

HVAC Control System Requirements for the Biotech Industry



Industry Requirements - Introduction

Good Manufacturing Practices (GMP) regulations require that manufacturers, processors, and packagers of drugs to take proactive steps to ensure that their products are safe, pure, and effective.

GMP regulations require a quality approach to manufacturing, enabling companies to minimize or eliminate instances of contamination, mix ups, and errors.

All GMP's have one common theme.....

“CLEANLINESS, CLEANLINESS and CLEANLINESS”

| Country | Standards |
|--------------------|---|
| United States | Federal Standard 209, Code of Federal regulations CFR 210 & 211 |
| European Community | "Guide to Good Manufacturing Practice for Medicinal Products" |
| United Kingdom | BS 5295 |

The GMP for HVAC services embraces 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 cleanrooms.

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.

Industry Requirements – 21 CFR Part 11

By affirming that electronic records and signatures are equally as legitimate as paper records and handwritten signatures, Part 11 has given companies the opportunity to automate and streamline manufacturing and quality processes.

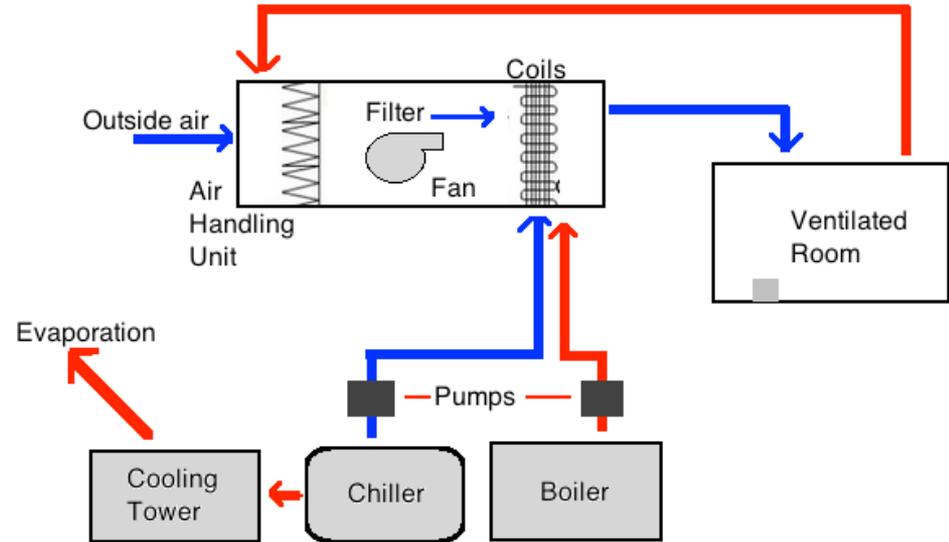
1. Authenticity of electronic records - A system that offers the ability to delineate user permissions for every document vault in the system. The system must also be able to generate an audit trail for any captured document.
2. The potential for a signer to repudiate an approval must be minimized - Users to enter two passwords to approve any type of document collaboration, one password for login and another for approval.
3. Electronic system must be validated - An electronic system with a proven track record of performance and validation can drastically reduce the time and money a company devotes to its overall validation efforts.
4. All users who have been approved to use the electronic system must be sufficiently trained to perform their assigned duties - A system that incorporates automated training capabilities and provides automatic triggers when an essential quality document is revised. A system with a proven training component should also be able to automate the follow-ups and escalations of past-due training tasks as well as create audit trails for all training data.
5. Document controls must provide revision controls, change controls, and time-based system modifications.
6. Signed electronic records include the following data: name, date and time of signing, and meaning of signature.
7. Electronic (and handwritten) signatures must be able to be linked to their corresponding electronic records.



Industry Requirements – HVAC Systems

HVAC system performs four basic functions:

1. Control airborne particles, dust and micro-organisms – Thru air filtration using high efficiency particulate air (HEPA) filters.
2. Maintain room pressure (delta P) – Areas that must remain “cleaner” than surrounding areas must be kept under a “positive” pressurization. This is achieved by the HVAC system providing more air into the “cleaner” space than is mechanically removed from that same space.
3. Maintain space moisture (Relative Humidity) – Humidity is controlled by cooling air to dew point temperatures or by using desiccant dehumidifiers.
4. Maintain space temperature - Temperature can affect production directly or indirectly by fostering the growth of microbial contaminants on workers.



Industry Requirements – HVAC Systems

In designing the air-conditioning system for pharmaceutical plants, 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?

Airborne particles are solids suspended in the air, acting as a vehicle for bacterial and gaseous contaminants brought in by the movement of people, material, etc.

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.

| Particulate Sources | Description | Control Actions |
|---------------------|--|--|
| External | <ul style="list-style-type: none"> • Outside make-up air introduced into the room | <ul style="list-style-type: none"> • Make-up air filtration • Room pressurization • Sealing of all penetrations into the space |
| Internal | <ul style="list-style-type: none"> • People in the clean area • Cleanroom surface shedding • Process equipment • Material ingress • Manufacturing processes | <ul style="list-style-type: none"> • Design airflow path to shield humans from surroundings • Use of air showers • Using hard-surfaced, non-porous materials • Proper gowning procedures |

Industry Requirements – Cleanrooms

A cleanroom is defined as a room in which the concentration of airborne particles is controlled.

Cleanroom classifications are established by measurement of the number of particles 0.5 micron and larger that are contained in 1 ft³ of sampled air.

| U.S FEDERAL STANDARD 209E | | | | | |
|---------------------------|---------|----------------|-----------------|----------------|-----------------|
| Class Names | | Class Limits | | | |
| | | 0.5 Micron | | 5 Micron | |
| SI | English | m ³ | ft ³ | m ³ | ft ³ |
| M 3.5 | 100 | 3,530 | 100 | - | - |
| M 4.5 | 1,000 | 35,300 | 1,000 | 247 | 7 |
| M 5.5 | 10,000 | 353,000 | 10,000 | 2,470 | 70 |
| M 6.5 | 100,000 | 3,530,000 | 100,000 | 24,700 | 700 |

| Comparison of US Federal standard 209E v/s EEC | |
|--|----------------|
| Class 100 | Grades A and B |
| Class 10,000 | Grade C |
| Class 100,000 | Grade D |

Industry Requirements – Cleanrooms

EUROPEAN COMMUNITY GUIDELINES

| Grade | At Rest | | In Operation | |
|------------------------------------|---|---|---|---|
| | 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 | Maximum permitted number of particles per m3 equal to or above 5 micron |
| A (Laminar Airflow Workstation) | 3500 | 0 | 3500 | 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 |

- “At –Rest” - ‘state of cleanrooms is the condition where the production equipment is installed and operating but without any operating personnel.
- “In- Operation” - state of cleanrooms is the condition where the installation is functioning in the defined operating mode with the specified number of personnel working.

There are generally two air supply configurations used in cleanroom design:

1. Non-unidirectional
2. Unidirectional.

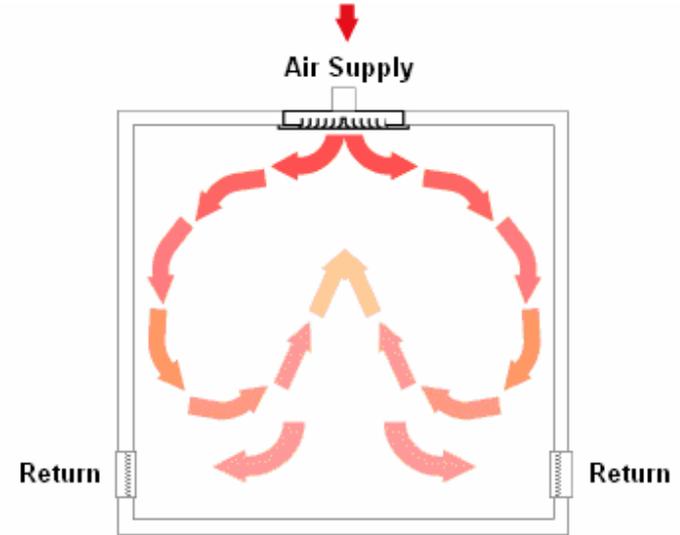
Non-unidirectional air flow

The 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:

1. 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.
2. 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.



Non-Unidirectional Air Flow Pattern

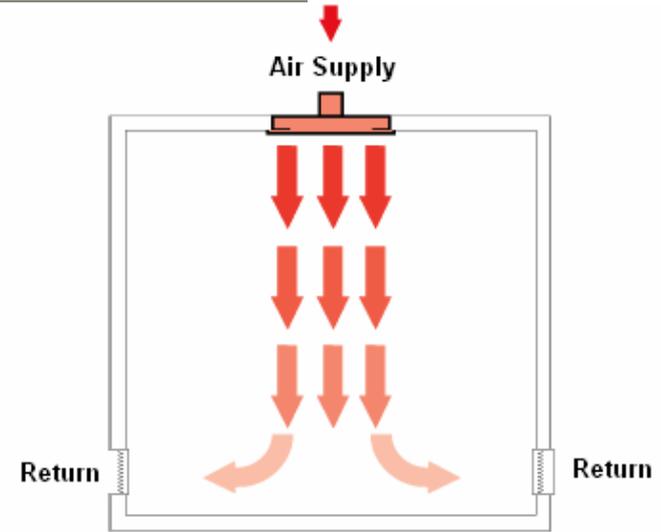
Unidirectional air flow / Laminar airflow

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.

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.



Unidirectional Air Flow Pattern (Vertical)

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

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.

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:

1. A written basis of design is produced that describes the regulations and codes that will govern the design
2. Spaces are defined by function, and temperature and humidity requirements are determined
3. Room classifications are listed and adjacency of spaces and pressure relationships are documented
4. 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
5. Alternate studies are conducted to compare options for the HVAC system
6. 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
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. Defumication requirement
10. Commissioning, performance qualification and validation
11. Testing and validation
12. Documentation

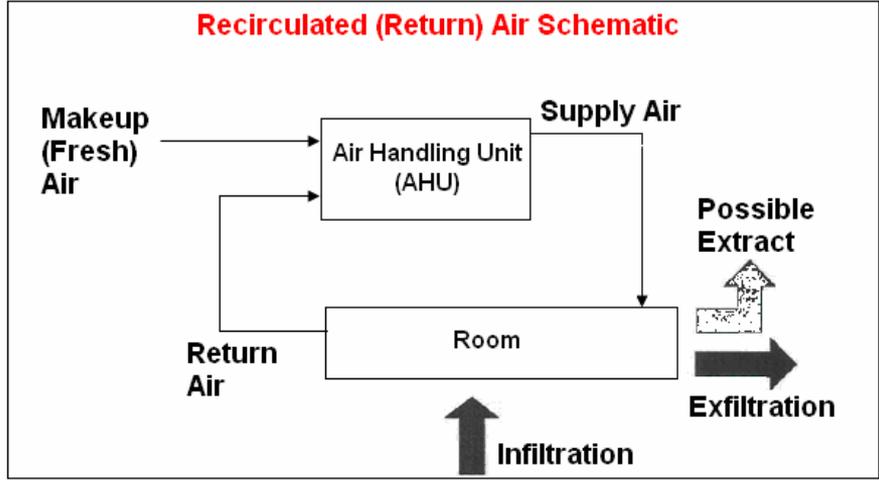
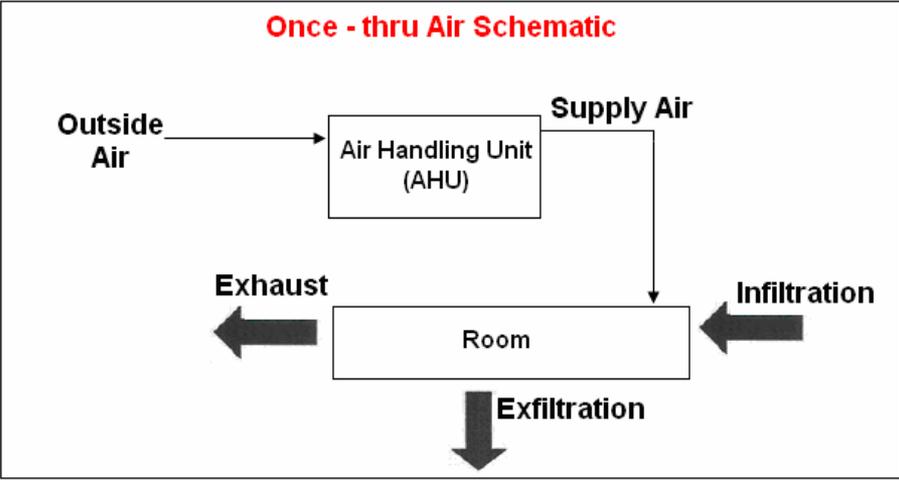
System Design – HVAC Requirements system-wise and room-wise

The requirements defined are:

1. Room temperature - Room temperature (T) is not critical as long as it provides comfortable conditions
2. Relative humidity - Relative humidity (RH) on the other hand, is of greater importance in all the production areas. 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.
3. Room pressure - Cleanroom positive pressurization is desired to prevent infiltration of air from adjacent areas.
4. Cleanliness level - Of all the design goals, it is the quality of air cleanliness of the space and prevention of contamination which are of utmost importance. Externally generated particulates are prevented from entering the clean space through the use of proper air filtration.

| Room Pressure Differential (DP) | | | |
|--|----------------------|-------------------------|-----------------------------|
| Operation | Parameters | United States | European Economic Community |
| Non-sterilized product or container (U.S : Controlled Area) | Space pressurization | 0.05 inch-w.g | Positive |
| Sterilized product or container (U.S: Critical Area) | Space pressurization | 0.05 inch-w.g or higher | Positive |

| | <u>Once –thru Air</u> Air is conditioned, enters the space and is discarded | <u>Recirculated Air - Air is conditioned, enters the space and portion is reconditioned. Some may be discarded.</u> |
|--|---|---|
| What are the advantages of this system? | <ol style="list-style-type: none"> 1. Fresh air – lots of it 2. Can handle hazardous materials, although will need to clean up air leaving the space 3. Exhaust duct is usually easy to route as high velocity = smaller diameter | <ol style="list-style-type: none"> 1. Usually less air filter loading = lower filter maintenance and energy cost 2. Opportunity for better air filtration 3. Less challenge to HVAC = better control of parameters (T, RH, etc) 4. Less throw-away air = lower cooling/heating cost |
| Disadvantages | <ol style="list-style-type: none"> 1. Expensive to operate, especially when cooling and heating 2. Filter loading very high = frequent replacement 3. Potential need for dust collection/scrubbers/cleanouts | <ol style="list-style-type: none"> 1. Return air ductwork routing to air handler may complicate above ceiling 2. Chance of cross contamination = requires adequate supply air filtration (an sometimes return air filtration) |
| Applications | <ol style="list-style-type: none"> 1. Labs with hoods, potential hazards 2. Bulk Pharmaceutical Chemical (API) plants handling flammable materials 3. Oral Solid Dosage (OSD) plants where potent products/materials exposed 4. Where high potential of product cross-contamination – segregation 5. Some bio API facilities with exposed potent materials | <ol style="list-style-type: none"> 1. Classified spaces such as sterile manufacture (few airborne materials, very clean return air) 2. Finished oral solid dosage (OSD) manufacture where product is not airborne with other products in the facility 3. Final bulk APIs, usually with dedicated air handler for each room |

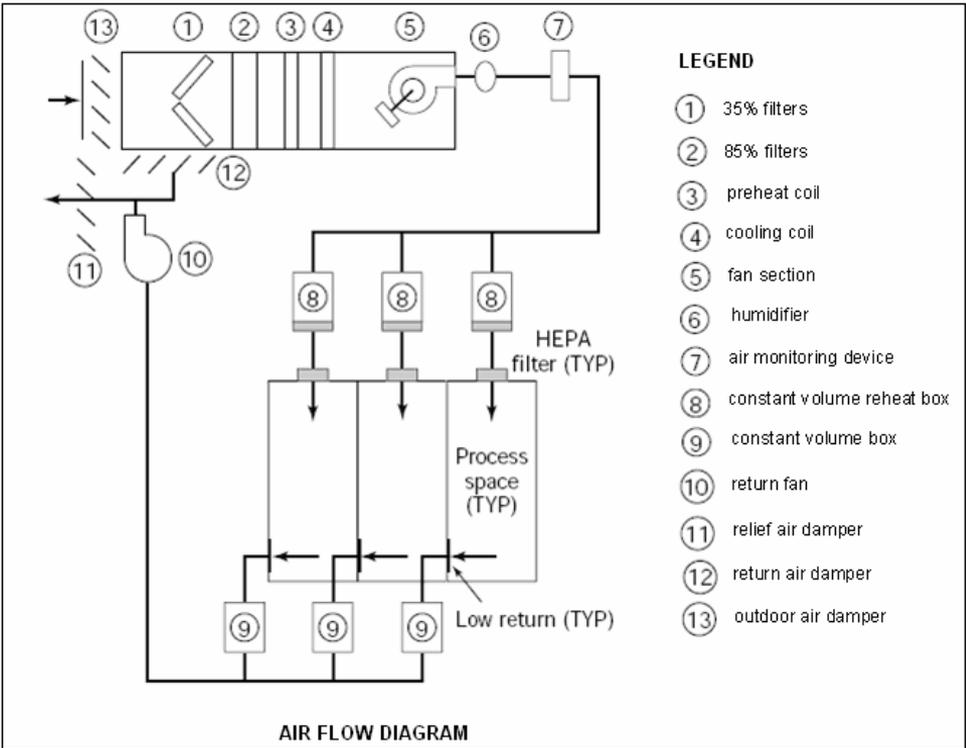


System Design – Basic HVAC Systems

Constant Volume Systems

The most reliable system for pharmaceutical manufacturing areas is constant volume system with terminal reheat (CVRH). This is because; ensuring constant pressure gradient between the adjacent areas is of prime importance.

In a terminal reheat system the air leaving the cooling coil is set at a fixed temperature, and the terminal reheat responds to a space thermostat, turning on heat to satisfy the load. This can waste energy, since air is cooled and then reheated. Many energy codes prohibit this practice for comfort applications, however, where close control of temperature and humidity is required for process areas the energy conservation requirement is waived. The advantages of reheat systems are that humidity is always controlled (since dehumidification always takes place at the cooling coil) and each space or zone that needs temperature control can easily be accommodated by adding a reheat coil and thermostat. Another advantage of the CVRH system is that airflow is constant, which makes balancing and pressurization easier to main maintain. A reheat system is probably the simplest and easiest of all systems to understand and maintain.



Variable Air Volume Systems

A variable air volume (VAV) system is generally used in administrative areas and some storage spaces where pressure control is not critical, humidity control is not essential, and some variations in space temperature can be tolerated.

The VAV system works by delivering a constant temperature air supply to spaces with reductions in airflow as cooling loads diminish.

This eliminates the energy used for reheat and saves fan energy, because the total amount of air moved is reduced.

Some form of perimeter heating must be supplied for spaces with exterior walls or large roof heat losses.

The perimeter heating can be baseboard radiation or some form of air heating using heating coils.

Finned radiation or convection heating devices should not be used in clean spaces, since they are not easily cleaned and allow places for unwanted particulate buildup.

Combinations of systems can be used, especially if variable quantities of supply and exhaust air are required for fume hoods or intermittent exhausts.

The automatic control system that controls and monitors the HVAC system is called:

- Automatic temperature control system (ATC)
- Energy management and control system (EMCS)
- Building automation system (BAS)
- Building management system (BMS)

The control system of choice for major facilities, and even for some small systems, is a direct digital control (DDC) system

The systems are computer based and have the ability to communicate within and outside the system by coded digital signals.

System architecture refers to the major components of the DDC system and their interrelationship. The architecture is developed by determining what components are initially required, what may be required in the future, and how the system may expand as additional requirements are added.

Sequence of Operations

- Description of the complete operation for each air handling system 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.
- What happens to system components during an abnormal occurrence.
- Any energy management strategies to be included in the system, such as a night temperature setback, unoccupied periods

Points List

After the sequence of operation is completed and the airflow diagrams are defined, the next step is to develop points list. This is an all inclusive list of points, which includes the alarm, control, and monitoring point, that are to be connected to the DDC system.

The points list should include analog control points such as cooling coil valves and room temperatures. Monitoring points can be digital or an analog, and can include fan run, room temperature indication, damper position, and room pressure indication.

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.

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.

Installation Qualification and Operation Qualification

The installation qualification document verifies the proper installation and configuration of a System.

1. Ensure that necessary files have been loaded, equipment has been installed, the necessary procedures have been approved, or the appropriate personnel have been trained.
2. The requirements to properly install the system are defined in the Design Specification.

Operation Qualification

This is a commissioning documentation which shall provide all the details of equipment various points of performance, test readings, statement of compliance and noncompliance with the acceptance criteria.

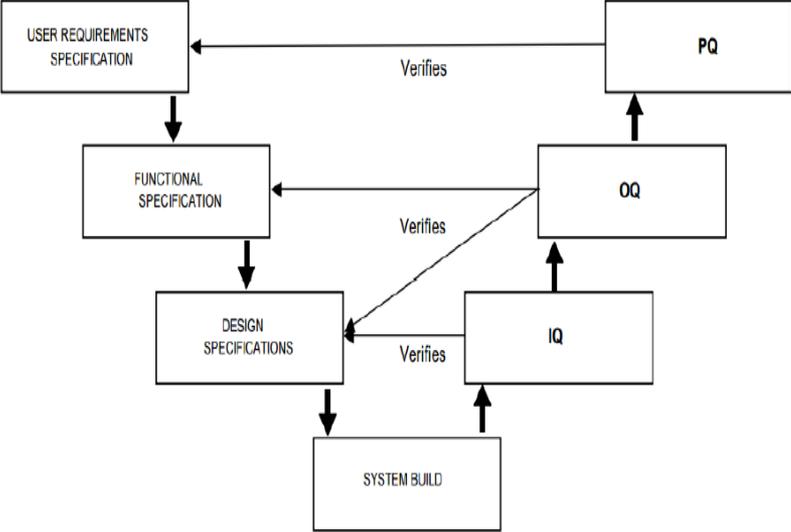
1. Installation date showing manufacturers, model no., ratings of all equipment such as fans, motors, cooling & reheat coils, filters, HEPA filters, controls etc.
2. As-built drawings showing equipment layouts, duct and pipe runs, control & fire dampers, settings of various sensors and controllers.
3. Contractor's test readings covering rotation tests, megger readings, air quantities, temperatures and RH pressures of each space, dry & wet run of controls, air and water balance, HEPA filter integrity tests at final operating velocities testing of limits & alarms.
4. Identification of items spaces, parameters not meeting the acceptance criteria but cannot be corrected.

Performance Qualification

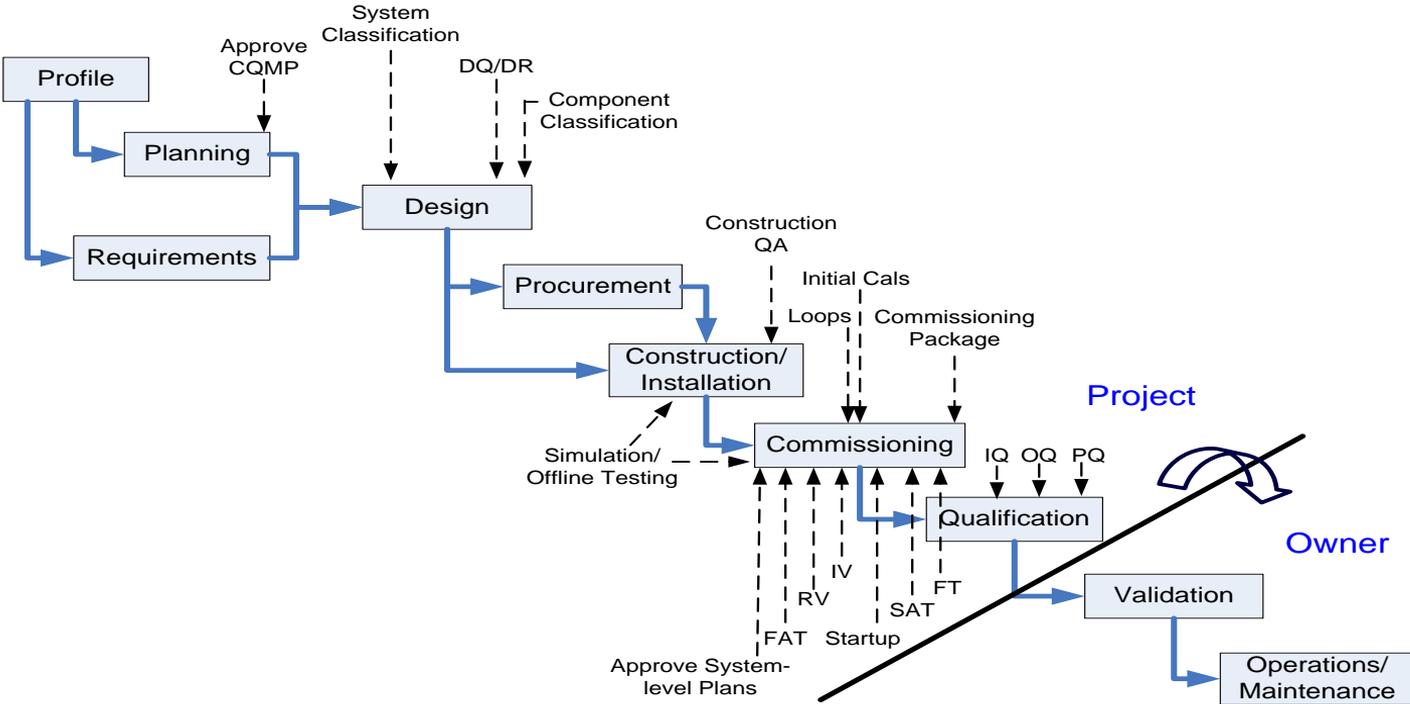
This is essentially for the system operating under full production conditions and covers among others:

1. Identification of agency for commissioning, for equipment and instruments and their calibration.
2. Test readings of all critical parameters under full operating conditions and full production, modification of readings in the contractors test results, acceptable and unacceptable departures from design qualification and acceptance criteria.

System Commissioning and Testing - Introduction



System Commissioning and Testing - Summary



Any Questions?