

Revolutionizing the Major Threat Challenges in Pharmaceutical Industries by Monitoring Heating, Ventilation and Air Conditioning Systems

Natarajan Tamilselvan, Appavoo Umamaheswari, Sakthivel Lakshmana Prabu

Abstract: *The environmental as well as personal individuals are mainly influenced by the air ventilation. In pharmaceutical industry the efficacy of substances including raw materials, in-process ingredients, finished products and machineries in the pharmaceutical manufacturing industry is mainly influenced by the air ventilation quality in interior area of the industry. Heating, ventilation and air-conditioning system plays a vital role in ensuring the quality pharmaceutical drug substances as well as drug products. It also protects the pharmaceutical products from contamination and cross contamination from various contaminants like dust or dirt particles and environmental other microorganisms. HVAC system design impacts the architectural design layout of the building as these sequentially have an influence on the room pressure, pressure cascades, pressure differentials, contamination and cross-contamination control. So, the design of the system must be considered carefully at the primary design period of the pharmaceutical industrial plant.*

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Цитирање: Тамилселван Н, Умамахешвари А, Лакшмана Прабу С (2023) Значај унапређења система за гријање, вентилацију и климатизацију у грађевинским објектима намијењеним за фармацеутску индустрију. У: Илић П, Говедар З, Пржуљ Н (уредници) Животна средина. Академија наука и умјетности Републике Српске, Бања Лука, Монографија LV:203-241

It also controls a variety of operating functions which are involved in regulating the acceptance criteria, quality assurance, validation and qualification of the building facility, operational documents and the documentation for maintenance. These protocols are mainly followed and performed for new equipment's, utilities, premises and systems, at periodic intermissions, as soon as major variations have been completed.

This chapter provides insight into the superlative necessities of HVAC system on the environmental protection in pharmaceutical industries and also about the role of it in manufacturing of drug substances and products in the production unit of the industrial plant. In addition, it summarizes existing information about the validation, qualification, maintenance, risk assessment and also highlights about the automation of HVAC system in the pharmaceutical industries.

Keywords: HVAC system, environmental protection, pharmaceutical industry, validation, qualification, FMEA, automation

7.1. Background

Manufacturing of pharmaceutical drug substances on the organic atmosphere is well identified to produce adverse effects and lethal influence on both the animals as well as human beings which endures through no distinct perception and remains basically unregulated. For throughout recent years, numerous worldwide associations and industrial organisations have started to understand the hindering effect of pharmaceutical drug substances due to atmosphere on a worldwide scale. They also pass in the milieu at numerous stages of their life-cycle, yet dominantly during the production phase.

On the way to safeguard the atmosphere from pollution and to help in the production of quality medicinal substances the World Health Organisation (WHO) has stepped up to take initiative and also framed the rules and regulations on Good Manufacturing Practices (GMP) which includes Heating, Ventilation and Air-Conditioning (HVAC) systems. As GMP plays a vital role in the API manufacturing and production units from preliminary processing steps to final process holding a certain number of problems along with the determination of important factors like pressures, temperature, humidity, filtration, airflow designs, typical heat and cooling pacts (Lakshmana Prabu et al. 2015). Also regulates the grade of operating numerous constraints for controlling the quality assurance, acceptance criteria, validation of the facility, and documentation for operation and maintenance. (WHO TRS 1010, Annex 8 2018). The WHO as a factor of GMP is used by pharmaceutical regulators and the pharmaceutical

industry in over one hundred countries worldwide, suggestively in the modernizing world according to the standards of pharmaceutical industries.

7.2. Introduction

Airborne viable microbes are the main critical contamination factor in the environmental monitoring programs. Concentration of the airborne viable microbes in environment indicates the functioning ability of the air handling units. Hence, adopt different strategic process during the manufacturing to control in the microbes number, survival and its proliferation. Contamination by these microbes can be controlled by defining the temperature, humidity, clean zone/clean room and its segregation.

Monitoring the environment provides a documentation evidence to prevent the microbial contamination by monitoring the efficiency of different systems. The effectiveness of various solutions to prevent microbial contamination can be evaluated using the evidence and documentation provided by environmental monitoring. The process of existence, movement, and survival of microorganisms in clean rooms and other regulated settings must be under control (Jimenez 2004; Gail and Stanischewski 2004).

The HVAC system plays a significant part in guaranteeing the production of quality pharmaceutical drug substances. The GMP necessities intended for the prevention of adulteration as well as cross-contamination are a crucial strategic deliberation of an HVAC system. A good designed HVAC system consistently provides protection for both the environment as well as the operators with comfortable working circumstances. The pharmaceutical rules and specifications often contain very precise but also generally formulated requirements of air conditioning technology, such as “temperature, humidity and ventilation of premises should be adequate”. A complete science as well as risk-based tactic must be accompanied all over the lifecycle of an HVAC arrangement, with its design, installation, qualification, and the maintenance. Along with the GMP, risk assessment is also a crucial parameter for the HVAC systems (WHO TRS 1019, Annex 3 2019). Numerous worldwide associations and industrial organizations started to understand the hindering effect of pharmaceutical drug substances due to this microbial environment on a worldwide scale. They also pass in the milieu at numerous stages of their life cycle, yet dominantly during the production phase.

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initiative and also framed the rules and regulations on GMP which includes Heating, Ventilation and Air-Conditioning (HVAC) systems. It holds a certain number of problems along with the determination of important factors like pressures, temperature, humidity, filtration, airflow designs, typical heat and cooling pacts. Also regulates the grade of operating numerous constraints for controlling the quality assurance, acceptance criteria, validation of the facility, and documentation for operation and maintenance. The WHO as a factor of GMP is used by pharmaceutical regulators and the pharmaceutical industry in over one hundred countries worldwide, suggestively in the modernizing world according to the standards of pharmaceutical industries.

Different GMP guidelines are framed worldwide, which are:

Pharmaceutical Inspection Convention (PIC) – Guideline is followed in the following countries like Austria, Australia, United Kingdom, Canada, France, Italy, Spain, Denmark, Finland, Ireland, Netherland, Poland, Switzerland, Belgium, Hungary, Latviam, Malaysia, Singapore, Norway, Romania, Portugal, Slovak Republic, Sweden and Liechtenstein.

Association of South-East Asia Nations (ASEAN) – Guideline is followed in the following countries like Brunei Darussalam, Malaysia, Singapore, Cambodia, Indonesia, Thailand, Lao PDR, Philippines, Myanmar and Vietnam.

European Economic Community (EEC) – Guideline is followed in the following countries like Austria, United Kingdom, Germany, France, Italy, Spain, Finland, Ireland, Netherland, Belgium, Greece, Denmark, Luxembourg, Portugal and Sweden (Karmacharya 2014).

7.3. Microbial Contamination

Environment in the earth is an incredible nutrient for microorganisms. Indulgently it has been named as “blue planet” or “water planet”. In another way in simple we can say “planet of the microbes”, because it can be found everywhere. Introduction of microorganism in the pharmaceutical premises are

1. Higher microbial load from the natural products utilized in the formulation.
2. Quality of air handling units.
3. Personnel in the premises because microorganisms are part of the human body as well as skin.
4. Quality of water utilized in the premises.
5. Building areas and equipment (Hyde 1998; Jimenez 2004).

If higher number of microorganisms are present in the manufacturing location can spoils the drug substances, drug products, integrity, and its stability. Manufacturing of pharmaceutical drug substances in this atmosphere condition is well identified to produce adverse effects and lethal influence on both the animals as well as human beings which endures through no distinct perception and remains basically unregulated. Major microbial contamination was observed for non-sterile products because of raw material or water may contain of microorganism (Baird 1985).

Among the different process parameters quality of air has been considered to have a significant role in ensuring the quality of products from these microorganisms. Intervention of human beings has been considered as major reason for contamination of products. In addition, gram negative bacteria could be a sign of uncontrolled processes in raw materials and water systems (Jimenez 2004).

7.3.1. Microbial specifications

Presence of 100 CFU and 10⁶ CFU can cause disease to the children's and adults respectively. Regulations were made to test for different microorganisms based on the form of different formulations are being tabulated in Table 7.1 (Rusin et al. 1997; Jimenez 2004; Ratajczak et al. 2015).

Table 7.1. Test for different microorganisms and limit tests

Таб. 7.1. Тест на различите микроорганизме и гранични тестови

| Products/Formulations | Organism |
|--|---|
| From animal, plant and mineral | <i>Salmonella</i> sp. |
| Topical products | <i>S. aureus</i> and <i>P. aeruginosa</i> |
| Vaginal, rectal and urethral | yeast and mould |
| Products/Formulations | Limits |
| Respiratory tract drugs, 100 CFU/g or mL | |
| transdermal patches and topical | |
| Oral and rectal route | Total viable count of NMT 1000 CFU/g or ml and not more than 100 CFU yeast and mold/g or ml |
| Raw materials from Plant origin, animal or mineral | Total count must be no more than 10,000 CFU/g or ml Not more than 100 enterobacteria; absence of <i>Salmonella</i> spp., <i>S. aureus</i> and <i>E. coli</i> . |
| Herbs | Total viable counts should range from 10 ⁵ to 10 ⁷ CFU/g or ml for bacteria and from 10 ⁴ to 10 ⁵ CFU/g or ml for mold and yeast. |

7.3.2. Microbial testing methods

All over the world, microorganisms such as *Acinetobacter* spp., *Enterobacter* spp., *Pseudomonas* spp., *Bacillus cepacia* and *Klebsiella* spp. are normally found in pharmaceutical products. Other gram-positive bacteria such as *Bacillus* spp., *Clostridium* spp., *E. coli*, *Streptococcus* spp., *Staphylococcus* spp., and *P. aeruginosa* are found in topical products and oral solutions. Irrespective of geographical location some gram-negative bacteria are found in non-sterile products (Jimenez 2004). Additionally, the aseptically manufactured drug substances and products are specified with the microbiological quality. As those new drug substances or products should meet the specification as per the acceptance criteria (Lakshmana Prabu et al. 2014a).

Both microscopic and macroscopic analysis results are based upon colony morphology, cell size, enzymatic profiles and carbon utilization profiles (Jimenez 2001). Hence, further studies are needed to be performed to identify the microorganism in the environment. Lately, biochemical indicators are used to identify the microbial population and its community. Fluorescent antibody technique has been used to identify the specific types of microorganism (Tabor and Neihof 1982). Extraction of DNA and RNA from the clinical sample and environmental helps to confirm the different microbial community (Torsvik et al. 1990; Kroes et al. 1997; Torsvik et al. 2002).

However, the testing methods accuracy, sensitivity and reproducibility are determined by inoculating the specific quantity of material from three batches in viable cultures. The observed results will provide the information about the validation of the method.

7.4. HVAC Systems – An Overview

To meet the regulatory requirement, monitoring and ensuring the drug substances/products safety, quality and purity during the manufacturing is the prime requirement of every pharmaceutical industry.

Products safety, quality and purity are ensured through a well-defined and validated HVAC system. It provides comfortable zone for the operators as well as prevents sterile products from bacterial contamination. It also prevents the spreading and adulteration of various microbial organisms which are used in the production of drugs. The validation and qualification of the HVAC system is very critical also to have a significant role important because the intent of qualification is to afford a written proposal for creating the standard document evidence of both the facility as well as reliability of the system.

As it is beneficial in reduce the capital costs, quality control, lifetime maintenance and monitoring costs. The production of drug substances and products must be carried out in the sterile areas and the entry of it should be over airlocks for personnel as well as for materials and equipment's. A standard cleanliness procedure should be maintained and followed for making a particular area sterile and the air need to be supplied should pass through various filters with suitable proficiency (Singh et al. 2016).

Significance of HVA

HVAC systems are very important to the architectural design of the pharmaceutical industries. The four major reasons are,

1. HVAC system avoids the airborne contamination by provides adequate temperature, weather condition and comfort to the operations.
2. Helps in the movement of air in the clean room. Also provide fresh oxygen and sweep off the expelled carbon dioxide in the manufacturing premises.

Provides sufficient ventilation and prevent the growth of bacteria and fungi in the manufacturing location (Haider 2006; Akers and Anderson 2006).

Operational Principle

Essential functions of HVAC system for control the airborne particles are:

1. Control dust and micro-organisms by means of air filtration system using High Efficiency Particulate Air (HEPA) filters.
2. To maintain the room pressure (ΔP)
3. To maintain Relative Humidity (RH) (space moisture) (Bhatia 2014).

7.5. HVAC System Description

HVAC system is a completely integrated for air filtration and air conditioning. It consists of various components like Air Handling Unit, filters, fans, gauges, ductwork, heating, and cooling system, as well as the control system. The features of these components are:

Air Handling Unit (AHU)

AHU is built in the parallel modular plane, and it is placed inside the system roof area. The air handler is generally built around a mounting system with metal infill panels. The outer metal exertion is typically galvanized for the long-term protection. It is a huge metal container comprising a heating or cooling

elements, blower, sound attenuators, filter racks or chambers, and dampers. Also, AHU connects to the ductwork ventilation system, so that it distributes the conditioned air all over the industrial building facilities and again returns it to the AHU (Bhatia 2014; Handbook ASHRAE 2016; Brambley 2005).

1. Air Filters – Air filters provide clean dust-free air to the production areas of pharmaceutical companies. Filtration process is always positioned first in the AHU to keep the entire downstream components clean.

2. Heating and cooling coils – Heating, cooling, or both coils are required to alter the temperature of air supply and humidity level. The coils used in this system are directly inclined to the intermediate which provides the cooling or heating effect. These kinds of coil are usually produced from copper or aluminium paddles to support heat transfer.

3. Humidifier – Humidifiers are used to maintain humidity level in the circulation air. Humidification process is regularly essential in the colder temperatures where nonstop heating will produce dry air, and results in poor air quality and improved stationary electricity.

4. Air mixing plenum – To maintain the indoor air quality, air mixing plenums are used to permit the entry of outdoor air into the fresh air filtered through opening controlled by manual damper. A large mixing chamber is being used for mixing with the manual dampers directing the proportion between the return, outside, and the exhaust air.

5. Blower fans – Large cage blower fans are used; it is being driven by the electric motor (AC) for the air suction. A Variable Frequency Drive allows the blower fans with a varied series of rate of air flow and the flow rate is controlled either by the inlet vanes or outlet dampers on the blower fans. Speed control is being regulated by the high proficiency electronically commutated (EC) motors.

6. Vibration isolators – The blower fans in the AHU produces more vibration while operating. A duct system associated with huge area besides it which transmits this vibratory noise to the workers of the core building facility and also to the manufacturing zones of pharmaceutical industry. The vibration isolators or the damper block helps in avoiding or reducing the noise by typically implanting it into the duct work instantly before as well as after the air handler and the blower fan compartment is operated.

7. Building management system (BMS) – It is used in the HVAC control simulation. It is a computer-based regulator system mounted in the building facilities so as to control and monitor the equipment's such as, air handling unit and ventilation unit of the HVAC systems.

7.6. Types of HVAC Filters

For keeping the industrial environment healthy and clean, various types of HVAC filters are being widely used. Industrial experts recommend that for every month's the filter being used should be cleaned or changed to ensure the deposition of dust or dirt in the porous filter membrane. There are four types of HVAC filters are used (Edelman 2008), they are:

1. HEPA Filter

HEPA filter provides the maximum level of protection in contrast to a diversity of dusty or dirty airborne substances. These filters have the proficiency to trap various kinds of dust particles which are as small as 0.3 microns. It has the highest trapping efficiency up to 99.97% of airborne particles.

Moreover, HEPA filters have a Minimum Efficiency Reporting Value (MERV) score ranging between 17 and 20. Even though it has more efficiency, this type of filter, generally doesn't suitable for the residential HVAC systems due to the airflow and sizing limitations.

2. Reusable Air Filters

Reusable air filters can be easily cleaned up and used again for various systems. These filters are washable filters, generally more costly. It is more expensive than the disposable type filters has very low MERV grade around 1 to 4. This makes the reusable air filters susceptible to the development of mold or fungus.

3. Flat-Panelled Fiberglass Filters

Flat-Panelled Fiberglass Filters are effortlessly disposable filters. It is being covered by means of fiberglass along with a metal-reinforcing grate. This filter has very low MERV score around 4, so it cannot be used for air purification.

4. Pleated Media Filter

It is also used as a disposable filter having MERV score ranging between 5 and 13. Though, it has a highly effective version which has a MERV rating around 14 to 16. The design of this kind of filter is proposed to rise the surface area, which progresses its purification effectiveness.

7.7. HVAC System Design

HVAC system regulates various parameters in the environment includes the temperature, pressure, relative humidity, air flow and quality. The major types of HVAC systems are (Yeotikar 2020):

- 1. Once-Through system** – This type of system is used in intermediate bulk Active Pharmaceutical Ingredient (API) plants, Oral Solid Dosage (OSD) and biotech API plants. In this system, air used in the maintenance of clean room and discarded afterwards.
- 2. Recirculated system** – This type of system is used in aseptic environment and finished bulk API plants. In this system, certain percentage of air is discarded and the remaining percentage is re-processed and re-used.

A comparative merits and demerits between these two systems are summarized in the Tab. 7.2.

Table 7.2. Merits and demerits of HVAC design types
Table 7.2. Merits and demerits of HVAC design types

| Topic | Once through | Recirculated |
|---------------|--|--|
| Advantages | - Easy duct routing due to one-way out and fresh air | - Low filter maintenance - Have good control over temperature and RH - Low cost |
| Disadvantages | - Less filter life due to regular introduction of fresh air - Additional cost for dust collection or removal system - High cooling or heating cost | - Complicated - Return line ducting and additional filtration required for preventing cross contamination |

7.7.1. Constant Volume Systems

The most frequently used and reliable system for the manufacturing of drug substances and products in the pharmaceutical industries are Constant Volume System with terminal reheat (CVRH). In this system, constant pressure gradient is maintained between the surrounding areas. The terminal reheat system is set at a fixed temperature so that when the air leaves the cooling coil, it responds to a space thermostat and turns on heat. Due to this, large amount of energy is wasted for cooling and reheating of the air:

Advantages

- Humidity is constantly controlled easily (as dehumidification takes place continuously at the cooling coil).

- Temperature control can be easily regulated by adding a thermostat and reheat coil.
- Airflow is constant in CVRH system.
- Very simple and simple maintenance.

7.7.2. Variable Air Volume System

A variable air volume (VAV) system is most commonly used only in the administrative areas, some of the storage areas where pressure and humidity control are not crucial, and also some differences in the temperature can be easily tolerated. The working principle of the VAV system is by distributing a constant air supply with very less variations in temperature to the spaces. This system eradicates the energy usage in reheating process and saves the fan energy. Limitation of this system is finned radiation or convection heating devices cannot be used in the clean areas, because this system device can't be cleaned easily and it may allow the spaces for undesirable particulate build-up.

7.7.3. Cleanroom design and operation

Airborne viable microbes contamination risk is depends on

1. Level of airborne microbes,
2. Personnel activities and
3. Condition of the process either open or closed.

The above said risk factors can be minimized by unidirectional airflow in high air change rate (Ratajczak et al. 2015). In the sterile processing areas, movement of material and personnel can create the airborne contamination risk, which can be diminished by controlling,

1. Material entry, supply and exit,
2. Personnel exit and entry,
3. Waste assortment and disposal and
4. Maintenance operations.

7.7.4. Optimization of environmental monitoring plan

In environmental monitoring plan the optimization and development process includes:

- Site map,
- Sampling procedure,
- Sample site and frequency,
- Sampling handling and incubation,
- Formation of alert/action limits and
- Personnel training.

Generally environmental microorganisms are present in the non-sterile manufacturing areas; however, the types and numbers of microbes in this location characterize the risk. Presence of higher number of microbes can affect the quality of the products. Deficiencies in the monitoring of environmental system includes:

- Not all aseptic process areas are monitored.
- Failing to act quickly when results are outside of acceptable limits.
- Insufficient corrective measures.
- Not adhering to written instructions.
- Defective documentation and follow-up.
- Derisory program for environmental monitoring.
- Not validating cleaning and sanitization techniques.
- Absence of program for monitoring the environment.
- Environmental monitoring data are not trended.
- Insufficient analysis of the underlying cause of the divergence.
- Unable to recognize common germs.
- Insufficient lab infrastructure facilities.
- Absence of proper written guidelines.
- Lack of a program to identify microbial isolates.
- Insufficient records of the divergence.
- Failure and deviation investigation reports are not finalizing in time (Gail and Stanischewski 2004).

7.7.5. Air

Air is the major source for the microbial contamination. Routine air sampling monitoring includes both viable and nonviable airborne particulates in the location. In non-sterile and sterile manufacturing area major source of microbial contamination is by viable particulates, whereas laboratory persons can be the source of both particulates (Baird 1985; Mestrandrea 1997; Akers and Agallaco 2001; Reich et al. 2003).

Level of microbial loads can be reduced and to provide a controlled environmental condition by utilizing adequate number of HEPA filters along with

uniform airflow pattern with sufficient velocity. Monitoring the microbes in the environment can be performed by performing different air sampling methods. The sampling methods are settling plates, surface air sampling system, centrifugal sampling system, slit to agar sampling system, gelatin filter sampling system, sieve impactor and Sterilized microbiological atrium.

7.7.6. Surfaces

Surface includes walls and floors are considered as critical area in the pharmaceutical facilities for environmental monitoring system. Surface sample method includes

1. Contact plates,
2. Swabbing and
3. Surface rinses (Denny and Marsik 1997).

7.7.7. Personnel

Persons can act as microbes hut and spreading of non-viable particulates. Proper gowning can reduce the spreading of non-viable particulates.

Smoke, pollen and dust are considered as the other sources for particulates for contamination. Regular monitoring of microbes in the garments and finger impression are done to ensure the aseptic techniques (Rutala and Weber 2002).

Micro-Contact plate samples are part of the personnel's microbiological sampling includes:

- Right and left chest,
- Right and left sleeve,
- Right hand and left-hand glove fingers and
- Forehead.

7.8. Facility Classifications

Pharmaceutical industries typically include a series of rooms to contest with the necessities of the industrial manufacturing processes. For the production of sterile (absence of living organisms) products, aseptic processing method is used by utilizing sterile rooms. Sterile rooms should be independent from the neighbouring sector to prevent cross contamination.

Objective – The aseptic processing systems includes the production of sterile products, closures and containers with special design in the controlled environments to maintain as well as to minimize the effect of microbiological and particulate contamination.

For sterile and non-sterile areas, the cleanroom classifications differ with various aspects. These are called by various names and they are (Bhatia 2014),

1. Sterilized operation = Critical Area = aseptic application
2. Non-sterilized operation = Controlled Area = non-aseptic application

1. Critical Areas

According to the U. S standards, “Critical Areas”, are defined as the areas where sterilized processes are being carried out. It should have aseptic cleanrooms.

Requirement – In the critical areas, air is normally of acceptable particulate quality if it has a per cubic foot particle count of less than 100 in size range of 0.5 micron. A prevalence of merely 0.1 colony forming units per cubic foot is tolerable as microbial quality. Air quality in sterile areas is maintained by laminar airflow with a velocity of 90 feet per minute \pm 20 and the pressure differential should be of no less than 0.05 inch of water gauge is suggested.

2. Controlled Areas

As per the U.S standards, the “controlled area” is defined as the area where non-sterilized substances and products are being prepared. The activities performed in non-aseptic environment are production, drug substances and products, equipment contact areas, in-process materials, closures and containers, are exposed to the surrounding environment of the industrial setup.

Requirement – In the controlled areas, air is normally of acceptable particulate quality if it has a per cubic foot particle count of less than 100,000 in size range of 0.5 micron. Regarding the microbial quality, a prevalence of merely 2.5 colony forming units per cubic foot is adequate. So as to maintain the air quality in controlled areas, airflow should be sufficient and also it helps to attain no less than 20 air changes per hour. In general, the overall pressure differential should be of 0.05 inch of water gauge is being recommended.

7.9. Clean Rooms and Sampling in Contamination Control

Cleanrooms are characterized based on the air supply and its distribution. Generally, two types of air supply configurations are used in cleanroom design (Yeotikar 2020):

1. Non-unidirectional air flow

- It has significant amount of turbulence.
- It is used in the rooms where major contamination is likely from external source.
- The turbulent flow improves the mixing of low and high particle concentrations.
- It produces a homogenous particle concentration for manufacturing process.
- Air is generally supplied into the space by two different methods.
 - o First method is by using supply diffusers and HEPA filters – The HEPA filter is essential to the supply diffuser or to the air handler.
 - o Second method – It has the prefiltered air supply in upstream of the cleanroom and then passed into the space over HEPA filtered places.
- This type of airflow affords an acceptable control for the cleanliness levels between Class 1000 and 100,000 (Bhatia 2014).

2. Unidirectional air flow:

- A Unidirectional air flow (*UDAF*) is also known as 'laminar' airflow and the pattern is being represented (Talukder 2016) in Scheme 7.1.
- The air flow pattern is a single pass and single direction air flow of parallel streams.
- UDAF must be used where it is suitable to afford product and substance protection by providing a clean air supply.
- Thus, minimizing the entry of impurities from the neighbouring areas.
- Provides protection to the operator and drug substances/products vice versa.
- They are commonly categorized into two different types:
 - o Vertical down flow – the direction of air flow is vertical laminar. The clean air is generally introduced through the ceiling and then returned by means of a raised floor and the base of adjacent walls.
 - o Horizontal flow – the direction of air flow is horizontal laminar. Here the supply of clean air is from one side of the wall and the return will be on the other side of the wall.
- Among the two types of UDAF, the vertical down-flow pattern provides better result and also it is more adaptable to the pharmaceutical industries (Talukder 2016).



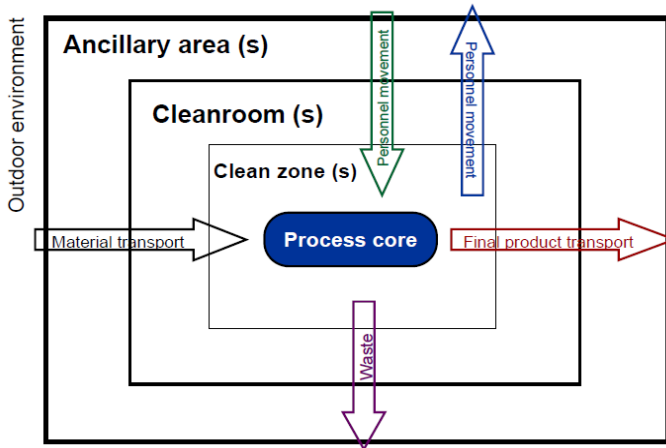
Scheme 7.1. Diagram for unidirectional airflow
Схема 7.1. Дијаграм за једносмерни проток ваздуха

7.9.1. Segregation of Cleanroom

Generally airborne particles are created during human activities and it has been considered as a most important source for the contamination.

Appropriate filtered airflow with differential positive pressure of 10–15 Pascal's from higher cleanliness to less clean areas can provide good clean room segregation. Clean room area should be minimum in size; however large space the area is divided into different clean room zones with suitable physical barriers (Gail and Stanischewski 2004).

Air supply from top to bottom with appropriate air change can confiscate the contaminant from the clean area. Also, persons entering between different zones should change the garments with respective to the zone. Shell type segregation (Quinto and Menezes 2010) of clean room is shown in Scheme 7.2.



Scheme 7.2. Shell type contamination control concepts

Схема 7.2. Концепти контроле контаминације типа шкољке

There are three different clean room segregation concepts which are utilized to maintain the clean room/zone in the pharmaceutical manufacturing premises. Clean rooms are segregated based on the three different concepts, they are:

- a) **Differential pressure concept:** Mostly utilized when ventilated rooms of various classifications are divided by a door or other tiny opening. Low turbulent displacement with velocity above 0.2 m/s airflow can provide low pressure different between the clean rooms.
- b) **Displacement airflow concept:** Utilized to create a controlled or unidirectional airflow between adjacent clean room zones of various classifications have differential pressure between 5 and 20 Pascal's. Airflow pattern is used to balance quantitatively both inflow and outflow of air in the area.
- a) **Physical barrier concept:** Utilized in isolator technology by providing impervious barrier between clean zone and less clean zone (Lakshmana Prabu et al. 2012).

7.9.2. Clean room classification

Clean room classification as per Grades is

- Grade A: Laminar flow system is furnished having the air speed in the range of 0.36 to 0.54m/s in homogenous way. Mainly installed in the high-risk operational areas like aseptic filling, open vials, stopper bowls and creating aseptic connections.

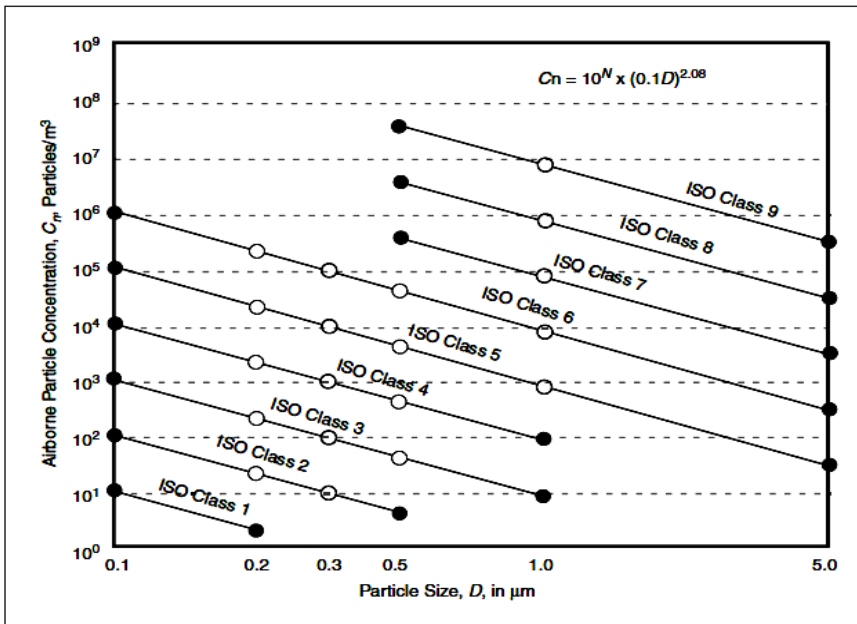
- Grade B: Clean area provides contextual environment for grade A zone.
- Grade C: Clean area for manufacturing of less critical stage activities of sterile products.
- Grade D: Clean area is not classified, used for change room especially gowning room (Jennie et al. 2014).

Clean room classification is determined by:

$$C_n = (0.1/D)^{2.08} \times 10^N$$

- C_n = Maximum permitted concentration (particles per m^3)
- D = Particle size in μm
- 10^N = Classification number

This graph plotted taking particle size in 'X' axis and airborne particle concentration in 'Y' axis, whereas slope of the curve is 2.08 for each class. Clean room classification as per ISO and its limit is depicted in Graph. 7.1. (Sandle et al. 2008).



Graph 7.1. ISO-Clean room classification and concentration limits

Граф. 7.1. ISO-Класификација чистих соба и дозвољене концентрације

As per ISO clean room, a comparison of various clean rooms and its airborne particulate limits (WHO TRS 823 1992; Chyan 1992; Postlewaite et al. 2013) are given in Tables 7.3 and 7.4.

Table 7.3. ISO Cleanroom and clean zones airborne particulate limits

Таб. 7.3. ISO Дозвољене вриједности честица у ваздуху чистих соба и зона

| Classification number (N) | Maximum concentration limits (particles/m ³ of air) for particles equal to and larger than the considered sizes shown below | | | | | |
|---------------------------|--|--------|--------|---------|--------|--------|
| | 0.1 µm | 0.2 µm | 0.3 µm | 0.5 µm | 1 µm | 5.0 µm |
| ISO Class 1 | 10 | 2 | - | - | - | - |
| ISO Class 2 | 100 | 24 | 10 | 4 | - | - |
| ISO Class 3 | 1000 | 237 | 102 | 35 | 8 | 8 |
| ISO Class 4 | 10000 | 2370 | 1020 | 352 | 83 | 83 |
| ISO Class 5 | 100000 | 23700 | 10200 | 3520 | 832 | 832 |
| ISO Class 6 | 1000000 | 237000 | 102000 | 35200 | 8320 | 8320 |
| ISO Class 7 | | | | 352000 | 83200 | 83200 |
| ISO Class 8 | | | | 3520000 | 832000 | 832000 |

Table 7.4. Airborne particulate classification system

Таб. 7.4. Систем класификације честица у ваздуху

| WHO (GMP) | United States (209 E) | United States (Customary) | ISO/TC (209) | EEC (GMP) |
|-----------|-----------------------|---------------------------|--------------|-----------|
| Grade A | M 3.5 | Class 100 | ISO 5 | Grade A |
| Grade B | M 3.5 | Class 100 | ISO 5 | Grade B |
| Grade C | M 5.5 | Class 10000 | ISO 7 | Grade C |
| Grade D | M 6.5 | Class 100000 | ISO 8 | Grade D |

7.9.3. Selection of sampling sites

Generally various types of sampling techniques are used based on the sampling sites, but the most desirable techniques used are Direct surface sampling, Swab sampling and Rinse sampling (Lakshmana Prabu and Suriyaprakash 2010). Identifying the sampling sites in the sterile and non-sterile manufacturing area can provide information about the microbial level. Ancillary areas like equipment disassembling, cleaning and assembling are also considered as critical areas. Common sampling environmental sites are (Jimenez 2004):

- a) Water pipelines,
- b) Dispensing room,
- c) Component preparations room,
- d) Mixing and filling rooms,
- e) Stoppering rooms and
- f) Air ventilation systems.

7.9.4. Sampling Frequency

Based on the rooms classification and activity the frequency of sampling will be varied for sterile products from daily to weekly, whereas for non-sterile products from monthly to quarterly (Denny and Marsik 2004; Ratajczak et al. 2015). Then the frequency of sampling is represented in Table 7.5.

Table 7.5. Sampling Frequency

Таб. 7.5. Фреквенција узорковања

| Sampling areas | Sampling Frequency |
|--|------------------------|
| Class 100 & Class 10,000 | Each operational shift |
| Class 100,000 & Product/container contact area | Twice a week |
| Other support areas to aseptic processing areas but not product contact (class 100,000 or lower) | Once a week |

Microbes in the environment are monitored by impaction and centrifugal samplers (Ljungqvist and Reinmuller 2000). For Impaction method – Slit to agar air sampler is an example. For centrifugal samplers – Settling plate is an example where particles from the environment are settled by gravity on the surface of the agar in open agar plates (Nagarkar et al. 2001). Surface sampling in the environment is another important component in monitoring the environment. Surface sample has been performed in different media's like D/E agar, R2A, SD and Soybean casein digest agar with or without neutralizers. Other media includes:

- a) Soybean casein digest agar
- b) Tryptone glucose extract agar
- c) Lecithin agar
- d) Brain heart infusion agar
- e) D/E neutralizing agar
- f) Lethen agar

7.10. Qualification and Validation of HVAC System

Validation is a very immense subject field in Pharmaceutical Industries which is a study of quality assurance affording the safety and quality of the product, manufacturing equipments and systems. It certifies about the accuracy of results obtained by any kind of system in industry. Maintenance of quality of the drug products and substances pharmaceuticals are of great importance, because they

have direct impact on the human beings externally as well as internally. Validation affords documentary evidence for the HVAC system, which describes about its design, installation, and performance condition as proposed (Gouveia et al. 2015).

7.10.1. Importance of qualification and validation

Validation is a mandatory field in the pharmaceutical manufacturing industries as it confirms the accuracy, precision and reproducibility of the results through determining the optimal performance of a system at various stages. Primarily qualification is a regulatory requirement for almost every process in the pharmaceutical industry, medical and biologic devices. The current movement towards synchronization of all the necessities will ultimately result in a good qualification standard universally (Singh et al. 2016).

7.10.2. Validation process of HVAC system

The validation of HVAC system generally comprises the assembling of various documentary evidences such as functional specifications (the conceptual design); design drawing, plans, and specifications; validation master plans; contractor's documents; testing, adjusting, and balancing (TAB); startup reports; commissioning reports (the actual execution of validation protocols); and validation (IQ, OQ, and PQ) (Singh et al. 2014). HVAC system is essential during the process validation to prevent the cross contamination (Lakshmana Prabu et al. 2014b, 2014c).

The validation process of HVAC system generally includes documentary evidence with regards to several characteristics of HVAC system such as:

Functional specifications (the conceptual design) includes system plans, design drawings and specifications of the HVAC system (Patil et al. 2018).

System Plans – It elucidates the detailed purposes that the producer targets such as, cleaning, maintenance and operation with very less dust as well as sound.

Design drawings – It relates to the measurement of the equipment (like length and breadth of it), efficiency of the equipment, quick services at practical costs and accessibility of the spare parts.

Specifications – Here, the industrial manufacturer describes about the qualitative and quantitative features of the equipment.

7.10.2.1. Validation master plans

Validation master plan is a very important document which consists of the contractor's document. It has critical details related to the manufacturer's necessities. It also consists of testing details in-terms of pictorial, physicochemical, adjusting, and balancing (TAB) particulars which is generally executed in the presence of a merchant (Patil et al. 2018).

7.10.2.2. Startup reports

Startup reports are documented evidence which comprises of commissioning reports. It is the authentic implementation of validation protocols and procedures at various stages such as Design Qualification, Installation Qualification, Operational Qualification, and Performance Qualification (Patil et al. 2018).

7.10.2.3. Design Qualification

Design Qualification (DQ) provides standard documentary evidence that the design specifications are accomplished or not and whether it is constructed into the design of building facilities and operations. If specific equipment is need to be created according to the user necessities, and then it is very important to design the detailed qualification documentary evidence. It is desirable to work out and design the complete equipment requirement by sitting in an organized manner with the producer. Once the DQ is prepared, it must be friendly to both the parties, that is, the manufacturer as well as the purchaser. At this stage it might be desirable to categorize the stages involved during the production of the equipment, where various visual and physicochemical tests are executed in the presence of purchaser. Commonly, the Factory Acceptance Test (FAT) is being executed at the producer's buildings before the dispatch of equipment systems to the purchaser. DQ must afford documentary evidence that the design specifications were met the specific equipment system (Singh et al. 2014; Handbook ASHRAE 2016).

7.10.2.4. Installation qualification

Installation Qualification (IQ) provides standard documentary evidence that the installation was complete, satisfactory and acceptable. The design drawings, vendor particulars, procurement specifications must be confirmed during the IQ (Tab. 7.6).

Table 7.6. Installation Qualification Acceptance Criteria

Таб. 7.6. Критеријуми прихватања за квалификацију инсталације

| Test | Acceptance criteria |
|--|--|
| Verification of approved or as-build (on site) HVAC system drawings. | HVAC system diagrams or drawings must be in accordance to the approved design. |
| Verification of critical instrument installation. | All critical or non-critical instruments must be in current state of calibration. |
| Verification of major component installation. | Major components or lesser importance components must be in accordance to the checklist provided during URS (User Requirement Specification). |
| Verification of support utilities installation. | All utilities stipulated in the approved design should not deviate during support utilities installation. |
| Audit of High Efficiency Particulates Air (HEPA) filter Integrity Test Critical Area Controlled area | The HEPA filters must pass the filter integrity test in accordance to the USP/EP Standards |
| Verification of receipt of all required system documentation/manuals. | All systems documents and instrument manuals must be in accordance to the checklist mentioned in URS. (Calibration manuals and calibration certificates for critical parts). |
| General system inspection | <ul style="list-style-type: none"> - Filters are properly seated. - No defective or missing filters. - The AHUs must be clean. - The ductwork is properly connected. - Pneumatic lines are properly connected |

IQ can be defined as the documented verification of all the important features of the installation stick to the producer’s recommendation, permitted design qualification, and appropriate codes (Singh et al. 2014).

The equipment can be installed only when it is qualified for installation, specifically, as soon as it passes the IQ test. IQ must afford documented evidence that the installation was complete and satisfactory. The manuals, spare parts lists, drawings, purchase specifications and merchant details must be confirmed during IQ. In this stage both controlling and measuring devices must be standardized according to the acceptance criteria depicted on Table 7.6.

7.10.2.5. Operational qualification

Operational Qualification (OQ) provides standard documentary evidence that systems and equipment utilities as well as its machineries function according to the operational specifications. Examinations must be planned to validate the operating procedure over the standard operating process in addition to the restrictions of its operational conditions (e.g. including the worst-case scenario).

OQ can be defined as the document verification that the equipment system executes as planned all over the quantified operational range. After installation the equipment must be operated only once it passes the OQ Test. In the OQ, alarms, operation controls, displays, switches, and some extra functioning components must be tested. Measurements are made in compliance with a statistical approach (Singh et al. 2014; Handbook ASHRAE 2016). For OQ, the acceptance criteria (Jennie et al. 2014) are shown in Table 7.7.

7.10.2.6. Performance qualification

Performance qualification (PQ) provides standard evidence that systems and equipment utilities as well as its machineries function according to the PQs specifications under routine usage. For determining the PQ, test results must be collected over a certain period of time to verify the consistency the systems performance. PQ is measured by various methods as identical with the OQ. Roughly some specialists consider OQ as the authentication performance of the system without load and PQ is the equivalent with the load. Though, these two relations continually go together and no difference can be completed (Singh et al. 2014). Various tests are being carried out to ensure the PQ and the PQ acceptance criteria (Jennie et al. 2014) are represented in Table 7.8.

7.10.3. Validation Methodology

On the whole, the numerous parameters need to be verified for the validation of HVAC system. The validation of HVAC system comprises of air flow pattern or smoke pattern, air flow velocity and changes per hour, filter leak test, filter integrity test (dioctyl phthalate (DOP)/polyalphaolefin (PAO) test), particle count, viable monitoring, pressure difference, recovery test (temperature and humidity), temperature and humidity uniformity test, and fresh air determination (Shukla et al. 2011).

Table 7.7. Operational Qualification Acceptance criteria

Таб. 7.7. Оперативна квалификација критеријума прихватања

| Test | Acceptance criteria |
|---|---|
| HVAC Start-up and Shutdown Operation Test. | The air-handling unit start-up and shutdown sequence must operate in accordance with the design specifications and accordance to URS. |
| Operational procedure compliance test | All the operational procedure must comply with Functional Requirement Specification. |
| Verification of Critical Instrument Calibration | All critical instruments must be in the state of calibration. |
| Airflow Velocities and pattern | The airflow velocity in a unidirectional airflow device should not exceed the limit set in the design criteria. The highest and lowest reading should not be more than 15-20% from the unit average velocity. |
| Loss of utility test | Loss of utility test must not interfere with other ongoing operations. |
| Audit of air balance reports/Air volume test | <ol style="list-style-type: none"> 1. The room air change must be not less than 20 air changes per hour. 2. Air balance report should include all the data within the pre-determined acceptance criteria. |
| HEPA Filter Leak Test | <ol style="list-style-type: none"> 1. Filter media integrity test should pass according to ISO 14644. 2. Filter seal integrity test should pass according to ISO 14644. |
| Relative humidity Audit / Monitoring | (30–65) RH% for all controlled rooms. |
| Temperature Audit / Monitoring | (22.0 ± 3.0) °C for all controlled rooms. |
| Differential air pressure test | <ol style="list-style-type: none"> 1. Differential air pressure (ΔP) between any room and the main corridor must be within the tabulated defined range, which ensures that the ΔP between two adjacent rooms, which have same/different classification levels, is not less than 12.5pa. 2. Absence of cross-contamination (measurement of pressure difference). |
| Alarm test and Interlock Test | <ol style="list-style-type: none"> 1. All alarms systems and interlock must comply with Functional Requirement Specification. 2. Door interlocking testing should pass for all doors in sterile area to insure there will be no contamination between each individual area. |
| Power-fail and Recovery test | The controlled environment should recover to the original setup after loss of power (within 15 min.). |

Table 7.8. Performance Qualification Acceptance criteria

Таб. 7.8. Квалификација учинка критеријума прихватања

| Test | Acceptance criteria |
|---|---|
| Verification of Performance Qualification prerequisites | All actions must be performed before starting execution of performance qualification activities. |
| Air Cleanliness Test | <ol style="list-style-type: none"> 1. <i>Critical Environment</i> – The particle concentration under dynamic conditions should not be more than 3.5 particles of 0.5 µm and larger per cubic meter (100 particles of 0.5 µm and larger per cubic feet). 2. <i>Other Environments</i> – Typically, a tenfold gradient must be used from critical to less critical environments (Ex. 1,000 for environment adjacent to critical environment 10,000 for those adjacent to it.) |
| Airborne Bioburden Test | <ol style="list-style-type: none"> 1. <i>Critical Environments</i> – Not more than 1 CFU/m³ or 0.03 CFU/ft³. 2. <i>Typical for other environments</i> – Adjacent to critical environment 5/m³ or 0.15/ft³. 3. <i>Controlled Environments</i> – 87/m³ or 2.5/ft³. |
| Temperature – Humidity Control test | <ol style="list-style-type: none"> 1. The specified temperature range must not be more than 22 ± 3 °C. 2. The specified relative humidity range must not be more than 30–65% in aseptic processing areas. Unless otherwise specified by the process requirements. |
| Differential Air Pressure and Direction Test – Dynamic Conditions | <ol style="list-style-type: none"> 1. Differential air pressure between any room and main corridor must be within the tabulated defined range, which ensures that the ΔP between two adjacent rooms, which have same/different classification levels, is not less than 12.5 Pascal's. The supply and return air volumes should conform within the range specified. Pressure differential between rooms should be maintained as indicated in the specifications. 2. Absence of cross-contamination (measurement of pressure difference). |
| Surface Bioburden Test | <ol style="list-style-type: none"> 1. <i>Critical Environments</i> – Not more than 1 CFU/12.9 cm² or 2 in². 2. <i>Typical for other environments</i> – Adjacent to critical environments: 5/12.9 cm² or 2 in². 3. <i>Controlled Environments</i> – 20/12.9 cm² or 2 in². |

The methodology for the validation of the HVAC system embraces:

Air flow or smoke pattern

For the determination of the air flow, a titanium tetrachloride stick is burnt and the burning stick is placed in front of the AHU and the distribution of smoke is observed. It should be uniform. Preferably class 100 is used for the determination of air flow pattern.

Velocity of Air flow and air changes per hour

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. The area of the HEPA filter inlet (A) is calculated in feet and the total air volume (T) is then calculated by multiplying the average velocity of air and the area of the inlet ($T = A \times V$). After this, the volume of the room is calculated and the air changes per hour are obtained by dividing the total air change by the volume of the room. According to the ISO classifications the air flow rate and airflow change per hour for clean room (Schneider 2001) are tabulated in Table 7.9.

Table 7.9. Clean room – Air flow rate and change per hour

Таб. 7.9. Чиста соба – Проток ваздуха и измјена по сату

| ISO Classifications | Federal Standard 209 E | Federal Standard 209 E | Guideline | Air flow (fpm) | Airflow w (ACH) |
|---------------------|------------------------|------------------------|------------------------|----------------|-----------------|
| 1 | No Equiv. | No Equiv. | Stringent | 70–100 | |
| 2 | No Equiv. | No Equiv. | Stringent | 70–100 | |
| 3 | 1 | M1.5 | Stringent | 70–100 | |
| 4 | 10 | M2.5 | Stringent | 70–100 | |
| 5 | 100 | M3.5 | Stringent intermediate | 70–100 | 225–275 |
| 6 | 1000 | M4.5 | Intermediate | N/A | 70–160 |
| 7 | 10000 | M5.5 | Intermediate | N/A | 30–70 |
| 8 | 100000 | M6.5 | Less stringent | N/A | 10–20 |
| 9 | No Equiv. | No Equiv. | Less stringent | N/A | As req. |

Particle count

A particle counter is used to perform the particle count. Particle count is taken before the operation as well as during the working condition.

Grade A and B, the total sample volume should be not less than 1 m³ even Grade C also can be performed in this sample volume range. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas. Based on the clean room's square meter area, the minimal amount of samples is determined and the sampling point number is determined by,

$$NL = \sqrt{A}$$

- NL is the number of sampling locations (rounded up to a whole number)
- A is the cleanroom area

Based on the different guidelines, maximum allowable permitted numbers of particles/m³ are tabulated in Table 7.10, 7.11 and 7.12.

Table 7.10. Airborne particulate limits as per PIC/S and EC

Таб. 7.10. Граничне вриједности честица у ваздуху према PIC/S и EC

| Grade | At rest | | In operation | |
|-------|---------|-------|--------------|-------------|
| | 0.5 µm | 5 µm | 0.5 µm | 5 µm |
| A | 3500 | 1 | 3500 | 1 |
| B | 3500 | 1 | 350000 | 2000 |
| C | 350000 | 2000 | 3500000 | 20000 |
| D | 3500000 | 20000 | Not defined | Not defined |

Table 7.11. WHO acceptable limits of Airborne Particulate

Таб. 7.11. Прихватљиве вриједности честица у ваздуху према C30

| Grade | At rest | | In operation | |
|-------|------------|---------|--------------|-------------|
| | 0.5–5.0 µm | >5.0 µm | 0.5–5.0µm | >5.0 µm |
| A | 3500 | 0 | 3500 | 0 |
| B | 3500 | 0 | 350000 | 2000 |
| C | 350000 | 2000 | 3500000 | 20000 |
| D | 3500000 | 20000 | Not defined | Not defined |

Viable monitoring

Viable monitoring is performed on daily basis by employing the swab test, viable air samplers and using nutrient agar medium for the incubation of microorganisms.

The different media plates are exposed in every manufacturing location including the reverse air duct of the HEPA filter at the back of the cubicle. The microbial count should be within the range and if it is found out of specification for consecutive two times, an effective corrective and preventive action must be taken. Schematic diagram for viable airborne particulate monitoring (Patil et al. 2018) is shown in Fig. 7.1.

Table 7.12. Maximum acceptable number of particles/m³

Таб. 7.12. Максимални дозвољени број честица/м³

| Guideline | Grade | At rest | | In operation | |
|-----------|--------|----------|--------|--------------|-------------|
| | | 0.5 µm | 5 µm | 0.5 µm | 5 µm |
| EU | A/B | 3520 | 20/29 | 3520 | 20 |
| ISO | 5 | 3520 | 29 | 3520 | 29 |
| FDA | 100 | - | - | 3520 | - |
| EU | - | - | - | - | - |
| ISO | 5 | 35200 | 293 | 35200 | 293 |
| FDA | 1000 | - | - | 35200 | - |
| EU | B*** | - | - | 352000 | 2900 |
| ISO | 7 | 352000 | 2930 | 352000 | 2930 |
| FDA | 10000 | - | - | 352000 | - |
| EU | C | 352000 | 2900 | 3520000 | 29000 |
| ISO | 8 | 3520000 | 29300 | 3520000 | 29300 |
| FDA | 100000 | - | - | 3520000 | - |
| EU | D | 3520000 | 29000 | Not defined | Not defined |
| ISO | 9 | 35200000 | 293000 | 35200000 | 293000 |
| FDA | - | - | - | - | - |



Fig. 7.1. Viable monitoring using viable air samplers

Сл. 7.1. Одржив мониторинг коришћењем узоркивача ваздуха

Filter leak test

For the leak test Velometer is placed at the front of the HEPA filter of the AHU system and the air velocity is checked at all the corners. The air velocity should be within the specification of the HEPA filter. In case it is found to exceed the upper limit, old gas cut (silicon) is replaced with new one to ensure the velocity.

Filter integrity test

The HEPA filter integrity is tested by generating a Poly Alpha Olefin (PAO) aerosol by an aerosol generator and allowing the upward flow of the aerosol. The 100% upward flow of the aerosol is ensured and then the receptor probe of the HEPA is monitored to know the amount of the aerosol reversed. It should not exceed the higher limit of the HEPA filter. Earlier to this test, Dioctyl Phthalate (DOP) was performed regularly. But nowadays, it is replaced by the PAO taking into consideration the carcinogenicity of the DOP. Different aerosols like Di-ethyl hexyl sebacate, Poly-alpha olefin, Di-octyl phthalate, Shell Ondina EL and Total Finaveston A80B (refined mineral oil) are frequently used in HEPA filter integrity testing. Filter integrity test for HEPA filter (Lakshmana Prabu et al. 2016; Singh et al. 2016; Patil et al. 2018) is shown in Fig. 7.2.

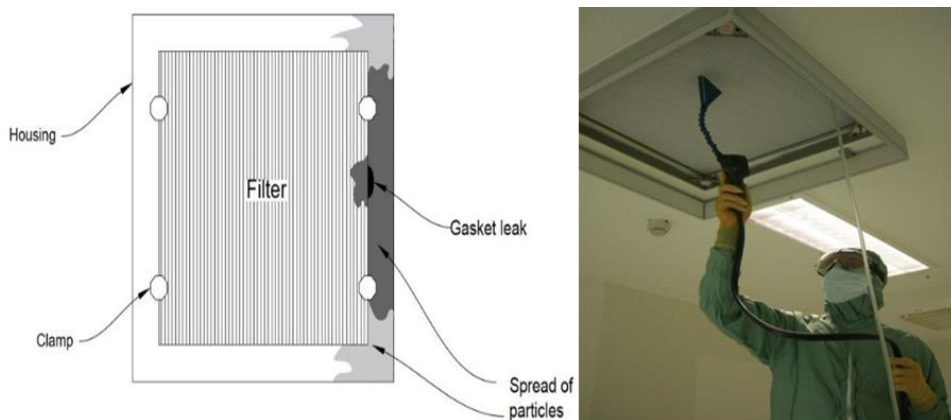


Fig. 7.2. Filter integrity test of HEPA filters
Сл. 7.2. Тест интегритета HEPA филтера

Pressure difference

It is calculated by making use of the manometer attached at the walls of the adjacent area. The pressure difference is generally kept between 5–20 mm Hg pressure.

Recovery test

The recovery of temperature and humidity is checked. For this, the humidity and temperature are checked at the off position of the HVAC system. Then the humidity is increased to 75% and temperature to 40 °C and again the temperature and humidity are measured after switching on the HVAC system, and the time required to stabilize the temperature and humidity are noted.

Temperature and humidity uniformity test

The uniformity of temperature and humidity are monitored by employing a calibrated thermometer and manometer respectively. The two parameters are monitored on daily basis, documented in the format and stabilization is ensured within the specified limit.

Fresh air determination

The intake of fresh air is observed at the inlet on the fresh air dumper and the total air change is calculated. The intake fresh air is divided by the total air change in the room and multiplied by 100 to obtain the percent fresh air intake on each cycle by the HVAC system (WHO TRS 1010, Annex 8 2018; Singh et al. 2014).

7.11. Maintenance of HVAC system

Maintenance of HVAC system is a major and crucial process in the pharmaceutical industries. All the procedures and records must be available in the operation and maintenance (O&M) manuals and should be updated regularly. The schematic designs, protocols, their reports and the O&M manuals must be kept as reference materials for all the upcoming changes and advancements to a particular system. Among all the O&M manuals, the available significant information's are:

- List of equipment suppliers,
- Spare parts list,
- Capacity schedules/equipment data,
- Supplier's literature,
- System description,
- Control system description,
- Operating instructions,
- Troubleshooting,
- Commissioning data,
- Maintenance instructions,
- Electrical drawings and

- As-built drawings.

For the HVAC system, there must be a strategic protective maintenance program. This the critical program should enlist about the critical parameters of the system also about its components. These kinds of maintenance activity must not have any undesirable effect on the quality of the product and this activity should be programmed to occur at outside the manufacturing hours. In case of any system stoppages, the root cause and impact procedure should be followed to assess and also to take necessary suitable corrective and preventive actions. If necessary, qualification or requalification protocol should be followed. Then the HEPA filters in a particular HVAC system should be replaced by a skilled person in time to time only after performing the installed filter leakage testing for proper filtration process. Finally, the observed results and the records should be maintained for an appropriate period of time (Au-Yong et al. 2014).

7.12. Risk assessment

Among the validation and qualification of the HVAC system, risk assessment also plays a major role in the continuous development process in pharmaceutical industries. It is a critical tool for the qualification of HVAC system in aseptic procedures. It is not just a means for current Good Manufacturing Practices (cGMP) compliance, but it aids in identifying the risks and ensures whether the critical measures are controlled or not. By means of managing the critical risks, pharmaceutical manufacturing industries can certify that the correct resources are applied at the exact place as well as at the right time thus by improving patient safety and eliminating the needless validation and qualification efforts.

Risk assessment is done by using the Failure Mode and Effects Analysis (FMEA) model. By this FMEA model, the overall risk of the validation and qualification steps can be evaluated. In the evaluation the severity value will be high for most of the direct impact systems. The risk priority ranking (RPR) is determined by the combination of severity, occurrence and detection. After the FMEA analysis of risk with RPR, if the level of risk is not in the acceptable value, modification should be done in the validation and qualification steps to decrease the RPR value to an acceptable limit or else improve the process of detection to lessen the RPR to an acceptable limit. Most probably, occurrence should be reduced rather than increasing the detection limit. The RPR system in accordance with the FMEA model is being represented in Table 7.13.

With the completion of the risk assessment with various models and ranking systems, the HVAC system will have very high level of quality, if the test results

are within the acceptable limit. In addition, if the test result is not in the acceptable limit, corrective action can be carried out which includes modification in the controls of the system (Shukla 2011).

Table 7.13. WHO acceptable limits of Airborne Particulate

Таб. 7.13. Прихватљиве границе честица у ваздуху према СЗО

| S.No | Occurrence | Risk associated with the probability of detection | | |
|------|------------|---|--|--|
| | | High | Medium | Low |
| 1. | Low | The cause will not occur if occurs also it will not be detected (Medium risk) | The cause will not occur if occurs also it will be detected (Low or medium risk) | The cause will not occur if occurs also it will be detected (Low risk) |
| 2. | Medium | Risk may occur and it will not be detected (High risk) | Risk can occur and will be detected (medium or high risk) | Risk can occur and will be detected (low or medium risk) |
| 3 | High | It is likely to occur and detection is not required (High risk) | It is likely to occur and detection is not required (High risk) | If risk occurs it will be detected (Low risk) |

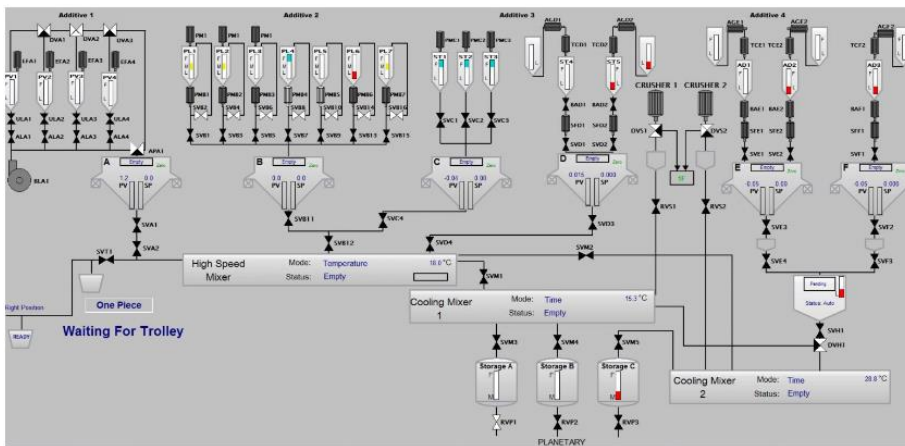
7.13. Automation of HVAC in Pharmaceutical Industry

HVAC system in the pharmaceutical manufacturing industries should be combined by means of a well-organized automation system to maintain the standard climatic constraints and to prevent any environmental contamination.

A statistic approach to deal with the association among the input and output factors with the information collected from the manufacturing or at the packaging areas of the industries (Shukla 2011).

Conventionally HVAC or Building Management System (BMS) is regulated by the Direct Digital Control (DDC) which is a closed control system with exclusive hardware as well as software packages. It is projected for the usage of Programmable Automation Controller (PAC) in consort with Supervisory Control and Data Acquisition System (SCADA) and Human Machine Interface (HMI) which

is a dedicated display with fixed structures is being depicted (Dhage et al. 2016) in the Scheme 7.3.



Scheme 7.3. SCADA screen in the HVAC plant control system

Схема 7.3. SCADA екран у контролном систему HVAC постројења

7.14. Conclusion

HVAC is a tool for monitoring the ambient environment for the pharmaceutical manufacturing processes. If a particular product is exposed to the environment the HVAC can directly influence the product quality by controlling the movement of unpleasant particles known as product contaminants. By means of the HVAC system in the pharmaceutical industry, the environment can be protected from the contaminated drug substances and products.

For accomplishing a high-quality HVAC system, validation and qualification is being carried out as per the standard protocols. Based on the results of the validation and qualification results only the HVAC system is concluded about its specifications and the quality attributes. Risk assessment using FMEA model is also important in the continuous development process of the industry as well as product. In the validation and qualification of the HVAC systems various methodologies and tests are performed and if the results are within the predetermined acceptance limits, then the HVAC system is prepared for routine usage by the qualified personnel. There is an increased interest for the automation of HVAC system among the pharmaceutical companies as the system plays a major role in every aspect of manufacturing processes. This software system unit aids in the monitoring and regulation of the production of drug product which will be free from the contamination of particulates.

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Значај унапређења система за гријање, вентилацију и климатизацију у грађевинским објектима намијењеним за фармацеутску индустрију

Натараџан Тамилселван, Апаву Умамахешвари, Сактивел Лакшмана Прабу

Сажетак

Систем гријања, вентилације и климатизације (*Heating, Ventilation, and Air Conditioning, HVAC*) има важну улогу у обезбјеђивању квалитета фармацеутских супстанци и лијекова. Такође штити фармацеутске производе од загађења и унакрсне контаминације разним загађујућим материјама, као што су честице прашине или друге прљавштине и микроорганизми из животне средине. У фармацеутској индустрији на ефикасност производње супстанци, укључујући сировине, састојке у процесу, готове производе и машине, највише утиче квалитет вентилације ваздуха у унутрашњости објекта. Вентилација ваздуха иначе има специфичан утицај на животну средину и на појединце.

Систем HVAC у згради регулише, између осталог, притисак у просторији, пад притиска, разлике притиска, контаминацију и контролу унакрсне контаминације. Зато се овај систем мора пажљиво размотрити и у периоду примарног пројектовања фармацеутског индустријског објекта. Такође приликом одобравања за употребу изграђеног фармацеутског грађевинског објекта потребна је опсежна контрола низа оперативних функција укључених у осигурање његовог укупног квалитета, али су важне и валидација и квалификација оперативне документације и документације за одржавање. Ови протоколи се периодично прате и спроводе и за нову опрему, комуналије, просторије и системе, чим се заврше велике промјене.

Ово поглавље даје увид о томе колико је потребно да HVAC систем у односу на заштиту животне средине у фармацеутској индустрији буде врхунски, јер је његова улога у производњи љековитих супстанци и производа у производној јединици индустријског погона велика. Осим тога, овај рад сумира постојеће информације о валидацији, квалификацији, одржавању, процени ризика у уградњи овог система у објекте фармацеутске индустрије и наглашава изузетно потребну аутоматизацију HVAC система у наведеним објектима.

Кључне ријечи: HVAC систем, заштита животне средине, фармацеутска индустрија, валидација, квантификација, FMEA (*failure modes and effects analysis*), аутоматизација

