakash TNK. 2010. Cleaning validation and its importance in pharmaceutical industry, PharmaTimes, 42, 21-24

[8] WHO GMP for sterile pharmaceutical products, WHO Technical Report Series, , Annex 6.

[9] WHO good manufacturing practices for biological products,2016 Annex 3, WHO 807 Technical Report

[10] Pharmaceutical Inspection Convention, 2007. "Recommendations on Validation Master Plan, Installation and Operational Qualification, Non-Sterile Process Validation and Cleaning Validation".

[11] International conference on Harmonization (ICH). 2005. Harmonised tripartite guideline Q2 (R1),Validation of analytical procedures: Text and methodology

[12] Supplementary guidelines on good manufacturing practices. 2006. Validation WHO Technical Report Series, No. 937, Annex 4

[13] Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for nonsterile pharmaceutical dosage forms (working document QAS/15.639/Rev.1) (Appendix 1)

[14] Carleton FJ and Agalloco JP.Validation of pharmaceutical processes, sterile products.,second edition., 1 to 16.

[15] Britain H.G. 2002. pharmaceutical technology; 68 to 70.

[16] Nash RA and Berry IR. Pharmaceutical Process Validation.,second edition, Marcel Dekker inc.,167-188,200-202,205.

[17] European Commission Enterprise Directorate General Single market,regulatory environment, industries under vertical legislation Pharmaceuticals and Cosmetics Brussels, July 2001. EU Guide to Good Manufacturing Practice, Qualification and validation.

[18] FDA guidelines on General Principles of Process Validation. 1987.

[19] Chapman KG.Amer G. Brower G. Green C. Hall WE and Harpaz D. 2000. Journal of Validation Technology.6:505-506.
[20] Health Products and Food Branch Inspectorate, Guidance Document Validation, Guidelines for Pharmaceutical Dosage Forms.
[21] The European agency for evaluation of medical products. 2001. London Note for Guidance on Process Validation.
[22] British Pharmacopoeia 2002, Department of Health, Scottish Home and Health department, Volume I,736.
[23] Howard T. Fuller Six Sigma for Validation. 2000. Journal of Validation Technology. 6(4):749-765,751
[24] ASHRAE Handbook. 1996. HVAC Systems and Equipment. Atlanta, GA: American Society of Heating, Refrigerating, and Air Conditioning Engineers; pp. 1-10.
[25] American Society of Heating, Refrigerating & Air-Conditioning Engineers. Heating, Ventilating, and Air-Conditioning: Systems and Equipment: 2000 ASHRAE Handbook: Inch-Pound. Amer Society of Heating; 2000.
[26] Brumbaugh JE. Audel HVAC Fundamentals.2004. Volume 1: Heating Systems, Furnaces, and Boilers. Vol. 17. Canada: John Wiley & Sons, Wiley Publishing, Inc.
[27] R. M. Barbosa and N. Mendes. 2003 "Dynamic simulation of fancoil systems," in Proceedings of the 17th International Congress of Mechanical Engineering (COBEM '03), Sao Paulo, Brazil.
[28] D. Fallman. 2003 "Design-oriented human-computer interaction," in Proceedings of the SIGCHI Conference on Human Factors in Computing Systems ACM, pp. 225–232, New York, NY, USA.
[29] G. Mustafaraj, J. Chen, and G. Lowry.2010. "Development of room temperature and relative humidity linear parametric models for an open office using BMS data," Energy and Buildings, vol. 42, no. 3, pp. 348–356.
[30] G. Knabe and H. Le, 2001. "Building simulation by application of a HVAC system considering the thermal and moisture behaviors of the perimeter walls," in Proceedings of the International Conference on Building Performance Simulation (IBPSA '01), vol.1, pp. 965–972.
[31] J. A. Orosa, 2011"A new modelling methodology to control HVAC systems," Expert Systems with Applications, vol. 38, no. 4, pp.4505–4513.
[32] C. Ghiaus and I. Hazyuk, 2010 "Calculation of optimal thermal load of intermittently heated buildings," Energy and Buildings, vol.42, no. 8, pp. 1248–1258.
[33] J. Wang, Y. Jing, and C. Zhang, 2008 "Robust cascade control system design for central air-conditioning system," in Proceedings of the World Congress on Intelligent Control and Automation (WCICA '08), pp. 1506–1511.
[34] R. Z. Homod, K. S. Mohamed Sahari, H. A. F. Almurib, and F. H.Nagi .2012. "RLF and TS fuzzy model identification of indoor thermal comfort based on PMV/PPD," Building and Environment, vol.49, no. 1, pp. 141–153.
[35] J. Liang and R. Du, 2005 "Thermal comfort control based on neural network for HVAC application," in Proceedings of the IEEE Conference on Control Applications, pp. 819–824.
[36] Quality Assurance of Pharmaceuticals, 2007 A Compendium of Guidelines and Related Materials. 2nd ed., Vol. 2.
[37] Guideline on General Principles of Process Validation.1987. FDA, CDRH/CDER.
[38] Potdar MA. 2012 Pharmaceutical Quality Assurance, Nirali Prakashan, Pune, Edition II.
[39]FDA/Global Harmonization Task Force (GHTF; medical devices). 2004. Quality Management Systems-Process Validation. 2nd ed. Guidance.
[40] Guidance for Industry, Process Validation. 2011. General Principles and Practices, U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), Current Good Manufacturing Practices (CGMP), Revision 1.
[41] Guidelines for the Validation of Chemical Methods for the FDA Foods Program .2012. Department of Health and Human Services, Public Health Service Food And Drug Administration.
[42] Scott B, Hargroves J and Bauers J. 2009 Validation of HVAC systems in pharmaceutical and biotechnology facilities-Part 1. 10. Goldschmidt N. First steps for sustainable bio/pharma HVAC.
[43] FDA. 2006. Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Veterinary Medicine (CVM), Quality Systems Approach to Pharmaceutical Current Good Manufacturing Practice Regulations, guidance for industry.
[44] Shukla A, Katole A, Jain N, Karthikeyan C, Mehta F and Trivedi P. Risk assessment approach: Qualification of a HVAC System in aseptic processing area using building management system.
[45] Guidance on Qualification of existing facilities, systems, equipment and utilities .2004. Active Pharmaceutical Ingredients Committee. p. 1-16.
[46] Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Fortieth report. Geneva, World Health Organization, 2006, Annexure 4 (WHO Technical Report Series, No. 937).

[47] Supplementary guidelines on good manufacturing practices for heating, ventilation and air-conditioning systems for non-sterile pharmaceutical dosage forms. WHO Expert Committee on Specifications for Pharmaceutical Preparations. 40th report. Geneva: World Health Organization; 2011. Annexure 5 (WHO Technical Report Series, No. 961).
[48] Guidance for Industry . 2001 Q7A Good Manufacturing, Practice Guidance for Active Pharmaceutical Ingredients, U.S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER).
[49] Deryck S. 2003 Supplementary guidelines on Good manufacturing practices for Heating, Ventilation and Air Condition (HVAC) Systems. Working document QAS/02.048/Rev.1. Geneva, World Health Organization, (unpublished document)
[50] Good manufacturing practices for pharmaceutical products. 2003. main principles. In : WHO Expert Committee on Specification for Pharmaceutical Preparations. Thirty-seventh report. Geneva, World Health Organization, Annex 4 (WHO Technical Report Series, No. 908)
[51] Guide to Good Manufacturing Practice for Medicinal Products. 2004. PE 009-2, Pharmaceutical Inspection Co-operation Scheme (PIC/S).
[52] Pharmaceutical Engineering Guides for New Renovated Facilities Volume 2 .1998. Oral Solid Dosage Forms, First Edition. International Society for Pharmaceutical Engineering.
[53] Chan CC, Lam H, Lee YC and Zhang XM (eds.). 2004. Analytical Method Validation and Instrument Performance Verification, New Jersey; John Wiley and Sons: pp. 11-
[54] PIC/S document PI 006-3: .2013. Preparation of Validation Master Plan Installation and Operational Qualification Non- Sterile Process Validation Cleaning Validation. A Regulatory Guideline ; 9-11.
[55] Lakshmana P .2010.Cleaning validation and its importance in pharmaceutical Industry. Pharma Times ; 42(7): 21—25.
[56] Amit Kailas chand M. 2011. Process validation of cephalosporin antibiotics cefuroxime axetil 500 mg tablets. Karnataka: Rajiv Gandhi University of Health Sciences.
[57] Kumar V S, Sanjeev T .2012. Overview of cleaning validation in pharmaceutical manufacturing unit. International Journal of Advanced Research in Pharmaceutical & Biosciences; 1(2): 154-164.
[58] Patel Hiren Popatbhai et al .2012. Process validation of Benzepril HCL 5 mg tablet. International Research Journal of Pharmaceutical and applied sciences ; 2(4): 1-16.
[59] Kathiresan K.2010. Cleaning validation of acetaminophen tablets. Rasayan Journal ; 3(3): 503-506.
[60] Robert A Nash and Alfred H W: .2003. A Text Book of Pharmaceutical Process Validation. Marcel Dekker, 3rd Edition 500-541.
[61] Agallaco J. Frederick Carelton J .2008. A Text Book of Validation of Pharmaceutical Process. Spring Publisher, 3 rd Edition : 525-565.
[62] Bodavula Samba Siva Rao. 2012. Cleaning validation of albendazole tablet 400 mg. Pharma Innovations; 1(4): 76-94.
[63] Kumar S .2012. A review on concept of cleaning validation in pharmaceutical Industry. International Research Journal of Pharmaceutical Sciences ; 3(7): 17-19.
[64] Active Pharmaceutical Ingredient Committee (APIC).1999. group of EEFIC: Guide to cleaning validation in API plants. APIC Publications; 2-23
[65] Sanjay Dey and Anindya G . 2010. Overview of cleaning validation in pharmaceutical industry. Indian Journal of Pharmaceutical Quality Assurance ; 2(2): 26-30.
[66] Lambert J. 2004.Validation Guidelines for Pharmaceutical Dosage Forms. Health Canada / Health Products and Food Branch Inspectorate ; 7-15.
[67] Tangri Pranshu, Rawat Prakash Singh and Jakhmola Vikash. 2012. Validation: A Critical Parameter for Quality Control of Pharmaceuticals. Journal of Drug Delivery & Therapeutics 2(3): 34-40
[68] Agalloco J. 1995. Validation: an unconventional review and reinvention, PDA J. Pharm Sci Tech ; 49, 175–179.
[69] Ramamurthy, M and Sarvanakumar.K. 1997. pharmaceutical validation. The Eastern Pharmacist. XL, 476, 45-47.
[70] Guidance for Industry, Sterile Drug Products Produced by Aseptic Processing. 2004. Current Good Manufacturing Practice, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Office of Regulatory Affairs (ORA), Pharmaceutical CGMPs.