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HVAC SYSTEM USED IN PHARMACEUTICAL INDUSTRY

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ABSTRACT

In the pharmaceutical industry, HVAC systems play a crucial role in maintaining the optimal environmental conditions necessary for the production, testing, and storage of pharmaceutical products. These systems are responsible for precise control of temperature, humidity, air quality, and pressure in various areas of pharmaceutical facilities, including production areas, laboratories, and storage areas. Despite their importance, HVAC systems in the pharmaceutical industry face challenges such as energy efficiency, system complexity, and cost considerations. However, investing in state-of-the-art HVAC systems and regular maintenance can yield significant benefits in terms of product quality, regulatory compliance, and personnel safety. HVAC systems are equipped with filters that capture airborne particles, such as dust, bacteria, and other contaminants. This helps maintain a clean and sterile environment, preventing contamination of pharmaceutical products and ensuring compliance with stringent regulatory requirements for cleanliness.

KEYWORDS: HVAC, Furnace, Thermostat, Evaporator, Refrigerant, Ductwork.

INTRODUCTION

HVAC is an important part of any pharmaceutical industry. HVAC abbreviated for Heating, Ventilation and Air Conditioning system.

HVAC has different parts that help to maintain the required temperature and humidity in the manufacturing area.

The HVAC system is used to control the environmental temperature and humidity in the manufacturing and storage area of the pharmaceutical industry.

Heating, Ventilation and Air Conditioning is a system that is used to control the air temperature by controlling the air filtration and the moisture in the air.

The HVAC system is used to control the temperature of a designated area with the control of the humidity in the air, supply the area with fresh air by controlling the level of carbon dioxide and oxygen. It also controls the contamination of airborne particles by regulating the air movement.

BASIC COMPONENTS OF HVAC SYSTEM

Figure-1: HVAC.

The following are the basic components of an HVAC system and the role they play to keep the condition suitable.

Furnace: This is the largest and main component of the HVAC system. It heats the air that is supplied the system; this can be done through the heat pump, solar energy, or the burning of the natural gasses. Inside the furnace, there is a heat exchanger which helps to switch on when the furnace is activated. It pulls the cold air and heats and circulates the air out through the vents.

Thermostat: The thermostat can either be set manually or programmed in advance to the desired temperature. It is easily visible and accessible part of the system. The thermostat can trigger the heat exchanger or evaporator coil-condensing unit to circulate a space with cold or warmed air.

Evaporator: It helps to cool the heated air. It is connected to the condensing unit which is filled with refrigerant gas. The unit is usually installed outside the room. It pumps the condensed liquid to the evaporator coil which is evaporated to gas again.

Refrigerant: This unit carries the refrigerant to the condensing unit for vaporization and returns it to the evaporator in liquid form. They are narrow tubes usually resistant to heating and cooling.

Ductwork: This unit transports the heated or cooled air across the room. The ducts are made of lightweight aluminium. The ductwork is connected with the vent that transfers heated or cooled air to individual rooms. They are usually located near the ceiling and are fronted with angled slats. It can be manually controlled to regulate the heating or cooling of space that they are directed.

- **The core functions of an HVAC system include the following**

1. Controlling micro-organisms, particles in the air and dust. A working HVAC system has to primarily control dust, which is eliminated through filtration. Dust can be a cause of contamination in the manufacturing process if not taken care of. Airborne particles that are found in the air can also interfere with the manufacturing process and result in contamination. Micro-organisms are also a potential threat to the successful processing of pharmaceuticals since the environment in the plant should be sterile. All these are eliminated through the HEPA systems.
2. Maintaining the right temperature in the production spaces. Temperature is very key in any pharmaceutical industry. if the temperature is not well controlled, it may cause micro bacteria to grow in the spaces or on workers, which may affect their health adversely.
3. Maintaining the right pressure in the room. In the pharmaceutical industry, there are areas and surfaces that must be kept cleaner at all times. These areas must, therefore, be kept at a positive pressurization at all times. The air floor at these areas should be more at the opening areas. The HVAC system ensures that positive pressurization is achieved by keeping the air flower into the clear spaces more than the air that exits at the same time. this ensures that there is no chance or space for the growth of micro-organisms.
4. Maintaining the right relative humidity. Controlling the moisture in the manufacturing spaces is achieved by the installation of desiccant dehumidifiers. Having the right humidity levels in the space is key to manufacturing stable drugs. The correct relative humidity is usually needed to ensure that tablets are well manufactured.

- **Functions of Pharmaceutical HVAC:** There are various applications of a pharmaceutical HVAC. The requirement of HAVC for a particular area depends on the manufacturing pharma product.

Some common functions of an HVAC system include the following

1. **Maintaining Temperature**
2. **Maintaining Humidity**
3. **Regulating air inside an area**
4. **Pressure regulation**

Maintaining Temperature: Temperature control is the basic and integral function of HVAC in the Pharmaceutical industry. This is necessary because uncontrolled temperature conditions can stimulate microbial growth. It can also increase the water activity in the area, which is also the basis of microbial growth.

Pharmaceutical HVAC provides suitable temperature conditions for a safe pharma product. It also prevents energy wastage by optimizing the temperature regulation process.

HVAC controls the temperature by continuously monitoring the area. When the temperature exceeds the required value, the AHU supplies cool air to reduce the area's temperature. Similarly, the supply air temperature increases when the temperature becomes lower than the desired value. In this way, the HVAC system regulates the area temperature.

Maintaining Humidity: Humidity control is also a critical feature of a Pharmaceutical HVAC system. Like temperature, humidity also stimulates microbial growth and increases contamination.

HVAC must maintain adequate humidity levels for pharma products and processes. If no product or process is involved, human comfort levels are considered.

A common humidity control method is supplying cooled air into a particular area. In this method, chilled water is supplied to cooling coils in AHU. When the supply air

passes through the cooling coil, its temperature drops and dehumidifies. When exposed to a particular area, this air lowers the dew point and decreases the relative and absolute humidity.

Regulating air inside an area: Pharmaceutical HVAC also regulates the airflow inside a designated area to provide a uniform airflow. It is necessary because non-regulated air flow can cause dust particles or foreign bodies to re-enter the air stream.

The blower maintains the airflow in the air handling unit. The required airflow is fed into the main control of the HVAC, and different sensors continuously monitor the airflow in an area. If the airflow inside an area changes, for example, due to man or material flow, the sensors sense the change and send the signal to the main controller, which calculates the difference. The main controller regulates the blower motor driver, such as the Variable Frequency Drive – VFD, to increase or decrease the blower speed Airflow can also be adjusted by opening or closing the air dampers installed at the supply air. Opening a damper increases the airflow, and conversely, closing the damper decreases the airflow. Dampers can be adjusted automatically through the main controller or by manual method.

Pressure regulation: Pressure regulation is another primary function of Pharmaceutical HVAC. Pressure regulation prevents air from uncontrolled areas to enter into controlled or clean area.

Pressure regulation is achieved by supplying air with higher volumes than adjacent areas. It makes the area more pressurized (also called positive pressure) than other areas and prevents air infiltration from non-critical or uncontrolled areas.

A super clean environment with controlled temperature and relative humidity has now become an essential requirement for a wide range of applications in Pharmaceutical Plants.

Cleanroom: A cleanroom is defined as a room in which the concentration of airborne particles is controlled. The cleanrooms have a defined environmental control of particulate and microbial contamination and are constructed, maintained, and used in such a way as to minimize the introduction, generation, and retention of contaminants.

Cleanroom classifications are established by measurement of the number of particles. 0.5 micron and larger that are contained in 1 ft^3 of sampled air. Generally class 100 to 100,000 rooms are used in the pharmaceutical industry. [Note - rooms may be classified as clean at class 1 or 10 for other applications, particularly in the microchip /semiconductor industry].

Notes

Grade-A classification is the most stringent of all. It requires air in the immediate proximity of exposed sterilized operations to be no more than 3500 particulates per cubic meter, in a size range of 0.5 micron and larger, when measured not more than one foot away from the work site and upstream of the air flow, during filling/closing operations. This applies both at "at rest" and "in-operation" condition. Grade-A areas are expected to be completely free from particles of size greater than or equal to 5 micron both "at rest" and "in-operation" condition.

Besides "at-rest" and "in-operation" cleanroom states, another condition most commonly used by HVAC contractors is "As – Built" condition. 'As built' cleanrooms are those which are ready with all services connected but without equipment and personnel.

The HVAC contractors responsibility generally lies up to the 'as built' or 'at rest' cleanroom stage and often the pharmaceutical companies specify higher cleanliness levels for these stages than the 'operational' stage.

Typical Examples

Typical examples of Grade- A areas include filling zone, Stopper bowls, Open ampoules and vials making aseptic connections.

Typical examples of Grade-B areas are Aseptic preparation and filling area, Aseptic receiving area, Aseptic changing room and solution preparation room.

These are less critical areas. Typical examples of these areas are 1) Changing room, 2) Material Entry air locks.

Facility Classification: Pharmaceutical facility typically consists of a series of integrating classes of rooms to match with the requirements of the manufacturing process. There are some basic requirements that must be satisfied so that the air in the sterile rooms is correct for the activities related to the manufacturing process. Each sterile room must be clinically independent from the surrounding area and are produced by "aseptic" processing. Aseptic processing is a method of producing a sterile (absence of living organisms) product. The objective of aseptic processing methods is to assemble previously sterilized product, containers and closures within specially designed and controlled environments intended to minimize the potential of microbiological or particulate contamination.

Cleanrooms classifications differ for sterile and non-sterile areas.

Non-sterilized operation = controlled area = non-aseptic application

Sterilized operation = critical Area = aseptic application

Controlled Areas: U.S standards define the "controlled area" as the areas where Non-sterilized products are prepared. This includes areas where compounds are compounded and where components, in-process materials, drug products and contact surfaces of equipment, containers and closures, are exposed to the plant environment.

Requirement - Air in "controlled areas" is generally of acceptable particulate quality if it has a per cubic foot particle count of not more than 100,000 in size range of 0.5 micron and larger (Class 100,000) when measured in the vicinity of the exposed articles during periods of activity. With regard to microbial quality, an incidence of no more than 2.5 colony forming units per cubic foot is acceptable.

In order to maintain air quality in controlled areas… airflow sufficient to achieve at least 20 air changes per hour and, in general, a pressure differential of at least 0.05 inch of water gauge (with all doors closed) is recommended.

Critical Areas: U. S standards define "Critical Areas", as the areas where Sterilized operations are carried out. These shall have aseptic cleanrooms.

Requirement - Air in "critical areas" is generally of acceptable particulate quality if it has a per cubic foot particle count of not more than 100 in size range of 0.5 micron and larger (Class 100) when measured in the vicinity of the exposed articles during periods of activity. With regard to microbial quality, an incidence of no more than 0.1 colony forming units per cubic foot is acceptable.

In order to maintain air quality in sterile areas… laminar airflow at velocity of 90 feet per minute ± 20 and, in general, a pressure differential of at least 0.05 inch of water gauge (with all doors closed) is recommended.

Types of Classification

Cleanrooms are also categorized by the way supply air is distributed. There are generally two air supply configurations used in cleanroom design:

1) Non-unidirectional and
2) Unidirectional.

Non-unidirectional air flow: In this airflow pattern, there will be considerable amount of turbulence and it can be used in rooms where major contamination is expected from external source i.e. the make up air. This turbulent flow enhances the mixing of low and high particle concentrations, producing a homogenous particle concentration acceptable to the process.

Air is typically supplied into the space by one of two methods. The first uses supply diffusers and HEPA filters. The HEPA filter may be integral to the supply diffuser or it may be located upstream in the ductwork or air handler. The second method has the supply air pre-filtered upstream of the cleanroom and introduced into the space through HEPA filtered work stations. Non-unidirectional airflow may provide satisfactory control for cleanliness levels of Class 1000 to Class 100,000.

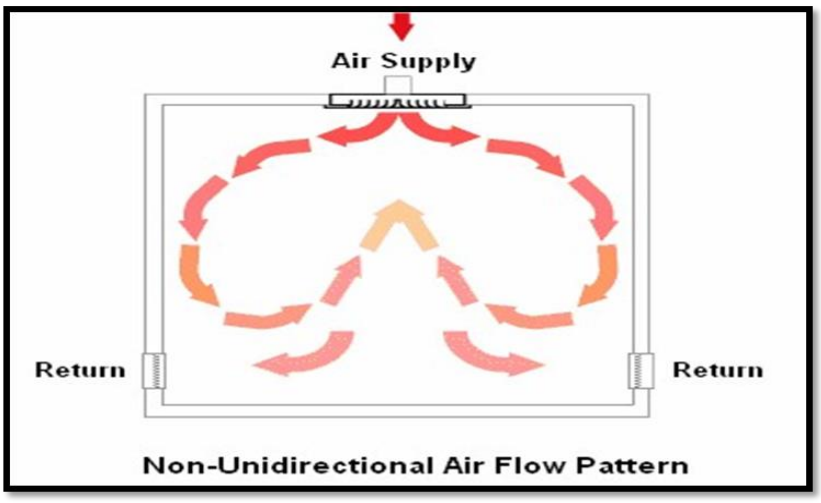

Figure-2: Air supply [non-unidirectional].

Unidirectional air flow: The unidirectional air flow pattern is a single pass, single direction air flow of parallel streams. It is also called 'laminar' airflow since the parallel streams are maintained within 18 deg - 20 deg deviation. The velocity of air flow is maintained at 90 feet per minute ±20 as specified in Federal Standard 209 version B although later version E does not specify any velocity standards.

Unidirectional cleanrooms are used where low air borne contaminant levels are required, and where internal contaminants are the main concern.

They are generally of two types:

1. Vertical down-flow cleanrooms where the air flow is vertical 'laminar' in direction.

2. Horizontal flow where the air flow is horizontal 'laminar' in direction.

In vertical down-flow arrangement, clean make-up air is typically introduced at the ceiling and returned through a raised floor or at the base of the side walls. Horizontal flow cleanrooms use a similar approach, but with a supply wall on one side and a return wall on the other.

Typically a down-flow cleanroom consists of HEPA filtered units mounted in the ceiling. As the class of the cleanroom gets lower, more of the ceiling consists of HEPA units, until, at Class 100, the entire ceiling will require HEPA filtration. The flow of air in a down-flow cleanroom bathes the room in a downward flow of clean air. Contamination generated in the room is generally swept down and out through the return.

The horizontal flow cleanroom uses the same filtration airflow technique as the downflow, except the air flows across the room from the supply wall to the return wall.

Between the two, the vertical down-flow pattern yield better results and is more adaptable to pharmaceutical production.

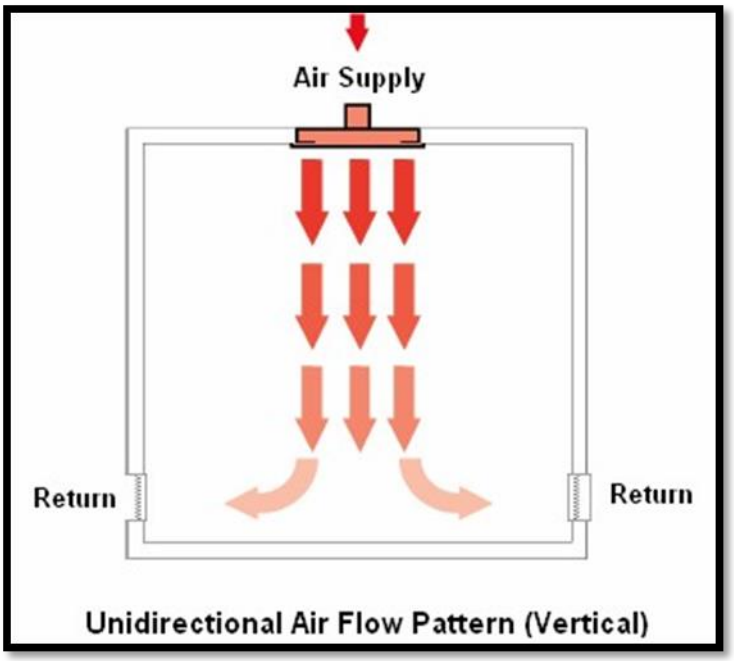

Figure-3: Airflow [vertical]

A cleanroom requires a very stringent control of temperature, relative humidity, particle counts in various rooms, air flow pattern and pressure differential between various rooms of the clean air system. All this requires:

1. **Increased Air Supply:** Whereas comfort air conditioning would require about 2-10 air changes/hr, a typical cleanroom, say Class 10,000, would require 50 - 100 air changes. This additional air supply helps, to dilute the contaminants to an acceptable concentration.
2. **High Efficiency Filters:** The use of HEPA filters having filtration efficiency of 99.97% down to 0.3 microns is another distinguishing feature of cleanrooms.
3. **Terminal Filtration and Air Flow pattern:** Not only are high efficiency filters used, but a laminar flow is sought.
4. **Room Pressurization:** With the increased fresh air intake, cleanrooms are pressurized in gradients. This is important to keep external particulates out of clean spaces.

- **SYSTEM DESIGN:** The HVAC design process begins with meetings with process engineers, architects, and representatives from the owner or facility user. The process and instrument diagrams (P&IDs) are reviewed, and a general understanding of the process is conveyed to all interested parties. Operation of the facility is reviewed, and any plans for future additions or modifications are discussed.

After the initial meeting, a written basis of design is produced that describes the regulations and codes that will govern the design. Spaces are defined by function, and temperature and humidity requirements are determined. Room classifications are listed and adjacency of spaces and pressure relationships are documented. Any unusual or unique facility requirements must also be designed into the HVAC system at this time, such as emergency backup or redundancy for HVAC systems. This is also the stage of the design process during which alternate studies are conducted to compare options for the HVAC system. The cost of a backup or redundant HVAC supply system

may be compared with the cost of product loss or experiment interruption should temperatures or airflow go out of control or specification. Heat recovery from exhaust systems and thermal storage are examples of other potential areas for study. Airflow diagrams are produced that show areas served by a particular air handling system including supply, return, exhaust, and transfer air between spaces. The basis of design also describes major equipment to be used and the level of quality of components and construction material.

The efficacy of the system design is based on proper consideration of the following factors:

1. Building construction and layout design
2. Defining the HVAC requirements system-wise and then room-wise.

– Cleanliness level
– Room temperature, relative humidity
– Room pressure
– Air flow pattern

3. Cooling load and Airflow compilation
4. Selection of air flow pattern
5. Pressurization of rooms
6. Air handling system
7. Duct system design and construction
8. Selection, location and mounting of filtration system
9. Defumigation requirement
10. Commissioning, performance qualification and validation
11. Testing and validation
12. Documentation

BUILDING DESIGN, CONSTRUCTION AND LAYOUT: Proper building design and planning of the flow of personnel, material and equipment is essential for achieving and maintaining the design levels of cleanliness and pressure gradients. If the building layout and its construction are poor there is very little that an air-conditioning system designer can do to satisfy the end-user needs.

Building Layout: From an HVAC standpoint it is desirable to keep similarly classified areas as physically close to each other as possible so they can be connected to the same air handling system, thereby minimizing duct runs, cost, and air system complexity. It is also imperative that spaces be arranged to allow people to move around without disrupting the cleanliness or containment of the spaces.

It is NOT desirable to mix dirty and clean systems or suites that may allow the possibility of cross-contamination from one suite to another. Leaks can develop in a filter, or some source of contamination could find its way through the air supply or return systems, providing a source for cross-contamination.

Sterile zones are normally divided into three sub zones:

1. Main sterile zone or white zone
2. Cooling zone which is also a white zone
3. Set of three change rooms: black, grey and white in ascending order of cleanliness

In order to achieve a pressure gradient, it is imperative that zones are located such that the gradient is unidirectional, i.e. the room with the highest pressure should be located at one end and the room with the lowest pressure should be located near the opposite end.

This type of planning can simplify balancing of system pressures to a great extent.

Entry for people to the main sterile room should be from a set of three change rooms: black, gray and white …in that order. Entry for equipment and material must be through "AIRLOCKS". No area should directly open into the sterile room.

Building Construction: The internal particulate generation always is the focus of any cleanroom design. The internal generation consists of those from building elements such as walls, floor, ceiling, etc., from equipment, and most importantly from operators. The building construction itself has to be "tight" with minimum of uncontrolled infiltration and leakages. This is very important in the case of buildings for formulation and sterile production. Materials used in the construction of the pharmaceutical facilities should be hard-surfaced. There are few special points of interest as noted below:

1. All material used is construction should be non chipping and cleanable. Wall and floor finishes should not shed particulates and should provide self-cleaning surfaces.
2. All exposed surfaces should be smooth, impervious and unbroken
3. No un-cleanable recesses and a minimum of projecting ledges, shelves, cupboards and equipment
4. Sharp corners should be avoided between floors, walls and ceiling
5. False ceilings and the tile joints in the floor should be completely sealed
6. Pipes, ducts and other utilities should be installed so they do not create recesses
7. Sinks and drains should be prohibited in grade Class 100 areas
8. All doors in the sterile area should have airtight construction. Special gaskets should be provided on the door frame and drop seals provided at the bottom of the door, if necessary.
9. Epoxy painting should be carried out in these areas.

Areas w/o False Ceiling: Special attention should be given to the type of ceiling. The commonly followed trend is to eliminate false ceilings and to provide instead a concrete slab on top of which are located the air handling units and ducting. Cut-outs in this slab are used for housing the terminal filters. Access to these filters is from top of the slab. Care should be taken to adequately reinforce this slab to accommodate the weight of the air handling units, piping and ducting.

In the case of NO false ceiling is considered, the air-conditioning system is required to be designed before slab construction is started. Make sure:

1. To correctly identify the location and size of the cut outs for terminal filters. Mounting frames for terminal filters/terminal filter boxes should be grouted at the time of casting the slab.
2. To correctly identify the location and size of the cut outs for return air risers and inserts in the slab.
3. To correctly identify additional cut outs required for other MEP services.
4. To correctly determine the air handling equipment size and location that should be matched with the cut-out location and size.
5. To provide curbing at the perimeter of the cut outs to prevent water seepage into the working area.
6. To correctly provide floor drain locations for air handling units.
7. To consider water proofing in areas where air handling units are located.

Areas with False Ceiling: In the case of a false ceiling in the sterile area, the following points should be considered:

1. Inserts should be provided for false ceiling supports and mounting of filters.
2. To prevent fungus growth and eliminate air leakage, the false ceiling should be of NON-shedding variety, such as aluminum or PVC coated CRCA sheet.
3. False ceiling members should be designed to support part of the weight of terminal filters.
4. Proper sealing must be provided between panels and between filters and panels to avoid air leakage.

Ceiling Construction: The ceiling of the cleanroom is another potential location for contaminants to enter the clean zone. Pressurization of the cleanroom helps to prevent this; however this can lead to contaminants from the processes in the cleanroom being forced out into the area surrounding the cleanroom. To reduce the chance of this happening, the cleanroom ceiling is sealed. The type of seal is determined by the cleanliness class of the cleanroom.

HVAC REQUIRMENTS: Define the HVAC requirements system-wise and then room-wise. The requirements defined are: 1) room temperature, 2) relative humidity, 3) cleanliness level and 4) room pressure.

Room Temperature (T): Room temperature (T) is not critical as long as it provides comfortable conditions. Generally areas are designed to provide room temperatures from 67 and 77°F with a control point of 72°F. Lower space temperatures may be required where people are very heavily gowned and would be uncomfortable at "normal" room conditions.

Relative Humidity (RH): Relative humidity (RH) on the other hand, is of greater importance in all the production areas. While most of the areas could have a RH of 50 ± 5%, facilities designed for handling hygroscopic powders need to be at 30 ± 5%. Automatic control of the RH is essential for maintaining continued product quality. Control of humidity is necessary for personal comfort, to prevent corrosion, to control microbial growth, and to reduce the possibility of static electricity. We will discuss more about the RH control in the subsequent sections.

COOLING LOADS: Pharmaceutical buildings as a rule are totally enclosed without any fenestrations. This is to maintain a 'tight' building to minimize uncontrolled infiltration. As a result, the room sensible loads are essentially a contribution from process equipment, lighting and personnel. Fan heat from recirculating fans can also be a large heat contributor in clean spaces. The density of equipment loads is low excepting in the tablet manufacturing facility covering granulation, drying and tabletting.

Heat-loss calculations must also be made to determine heat loss through walls, roof, and floor. No credit should be taken for process heat gain in this calculation, since the process could be dormant and the space would still need to be maintained at proper temperature.

AIRFLOW SHEETS: Once the cooling load is determined, the next step is to calculate the dehumidified airflow using psychrometric analysis or computer analysis. These results are compared with airflow quantities required to establish the minimum air required to satisfy both the space cooling load requirements and air cleanliness classification.

The airflow sheets should be developed on full-size drawings and should show air quantities supplied, returned, and exhausted from each space. They also must show air transferred into and out of spaces, and, while quantities should be shown, they will probably require field modification to attain pressurization. The airflow sheet is a useful tool for transfer of information to the owner or user, for agency reviews, for transmission of information to HVAC designers, and for other engineering disciplines.

AIRFLOW PATTERN: The air distribution has to be appropriate with the class of cleanroom. Air turbulence in the space can cause particulates which have settled onto the floor and work surfaces to become re-entrained in the air. Air turbulence is greatly influenced by the configuration of air supply and return grilles, people traffic and process equipment layout.

The following measures are normally taken to control the air flow pattern and hence the pressure gradient of the sterile area:

1. Class 100 and lower zones must necessarily have unidirectional (laminar) flow with 100% HEPA

filter coverage in the ceiling or wall. Return must be picked up from the opposite side.

2. Air flow velocities of 90 rpm ±20 (70 rpm to 110 fpm) are recommended as standard design for Class 100 cleanroom systems.
3. The vertical down-flow configuration is preferred. Per EEC standards, laminar work station with vertical flow requires 0.3 m/s velocity whereas the horizontal work stations require 0.45 m/s velocity. When horizontal flow is used the work place must be immediately in front of the clean air source so that there is nothing in between which could emit or cause uncontrolled turbulence and consequent contamination.
4. Class 1000 and above are generally non-unidirectional with
5. Ceiling level and the return air at the floor level.
6. This air should be supplied at a much higher volume than its surrounding area ensuring a higher velocity and pressure in the clean zone relative to the perimeter.

Return Air System: The air return system is another critical component of the cleanroom air distribution system. The return points shall be positioned low down near the floor in the walls and spaced as symmetrically as building construction allows. Return grilles shall be made as long as convenient to increase the collection of dust particles over a larger area.

Return air grilles in the main sterile zones should be located to avoid dead air pockets. While locating the return grille, care should be taken to avoid placing the grille near a door opening into an adjoining lower pressure room. This is done to prevent creation of a low pressure zone near the door, thus preventing air leakage from the low pressure to high pressure room at the time of door opening.

On each return air riser manually operated dampers shall be provided for control. These dampers should preferably be operated from the non-sterile areas.

Mixed Areas: It is possible to create Class 100 space within Class 10,000 areas at background. For example, if a small localized operation in big Class 10,000 volume requires Class 100 standard, there is no point to put the entire area as Class 100. This will be very expensive. For such areas, install “localized laminar flow workstations”, which are commercially available in horizontal or vertical flow patterns generally recirculating within the clean space.

It is important to note that high air change rate (ACR) equate to higher airflows and more energy use. In most cleanrooms, human occupants are the primary source of contamination. Once a cleanroom is vacated, lower air changes per hour to maintain cleanliness are possible allowing for setback of the air handling systems. Variable speed drives (VSD) should be used on all recirculation air systems allowing for air flow adjustments to optimize airflow or account for filter loading. Where VSD are not already present, they can be added and provide excellent payback if coupled with modest turndowns. The benefits of optimized airflow rates are:

1) Reduced Capital Costs - Lower air change rates result in smaller fans, which reduce both the initial investment and construction cost. A 20 percent decrease in ACR will enable close to a 50 percent reduction in fan size.
2) Reduced Energy Consumption - The energy savings opportunities are comparable to the potential fan size reductions. According to the fan affinity laws, the fan power is proportional to the cube of air changes rates or airflow. A reduction in the air change rate by 30% results in a power reduction of approximately 66%. A 50 percent reduction in flow will result in a reduction of power by approximately a factor of eight or 87.5 percent.

Designing a flexible system with variable air flow can achieve the objectives of optimized airflow rates. Existing systems should be adjusted to run at the lower end of the recommend ACR range through careful monitoring of impact on the cleanroom processes.

PRESSURIZATION: Pressurization prevents the infiltration from adjacent spaces. Pressurization of clean areas is required to keep products from being contaminated by particulate and/or to protect people from contact with harmful substances by physical means or inhalation. This can be easily accomplished by supplying more air than the cumulative of what is returned, exhausted or leaked from the room.

The pressure gradients are monitored with 'U' tube manometers or magnahelic gauges. Alarm and warning systems may also be provided when the pressure gradients are disturbed.

Pressure Gradient: There should be a net airflow from aseptic rooms to the non-aseptic areas. This is possible only if there is pressure gradient between two adjacent rooms. Air always flow from high pressure to low pressure region. Pressure between two rooms is differential pressure “DP”.

With reasonably good building construction and airtight doors and windows, it is normally possible to achieve and maintain the following pressures between various zones.

Where major demarcations of pressure are required, air locks are used. These are small rooms with controlled airflows acting as barriers between spaces. It minimizes the volume of contaminated air that is introduced into the cleaner room when its door is opened…remember, with ZERO pressure differential and on open door, the entire

volume of the dirtier room can eventually find its way to the cleaner room. It is important that

- Doors open/close FAST (to minimize time of contamination). Both airlock doors should not be opened simultaneously.
- High air changes (high airflow or small volume room) to permit faster "recovery".
- People use smaller airlock (faster recovery time = less time to wait in airlock)

Table 1: Pressure gradients.

Atmosphere	0 Pa
Change rooms	25 Pa
Non-aseptic areas	25 Pa
Aseptic areas	
Cooling corridors	45 Pa
Access corridors	35 Pa
Manufacture laboratory	55 Pa
Filling rooms	55 Pa
Change rooms	25 Pa

The pressure differential exerts a force on the door. If the force is too great (0.15 in water/36 Pa), the door may not close fully or may be difficult to open. This is particularly important in large complex facilities where many levels of pressurization may be required. Many facilities now use sliding doors, and it is essential that the seals be carefully designed to allow minimum leakage and proper containment or pressurization.

Alarms that sound to indicate loss of pressurization are valuable features and essential in the HVAC design of critical areas.

Room Seals and Doors: In most facilities the openings around the doors between rooms are where leaks occur due to pressure differentials between rooms. In making rooms tight any room openings must be sealed with a proper sealant that will not promote growth of organisms and can be easily cleaned. Areas to be sealed include ceiling tiles, lighting fixtures, pipe penetrations, telephone outlet penetrations, and any cracks or openings that appear in the structure. A typical door would have the following dimensions and crack area at the perimeter: door size, 3 ft.wide by 7 ft high; cracks at top and sides, 1/8 in with an undercut of 1/4 in. The calculated area around the door is equal to 0.24 ft^2. To achieve 0.05 in water pressure differential across the door, approximately 215 CFM of airflow through the cracks is required. Door seals around the top and sides are usually made of closed cell neoprene and should generally be used to reduce the crack area. To reduce the undercut, a drop type seal, which is commercially available, should be used. The drop type is preferred to a wipe type, since it will not mar or leave residue on the floor. Air used for pressurization must be accounted for in system calculations. Air through cracks or openings is accounted for as transfer air and shown in the HVAC room balance table.

FILTRATION: Proper air filtration is crucial for cleanroom controls. In dusty production areas such as grinding, granulation, coating, tabletting etc., the filters not only control the atmosphere contamination but also hold the internally generated particulates.

Atmospheric dust is a mixture of dry particles, fibers, mist, smoke, fumes, live or dead organisms. The air-borne particle size varies from 0.01 micron to as much as 100 microns. Less than 2.5 micron particles are considered as fine and particles over 2.5 micron is regarded as "coarse". Fine particles are airborne for a longer time and could settle on vertical surfaces. Coarse particles, products of mechanical abrasion like in grinding and granulation departments, have lower airborne life time and are subject to gravitational settlement. The air conditioning systems in the pharmaceutical industry have to handle both fine and coarse particulates depending on the production pattern and the filter regime has to be appropriate.

Air Filters

- Air filters capture solid materials
- Can be "roughing" filter to capture a significant percentage of total mass (30%)
- Can be "high efficiency" to capture a higher percentage of mass, plus some of the "weightless" fine particles (85% - 95%)
- Can be "high efficiency particulate" to remove virtually 100% of the material weight and 99.97% or more of all particles

Terminal HEPA Filters: HEPA (High efficiency particulate air) filters have 99.97% to 99.997% removal efficiency on 0.3µ particles. In other words, only less than 0.03% of all particles of 0.3 microns or larger can get through such a filter. So if the return air contains 10,000 particles per ft^3, its concentration would be reduced down to three particles per ft^3 after it goes through the filter. Ultra low particulate air (ULPA) filters have 99.9997% removal efficiency on 0.12µ particles, but these are generally recommended for cleanliness lever of Class 10 and low (more cleaner classification), primarily for semi-conductor industry.

HEPA filters use sub-micron glass fiber media housed in an aluminum framework and are available in two types of constructions: 1) Box type and 2) Flanged type.

Box type filters are more suitable for housing within the ceiling slab cutout where removal of filter is from above. Whenever filter removal is not from above e.g. in case of filter being mounted in false ceiling, flange type of filters is required. With flange type of filters, additional housing is also required to facilitate the mounting of filters and transfer the load to false ceiling members. Aluminum / stainless steel slotted type protective grilles

can be provided under the terminal filters. The housing and grilles should be epoxy/stove enamel painted. Sealing of filters to frames is an installation problem and is best solved by using a filter frame with a gel-like seal into which the filter fits. The sealant selected should not promote growth of organisms and can be easily cleaned.

Pre-filters to HEPA Filters: In order to prolong the service life of HEPA filters, pre-filters are recommended to filter out majority of particles above 1 micron. However, dust holding capacity of these filters is poor. Therefore, in case the application requires a filtration system with good dust holding capacity, bag type filters with fiberglass scrim cloth media are recommended to give efficiencies ranging from 85% (down to 20 microns) to 99.97% (down to 5 microns).

Pre-filters are available in various sizes with 6" and 12" thickness and with pressure drop in the range of 0.2 to 0.25 inch- w.g. Pre-filters are normally mounted in a separate plenum with access door after supply air fan discharge at an appropriate location. Normally flanged filters are used for mounting in such plenums. It should be convenient to clean and replace these filters without disturbing the rest of the filtration system.

Roughing Filter: These filters are normally provided before the cooling coil in the air handling unit and at fresh air intakes. Efficiency of these filters is in the range of 80% down to 20 microns and they can be easily cleaned by washing.

Filter Testing: The efficiency of a filter is of paramount importance and must be measured in an appropriate way. The common tests on the filters include the dust spot test and DOP tests. The dust spot test is a measure of the ability of the filter to reduce soiling and discoloration. High efficiency filters are tested using Di-octyl Phthalate (DOP) method.

The DOP test is conducted by counting upstream and downstream particulates through a light scattering photometer or any other particulate counter.

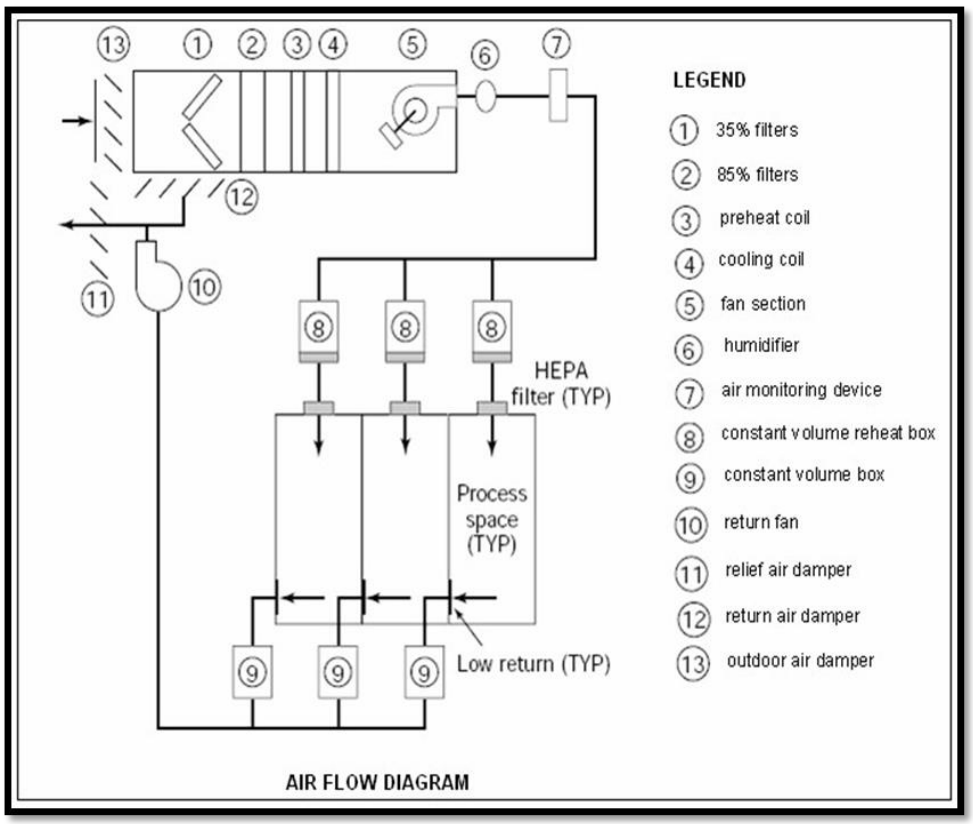

Figure-4: HEPA Filter.

- **HVAC EQUIPMENT SPECIFICATIONS**

Air Handling Unit: The air handling unit is Pharmaceutical HVAC's brain and performs major area conditioning functions. It consists of a filter, coils, and a fan section in a single casing. The casing is sealed and insulated to prevent leakage from and into the AHU. It also contains access doors and view ports for maintenance and inspection purposes.

Air handling unit (AHU) is one of the most important equipments in HVAC (heating, ventilation, and air-conditioning) system particularly in large-scale buildings for providing both heating and cooling for multiple zones. AHU operations not only significantly impact supply air temperature and humidity levels, but also the energy consumed for heating, cooling, and ventilation. It

is essential to implement measures to reduce energy consumption.

Two types of coil in an AHU are cooling and heating. Commonly, chilled water circulates in cooling coils and hot water in heating coils. When the supply air passes through the cooling coils, it lowers its temperature and, as a result, decreases the temperature of the serving area. Similarly, when supply air passes through the heating coil, it heats the air and, as a result, increases the temperature of the serving area. Air Handling Unit also contains filters for air purification. There can be different classifications of filters depending on the area requirement. Blowers in the AHU are used to create airflow. They can operate at varying speeds to create the desired airflow. These blowers can operate manually or automatically through the main controller. Sensors installed across different locations of AHU and in the area constantly monitor the airflow. The main controller immediately compensates for any difference in the required airflow.

The conditioned air from the HVAC flows through the ducting to the target area. If ducting is not designed carefully, it will disturb the characteristics of airflow and will also contaminate the conditioned air. The characteristics and cleanliness requirements of a particular area define the ducting's design and profile. AHU operations not only significantly impact supply air temperature and humidity levels, but also the energy consumed for heating, cooling, and ventilation. AHU oper- ations greatly affect building energy use, thermal comfort, and health of occupants. In addition, to control building ventilation intake, AHUS connect primary heating and cooling plants with building zones .To perform ventilation functions, various dampers are provided to connect to air ducts including return air duct, exhaust air duct, fresh air duct, and supply air duct.

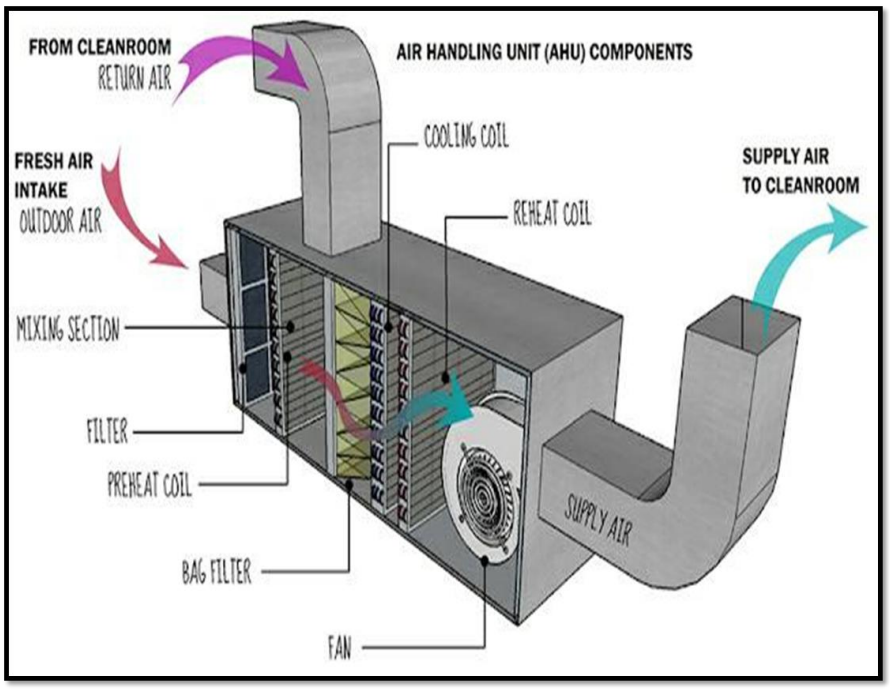

Figure-5: AHU.

COMPONENTS OF AHU

Filters - Air filtration is almost always present in order to clean dust-free air to the building occupants and to the core areas and manufacturing areas of pharmaceutical firms. Filtration is typically placed first in the AHU in order to keep all the downstream components clean. Depending upon the grade of filtration required the types of filters used are G-4, F-6, F-9 and H-13 hence, G-4 filter is cheaper to replace and maintain thus saving other expensive filters from getting replaced within short interval of time. The span of a filter maybe assessed by monitoring the pressure drop through the filter medium at design air volume flow rate. This is done by means of a visual display using a pressure gauge. Failure to replace a filter may eventually lead to its collapse, as the forces exerted upon it by the fan overcome its inherent strength, resulting in collapse and thus contamination of the air handler and downstream ductwork.

Heating & Cooling coils - Air handling units requires providing heating, cooling, or both to change the supply air temperature, and humidity level depending on the areas and the application. Such conditioning is provided by heating and cooling coils within the air handling unit air stream; such coils are directly influenced to the medium providing the heating or cooling effect. Coils are typically manufactured from copper for the tubes, with copper or aluminum fins to assist heat transfer. Cooling coils will also employ eliminator plates to remove and drain condensate water. The hot water is provided by hot water generator and the chilled water is provided by chiller. Downstream temperature sensors are typically

used to monitor and control "off coil" temperatures, in conjunction with an appropriate motorized control valve prior to the coil. Dehumidifier is required, and then the cooling coil is used to over-cool so that the dew point is reached and condensation occurs. A heater coil placed after the cooling coil re-heats the air to the desired supply temperature. This has the effect of reducing the relative humidity level of the supply air. During colder climates, where winter temperatures regularly drop freezing point, then heating coils are often used as a first stage of air treatment to ensure that downstream filters or chilled water coils are protected against freezing. The control of the chilled

Humidifier - Humidification is often necessary in colder climates where continuous heating will make the air drier, resulting in uncomfortable air quality and increased static electricity.

Blower fan - Air handling units generally employ a large squirrel cage blower driven by an AC induction electric motor to suction the air. The blower is driven by a Variable Frequency Drive to allow a wide range of air flow rates. Flow rate is controlled by inlet vanes or outlet dampers on the fan.

Vibration isolators - The blowers in an air handling unit can create substantial vibration and the large area of the duct system would transmit this noise and vibration to the occupants of the building situated in the core and manufacturing areas of pharmacy plant. To avoid this, vibration isolators or damper block are normally inserted into the duct immediately before and after the air handler and often also between the fan compartment and the rest of the AHU. The rubberized canvas-like material of these sections allows the air handler components to vibrate without transmitting this motion to the attached ducts. The fan compartment is further isolated by placing it on a spring suspension, which will palliate the transfer of vibration through the floor.

Humidifiers - In drier locations, makeup air may require the addition of moisture for RH control. There are many commercially available humidifiers, but the most commonly used is "steam grid" humidifier. These are controlled by modulation of a steam valve at the humidifier, and include a chamber to prevent condensation and water droplets in the duct. The valve is controlled by a signal located in the return or exhaust airstream or in a room humidistat. A high-limit stat is placed in the duct downstream of the humidifier to override the controlling stat and prevent condensation in the duct. Placement of the humidifier in the duct is critical and must follow the manufacturer's recommendations to prevent condensation and provide proper dispersion space. It is important to use clean steam, not plant steam, which may contain boiler chemicals and impurities from deteriorating piping and equipment.

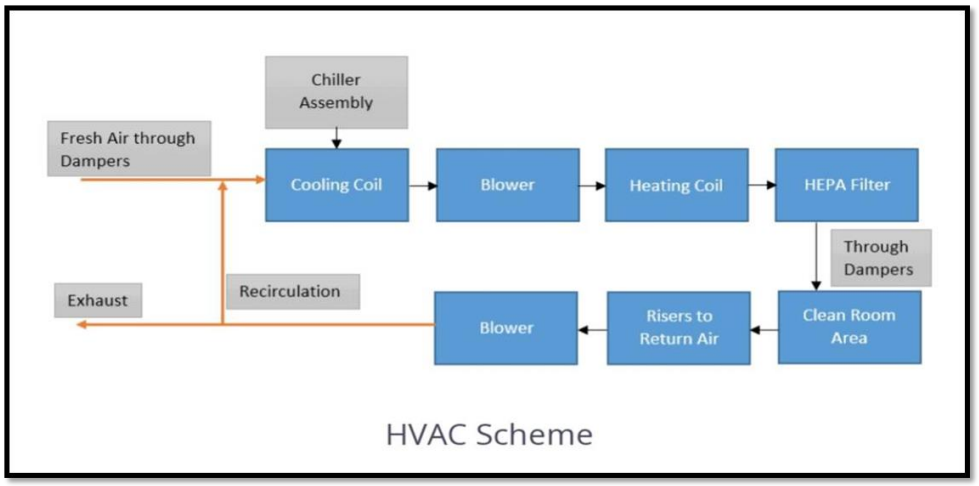

Figure-6: HVAC scheme.

Ductwork Design, Materials & Cleanability

Duct Pressures: Ductwork in pharmaceutical facilities tends to have higher system pressure due to extensive use of filters, volume control devices, and physically complex arrangement.The duct system pressures must be calculated and clearly stated on the contract documents to allow the fabricator to provide the proper metal thickness and construction methods for the required system pressures. System pressures will also change as the system is operated with filters that get dirty or space pressure conditions that vary. Duct systems must allow for these pressure fluctuations and the fans may require speed controls, inlet vanes, or variable pitch blades to match the varying flow and pressure conditions.

Duct materials and shape: Unlined galvanized steel, stainless steel or aluminum ductwork is used in rectangular, round, and elliptical (or flat oval) configurations for the majority of the systems. Round ducting is a natural choice, being self cleaning in shape, wherever space permits.

Because galvanized duct can flake off or rust, it should not be used downstream of the HEPA filters to avoid contamination from the duct system itself. When the HEPA filter is located upstream of the room terminal and a long run of duct is present, the material of choice for the duct is stainless steel, but this is expensive and its use should be minimized. Many systems may also be fumigated or cleaned in place, and the duct material chosen should not be affected by the cleaning agent.

Cleanability: Clean ability of duct systems is important to ensure that if an installed system gets dirty or contaminated it can be cleaned. In the design stage care must be taken to locate access doors in the duct, where they can be easily reached without compromising a process or violating a controlled space. All sealed duct shipped to the site should have only end seals broken, and then quickly resealed, during final installation. In very critical applications the duct is factory cleaned and sealed before shipment to the site. This step removes the oil and other contaminant present during duct construction but is expensive. It may be difficult to find sheet-metal fabricators willing to do this work, since they are not always set up for such procedures.

Following precautions should be taken:

1. Ducts should be sealed with silicone sealant at longitudinal joints in order to make the system airtight. Rubber gaskets should be used at transverse joints.
2. GI flanged joints must be avoided and instead pocket slips or angle iron flanged joints should be used.
3. No acoustic insulation should be provided inside the ducts.
4. Dampers provided in the system should be of compatible duct materials and should have extended handle to accommodate insulation thickness.
5. Return air risers should be designed for velocities not exceeding 1800 fpm with a minimum velocity of 1200 fpm at the highest point in order to carry particulate matter along with return air. However, the inlet velocity at the return grille should be in the range of 300 to 400 fpm gradually increasing the same to 1200 to 1800 fpm.
6. Grilles and diffusers should be flush mounted into ceiling, walls or duct work and all such grilles shall be fabricated from stainless steel or stove enamel/epoxy coated construction.
7. Whenever terminal filters are mounted in the false ceiling, proper sealed access door should be provided to reach the dampers above each filter.

Sequence of Operations: The first element in the design of the system is the development of a sequence of operation, which is a written description of the HVAC and related systems operation. A separate sequence is usually written for each air handling system, describing the complete operation of the system from control of coils and humidifiers to control of the room temperature and humidity. Starting and stopping of the air handling unit fans is outlined, along with interlocking of exhaust or return fans in relation to the main air system fan operation. Generally all fans operate at the same time, which is necessary to maintain pressurization. The sequence also addresses abnormal occurrences such as a smoke detection alarm or failure of an exhaust fan. The sequence describes what happens to system components during an abnormal occurrence. It may be necessary to shut a supply fan down if a major exhaust fan should fail to prevent or minimize the loss of pressurization. The sequence also describes any energy management strategies to be included in the system, such as a night temperature setback or reduced ventilation and exhaust rates during unoccupied periods.

TESTING, BALANCING, AND CLEANING: For pharmaceutical facilities, establishing pressure differentials between adjacent spaces is the most critical and is very tedious to balance. These differentials are obtained by adjusting airflows, smoke tests, taking pressure readings, and setting controls. This effort can take some time as each facility is different and each room has different leakage characteristics that affect pressurization.

VALIDATION: NO production can start until the cleanroom is validated. When a pharmaceutical facility is to be validated, the validating agency will peruse the HVAC documentation and should communicate with the design engineers to establish the validation protocol as it relates to the HVAC system. If the design is proper, the system is properly installed, and the components perform as specified, the systems should be easily validatable. The validator will follow a master plan and protocols to verify the actual system installation and operation against design values and intent. The physical parameters reported by the BMS system shall be verified by measurements using calibrated instruments to verify accuracy.

DOCUMENTATION: Good manufacturing practices govern the level of control of various parameters for quality assurance, regulating the acceptance criteria, validation of the facility, and documentation for operation and maintenance. The documentation should cover design, operation and performance qualifications of the system.

Design Qualification: The design qualification document should cover all the following issues:

1. Identification of various systems, their functions, schematics & flow diagrams, sensors, dampers valves etc., critical parameters & fail-safe positions.
2. Layout plans showing various rooms & spaces and the critical parameters like:

- Room temperature
- room humidity
- Room pressures and differential pressures between room and room and passages

- Process equipment locations and power inputs
- Critical instruments, recorders and alarms, if any

3. Equipment performance and acceptance criteria for fans, filters, cooling coils, heating coils, motors & drives.
4. Duct & pipe layouts showing air inlets, outlets air quantities, water flows and pressures.
5. Control schematics and control procedures.

- **THE IMPORTANCE OF HVAC SYSTEMS FOR THE PHARMACEUTICAL INDUSTRY**

1. Modern diagnostic machines need to operate within very strict temperature and humidity tolerances so that the integrity of powdered and fluid reagents is not comprised. The consequences of a misdiagnosis or false reading from the introduction of unanticipated moisture, for example, could be serious for both patient and medical provider alike. Customized HVAC units that ensure stable environmental conditions—whether cold, hot, or dry—and integrate well into often limited space, are key pieces of an effective diagnostic process.
2. Moisture can be one of the worst enemies of modern medicine production. In every phase of production—from milling to compounding to coating—excess moisture can cause manufacturing inefficiencies, weaken the medicine's effect, or in the worst-case scenario, completely ruin an entire batch of product. Specialized HVAC units that enforce a specified dew point based on the application all but guarantee that there will be no excess moisture from the air to cause production issues.

CONCLUSION

The main reason why each pharmaceutical industry strives to have a working HVAC system is to ensure that the quality of the products they manufacture is not to be compromised. Also, the manufacturing process sometimes includes emission of harmful by-products such as gases, This is controlled by these systems through proper ventilation. With that in mind, we can say that working HVAC systems are part of upholding the health and safety of operators as well as to provide comfortable working zone.

HVAC is Heart of Pharmaceutical Industries that purify the outside air and circulate all over the areas, it also provides desired temperature as well as humidity and pressure, HVAC system provide specific set of environment condition which required to make quality product therefore it must be validated periodically.

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