Serum Institute, Pune is India's largest vaccine manufacturer

Role of HVAC in a Vaccine Manufacturing Plant

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Introduction

Air, whether it is from outside or re-circulated within the area, acts as a vehicle for bacterial and gaseous contaminants brought in by the movement of people, material, etc. Since many of these air-borne contaminants are harmful either to products or people working in such environments, their removal is necessary on medical, legal, social and financial grounds.

Pharmaceutical facilities are closely supervised by the Food and Drug Administration (FDA), which requires manufacturing companies to conform to current Good Manufacturing Practices (cGMP). These regulations, which have the force of law, require manufacturers, processors and packagers of vaccines to take proactive steps to ensure that their products are safe, pure, and effective.

The cGMP for HVAC services embraces a number of issues starting with the selection of building materials and finishes, the flow of equipment, personnel and products, determination of key parameters like temperature, humidity, pressures, filtration, airflow parameters and classification of clean rooms. It also governs the level of control of various parameters for quality assurance, regulating the acceptance criteria, validation of the facility and documentation for operation and maintenance.

What can HVAC do?

HVAC system performs four basic functions:

1. Control air-borne particles, dust and micro-organisms: Through air filtration using high efficiency particulate air (HEPA) filters.
2. Maintain room pressure (ΔP): Areas that must remain 'cleaner' than surrounding areas must be kept under 'positive' pressurization, meaning that air flow must be from the cleaner area towards the adjoining space (through doors or other openings) to reduce the chance of airborne contamination. This is achieved by the HVAC system providing more air into the cleaner space than is removed from the same space in the form of return air, exhaust air and leakage.
3. Maintain space moisture (Relative Humidity): Humidity is controlled by cooling air to its dew point temperature or by using desiccant dehumidifiers. Humidity can affect the efficacy and stability of drugs and is sometimes important to effectively mould the tablets.

About the Author

Kedar Gokhale is a mechanical engineer with 21 years of experience in field projects and engineering for biotech and pharmaceutical industries. He is responsible for all the domestic and international projects of Serum Institute of India, the largest manufacturer of human vaccines. He is also responsible for maintenance and engineering of all the running facilities.
He has been handling multiple EPCV projects, and has created state-of-the-art facilities for various products including human vaccines, MABs, blood plasma products and large volume parenteral drugs, approved by regulatory agencies.

continued on page 70

continued from page 68

4. Maintain space temperature: Temperature can affect production directly or indirectly by fostering the growth of microbial contaminants on workers. HVAC system will take care of the heat load generated by people and the equipment in the clean room and maintain the desired temperature.

Each of above parameter is controlled and evaluated in the light of its potential to impact product quality.

While designing the air conditioning system for a vaccine manufacturing plant, it is very important to study the application, identify various factors affecting the particulate count and decide the level of contamination that can be permitted.

What is Particulate?

Simply stated, airborne particles are solids suspended in the air. The size of contaminants and particles is usually described in microns; one micron is one-millionth of a meter. In English units one micron equals 1/25,400 inch. To give a perspective, a human hair is about 75-100 microns in diameter.

Air, whether it is from outside or re-circulated, acts as a vehicle for bacterial and gaseous contaminants brought in by the movement of people, material, etc. There are two main sources of particulates: external and internal sources.

External sources consist of the following:

- Outside make-up air introduced into the room; this is typically the largest source of external particulates.
- Infiltration through doors, and other penetration through the clean room barriers.

Control action for external sources comprises of:

- Make-up air filtration.
- Room pressurization.
- Sealing of all penetrations into the space.

Internal sources consist of the following:

- People in the clean area: people are potentially the largest source of internally generated particulates.
- Cleanroom surface shedding.
- Process equipment.
- Material ingress.
- Manufacturing processes.

Control action for internal sources comprises of:

- Design of airflow path to shield humans from surroundings.
- Use of air showers to continually wash occupants with clean air.
- Use of hard-surfaced, non-porous materials such as polyvinyl panels, epoxy painted walls and glass board ceilings.
- Proper gowning procedures and head wear.

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

Fact File – Serum Institute of India

Founded in 1966 in Pune.
Manufactures life-saving immuno-biologicals.
Major producer of tetanus anti-toxin, anti-snake venom serum, DPT (Diphtheria, Pertussis and Tetanus) group of vaccines, hepatitis B and MMR (Measles, Mumps and Rubella) group of vaccines.
World's largest producer of Measles, DPT and Pentavalent vaccine.
Vaccines used in 140 countries across the world.
Recently set up Serum Bio Pharma Park, India's first biotech Special Economic Zone.

Air Conditioning System Design in Vaccine Manufacturing Plant

Design Objectives

Within the vaccine manufacturing facility, there are some basic requirements which 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, i.e. its temperature and relative humidity should be controlled and air pressure regulated.
- Contamination due to air borne particles should be controlled by an efficient filtration system.
- Contamination generated within the sterile area, for instance from people, must be contained and removed before it can cause any harm, by carefully selecting the air flow pattern.
- Effective monitoring of conditions in the system must be carried out from time to time to ensure that the right conditions are being maintained for the manufacturing process. It is important to understand that the design and function of the pharmaceutical manufacturing area forms a significant part of Good Manufacturing Practices (GMP), these being the requirements laid down by governmental agencies like the FDA and followed by most of the pharmaceutical companies.

Design Methodology

Based on several years of experience in the design and installation of HVAC systems, it is possible to use a systematic approach to the design of clean rooms for the vaccine industry. This step by step approach is briefly as follows:

- Analyse the production process, especially the flow of materials and personnel. This helps to define the activities in the various rooms and group the rooms having similar environmental requirements.
- Define the HVAC requirements system-wise and then room-wise. The requirements defined are:
  - Cleanliness level
  - Room temperature, relative humidity
  - Room pressure
  - Air movement direction
- Carry out detailed heat load calculations room-wise, taking into account fresh air quantity requirements.
- Air handling system design and selection.
- Prepare air flow diagrams based on the above mentioned load calculations and room pressure requirements.
- Develop detailed layouts, after preparation of design specifications and any specific requirements. *Figure 1* is an air flow diagram of a typical sterile system.

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

- Building construction and layout design

continued on page 72

continued from page 70

- Air handling system
- Selection of air flow pattern and pressurisation of rooms
- Fresh air quantity
- Duct system design and construction
- Selection, location and mounting of filtration system
- Defumigation requirement
- Performance qualification and validation
- Documentation

Since we are engaged in supplying vaccines to WHO and UNICEF, it is mandatory to get the vaccine manufacturing facility audited and approved by European authorities.

European Community defines clean rooms in Grades A, B, C and D. The classification is given on two different conditions: 1) At-Rest and 2) In-Operation

At-Rest state of clean rooms is the condition where the production equipment is installed and operating but without any operating personnel.

In-Operation state of clean rooms is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

Table 1: Maximum permitted number of particles per m³

Grade	At Rest		In-Operation	
	Maximum permitted number of particles per m³ equal to or above 5 micron	Maximum permitted number of particles per m³ equal to or above 0.5 micron	Maximum permitted number of particles per m³ equal to or above 5 micron	Maximum permitted number of particles per m³ equal to or above 0.5 micron
A (Laminar airflow workstation)	3,500	0	3,500	0
B	35,000	0	350,000	2,000
C	350,000	2,000	3,500,000	20,000
D	3,500,000	20,000	Not defined	Not defined

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 at-rest and in-operation condition.

Typical examples of Grade A: Essentially this covers areas where vaccine filling, stoppering and sealing is taking place.

Typical examples of Grade B : Areas like aseptic preparation, aseptic change rooms and solution preparation comes under this grade.

Typical examples of Grade C and Grade D : These are less critical areas like change rooms, washing areas, material entry and outer corridor.

Basic HVAC Systems

1. Once-through Air: Air is conditioned, enters the space and is discarded. Normally this type of system is used in animal houses, or where there is high potential of cross contamination.
2. Re-circulated Air: Air is conditioned, enters the space and a portion is reconditioned. Some may be discarded. This is an economical HVAC design.

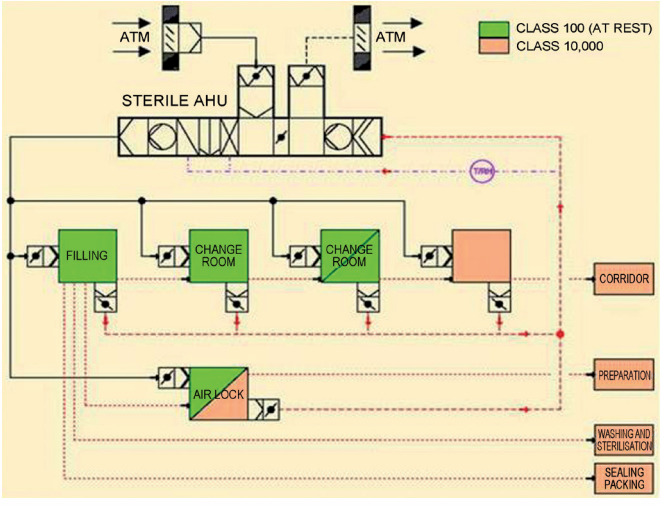

Figure 1: Typical airflow diagram for sterile area

HVAC 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 stakeholders. 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.

Air Changes

Air change rate is a measure of how quickly the air in an interior space is replaced by outside (or conditioned) air. For example, if the amount of air that enters and exits in one hour equals the total volume of the clean room, the space is said to undergo one

continued on page 74

continued from page 72

air change per hour. Air flow rate is measured in appropriate units such as cubic feet per minute (cfm) and is given by:

Air flow rate = air changes x volume of space/ 60

The normally accepted air change rates for both sterilized and non-sterilized areas are given in *Table 2*.

Table 2: Air change rates for sterilized and non-sterilized areas

Class	ACH	% HEPA Coverage	Air Velocity (fpm)
100,000	< 20	10 - 20%	5 -10
10,000	<40	20 - 40%	10 - 20
1,000	<60	40 – 60%	25 - 35
100	<150	80-100%	70-110

Pressurization

Pressurization prevents infiltration from adjacent spaces. Pressurization of clean areas is required to keep products from being contaminated by particulates and 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.

Filtration

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

Atmospheric dust is a mixture of dry particles, fibers, mist, smoke, fumes and live or dead organisms. 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 are 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. 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.

Terminal HEPA Filters

High Efficiency Particulate Air (HEPA) 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 level of Class 10 and cleaner classification primarily for the semi-conductor industry.

Testing, Cleaning and Validation

For any vaccine manufacturing facility, establishing pressure differentials between adjacent spaces is the most critical and 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.

No production in vaccine facility can start until the clean room is validated. When a vaccine facility is to be validated, the validating agency will peruse the HVAC documentation and communicate with 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 validable. The validator will follow a master plan and protocols to verify the actual system installation and operation against design values and intent. Physical parameters reported by the BMS system will 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.

Conclusion

HVAC systems in manufacturing facilities are closely supervised by the FDA and must meet other global current good manufacturing practices (cGMP). As per US GMP, *Design and Construction Features Standard 211.42*, sterile area cleanrooms have the following distinct characteristics:

1. Air is of a high microbial quality.
2. Air handling system is provided with a central HEPA filter bank along with mandatory terminal filters in order to extend the life of terminal filters.
3. The filtration regime is generally three stages with two stages of pre-filters, 10 micron (EU 4), 3 micron (EU 8) and one central final filter 0.3 micron (EU 12) along with terminal HEPA filter.
4. All sterile critical operations are in a laminar flow work station.
5. Critical areas have a positive pressure differential relative to adjacent less clean areas: a positive pressure differential of 0.05 inch of water (12.5 Pa) is acceptable.
6. Supply air outlets are provided flush at the ceiling level with perforated stainless steel grilles and terminal absolute filters. Return air grilles are provided at the floor level with a return air riser for better scavenging.
7. Walls, floors, and ceilings for cGMP areas are constructed of smooth, cleanable surfaces impervious to sanitizing solutions and resistant to chipping, flaking, and oxidizing.

Maintaining proper pressurization gradient between adjacent spaces is important to prevent infiltration and cross-contamination. Air filtration techniques and air conditioning components should be constantly monitored and upgraded in order to improve the finished product and reduce energy consumption.

Remember, overstating quality requirements and tolerances may result in unnecessary costs. Higher air flows and pressures require more HVAC capacity. Since most engineering decisions will have an impact on HVAC systems, it is important to recognize opportunities to seek the best engineering solutions. ❖