



**Good
Practice
Guide**

Heating, Ventilation, and Air Conditioning (HVAC)



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Heating, Ventilation, and Air Conditioning (HVAC)

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Preface

Heating, Ventilation, and Air Conditioning (HVAC) systems can critically affect the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. The design of these systems requires a blend of Good Manufacturing Practice (GMP) and Good Engineering Practice (GEP) to help provide a safe and healthy work place, protect the environment, and manage energy responsibly. HVAC can consume a major portion of the energy used by a facility and must be considered in any company's sustainability and carbon management policies.

This Guide aims to clarify GMP HVAC issues, those critical to the Safety, Identity, Strength, Purity, and Quality of pharmaceuticals, biopharmaceuticals, and medical devices from raw materials to finished goods, including the requirements for HVAC control and monitoring. This Guide also addresses issues of GEP related to sustainability, economics, and environmental health and safety.

To achieve these goals, the Guide Team aims to provide the Life Science Community with common language and understanding of critical HVAC issues, guidance on accepted industry practices to address these issues, and a common resource for HVAC information currently included in appendices of the various ISPE Baseline® Guides.

The intended audience for this Guide is global with particular focus on US (FDA) and European (EMA) regulated facilities.

The information provided in this Guide reflects the cumulative knowledge and experiences of the authors, editors, and reviewers with input from members of the ISPE HVAC Community of Practice (COP). There is no single approach to satisfy every HVAC situation; therefore, this Guide cannot address every HVAC situation. A recurring theme throughout the Guide is the importance of understanding the role of HVAC performance in protecting product, personnel, and the environment.

This Guide includes appendices which provide industry examples and templates that may be of use to the reader.

Disclaimer:

This Guide is meant to assist pharmaceutical companies in determining a common understanding of the concept and principles of HVAC. The ISPE cannot ensure and does not warrant that a system managed in accordance with this Guide will be acceptable to regulatory authorities. Further, this Guide does not replace the need for hiring professional engineers or technicians.

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1 Introduction

1.1 Background

Heating, Ventilation, and Air Conditioning (HVAC) can be a critical system that affects the ability of a pharmaceutical facility to meet its objective of providing safe and effective product to the patient. Environmental control systems that are appropriately designed, built, commissioned, operated, and maintained can help ensure the quality of product manufactured in a facility, improve reliability, and reduce both initial costs and ongoing operating costs for a facility.

The design of HVAC systems for the pharmaceutical industry requires additional considerations, particularly with regard to providing a clean and safe space environment. HVAC can consume a major portion of the energy used by a facility, and requires a blend of Good Engineering Practice (GEP) and Good Manufacturing Practice (GMP).

1.2 Purpose

This Guide is intended to supplement published ISPE Baseline® Guides for facilities (Reference 13, Appendix 12), providing detailed information and to recommend practices for implementation of HVAC systems in pharmaceutical facilities.

This Guide emphasizes the importance of understanding the role of HVAC system performance in protecting product, personnel, and the environment. Air filtration, Differential Pressure (DP), and airflow/air change rates are covered in detail to assist comprehension of airborne particulate control.

The information provided in this Guide reflects the cumulative knowledge and experience of the authors and reviewers with input from members of the ISPE HVAC Community of Practice (ISPE HVAC COP).

1.3 Scope

The ISPE Good Practice Guide: HVAC provides:

- supporting information and HVAC practices for facility types covered by ISPE Baseline® Guides
- an overview of the basic principles of HVAC to facilitate a common understanding and consistent nomenclature

This Guide addresses HVAC requirements in areas of the facility life cycle, including:

- establishing user requirements
- design, including the requirements of outdoor conditions
- construction, including good practices for equipment specification and installation
- commissioning/qualification
- operation/maintenance

Requirements of regulatory agencies other than the FDA may differ significantly and may not be covered in the facility ISPE Baseline® Guides (Reference 13, Appendix 12), and therefore, they may not be considered by this Guide.

This Guide references ISPE Baseline® Guides (Reference 13, Appendix 12) and provides associated examples. The relevant Baseline® Guide should be consulted for regulatory expectations in a specific topic area.

GEP should be applied in assessing which of the recommended practices is most applicable to a situation.

This Guide refers to recommendations, standards, and guidelines published by:

- World Health Organization (WHO)¹
- International Conference on Harmonisation (ICH)
- International Standards Organisation (ISO)
- Institute of Environmental Sciences and Technology (IEST)
- European Medicines Agency (EMA)
- US Food and Drug Administration (FDA)
- Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme (PIC/S)
- American Society of Heating, Refrigeration and Air Conditioning Engineers (ASHRAE)
- International Society for Pharmaceutical Engineering (ISPE)
- American Society for Testing and Materials (ASTM) International
- Chartered Institute of Building Services Engineers (CIBSE, UK)
- American Council of Government Industrial Hygienists
- Instrumentation, Systems, and Automation Society (ISA)
- Sheet Metal and Air Conditioning Contractors National Association – (SMACNA (North America))
- National Environmental Balancing Bureau – (NEBB (US))
- Heating and Ventilating Contractors Association (HVCA) (UK)

The Guide is not intended to be a complete handbook for HVAC design and does not address every HVAC situation.

1.4 Benefits

This Guide introduces the fundamentals of HVAC systems that control the GMP workplace environment and provides:

- the life science engineering community with common language and understanding of critical HVAC issues

¹ The WHO TRS 937 reference document, (Reference 2, Appendix 12) aims to promote discussion regarding quality in preparation of Oral Dosage Pharmaceuticals and provide practical guidance for inspectors in countries without a robust history of GMP regulations (particularly in support of WHO HIV/AIDS, Tuberculosis, and Malaria programs). Per the WHO purpose statement:

"These guidelines are intended as a basic guide for use by GMP inspectors. They are not intended to be prescriptive in specifying requirements and design parameters. There are many parameters affecting a clean area condition and it is, therefore, difficult to lay down the specific requirements for one particular parameter in isolation. Design parameters should, therefore, be set realistically for each project, with a view to creating a cost-effective design, yet still complying with all regulatory standards and ensuring that product quality and safety are not compromised."

WHO TRS 937 (Reference 2, Appendix 12) has been adopted as the GMP standard in some countries where prior regulation was inadequate or did not exist. (In regions with existing regulation (e.g., the US, Japan, Australia, and the EU) this document normally does not carry the force of law.)

HVAC engineers should understand the applicability of WHO TRS 937 before discussing user requirements for new OSD facilities.

- guidance on accepted industry practices to address these issues
- a common resource for HVAC information currently included in appendices of the various ISPE Baseline® Guides
- help to less experienced personnel in understanding the options available to HVAC designers
- assistance with prevention of airborne product contamination to assure product quality
- quality professionals with an understanding of which HVAC parameters are important to product quality and patient safety
- information on how to avoid increasing facility costs without providing benefit (e.g., over-designing of room classifications for aseptic processing)
- highlights on the differences between HVAC parameters that address product requirements and “discretionary” HVAC specifications that tend to be more business driven, such as custom air handlers, redundant systems, all stainless air duct, and DP controls

1.5 Objectives

The Guide:

- aims to clarify HVAC issues critical to product quality for the production of drug substances and drug products, and biopharmaceuticals
- considers the requirements for HVAC control and monitoring systems
- addresses how to implement the recommendations provided in relevant ISPE Baseline® Guides to meet FDA and EMEA regulatory expectations for HVAC system design

This Guide is intended for a global audience with particular focus on US (FDA) and European (EMA) regulated facilities, including:

- HVAC personnel, including those less experienced with HVAC systems
- quality professionals

1.6 Key Concepts

This section is intended to introduce Key Concepts, which are essential to understanding this Guide. Further detailed information on these concepts is provided in Appendices 1 to 3, in addition to a primer for readers unfamiliar with HVAC equipment and theory. Readers with limited experience in either HVAC or design for pharmaceuticals, biologics, and medical devices are encouraged to examine Appendices 1 to 3 before reading and interpreting this Guide.

1.6.1 Ventilation

Ventilation is the movement and replacement of air for the purpose of maintaining a desired environmental quality within a space. The term “Ventilation” has two common uses:

- It may refer to the movement or exchange of air through a space, which is responsible for the transport of airborne particles, the mixing, or displacement of masses of hot or cold air, and the removal of airborne contaminants (e.g., vapors and fumes).

- It may refer to the supply of “fresh” oxygen-rich air.

This Guide uses the definition only for movement or exchange of air through a space (see Appendix 1).

1.6.2 Product and Process Considerations

HVAC aims to make personnel comfortable and to protect both workers inside a facility and the environment outside a facility from airborne materials that could be hazardous. In pharmaceutical manufacturing facilities, there also is a specific requirement to control the impact of the environment on the finished product (to assure product quality).

Products may be sensitive to temperature, humidity, and airborne contamination from outside sources or cross-contamination between products. Process operators may need protection from exposure to airborne hazardous materials.

Understanding the product and process is the key to good HVAC design (see Appendix 1).

1.6.3 Contamination Control

Pharmaceutical HVAC should control airborne contamination and needs to help to ensure the “...purity, identity and quality...” of the product (21 CFR Part 211) (Reference 8, Appendix 12). Room contamination control generally is achieved by filtering the incoming air to ensure that it does not carry unwanted particles, then introducing the air to the work space to mix with ambient air and dilute any contaminants (see Appendix 1).

1.6.4 Impact of Temperature and Humidity on Contamination Control

Comfortable personnel produce fewer environmental contaminants: a typical worker will discharge 100,000 particles (sized 0.3 µm and larger) a minute doing relatively sedentary work. A worker who is hot and uncomfortable may shed several million particles per minute in the size range, including a greater number of bacteria. Additionally, environmental conditions inside a building, such as high humidity, can influence the product by increasing microbial and mold growth rates on surfaces (see Appendix 1).

1.6.5 Total and Viable Particulate

The majority of airborne particles are non-viable. A fraction (< 1%) of airborne particles are viable, e.g., bacteria and viruses; however, these can multiply. Viable particles travel with non-viable particles; therefore, controlling the total number of airborne particles also controls the number of viable particles (see Appendix 1).

1.6.6 Classified Space

The concentration of total airborne particles and microbial contamination within the space is a key measurement of room environmental conditions for pharmaceutical operations, particularly for sterile products and some biopharmaceutical API. The target maximum reading for these measurements is referred to as the “classification” of the space.

Several similar systems exist for the classification of space; however, there is no consensus on a single terminology for classification. This Guide uses the term “Grade” (from the EMEA standard) followed by an ISO level number. Therefore, “Grade 7” meets ISO 7 (10,000 0.5 micron particles per cubic foot or 352,000 per cubic meter) in use only with bioburden limits of 10 per cubic meter. By comparison, a Grade 7 space looks much like a European Grade B space, but the European Grade (A, B, C, D) also has at-rest limits. This terminology was developed within ISPE to help bridge the gap between the various standards (see Appendix 1).

1.6.7 Maintaining Classification

Designers may default to “rules of thumb” for ventilation rate by the class of a space. Knowledgeable designers use rules of thumb for only conceptual design with the intent of later reducing air changes, based on further knowledge of the process.

The relationship between air change rate, ventilation rate, air particle concentration in the space, and recovery rates from in-use to at-rest conditions should be considered. Although “air change rates” are important parameters in pharmaceutical HVAC system design, air change rates are more related to a room’s ability to recover from an upset, rather than the room classification. Arbitrary air change rates associated with area classifications may be either excessive or insufficient. Arbitrarily set air change rates often drive decisions regarding room size and airflows. This can have significant cost implications, but does not relate directly to the particle count in a room (see Appendix 9).

1.6.8 Particle Generation Rate

The Particle Generation Rate (PGR) for an existing process may be calculated if the steady-state room particle count, the room supply airflow, and the supply airflow particle level are known (see Appendix 9). The calculated value of PGR can then be used for the same process in a new facility.

When using empirical data for airborne particulate monitoring, it should be taken into consideration that particulate of the product being processed is not a contaminant. This is of particular interest in aseptic powder filling operations, where high particle counts may be associated with the filling process, but do not indicate failure of a cleanroom design.

Although equipment in operation can generate many times more particles per minute, personnel are a primary source of viable contamination. Increased control of total particles released from personnel leads to an increased control of viable particles in a room (see Appendix 1).

1.6.9 Effective Ventilation Rate

The relationship between air change rate, supply and extract locations, filtration, terminal devices, contaminations sources, etc., is expressed in the “effective ventilation rate.” This measure expresses the efficiency of the dilution air supply at removing contaminants expressed as a percentage of the theoretical performance with perfect (complete) dilution. For further information and calculations, see Appendix 9.

A comparison of the effective ventilation rates of various designs indicates that good air supply layout, good return/exhaust layout, and effective supply filtration may produce desired airborne particulate levels and recovery rates with less air change rates than used traditionally (see Appendix 1).

1.6.10 Impact of Unidirectional Flow Hoods (UFHs) on Air Change Rates

Air leaving the processing space inside a hood is often significantly cleaner than the air of the room into which it moves. The relatively clean air from the hood may help, along with the supply air from the HVAC system to dilute airborne particles in the room.

In addition to reducing airborne particles, air flow from a hood may accelerate the recovery time of a room from in-use to at-rest conditions. The entire air flow from a hood may not be available to include in air change calculations because the added dilution will affect only areas near the airflow path. Short circuiting of filtered air back to the air intake may create only localized “super-clean” areas, as with UFHs.

Similar increases in room air cleanliness and recovery can be accomplished with HEPA-equipped Fan-Filter Units (FFU) operating inside a room (see Appendix 1).

1.6.11 Room Airflow Patterns

The locations of air inlets and outlets relative to the location of sources of contamination/heat and to expected airflow obstructions are crucial to controlling contamination. The orientation of airflows can be aligned to protect product or personnel by sweeping across one or the other (or both) between the supply terminal and the extract point. Local (usually high level) supply or extraction, or complete enclosure of the process also can create a local environment that excludes or removes particulates. Air velocity that is too high can create eddies and vortices near operators and increase the risk of exposure to hazardous material. Local supply or extraction is considered most effective when located near the point of contaminant generation.

Contaminants may be removed more rapidly using displacement airflow of adequate velocity and direction (e.g., in a unidirectional flow hood, local extraction vent, or via non-aspirating diffusers) than with dilution ventilation. Numerous air outlets equally spaced with equal flow rates, can create a “plug flow,” which is a situation where air generally moves downward from ceiling to floor, but not at constant velocity. This can lead to faster recovery (often less than 10 minutes for 20 ac/hr) and also prevent “hot spots” of high particle count in a room. The number and intensity of contamination sources in a room should be considered; if low, a displacement airstream may be more useful in controlling airborne contaminants than dilution (see Appendix 1).

1.6.12 HVAC Relationship to General Construction

Pharmaceutical HVAC can help control contaminants within a space, but facilities should be designed with physical architectural features, such as airlocks, which limit the migration of contaminants (see Appendix 1).

1.6.13 Airflow Direction and Pressurization

A continuous flow of air in the desired direction through the cracks in building construction (door gaps, wall penetrations, conduits, etc.) can reduce unwanted passage of airborne particulates. A velocity of 100 to 200 FPM (0.5 to 1.0 m/sec) usually will capture and transport light powders and bioburden, assuming there are no strong drafts.

One method to control the direction of airflow is to control the relative pressurization of adjacent spaces. GMPs for classified spaces, such as EMEA Grade B or FDA ISO7/Grade 7, require a measurable Differential Pressure (DP) between cleanrooms and adjacent less clean spaces, suggesting 10 to 15 Pa (0.04 to 0.06 inch wg) DP between air classes.

Products in rooms that are not classified may be protected by measurable DP or by airflow velocity and direction that cannot be measured with traditional DP instrumentation.

A simplified method (neglecting the orifice coefficient for the opening) to calculate the expected velocity of airflow through a “crack” (e.g., around a closed door) resulting from a given pressure differential is given in Chapter 7 of this Guide.

Other “cracks” in the fabric separating a pressure controlled room from other spaces may not be accounted for using this calculation. A common method to account for this additional airflow is to allocate 0.05 to 0.5 CFM per square foot of room surface, depending on construction and (DP) (see Appendix 1).

1.6.14 Automated Differential Pressure Control

There is no GMP requirement that DP or airflow direction be automatically controlled (such as by using actuated dampers or CV devices). Satisfactory designs using “static” air balance to achieve desired DP values are common in the pharmaceutical industry (see Appendix 2).

1.6.15 Airlocks or “Ante Rooms”

The primary role of airlocks is to provide an effective obstacle to airborne contamination. These rooms control traffic into and out of a space through a series of doors and also provide a location for gowning/de-gowning, sanitizing/decontamination, etc. Airlocks can prevent DP between air classes from dropping to zero when doors are opened between the classes (see Appendix 2). Three primary types of airlock pressure arrangements are common:

1. Cascade – air flows from area at highest pressure, through the airlock to the area of lowest pressure.
2. Bubble – airlock is at highest pressure, air flows from the lock to the cleanroom and corridor.
3. Sink – airlock is at lowest pressure, air flows from the cleanroom and corridor.

1.6.16 Differential Pressure Measurement

Two methods of measurement are commonly used to monitor room pressure relationships:

- room-to-room
- room-to-common reference point

Small or simple facilities with just a few DP sensors may prefer to read pressures from area class to area class (or from room to room if there are no airlocks). Larger facilities needing to record numerous pressure differentials usually use the common reference point method to minimize the number of pressure sensors and to minimize compounded error. The size of the pressure reference piping can be small, because the flows are very small; the only effect of pipe sizing is to slow the progress of pressure waves. The ideal pressure reference location has a large volume, few openings, and an unvarying or slowly changing pressure relationship to the outdoors (see Appendix 2).

1.6.17 HVAC Controls and Monitoring

It is common practice to qualify monitoring systems (sensors, transmitters, indicators, recorders, alarms, etc.) for those parameters defined as critical and to use GEP to ensure the development and maintenance of a robust control system.

HVAC control systems or multi-use systems, such as Building Management System/Building Automation System (BMS/BAS) also can act as the quality ‘system of record’ to provide electronic data records, as well as direct environmental monitoring data that may be used to support product release or other GMP processes.

A common alternative approach is to employ an independent system for alarming and managing critical data. The HVAC control system is limited to control and maintenance information. A BMS/BAS could be used as a data source interface to equipment and instruments, transmitting information to the monitoring system, which is responsible for all other data management and backup/archiving functionality. In smaller facilities needing to monitor just a few HVAC parameters, the data management and the control of all HVAC points can be included in the process control system (Distributed Control System (DCS), Direct Digital Control (DDC), PLC, etc.). The critical parameter data may originate from a common device and be relayed to the BMS/BAS or the output may go to both systems (see Appendix 2).

1.6.18 Alarm Time Delays

Rapidly changing parameters, such as room pressure, have the potential to create frequent (nuisance) alarms, such as when a door is opened. Differential Pressure alarms often have time delays, the duration of the time delay should be sufficient to permit normal passage through a door (see Appendix 2).

1.6.19 Time Weighted Averaging

Measurements with “noisy” (rapidly changing) signals, such as airflow measurements, may require filtering to avoid nuisance alarms. A commonly used filter is to use a rolling time weighted average signal, rather than an instantaneous signal for recording and alarming. A rolling average of readings from 4 to 10 seconds typically is capable of smoothing out signal noise without missing significant failure events (see Appendix 2).

1.6.20 Airborne Particle Monitoring

The 2004 FDA Guidance for Industry, “Sterile Products Produced by Aseptic Processing – Current Good Manufacturing Practice” (Reference 9, Appendix 12) states “Regular monitoring should be performed during each production shift.”

More recent guidance also is available from the EMEA (EU GMP Annex 1) and ISO (14644-1).

Based on this guidance, there is a trend toward the installation of continuous monitoring systems since they provide a better understanding of the process, and the data can be used to support a reduced frequency of testing, while assuring continued levels of control (see Appendix 2).

1.6.21 Air Handling Unit Zoning

A manufacturing area often is divided into zones with a separate AHU used for each zone. In the pharmaceutical industry, a zone is usually considered to be an area with one type of manufacturing process or area cleanliness classification, e.g., a tablet compression suite in an oral solid dosage facility or all classified areas for aseptic product. The decisions for zoning should be based on risk to product and to operators; taking into account the preferred air filtration and monitoring technology (see Appendix 2).

1.6.22 Use of Air Handling Units in Parallel or Series

Air Handling Units (AHUs) may be placed in series, e.g., if a higher air pressure is required to offset the pressure drop through HEPA filters in ductwork to just one area served by the primary HVAC system. A common series configuration uses an AHU to precondition outdoor air as makeup air to one or more ‘local’ AHUs downstream. The use of parallel AHUs is common practice where large areas are being conditioned, e.g., warehouses and large research laboratories. This approach increases reliability allowing acceptable conditions in the area to be maintained if one unit fails or when the load on the system is light (see Appendix 2).

1.6.23 Psychrometrics

Sensible (dry) heat causes a change in the temperature of a substance. Addition or removal of sensible heat will cause the measured air temperature to rise or fall.

Latent heat is the heat of vaporization carried by the moisture in the air/water mixture. The addition of water vapor to air may increase the humidity of the air without changing the temperature of the air.

Relative Humidity is the amount of moisture in the air versus the air’s capacity to hold moisture.

The Dew Point temperature is the temperature at which water vapor leaves the air and collects on cool objects in the form of fine droplets or bands together and becomes fog.

See Appendix 3 for further information on Psychrometrics.

1.6.24 Life Cycle Cost Approach

In addition to protecting the product and patient, HVAC designs need to consider economics. Overall cost is a major factor in deciding which options to implement for an HVAC system. Life cycle cost is usually much greater than the initial (capital) cost of an HVAC system.

The impact of an HVAC system failure could be financially significant in the pharmaceutical industry, possibly causing loss of a batch of product or the loss of control of the conditions in a research laboratory and potentially invalidating the results of a long term test (see Appendix 9).

1.6.25 Sustainability

For a facility that is aiming to be considered as “green” or sustainable, HVAC systems are an important component. Compliance with sustainability guidelines has been optional and considered progressive, and provided market differentiation for the building owners. Compliance with sustainability guidelines and standards is becoming required in some regions (see Appendix 9).

1.6.26 Key Terms

This Guide uses the term ‘controlled space’ to refer to an enclosed volume that is provided with HVAC for control of one or more environmental parameters. (See Glossary for possible alternative terms.)

Air Flow: the volume per unit time of air moving through a duct or space.

Air Change: the volume per unit time (in this case hours) of air entering a space, divided by the total volume of that space. As an example: 1000 cfm (cubic feet of air per minute) delivered into a room measuring 10 ft × 10 ft × 10 ft would have an air change rate of 60/hr ($1000/\text{min} \times 60\text{min/hr} = 60000 \text{ ft}^3/\text{hr} / 1000 \text{ ft}^3 = 60 \text{ ac/hr}$).

Psychrometrics: the measured properties of air/water gaseous mixtures. The science of psychrometrics tells us the energy states, density, and makeup of ambient air at various temperature and humidity levels.

Static Pressure: similar to atmospheric pressure, that component of total pressure which is exerted equally in all directions (as described by Pascal). This pressure represents potential energy in a fluid system and can be converted to velocity across any opening to a lower pressure space.

Velocity Pressure (VP): the component of total pressure that is exerted only in a single direction (or vector) because of the velocity of a fluid. This pressure represents the kinetic energy in a fluid system and can convert back to static pressure (potential energy) when flow is stopped.

Total Pressure: a measurement taken by a tube or probe facing upstream, it has both the components of velocity and static pressure.

Differential Pressure (DP): the difference in static pressure between two spaces. DP between spaces results in airflow through any openings between spaces to help control contamination.

Dalton’s Law of Partial Pressures: states that the pressure of any gas in a space is independent of the pressure of every other gas in that space. This is important in HVAC because, while air pressure within a low humidity space may be higher than ambient, the pressure of the water vapor may be lower, and therefore, moisture will flow into the higher pressure space.

Classified Space: a space in which several parameters (e.g., temperature, relative humidity (RH), total particulate, and viable particulate) are maintained within specified limits. In classified spaces, total particulate is defined and controlled. In the pharmaceutical industry, viable particulate is controlled, and temperature, RH, DP, or direction of airflow usually are controlled.

OR

The concentration of total airborne particles and microbial contamination within the space is a key measurement of room environmental conditions for pharmaceutical operations, particularly for sterile products and some biopharmaceuticals. The target maximum reading for these measurements is referred to as the “classification” of the space.

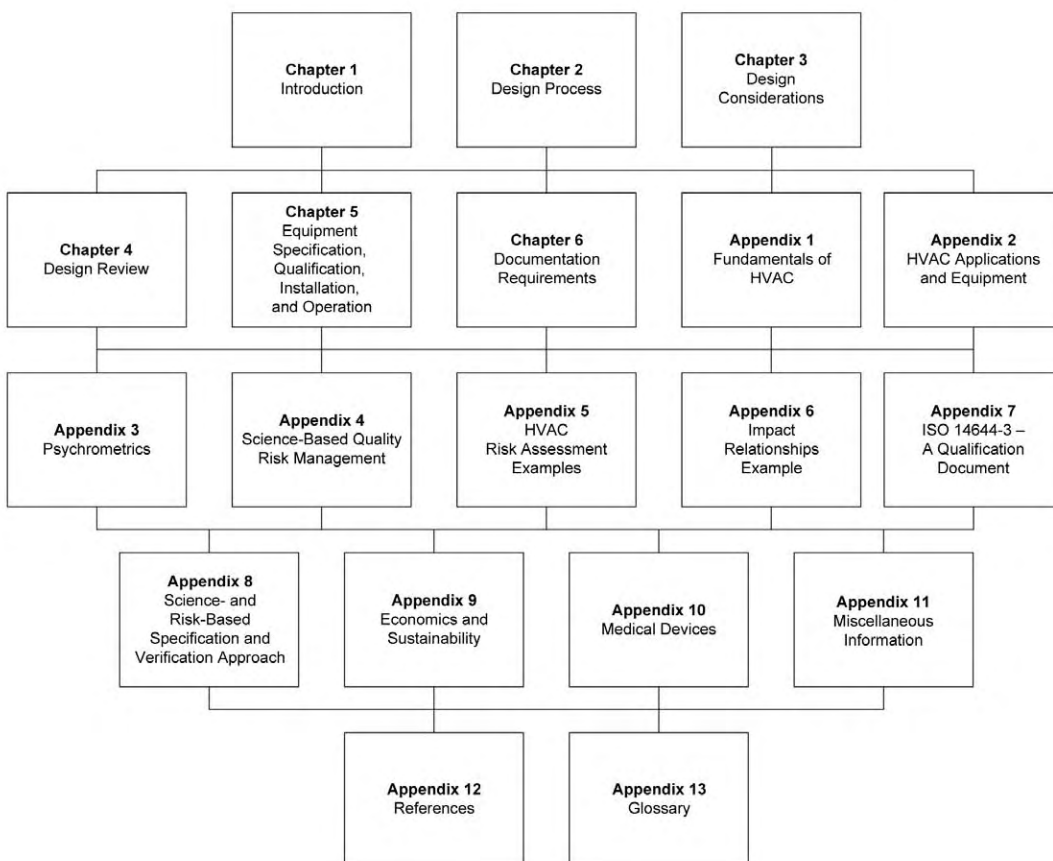
This Guide uses terms as defined in the online ISPE Glossary of Pharmaceutical Engineering Terminology (Reference 17, Appendix 12). New terms or terms specific to the content of this Guide are defined in the Glossary.

1.7 Structure

This Guide is divided into three main topic areas:

- introduction, principles, and recommended practices for HVAC systems
- appendices on fundamentals of HVAC, and HVAC applications and equipment
- appendices containing additional topics, detailed information on specific topics and examples, such as controls, science- and risk-based specification and verification approach, HVAC economics and sustainability, HVAC equations, and psychrometrics

Figure 1.1: Chapter Structure



This Guide is written in inch-pound (I/P) units with reference to metric units (the International System of Units (SI)), where practical.

2 Design Process

2.1 Introduction

The objectives of HVAC design are to provide GMP compliant systems that meet product and process needs, along with GEP and business requirements (such as reliability, maintainability, sustainability, flexibility, and safety). In addition, the design needs to comply with local codes and standards.

Therefore, the HVAC design team should understand both advanced HVAC system design and the current requirements of regulatory authorities that govern a facility's operations. This includes the GMPs of the regions where a facility's product will be sold, as well as where a facility is located. The team also should consider how HVAC systems integrate with, and are affected by, other aspects of the facility design and expected operation. Issues that are typically associated with HVAC design are:

- personnel, equipment, and material flow patterns
- open or closed manufacturing
- manufacturing activities envisioned in each room
- architectural layout
- finishes and tightness of room construction
- door selection and location
- air lock strategy
- gowning and cleaning strategy
- spatial requirements for HVAC equipment and ductwork
- intake locations and exhaust locations

The requirements of pharmaceutical regulatory bodies, such as the FDA and the EU regulators, will affect the project design at the HVAC system design level, particularly relating to establishment of critical parameters. For further information, see the relevant ISPE Baseline® Guides (Reference 13, Appendix 12).

The design team should deal with conflicts between GMP requirements and local building codes/standards that apply to the design of facilities and HVAC systems. These include applicable local building, mechanical, electrical, fire, energy, and seismic codes circulated by organizations, such as the International Code Council (ICC), National Fire Protection Association (NFPA) (US), and local building authorities. Other compliance related requirements from organizations such as Occupational Safety and Health Administration (OSHA) (US), Health and Safety Executive (HSE) (UK), and European Union – Occupational Safety and Health Administration (EU-OSHA)/European Agency for Safety and Health at Work (EASHW) deal with employee health and safety and process safety. The owner's insurance representative also may have requirements beyond those of the local codes authority.

HVAC design engineers should work closely with other disciplines to maximize the success of a project. This chapter provides suggestions to help determine the user requirements (the 'what') and the functional design (the schematic 'how to') that define a facility's objectives. It also provides options to be considered in creating a design that has low life cycle cost and is sustainable.

HVAC Design Process

The design process may be considered as several steps; each step provides a deliverable:

<u>Step</u>	<u>Deliverable</u>
1. User Requirements/Conceptual Design	User Requirements/Conceptual Design Report (CDR)
2. Functional (Schematic) Design	Functional Design Specification (FDS)/Basis Of Design (BOD)
3. Detailed Design	Design Documents
4. Construction Documents and Support	Construction Documents (CDs), Revisions/Bulletins

2.1.1 User Requirements

The first step in the design process is the definition and documenting of the key requirements of the user (process and quality criteria, maintainability, etc.) by the HVAC design engineer. This requires collaboration with both the user and the Quality Unit to determine critical HVAC performance parameters, and therefore, the environmental requirements for the facility design. Some parameters are directly controllable (such as room temperature), while other parameters (such as airborne particles) cannot be controlled directly, but are the result of controllable parameters (room DP, airflow, filters, etc.).

Performance parameters may have been established through a user's internal standards. The definition of user requirements is a critical step in the design process and has the greatest effect on the size and complexity of the facility, and ultimately, the cost to construct, commission, qualify, operate, and maintain that facility. Small incremental increases in the level of cleanliness or in the area of classified space can result in relatively large increases in the initial cost and ongoing operating costs of a facility. The required levels of cleanliness for airborne particles, biological or chemical contamination for processes, equipment, and personnel in a facility should be carefully considered, via risk assessment and established explicitly.

HVAC engineers should play a key role throughout the design process in helping project teams to understand the implications of requirements on product quality and life cycle cost of a facility or process. Time should be allowed to establish user requirements thoroughly and to ensure that they are understood by all parties involved. This should provide benefit in the long term with fewer changes (and costly changes/delays) in the detailed design.

User requirements for HVAC typically include:

- A room schedule with environmental parameters:
 - Temperature
 - RH
 - Classification (if any)
 - Recovery time (if any)
 - Air change rate requirements
 - Particulate control or filtration expectations (if not classified)
 - DP or direction of airflow requirements

- Ancillary ventilation or extraction requirements (e.g., dust collection)
- Preliminary AHU count or list with zoning assumptions:
 - Areas served
 - AHU basic configuration (e.g., recirculated or 100% fresh air)
- Ancillary HVAC systems list:
 - Dust collection
 - Chilled water
 - Cooling Towers
 - Scrubbers/Carbon Adsorption
- System Qualification Philosophy (e.g., system boundaries at room or AHU level)

2.1.2 Functional Design

Once user requirements are established, HVAC engineers should work with other disciplines to develop a functional (or schematic) design. The functional design should include:

- flow patterns of people, product, equipment, and other materials; a basic layout
- further clarification of the requirements established in the user requirements
- a basic AFD and critical elements of an AF&ID for each system
- AHU zoning map
- room classification map
- pressure or direction of airflow map
- airlocking schemes
- potential contamination sources, paths, risks and their control
- a risk assessment of alternative engineering solutions that can meet the user requirements
- preliminary sections or service zoning
- preliminary specifications

The risk assessment can be combined with an economic analysis to assist in design choices that yield a facility and HVAC system that will meet requirements effectively with best total cost of ownership.

The project teams should consider the following issues during development of the functional design:

- relationship between room cleanliness and contamination risks to product

- procedures to control deposited contamination (i.e., cleaning or sanitization)
- reliability and redundancy of equipment and systems
- flexibility of the facility and systems
- ease of construction and of startup/commissioning
- ease of maintenance, servicing, and operation
- qualification strategy
- commissioning and qualification plan
- economics and facility life cycle cost

2.1.3 Detailed Design

Once the BOD is approved the project moves into Detailed Design. During this phase, the technical details of how the systems will work should be established. The Detailed Design for HVAC systems should include:

- updates and further detail for all documents produced previously
- draft ductwork plans
- detailed AHU layouts with performance specifications
- draft sections, elevations, and coordination drawings
- final AF&ID for each system
- control system sequences of operation
- final equipment selections
- final specifications
- system commissioning and qualification draft protocols

Commissioning and qualification requirements should be considered during the design phase to avoid a negative impact on the project in scope, cost, and schedule. HVAC engineers should include planning for commissioning and qualification activities during the design phase, before detail design is complete, because flaws in HVAC system design often initially become apparent during commissioning.

2.1.4 Design Review and Qualification

At specific points in the design process (e.g., at the end of functional design and at the end of detailed design) a formal design review/design qualification should be performed to verify that the project design to date is fit for use. This review should focus two main areas:

- GEP
 - Is the design technically robust?

- Does the design satisfy user preferences as expressed in the user requirements?
- Can the design be constructed, commissioned, operated, and maintained?
- GMP
 - Does the design meet the product requirements as expressed in the user requirements?
 - Is the design aligned with the risk assessment?
 - Does the design meet regulatory expectations?

For HVAC systems, typical areas to check during design qualification include:

- compliance to temperature, humidity, and classification requirements
- use of classified space, where required
- AHU system map coordination with manufacturing activities
- dust or contaminant generation coordination with mitigation (e.g., LEV)
- cross-contamination controls
- airlock plan coordination with pressure regime
- air change rates used
- compliance with fire and smoke codes, compliance with emissions permits
- maintenance, testing, and commissioning access and clearances
- redundancy and reliability
- integration of process systems with facility

For further information on Design Review, see Chapter 4 of this Guide.

2.1.5 Construction Documents and Construction Support

After detailed design is completed the HVAC design team should complete bid documentation, resolve construction questions, and perform on-site construction reviews. HVAC engineers also may be involved in activities related to the receipt and installation of equipment and systems, to verify that they were delivered and installed in a manner consistent with the design.

2.2 Developing User Requirements

2.2.1 Introduction

Users should define the quality critical environmental requirements (the HVAC critical parameters and their acceptance criteria), typically in a User Requirements document. This may include the following:

- temperature for product, process, or worker comfort

- humidity for product, process, worker comfort, or microbial control
- air flow directions/DPs for contamination control, properties of expected airborne contaminants
- area classification – airborne particles – viable and non-viable (classified spaces)
- clean up (recovery) times from in-use to at-rest (classified spaces)
- process containment and exposure sites (high contamination risk areas)

User requirements provide information that defines the processes, activities, and environments for an operating facility. Assembling programming data for a facility early in the design process is critical to a successful project, both in terms of production output and efficiency, and in delivering the asset at the right time to maximize Return on Investment (ROI) and provide the lowest Total Cost of Ownership (TCO).

HVAC costs, both operating and initial capital costs, usually account for a significant portion of a facility's cost. Decisions and commitments made in the early phase of project planning often are too costly to change as the project advances to the final design and then to the execution phase. User requirements should be understood, agreed to by all parties, and properly applied early in the design process. Establishing, early in the project planning, fixed user requirements that drive HVAC design criteria is critical to the overall HVAC strategy for a facility.

For HVAC systems, user requirements are developed as a result of gathering relevant data with regard to:

- process: critical environmental parameters that must be achieved and maintained
- quality: regulatory guidance and quality principles to guide decision making on HVAC parameters that can have product impact
- operations: correct environment for working conditions that affect the HVAC system design
- maintenance: provide input on critical aspects of the HVAC system design that would ensure a low TCO

Critical HVAC parameters often associated with qualification (e.g., temperature, humidity, DP, air quality, etc.) are treated differently from non-critical HVAC parameters. Critical HVAC parameters are part of direct impact systems, while systems providing only non-critical HVAC parameters are either indirect or no impact systems as defined in the ISPE Baseline® Guide for Commissioning and Qualification.

HVAC systems are commissioned following GEP, while those that provide critical HVAC parameters (direct impact systems) are further qualified.

User requirements can either be in the form of performance-based information that describes an operation and sets expectations, or may be strict criteria where critical HVAC parameters are defined by the product or regulations, e.g., air classifications (operational, or possibly at-rest or as-built).

For performance based information, relevant information should be obtained and the necessary criteria to meet the user requirements should be proposed. It is accepted practice to copy (similar) HVAC criteria from one facility to another facility, as long as the rationale for the original criteria is properly understood. For example, temperature and RH design criteria in an aseptic environment depend on:

- the type of process (closed or open)
- powder or liquid
- local regulatory expectations

- gowning procedures
- environmental monitoring procedures
- the level and type of activity in the area
- required alert and alarm limits

Each of these variables should be considered when proposing criteria. Using “industry norms” or “accepted industry practices” without understanding the variables involved should be avoided.

Once user requirements are established, design strategies and their effects should be considered. It may be desirable to segregate HVAC systems, such that only one system deals with critical parameters, and therefore, has direct impact (e.g., processing areas on one HVAC system, support areas on another HVAC system). This may help simplify the scope of qualification.

The flow diagrams shown in Figure 2.1 are a simple model segregating critical HVAC parameters with separate HVAC systems versus combining critical and non-critical areas in a single HVAC system. Both design approaches would meet user requirements, but illustrate the potential complexity when using a single HVAC system to serve areas with both critical HVAC parameters and non-critical HVAC parameters. It should be noted that not every room parameter affected by a direct impact system will be critical (e.g., humidity may not be critical in a storage area inside a production facility where humidity is critical elsewhere although both areas are on the same AHU).

The impact assessment methodology evaluates the HVAC system at the component level to identify critical (with potential impact on product) and non-critical components; therefore, making it possible to have a single HVAC system that can serve all areas. Well-defined and accepted procedures should be established, or agreed upon, when defining user requirements, allowing a single HVAC system with perhaps a lower total cost of ownership. If these concepts are not well understood, or if established procedures or practices do not recognize this methodology, the HVAC design may increase the total cost of ownership.

Figure 2.1: User Requirements that Drive HVAC Critical Parameters

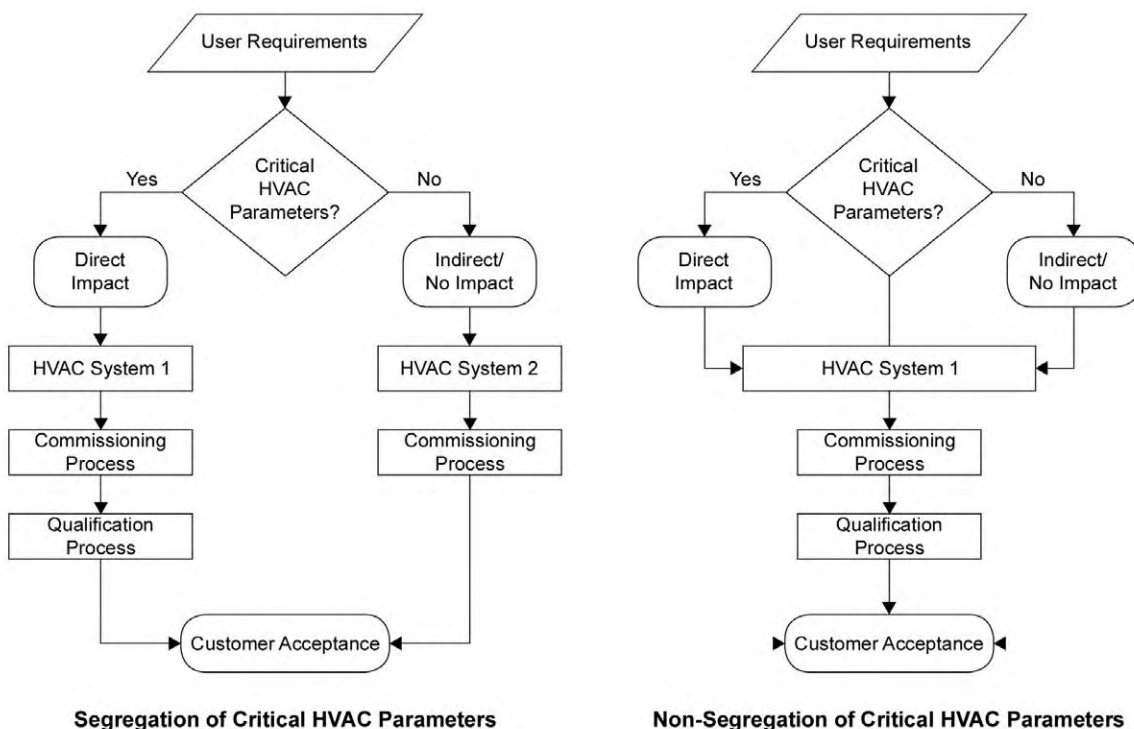


Figure 2.1 reflects a traditional approach, as described in the ISPE Baseline® Guide on Commissioning and Qualification, (Reference 13, Appendix 12) where two systems, one direct impact and one indirect or no impact, can serve a facility. The second approach is a single system that is qualified to serve both process and support areas in the facility with a focus on critical components where the system has direct impact on the process/product.

An alternative approach is to define systems by function, rather than by AHU. For example, monitoring systems for critical HVAC parameters are direct impact. If all the room DP monitors were grouped as the DP monitoring system they could be qualified as a single system, the air handlers themselves being indirect impact systems. Should any AHU fail to deliver the correct quantity of air, the direct impact system (the DP monitoring system) would detect it. Other grouped systems can be temperature monitoring, HEPA filtration (periodic testing), airflow monitoring (to verify air changes and recovery), RH monitoring, etc.

An enhanced science- and risk-based approach to verifying that HVAC systems are fit for intended use are currently being developed based on recent regulatory and industry trends and guidance. For further information, see Appendix 6.

References for User Requirements

ISPE Baseline® Guides (Reference 13, Appendix 12) provide a framework to understand the different products and processes within pharmaceutical and biopharmaceutical manufacturing facility. Section 2.2.2 describes HVAC parameters as covered in the ISPE Baseline® Guides (Reference 13, Appendix 12) and the importance of each parameter to each type of facility.

2.2.2 HVAC Parameters

HVAC parameters that may have an effect on product generally include:

- temperature
- RH (dry products, some liquids)
- airborne contamination (viable and non-viable particles) which is affected by:
 - room relative pressure
 - airflow patterns (especially Unidirectional Flow Hoods (UFHs))
 - air flow volume and air changes
 - air filtration

Within the context of the ISPE Baseline® Guides (Reference 13, Appendix 12) some parameters are common to all facility types, while other parameters apply only to specific facilities. Table 2.1 depicts an overview of typical HVAC parameters that would generally apply to each facility type.

Table 2.1: Typical HVAC Critical Parameters by Facility Type

HVAC Parameter Facility Type	Temperature	Relative Humidity	Room Relative Pressure	Airborne Particles	Air Changes
Pharmaceutical Ingredients	X	Final API Powder	Low Bioburden API	Low Bioburden API	Low Bioburden API
Oral Solid Dosage Forms	X	X	Air Direction	Cross Contamination	
Sterile Manufacturing Facilities	X	X	X	X	X
Biopharmaceuticals	X	X	Classified Space	See Baseline® Guide	Classified Space
Packaging, Labeling, and Warehousing	X	Exposed Product			
Quality Laboratories	X	X			
Notes: - Shaded areas represent HVAC parameters that commonly have a product impact or are required for operator comfort to keep airborne contamination low. Some products may not have temperature, humidity, or particulate limits, but USP temperature and humidity limits may apply. - Non-shaded areas are HVAC parameters that normally do not have product impact. However, there may be other requirements, such as local codes or regulations that may require specific parameters be considered in the design. For example, room relative pressure may not have product impact in an API facility where processes operate closed, but because of governing codes, the design may include room negative pressurization in order to meet fire safety requirements because of the presence of flammable liquids or vapors.					

Individual HVAC parameters are discussed with an emphasis on minimum requirements to achieve “compliance,” the importance of the parameter, the impact on design, and the challenges faced in determining these requirements.

2.2.2.1 Temperature and Humidity

General Requirements

Room temperature and RH requirements depend on the application (process design), product requirements, and operator comfort.

When operator comfort is the only requirement, the ranges, e.g., 65-74°F (18-23°C)/30-60% RH, are well understood and usually are based on historical operating practices that include gowning requirements, type of work being performed, and local climate (e.g., tropic or temperate zone).

EU Guide Annex 1² reinforces that the temperature and humidity within a sterile facility be kept at a comfortable condition, presumably to avoid shedding of particles and bioburden from excessive perspiration.

² “The ambient temperature and humidity should not be uncomfortably high because of the nature of the garments worn.”

Specific Requirements

Room temperature and RH requirements at which product quality is adversely affected should be based on stability studies or process parameters that demonstrate the acceptable operating ranges for the product or process. In the case of sterile facilities, where air is in direct contact with the product (Grade A/Grade 5 open processing areas) temperature may have an effect on product quality, and therefore, the temperature range may be limited to plus/minus a few degrees.

Room temperature and RH for bulk biological processing areas generally are maintained just for operator comfort. Most product processing occurs in Grade C or D (Grade 8 or CNC) areas with closed operations. In areas with unjacketed processing, when it can be demonstrated that room temperature and RH may affect product quality or processing, these HVAC parameters are considered critical.

For solid dosage facilities, although air is in direct contact with product, temperature generally is not as critical to product quality. Set points often are based on operator comfort for the level of gowning. Many powder products are hygroscopic and require lower humidity than usually provided for operator comfort. Products or processes may require strict environmental room conditions for production or to maintain product quality (e.g., where the hygroscopic nature of an ingredient causes a weight gain when exposed to ambient humidity, which may affect weight upon formulation).

Storage of finished goods or raw materials, as stated by regulatory requirements, requires environmental control and monitoring of storage conditions. Generally, space temperature and humidity are monitored and controlled because of labeling requirements of the finished product or raw material. For closed and sealed containers, humidity requirements usually are not as stringent.

2.2.2.2 Airborne Particles

Airborne particles should be controlled in classified facilities; i.e., Grade A, B, C (Grade 5, 7, 8), etc. Other types of facilities, e.g., oral solid dosage, bulk chemical, warehouse/storage, and packaging/labeling, generally have no specific criteria for airborne particulate, except that filtration is provided to reduce particulates below ambient levels. Local requirements may stipulate a minimum level of particulate control in specific types of facilities or product manufacture. These should be reviewed with the local quality unit for application and impact. In general, user requirements should not specify space classification for applications that do not require them. See the appropriate facility ISPE Baseline® Guide (Reference 13, Appendix 12).

Airflow patterns can influence local airborne particle levels significantly. For aseptic and classified areas, a protective isolator or UFH can isolate the product area from the room substantially. Although airflow patterns are not monitored, the performance of the protective device (isolator, UFH) can be monitored (e.g., pressure monitoring for an isolator or air flow monitoring for a UFH).

Elevators present a particular challenge in the control of airborne particulates. The piston action of the cab in the elevator shaft causes DPs change as the elevator cab moves. This makes elevators and elevator shafts difficult to construct as classified space. If elevators are needed for transport of material, closed transfer procedures are recommended.

For further information on the requirements for routine particle monitoring see Appendix 2. Continuous particle monitoring systems may provide a financial benefit by allowing the period between formal re-qualification and a quality benefit by providing a continuous set of environmental data.

2.2.2.3 Room Relative Pressure/Direction of Airflow

General Requirements

Room relative pressurization (direction of airflow control) is critical to protecting most manufacturing operations and often becomes the most challenging part of commissioning and qualification. A pressurization or airflow direction scheme should be established early in the design process to integrate the HVAC design with the architectural features of the facility, for example:

- door swings
- airlock strategy
- wall and floor openings
- pass-throughs

HVAC engineers should assist in the selection of the building and room fabric (i.e., walls, ceilings, etc.) during building design. Control of room pressurization can range from simple (manual balancing) to complex (fully automated dynamic control).

Manual systems are less complex, less expensive, and require less effort to commission and qualify, but are not flexible and may need to be checked and adjusted periodically.

Fully automated systems are more complex and expensive, can take considerably more effort to commission and qualify, have a greater tendency to tuning upsets, but are very flexible, provide consistency in measurement, and have a high degree of reliability (as long as the correct hardware has been specified). Door closure devices that can work against the anticipated pressure differential should be specified by the architect.

Specific Requirements

Sterile Facilities

Room pressurization for sterile facilities normally is designed to cascade from areas of highest cleanliness to areas of lower cleanliness. The design DP measured between different grade rooms, inclusive of airlocks, should be held between 10 Pa to 15 Pa with the doors in their normal closed positions. For complex facility designs, where there are many different levels of pressurization, consideration should be given to avoiding an absolute pressure above 37 Pa, which could lead to excessive air leakage, building fabric failures, and difficulty in opening/closing doors. Special consideration should be given to product conveying lines that pass from a higher-pressure area to a lower pressure area. Such high differential room pressures also create significant air velocity through the “mouse hole” that can lead to toppling of vials or product. This DP is critical, and generally, will tend to be the highest DP across one wall in a facility.

Where rooms are of the same cleanliness class, a more critical room may be the same pressure, but is usually slightly higher. General industry practices have shown that, while DPs as low as 1.2 Pa are achievable, DPs of approximately 5 Pa between rooms are easily measurable and controllable.

Bulk Biological Facilities

Bulk biological facilities generally will operate under the same principles for pressurization as sterile facilities, where open operations are performed. Closed processes may be in a CNC space. In both types of facilities, where there are live viruses, organisms, or open powder handling, rooms may be designed as containment areas. In these cases, there should be a negative pressure “sink” or pressure “bubble” airlock to interrupt the path of fugitive airborne particles.

Oral Solid Dosage Facilities

In oral solid dosage facilities where airflow direction is considered critical to maintaining room cleanliness, the direction of airflow at room interfaces (doors, pass-through(s) or other openings) can be controlled by an offset between supply and return/exhaust with periodic verification. DP also can be used to ensure the direction of airflow and can be a critical parameter. Although there are no regulatory guidelines that state DP values for these facilities, internal company guidelines or policy may stipulate criteria. Generally, any measurable DP will work. Room DP strategy is influenced by the following:

- facility usage (dedicated, multi-product, or flexible/campaigned)
- product mix
- process characteristics (open or closed)
- unit operations
- air filter capture and location
- material and people flow

Solid dosage facility pressurization strategies focus on airflow direction that minimizes contamination from extraneous matter and cross-contamination from one product to another.

In general, measurement of DP is performed directly (room-to-room) or indirectly (room-to-reference) and may employ both strategies. Alert and alarm levels that a facility will be observing should be considered when choosing a measurement strategy.

Action alarms (unusual events for the most critical rooms) may be measured directly (across the airlock) to ensure end-to-end data accuracy, rather than indirectly where DP is calculated in a control system (computer based).

Alerts (maintenance/operations notification of potential problems) can be measured indirectly.

2.2.2.4 Air Changes

There is a common understanding in the Pharmaceutical Industry of a regulatory requirement for a minimum air change rate for an area – typically a rate of 20 per hour for classified areas. There is no minimum air change rate for non-classified areas, except as defined in local Building Codes (often 4 or 6 per hour), although the WHO guidance for OSD HVAC (Reference 2, Appendix 12) suggests that a room class, air change rate, and recovery period be established by the facility owner. The European GMP (Reference 4, Appendix 12) regulations have a requirement for a “clean up” time of 15 to 20 minutes in a sterile product processing facility. The 2004 FDA “Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice” (Reference 9, Appendix 12) gives the following guidance:

“For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas.”

There is no minimum air change rate for non-sterile product facilities, except as defined in local Building Codes (often 4 or 6 per hour due to chemical storage) although the WHO guidance for OSD HVAC (Reference 2, Appendix 12) suggests that a room class, air change rate, and recovery period be established by the facility owner.

The resultant particulate level achieved in the various operating states (at-rest and dynamic) that are affected by the supply airflow volume, which can then be translated to air changes for a particular room is more important than the number of air changes. For further information, see Appendix 1.

However, the recovery of a room from in-use to at-rest is directly related to its air change rate; the higher the air change rate, the quicker the recovery. As shown in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12), calculating recovery based on 20 AC/hr of clean air supplied to a Grade B (Grade 7) room with completely uniform mixing, the recovery time from ISO 7 in use to ISO 5 at rest is 14 minutes, which meets the EU requirement.

Designers may default to “rules of thumb” for ventilation rate by the class of a space, rather than calculating the actual airflow required by the process. Knowledgeable designers use rules of thumb for only conceptual design with the intent of later reducing air changes (and thus overall capital and energy costs) in detail design, based on further knowledge of the processes to be protected. Typical values of rules of thumb are:

- 6 to 20 AC/hr for CNC, EU Grade D) spaces
- 20 to 40 AC/hr for Grade 8 (EU Grade C) spaces
- 40 to 60 AC/hr for Grade 7 (EU Grade B) spaces
- Grade 5 (EU Grade A) spaces

For unidirectional flow, air changes do not matter; air flow velocity and pattern are important.

The number of air changes can have a significant influence on system cost and should be considered carefully and defined. Organizations may require air change rates that are not based on operating data. Airflow (volume/time) determines steady state particle levels, and should be used where historical process data are known. Utilizing arbitrary air change rates throughout a design should be avoided; the designer and owner should take responsibility for defining the required airflow based on a number of factors as discussed in this Guide.

In order to define the actual volumetric flow rate required (CFM or cu.M/hr), the following interrelated factors should be considered:

- heat gain to the conditioned space due to external influences, e.g., solar gain, wall gain
- heat gain to the space because of internal influences, e.g., equipment and people
- moisture gain to the conditioned space because of external influences, e.g., external humidity
- moisture gain to the space because of internal influences, e.g., occupants, processes, such as washing activities
- the number and location of the occupants in the space
- the tasks the occupants are doing
- the clothing (gowning level) of the occupants
- the process and its particle generation rate (PGR) (generally, the driver requiring the most airflow)
- the cleanliness of the supply air
- the means and efficiency of coverage of distributing the supply air

- the means and location of extracting the air from the conditioned space
- the locations where the specified conditions are critical, e.g., in a tablet compression room, the process will add a considerable amount of heat to the product; the critical area is likely to be where the raw material is exposed
- airflow required to achieve required DPs (usually small compared to other factors)

Heat and humidity gain typically are more easily offset, and therefore, less critical for establishing airflow for classified space than particulate load. The cost of installing a system to deliver higher than required air change rates is significant both in terms of the capital and system operating costs. A process that generates low volumes of particles in a large room may need fewer air changes to maintain desirable particle levels. For classified spaces (Grade C/Grade 8 or cleaner), however, 20 AC/hr is a common minimum design target, as it is cited in the FDA Sterile Guidance and meets EU Annex 1 recovery (Reference 4, Appendix 12) requirements. Acceptable recovery tests and particle measurement during HVAC and process qualification may justify setting lower air change rates after startup of process equipment. (Air changes should not be reduced to the point that HVAC equipment is significantly oversized and difficult to control.)

2.2.3 Managing Critical HVAC Criteria and Non-Critical HVAC Criteria

2.2.3.1 Alarming of Parameters

Temperature, RH, and room pressurization may be critical to product quality or patient safety; organizations may decide which through policy, internal guidelines, or operating experience. Critical parameters should be defined during the creation of the User Requirements document with the involvement of the HVAC design, development, production, and Quality Assurance groups.

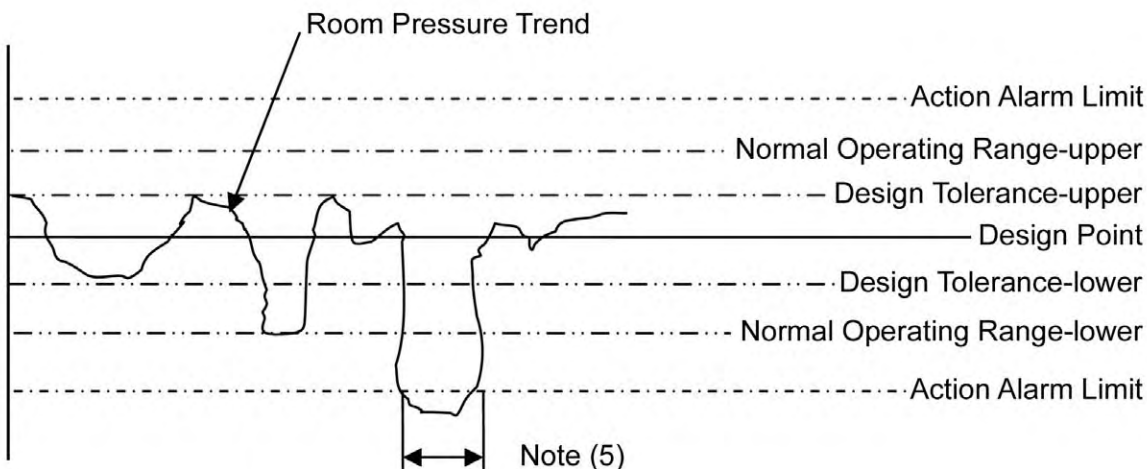
Specific terms should be understood in context (for definitions see Appendix 13):

- Action (or Alarm) Limit
- Alert Limit
- Design Point
- Design Tolerance
- Normal Operating Range

The illustrations provided are intended to assist in establishing ranges of critical HVAC parameters within a facility and describe critical HVAC parameters that are normally monitored. For further information, see Appendix 2. They are intended to help to illustrate the difference between design criteria and operating values; to provide a sample framework to show how critical HVAC parameters are controlled, monitored, and communicated.

Figure 2.2 shows a room pressure plot. The design point is the target value for the control system to achieve. The design tolerance is the expected variance of the measured pressure around the design point, given instrumentation accuracy, drift, and normal activity in the room. Alert and Action Alarm limits are the points that lie beyond the design point and tolerance, and also should lie beyond the Normal Operating Range.

Figure 2.2: Example 1: Pressurization – Monitoring and Control Diagram

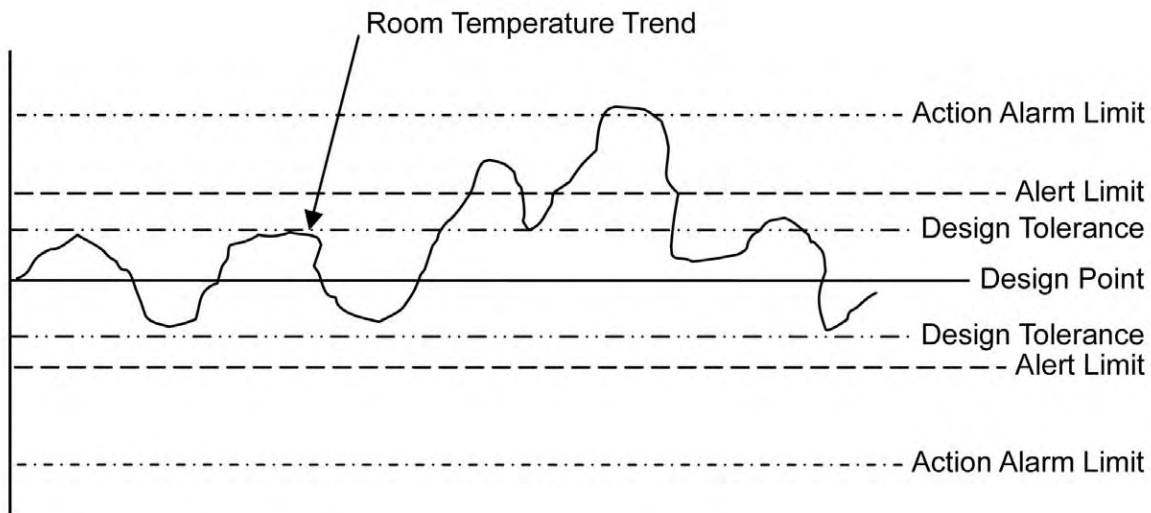


Notes:

1. When pressurization is critical to product quality or patient safety, such as for a Grade 7/Grade B space, an action alarm should indicate an atypical event. If pressure differential is not critical to product, it may still be monitored as good engineering practice but would not trigger an action event.
2. Alert limits may be used as pre-cursors to signal staff that an action alarm event may be imminent unless some correction is made.
3. Alert limits for pressurization may have the same pressure value as action alarm limits. Typically, what distinguishes a pressure alert limit from an action alarm limit is the length of time that is allowed to pass before signaling an alert and then an action alarm (time delay). i.e. alert limit time delay = x seconds (such as a door opening and closing), alarm limit time delay = (1.5) x (alert Limit time delay x) (door held open too long)
4. Time delays for alert/alarm limits are based on normal operating activities. The length of time delay should be justified and documented e.g., written procedure, policy, and standard operating procedure. Pressure alarm time delays should be justified during facility commissioning using particle counting at the critical site.
5. When pressurization levels reach the alert alarm limit, as illustrated in the graph, the first notification is an alert signal once time period x has elapsed. If conditions continue to remain outside the alert/alarm limit after the action alarm time period has elapsed, an action alarm signal is generated.

Figure 2.3 shows a similar profile for room temperature. Unlike the pressurization profile, most HVAC parameters will have different set-points for alert and action alarm limits. Usually temperature has a wider range in which to operate and changes slowly, allowing different alert and alarm limits. For example, if a chiller fails, a high room temperature alert would signal that something is happening and provide time to react to a potential action alarm. If product requirements have tight environmental limits, however, it may not be practical to have alert and alarm levels at widely different set-points. Therefore, alarms would revert to the same alert/alarm strategy as for pressurization, setting time delays around the same set point. This is usually not necessary with temperature or humidity.

Figure 2.3: Example 2: Temperature – Monitoring and Control Diagram



Notes: (the notes for pressurization apply except for the following clarifications)

1. Alert limits for temperature may vary based on the application; very few products or processes need the same temperature alert limit value as alarm limits. Most temperature alert limit values will fall between the normal operating range and action limit. In the case where action and alert limits have the same value, time delays to distinguish alert and action alarm are needed.
2. Time delays for alert/alarm limits are based on product impact, labeling requirements, or process requirements.
3. The same approach can be used for relative humidity.

2.2.3.2 Managing HVAC Parameters (Monitoring)

Considerations for a monitoring system for the critical parameters (see Appendix 2) include:

- Accountability for alerts and alarms:
 - Who deals with them?
 - Written procedures should be established.
 - The location of alarm indicators affects design of monitoring systems.
- Methodology in determining appropriate alarm delays:
 - Will they be based on actual operating data or upon predetermined values?
- How to monitor In the DCS:
 - Process control system, in the BAS, by procedural means, or by manual monitoring?
- What should be monitored:
 - Every room or select representative rooms?

2.3 HVAC System Risk Assessment

2.3.1 Introduction

Risk assessment is used as a process to evaluate the impact of systems or components on product quality. The risk assessment is performed by dividing the systems into components and evaluating the impact of those systems/ components on the Critical Process Parameters (CPPs) (derived from the relevant Critical Quality Attributes (CQAs)). As the components included within a system can significantly affect the ability to maintain CPPs within their acceptable limits, the definition of system boundaries is a critical step in a successful risk assessment.

The risk and potential impact of system failure should be reviewed by HVAC engineers with consideration given to the potential modes of failure, for example:

- airflow failure
- filter failure (loss of control of airborne particles or cross-contamination)
- failure of temperature control
- failure of humidity control
- failure of one AHU, upsetting DP created by other AHUs

The potential impact of system failure can influence significantly the HVAC system design and maintenance, as well as the design of the supporting utilities. The scope of the analysis may include business as well as quality aspects. (If a system fails and the qualified (verified) monitoring system advises the Quality Unit that the area is not within specifications, there is no risk to patient, but the cost to the business could be considerable.)

The risk assessment process may be used to determine:

- the testing (commissioning, qualification) requirements for the system and its controls
- the level of documentation that is appropriate
- the individual components that should be verified (commissioned/qualified)
- the necessary level of change control to apply to system components

Typical HVAC performance parameters that may affect CPPs include the following:

- temperature
- RH
- particle count at rest
- total particle count in use (area classification)
- clean up and room recovery time from in-use to at-rest
- supply air HEPA filter performance (capture of contaminants)
- air change rates/airflow volumes (affecting particle counts and recovery)

- area DPs (room protection)
- airflow patterns at critical site
- microbial viable particulate test results – in air (related to total airborne particles)
- microbial viable particulate test results – swab tests (indirectly affected by HVAC)

The list of critical parameters should be reviewed to ensure it minimizes risk to product quality and patient safety. The impact of the failure of a component should be assessed.

2.3.2 Impact Assessment

A recommended practice is to begin the impact assessment process with a table of HVAC monitoring points and evaluate them for impact on product quality or patient safety. Table 2.2 is intended to encourage discussions between the Quality Unit, process, and engineering to identify and segregate critical and non-critical HVAC points using appropriate risk analysis when no formal guidance or written procedures exist.

Table 2.2: Parameter Risk Assessment Table

Monitored Area	Point Name	HVAC Critical Parameter? (Y/N)	Alert Limit	Delay (x ₁)	Alarm Limit	Delay (x ₁)
AHU	Supply Airflow					
	Return Airflow					
	Supply Temperature					
	Supply Humidity					
	Return Temperature					
	Return Humidity					
	Supply Static Pressure					
	Return Static Pressure					
	Mixed Air Temperature					
Grade A/B Room	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow AC/hr					
Grade C Room	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow AC/hr					
Grade D or Controlled Unclassified Room	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow AC/hr					

Table 2.2: Parameter Risk Assessment Table (continued)

Monitored Area	Point Name	HVAC Critical Parameter? (Y/N)	Alert Limit	Delay (x ₁)	Alarm Limit	Delay (x ₁)
Oral Solid Dosage Film Coater Room	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow					
Controlled Storage Warehouse Area	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow					
Drug Substance Room – Dry Area	Room Pressurization					
	Room Temperature					
	Room Humidity					
	Room Supply Airflow					
Notes: - Although one room for various facilities is included, the intent is to develop a room-by-room analysis for each facility, segregating critical HVAC parameters from non-critical HVAC parameters. - Parameters inside the AHU (except possibly supply airflow) usually are not considered critical, as they are the value needed to satisfy room parameters. Excessive constraints on parameters inside the AHU or ductwork should be avoided.						

Typical critical HVAC parameters under a given process or classification should be identified, i.e.:

- Product Driven
- Flammability or Hazard Issues
- Environmental Air Classification
- Open/Closed processes
- Terminally Sterilized
- Oral Solid Dosage Forms

Assumptions or clarifications should be discussed and documented.

2.3.3 Risk and Components

The risk assessment process is used to determine which HVAC system components are critical to the product quality. These components then require additional attention through qualification and may require installed redundancy to avoid business impact. This could be extended to determine which components should be under GMP change control with the remainder of the direct impact system under GEP change control.

One method to address this is a matrix in which the individual components of the HVAC system (e.g., preheat coil, fan, temperature sensor, HEPA filters) are listed on one axis, and a series of challenge questions to aid in determining the GMP-critical nature of that component are listed on the other axis. Generally, failure does not make a component critical if its failure can be detected quickly (through monitoring, see Appendix 2).

There are several approaches to performing a risk assessment, for example:

STEP 1.0 Define the CPPs for the area served by the HVAC system, together with the supporting rationale. Some examples may be:

- *Humidity is not a critical factor for the product as it is an aqueous liquid.*
- *Temperature is not a critical factor as the product is contained in temperature-controlled vessels.*
- *Air quality is considered a critical factor – the room supplied is classified as Grade 8 (EU Grade C) because product-contact equipment is exposed.*
- *Room pressure differentials are considered critical to maintain the room environment, minimizing the risk of contamination/cross contamination, because the room is classified Grade 8.*

STEP 2.0 Define system boundaries for HVAC systems:

- *Systems can be organized by components of like type (i.e., system that is all one type of components, such as only HEPA filters).*
- *Systems can be organized geographically (i.e., at room level).*
- *Systems can be organized by connected components (i.e., an AHU system).*
- *Control and monitoring system can be either a separate system, or may be included as part of another system.*

STEP 3.0 Define how the CPPs are monitored. Some examples may be:

- *Humidity is monitored by an independent SCADA based environmental monitoring system.*
- *Temperature is monitored by an independent SCADA based environmental monitoring system.*
- *Air quality is monitored by a routine test using a particle counter to per ISO CEN 14644-2 (Reference 3, Appendix 12) for particles, and also via microbial testing.*
- *Microbial monitoring for viable particles is tested per local SOP.*
- *Room pressure differentials are monitored by an independent SCADA based environmental monitoring system.*

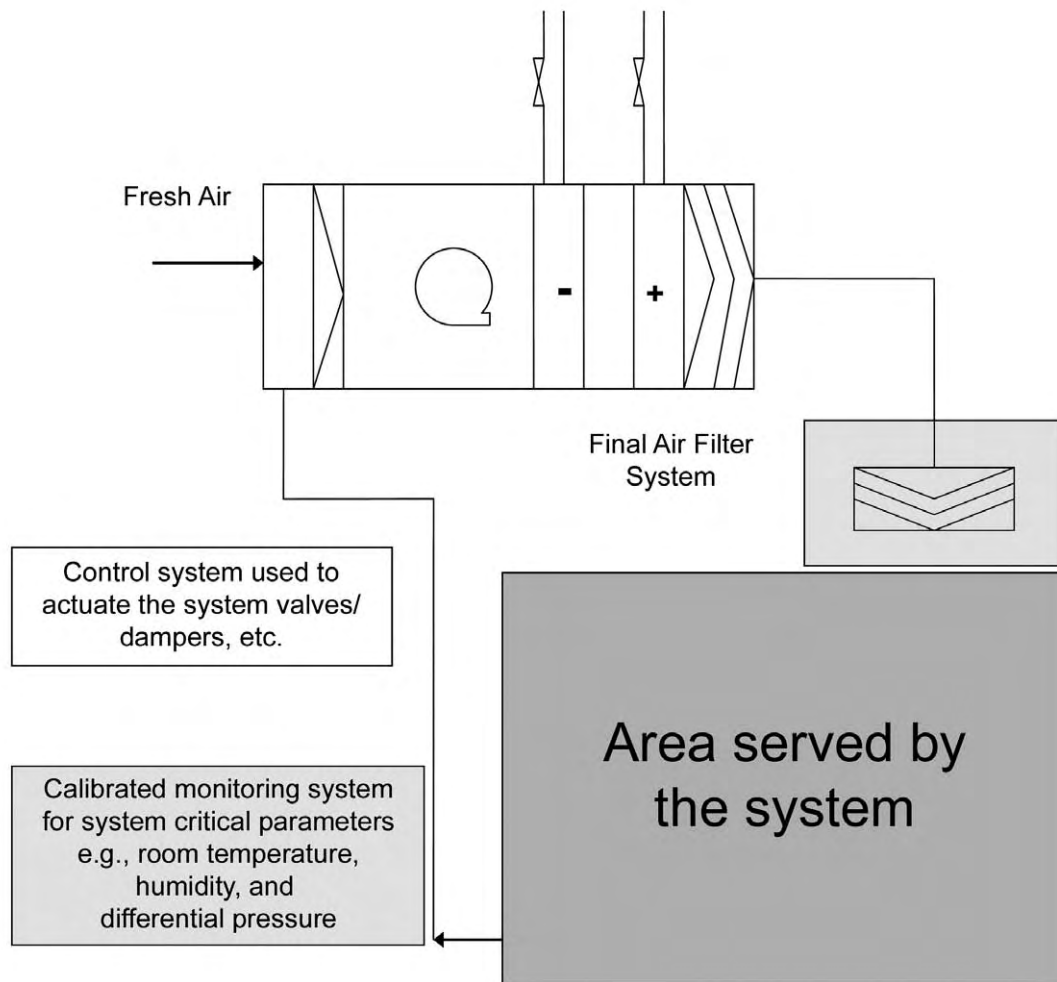
STEP 4.0 Define how the CPPs are achieved, and any associated equipment risks of failure and the probability of detection of those failures. Some examples may be:

- *Humidity control is achieved by either dehumidifying (through cooling or desiccant) or by adding moisture with a steam humidifier. As humidity is continuously monitored by a verified system, it is considered adequate to commission the humidifier/dehumidifier system, and maintain it under engineering change control*
- *Temperature control is obtained through the use of the heating or cooling coils. As temperature is continuously monitored by a verified system, it is considered adequate to commission the heat system, and maintain it under engineering change control.*

- *Air quality in Grade 8 is obtained through the final HEPA grade filter, which is leak tested annually with a particle count conducted periodically. As the HEPA filter integrity is not continuously monitored and is directly responsible for this aspect of the system performance, it will be verified and maintained under quality change control.*
- *Room pressure differentials are the result of resistance to leakage from and to the conditioned space from adjacent areas. As pressure is continuously monitored by a verified system, it is considered adequate to commission the duct/damper system and maintain it under engineering change control.*

Based on the above examples, the equipment to be verified and maintained under formal Change Control is shown as shaded boxes in Figure 2.4.

Figure 2.4: A Typical Schematic of Critical Devices



Examples of other methods for performing an HVAC risk assessment, including some typical risk assessments of HVAC components are included in the appendices.

2.4 Programming for Detail Design

2.4.1 Programming and Layout Considerations (Schematic Design)

Issues with HVAC systems may affect the programming and layout of a facility design to avoid future problems in the construction, commissioning and qualification, operation, and maintenance of the facility. The impact of HVAC varies by type of facility, generally increasing as the complexity of the facility increases from general administrative office areas to more complex facilities for aseptic or potent compound processing.

In general, the larger the classified area and the more stringent the environmental cleanliness class, the more complex and costly the HVAC system, both in first cost and ongoing operating costs. Once the user requirements document is formally approved, design can begin. Changes in scope that affect the user requirements should be formally approved before design can be changed.

Special requirements should be determined for temperature or RH for specific rooms (freezers, chill rooms, stability storage chambers, R&D suites, etc.).

HVAC engineers should understand the flow of materials, equipment, and personnel (unidirectional flow; gravity flow, etc.) in determining area classifications, pressurization strategies, and airlock strategies (the use of airlocks to separate areas of different requirements for cleanliness, pressure, temperature, and RH), their classification, HVAC system zoning, etc., and location of changing rooms and their classification. **Note:** Elevators serving classified spaces should be located outside those classified spaces.

Area functionalities and adjacencies (both horizontal and vertical) should be determined.

Functional/relational adjacencies should be determined (e.g., avoid placing large AHUs next to a laboratory with vibration-sensitive precision analytical equipment).

There may be special considerations in the layout and adjacencies for projects employing prefabricated modular construction.

HVAC and utilities equipment, duct/pipe routing and supply/exhaust/return, and diffusers/grilles locations and issues should be considered. Outside air intakes and exhaust stacks should be located to avoid entrainment/re-entrainment of unwanted fumes and odors, such as laboratory fume hood exhausts, process vents, and fumes from idling trucks near docks and other loading/unloading facilities. Major equipment may be located, e.g., in a basement, penthouse, or roof, accordingly. Building configuration ($H \times W \times L$) may affect the location of central services and how they are distributed.

Maintenance

The requirements for maintenance, testing, repair, and replacement should be considered, including the locations for access doors/panels for HVAC system inspection, testing, maintenance, and HEPA filter scan testing and replacement.

Access to field instruments for calibration, testing, and repair also should be considered.

For AHU maintenance, removal or replacement of large motors and fans, dehumidifier wheels, coils, and filters should be considered. Access to AHUs should allow the removal and replacement of large equipment (clear pathways, hoists/elevators, etc.).

Locations and access requirements for BMS/EMS data and control should be identified. Requirements for local indications and control features for BMS/EMS should be determined.

Facility maintenance philosophies (i.e., maintain from inside or outside of room) should be defined.

Process

Materials to be used in a process (i.e., potent, solvents, cytotoxic, sterile) and the approaches and technologies for product containment and clean/sterile processing should be determined.

The use of micro-environments (barrier isolators, Restricted Access Barrier System (RABS), biosafety cabinets, etc.) may reduce both the required amount and grade of classified space, compared to traditional dedicated classified rooms for open pharmaceutical processing. This may result in a smaller facility footprint, fewer airlocks, and lower overall HVAC system life cycle cost.

The location and associated maintenance of hazardous equipment and ductwork may affect facility layout.

Process issues related to codes and standards, include:

- codes and standard applicable to the region (e.g., Americans with Disabilities Act (ADA), Fire, OSHA, Energy, IMC)
- ease of egress and other safety considerations
- risks associated with various layout and programming issues (i.e., area electrical classification, explosion-relief panels, product risks)
- special considerations associated with hydrogen or nitrogen operations
- Where facility modules are prefabricated in a jurisdiction different to that of the facility location, special attention should be given to requirements of local codes and standards. Applicable requirements should be identified early in the design process.

Process issues within a room which should be considered include:

- locations of personnel, processes, and product with respect to HVAC supplies and exhaust/returns
- equipment heat loads (where is heat generated and how is it cooled or extracted?)
- Locations of utilities connections in regard to the operations to be performed. Room HVAC system should be designed as an integrated system in rooms with fume hoods, biosafety cabinets, LEV systems, and process equipment HVAC systems. Using a manifold exhaust system rather than one fan per hood may affect facility layout.

2.4.2 Architectural Considerations

HVAC engineers and the project architects should coordinate HVAC on issues and considerations which affect both the architectural aspects of a project and HVAC systems. Problems in the construction, commissioning and qualification, operation, and maintenance of a facility may be avoided.

The materials of construction of a facility include:

- Room Finishes: these should be cleanable, resistant to cleaning and sanitization chemicals, suitable for the environment, and be wear/bump resistant.
- Flooring: appropriate flooring materials should be selected for an application. The technique and skills of flooring installers should be verified. Installing test patches of the materials and the techniques being considered may be used to evaluate their performance in a specific application. Poor flooring can add to airborne particle levels.

For further information, see relevant ISPE Baseline® Guides (Reference 13, Appendix 12).

Construction methodologies for both architecture and HVAC designs should be coordinated:

- Room tightness: where pressure differential is significant, floor to ceiling walls should be used. Hard (gypsum or gasketed, interlocking, steel or FRP panels) ceiling construction may be used for pressure-controlled spaces. In addition, air migration above a ceiling should be minimized between controlled and uncontrolled spaces. If RH is significant, reducing moisture migration through unsealed penetrations, drains, door seals, and porous wall materials should be addressed. Door specifications should address seals, windows, interlocks, construction of the door, actuation, direction of swing, and hardware.
- To minimize air leakage, the gap between finished floor and the bottom of door should be uniform (typically approximately .125 to .5 inch (3 to 14 mm)) when closed. Door sweeps are typically not recommended for swinging doors in manufacturing spaces, because of their accumulation of dirt, scratching of the floor, and increased maintenance.
- A commissioning test to verify room tightness (i.e., room leakage test or room integrity test per ISO 14644-3) should be considered.
- The use of prefabricated modular facility construction techniques may impose additional restrictions on a HVAC design (e.g., design may be limited to equipment suppliers with which the module contractor has an established relationship; the size of AHUs may be limited to the size of a standard module). Owners should understand the limitations and preferences associated with each module supplier, for example:
 - duct and piping joints at each module interface, misalignment, and leakage potential
 - limited height
 - constraints on duct routing
 - tight access to mechanical spaces for service and removal/replacement
- Where possible, service distribution and pipe work should be located outside a cleanroom in an adjacent utility space to promote better airflow patterns and to produce fewer pockets for dirt to accumulate. In addition, this location is helpful for the maintainability of equipment.
- The effect of HVAC systems on programming and layout will vary depending on the type of facility. See Chapter 3.

2.4.3 AFD and AF&ID

Once functional relationships between areas are established along with their HVAC requirements, and product contamination and operator risks are identified, a simple AFD can be created. Critical components of filtration or parameter monitoring systems also may have been identified, and provide the initial elements of an AF&ID. (On completion, an AF&ID should show all instrumentation.)

An AF&ID may be considered the HVAC version of a P&ID. For a definition of P&ID, see Appendix 12.

An AF&ID usually will include:

- instrumentation with tag numbers
- equipment with tag numbers

- control and manual valves/dampers with tag numbers
- duct and piping, sizes, and identification references
- vents, drains, fittings (e.g., reducers, increasers), sample points
- flow directions
- control inputs and outputs, interlocks
- safety and regulatory requirements, including seismic category
- annunciation inputs
- supplier and contractor interfaces
- identification of components and subsystems delivered by others, i.e., system boundaries

This should be supplemented by documentation of intended physical sequence of the equipment, startup, and operational information.

An AF&ID typically does not include:

- instrument root valves
- control relays
- manual switches
- equipment capacity
- pressure temperature and flow data

An AFD will usually include:

- ductwork
- major HVAC equipment with tag numbers
- valves and dampers that affect operation of the system, including balancing dampers
- interconnections with other systems
- system ratings and operational values as a minimum, normal and maximum flow, temperature, and pressure

An AFD typically does not include:

- duct classification and material
- line numbers
- minor bypass duct
- isolation and shutoff dampers

- access points
- safety and regulatory requirements, including seismic category

As there is no standardized in its approach, organizations may have “standard practices” that fall between AFDs and AF&IDs.

An AFD/AF&ID may be used as a master “record” that is maintained on an ongoing basis for regulatory purposes. The master record AFD/AF&ID should include:

- the volumetric airflows to the rooms and acceptable tolerances
- the design and operating limits for room temperature and humidity
- area classifications
- airflow directions/pressure differentials and infiltration/exfiltration
- the process flow
- critical instruments

Note: References pipe and ductwork routing (dimensional) drawings may be included in the list of requirements for an ‘as built’ record drawing, but these are not considered to be critical for an HVAC application.

Other drawings, such as installation drawings which are kept for engineering record purposes, may be updated on an ‘as needed’ basis.

A nomenclature for “tag numbers” shown on AF&IDs should be established to help improve understanding between designers, contractors, and operators. Industry systems, such as the tagging nomenclature established by ISA, commonly are used. For example, in ISA TE-209 is a Temperature Sensing Element (TE) on control loop 209 or room 209.

As the AF&ID develops, a description of **how** a HVAC system satisfies User Requirements can be developed (i.e., the ‘functional design’). Programmers of the HVAC control and monitoring systems, commissioning personnel, and regulators who need to understand the role of the HVAC system in protecting product should find this helpful.

3 Design Considerations

3.1 Introduction

This chapter is intended to assist HVAC system design and commissioning personnel; providing suggestions and a selection of typical schematics.

Specific regulatory requirements are covered in the relevant ISPE Baseline® Guides (Reference 13, Appendix 12). As there is no Baseline® Guide for medical devices, a brief overview is provided in Appendix 3.

Air handling systems should provide physical separation to prevent airborne cross contamination between products. Cross contamination control can be achieved with stringent air filtration, by using only once-through air, or by the use of separate (dedicated) air handling units. Separate air handling units may be used for different product areas to prevent cross contamination via ductwork, and are often used to segregate different building functions, such as:

- production
- production support
- warehouse
- administration
- mechanical areas

Within production areas for a given product, the cost of further segregation may be justified for various unit operations, e.g., upstream cell culture versus downstream purification, pre- versus post-viral processing, or aseptic filling. See the appropriate facility Baseline® Guide for considerations (Reference 13, Appendix 12).

Manufacturing areas supporting key unit operations usually require maximum on-stream reliability. The air-handling units supporting these areas may be configured for partial operation during routine maintenance operations to support areas still in production. Shutdowns for routine maintenance are permissible for specific product forms, while not in production.

It should be noted that simplicity of design often assures greater uptime and compliance with fewer maintenance procedures.

3.2 General Design Considerations

3.2.1 Heating and Cooling

- Heating coils may be required for air handler systems in cold climates with higher percentages of outside air.
- Energy recovery may be justifiable. Enthalpy wheels may be justifiable for non-production areas.
- Unidirectional flow hoods that have recirculation may be supplied with a small percentage of fresh (or cooled) air to offset fan heat. This is usually not a problem in smaller UFHs.
- Use of energy conserving enclosures such as glove boxes is encouraged.

3.2.2 Humidity

- Humidification should be considered for cold or arid climates where static control is a concern.
- Desiccant dehumidification and post cooling coils should be considered for low humidity room control (i.e., powder handling). Desiccant dehumidifiers should be used sparingly, usually when a dew point below 40°F (5°C) is needed, because of high capital and energy cost. If humid outdoor air can leak directly into a processing room, however, cooling/condensing coils alone may be incapable of meeting room humidity requirements and a chemical dehumidifier may be needed. Room pressurization may be considered to improve this situation.
- Exposed powder products may require RH below 40% to prevent absorption of moisture. If RH is too low (below 20 to 30%), workers may experience irritation of throat and eyes.
- Where low RH is required, special attention may be given to sealing the return duct systems to prevent inward air leakage from uncontrolled spaces and resultant high humidity.
- Humidifier locations can vary with the most common being AFTER final filters in the AHU, and before cooling coils in climates where cooling and humidification are unlikely to occur simultaneously. Designs with humidifiers before fans should be sure that water droplets do not impinge on the fan inlet, possibly leading to corrosion. Humidifiers are covered in more detail in Chapter 5 of this Guide.

3.2.3 Hazardous Materials and their Removal

- Where solvents are handled, 100% exhaust (once-through) systems are recommended. Oxygen depletion and LEL monitors may be employed, as appropriate, to assure that dangerous conditions do not occur, especially when using recirculated systems. Such systems should also comply with fire and building codes.
- Once-through air systems are common where potent compounds are handled in the open.
- Recirculation of room air is not allowed by most codes and insurers when solvents may be present above 25% of LEL. Where solvent use is occasional and small in volume, return air ducts should be equipped with control device sensors to switch the system to 100% outdoor air in the event of a spill.
- There may be specific requirements for storage and handling of hazardous materials, e.g., once-through ventilation and high extract rate capability in the event of smoke detection (see applicable Fire/Safety Codes).
- The storage of incompatible materials may dictate specific HVAC design requirements (see applicable Fire/Safety Codes).
- Exhaust should be hard connected wherever possible. Movable arms (trunks) should be provided for point exhaust sources that do not support hard duct connections or fixed exhaust hoods. These supplemental point exhausts should be served by an independent exhaust box (where possible) or connected directly to the main (with a volume damper or blast gate).
- Exhaust ductwork does not normally require insulation except if part of a heat recovery system or where internal condensation is possible (high concentration of corrosive vapor).
- The use of emergency power for exhaust systems should be considered on a case-by-case basis. In multi-fan manifolded systems (such as in laboratories or API chemical facilities), the use of emergency power for at least one fan should be considered.
- Where emergency power is not provided for exhaust fan(s) alarms should be connected to emergency power or furnished with UPS to signal exhaust failure. (Recommended for fume hoods in laboratories without room pressure monitoring.)

- Provide LEV for control of fugitive active dusts or aerosols in the room; LEV should be provided at emission points and equipment break points. Containment devices with leak free equipment connections are recommended.
- Provide LEV for containment devices, such as glove boxes, isolators, and powder transfer equipment.
- A testing and preventive maintenance program should ensure the integrity of exhaust cleaning system and LEV performance.
- Dust collection systems designed to allow removal of contaminated media without contact or exposure with harmful compounds (e.g., bag in/bag out filters) should be considered where handling potent compounds.
- Spark-proof exhaust equipment should be provided when serving process areas where flammables are handled. As a minimum, exhaust fans should be AMCA Type B spark resistant construction.
- Explosion proof or intrinsically safe electrical components should be provided in potentially flammable exhaust air stream. Non-explosion proof fan motors may be used if outside the air stream.
- Wherever exhaust to atmosphere is shown, the contents of the exhaust stream should be evaluated, e.g., material, form (solid, vapor, etc.), expected quantity, and times when exhausted. Scrubbers, dust collection, thermal oxidation, carbon adsorption, and “polishing” filters may be required to protect the outdoor environment and prevent re-entrainment into HVAC systems. If used, energy from exhaust streams should be recovered before scrubbers in order to capture as much of the wasted energy as possible. The recovery unit’s construction should deal with the contents of the exhaust stream.

3.2.4 Product Contamination Control

- If near a production area, schemes using return air from a general area to a common plenum (such as to the plant room) may create pressure control problems in the production area.
- Manufacturing rooms should be protected from migration of contaminants or solvent vapors via the use of room pressure or differential airflows. Where multiple products are handled concurrently, HEPA air filtration is recommended; once-through air or dedicated air handling systems for each product area also are options.
- Monitoring and alarm of direction of airflow or DP (for classified areas) is suggested where airborne cross-contamination is an issue.
- A remotely operated or automatic damper may be provided in the return air duct from each room as a means of setting the desired pressure differentials. Duct pressure control also may be needed. Simple facilities may be balanced successfully using only manual dampers, especially if terminal HEPA filters do not load quickly or differentially, and therefore, change supply airflow (i.e., are preceded by high efficiency filters in the AHU).
- If manual/remotely operated dampers are used, the damper controls should be tamper-proof or concealed in a lockable cabinet accessible only to authorized personnel. A DP gauge should be provided for each room adjacent to the damper controls to facilitate balancing.
- Packed silencers are not recommended where they can harbor contaminants and viable organisms.
- Low returns in CNC (with local monitoring, equivalent to EU Grade D) processing areas are recommended and should be located behind process equipment where applicable and where clearance is sufficient to allow proper air extraction from the space. CNC areas (airflow filtration on supply air with personnel access control) do not require low level returns, but can be used if deemed necessary by the design team.

- Grade 5 (Grade A) rooms and large UFHs may be unavoidable (such as for manual multiple lyophilizer loading) but are not recommended because:
 - They place the operator in the clean space with the product. Special procedures are needed and should be verified with airflow visualization (smoke tests).
 - Airflow pattern tests may reveal a “dead zone” near the area of the room farthest from low wall air returns, often in the center of the room where critical activities are located. This problem is solved in the electronics industry with perforated floors and a return air plenum below the floor. However, this solution creates a cleaning issue and is a potential harbor for bacteria so it is not recommended for pharmaceutical cleanrooms. A low wall return below a lyophilizer door can improve patterns in front of the door.
 - If the supply air filters are too high, airflow patterns can greatly deteriorate before the air reaches the critical site. Open Grade 5 areas should be kept small with HEPA filters as near as possible to critical sites.

3.2.5 General AHU and Control Considerations

- Air systems may recirculate with the minimum outdoor air necessary to maintain pressure relationships, in support areas, and where no solvents or potent compounds are handled.
- HEPA filtration should be considered to prevent cross-contamination and limit operator exposure in manufacturing area recirculation systems.
- Once-through systems do not require HEPA filtration for cross-contamination control.
- Recirculation of return air from production areas as supply to non-production areas is not recommended.
- The most common air handling system for pharmaceutical production is the Constant Volume (CV) terminal reheat type.
- The supply fan should be equipped with variable dampers, vanes, or speed controls that can be reset in order to maintain design airflow for the life of the air filters (whose pressure drop increases with time).
- Risk assessment should be performed to determine the need for fan redundancy (parallel fans or multiple plug fans in the AHU). Use of standby electric power systems to maintain fans and design pressure differentials in the event of local power failures should be considered.
- 100% outside air handling units are prone to freezing in preheat coils; variable temperature constant internal flow volume pumped preheat coils or Internal Face and Bypass (IFB) steam coils help to reduce this risk. Propylene glycol solution for preheating also may prevent freeze-ups.
- Backup power for monitoring systems to determine if critical parameters are compromised during a power outage should be considered.
- Successful HVAC systems may not have DP controllers, constant air volume boxes, or HEPA prefilters, etc. The need for complexity and its added cost should be justified.
- Access doors are suggested wherever maintenance or testing is required. Minimum locations include access to key air handler components and in-duct sensors. Access doors provide a route for leakage and contamination, so keep their use to a minimum.

For further information on additional equipment considerations, see Chapter 5 of this Guide.

3.2.6 Application of Outside Air Pretreatment

It may be more energy efficient to pre-treat incoming outside air and supply it to one or more recirculation units, rather than overcooling or desiccant dehumidification of an entire recirculated air stream.

Applicability:

- The desired mixed air condition should be established; there will be a limit to the achievable humidity levels.
- The moisture load in the return air should be less than the desired mixed air condition (low internal latent load).
- Outside air volume requirements should be sufficiently understood to size the pre-conditioning equipment.
- Excursions above humidity setpoint, because of intermittent activities that create additional latent load (e.g., cleaning), should be tolerable.

Configuration Options:

- Where internal sensible heat gains are low or where outside air is a large percentage of the total airflow, the pre-treated air may provide all cooling for a space. This configuration has a low first cost and low energy cost, but may lead to temperature variations within a controlled space. It should be employed only when the processes, systems, and environment are sufficiently understood.
- Where multiple recirculation units are employed, a central pre-treatment system may provide outside air to all AHUs.
- Coils in the recirculation airstream may be configured for sensible cooling only with fewer rows, lower air pressure drop, and no drainage pans. Alternatively, larger coils and drainage pans may be installed in the recirculation unit for flexibility and faster recovery from excursions.
- The use of a small dehumidifier to provide pre-treated air at low moisture levels may eliminate the need for moisture reduction (via over-cooling and reheat) in the recirculation air stream.
- It is recommended that air from the pretreatment system is introduced into the inlet of the recirculation system to ensure acceptable blending and temperature control, ease of balancing, and duct pressure control; however, it is possible to blend the air downstream of the recirculation unit.

Advantages:

- eliminates wasted energy from overcooling and reheating or dehumidifying the entire recirculated airstream
- lower first cost, because of elimination of drain pans, smaller (fewer rows) cooling coils, smaller dehumidifier (if applicable)
- lower energy cost, because of lower air pressure drop over smaller cooling coils
- effective where most humidity is from external sources

Disadvantages:

- may not be able to achieve low humidity, where required, because of internal latent heat gain or leakage into return air ducts from unconditioned spaces
- has limited flexibility for later changes to conditions

- may not be applicable if return humidity is too high (high internal latent load)
- additional maintenance (for pretreatment equipment)
- additional space required for pretreatment equipment and associated ductwork
- if a desiccant dehumidifier is added to the pretreatment system, in place of over-cooling and preheat in recirculation, it increases complexity and may add a new type of equipment

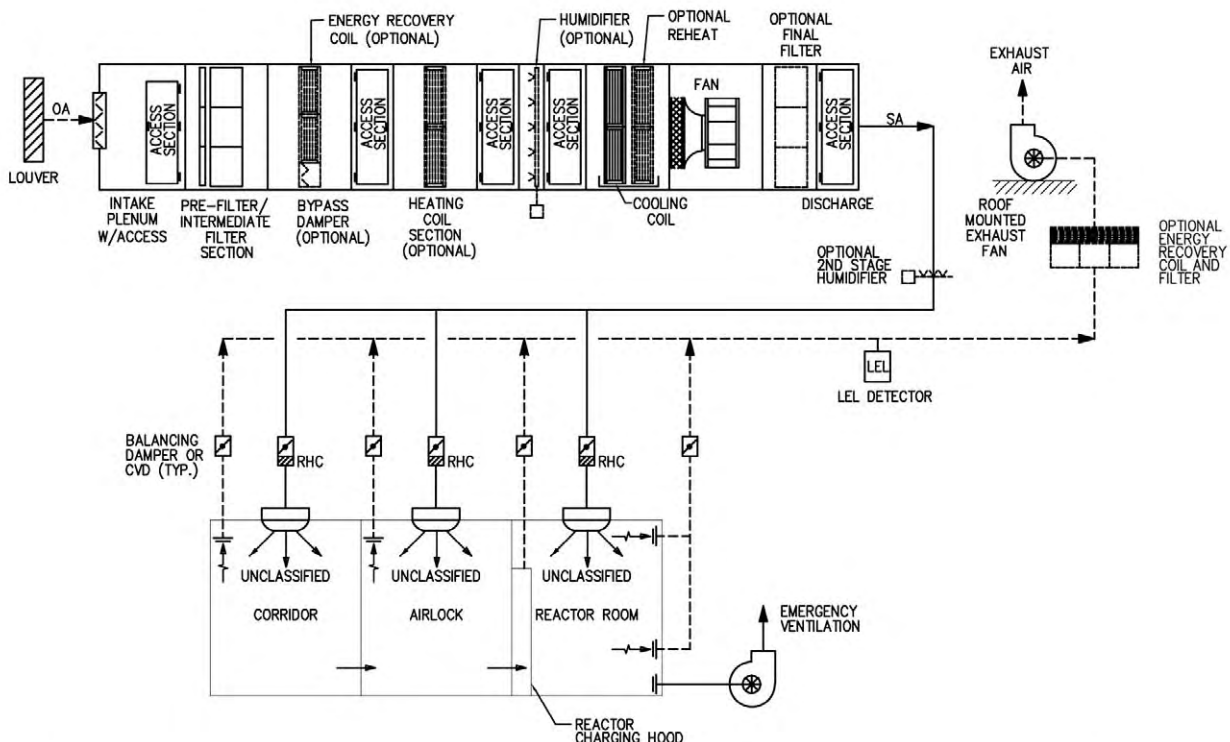
3.3 Air Flow Diagrams by Facility Type

The typical basic (AFDs) included in this section were developed as examples and *may not be appropriate for all products or facilities*. Some instrumentation (as found on an AF&ID) is shown. The detail of design and the extent of control are meant **for example only** and do not constitute recommended practice.

Note that RHC stands for Reheat Coil, and Constant Volume Damper (CVD) is an airflow flow control device to hold air flow constant.

3.4 Active Pharmaceutical Ingredients (APIs) – (Wet End)

Figure 3.1: Chemical APIs



Note: Instrumentation – RH stat in reactor room controls cooling coil and humidifier. Thermostat in reactor room controls reheat coil. Thermostat set at 50°F (10°C) controls preheat coil. DP gauges on each filter bank. Emergency ventilation controlled by Spill Help alarm. Not shown – DP gauges on air filter banks.

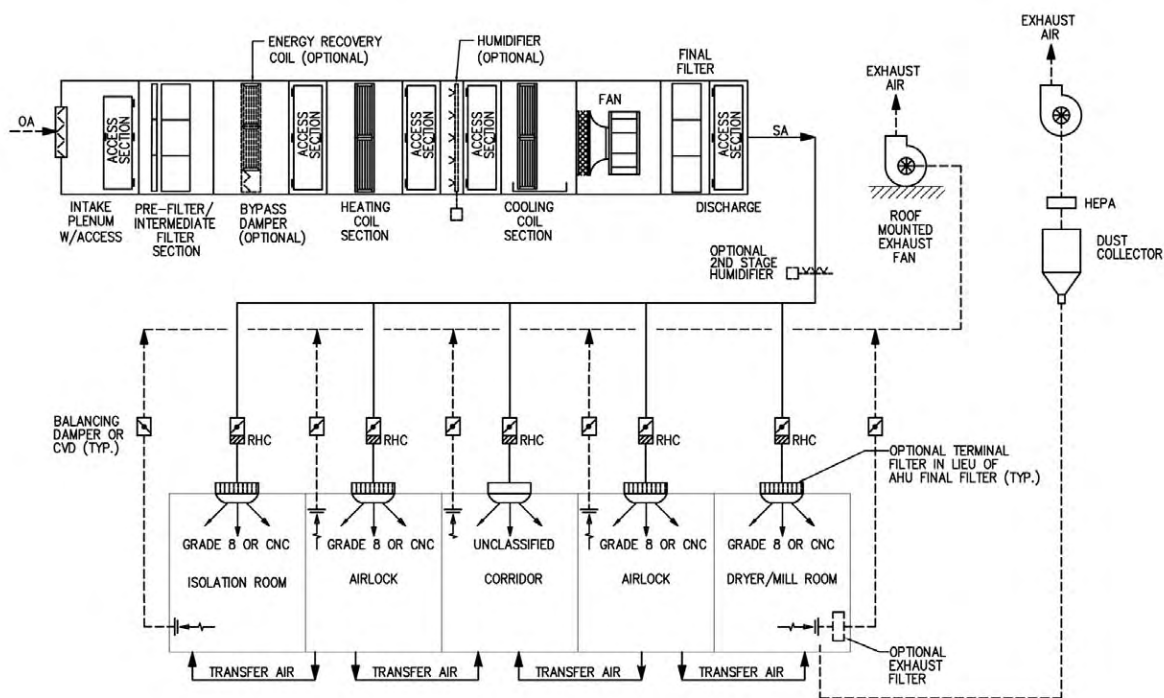
3.4.1 System Design Considerations

- Product-specific requirements are covered in the ISPE Baseline® Guide on APIs (Reference 13, Appendix 12).

- Air systems should be once-through where solvents or potent compounds are handled in the open. Additional emergency ventilation may be required by local code or by insurers, activated by manual “help/evacuate” alarm or by sensors.
- Where processes are proven closed, air recirculation may be considered with LEL monitoring in return air to detect a flammable spill. If processes are in closed temperature controlled vessels, room HVAC should satisfy operator comfort requirements.
- Use of adequate dilution ventilation and exhaust on emergency power may be used to minimize electrical classification requirements in some jurisdictions. AHU should have MERV 7 followed by MERV 13 filters for good housekeeping.
- Manufacturing rooms should be fitted with low or combination high/low returns.
- Provide LEV for dry product addition sites, drum handling, manways, and spills in wet areas. The use of charging isolators or booths to minimize the flammable and potent /hazardous material exposure in the room should be considered.
- Aqueous chemistry usually does not require once-through air; the AF&ID for OSD may be applied in these areas.

3.5 Active Pharmaceutical Ingredients (APIs) – (Dry End)

Figure 3.2: Final API Dry-End Schematic (Once-Through for Solvents or Potency)



Note: DP gauges on filter banks, room thermostats controlling RHC, one RH-stat controlling cooling coil and humidifier.

3.5.1 System Design Considerations

- Oral dosage (“dry”) API product handling areas (i.e., centrifuge, dryer, blender, mill, pack-off rooms) do not require classified cleanrooms; however, they should be designed in a manner consistent with CNC, OSD design concepts as described in various ISPE Baseline® Guides (Reference 13, Appendix 12) (similar to European grade D – capable of meeting ISO 8 AT REST, but not monitored).

- Areas serving final bulk product that will become sterile product (including bulk biopharmaceuticals) should meet Grade 8 (Grade C). This generally requires HEPA filtration on the supply air, low returns, pressure airlock (to keep exposed powders in the room), and instrumentation for verification of room conditions. Final drug substances areas may need to meet the requirements for dispensing of API in the finishing facility. For sterile or API that will become sterile, the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12) should be consulted (may be Grade C or D with air filtration, DP control, airlock, etc.)
- Manufacturing rooms should be fitted with low or combination high/low returns.
- LEV should be provided for dry product addition, drum handling, manways, and where spills are likely in wet areas.
- See Chapter 3 of this Guide (API-Wet) for considerations if solvents are used in the process.
- Closed intermediate product processes are usually in temperature-controlled vessels and have no area requirements. See the ISPE Baseline® Guide on APIs (Reference 13, Appendix 12).
- In general, where flammability is not an issue, recirculated HVAC is possible.
- AHU filtration should be MERV 7 followed by MERV 13. Final filter grade should assess potential product size and potency. See note above for final aseptic API steps.
- Potent API containment exhaust should not be returned to the room. Scrubbers or HEPA filters are recommended in exhaust for potent products.

3.6 Biologics

Figure 3.3: Biologics Upstream Processing System Schematic

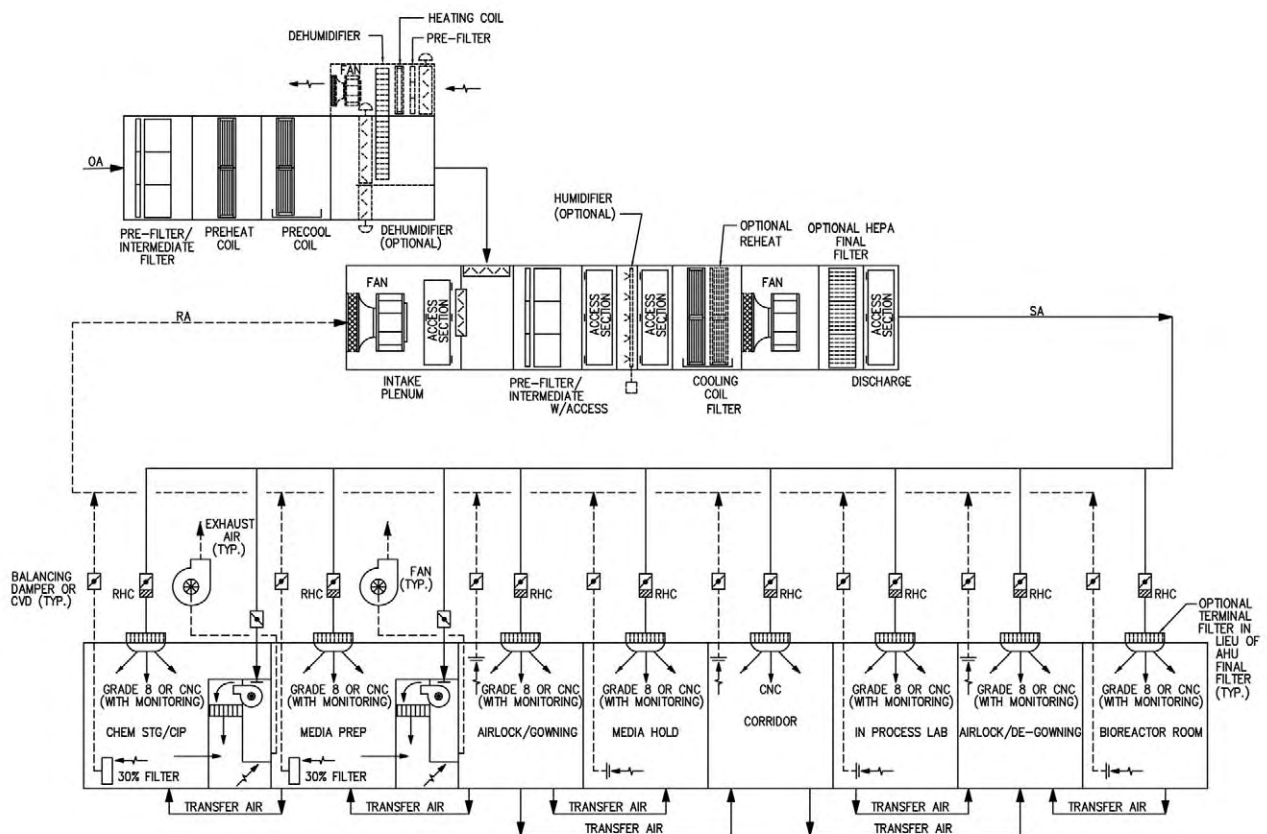
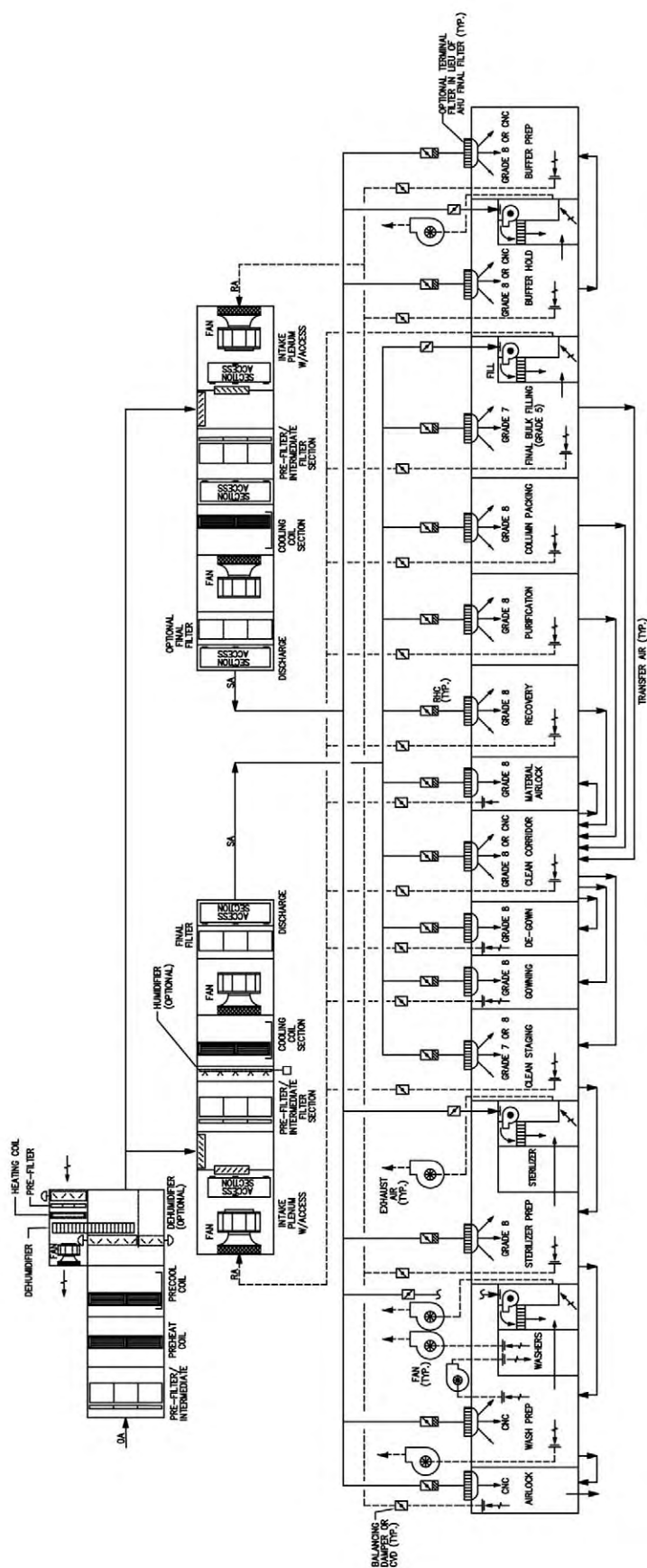


Figure 3.4: Biologics Downstream Processing System Schematic



Note: Separate AHUs are commonly used to enhance the separation of pre-viral from post-viral purification. The distinction between pre- and post-viral is hard to discern and may differ by product and process.

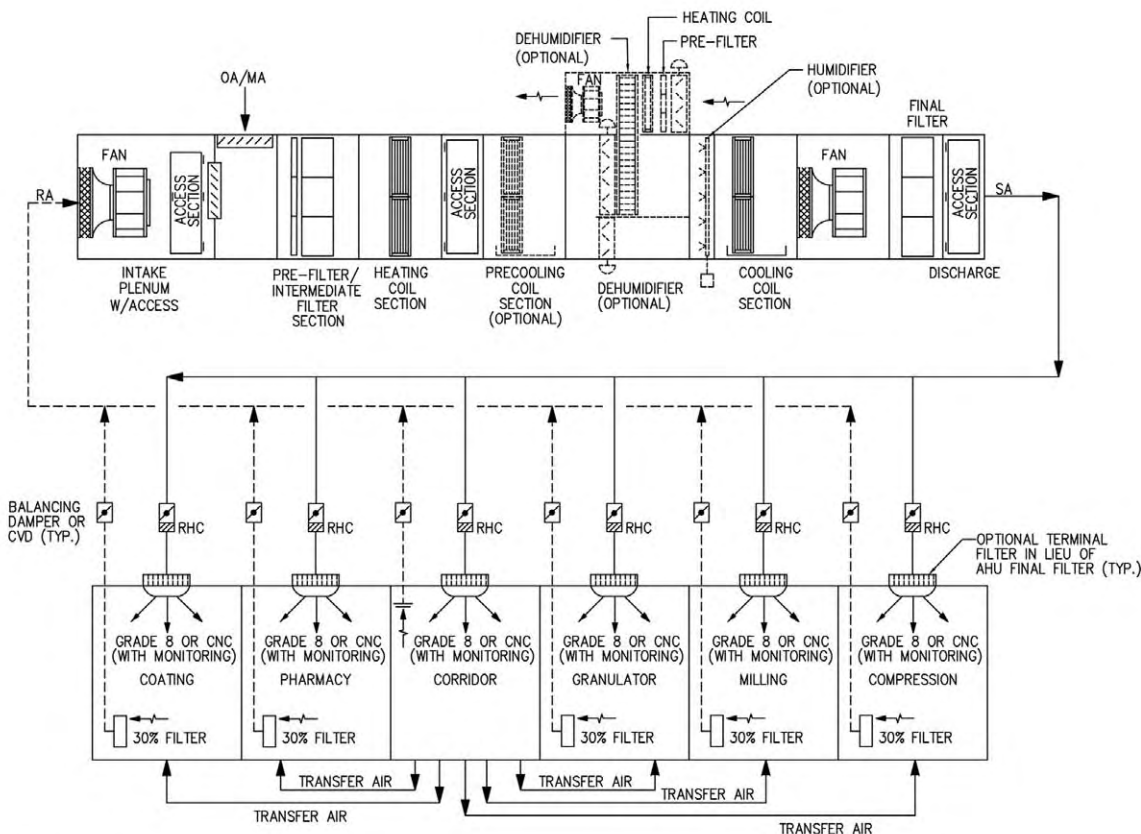
3.6.1 System Design Considerations

- Bulk biopharmaceutical products may require area classification. See the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities (Reference 13, Appendix 12) for requirements. Upstream Biopharmaceutical API AF&IDs are similar to diagrams for chemical API.
- Downstream biopharmaceutical API AF&IDs are similar to Oral or Aseptic systems (depending on the CPPs of the particular process and product). Areas needing classification can follow the recommendations for Aseptic Processing HVAC. Reference also should be made to the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities (Reference 13, Appendix 12) for area classification requirements for biopharmaceutical API and for Biosafety Level (BL) information.
- A desiccant dehumidifier rarely is needed for biopharmaceutical processes, except in cold (5°C/40°F) rooms where high humidity can lead to “fogging” and standing water on the floor (a safety and microbiological concern).
- It is common for room air, especially from a Grade 5 (Grade A) area to be recirculated rather than discharged to atmosphere with enough additional supply volume to exfiltrate to lower class areas.

3.7 Oral Solid Dosage (Non-Potent Compounds)

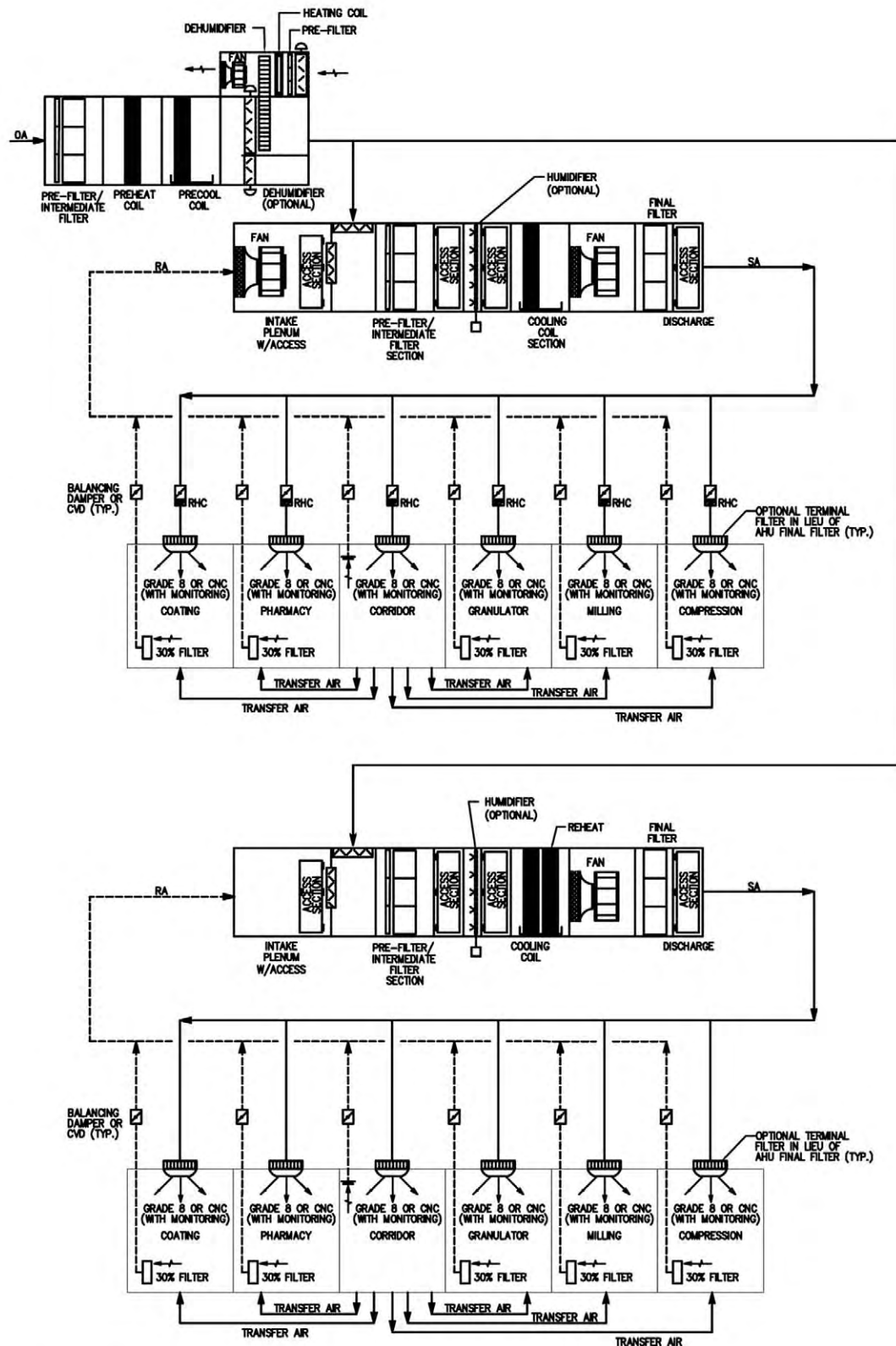
In Figure 3.5, return air filters are located at the rooms, which can cause room DP relationships to change with filter loading. For this reason, CVDs are provided on return air to keep airflow constant.

Figure 3.5: OSD Non-Potent System Schematic (Sample)



Note: 1 CVD on every room return is required due to uneven loading of return air filters. Alternative is for ONE return air filter bank and a constant volume control on return fan. Note that DP gauges on rooms and filters, room temp and RH control, and supply fan control are not shown.

Figure 3.6: OSD System Schematic with Pretreatment (Sample)



- Notes:**
1. The example is appropriate for single product or multi-product campaign production.
 2. Multi-product concurrent production requires the addition of a HEPA filter, preferably in the return.
 3. For potent products, add HEPA filter in the return, preferably in the room.

3.7.1 System Design Considerations

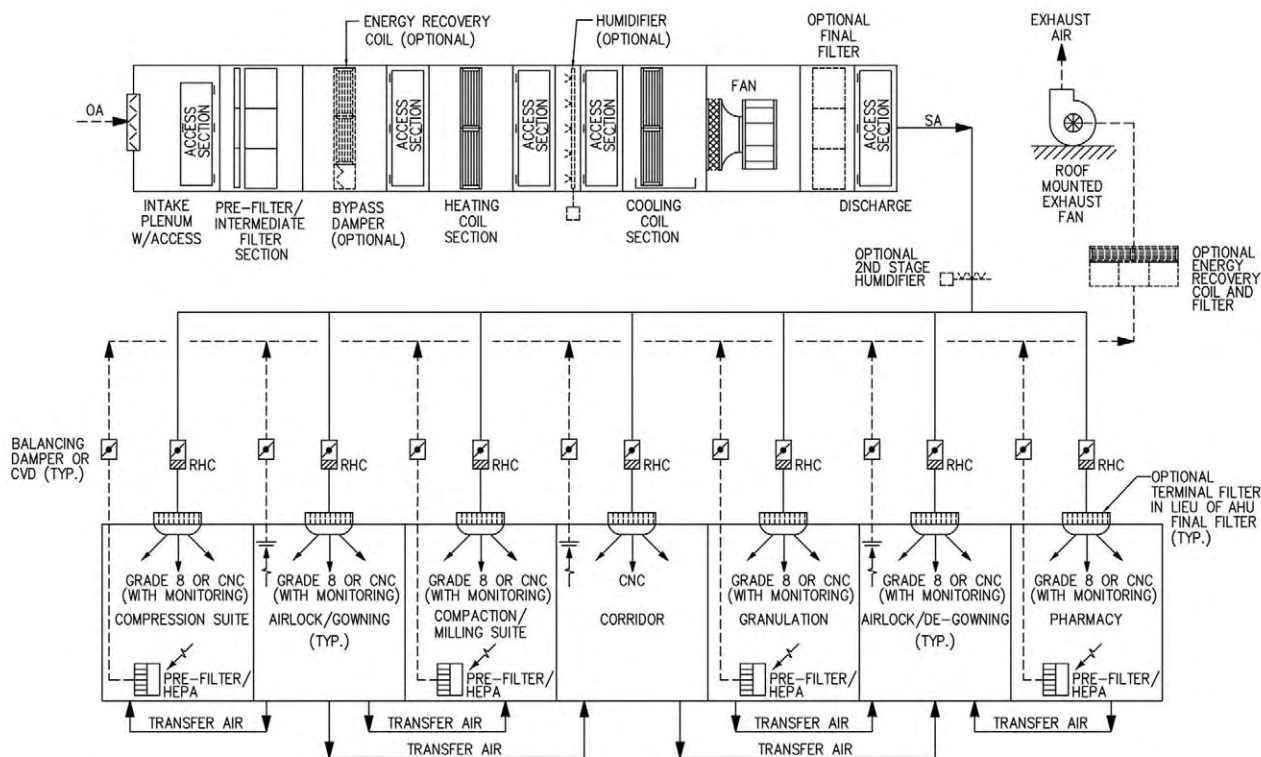
- Further discussion for Oral Solids Dosage facilities is covered in the ISPE Baseline® Guide on Oral Solid Dosage Forms (Reference 13, Appendix 12).
- Oral dosage facilities usually do not require manufacturing activities to take place in areas with assigned cleanliness classifications. While many processing rooms are designated CNC and are capable of meeting EU Grade D (ISO9 or ISO8 at rest), they are not normally monitored for particles. Facilities designed in alignment with WHO 937 Annex 2 (Reference 2, Appendix 12) may be classified by the Owner and periodically monitored for airborne particulate. If aligning with WHO guidance, these facilities may be designed to maintain a DP of 10-15Pa from adjacent, unclassified, spaces.
- However, process and process support areas require critical parameters to be controlled and maintained to protect the product from contamination, whether from another product in a multi-product facility or from external or personnel contamination. Airlocks or anterooms are suggested to enhance segregation.
- Cleanliness of open processing areas should be maintained via control of airflow between product handling area or airlock and surrounding spaces.
- Isolation via a clean airlock (pressure bubble or pressure sink) into the area of highest contamination is strongly recommended. Where solvents are used, this configuration is recommended to prevent migration of flammable vapors to the building.
- Monitoring and alarming of direction of airflow (through DP, hotwire velocity sensors, air balance, flow tracking, etc.) to surrounding rooms is recommended.
- AHU filtration – MERV 7 followed by MERV 13/14 filtration is recommended.
- Final filtration – 95% DOP/PAO efficiency is recommended in exposed Oral Solid Dose and dry bulk (non-Aseptic) product areas, but terminal HEPA filters may be more practical for multiple product facilities. Where terminal HEPA filters are employed for cross-contamination control, 95% pre-filtration can help to maximize terminal filter life.
- Large facilities may consider preconditioning outside air for distribution to local recirculated AHUs, each dedicated to one product suite.
- Low RH may be required; desiccant dehumidification is not uncommon.
- Return or exhaust air grilles may be equipped with easily removable 30% “dust stop” filters. The effect of filter loading on room pressurization or direction of airflow should be considered.
- Recirculation systems with adequate filtration may be applied in multi-product areas where solvents are not present. Precautions are covered in the ISPE Baseline® Guide on OSD Facilities (Reference 13, Appendix 12) as well as in other parts of this Guide.
- Airflow and makeup air delivery should be directed to flow from the operator’s breathing zone and the room entrance toward the source of airborne dust.
- Non-aspirating supply diffusers are recommended to minimize air disturbances, eddies, and re-entrainment of dust.
- LEV for open operation (i.e., open coating, tableting, and capsule fill) should be designed and engineered according to ACGIH standards.

- If risk to workers is assessed to be low, recirculation of LEV exhaust within a production room requires HEPA filtration. The ACGIH Industrial Ventilation Manual (Reference 19, Appendix 12) decision analysis and design criteria should be consulted for guidance on when recirculation is up to standard.
- Recirculation of LEV exhaust to the AHU or the general building is not acceptable.
- Multi-product concurrent manufacturing may require dual HEPA filtration (one supply and one return) for recirculation systems.
- Multi-product concurrent manufacturing typically uses pressure bubble or pressure sink airlocks to avoid contamination of the common corridor.
- Single-product or multi-product campaign facilities may employ a pressurized (bubble) common corridor as an airlock to the process (as suggested in WHO TRS 937 Section 4.5 (Reference 2, Appendix 12)).
- Multi-product concurrent manufacturing facilities may be organized in single product suites to employ the pressurized corridor/airlock concept described in this section.

3.8 Oral Solid Dosage (Potent Compounds)

The typical AFD shown below introduces a number of key concepts that apply to non-potent as well as potent OSD HVAC:

Figure 3.7: Potent OSD System Schematic (Sample)



- Notes:**
1. The example is appropriate for single product, multi-product campaign, or multi-product concurrent operation.
 2. Optional dehumidifier not shown.

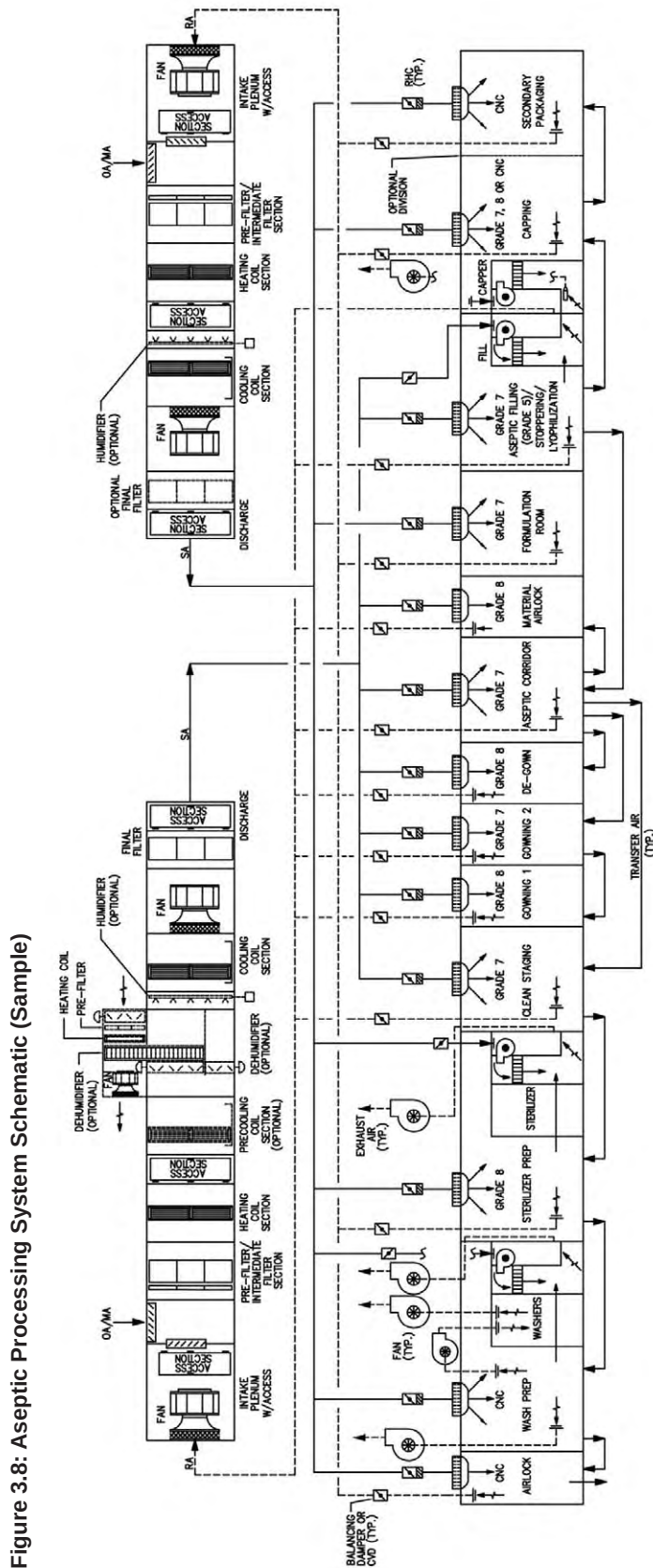
3.8.1 System Design Considerations

Potent OSD facilities should follow the guides above for OSD with the following exceptions:

- A minimum filtration of ASHRAE 85% (MERV 13 or 14) in the Supply Air if a 100% once-through system.
- Closed containment is the primary means of airborne contamination control for this class of material. If processes are proven closed, recirculated air should include HEPA filtration. If the process is not proven closed, once-through air or double HEPA filtration should be considered.
- LEV should be provided at locations where containment is opened for introduction or removal of materials or in conjunction with other technologies, as required.
- LEV should be used for solvent extraction only where containment is not technically feasible (i.e., maintenance activities, etc.). Where LEV is used with any possibility of duct contamination by solids, HEPA filters should be installed near the room, before the AHU, preferably in a bag-in/bag-out enclosure in the return duct.
- Isolation via active control of direction of airflow (using DP, hotwire velocity sensor, flow tracking) into the area of highest contamination from surrounding areas is strongly recommended.
- Audio-visual alert on loss of airflow or containment should be transmitted to the controlled space for personnel safety.
- Room air locks/anterooms are recommended for powder handling areas to provide a barrier that maintains a positive airflow differential with respect to the corridor and the processing room (this may also serve as a gowning area).
- Airflow into de-gowning areas should be negative with respect to the corridor and processing area to contain particles shed from clothing.
- A secondary control against the spread of active materials is direction of airflow within the room. Supply air should be directed to flow across the operator's breathing zone before crossing the source of dust. Wherever possible, supply air should be directed to flow from a location near the room entrance toward the source of dust and finally out low returns mounted on the far wall.
- A dedicated HVAC system is recommended for the controlled space where product is exposed.
- It is recommended that air leaving an **open-processing** room is **not** recirculated. Main air systems for these rooms should be designed for 100% exhaust, once-through supply. However, most processes are enclosed and recirculation with HEPA filtration may be justified.
- Recirculation of air from the controlled space into other areas is not recommended.
- Recirculation of local exhaust (LEV) from equipment back to the room is not recommended.
- Filtration of exhaust from potent dry product handling areas and LEV through HEPA filters, scrubbers, or other equivalent treatment methods prior to release outdoors may be required.
- Where containment equipment is provided and PPE is not required, HEPA filters can protect the AHU and facility in case of an accidental release. These may be a room-accessible type with PPE used for change-out, if needed.
- Exhaust/return filters should be located as near to processing area as possible to reduce the length of potentially contaminated air ducts. Control dampers may be needed to offset the rise in room pressure due to dirty exhaust/return filters.

- Exhaust/return HEPA filters not located within a room or where high levels of airborne powders are expected should be safe-change type with Bag-In/Bag-Out housing and bubble tight dampers.
- Terminal HEPA supply filters can protect against backflow to ductwork if product containment should fail because of AHU failure.
- An annual testing and preventive maintenance program to ensure the integrity of HEPA filtration systems is suggested. Filters on processes requiring PPE should be tested more frequently.
- Appropriate monitoring and interlocking of HVAC with process equipment should be considered to maintain containment integrity and to control cross contamination and emissions. Performance of isolator protection (DP) should be monitored.

3.9 Aseptic Processing Facility



3.9.1 System Design Considerations

- Considerable background on product requirements and the design of HVAC systems is covered in the ISPE Baseline® Guide for Sterile Manufacturing Facilities.
- The impact of closed barrier devices and open isolators (such as RABS) is covered in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12) and Chapter 3 of this Guide.
- Area classification requirements for bioburden-controlled processing (biotech) are covered in the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities (Reference 13, Appendix 12).
- Closed wash equipment may not require room exhaust. Room pressure control may be needed if the exhaust fan can be turned on and off.
- Revisions to EU GMP Annex 1 which went into effect in 2009 suggest that capping be accomplished under Grade A conditions or if outside the aseptic space, under Grade A “airflow.” Some may interpret this as meaning that capping equipment should be in a Grade 7 (EU Grade B) room under Grade A hood. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12), which recommends that “Grade A airflow” is provided by a unidirectional airflow module, which provides HEPA filtered air directly to the uncapped vials until the crimp is complete.
- EU Annex 1 requires exhaust from the crimping operation. This should be located as near as possible to the crimping head(s) to minimize aluminum particulate in the capper. Contamination from the air conditioning supply system should be eliminated with properly installed and integrity tested ceiling mounted terminal HEPA filters for Grade 7/8 (EU Grade B/C).
- AHU filters – MERV 7 followed by MERV 13/14. A HEPA filter in the AHU should extend the life of the terminal HEPA filters. Draw-through AHU is acceptable if the final filter is after the fan and cooling condensate trap has sufficient height.
- RH is normally controlled by condensing cooling or by humidification. Desiccant systems are often used for dew points below 40°F (5°C).
- Outside air may be pre-conditioned and distributed from a central AHU, because of high airflow (air change) requirements.
- Infiltration of contamination from uncontrolled spaces should be minimized by the use of room pressure differentials and airlocks between air classes.
- Continuous room pressure monitoring with alarms and recording devices that indicate out of specification conditions are recommended. Rooms with stringent environmental parameters or where the product is exposed to the environment may require continuous monitoring. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Consider automatic pressure controls to keep the spaces within specified pressure limits where process exhaust volumes can change or where doors and hatches are frequently opened or door seal integrity changes over time.
- Desiccant dehumidification with post cooling coils should be considered for low humidity room control. Low humidity and desiccant dehumidification usually are not needed, as most products are liquid.
- A dedicated air handling system is recommended to serve only the aseptic areas and to remain operational to maintain pressure control when other building systems are shut down during unoccupied periods.

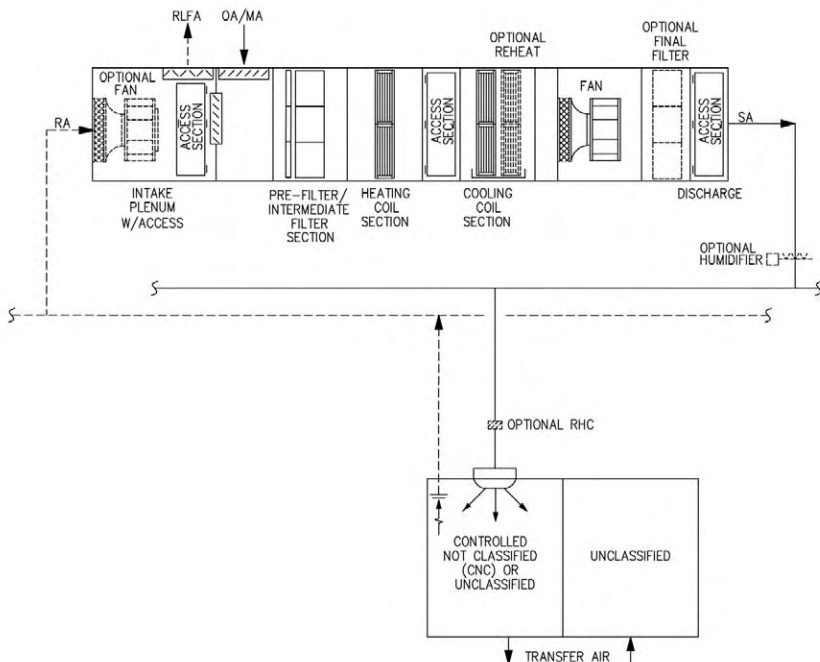
- HVAC systems for classified spaces should operate 24hours/day, 7 days/week. After system shutdown or setback, a protocol for returning a room to proper operating condition should be developed with QA. This does not remove the possibility of reduced airflow during idle periods.
- Ductwork should be designed per SMACNA standards (Reference 30, Appendix 12) and should be constructed for 4 inch or greater water gauge duct static pressure and SMACNA seal Class "A."
- Ductwork should be galvanized steel except where exposed (to a minimum extent) in production areas or subject to moisture, in which case it should be a minimum 304SS stainless with cleanable finish. Cleaning materials used in the room should be considered.
- Air to an aseptic area should be supplied through ceiling mounted terminal HEPA filters. These terminal HEPA filters become part of the aseptic boundary and protect the room from outside contamination. The use of only remote bank mounted HEPA filters in the supply duct is not recommended. Access ports to introduce and monitor PAO (test aerosol) challenge materials upstream on the non-aseptic side of the HEPA diffusers are suggested for filter integrity testing.
- Air supplied through ceiling mounted terminal HEPA filters should be returned at floor level through multiple return duct drops. Return air in the air handling unit should be filtered through MERV 7 pleated and MERV 13 or 14 bag filters to extend HEPA filter life. Recirculation HEPA/fan units mounted below the ceiling as terminal HEPA units are not recommended (unless an alternative is unavailable), as they require service within the aseptic area and do not normally use low returns.
- The return air openings in the aseptic area should be located near the floor, preferably on at least two (2) walls and along the long dimensions of a room to ensure maximum uniformity of airflow. More return openings are better than too few. Equipment and furniture should not block return openings.
- Differential air pressure is needed to minimize infiltration of contaminants from outside the controlled space. The aseptic area should be designed for a positive pressure with all doors closed in relation to less clean adjacent areas outside the controlled space (refer to second edition of ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12). Gowning areas are treated as airlocks with supply and return air, and are maintained at a negative pressure relative to the controlled aseptic area and at a positive pressure relative to the outside and uncontrolled spaces. DPs are measured across airlocks. See the ISPE Baseline® Guides (Reference 13, Appendix 12).
- Each area should have an air supply and return with dampers to permit proper balancing. The room layout of the aseptic suite will dictate the pressure relationships to be maintained. The room with exposed product is to be maintained most positive; while anterooms leading to this room are to be maintained successively less positive down to the zero reference level of uncontrolled spaces (the general building). Where potent product is open-filled and may become airborne, a high-pressure containment airlock that meets the filling room air grade may have pressure higher than the aseptic filling room. A control range should be established for each room pressure level, such that the pressure can float within the range and continue to satisfy the specified differentials.
- The manual/remote gauges and controls or automatic controls should be mounted in a common panel outside the controlled space. An audible alarm may be provided to indicate loss of area pressure control. This alarm may be a manual reset type and equipped with a hard copy printout that indicates the out-of-range alarm.
- Unidirectional airflow serves as a barrier between product and microbial and particulate contamination generated by the equipment and personnel within an aseptic area. Where components and equipment are not protected by unidirectional airflow, terminal HEPA filters should be located directly over the exposed product.

- When the central system air conditioning air quantity required to maintain room conditions is not sufficient to provide adequate air changes for recovery or protection over the product, components, and equipment, a supplemental (“local”) HEPA filtered air recirculating system may be employed. The cooler central system conditioned air may be distributed into the local recirculating AHU or UFH (preferably at the fan inlet) to maintain room temperature. The heat generated from the local recirculating system fan motor should be considered; failing to do so can lead to serious temperature stratification and overheating in the aseptic area. Fan-filter (HEPA) units may add protection or air changes to speed recovery when inlets are ducted to create return airflow from low level.
- Airflow patterns within the workspace (inside the UFH) should be uniform with minimum turbulence. Ambient air may not aspirate into the work areas along the perimeter of the unidirectional airflow barrier. The hood filter area should deliver ISO 5 air at a target velocity of 90 feet per minute (0.45 m/sec) with uniformity within plus or minus 20%, measured just below the filter face (6 to 12 inches, 15 to 30 cm). Velocity at the work height also should be measured although it may measure close to zero if it is far from the filter face. The optimal filter face velocity should be determined during qualification of the UFH using airflow visualization (“smoke testing”). The performance of the UFH should be monitored and alarmed (current sensing relay). See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Room temperatures should be controlled by maintaining constant airflow through a cooling/dehumidification coil (humidity control), and possibly modulating a heating coil for temperature control. Systems that vary cool airflow to control room temperatures are not recommended because of adverse effects on room pressures.
- The HVAC system may be required to quickly return room conditions after sanitization. Sanitizing chemicals and frequency and duration of sanitizing may have an effect on HVAC materials.
- Since a Grade 5 room requires a very large treated airflow to create the unidirectional condition, air from the Grade 5 room is normally recirculated rather than exhausted with some excess supply air to create room DP. A Grade 5 (Grade A) room would be unusual; the Grade 5 area is usually a UFH or RABS inside a Grade 7 (Grade B) room. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Dampers on return air may be modulated to maintain room pressure, while CV units on supply air help maintain constant flow to the room (particularly when there is no high-efficiency final filtration in the AHU).
- A desiccant dehumidifier may be required for aseptic liquid filling facilities.

- Processes should be contained in isolators with dedicated HVAC for the containment enclosure.
- Where the process leaks into a room, protect the HVAC system and other rooms on the system from hazardous compounds by using non-recirculating primary air conditioning systems.
- The exhaust or return air ducts may be kept clean with HEPA filters protected from physical damage with a pre-filter or equivalent. These filters should be located within the room where properly gowned and protected personnel can service them. Frequent filter change out or active room pressure controllers may be needed to offset loading of return air filters.
- If return filters are located remote from the room where open processing occurs, they should be housed in a high containment bag-in/bag-out filter housing and identified as such. These filters contain the potentially hazardous compounds and minimize particulate “fall back” during fan failure.
- Gowning areas should be supplied with HEPA filtered air and maintained at a negative pressure relative to the controlled aseptic area and at a positive pressure relative to the uncontrolled spaces. Local regulations may prefer two-stage gowning. The gowning area should be separated from the Grade 7 (EU Grade B) aseptic filling room by a high pressure Grade 7 (Grade B) airlock.
- The de-gowning area should be separated from the aseptic filling room by a low-pressure airlock. The de-gowning room shall be maintained negative relative to adjacent spaces on the uncontrolled side.
- Material entering the aseptic filling room should be transferred via a HEPA filtered, high-pressure tunnel, box, or sterilizer. Contaminated material leaving the aseptic filling room should be transferred via a low-pressure tunnel or box.
- If aseptic product is a powder, very low RH may be required. Minimize leakage into the AHU after the dehumidification step (blow-through AHU is preferred).

3.10 Packaging/Labeling

Figure 3.10: Packaging and Labeling System Schematic



3.10.1 System Design Considerations

- Primary packaging for sterile products is covered in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Primary packaging areas should have the same area requirements as that used for manufacturing. Handling of product exposure and potent compound issues should be addressed. Room pressure or airflow direction may be required.
- Secondary packaging (e.g., sealed bottles into cartons) is usually CNC with worker comfort conditions. Tight humidity control may be needed for specific labeling operations. Room pressure control usually is not required.
- Some raw material warehouses in temperate climates need meet only USP storage requirements (Reference 30, Appendix 12), sometimes with only supplemental heat in winter provided by steam, gas, or electric unit heaters.
- As materials, drug substances, and drug products usually are stored closed and isolated from the room environment, humidity control may not be required.
- Draw-through AHU is considered acceptable with MERV 7 and MERV 13 filtration. Terminal filtration usually is not required.
- The use of more elaborate HVAC normally would be driven by business needs, where higher HVAC life cycle costs can be offset by the risk of loss of expensive product.

3.11 Laboratories

3.11.1 System Schematics

Figure 3.11: Laboratory

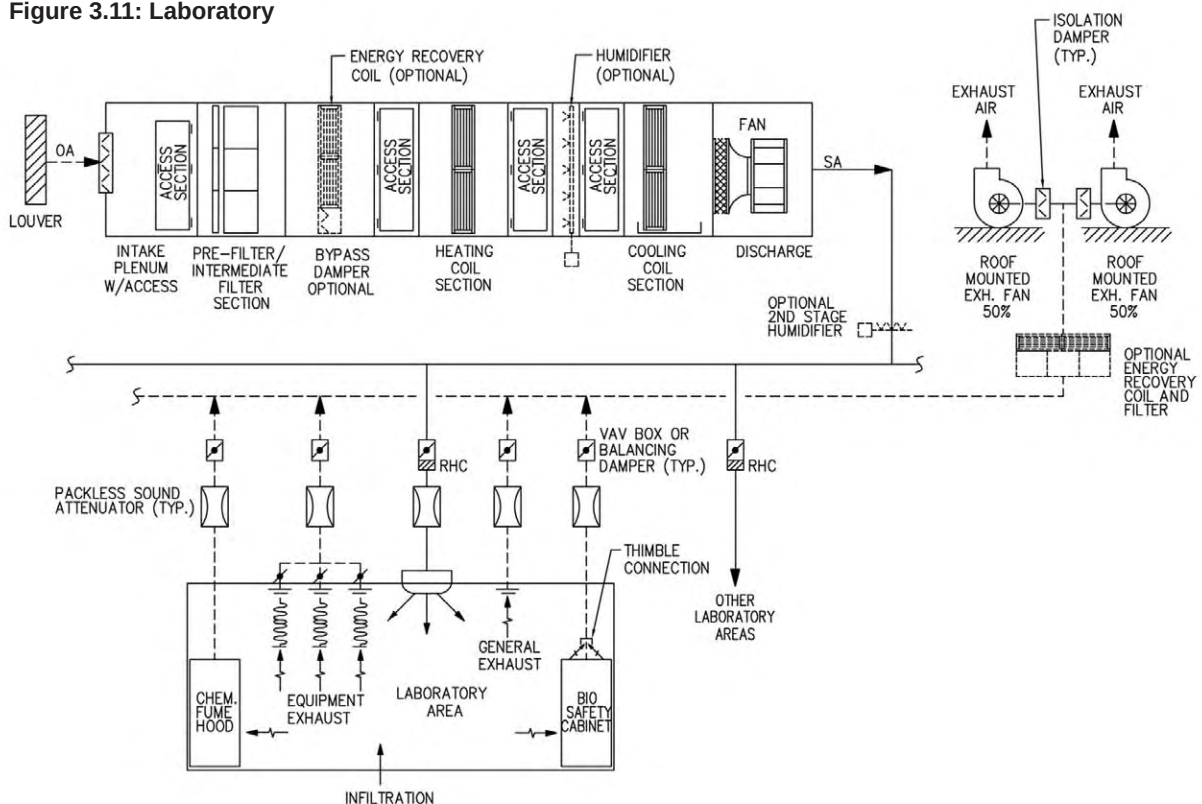
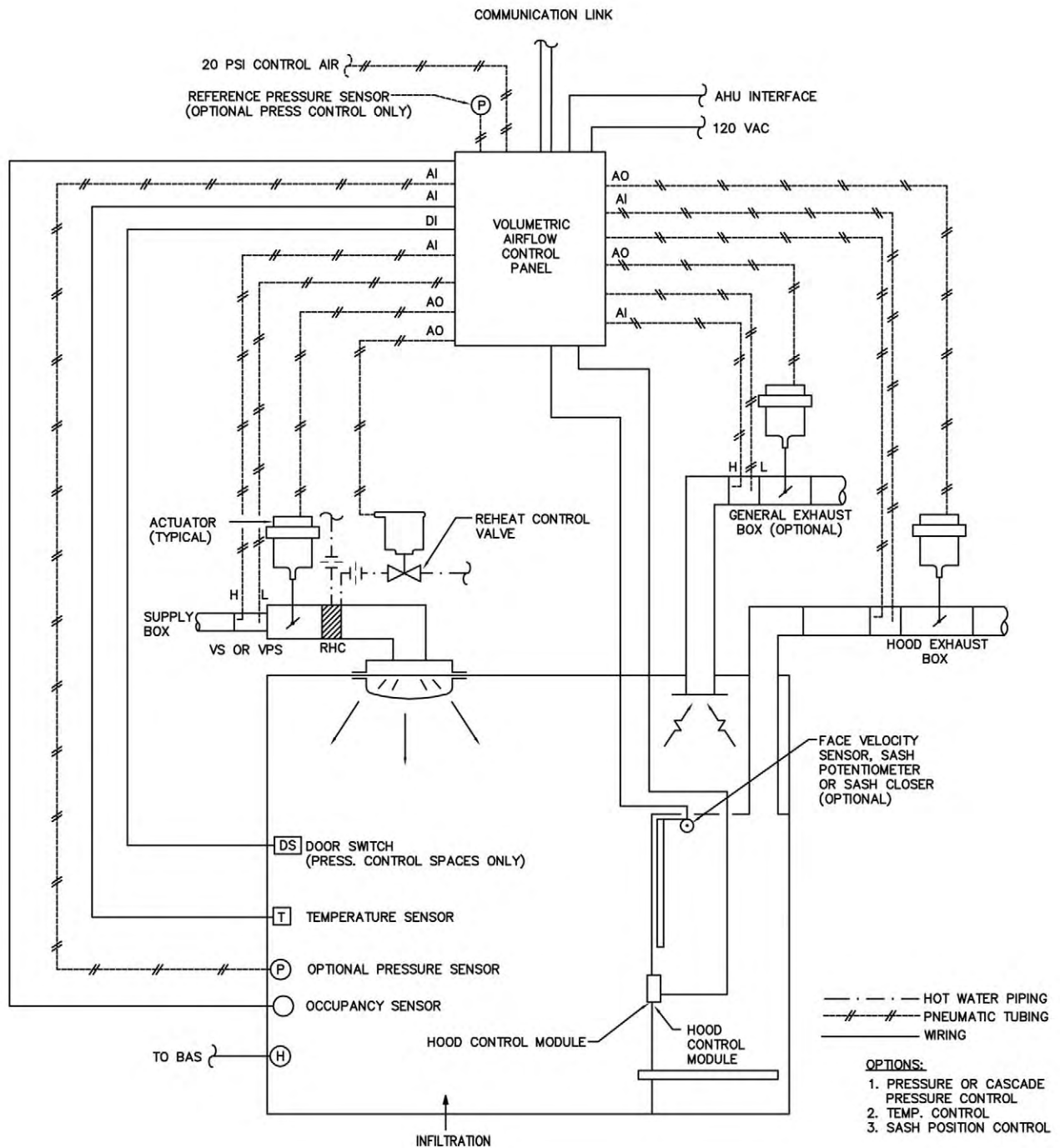


Figure 3.12: Typical Laboratory Room HVAC Detail (with Pneumatic Actuators)



3.11.2 System Design Considerations

- There are four exhaust ducts shown for the laboratory, two of which service fume hoods. One services analytical equipment through flexible drops and the other keeps the laboratory at negative pressure in relation to the corridor or other adjacent spaces when fume hood airflow is low or when room cooling requirements require additional supply air. Laboratory facilities may serve these ducts with individual fans or with a single exhaust plenum held at constant pressure and serviced by one or two larger exhaust fans. This is common for facilities with a number of rooms and hoods. In such a design, care should be taken to avoid settling of exhausted solids inside the duct when fume hood flow is low.

- Laboratories using volatile solvents or radioisotopes should be negative (commonly via airflow tracking) relative to corridors, offices, and adjacent occupied space. Air from offices or technical spaces adjacent to laboratories should transfer into the laboratory. Classified clean laboratory spaces should be positive (via airflow tracking) relative to corridors, offices, and adjacent occupied space. A high pressure bubble airlock should be provided where activities in positively pressurized spaces pose a threat to corridor air quality.
- Where chemicals or other hazardous materials are handled in the open, air systems should be 100% exhaust. Risks of recirculation of laboratory air should be evaluated if energy costs become prohibitive. Glove boxes to reduce dilution volumes and total airflow may be justified.
- Recirculation of air in microbial and in-process or materials testing laboratories that do not employ volatile organic solvents may be considered. A ductless laboratory hood may be justifiable. These hoods recirculate air to the room through activated carbon filters that remove vapor contamination. It is important that the carbon is prevented from becoming saturated, and therefore, ceasing to absorb airborne vapors. This type of hood is uncommon, because maintenance is critical to the safety of the user.
- VAV control systems are recommended for increased safety through monitoring capabilities and decreased energy usage (using hood diversity and variable flow). Airflow tracking (fixed difference between supply and exhaust) is common.
- Occupancy sensors and night setback can enhance the energy saving potential of VAV systems. Where the minimum ventilation rate (for building or fire code) is greater than the total exhaust from hoods, VAV supply is **not** recommended. Minimum ventilation rates of 8 to 12 are recommended for most laboratories. Minimum ventilation rates below 6AC/hr for occupied laboratories are not recommended.
- Non-aspirating type diffusers are recommended to be selected and located to minimize velocity and turbulence near the hood face; design cross drafts should not exceed 30 FPM within 24 inches of the hood opening.
- Galvanized exhaust ducts, boxes, and attenuators may be used except where process or research activity requires special corrosion resistance. Laboratory hood exhaust ducts and accessories that are inaccessible should be stainless steel (304). Laboratory hood exhaust ducts which handle large quantities of acids should be high grade stainless steel, Hastelloy, FRP, or other suitable material (stainless steel will corrode rapidly in the presence of high molarity concentrations of hydrochloric acid).
- Perchloric acid digestion hood exhaust requires special handling and cleaning systems. These systems represent an explosion hazard, should be segregated, and designed by experienced professionals. The use of dilution air fans to maintain stack velocity creates noise and requires extra energy. The exhaust from most chemical laboratories primarily is composed of air. As the objective is to get exhausts to a height where prevailing winds can carry them away, high exhaust stacks are preferred. Stack height above a building roof should be maintained at a 10 ft 0 inch minimum; although a stack height equal to 30% of the building height is preferred. If necessary, variable geometry stacks can maintain velocity at reduced airflows. Stacks should be located to avoid re-entrainment of air into HVAC systems (considering the prevailing winds although many locations will experience winds from all directions).
- Automatic hood closing systems with obstruction detection should be considered for energy savings. VAV boxes should not be oversized. Oversized boxes yield poor airflow control and have a limited range.
- VAV systems should be sized with a diversity factor to allow for savings in airflow and first cost of central heating and cooling equipment. A factor of 70% of installed load is common; however, the diversity factor should take in to account the anticipated hood use. If 50% sash height is considered as full flow, a further diversity factor should not be used.
- A general room exhaust should be provided only when the hood flow at minimum sash position requires an air supply rate less than that required to satisfy heat loads or the specified minimum air change rate.

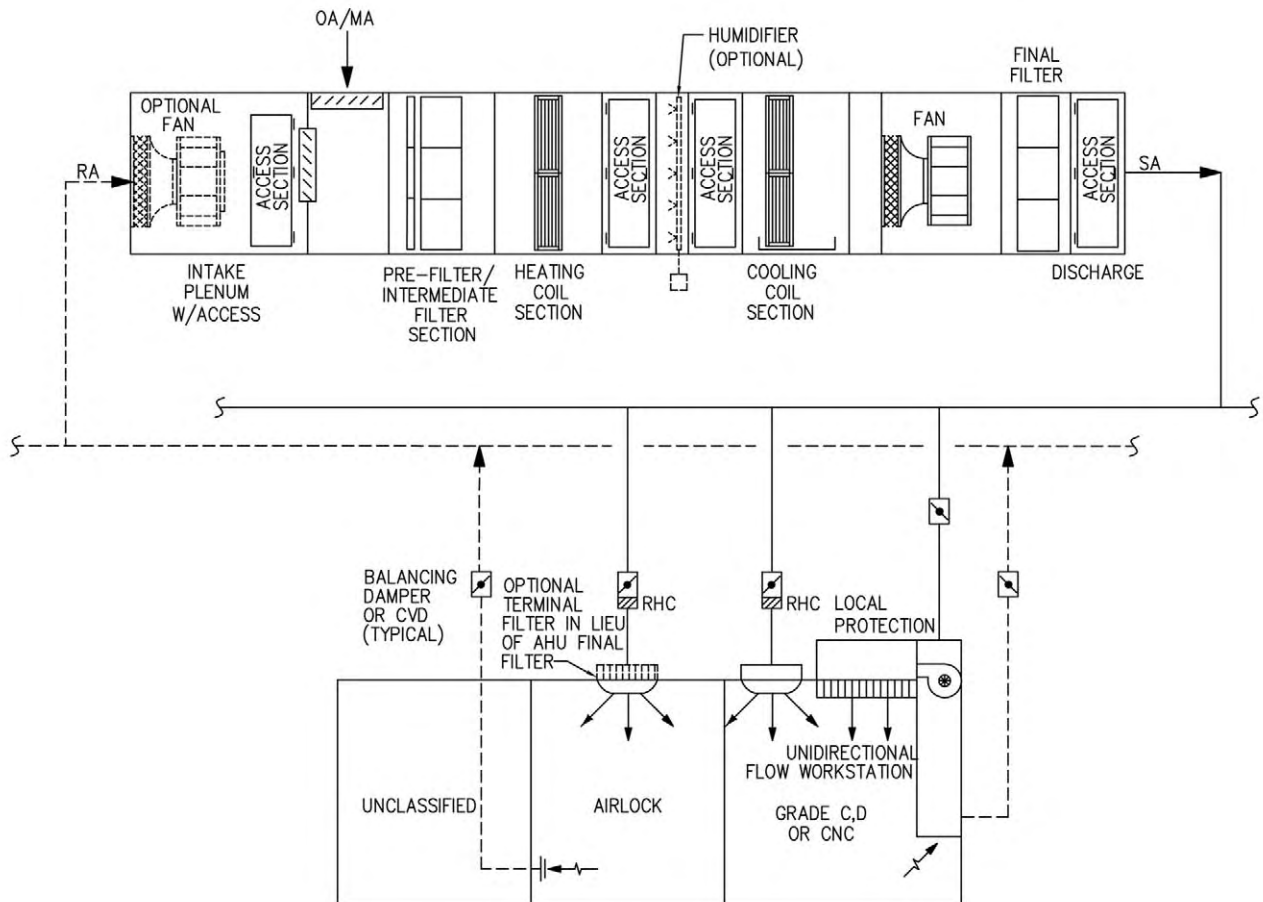
- Air change rate or exhaust quantity will usually dictate the supply air quantity. Exhaust quantities should be reset upward when additional cooling is required.
- Mounting VAV laboratory controls in accessible panels either flush in alcove outside laboratory or in dedicated rooms should improve ease of maintenance.
- Manifolded exhaust systems are considered acceptable, except for perchloric acid hoods which should be on a dedicated exhaust system.
- Approved exhausted chemical storage cabinets should be considered for solvents and hazardous materials.
- Heat should be recovered from laboratory utility equipment, wherever possible.
- Temperature alarms should be provided on refrigerators or freezers. Where critical, these should be connected to the BAS.
- Where laboratory offices are on the exterior wall, heating at the perimeter wall is recommended.
- Central draw-through air handlers are common. Distributed AHUs may be justified for areas that are frequently shut down.
- Supply Air Filtration – MERV 7 and MERV 13/14 (in series). If required by product, HEPA may be needed for classified rooms.
- Exhaust Air Filtration – As required by application. Where energy recovery is employed MERV 7 filters are required. Scrubbers may be required for some dedicated hoods. HEPA filtration may be required for formulation laboratories, BSL3&4, etc.
- While discouraged in supply duct to product processing areas, in-duct silencers can help decrease noise from exhaust manifold valves. Packless type silencers can be used for chemical exhaust applications located between the volume control box and hood.
- Biosafety laboratories are outside the scope of this Guide. Biosafety levels are described in the ISPE Baseline® Guide on Biopharmaceutical Manufacturing Facilities (Reference 13, Appendix 12).

3.11.3 Vivarium

Vivarium facilities should consist of individual suites, each capable of maintaining its own microenvironment for the duration of the product study. Guidances are published by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC), ASHRAE, and others.

3.12 Sampling/Dispensing

Figure 3.13: Sampling and Dispensing



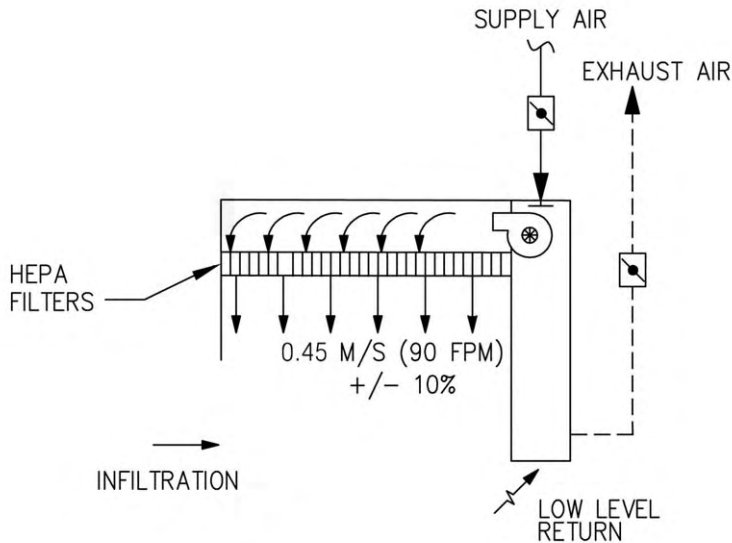
3.12.1 System Design Considerations

- Specific product requirements are in the appropriate ISPE Baseline® Guide (Reference 13, Appendix 12).
- Once-through air may be applied for solvent use. Recirculated room air is possible with adequate air filtration. Exhaust air for sampling stations should not be recirculated.
- Central Filtration should be minimum MERV 7 followed by MERV 13/14. Starting materials for aseptic processing may require HEPA filtration to meet Grade C or D. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Airflow Tracking or room pressure control are recommended for room segregation.
- Powder sampling/dispensing may require low RH.
- Airlocking between warehousing and sampling spaces is expected.
- The area classification and environmental conditions in sampling and dispensing should reflect the conditions used when charging materials to the process.

- Unidirectional Flow modules are, typically, employed as local protection for sampling activities, this gives greater flexibility when multiple materials are sampled or dispensed in a given area.
- LEV should be considered for sampling or dispensing of hazardous materials. Exhaust hoods designed for this purpose are commercially available.

3.12.2 Downflow Booth

Figure 3.14: Uni-Directional Flow Booth for Local Protection



The downflow booth is a “packaged” HVAC system integrated into a booth that has sidewalls, a ceiling plenum, and a low level return inside the booth at the front. The unit is designed to provide operator protection when handling hazardous materials.

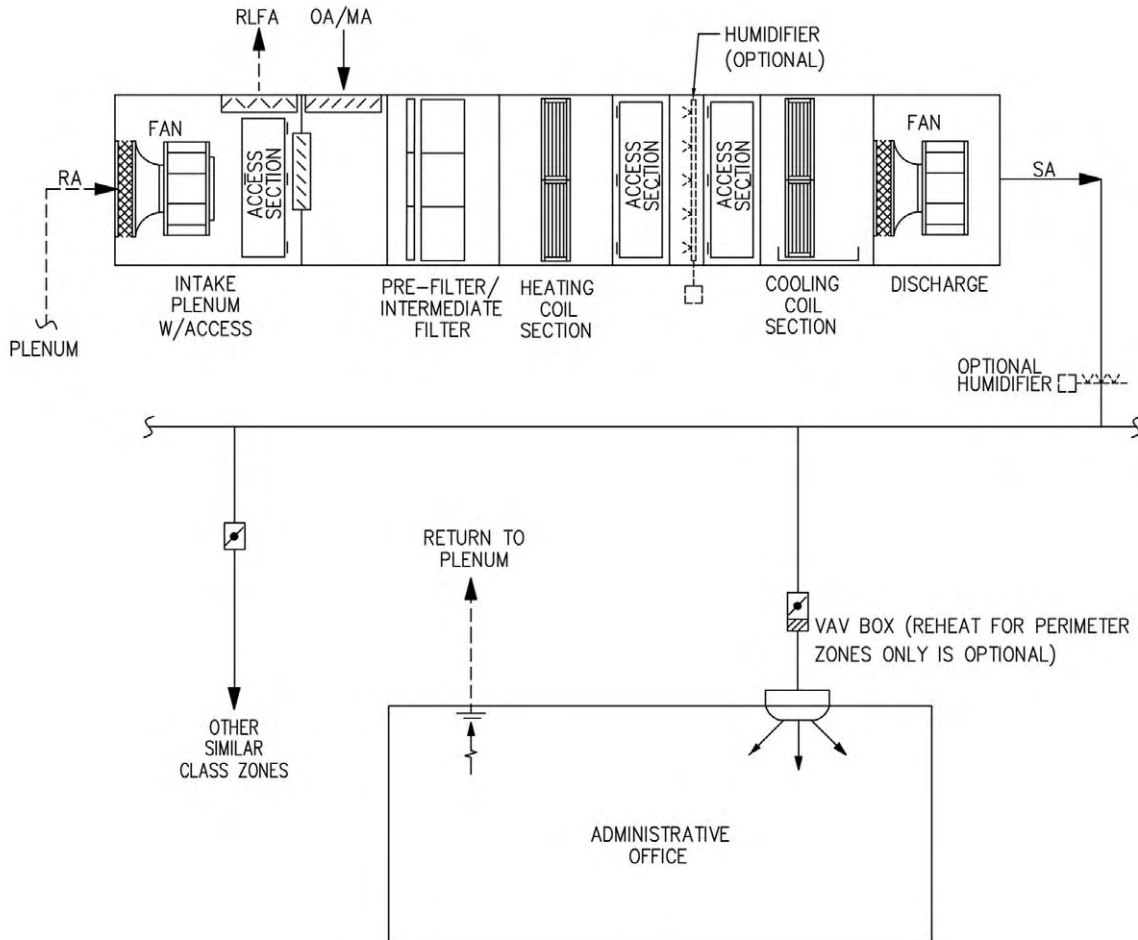
The design concepts are shown in Figure 3.14. The discharge HEPA filter (usually a safe change unit) may be mounted in the ductwork from the fan to the ceiling plenum with the ceiling a proprietary material designed to provide uniform laminar downflow of air or the booth ceiling can be made up of HEPA filters. By introducing a material with a high pressure drop, the system creates a uniform high velocity downward flow from the ceiling. The advantage of the material based systems is that lighting can be mounted above the screen, minimizing any gaps in the airflow.

The high air change rate means that heat builds up in the booth from the fan energy; therefore, the system usually has a cooling coil mounted in the airstream controlled to maintain the temperature in the booth.

A small portion of air (usually around 10%) is bled from the plenum in order to create an inward flow of air in the front of the booth to provide containment; usually the systems have vinyl curtains mounted on the front to encourage the inflow at a low level.

3.13 Administrative and General Building

Figure 3.15: Admin Area System Schematic (Sample)



3.13.1 System Design Considerations

- See general design considerations in Section 3.2.
- Most office areas use VAV HVAC, which is more energy efficient, but may, by its nature, create variable room pressures inside the office. If the administrative area borders on a pressure controlled processing area or the area of common pressure reference, there may be a disturbance of pressures inside the processing area. However, careful HVAC design can solve this problem.

3.14 Warehouse

3.14.1 System Design Considerations

- Many warehouse facilities do not have central air handling, using only unit heaters. Be sure that their very warm air outlets do not overheat high-stacked material.
- See product data or the USP (Reference 30, Appendix 12) or equivalent pharmacopoeia for finished product temperature and RH requirements. The USP defines a limit for “controlled room temperature storage” of 15 to 30°C (59 to 86°F) with a Mean Kinetic Temperature (MKT) below 25°C (77°F).

- Biological products may require lower temperatures than the USP specifies and may require a “cold chain” or series of cold storage and handling areas to meet stability criteria. AF&IDs for warehouses can be similar to that for administration or packaging areas. AF&IDs may be as simple as employing only unit heaters where high summer temperatures are not an issue.
- The warehouse should be “temperature mapped” to identify normally “hot” and “cold” locations and define the relationship between these locations and the measured temperature at the control sensors.
- Mapping of temperature extremes in high bay warehouses is recommended.
- Dedicated exhaust may be required for battery charging areas to remove hydrogen gas emitted by charging lead/acid batteries.

3.15 Process Equipment Integration

There are specific requirements for process equipment. Specific aspects for the area containing process equipment should be considered in the design of HVAC systems.

3.15.1 Dust Extract Systems

Where there is a common dust extract system, aspects to consider in the HVAC system design include:

- What happens if the unit fails?
 - Does the unit have a damper that closes, preventing air leaving the system? Is the pressure difference between the rooms served by the system adequate to obtain flow with a consequential risk of cross contamination?
- How does the dust collector clean itself?
 - Some units are cleaned by a shaker mechanism; others use a pulse of compressed air. During this pulse, which is in the opposite direction to the normal airflow, the extract air flow can halt or even reverse for a short period, is this acceptable?
- It should be noted that one of the advantages of a remote system (regardless of whether it is a common or a dedicated system) is that the system heat gain is outside the room and the extract normally is located near an area where the equipment heat gain is high, so heat gains are extracted from the room, reducing the load on the area HVAC system. In addition, duct pressure is negative; keeping contaminants in the system should the duct develop a leak. Being remotely located, fan noise is not an issue.

3.15.2 Granulators/Coaters/Fluid Bed Dryers

These units typically have dedicated air-handling systems that are independent of the area HVAC. See the ISPE Baseline® Guide on Oral Solid Dosage Forms (Reference 13, Appendix 12). The design should consider what happens during periods of non-use and whether there is potential for moisture to migrate from an outside high-humidity environment into the system. Other aspects to consider include:

- Assess the risks of corrosion during use – what ductwork materials should be used?
- What areas of the duct are pressurized? What is the risk of drawing in untreated air? What is the risk of potentially contaminated (with product) air leaking out?
- If for multiple campaigned products, does the duct need Clean In Place (CIP)?

3.15.3 Glassware Depyrogenation Tunnels

Glassware depyrogenation tunnels generally are located between rooms with different area classifications (grades) and operate intermittently. They present a challenge to HVAC system designers. Area pressure differentials typically need to be held at a consistent level, usually requiring some type of active pressure control. (Risk analysis to determine areas of patient/product risk may present opportunities to reduce the room pressure differentials during periods of no production).

As tunnels are started up and the temperatures and volumes stabilize, there is a dynamic period in terms of changing airflow during which filling is not in operation. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12). Without a pressurized cool in-feed zone between the washer and the heat zone of the tunnel, held at the same pressure as the sterile filling line, extremely hot air can exit the front of the tunnel, creating a need for local exhaust to remove the excess heat and potentially creating a hazard.

Other issues with depyrogenation tunnels include the testing and integrity of high temperature HEPA filters and the monitoring of particle levels in the hot zone (sometimes over 325°C). These issues are discussed in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12) and in online discussion groups such as the ISPE Sterile Processing COP.

3.15.4 Isolator Systems

Figure 3.16: Isolator System Schematic 1

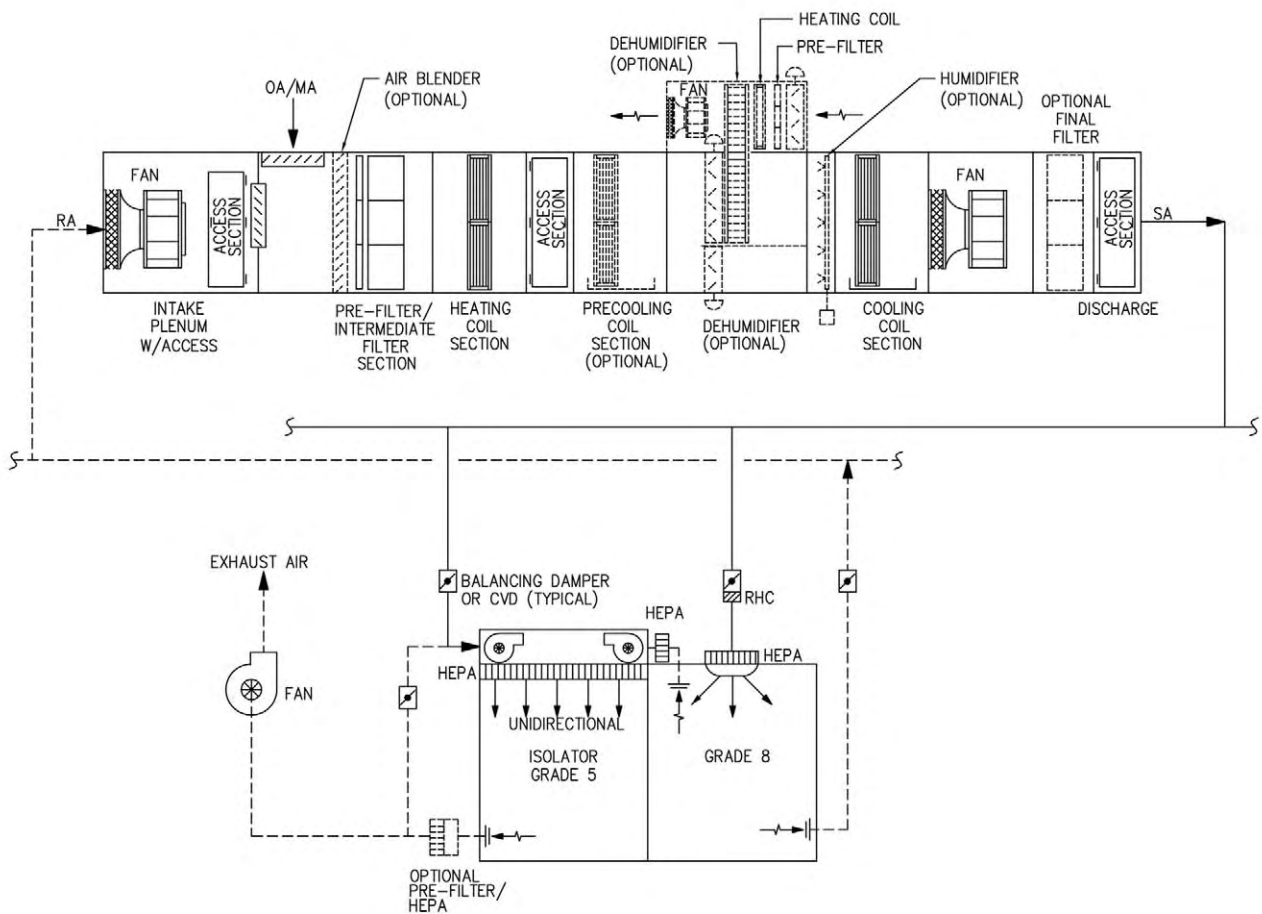
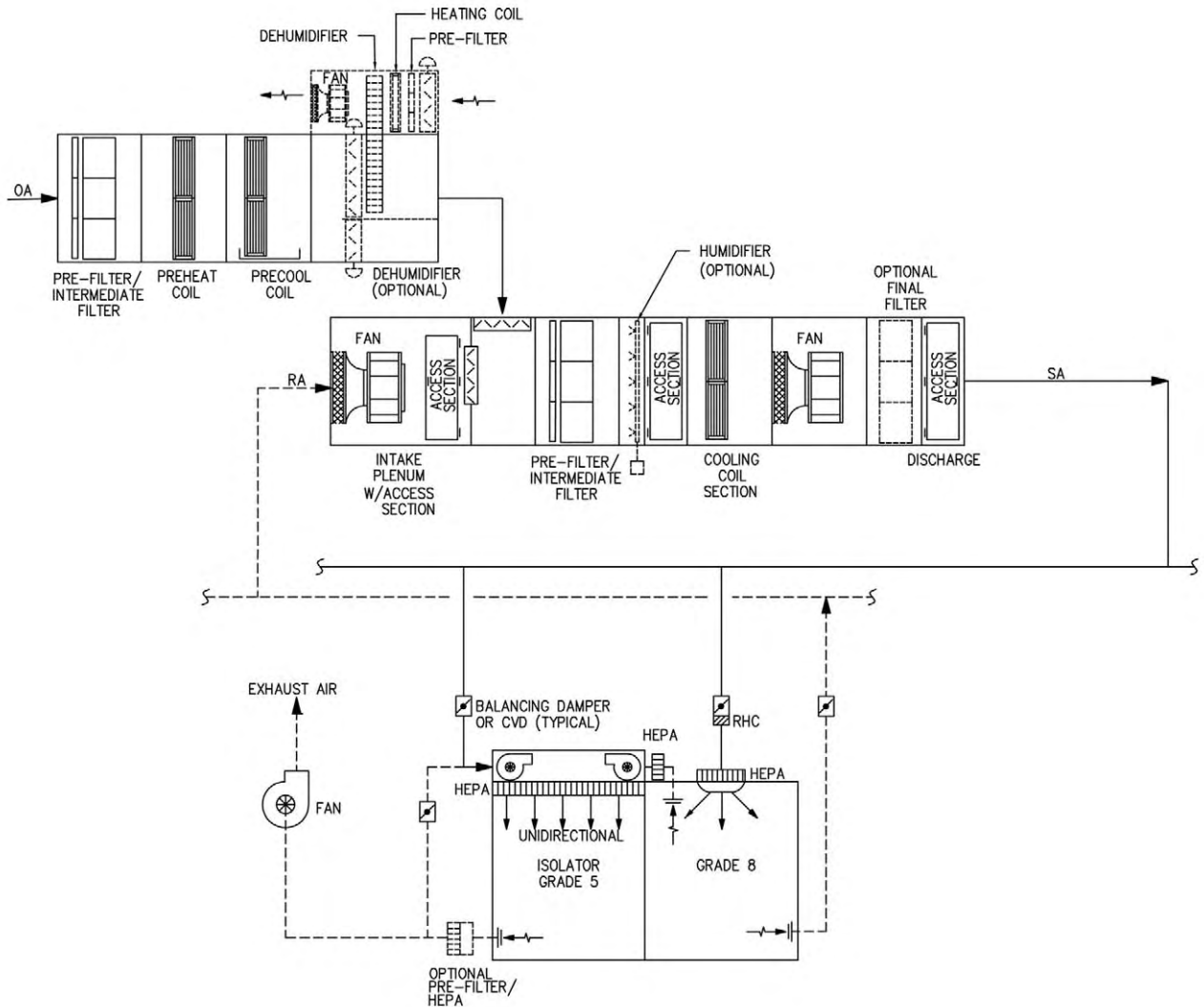


Figure 3.17: Isolator System Schematic 2



Where aseptic processing or containment of hazardous materials is required, barrier-isolator technology may be applied. Generally, when a closed isolator is used in aseptic processing and can be pressurized, room air class can be relieved by one or (often) two levels, requiring fewer air class zones, less gowning, and lower HVAC airflow. When an isolator is used as containment for non-sterile products, potential for product release to the air and cross-contamination often is greatly reduced, lessening risk to product and operators and requiring less rigorous HVAC systems. See the appropriate ISPE Baseline® Guide (Reference 13, Appendix 12) for further information. Considerable discussion on closed isolators (barriers) and open isolators (RABS) is provided in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).

Isolators are a microenvironment and the area of greatest risk, and therefore, greatest environmental control is minimized. This design makes isolators a “green” technology with lower energy consumption than conventional processing.

Isolator technology for aseptic processing or containment of hazardous material can reduce the exposure of operators to product and the exposure of product to disinfection chemicals that may be used in a conventional aseptic processing suite.

Isolators may be fed with room air (as shown in Figure 3.16 and Figure 3.17) or by dedicated air handlers. The use of dedicated air handlers decreases the risk of vapor phase hydrogen peroxide (VPHP) escape from the isolator and simplifies balancing of the room and enclosure. Use of room air is more energy efficient and potentially demonstrates less impact on isolator pressurization relative to the room because of changes in the isolator operating mode (or phase).

Depending on the source of makeup air to an isolator's air handling system, there may be an effect on room pressure when an isolator is in use. When an isolator draws air from the room and returns it all to the room, there should be no effect during normal operation. If an isolator draws air from outside the room, air leaking from the isolator will further pressurize the room. Most isolators have multiple operating modes for open setup with unidirectional flow, CIP, closed-operation. The integration of an isolator to a processing room requires careful consideration of all operating phases and conditions. The effect of the transition between isolator operating modes on the surrounding room should be carefully considered, as it may impact the relationship of the processing room to surrounding spaces. HVAC control designs for the room should account for planned isolator operating modes and transitions. Isolators decontaminated by VPHP and then aerated present additional challenges, as the air removed from the room is not returned during the aeration phase. VPHP sensors should monitor the room around the isolator and mechanical spaces outside the room as a further safety measure.

The air classification required for the background environment depends on the design of an isolator and the application. Room cooling loads should account for the heat generated by the isolator fan system(s).

3.15.5 Vial Capping

The 2008 revision to EU GMP Volume 4 Annex 1 provides specific requirements for finishing of sterile products, specifically for freeze drying vials:

"Partially stoppered freeze drying vials should be maintained under Grade A conditions at all times until the stopper is fully inserted."

It also gives specific requirements for stoppering/crimping, to be implemented by 1 March 2010.

"As the equipment used to crimp vials can generate large quantities of non viable particulates, the equipment should be located at a separate station equipped with adequate air extraction."

"Vial Capping can be undertaken as an aseptic process using sterilized caps or as a clean process outside the aseptic core. Where this latter approach is adopted, vials should be protected by Grade A conditions up to the point of leaving the aseptic filling area, and thereafter, stoppered vials should be protected with a Grade A supply until the cap has been crimped."

Where facilities are being modified to comply with these regulations, the following factors should be considered:

- A UFH can be used to provide a robust Grade A (Grade 5) local airflow.
- The loss of air from an area due to an extract system for capper particles should be considered during balancing, unless the air is re-introduced into the room (in this case, via a HEPA filter in order to maintain environmental conditions).
- The heat gains from the fans of unidirectional flow and extract systems should be considered.

3.15.6 Lyophilizer

As the loading and unloading of a freeze dryer should be under Grade 5 (Grade A) conditions, it is usual to place a large UFH over the lyophilizer door. Smoke tests (with and without operator presence) may reveal poor air patterns near the bottom of the door opening. A low level return (with considerable airflow) below the lyophilizer door may help improve patterns.

3.16 Medical Devices

Figure 3.18: Typical AF&ID for “Clean” or Bioburden Reduced, Device Assay

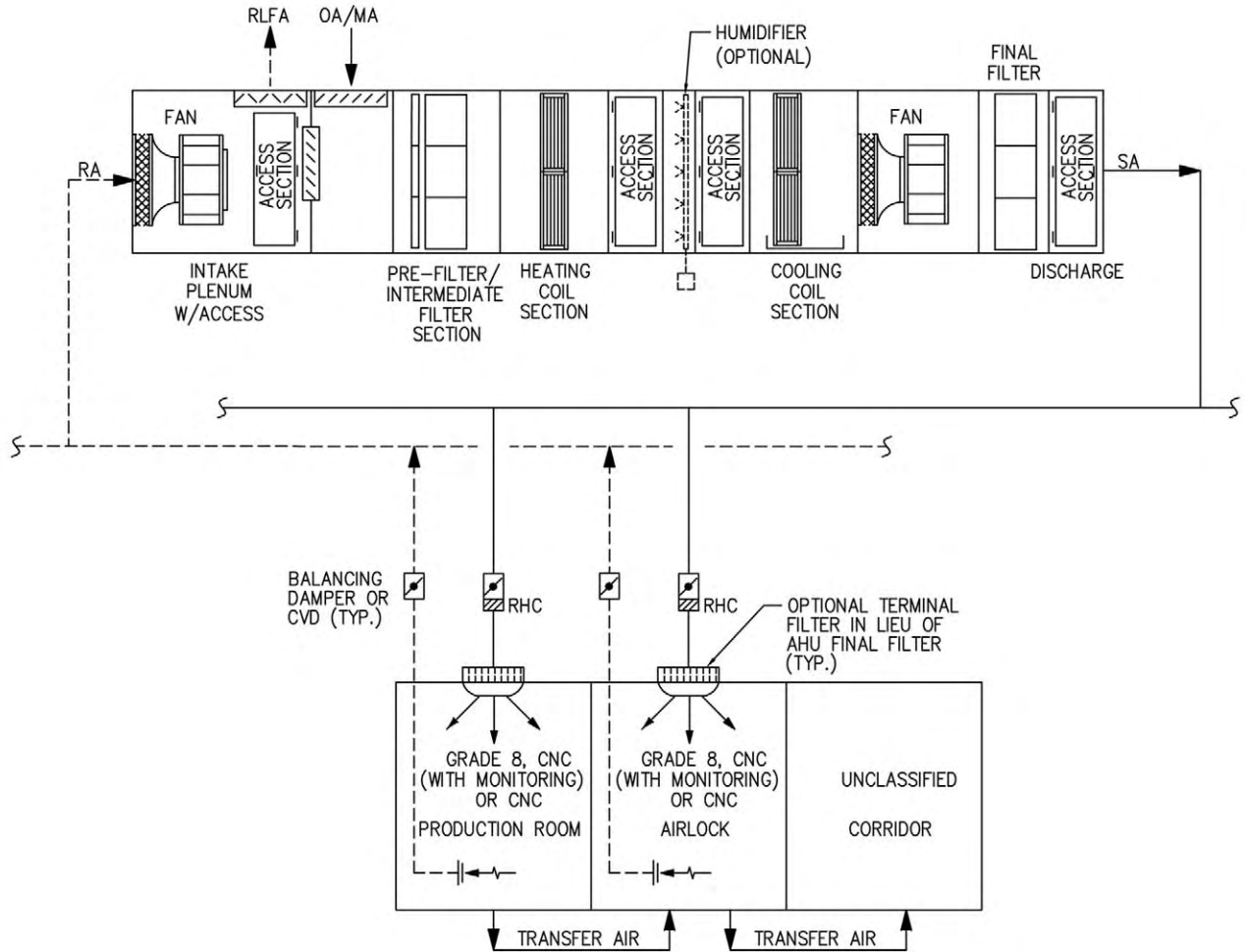
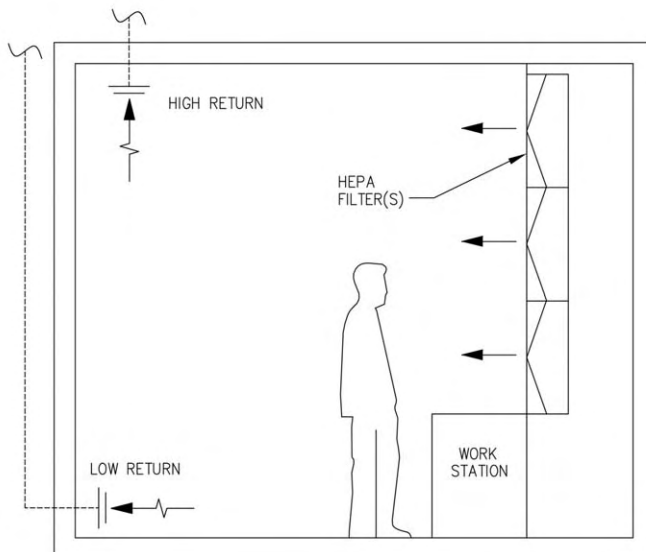


Figure 3.19: Horizontal Flow Clean Workstation



Requirements for environmental control in medical device facilities are based on the risk to patients from a medical device and downstream processing. For further information on the risks and classification of medical devices, see Appendices 8 and 10.

Where devices do not contact the patient or contact the patient only externally, cleanliness requirements may be equivalent to those for packaging areas.

Where medical device components are used internally, but are processed downstream (e.g., terminally sterilized) processing typically should be performed in a classified space, as with other sterile products.

Where devices or components of a device are used internally for patients, aseptic considerations should be applied.

Cleanliness of open processing areas should be maintained via control of airflow between product handling area or airlock and surrounding spaces:

- Isolation via an airlock should be used. Where solvents are used (e.g., for welding plastics), pressure bubble airlocks are recommended to prevent migration of flammable vapors to the building.
- Monitoring and alarming of direction of airflow (through DP, hotwire velocity sensors, air balance, flow tracking, etc.) to surrounding rooms is recommended.
- AHU filtration – MERV 7 followed by MERV 13/14 filtration is recommended.
- Final filtration – 95% DOP/PAO efficiency is recommended in non-aseptic product areas; terminal HEPA filters may be appropriate.
- Return or exhaust air grilles may be equipped with removable 30% dust stop filters. The effect of filter loading on room pressurization or direction of airflow should be considered.
- Airflow and makeup air delivery should be directed to protect the product.
- Dust collection with high transport velocities (3000 to 5000 fpm, 15 to 25 m/s) may be required where plastics or metals are machined.
- LEV for smoke and solvent vapor removal may be required where machining metal, welding metal and solvent, or heat welding plastics. These should be designed and engineered according to ACGIH standards.
- The ACGIH Industrial Ventilation Manual decision analysis and design criteria should be consulted for guidance on recirculation.
- Recirculation of LEV exhaust to the AHU or the general building usually is not acceptable.

4 Design Review

4.1 Design Review (Design Qualification)

This chapter provides guidance on verifying that the design as issued for construction will meet the user requirements.

It is easier and more cost effective to change a design before it is constructed than during or after construction, and therefore, there is less impact on capital cost and schedule. As the design develops, input from all interested parties should be considered to avoid later changes.

The process of reviewing a design (drawings and specifications) as it develops from concept to issued-for-construction status has several objectives:

- to ensure that a design follows preferred custom and practice
- to ensure that the concepts proposed are capable of meeting the requirements defined in the User Requirement documentation, i.e., user expectations
- to ensure that a design minimizes risk to product quality/patient safety
- to ensure that a design is robust and will perform reliably and that performance can be documented
- to ensure that a design proposed is cost effective
- to ensure that design options, the life cycle costs, and the risks have been identified and addressed
- where an end user has preferred suppliers, the review should confirm that these have been specified

Common practice is for a design to receive comments for the designer (engineer of record) to incorporate or provide a rationale for not incorporating. Users usually do not approve a design to avoid making design responsibility unclear.

For systems that may affect product quality, it is a common practice to split design reviews into two categories:

1. engineering or technical reviews
2. quality (or GMP) focused reviews

A final specific “quality” review usually is performed to confirm that the HVAC system (and the specified related conditions for the areas it serves (temperature, humidity, classification, DPs, etc.) comply with GMP regulations/organizational standards. This review may be called Design Qualification, allowing the statement to be formally made that the design as reviewed is fit for its intended use, as well as confirming that the user requirements are met.

It should be noted that there are regulations requiring this review. ICH Q7 suggests a design review and the European regulations state:

“The first element of the validation of new facilities, systems, or equipment could be design qualification (DQ).”

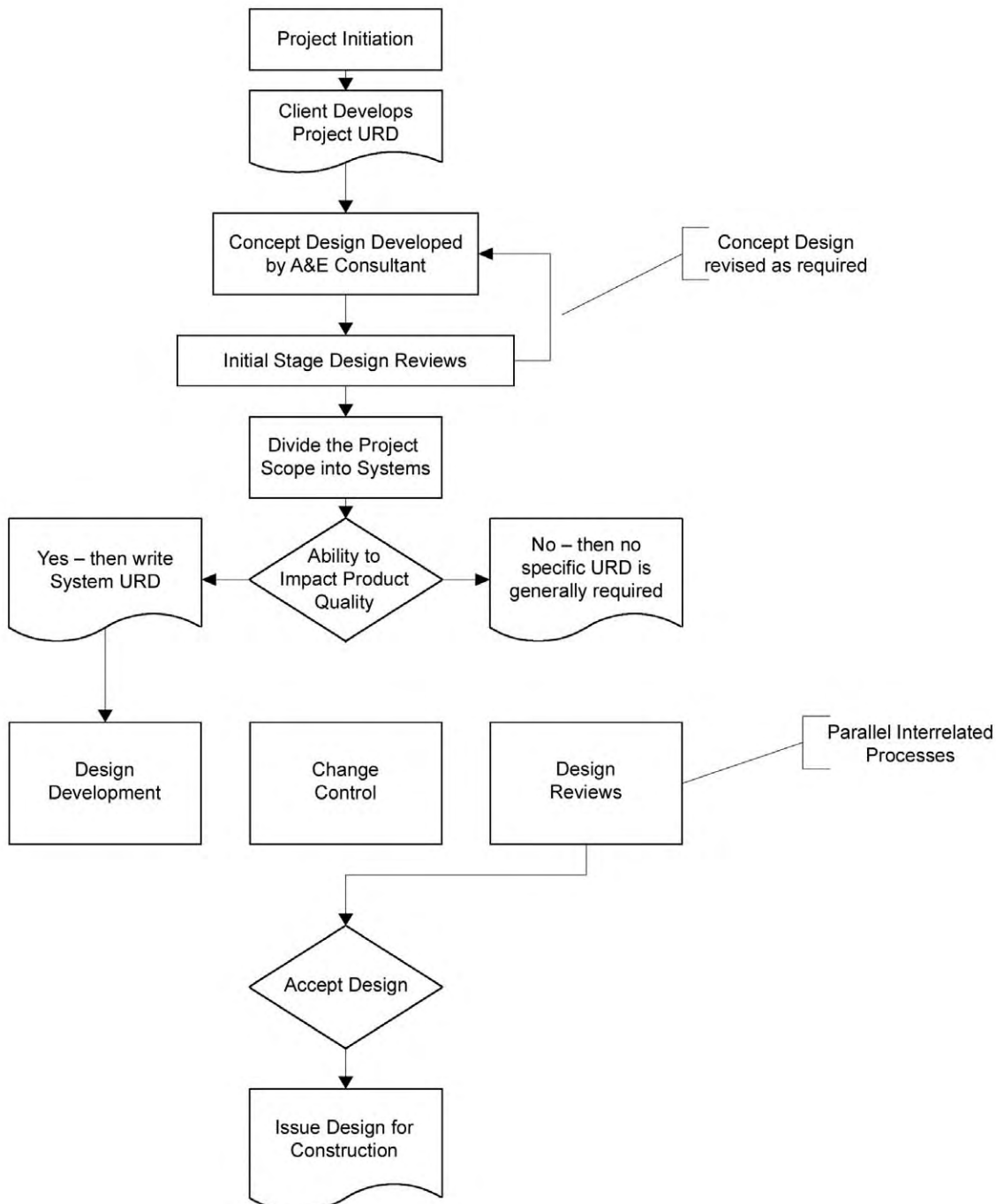
“The compliance of the design with GMP should be demonstrated and documented.”

The process of reviewing and accepting a design to be released for construction or the overall review process also may be considered a qualification of the design, because it confirms that the user organization has reviewed the design (documented through the design review process) and agrees to release the design for implementation.

Once a design has been accepted as fit for its intended use, formal change control should be applied. Formal change control should ensure the system remains in compliance and is fit for its intended use. Individual change requests may be reviewed or a single review of the system and all changes may be performed during installation qualification.

Figure 4.1 shows (diagrammatically) an overview of a typical design/design review process:

Figure 4.1: Design Review Process



Organizations may develop knowledge capture systems such as:

- design review checklists (see Table 4.1 to Table 4.4)
- design guides: defining the preferred way of designing a given system type, e.g., HVAC systems or compendial water systems

These approaches should ensure that organizational experience and preferences are both captured and considered. They also should consider novel concepts.

The review method to be used should be defined and review participants should agree to the method. The method and participants may vary depending on the system type.

A preferred approach for design review is for a multi-disciplinary team to ensure that key viewpoints are considered with SMEs in HVAC, controls, commissioning, and regulatory requirements.

For areas where high system reliability is required, e.g., vivariums, a formal review may be conducted, such as using a Failure Modes and Effects Analysis (FMEA) to ensure that the design is adequately robust. A simplified version of this approach may be beneficial, considering the effect of system failures on adjacent areas to ensure that the design is robust and that system failure will not compromise product.

Notes taken from the design review should be implemented through drawing and specification changes. If the revision cross references the notes, it may not be necessary to formally close out all actions in a GEP environment. SMEs who sign off drawings for construction are expected to check that necessary changes have been incorporated in the drawing.

Large projects usually have multiple reviews at key stages, e.g., a review at the concept stage (to ensure that the user team agrees with the proposals from the A&E design company), interim design reviews, and a final review. These may focus on individual systems, or on specific areas of the design, e.g., HVAC systems or chilled water systems.

For smaller projects, e.g., with one system, there may be fewer reviews, but there should be one review before design release, as a minimum. The project team should agree the approach to be applied to a specific project.

4.2 Design Review Process

Typically, the review process is formalized to make it more efficient and to ensure that all interested parties are involved the process.

The review may be structured to cover all design aspects or divided into two:

1. A GEP review: to ensure that GEPs are incorporated; this may include a review of maintainability of the systems.
2. A GMP review: to ensure that compliance requirements are adequately addressed by the proposed design.

(A Health and Safety review also may be justified for facilities handling potent or flammable compounds.)

The GEP review may be complex, (a significant amount of knowledge and experience within an organization can be captured and used in the review process). A formal audit trail usually is not required for GEP observations. Typically, reviewers ensure that comments have been addressed; therefore, there may be a benefit in keeping separate reviews.

The GMP review typically is simple and consistent; observations should be tracked to ensure that they are addressed and an audit trail established.

A series of typical categorized design challenges may be developed. See Table 4.1 to Table 4.4:

Table 4.1: Typical Design Concept Stage GMP Review

Design Challenge	Response	Action
Are critical parameters and acceptance criteria defined/Are the reasons for making them critical (risk assessment) documented?		
Are the units and associated controllers located in a controlled access space?		
Is the equipment maintainable? (Consider accessibility to key components of the system, filter maintenance requirements, filter integrity testing (if required), regeneration requirements, emissions, etc.)		
Review and evaluate the AHU service distribution drawing and consider the following:		
How many AHU units (zones) are proposed, is the zoning based on the process requirements?		
Are the airflow directions/differential pressures correct to control product exposure/cross contamination?		
Are the temperature and humidity design and operating conditions defined?		
Are any area classifications required/defined?		
Are the systems once-through or recirculating? (Are there provisions to handle solvents, high potent compounds or high particle generating operations, as required by the product/process operations?)		
Is the control scheme clearly defined, including monitoring and alarm requirements?		

Table 4.2: Detail Design or Issue for Construction Stage GMP Review

Design Challenge	Response	Action
Have the peak external design conditions been established from a reliable source, which considers local geographical features/ meteorological factors, e.g., lakes/prevaling wind direction?		
Has the user defined availability requirements for the products to allow the design external conditions to be defined? (i.e., the percentage of time that the facility will be able to maintain the manufacturing conditions)		
Are the internal requirements specified: temperature/humidity/ airflow direction – area DPs/classification?		
Review location of outside air intake and exhaust. Is the prevailing wind direction defined for the site with the HVAC inlet and outlet locations defined to demonstrate no risk of recirculation?		
Is the facility divided into manufacturing zones (areas)? What rationale is used to divide the facility into zones?		
Is the location of the monitoring sensors specified, such that they will give representative readings of the space conditions: are they easily accessible for maintenance and calibration activities? (For large areas, such as a warehouse multi-point mapping and monitoring may be required; for smaller areas, 1 or 2 points generally are adequate with the reading demonstrated as representative of the areas where product is susceptible to conditions during qualification using sensors. Consider the size of the room and the location of key process operations (e.g., product exposure) in establishing the location and number of monitored points.)		
If there are multiple AHUs servicing the manufacturing area, how will failure modes affect the intended operation? Will failure of one unit increase the risk of cross contamination?		
Is there a site drawing/component numbering system which has been used?		
Are airflow directions/DPs (from clean to less clean) appropriate to provide the minimum risk of product contamination/cross contamination, considering potential system failure modes?		
Are there airlocks that separate areas of different classifications with a design DP of at least 15 Pa across the airlock? The design airlock classification should be same as the area served when measured at rest.		
Are the airlocks specified with interlocked doors? (It is recommended that the design DP is a minimum of 20 Pa to allow for construction issues.)		
Does the process require containment; if so, is exhaust air filtered using safe change high efficiency filters with suitable re-filters (bag-in, bag-out)?		

Table 4.2: Detail Design or Issue for Construction Stage GMP Review (continued)

Design Challenge	Response	Action
Are there any provisions to handle solvents, high potency drugs, and/or high particle generating materials? If so, are the provisions in line with the area GMP operational requirements? (Airflow should be designed to contain high potency compounds. Biotech facilities design should conform to the US Center for Disease Control biosafety control levels.)		
Are the air handling systems designed for re-circulation where appropriate and with suitable return air filtration?		
What assumptions have been made to specify the position of the temperature sensor to ensure that it is representative of room conditions?		
What assumptions have been made to specify the position of the humidity sensor to ensure that it is representative of room conditions?		
Is there a qualified system for manufacturing areas to monitor and maintain records of temperature, humidity, and airflow direction? (Define what will be the system of record and what will be the system of control.)		
Is there a locally mounted alarm indicator for any out of limit environmental condition: temperature, humidity, airflow direction? Have alarm limits been defined based on product and process requirements?		
Has the position of inlet/outlet grilles been specified where necessary? (If the area is classified, it is common practice to design with ceiling mounted supply grilles and return air taken at low level in the room?)		
Is the area served a laboratory, if so, what considerations have been made for: • Fume hoods? • Microenvironments, e.g., low humidity rooms? • Sensitive scales?		
Does humidification use plant steam, if so, does it use approved additives (21 CFR 173.310) (Reference 8, Appendix 12) or chemical free steam? (If so, it should be injected before the final HEPA filter, where one is used.)		
Is the ductwork specified using an appropriate allowance for leakage – is it shown on the design?		
Are the AHUs mounted inside, if not, what provision is there to protect them and the personnel from the weather during maintenance?		
Does the specification for the AHUs include access panels and test ports to facilitate maintenance and HEPA filter testing if required?		
Are AHUs designed for CV and low leakage of conditioned air?		

Table 4.2: Detail Design or Issue for Construction Stage GMP Review (continued)

Design Challenge	Response	Action
How does the specification of the AHU ensure that it will not degrade or corrode during its working life to affect its performance?		
Are progressive pre-filters specified – what is the basis for their selection?		
What final stage filters are specified? Are all classified areas served via 99.97% efficient HEPA's? (Note terminal filtration is preferred). (H13 specified for in situ leakage testing, or H 14).		
Are lockable dampers specified, and is there a requirement to record the as balanced setting in the commissioning records?		
Confirm that the specification permits no interior lining of ductwork with any sound attenuators specified using non shedding lining.		
What security arrangements are there for controls?		
What happens in the event of power failure?		
Is the ductwork made of galvanized steel or are there special requirements; for non classified areas, does the specification limit the use of flexible ductwork to 4 feet long? Confirm that for classified areas the use of flexible ductwork is not permitted. What are the leakage allowances – are they appropriate? (The use of flexible hosing must be carefully evaluated. Maintenance requirements must be discussed as part of the review process.)		

Table 4.3: GEP Design Review High Level Challenges

Design Challenge	Response	Action
What considerations are made for reliability/robustness?		
Does the design proposed demonstrate current best practices?		
How are maintenance/calibration requirements addressed?		
How are failure modes considered?		
Are ceiling plenum returns proposed; if so, how would the ceiling void be cleaned?		

Table 4.4: Detail Design or Issue for Construction Stage GEP Review

Design Challenge	Response	Action
What arrangements are made to facilitate cleaning the system internally?		
How does the design consider the risk of building sickness syndrome?		
Are airflow directions proposed for any catering areas to contain odor?		
Are there arrangements to extract from copier rooms?		
Is the AHU construction specified to avoid risk of external condensation?		
If not, are the air handling systems designed for re-circulation where appropriate and with suitable return air filtration?		
What assumptions have been made to specify the position of the temperature sensor to ensure that it is representative of room conditions?		
What assumptions have been made to specify the position of the humidity sensor to ensure that it is representative of room conditions?		
How does the design allow for future changes in the room layout in terms of sensor locations and zoning?		
Are the site-specific requirements defined in terms of preferred suppliers?		
Are AHUs located in an area suitable for easy maintenance, suitably protected from the external environment to facilitate maintenance?		
Does the specification for the AHUs include access panels and test ports to facilitate maintenance?		
Is the system designed with progressive filtration?		
How have filter grades been decided – are they a site standard?		
Are lockable dampers specified and is there a requirement to record the balanced setting in the commissioning records?		
What security arrangements are there for controls?		
What happens in the event of power failure?		
Is the fan drive external or a high efficiency/low loss design e.g., flat belt? What is the bearing design life at the maximum rated fan speed?		
Is the ductwork made of galvanized steel, how is the internal finish specified, to ensure that the galvanizing is of good quality and finish?		
Does the ductwork specification limit the use of flexible ductwork to 4 feet long?		

5 Equipment Specification, Qualification, Installation, and Operation

5.1 Equipment Specification

5.1.1 Introduction

This section focuses on the design and specification of components that deliver conditioned air to GMP spaces. The equipment should meet safety, product, and regulatory requirements, while providing environmental comfort and protection to employees. Generally, to optimize life cycle cost, equipment should have:

- robust capabilities for achieving initial, continuous, and long-term operation
- ease of maintenance
- low energy use

The guidance in this section suggests materials and construction that may help to assure reliability and uptime, leading to lower operating and maintenance (life cycle) costs. Economic analysis may justify the use of less expensive or “off the shelf” HVAC equipment.

Installation, startup, and ongoing maintenance aspects should be considered. See Sections 6.3 and 6.4.

5.1.2 Air Handler Unit

HVAC equipment manufacturers may specialize in “pharma grade” air handlers, particularly in large capacity custom units. Smaller HVAC systems have been successful using “off-the-shelf” HVAC equipment from acceptable manufacturers. As both options can satisfy product requirements, the driver usually is economics, not GMP. The selection of equipment should satisfy user requirements; less elaborate equipment may require more maintenance and may be less energy efficient, but may be acceptable.

Aspects that should be considered in creating purchase specifications for bespoke HVAC systems include:

- GMP air-handlers should be constructed to meet stringent performance, improved reliability, and maintenance requirements for critical areas
- Air handler components, such as coils, humidifiers, dehumidifiers, dampers, fans, motors, and filters should be designed and constructed to provide 115% of design capacity to accommodate potential increased demand or future expansion

5.1.2.1 Cabinet Construction

In geographic regions of moderate to high ambient humidity levels, condensation on the exterior of the AHU casing may be an issue. Where high humidity is relatively persistent, this condensation may lead to exterior rust, mildew, and mold growth. Consideration should be given to no through metal (a thermal break) on wall, floor, doorframe, ceiling sections, and doors. If thermal breaks are not correctly designed and implemented, there is a potential for exterior condensation.

To minimize leakage of expensive conditioned air, total air leakage rate from the casing may be specified at no greater than 0.5% of rated flow at 150% of the design pressure or 50 CFM (1.42 m³/min), whichever is greater, or the requirements stated in EN 1886 standard (Reference 6, Appendix 12) for the most severe “leakage class” operation. As eventual deterioration of seals on doors, dampers, and other components will lead to increased air leak rates, the initial measured air tightness can be used as a gauge to identify future loss of air flow.

5.1.2.2 *Insulated Wall Panel Construction*

For larger air handlers, the roof, floor, and ceiling may be constructed of “sandwich” panels that are insulated with foam (polyisocyanurate) that is approved by the insurers and meets local fire ratings. Foam should not be exposed to the air stream and should be covered to isolate it from the surrounding area. Other insulating materials may be used, but foam panels are:

- structurally superior
- eliminate migration of moisture and air
- less subjected to deflection due to air pressure
- have better insulating properties

The interior panel surfaces and joints should be smooth and continuous, constructed of a material such as aluminum, galvanized steel, or stainless steel that can be wiped clean and will not easily rust or corrode. In AHU compartments serving cooling coils or steam humidification injection, 304L SS should reduce rusting effects. Insulation or sound attenuation lining should not be exposed inside an air handling system serving a GMP area because of the potential of providing an area for mold and bacteria growth.

To minimize leakage, interior joints may be sealed with food grade RTV silicone sealant caulk, with exterior joints sealed with caulking having at least a 25 year life with a mold inhibitor.

5.1.2.3 *Removable Wall Panels*

Removable panels in large AHUs provide a method to remove large components, such as fan assemblies and coils that would not fit through the AHU access door. The panel should be removable with simple hand tools to avoid cutting or sawing and creating a leakage problem after reassembly.

5.1.2.4 *Flooring*

Flooring in large AHUs should be of a sufficient thickness to prevent “oil canning” (deformation) when walked upon and damage from dropped tools or equipment. The floor may be designed to have a capacity of 100 pounds per square foot (psf) live load to accommodate a service mechanic working inside the unit. Flooring should have a non-slip texture for the safety of personnel standing within the unit. Floor seams should be sealed to the wall for a watertight floor system.

5.1.2.5 *Condensate Pan*

The cooling coil condensate drain pan (upstream and downstream) should be of 304L SS to maximize its life. The pan should slope to enhance total drainage (minimum 1.5%) with a minimum depth to prevent overflow during normal operation. Its length should extend beyond the coil's downstream face a minimum of 12 inch (30 cm) or half the height of the coil, whichever is greater, and a minimum of 6 inch (15 cm) beyond its upstream face. Refer to the ASHRAE – Systems and Equipment Handbook, Chapter 21.4 (Reference 22, Appendix 12).

Each stacked cooling coil should have a drain pan with drainage into the lower coil section(s). The length of a stacked cooling coil should extend beyond its downstream face a minimum of 12 inch (30 cm) or half the height of the coil, whichever is greater, and a minimum of 15 inch (40 cm) beyond its upstream face.

Condensate drain pans should not leave puddles (which can lead to biological growth). Drain pans should slope a minimum 1:100 (1%) toward the drain outlet. Connections should be piped through the casing wall and sealed. Condensate drain traps should be tall enough to prevent air movement into or out of the air handler during operating conditions.

5.1.2.6 Wash Down Capability

In specific applications, the interior of the air handler may require cleaning and wash down. In these applications, AHU sections (excluding condensate pans) requiring drainage capability for wash down should have a drain opening fully sealed around its perimeter and fitted with a secured/removable, flush-mounted, airtight cover plate or plug to prevent entry of contamination during operation.

5.1.2.7 Roof

AHUs located outdoors should be provided with roof panels sloped to drain. The entire roof should be fully insulated without gaps at the peak. If deemed necessary, all outside AHUs should be fitted with a perimeter roof gutter and down spouts, along with rain guards above all exterior access doors.

5.1.2.8 Hardware

Hardware (i.e., screws, nuts, washers, etc.) should be corrosion resistant (e.g., 300 series SS) with flexible washers to minimize air leakage in the exterior. Materials that oxidize or promote rust should not be used in the construction of equipment. Adequate materials of construction along with painting of components (valves, fittings, etc.) should help protect against deterioration (i.e., corrosion) dependent on the environment the unit will encounter.

5.1.2.9 Doors

Access doors should be installed on each section of the AHU (i.e., coils, filters, fan, humidifier, etc.), sufficiently wide (e.g., minimum 24 inch = 610 mm) to allow entry by an operator for cleaning and maintenance. Coils should have an access door upstream and downstream. Access doors should open against the direction of higher relative pressure for safe use and positive air seal. Positive pressure sections of the air handler should have doors labeled as such to protect operators if opened during AHU operation. Doors should be of a double gasket compression design to minimize leakage. Each access door may be fitted with an instrument test port to allow temperature and pressure readings to be collected without drilling into the cabinet during air balancing commissioning.

It is considered advantageous to be able to visually inspect the interior without opening casing doors. Doors may have impact, mar-resistant, clear view ports (such as double pane wire, Mylar-backed glass, or polycarbonate (Lexan)), usually sized 12 inch × 12 inch (305 mm × 305 mm), or 12 inch (305 mm) diameter.

Doors should have latch handles located inside of the AHU to prevent personnel becoming trapped inside of the unit. Doors may have static pressure ports with threaded caps. The port should not rotate when tightening or loosening the cap.

5.1.2.10 Mixing Plenum

The mixing plenum is where outdoor air is mixed with return air. Outdoor air louvers in mixing plenums should be aligned to promote mixing with return air to avoid stratification.

5.1.2.11 Duct Connections

Cabinet duct connections can significantly reduce the system's delivery capacity if sized to match the size of ductwork mains. It is recommended that return and supply duct connections be sized sufficiently large to ensure lower air velocity at the connection (e.g., no greater than 1,100 fpm = 5.5 m/s). Suitable transitions can then be connected to the main ductwork to ensure smooth transfer of air to/from duct mains.

5.1.3 Fans

Fan selection is critical to efficiently moving the proper quantity of air (supply, return, and exhaust/extract) and creating required pressure to overcome losses because of:

- dampers
- coils
- filters
- silencers
- ductwork

When selecting fans to operate smoothly over their intended life, aspects to consider include:

- materials of construction (rigidity, weight, corrosion, cleanability) determined for the type of operation (clean/contaminated air, humidity, temperature, severity)
- bearing
- lubrication
- direct versus belt driven
- static pressure flow sensing
- safety guards

Air handlers are configured as either a draw-through or blow-through operation; draw-through typically are used. Draw-through units have the fan located downstream of the pre-filters, coils, and humidifier. Their advantages include a shorter unit length, negative pressure on all access doors except the fan discharge section, and reheating of air leaving the fan section, which will reduce reheat coil requirements.

Fan pressure performance and construction are identified as Class I, II, III, or IV by AMCA, based on certain minimum operating criteria. A Class I fan offered by any particular manufacturer has a lower allowable minimum operating range than its Class II counterpart. As a result, a Class I fan has less mechanical design strength and with less first cost than a Class II fan. Typically, Class II and Class III fans are sufficient to handle pharmaceutical applications. Fans should not be sized too small, such that they operate above 1800 RPM, shortening bearing life. High fan RPM also has a risk of dangerous vibration (operating too near a fan's critical speed) and has more noise.

Fans typically used in air handlers on the supply side are either plug/plenum fans or centrifugal fans fitted with a drain plug and cleanout panel. Fans can be direct driven or belt driven. Exhaust/extract operations typically use direct or belt driven vane axial or centrifugal fans.

Plenum fans should be selected for high efficiency with non-overloading airfoil aluminum wheels. They should include inlet cones matched to the wheel intake rim to ensure efficient and quiet operation.

Vane axial fans are used where large volumes of air need to be moved at low to moderate pressures. The tubular design, high efficiency rotor, and integral straightening vanes provide high performance using minimal space. These fans are considered a suitable choice for HVAC systems using variable air volumes, high airflow to cleanrooms, and exhaust/extract. They are efficient as return fans to air handlers and for exhaust/extract applications (fume hoods, bio-safety cabinets.) These units should be configured for direct drive (motor in the air stream) although a belt drive could be used.

Another variation of the direct drive fan configuration is an array of smaller plug fans (commonly called a “fan wall”) to replace a traditional single large fan. This arrangement reduces the overall footprint of the air handler, allows design flexibility, simplifies maintenance, reduces downtime, reduces low-frequency noise (rumble) within the air handler, and usually saves energy. Such use of multiple direct-drive fans operating in parallel improves reliability by providing redundancy.

Direct driven fans eliminate belt replacement, guards, and belt shedding and alignment. In addition, there are no shaft bearings present, which eliminates lubrication requirements.

Belt-driven fans should have their motors and fan belt/sheave assemblies completely enclosed (front and rear) in a rigid 304 SS or painted steel guard that protects personnel from injury, while prodding for tachometer readings. These guards should be removable without the use of tools, but should include a warning label to notify the operator to secure the equipment prior to opening. The fan motor base should automatically control belt tension and be permanently aligned to allow belt changes without realigning. For multiple belt systems, belts should be matched sets. Entire fan assembly should be centered in the air stream both vertically and horizontally to assure efficient airflow. Fan inlets and discharges should have operator protective screens.

Belt driven fans may be laser aligned to decrease bearing, shaft, and belt failures and to reduce energy consumption. Correct fan belt tension should be maintained and requires special attention, particularly when installing new v-belts. Once new belt(s) have operated for a short time, they usually will need to be readjusted because of belt wear-in. Improper under-tensioning will result in premature failure and increased energy usage. Over-tensioning can reduce bearing life. Synchronous belts can reduce energy consumption, as they do not slip during startup and operation.

The best fan housings are continuously welded to provide strength and durability and extended service life. They have a primer with at least one coat of industrial strength or epoxy paint finish to eliminate rusting. For centrifugal fans, a drain connection should be located at the bottom of the fan housing for fluids that may accumulate, such as in a draw-through fan downstream of a condensing cooling coil.

If possible, fan wheels should be of aluminum construction to reduce weight and rusting and be fully welded and non-overloading. Wheels should be both statically and dynamically balanced. Fan shafts should be precision ground, polished, and sized so that the first critical speed is at least 25% over the maximum operating speed. A shaft seal should be included to reduce leakage or to protect the bearings from a contaminated air stream.

To minimize bearing problems, fan shaft bearings should be selected for a minimum average life of ABMA L10 200,000 hours. Automatic bearing lubricators may be installed to increase bearing life and reduce maintenance. This will eliminate the possibility of over/under lubrication, resulting in premature bearing failure. The lubricator should be installed directly on the bearing housing and be sized to supply lubricant for a minimum of 6 months without refill or replacement. The fan supplier should work closely with the lubricator supplier to provide the proper lubricant and device for the intended operation of the air handler. **Note:** The lubricator should not be mounted or activated until the fan is put into full operation to eliminate automatic excessive lubrication and damage.

Removable inlet and outlet fan guards should be included to provide protection for personnel and equipment meeting OSHA or local safety standards.

Fan inlets should be centered in both the horizontal and vertical planes within the air handler to promote more even airflow through filters and coils.

Bearing failure is the most common failure encountered within air handlers. Unbalanced fan wheels increase stress on bearings, leading to increased vibration and the likelihood of early bearing failure. Vibration should be minimized to conform to ANSI/AMCA Standard 204-05, “Balance Quality and Vibration Levels for Fans” (Reference 20, Appendix 12) and have a maximum balance and vibration BV-4 category. Balance readings should be checked by electronic type equipment in the axial, vertical, and horizontal directions on each of the bearings.

Fans and motors for critical applications should be provided with vibration sensors to provide early warning and trending of bearing performance with signal wiring brought out to a vibration interface enclosure mounted on the outside of the AHU.

One method of reliably measuring fan airflow without impeding air movement in or near the fan inlet is to install a combination piezometer ring and static pressure tap integrated into the fan inlet cone. The inlet cone of the fan is then used as the flow nozzle. The flow sensor should be provided with the fan.

5.1.4 Motors and Drives

Variable Frequency Drives (VFDs) are recommended to control the volume of air delivered to the various spaces. The advantages of the VFD in place of variable inlet guide vanes include:

- better volume control
- better energy usage
- less maintenance
- soft start of fan motor reducing the in-rush of electrical current and stress on the fan
- positive control feedback to the building automation system

Invertors should include line and load reactors to eliminate motor failure.

The cost of VFD controls may allow VFDs to be used on small air systems. Motors that will operate at various loads should be inverter duty, rated NEMA premium efficiency, and should comply with NEMA MG1, Part 31 (Reference 28, Appendix 12). A shaft grounding system or isolated bearings should be installed to prevent bearing failures caused by induced electrical current.

Motor bearings should have a minimum average life of ABMA L₁₀ 100,000 hours. Automatic bearing lubricators should be installed for the same reasons and with the same requirements as for fan bearings. For further information see Chapter 5 of this Guide.

Fans with belt drives use a synchronous belt with matching sprocket in place of v-belts and sheave. The advantages include:

- non-slip operation
- longer life
- less maintenance
- little to no belt shedding
- single synchronous belt versus multiple v-belts for same operation
- reduced energy consumption

The one disadvantage is that it may produce higher noise levels.

A disconnect inside the AHU casing is recommended for maintenance personnel use, as motors usually are controlled remotely.

5.1.5 *Electrical*

For operator ease, particularly in larger AHUs, interior lights may be more convenient than portable lighting. Lighting may include vapor tight fluorescent fixtures (typically 4 ft (1200 mm)) tubes with two T8 lamps and electronic ballasts with one fixture in each section. The lighting should be controlled with a one 6-hour maximum waterproof, light switch timer, as a minimum.

Junction boxes should be weatherproof and conduit penetrations should be sealed airtight.

Electrical components, wiring, and terminals should be tagged. High voltage terminals must be labeled as such. Internal power cabling should be shielded.

Materials and installation methods should comply with NFPA and NEC or the local electrical code.

Sections with fans and moving parts should have warning signs, such as **'isolate before entry'** affixed to doors. AHUs manufactured for Europe should have a Conformance Européenne (CE) mark. A Canadian Standards Association (CSA) rating should be placed on electrical devices.

5.1.6 *Heating and Cooling Coils*

Coils should be fully drainable with vent and connections extending outside the AHU or ductwork. Full port shut-off valves with hose connection with cap and chain should be included. Steam coils should be fitted with vacuum breakers. Water coil velocities should be kept between 2 and 6 fps (0.61 and 1.83 m/s) to provide turbulence, but to minimize erosion. Without turbulence, reduced heat transfer can result.

Coils exposed to salt or corrosive conditions should use a fin material of copper rather than aluminum, which degrades in corrosive atmospheres, or be coated with a protective film. Cooling coils in condensing service may be coated to minimize corrosion and reduce biological growth.

Coil performances should be rated in accordance with ARI Std. 410 (Reference 21, Appendix 12).

Coil sizing, configuration, and installation will affect the ability to meet the requirements for delivery of conditioned air. Peak moisture load should be considered for cooling coil design using the climatic data from the ASHRAE Fundamentals Handbook or CIBSE Guide A (References 22 and 24, Appendix 12).

Air handler cooling coils should have a maximum average face velocity of 450 fpm (2.29 m/s) to eliminate condensate carry over and optimize heat transfer capacity. Cooling coil face velocities should be fairly uniform. Steam and hot water coils should have a maximum face velocity of 600 fpm (3.0 m/s) to minimize static pressure drop, resulting in a lower (coil to energy) cost ratio compared to coils having velocities of 800 fpm (4.06 m/s) and higher.

Air handler coil tubing should be of nominal 0.035 inch (0.89 mm) thick seamless copper with aluminum fins of at least 0.0095 inch (0.24 mm) thickness. Coil casings and frames of 304L SS have better longevity and no rust. A center tube support for coils greater than 48 inch (1.2 m) in width is advised. Cooling coils should be no more than 10 rows deep and 10 fins/inch to enhance cleaning and heat transfer. Preheat steam and hot water coils should have no fewer than 2 rows to minimize downstream face temperature variation.

Duct mounted coil tubing should be 0.025 inch (0.64 mm) thick seamless copper with aluminum fins of at least 0.008 inch (0.20 mm) thickness.

Coil piping should have shut off valves and union fittings to facilitate coil removal for repair.

Steam supply should be taken off the top of the steam main.

For better control of liquid flow and proper venting through coils, control valves should be placed in the return piping.

Supply and return line shut-off valves should be provided to facilitate service and maintenance.

5.1.7 Steam Humidifier

Low-pressure steam is preferred over water for pharmaceutical HVAC humidification, because it is bacteria free and often available. Humidifiers should have steam injection dispersion/sparge tubes and accessories to provide drip-free steam absorption without downstream condensate droplets. When clean steam is required for humidification, such as for humidity controlled product dryers and coating pans, sanitary tri-clamp connection control valves, and thermostatic steam traps, along with other components made of 316L SS, should be used. Modulating steam control valves should be included to provide accurate control. A wye (Y) strainer should be installed upstream of the control valve to protect it from dirt. See Appendix 2 for a discussion of steam sources.

When located in the air-handling unit, the humidifier section should be located directly upstream of the cooling coil section (which should be off in the winter) to ensure efficient distribution and absorption of vapor into the air stream. The humidifier condensate drain pans (up and downstream) should be 12 gauge 304L SS, and at least 2 inch (5 cm) deep. Its length should extend beyond its downstream face to the upstream side cooling coil pan, and also extend a minimum of 6 inch (15 cm) beyond its upstream face. Connections should be piped to exterior of unit casing.

When the humidifier is located within ductwork, the ductwork should be constructed of fully welded 304L SS, 2 ft (0.6 m) upstream, and 5 ft (1.5 m) downstream of the humidifier for corrosion control. Humidifier ductwork sections should pitch downstream of the humidifier to a drain in the stainless section with a sufficiently tall trap to prevent air leakage through the trap.

Steam supply should be taken off the top of the steam main rather than off the bottom to ensure the driest steam is provided to the distribution manifold.

A high limit humidity sensor should be located within a relatively short distance of the humidifier, but after absorption of the steam has occurred to shut the humidifier control valve if air stream RH typically exceeds 85%, preventing accumulation of moisture onto downstream surfaces or air filters.

5.1.8 Dehumidification

Where standard chilled water or glycol systems are not available or unable to sufficiently reduce RH levels, several dehumidification systems are available to provide lower relative humidity.

These include:

- run-around coil systems – provide humidity levels equal to standard chilled water/glycol, but at lower energy cost
- heat pipe systems
- dual-path systems
- desiccant systems

Desiccant systems have been the most widely used method for dehumidification in the pharmaceutical industry, because they are capable of delivering air at much lower dew point than coils.

Layout of dehumidification equipment should include filters upstream of the coils and fans downstream of coils (in draw-through systems) to provide a small amount of reheat. Lower face velocity will reduce air pressure drop and improve the coil's dehumidification performance.

When dehumidification is integrated into a cooling system, attention should be given to:

- Selection and size HVAC equipment (coils, fan, pump, damper, etc.) for sensible and latent cooling at peak load conditions. These usually do not occur simultaneously (highest temperature day usually is not the most humid day).
- Designing for energy efficiency at part-load conditions because peak load usually occurs only about 2% of the operating time.

A desiccant dehumidification wheel should be upstream of final air filters to capture loose desiccant and contaminants deposited from reactivation air that may be shed from the wheel. Prefiltration of the reactivation air should be matched to the prefiltration of the process air to minimize the load on the final filters.

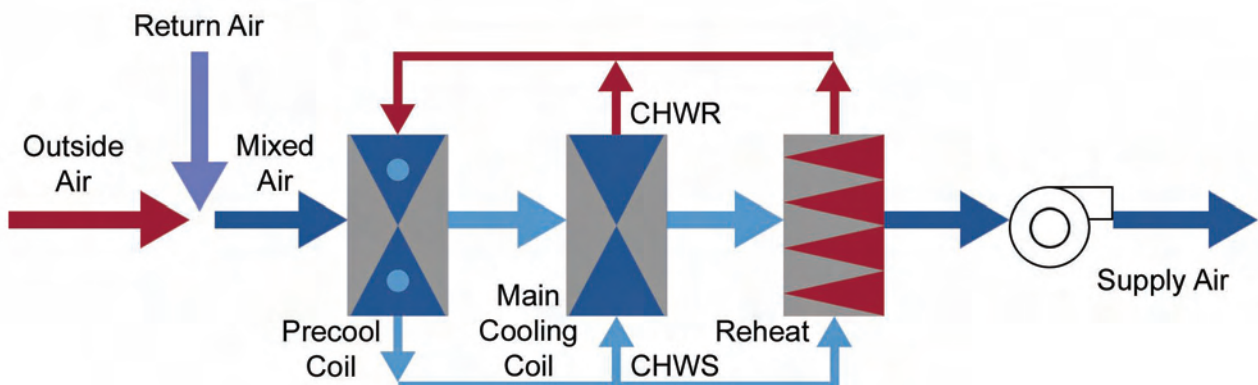
Cooling is required downstream of a desiccant wheel to remove the heat gained in the wheel. Pre-cooling (and even condensing) the air entering the wheel can enhance the drying capacity and energy efficiency of a desiccant wheel.

5.1.8.1 Run-around Coil System

A run-around coil system is a simple piping loop with an upstream pre-cooling coil and a downstream reheating coil that sandwiches the main cooling coil. A circulating fluid is pumped to transfer heat from the warm mixed air to the reheat coil, which heats the cold supply air coming off the main cooling coil. The run-around system reduces the cooling load on the main cooling coil; reheat energy is provided by the heat picked up by the circulating fluid in the pre-cooling coil instead of by an external source of energy.

The run-around loop requires a fractional horsepower pump and a three-way valve or a Variable-Frequency Drive (VFD) for the pump. For bigger systems, an expansion tank with air vent may be needed.

Figure 5.1: Run-Around Cooling Loop



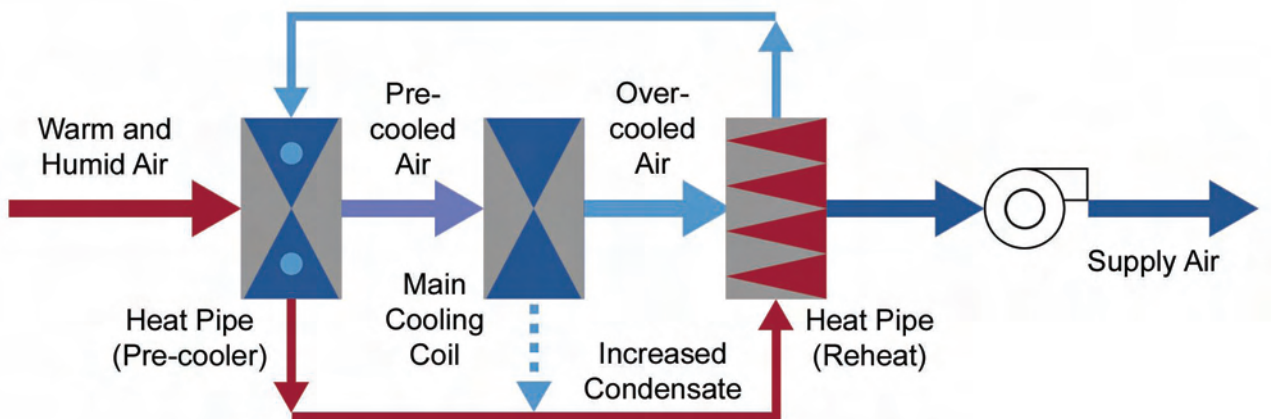
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5.1.8.2 Static Refrigeration/"Heat Pipe"

Heat pipes increase the effectiveness of air conditioning systems by helping to decrease the total cooling load of the air. The typical design consists of a refrigeration loop with two connected heat exchangers, (or one heat exchanger divided into two sections) one upstream (evaporator coil section) and the second one downstream (condenser coil section) from the main cooling coil. As the air passes through the first heat exchanger it vaporizes the refrigerant and is pre-cooled. This allows the main cooling coil to more effectively cool the air to a point below the dew-point temperature and to extract more moisture. The air then passes through the second heat exchanger and is reheated by the warm refrigerant coming from the first exchanger, cooling and liquefying the refrigerant, causing it to flow back to the first heat exchanger. Single heat exchanger type heat pipe systems are hermetically sealed, using a wicking action, and requires no pump. The increased dehumidification capacity provided by heat pipes allows for a smaller cooling system. However, the addition of heat pipes will increase the pressure drop and fan power should be adjusted

accordingly. For air dew points below 32°F (0°C), there is a risk of freezing condensed moisture from the air onto the surface of the main cooling coil with ice building up and reducing airflow over time. Often, a second cooling coil is installed in parallel to the first with dampers to switch over to the de-iced coil, while the first (iced) coil thaws.

Figure 5.2: Heat Pipe System



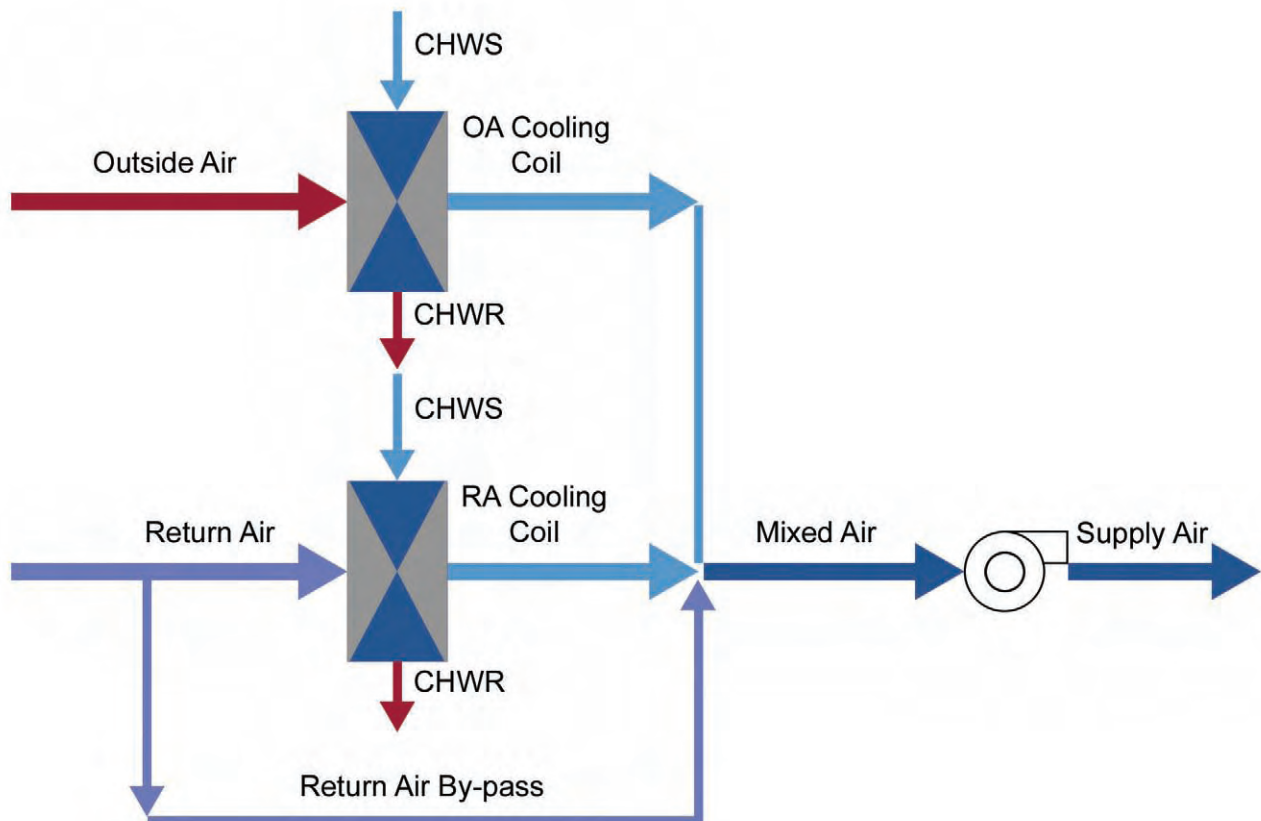
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5.1.8.3 Dual Path System

A dual-path system uses two coils (either chilled water or direct expansion -refrigerant) to separately cool the incoming outside air and return air. The hot and humid outdoor air is cooled by a 'primary' coil to 42 to 45°F (5 to 7°C) for dehumidification. The 'secondary' coil furnishes the sensible cooling of part of the relatively cool and dry return air. A portion of the return air may bypass the secondary coil and mix with the cooled return air stream. These two air streams (outside and return air) are then mixed into supply air with appropriate temperature and humidity.

Dual-path systems offer competitive energy efficiency with run-around loop systems and provide better control of the outside air ventilation rate. Dual-path systems decouple sensible cooling and latent cooling for easy control of the supply air temperature and humidity. Dual-path systems can be installed separately or integrated with additional HVAC/return equipment. The outside air cooling coil should be sized for peak latent load, while the return air cooling coil should be sized for peak sensible load. The outside air path controls the humidity of the mixed supply air by modulating the chilled water flow, while the return air path controls the mixed supply air temperature by adjusting the bypass damper position. As with the heat pipe, there is a risk of ice buildup for dew points below 32°F (0°C).

Figure 5.3: Dual Path Cooling



Used with permission from AEC and Department of Business, Economic Development and Tourism, State of Hawaii,
www.archenergy.com/library/general/hawaiiig/

5.1.8.4 Desiccant Systems

Desiccant systems are applicable and commonly used when operations require large dehumidification and low space humidity levels (dew points at or below 37°F/3°C) that would be difficult to achieve with cooling-type dehumidification. They can be configured to condition part or all of the incoming air depending on percentage of outside air versus return air, outside and space RH levels, and the quantity of air flow for the conditioned spaces.

Desiccant materials have an affinity for water vapor greater than that of air. They can either be solid or liquid, as absorbents or adsorbents. Both solid and liquid desiccants are used in cooling systems, but solid desiccants are the most widely used for HVAC operations and less difficult from a corrosion perspective.

Absorbents generally are liquids or solids that gradually become liquid as they absorb moisture, i.e., they undergo a physical or a chemical change when they collect too much moisture. Typical absorbents include Lithium Chloride (LiCl) and Sodium Chloride (NaCl).

Adsorbents are mostly solids and do not undergo physical or chemical change when they contact moisture. Water is adsorbed or held on the surface of the material and in its pores. Typical adsorbents include Silica Gel, Molecular Sieve, and Activated Alumina with Silica Gel being the most widely used.

The choice of desiccant material should take into account the amount of moisture to be removed, the degree of air filtration following the desiccant, and operating and maintenance costs. LiCl and silica are most commonly used in pharmaceutical HVAC.

The choice of a desiccant system affects the sizing of the main cooling coil, because the cooling coil needs to handle only the sensible (dry heat) load of the supply air, which permits higher chilled water temperature and more efficient operation. However, the total sensible cooling load will be higher, because of the hot dry air leaving the desiccant wheel (due to heat of adsorption).

Typically, the space RH controller modulates a bypass damper around the dehumidifier, such that a need for lower room RH causes more air to pass through the desiccant wheel. Because of variability of airflow caused by the multiple paths, pressure and air volume controls are needed in the duct system to maintain constant airflow at the main AHU. Attempts to control RH by modulating the steam flow to the reactivation coil have been made, but this method is less effective because of the long time lag before a change in room RH and because of potential damage to absorptive desiccants through under-drying.

When the dehumidifier is idle (such as in cold winter weather when humidity is needed), it should be bypassed fully, but the wheel should be kept dry (i.e., keep the wheel running and the heat on). This is particularly true for absorptive desiccants (such as LiCl) that can “self-destruct” if allowed to absorb moisture without being regenerated.

The addition of a desiccant wheel increases the overall air pressure drop, fan power, and maintenance, and an additional small motor is required to rotate the wheel. This extra energy usage affects the overall life cycle cost. Desiccant systems may use steam, electricity, natural gas, low-cost surplus heat, waste heat, or solar heat for desiccant reactivation. Typical reactivation temperatures exceed the boiling point of water and usually exceed 250°F (122°C).

Units should be capable of sustained operation without damage to the desiccant. The dehumidifier often is a fully factory assembled package unit, complete with:

- desiccant rotor
- desiccant rotor drive assembly
- reactivation heat source
- filters
- motors
- reactivation fan
- access panels
- volume dampers
- dust-tight electrical enclosure
- component auxiliaries (recommended by the manufacturer for safe, unattended automatic operation)

The fan for the process airflow, needed to overcome the pressure drop induced by the wheel, is often purchased separately. The unit should be fully automated and equipped with DP gauges and temperature transmitters to measure and display the pressure drop across the desiccant wheel and the reactivation and pre-cooling air discharge temperatures.

The unit casing should be fabricated of strain-hardened aluminum for torsional rigidity and corrosion resistance. The casing should be welded, gasketed, and sealed to be air and vapor tight at design pressures and airflows. Air seals and internal partitions should separate the process and reactivation air streams at operating pressure differentials of up to 8 inch wg (1.99 kPa). The dehumidifier should have full-face seals on both the process air entering and the process air leaving sides of the wheel. These should seal the entire perimeter of both air streams as they enter and leave the wheel. The seals should have a minimum working life of 25,000 hours of normal operation.

The desiccant wheel medium should be bacteriostatic, non-toxic, non-corrosive, and nonflammable, and fabricated entirely of inert, inorganic binders and glass fibers with the desiccant uniformly and permanently dispersed throughout the matrix structure to create a homogenous media. The desiccant wheel should have the capability of delivering nearly 100% of its drying capability for a minimum of 5 years.

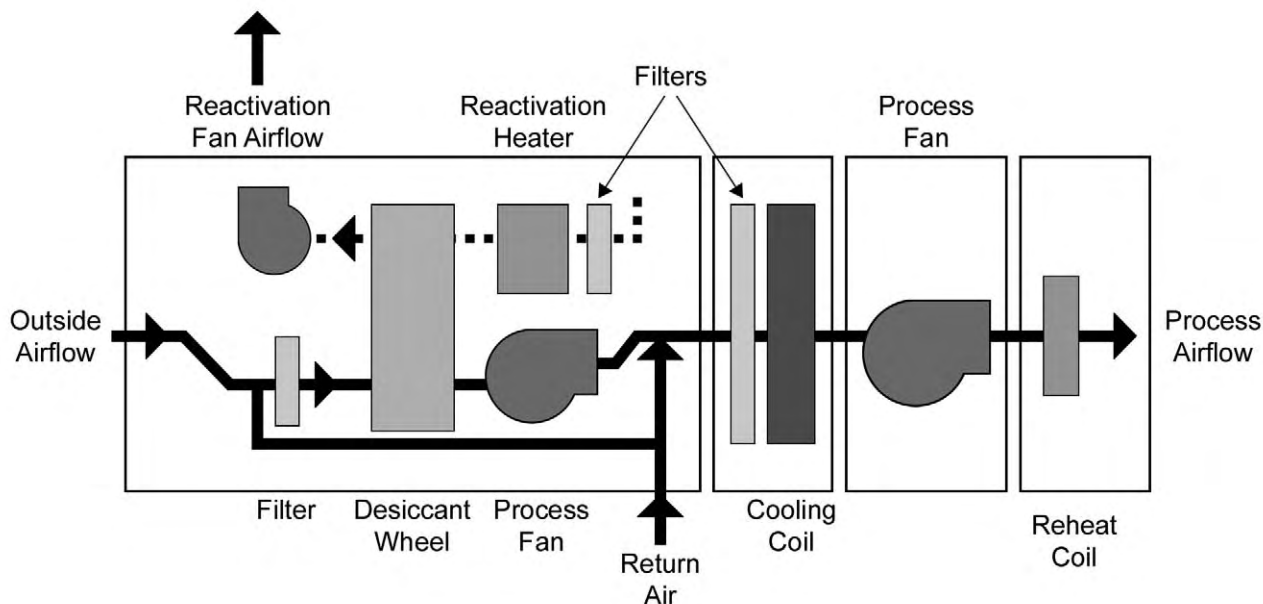
Desiccant systems are more competitive when:

- a low supply air dew-point temperature is required
- latent load fraction is high
- low or no-cost reactivation heat from steam, hot water, or waste heat is available
- electricity costs (for refrigeration dehumidification) are high when compared to gas or steam costs

There are several circumstances that may favor desiccant systems rather than cooling-based dehumidification systems. These include:

- economic benefit from low humidity in the facility (often product-driven)
- high moisture loads with low sensible load
- need for more fresh dry air
- exhaust air available for desiccant post cooling using energy recovery
- low thermal energy (steam, gas) available or high electrical cost
- economic benefit and bioburden benefit of dry supply air duct work
- low-cost heat available for desiccant regeneration

Figure 5.4: Package Desiccant HVAC System



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5.1.9 Ductwork Design

Ductwork should be in accordance with Sheet Metal and Air Conditioning Contractors' National Association (SMACNA) (Reference 30, Appendix 12) and Heating and Ventilating Contractor's Association (HVCA) (Reference 26, Appendix 12) standards. Local standards may be similar to these US standards. Supply and general return air ductwork should be constructed of galvanized steel. Stainless steel should be used when corrosion or continual cleaning occur, such as inside a cleanroom. There should be no interior insulation that can add particles or harbor growth. Ductwork should be adequately supported so as to easily carry its weight and insulation along with in-line equipment and controls. If noise is a concern, in-line silencers may be installed ahead of HEPA filters. If vibration is an issue, flexible support and connections should be considered. When flexible ductwork is required to tie the branch to the terminal air device, its length should be kept to a minimum and should not exceed 10 feet (3 m).

Abrupt changes in the size and direction of ductwork can lead to increased noise, vibration, and pressure drop. Duct leaving fans and air handlers should be straight for as long as possible, and if elbows are required near the fan, they should not cause "system effects" that can greatly reduce system performance and consume horsepower. Sufficiently sized duct access doors should be provided at appropriate locations to equipment (e.g., at coils, humidifiers, control boxes, dampers). To preclude leakage of expensive conditioned air and to avoid larger leakage in the future, ductwork should be sealed with approved fire and smoke rated sealant in accordance with NFPA 255 or UL 723 (Reference 29, Appendix 12) or equivalent. Ductwork leakage percentages will vary from site-to-site, air system, and areas served. In general, ductwork should have no more than 1% leakage (with 0% leakage on positive pressure exhaust duct and positive pressure duct carrying hazardous materials), 4 inch wg (1 kPa) minimum static pressure class, and a SMACNA seal class A. Duct sealant should be carefully chosen to ensure long-term adherence to galvanized steel. Solvent or oil-based sealants are more difficult to work with and may have environmental restrictions, but they have usually provided good long-term service.

5.1.10 Dampers and Louvers

Dampers redirect, stop, or vary the amount of air traveling within an HVAC system. Damper blade movement can be either parallel or opposed. Parallel blade dampers rotate in the same direction, staying parallel to each other throughout their travel from fully open to fully closed. Opposed blade dampers operate such that adjacent blades rotate in the opposite direction from each other.

Opposed blade dampers are preferred for their smooth throttling flow with more linear performance because of less turbulence. More sophisticated designs are available to provide better control, but at more cost. See Section 2.7 of this Guide.

For mixing applications, parallel blade dampers are preferred since they deflect air streams to encourage mixing. It is preferred to orient the locations of the outdoor air and return air entry points into the mixing plenum to direct the air streams into each other.

Louvers usually have no moving parts, and typically, are used for outside air intake. Outside air inlet velocities should prevent drawing in rain (recommended maximum of 3.05 m/s (500 fpm) through the louver's free area). For areas that experience significant snow, openings should be equipped with a 90-degree gooseneck inlet sized for a maximum of 1.02 m/s (200 FPM) and be equipped with an inlet louver sized for the same velocities. Louvers should be drainable and may be constructed of anodized aluminum or stainless steel with 304 SS hardware and include 304 SS bird screens.

Wind driven rain can be forced into outside air intakes with such force that the rain can be pulled through the air handling sections and then sent down the supply ductwork. A storm louver for outside air intakes to handle unseasonable weather should be selected to avoid pulling moisture into the system.

The outdoor air intake, return, exhaust, and relief dampers should be rated for low leakage to prevent the infiltration of air when the systems are off or during hostile weather conditions. Low leakage dampers should have vinyl seals that are mechanically attached (not glued) to the damper blade and jamb seals to prevent leakage around the ends of the damper blades.

Sufficient space should be provided to remove and install damper actuators without the need to remove dampers or other equipment. Dampers should be made of corrosion-resistant materials, such as aluminum or 304 SS. Damper jackshaft should be extended to the exterior of the AHU casing for actuator mounting.

The placement of outside air intake louvers for an air handler must take into account the location of fume and exhaust stacks, sewer vent pipes, and cooling towers that can affect Indoor Air Quality (IAQ). Avoid intake locations near where trucks may be running, such as loading docks. Local and regional codes provide minimum separation distances.

5.1.11 Diffusers and Registers

These devices are critical to the air distribution in and out of rooms/spaces. Proper positioning is vital for providing good distribution and a sweeping action of the air from the supply to the return side of the space to deliver uniform air patterns that cleanse the environment and displace contaminants. Poor positioning can result in either dead zones with increased local particulate levels or excessive airflow with unwanted air turbulence. For classified spaces requiring low in-use air counts, it usually is better to have more air outlets at low flow than to have one air outlet at high flow.

Since these devices are located at the perimeter of the space (usually in the ceilings), the choice of materials should be compatible with the room's function. For cleanroom operation, stainless steel is preferred, to eliminate corrosion and rusting resulting from wash downs with aggressive cleaning agents.

Terminal filtration modules (boxes) are used with room side accessible HEPA filters to supply clean air and to prevent contaminated air from leaving the room when the AHU is not running. Refer to the Filtration section for more detail.

5.1.12 Ultraviolet (UV) Light

Ultraviolet light is an emerging bioburden control technology that may continuously supplement the existing filtration device(s) in a building's HVAC system, where biological growth can lead to energy losses because of heat transfer reduction caused by fouling on the cooling coil. This growth may be released into the air stream. Safety of maintenance personnel and materials in proximity are a concern. Manufacturer's recommendations should be followed.

To protect personnel from UV exposure, the UV power supply should be de-energized when the lamp access door is opened or when the door of the air handler is opened.

5.1.13 Fume Exhaust/Extract System Design

5.1.13.1 Dust Collection Systems

There are three methods of controlling contaminant levels:

1. dilution ventilation
2. LEV
3. containment inside the process

LEV uses the concept of extracting the contaminant as soon as it is generated as close as possible to the release point, removing it before it can be inhaled or become a source of contamination. It is generally less expensive to operate than an equivalent dilution ventilation system.

The system usually consists of a local hood or enclosure, a ductwork system, a filter (typically a self cleaning bag filter), a fan, ductwork to discharge the cleaned air from the system, and often for pharmaceutical applications, a “policing” (usually HEPA) filter to provide a final protective filter before air is discharged to atmosphere. This filter and seal should be routinely leak tested at change-out, at least annually or at intervals designated by local codes or internal company policies.

Table 5.1: Types of airborne contaminant (1 μm = 0.000001 meter = 0.00004 inch)

Type of Contaminant	Typical Particle Size (μm)
Dust	0.1 – 75 μm
Fume	0.001 – 1.0 μm
Smoke	0.01 – 1.0 μm
Mist	0.01 – 10.0 μm
Vapor	0.005 μm
Gas	0.005 μm

The design of the local hood is critical to obtaining the correct capture velocity for the size of particle and its means of dispersal. The design should also strive for reasonable noise levels and exhaust volumes.

The ductwork design should be based on constant velocity to ensure that particles remain suspended and do not accumulate in ductwork. Table 5.2 suggests typical minimum velocities.

Table 5.2: Suggested Typical Minimum Conveying Velocities

Contaminant	Duct Velocity m/s	Duct Velocity ft/min
Gases (non condensing)	No minimum limit	No minimum limit
Vapors, Smoke, Fume	10	2000
Light/Medium Density Dust, e.g., Sawdust	15	3000
Average Density Dust	20	4000
Heavy Dusts, or Damp Dust which may agglomerate	25	5000

Ductwork is usually made of electrically conductive material, grounded (earthed) to prevent risk of explosion, and designed to either withstand or vent an explosion if one should occur. Duct for corrosive vapors may be non-metallic with conductive filler if the conveyed powders or vapors are flammable. Where positive pressure duct conveys hazardous material, zero leakage should be specified.

Duct thickness should account for erosion from solid impingement and incorporate smooth transitions with minimum bends to minimize energy consumption, erosion, and the potential of dust deposit build up. Access doors can facilitate routine inspection and cleaning.

The system may be designed for continuous operation to minimize risk of contamination due to cross flow within the facility if the HVAC system is turned off (thus influencing room pressures). Exhaust air volumes should be considered during balancing of the HVAC system. If the main dust collector is self cleaning, using a reverse flow of compressed air; the design and commissioning should consider the effect of the periodically reduced flow in the system ductwork to ensure that it does not present contamination risk due to momentary changes in room DPs when the exhaust flow is reduced during the cleaning cycle.

Dust collectors should normally be located outside the building served, typically in a separate building, to facilitate dust control during maintenance, and should be provided with explosion relief. Dust collectors may be located inside buildings if adjacent to an exterior wall, are vented to the outside through straight duct, typically not exceeding 10 ft (3 m) in length, and have explosion vents (depending on local regulations). Dust collectors may be located anywhere in a building if protected with an explosion suppression system. For further information, see NFPA Standard 654 (Reference 29, Appendix 12). The dust filter arrangements should be considered with safe change (bag in – bag out) housings provided where necessary.

Considerable information on the design of capture hoods and duct systems is found in the Industrial Ventilation Manual, ACGIH (Reference 19, Appendix 12).

5.1.13.2 Exhaust to Atmosphere

Laboratory and process fumes should be directly exhausted to a safe location outside the building. The effective stack height (exhaust stack height plus plume height) should be sufficiently large to avoid re-entrainment of exhaust air into air inlets or onto roofs and to disperse the exhaust effectively. The effective stack height should be used when analyzing design issues. Local regulations may limit stack heights, requiring more stack velocity or exhaust treatment.

Wherever an occupational or environmental risk may be attributed to the LEV system installation, a building airflow wake simulation (wind tunnel test) may be performed to verify the effective dispersal of aerosol contaminant. Factors affecting the wake flow study include: toxicity of the material, quantities, and frequency of generation, inlet and exhaust placement, discharge filtration and velocities, prevailing wind directions and velocities, proximity of adjoining buildings or structures, and area topography.

Discharge velocities from exhaust stacks should be equal to or greater than 3,000 fpm (15.24 m/s) if exhaust air is contaminated.

Exhaust from capture hoods, bio safety cabinets (BSCs), or process equipment can be achieved by ducting each piece of equipment to a dedicated fan or by manifolding the ducts to a centralized fan system that may have a number of fans to handle varying airflow, each with its own stack operating at more than minimum stack velocity.

The manifolded system is preferred as it has full fan redundancy (with one additional fan needed) and reduced energy and maintenance costs. When only a few hoods exist and hood locations are remote from one another, or exhausted materials are incompatible, then individual dedicated fans may be justified.

Fans and air cleaning equipment may be located exterior to the building to establish a negative pressure within the entire length of the indoor exhaust ductwork. Where external location is not possible and when air cleaning is not thorough, the positive pressure ductwork on the discharge of the fan should be welded and pressure tested for zero leakage. Automatic full shut-off dampers should be installed to prevent exhaust air being drawn back down into the building or short cycled through the idle fan.

The location of the fans and stacks and their operation should address noise sensitive areas and aesthetics. This may include acoustical silencer nozzles and roof sound barriers. A sound barrier wall effectively increases the height of the building; therefore, requiring more stack or discharge velocity to disperse the stack discharge.

Two fan types are considered acceptable for this exhaust service:

- the mixed-flow impeller is recommended (this combines the benefits of axial flow and centrifugal flow fans)
- the centrifugal fan

The fan application should provide for safe, easy inspection and maintenance of the fan drive components. Fans should meet AMCA type B or C spark-resistant construction. Metal surfaces should be coated with epoxy for protection against weather, UV, and chemical vapors. Fans and accessories should have internal drain systems with tall traps to prevent rainwater from entering the building duct system.

For safety and longer life, the motor, belt drive, and bearings should be located outside the contaminated air stream. Replacement of these components should not require removal of the fan from the system or expose maintenance and service personnel to the potentially contaminated interior of the fan.

Electric motors outside the air stream can be standard chemical duty with a 1.15 service factor for continuous duty operation, similar to NEMA Design B with class F insulation, and sealed bearings with a minimum bearing life of L_{10} 100,000 hours. A non-fused disconnect switch should be provided, mounted, and wired to the motor. If it is the only acceptable option, an Explosion Proof direct drive motor may be located inside the fan housing. For energy efficiency, NEMA rated premium efficient motors (or local equivalent) are recommended.

Fans should be tested under ANSI/ASHRAE 51 or BS 848 (Reference 20 and 23, Appendix 12). Sound testing should be in accordance with AMCA 300. Fans should be UL and CUL listed per UL 705 safety standard, ENEC (European Norms Electrical Certification), or country-specific requirements, and should meet the criteria of NFPA-45 and ANSI/ AIHA Z9.5 (Reference 29 and 20, Appendix 12).

5.2 Air Filtration

5.2.1 Introduction

This Guide does not discuss in detail the construction of filters.

Air filtration is the primary method to reduce the contaminant levels in an air stream. Clean air also provides advantages, including:

- maintaining the heat exchanging capability of heating and cooling coils
- maintaining motor heat dissipation
- minimizing ductwork contamination from dust, bioburden, and allergens
- minimizing material buildup on the fan wheel that can cause unbalance

- maintaining room cleanliness

Air filtration is performed at various locations within an HVAC system to achieve the air cleanliness needed to protect the process (room airborne particles), occupants, and the air handling equipment and ductwork.

Pre-filtration and secondary/intermediate filtration (Level I and II Filtration) usually are located within AHUs, where outside and return air streams enter. The efficiency of the filters should be sufficient to keep the internal components (coils, fan) and the AHU relatively clean over an extended period of time so that they can perform as intended.

Final filtration (Level III Filtration) is located at or after the discharge section of the air-handling unit (after the air stream has been conditioned) and keeps the ductwork clean, extends the life of terminal filtration (when provided), and (if no terminal filtration) protects personnel and the work space from airborne particles that pass through the AHU.

Terminal filtration located at the room perimeter (at ceilings and sometimes at walls) assures that the cleanest air possible is supplied to dilute or convey particles released in a room.

The cleanliness of the air leaving the filter depends on the filter's construction and the quantity and quality of the upstream air "challenge."

5.2.1.1 Filter Types

Filters are designated as either non-HEPA or HEPA filter types:

- Non-HEPA filters typically are known as pre-filters, as designated by ASHRAE or EUROVENT. Their intended use primarily is to remove larger size (> 1 micron) particles with efficiencies up to 95%, but they can also help in reducing many sub-micron particles that would normally collect on downstream HEPA filters.
- HEPA filters are used as final filters when sub-micron size particles need to be almost completely eliminated (99.97% or more) from the supply airstream, typically for classified spaces or for health concerns.

Air filters are fire rated as Class 1 or 2 in accordance with UL 900 (Standard for Safety Air Filter Units), with Class 1 being the most fire resistant. Typically, most filters for general use are Class 2 rated, unless conditions exist that warrant the more stringent fire rated Class 1 filters. Local regulations may justify the use of Class 1 rated filters.

Filters should be of standardized sizes and model numbers to limit inventory and simplify ordering and replacements. Face velocities should not exceed manufacturer's ratings and generally should be less than 450 FPM (2.3 M/sec). HEPA filter air velocities should be designed at a maximum of 100 fpm (0.51 m/s) when positioned as terminal supply air filters, and 450 fpm (2.3 m/s) when positioned in ductwork or in the air handler. Designers may choose to lower the design specification by 10 to 20% to allow for future airflow capacity.

A TCO filter analysis based on real-life performance should be conducted to provide the lowest life cycle cost (energy, maintenance, filter cost, and disposal). More than half of the total cost of filter ownership is related to energy. Choosing filters based on first cost alone, typically will cost more over time.

5.2.2 Filter Installations

Pre- and final-filtration mounting grid systems should be of rigid construction, usually aluminum or 304 SS. The air should not bypass around the filters or the grid. Filters should be front-loaded so the airflow pushes them into the mounting frame to eliminate air bypass. Filter frames should have closed cell rubberized/neoprene-type gaskets to prevent shedding. A separation of at least 1 inch (25 mm) should exist between the filters in the pre-filter section to reduce static pressure drop and increase the performance of the filters and permit pressure measurement between the filters.

Each filter bank within air handling units and ductwork should have a DP gauge (Magnehelic or manometer) to monitor increase in pressure drop because of loading. Filters may be replaced based when an established optimal DP limit is reached. Changing filters based on time only can result in excessive change out costs or possibly insufficient change out frequencies that can result in excess energy costs, possible filter failure (blowout), and reduction in delivered air flow. Where filters can load quickly, a high DP alarm to the BAS may be justified. In general, alarms on every filter remove the need for the HVAC system operator to visit the AHU. This may save labor, but also may prevent noticing other problems at the AHU.

5.2.3 Air Filter Nomenclature

Table 5.3 and Table 5.4 provide the various filter classifications, ratings, and comparisons from ASHRAE 52.2 and EN 779/1822 standards, and IEST RP-CC001 recommended practice (References 22, 6, and 12, Appendix 12).

Table 5.3: Filter Comparison – Pre-filters

These comparisons of filter rating systems are only approximate as the test methods are different.

ASHRAE 52.2 MERV Composite Average Particle Size Efficiency, % in Size Range, μm			ASHRAE 52.2	EU type	EN 779
E1 – Range 1 0.30 – 1.0	E2 – Range 2 1.0 – 3.0	E3 – Range 3 3.0 – 10.0	MERV Designation	Designation	Designation
n/a	n/a	$E_3 < 20$	1	EU 1	G 1
n/a	n/a	$E_3 < 20$	2	EU 2	G 2
n/a	n/a	$E_3 < 20$	3	EU 2	G 2
n/a	n/a	$E_3 < 20$	4	EU 2	G 2
n/a	n/a	$20 \leq E_3 < 35$	5	EU 3	G 3
n/a	n/a	$35 \leq E_3 < 50$	6	EU 4	G 4
n/a	n/a	$50 \leq E_3 < 70$	7	EU 4	G 4
n/a	n/a	$70 \leq E_3$	8	EU 5	F 5
n/a	$E_2 < 50$	$85 \leq E_3$	9	EU 5	F 5
n/a	$50 \leq E_2 < 65$	$85 \leq E_3$	10	EU 5	F 5
n/a	$65 \leq E_2 < 80$	$85 \leq E_3$	11	EU 6	F 6
n/a	$80 \leq E_2$	$90 \leq E_3$	12	EU 6	F 6
$E_1 < 75$	$90 \leq E_2$	$90 \leq E_3$	13	EU 7	F 7
$75 \leq E_1 < 85$	$90 \leq E_2$	$90 \leq E_3$	14	EU 8	F 8
$85 \leq E_1 < 95$	$90 \leq E_2$	$90 \leq E_3$	15	EU 9	F 9
$95 \leq E_1$	$95 \leq E_2$	$95 \leq E_3$	16	EU 9	F 9
					EN 1822*
			16	EU 10	H10
*All EN 1822 tests at MPPS H = HEPA; U = ULPA					

Table 5.4: Filter Comparisons – HEPA/ULPA

These comparisons of filter rating systems are only approximate as the test methods are different.

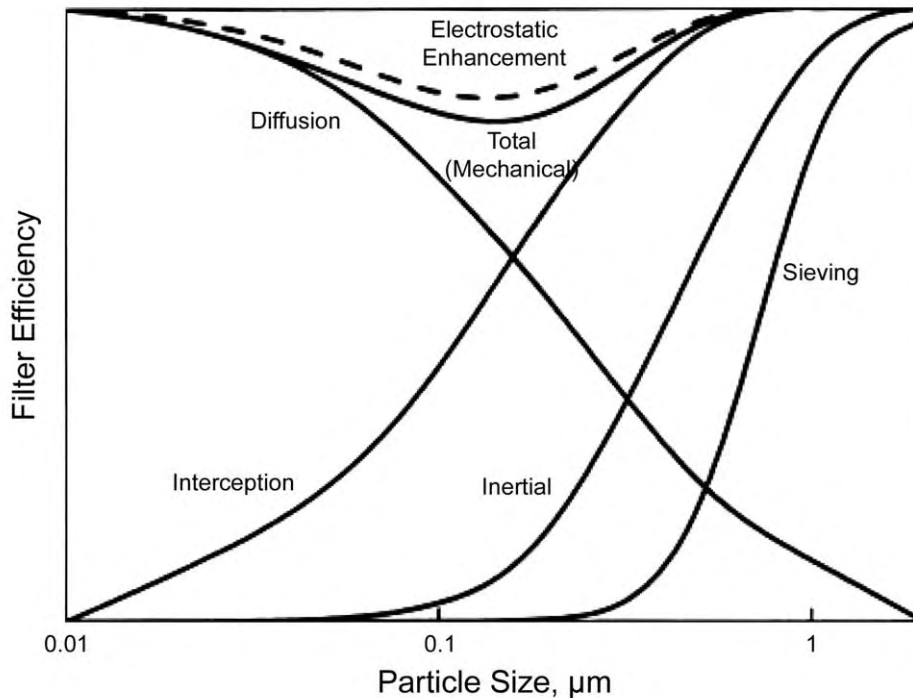
EU Type	EN 1822 HEPA/ULPA*		IEST Type (RP-CC001.4)	
Designation	Designation	Efficiency	Efficiency	Designation
EU 10	H10	85% @ MPPS		
EU 11	H11	95% @ MPPS		
EU 12	H12	99.5% @ MPPS		
			99.97% @ 0.3 mm**	A, B, E
EU 13	H13	99.95% @ MPPS	99.99% @ 0.3 mm**	C
EU 14	H14	99.995% @ MPPS	99.999% @ 0.3 mm**	D, K
	U15	99.9995% @ MPPS	99.999% @ 0.1 – 0.2 mm**	F
	U16	99.99995% @ MPPS	99.9999% @ 0.1 – 0.2 mm**	G
	U17	99.999995% @ MPPS		
*All EN 1822 tests at MPPS H = HEPA; U = ULPA HEPAs = H10-H14, A, B, E, C, D, K; ULPA = U15-17, F, G **All tested with thermally generated DOP aerosol (0.3 mm MMD; i.e., CMD is near MPPS). F, G and K type filters are tested at either 0.1 – 0.2 or 0.2 – 0.3 mm. K type filters are 99.995%.				

Filters typically are classified by IEST Recommended Practice RP-CC001, ASHRAE Standard 52.2, or EN 779/1822 (European standards for general ventilation filters and HEPA/ULPA filters) (Reference 12, 22, and 6). As the grading systems are based on different challenge materials and sizes and use different measurement methods, comparisons between the grading systems are not exact.

5.2.4 How Air Filters Work

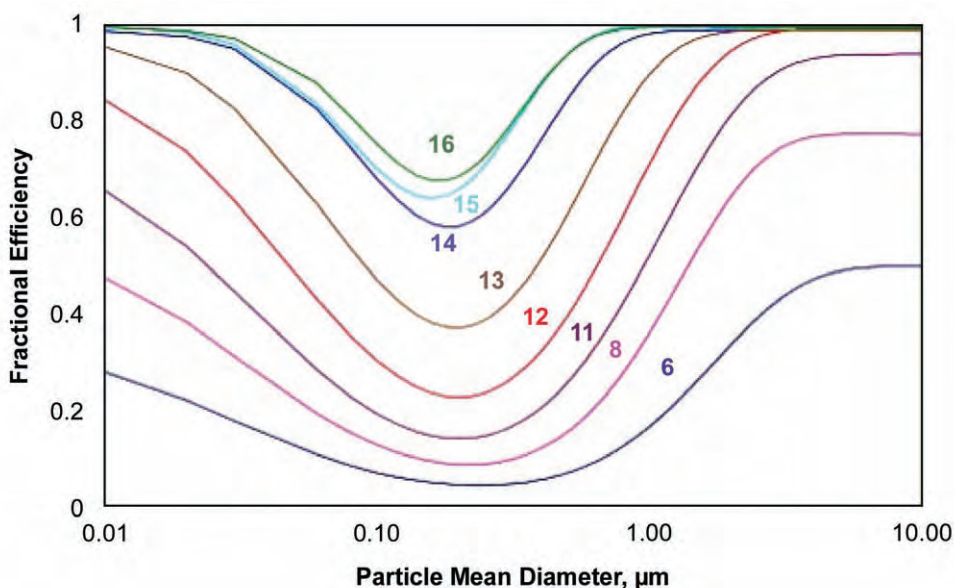
Particles are captured within the depth of filter media as the air follows a convoluted flow path through a series of interconnected void spaces formed by the micro filter structure (e.g., fibers, membrane). As the air flows around the structural elements, particles are removed from the air stream via the particle collection mechanisms of diffusion, interception, inertial impaction, and an enhancement through electrostatic deposition. Mechanisms of lesser importance include sieving and gravitational sedimentation. The particle capturing effectiveness of each mechanism is primarily dependent on the particle size, air velocity, and size of the filter structure (e.g., fiber diameter).

Figure 5.5 shows the cumulative effect of the various collection mechanisms. The lowest filter efficiency occurs at the most penetrating particle size (MPPS), which is typically in the 0.1 to 0.2 micron size range.

Figure 5.5: Effect of Particle Capture Mechanisms on Filter Efficiency

Used with permission from the American Filtration & Separations Society (AFS), www.afssociety.org

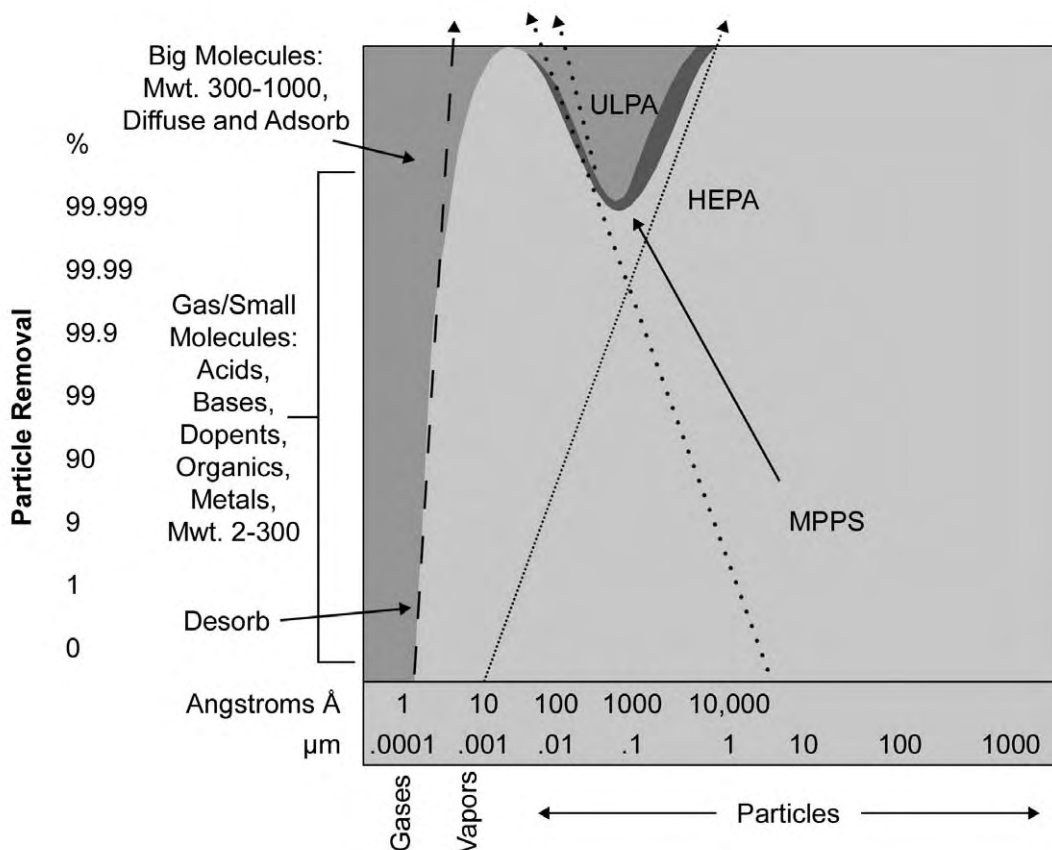
Figure 5.6 provides a composite of various MERV rated prefilters and their initial fractional efficiencies versus particle size. They are all least efficient at the MPPS. They are most efficient as the particle size increases from the MPPS and efficiency increases again as the particle sizes decrease, but they do not achieve the same efficiencies as compared to the larger size particle capture rate and decrease rapidly once particle sizes are reduced below what is shown on the left side of the graph.

Figure 5.6: Prefilter Efficiencies for MERV Rated Filters

Used with permission from the National Air Filtration Association (NAFA), www.nafahq.org (source: Summer 2002 issue of Air Media, Figure 4 Composite of all MERV filter models, based on initial conditions, Author(s): W.J. Kowalski, PE, PhD; W.P. Bahnfleth, PE, PhD, The Pennsylvania State University)

Figure 5.7 shows HEPA/ULPA filter particle removal efficiencies versus particle size. The MPPS is around $0.1\ \mu\text{m}$, and most HEPA filters maintain very high efficiencies down into vapor size particles at $0.0005\ \mu\text{m}$ and even some gases. The particles of interest in this Guide are either larger than $0.1\ \mu\text{m}$ (dusts, bacteria, and spores) or smaller (viruses) and can be captured effectively.

Figure 5.7: HEPA/ULPA Filters: Particle Removal versus Size



Used with permission from Camfil Farr, www.camfilfarr.com

5.2.5 Filter Applications

Level I through Level III and Terminal Filtration parameters are outlined.

5.2.5.1 Level I Filtration (Pre-filter)

Level I Filtration is the lowest efficiency (and lowest cost) level used for pre-filtration, intended to capture larger particles ($3\ \mu\text{m}$ and larger such as insects or vegetation) typically found in the outside air. It also is used as a pre-filtration to extend the life of Level II filtration. MERV 7 (EN G4) filter is recommended.

5.2.5.2 Level II Filtration (Intermediate Filter)

This more expensive filter typically is located directly downstream of Level I filtration to capture smaller sized ($0.3\ \mu\text{m}$ and larger) particles to protect the coils and fan in AHUs, ductwork, and personnel. A MERV 14 (EN F8) filter is recommended.

5.2.5.3 Level III Filtration (Final)

This filtration is located at the discharge section of the AHU downstream of Level I and Level II filtration and fans/coils, and may use either ASHRAE or HEPA type filters.

ASHRAE Type: captures released mold and other material, which may have grown or been collected on the condensing (wet) cooling coils as well as dust from belts, etc. Movement of this material through the ductwork and its possible contact with personnel is prevented. A MERV 14 (EN F7/8) efficient filter is recommended.

HEPA Type: used when the controlled space requires a cleanroom classification (typically limited to Grade 8 (Grade C) if used alone without terminal filtration), when redundancy (with a terminal HEPA) is deemed necessary, or to extend the life of downstream terminal HEPA filters, which by themselves are capable of providing acceptable supply air quality, but because of their cost and limited accessibility, should have a service life as long as possible. (For further information on redundant HEPA filtration, see Appendix 9). These filters should have a seamless sealing gasket (preferred) or a silicone gel seal on the downstream side of the filter to form a positive seal to eliminate air bypass around the filter perimeter. Permanent upstream and downstream media protective screens (media guards) should be considered to prevent physical damage to the filter media. Individual HEPA filters should be able to be replaced without disruption of adjacent filters. H12 (99.5%) to H14 (99.995% at MPPS) filter is recommended. High efficiency filters should precede HEPA filters to extend their service life.

5.2.5.4 Terminal Filtration

This point of filtration uses HEPA filters typically at the supply air terminal and is associated with cleanrooms classified as cleaner than ISO 8 in use (such as EU Grade C) and where particles generated in ductwork could adversely contaminate supply air. A terminal-style filter also may be used on return/exhaust air when process room air is contaminated with environmentally sensitive particulate (hazardous airborne materials). Caution is advised, as return air filters can adversely affect room air pressure values, requiring more complex pressure controls for room or return ductwork.

These filters should have a silicone gel seal on the downstream side of the filter to form a positive seal to eliminate air bypass around the filter perimeter. Permanent downstream media protective screens (media guards) should be included to prevent physical damage to the filter medium. Individual HEPA filters in filter banks should be capable of replacement without disruption of adjacent filters. H13 (99.95%) to H14 (99.995% at MPPS) filter is recommended.

A Terminal Air Filter Module is constructed either as a single or multiple HEPA filter housing structure. Terminal filters should be positioned at the entry (ceiling) of a room to supply clean air into the space.

A terminal module usually houses a single filter. The module should be complete with:

- insulated housing (if ambient conditions surrounding the module would result in external condensation)
- filter
- filter aerosol and pressure test ports
- damper adjustment
- grille
- trim
- hardware

The body of the module should be solidly constructed of cleanable rigid material (such as stainless steel or aluminum) with the exposed trim usually being stainless steel. It should be designed for room side filter replacement, unless the terminal unit is a self-contained (throwaway) lay-in enclosure with filter sealed inside, in which case, it is installed from above the ceiling.

A terminal plenum module or unidirectional air flow unit is intended to house at least 2 filters to distribute unidirectional airflow over a specific area (typically a Grade 5 – Grade A classified space). It is a fabricated structural plenum that houses the air inlet opening with:

- prefilter
- HEPA filters
- dampers
- challenge dispersion manifold
- test ports
- optional sprinkler system
- an integral grid for support of gel seal filled framed filters
- flush mounted lighting and perforated grill

A HEPA/UPLA filter used in UDAF hoods or to capture hazardous materials is usually “pinhole scanned” over 100% of its face area with a penetration not exceeding 0.01%. If the challenge aerosol is oil (DOP, PAO), it will be captured and absorbed into the filter medium, and the filter needs to be permitted to “dry out” for some time after testing to let the oil evaporate and pass through as a vapor. If upstream challenge concentrations are high, or if the test takes many minutes, a significant quantity of aerosol oil can be absorbed, perhaps to the point of “wetting” the filter medium. For this reason, it is recommended that aerosol testing be brief (one filter at a time, if possible), and that upstream aerosol concentration be kept at the low end of the sensitivity range of the photometer. Other filters (such as in air handlers) usually are not scanned, and the test of the entire filter bank efficiency may take but a few minutes.

Bag-in/bag-out housing is a side-serviced filter housing to capture dangerous or toxic biological, radiological, cytotoxic, or carcinogenic materials. It prevents hazardous airborne materials from escaping into the exhaust or return duct system. It typically is positioned at the perimeter (near floor) of the room where the material is generated, but may be located in a central site.

The housing is constructed of stainless steel, should have zero leakage, and uses a control barrier to isolate personnel from hazardous materials during change-out of the HEPA filter. The housing should have a silicone gel seal and be adequately reinforced to withstand a negative or positive pressure of 15 inch wg (3.75 kPa).

A fan-filter unit (FFU) is a self-contained filter assembly similar to a small UFH with fan, prefilter, speed control, and a single shallow-medium HEPA filter (99.97 or 99.99% scanned) sealed into a lightweight enclosure. Preferred construction is stainless or aluminum. Fan-filters can be used as “clean air projectors” to protect small areas (sample points, manways, etc.), to augment movement of HEPA filtered air in a cleanroom, and to add air changes for dilution. Capacity is adjustable, often from 70 fpm (0.35 m/s) to 150 fpm (0.75 m/s). Some FFUs have extra fan capacity that permits the unit’s air inlet to be ducted from floor level, making it usable as a retrofit for small rooms (such as older poorly-ventilated gowning rooms and airlocks) needing HEPA filtered airflow. When selecting FFUs, consideration should be given to:

- service life

- replacement of filter media
- electrical ratings
- excess capacity

Many low cost FFUs are meant for “throw-away” applications, while some other units may provide years of service with replaceable filters. Although several FFUs may be used together to serve as a Grade 5 UFH, care is needed to assure that the entire filter assembly provides acceptable airflow patterns. For this reason, few have been used as Grade 5 hoods. As an FFU is self-powered (it has its own fan), it may be used where the addition of a HEPA filter to a duct system would add unacceptable pressure drop or create imbalance in the system, such as a return air filter in a room. If mounted in a wall, an FFU can be used to create a DP between the two areas separated by the wall (such as the retrofit of an OSD facility to improve cross-contamination protection).

During commissioning of a clean space, areas of high particle concentration, slow recovery, or poor airflow patterns may be discovered. Prudent placement of an FFU may significantly reduce the issue. A lightweight FFU may be kept for troubleshooting to be replaced with a more expensive stainless unit for permanent use.

5.2.6 Airborne Particle Sizes

Airborne particles can range for sub-micron size (0.01 micron) to many microns.

Viable particles (viruses, spores, and bacteria) are present as a very small fraction of total particles. For example, in outdoor air, there may be a million particles in a cubic foot (35 times more per cubic meter), but only a few hundred or a few thousand viable particles per cubic foot).

It is estimated that over 90% of airborne particles in outdoor air are under 0.5 micron in size and comprise less than 1% of the mass. Fewer than 2% of particles are over 1 micron in size and comprise 97% of the mass, meaning that pre-filters do most of the mass removal. Typical approximate particle sizes include:

- viruses – 0.002 to 0.05 micron
- bacteria – 0.4 to 20 micron
- plant spores – 10 to 40 micron
- smoke – 0.01 to 1 micron
- test aerosol (DOP, PAO) – most particles are 0.1 to 0.7 micron
- dust and ash – mostly 0.5 to 1000 micron (the large particles fall out quickly)

A filter with an MPPS of 0.1 to 0.3 microns should perform well against viable particles, capturing them at efficiencies greater than its rating at MPPS.

5.2.7 HEPA Filter Performance Issues

Specific issues with HEPA filters have been observed in pharmaceutical cleanrooms, two of which are:

1. HEPA filter gel seal degradation
2. HEPA filter bleedthrough

5.2.7.1 HEPA Filter Gel Seal Degradation

Degradation of gel seals has been observed in cleanroom applications as the silicone (siloxane) gel seal material appears to revert to a liquid state and begins dripping out of the gel track. This may be accompanied by a color change, such as fading to a clear or translucent appearance. This usually does not result in a measurable integrity failure of the filter, but does present sterility, appearance, and safety issues. Studies have determined that this failure is because of the migration of unbonded polymer components out of the gel matrix, forming a slimy liquid on the surface of the gel. Factors which contribute to this include:

- Crosslinking of the gel components
- the more complete the crosslinking, the less unbonded polymer that can migrate to the surface
- the specific gel type and the mixing (ratio of components, environmental conditions, time to complete the reaction, etc.) are key to amount of crosslinking
- molecular weight of the gel
- higher molecular weight reduces the diffusion and migration of unbonded polymers
- narrow weight distribution is desired at the higher molecular weights
- certain challenge aerosols (PAO, DOP, etc.) accelerate the rate of unbonded polymer diffusion
- aerosol acts as a solvent, increasing migration of unbonded polymers to the surface
- typical pharmaceutical cleanroom cleaning and sanitizing agents (such as bleach or hydrogen peroxide) do not seem to affect the rate of unbonded polymer diffusion

It is recommended that miter joints and penetrations in the filter gel track are sealed with a material proven to be impervious to the silicone gel components (i.e., silicone gel components will penetrate silicone caulk).

Urethane gels are not recommended as replacements for silicone gels in pharmaceutical cleanroom applications that will be exposed to cleaning and sanitizing chemicals, as their performance is affected by those chemicals, as well as being affected by aerosol challenge materials, such as PAO and DOP.³ Filter manufacturer should be able to help determine the appropriate silicone gel that maximizes crosslinking and molecular weight, and that provides satisfactory sealing characteristics (resiliency, adhesion, etc.). Reducing the amount of aerosol challenge to which the filters are exposed will also reduce the risk of gel degradation.

Since urethane gels are hydrophilic, high humidity can affect the ability of the gel to cure properly.

5.2.7.2 HEPA Filter Bleed-through

HEPA filter bleed-through is a phenomenon in which a filter appears to fail a field integrity (leak) scan test using an aerosol challenge and a photometer with an observed leakage across the entire face of the filter media (not localized as with a pinhole or tear). This often occurs with filters that had previously passed a factory efficiency and scan test. It has been observed worldwide and is not limited to one filter or paper manufacturer. Further, it appears to be limited to HEPA (not ULPA) filters and to applications in which thermo-pneumatic (hot-block) aerosol generators were used for testing.

³ Urethane gel can fail in a mode similar to that of silicone gel failure, reverting to a liquid state. It also may form a tough skin on its upstream side, leading to poor bonding at the gel/knife edge interface. Fading of color does not appear to affect seal integrity.

Bleed-through of HEPA filters occurs when they are subjected to field testing conditions that are more stringent than their factory test conditions. This may occur when:

- actual field velocities are higher than factory tests
- actual field aerosol challenge particle sizes are smaller than factory tests
- HEPA filter is not specified appropriately for actual field conditions

Studies into the nature of this problem have resulted in determining that the following factors are fundamental to understanding and avoiding bleed-through issues:

- particle size distribution of the challenge aerosol from the generator
- impact of velocity on filter efficiency and bleed-through
- specifying and testing HEPA filters

Particle Size Distribution of the Challenge Aerosol from the Generator

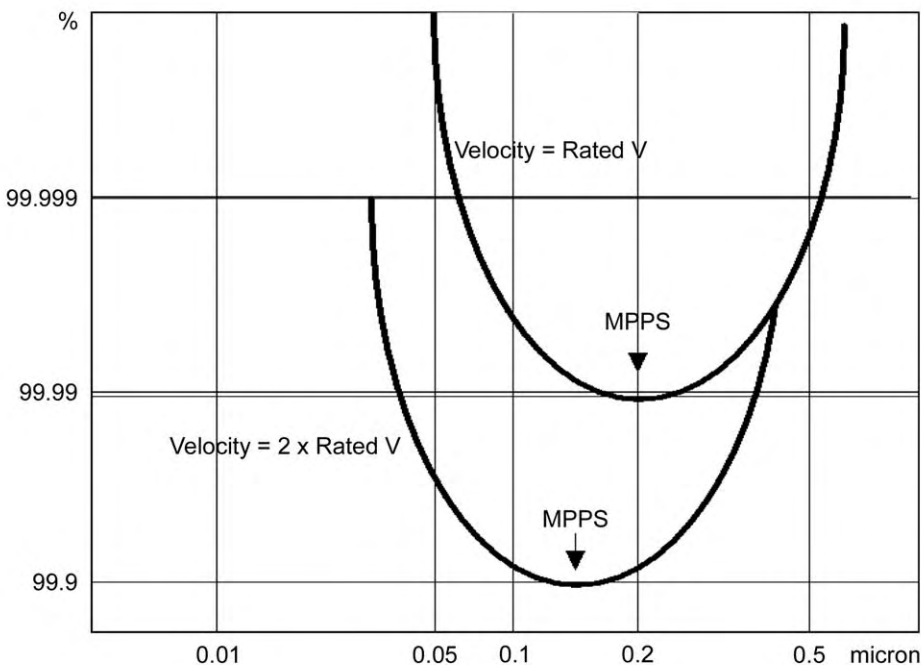
Aerosol particle sizes generated by pneumatic Laskin-nozzle type generators are larger than those from hot-block generators (mean diameter – MMD – size of 0.5 to 0.7 microns versus 0.2 to 0.3 microns). Although HEPA filters often are efficiency tested and rated at 0.3 microns, the filters' actual MPPS is less than 0.3 microns, often in the 0.12 to 0.25 micron range. HEPA filters which may pass an integrity scan test in the factory with a Laskin nozzle generator (at 0.5 to 0.7 microns) may fail a scan test in the field with a hot-block generator because of bleed-through of too many small particles at the MPPS. The filter supplier should know the field test challenge method to be used in the field so that the appropriate filter paper can be provided. Many issues can be avoided by stating the efficiency of the filter at the filter's MPPS.

Impact of Velocity on Filter Efficiency

Air velocity has a significant impact on filter performance. Increasing the velocity will decrease both the filter efficiency and the MPPS for that filter (more smaller particles will pass). For example, factory testing a specific filter for efficiency and integrity at 100 fpm face velocity and then field integrity testing at 150 fpm likely will result in different results. Filter performance should be specified for the intended face velocity.

Figure 5.8 indicates a decrease and shifting of efficiencies at the MPPS points as air velocities increase. Note that the air velocity through the medium is much less than the face velocity through the filter, because of the added medium area created by numerous folds in the medium.

Figure 5.8: Air Velocity Impact on HEPA Filter Efficiency (Typical)



Specifying and Testing HEPA Filters

Recommended practices to avoid the bleed-through problem:

- specify the filter for the maximum velocity it will see in operation
- factory test for efficiency and leakage at that velocity at the filter's MPPS
- If the filter will be field integrity tested with a hot-block generator, the filter should meet (as a minimum) the requirements for an IEST Type K or an EN-1822 Type H14 with a local penetration limit of two times the global penetration (i.e., 0.01%) instead of the standard five times (0.025%) as called for in EN-1822.
- If bleed-through presents an insurmountable obstacle, ULPA filters may be used. In addition, HEPA filters that use Teflon media (ePTFE) can give better performance than other HEPA filters, but may present their own testing problems in the field. As ULPA and Teflon filters are more expensive than HEPA filters, their use should be justified and manufacturers consulted before specifying.

5.3 Equipment Installation and Startup

5.3.1 Introduction

The guidance in this section should be considered for HVAC design drawings, as well as in the construction specification.

Care should be taken during installation and startup to preclude operational and maintenance problems. It usually is helpful for the HVAC system installer to follow “build clean” practices, such as cleaning duct and components prior to installation, cleaning after installation, and sealing installed ductwork to prevent ingress of contamination. A “white glove test” may not be specified, but systems should be capable of passing this test.

This section is not all-inclusive, and the user should consult with the equipment manufacturer for detailed specifics and procedures. Guidance for startup also may apply to ongoing operation and maintenance.

Air system startup usually is contracted to trained and certified professionals. Organizations such as NEBB have offered specific cleanroom certification. Occasionally, a “facility HVAC engineer” may be called upon to solve an immediate problem. The solution depends on the engineer’s skill and access to specific tools:

- hot-wire anemometer
- pressure sensor, 0.01 inch (2.5 Pa) accuracy to 0.5 inch full scale (125 Pa). Higher pressure range is needed to troubleshoot fan and duct problems.
- flow hood (used to measure supply outlet or return airflow)
- hand-held thermometer, RH meter
- particle counter
- cold aerosol generator (for HEPA test)
- smoke source (smoke sticks, smoke candles) for air pattern visualization
- duct tape and cardboard (used to temporarily block openings, divert airflow patterns, change the shape of equipment under UDAF hoods, etc.)

5.3.2 Air Handling Units Shipping, Storage, Installation

Larger air volume AHUs typically are disassembled after factory testing, and each section is separately wrapped for shipment. The unit or sections should be lifted vertically on a level plane by their lifting lug bracket arms to prevent distortion and stress on the components. It is recommended that an experienced rigger supervise the lifting and installation of the equipment.

The air-handling units should be stored in a dry area to protect components (fan- shaft, bearings and wheel, coils, humidifiers, and filters) against dust and corrosion. If a unit is idle for more than one month prior to startup, equipment with bearings should have their shafts manually rotated every two weeks to prevent premature bearing failure and redistribution of the lubricant.

The AHU position should allow sufficient free space for servicing its utility connections (steam, chilled and hot water, and electric) and internal components (e.g., coils, motors, filters). It should be mounted on a rigid, level foundation for correct alignment of the fan and drive equipment, for freedom from excessive vibration, and for the removal of condensate. It should be set sufficiently high to allow for correct condensate drainage using a P-trap and cap for ease of the trap’s priming, removal, and cleanout.

When reassembling sections of the AHU, gaskets, and RTV sealant should be used to eliminate air leakage. Minimal sealant should be applied to produce a clean, smooth, and level bead surface.

Procedures during the installation and startup of the unit should preclude dirt and debris accumulating within and around the unit. The interior of the air handler should be wiped down to remove residual oil and grease.

Prior to startup, a checklist can encourage smooth operation. Items that may be considered are covered in ASHRAE Guideline 1 (Reference 22, Appendix 12).

Fasteners, bolts, wheel hub set screws, and bearing locking collars should be checked for tightness before equipment startup.

Shipping tie down bolts and shims also should be removed before air handler startup.

Dampers on air handlers should operate freely and blades close tightly.

When supplied with a variable frequency drive, the unit should be started at low rpm and its speed increased slowly up to its maximum capacity. Unusual noise should be listened for and inspection should be performed for increased vibration and overheating of bearings.

Tests to be considered include:

- a pressurized leak test to ensure joints/connections are correctly aligned and the air handler cabinet is not leaking in excess of the specified value
- condensate drain pans and traps should be filled with water to confirm correct drainage, while the unit is operating

5.3.3 Fans

Correct fan installation and startup are critical to providing sufficient airflow in a safe manner, as a tremendous amount of kinetic energy is produced, and potentially, catastrophic results can result.

Laser alignment on the fan and motor shafts should be performed after the fan has been installed at the site, because shipping and installation can alter the factory alignment.

Drive belts should be adjusted to their proper tension prior to startup. Following 24 hours of operation, the belts should be re-tensioned.

Bearings should be checked for correct lubrication. If automatic lubrication units have been installed, they should be activated only at the time of startup.

Fan wheels should be turned over by hand to see that they run free and do not strike fan housings. The location of wheels in relation to fan inlets should be checked and fan housings should not be distorted. The fan should be jogged electrically to check for correct rotation.

Vibration testing should be performed following installation and startup to promote longevity and reliable operation of the equipment. It should be verified that the fan will not operate near its critical speed.

5.3.4 Heating and Cooling Coils

Coils should be inspected for concealed or visible damage prior to acceptance of delivery. The coil fins should be combed after installation to foster good air distribution and heat exchange.

Piping to the coil should be independently supported to avoid deforming the coil nozzle, headers or tubes, and stressing the brazed joints.

Insulation with protective jackets should be installed on hot and cold piping to eliminate hazard to personnel, reduce surface condensation, and reduce heat loss/gain.

Coils should be vented of air on initial startup and should include a manual or an automatic air vent.

For cooling coils, the term “moisture carry-over” describes the action of condensate being blown off the coil’s surface with cooled air. Following startup when condensing occurs, observation should be made for moisture carry over. If carryover occurs, then the following resolutions are available:

- reduce the coil face velocity (may not be possible if rooms need more airflow)
- install a perforated screen upstream of the coil to evenly distribute air across the coil, producing a more even face velocity
- install a mist eliminator after the coil

5.3.5 **Steam Humidifiers**

The steam distribution manifold should be placed where the supply air temperature is sufficiently warm to absorb steam being discharged without causing condensation at or after the unit. Inside an AHU, this may be downstream of the pre-heating coil and upstream of the cooling coil (which acts as a mist eliminator). Do not place the steam distribution manifold too near to the face of air filters where saturation of the filters will greatly shorten their life. Avoid placing the steam distribution manifold where visible discharge mist will impinge directly on a metal surface.

Another common location is in the ductwork after the reheat coil and air filters. When the humidifier is located in ductwork, a downstream section of the ductwork should be constructed of stainless steel to eliminate the possibility of rusting (consult with humidifier manufacturer). Access panels should be located both upstream and downstream of the humidifier for servicing.

Drain pans and condensate piping should catch and carry away water that can occur from humidification ‘spitting’ during startup. The drain and trap should flow and the water column will not drain completely when the duct is pressurized.

Uniform airflow over the cross section of the steam distribution manifold should be verified to assure absorption of steam.

The airflow sensor (“sail switch” or a signal from the AHU airflow monitor) should prevent the steam valve from opening unless air is moving in the duct.

5.3.6 **Desiccant Dehumidifiers**

Desiccant dehumidification systems are the most common means of achieving low RH for the pharmaceutical industry.

Desiccant units should be clear of surrounding obstructions to allow removal and replacement of the desiccant wheels, fans filters, etc.

The air from the reactivation portion of the wheel should be ducted (sloped to the outside, if horizontal path) to the exterior of the building due to its high moisture and heat content. The intake and outlet for the process and reactivation air streams should not be located close together to avoid short cycling that can reduce overall dehumidification capacity.

Operation of bypass and humidity control dampers should be verified.

Manufacturer’s recommendations should be followed for starting up their particular dehumidifier. This includes verifying wheel rotation and reactivation discharge temperature to dry the wheel before applying load to the wheel.

Wheels using lithium chloride should be kept hot and rotating, even when dehumidification is not required, to avoid damage to the desiccant due to over-absorption.

5.3.7 Air Filtration

Temporary filters should be installed during construction to keep the AHU, components, and ductwork clear of contaminants if the system is energized to provide temporary conditioning to the workspace. Once construction of the building and spaces has been completed, these filters should be replaced with clean filters.

HEPA/ULPA filters should be handled with special care. Consideration needs to be taken in the selection of the method and carrier used for filter shipment. Each pallet of filters should be checked before accepting shipment from the carrier. Pallets of filters that have been damaged or broken down should not be accepted without a thorough inspection and appropriate comments noted on the shipping documentation.

The filters should be stored to prevent damage or intrusion of foreign matter. Storage should be indoors, under roof, within 40 to 100°F (4 to 38°C) and 25 to 75% RH and be thoroughly protected from moisture.

Competent personnel and proven techniques and procedures should be employed for the installation of the filters. Prior to installation of HEPA/ULPA filters, duct and filter housings should be checked for cleanliness and obstructions that might impair filter operation. Filters should be unpacked and inspected for damage. Damaging the filter media should be avoided. If the media are damaged or have visible holes, filters should not be installed.

Filter clamping mechanisms should ensure that air does not bypass around filters or their supporting grid. This is particularly important at terminal filters mounted in ceiling frames.

Penetration (pinhole) testing is usually performed on only filters that provide direct contact air over product and critical locations, i.e., Grade A/Grade 5 hoods, and on occasion, for filters used to capture hazardous materials. There is little value in testing for pinholes in HEPA filters installed in ductwork and air handlers, where overall capture efficiency testing is more valuable. For further information see ISO 14644-3.

5.3.8 Ductwork

Ductwork typically is found in locations difficult to access. Sufficient access to service components, such as volume control devices and reheat coils, should be provided. Protection of the ductwork during construction and access to and around it should be provided; otherwise, damage to the ductwork may result in airflow leakage or increased air pressure drop and velocity. In addition, ductwork insulation that has been compromised will result in condensation and rusting and loss or gain in heat.

The use of flexible ducting should be limited to minimum lengths, properly supported, and securely fastened at each end. Sharp bends and turns, which will reduce the cross-sectional area of the flexible duct and result in reduced air volume delivery, should be avoided.

Ductwork should be wiped and cleaned of oil, dirt, and metal shavings prior to field installation. A solution of alcohol and lint free wipes may be used to remove oils or grease that may have accumulated during the fabrication and installation of the ductwork.

After ductwork is cleaned, openings should be covered with plastic sheeting and tape to keep them clean.

Avoiding the use of self-drilling sheet metal screws is recommended, as they generate small metal chips inside the cleaned ductwork. Self-piercing (zip) screws are preferred when there is concern for loose contamination inside the ductwork.

Installation of pressure test ports, smoke detectors, temperature sensors, and duct traverse testing ports at a later date can contaminate interior of ductwork with metal chips as a result of their field penetrations into a duct. Penetrations of the duct wall should maintain ductwork interior cleanliness. Where metal shavings or debris may have been produced, the interior of ducts should be cleaned, providing access as required, and the access opening sealed. Failure to follow these practices can result in sharp metal fragments being blown into the delicate HEPA filter media, causing filter integrity failures.

Prior to insulating and pressure testing new ductwork, a field inspection should be performed to ensure installation complies with design specifications. A simple checklist can be developed.

Unusual changes in duct direction that can cause “system effects” with significant reduction in the system’s capacity to deliver air should be corrected.

5.3.8.1 *Duct Leakage Test*

Pressure testing is recommended for ductwork systems serving a GMP system to avoid:

- increased use of outside air to overcome supply air losses and maintain adequate flow
- increased energy costs to operate system
- operating equipment at its maximum capacity with no reserve capacity
- unwanted air leaking into surrounding (mechanical) spaces from positive pressurized ductwork or room air leaking into negatively pressurized ductwork, requiring more airflow through fans

The “Total Percentage Leakage Method” is recommended: a percentage of total air delivery of duct section under test at a specific static pressure for performing duct leakage. See SMACNA or HVCA DW143 (Reference 30 and 26, Appendix 12). Typical leakage percentages for various operations include:

- 0% (essentially) leakage for positive pressure exhaust duct on hazardous operations to avoid release of harmful materials to the plant room
- no more than 1% for product processing areas

Evaluation of leakage versus energy cost should be performed for laboratory supply systems and support and administrative areas.

Other leakage testing methods may be employed. It is generally not a GMP requirement for ducts to be leak-free; energy savings are a bigger driver for lower leakage. Risks associated with leakage should be assessed.

Table 5.5: Ductwork Testing Requirements

Classified and Rooms Requiring Pressure Differential Duct Conveying Hazardous Materials	Test 100% Supply and Return
Laboratories, Ducted Bio Safety Cabs and Hoods	Test 100% Exhaust

Duct leakage testing should be performed with traceable calibrated test instruments and documented with signed approvals.

Leakage from non-duct components (fire dampers, smoke dampers, air flow monitors, duct heating coils, manual volume damper quadrants, and access doors) is an integral part of the overall system leakage, and these components should be included in the duct leakage tests.

Once construction is completed, the system should be blown down for at least 1 hour to purge the ductwork of loose and light debris that may have accumulated. Blow down will not flush the system of metal fragments that result from poor ductwork cleanliness control.

5.3.9 Dampers and Louvers

Actuators should be accessible for service and maintenance. Drive linkages should be secure and should operate without binding over their full range of travel.

Assemblies should be sealed to the framing of the opening to reduce bypass around damper perimeters.

5.3.10 Diffusers and Registers

Diffusers and registers should prevent poor distribution of air and to minimize drafts and short-circuiting of supply air.

5.3.11 Ultraviolet Lights

UV wavelength lighting degrades many plastics, including:

- synthetic air filter media and frames
- plastic coated wires
- gaskets
- grommets
- duct insulation

These materials should be at least 3 ft (~1 m) from the light source.

UV power supply circuits should be interrupted upon the loss of airflow past the lighting elements.

There should be no escape of UV light through direct or indirect transmission. In addition, warning signs should be placed in the area to advise personnel.

Gloves should be worn when handling emitters. Oil from fingerprints can permanently etch emitter glass and weaken its structure. If necessary, emitter should be cleaned using isopropyl alcohol and lint free wipe.

5.3.12 Exhaust/Extraction Systems

Ductwork or stacks should be independently supported, as the additional weight may stress the fan housing and result in vibration that can transmit to building structures. Guy wires (supports) may be needed for adequate stack bracing, but will themselves cause additional downward force on the stack mounts.

Positive pressure process ducts handling contaminated exhaust inside a building should be leak-free.

Install fire dampers and explosion vents in accordance with the US National Fire Protection Association Codes and other applicable codes and standards.

Fans and filtration equipment should be located, such that maintenance access is serviceable.

5.3.13 Unidirectional Airflow

UDAF hoods should be commissioned and then verified fit for use:

- Airflow face velocity is usually measured 6 to 12 inches (15 to 30 cm) from the filter face. Uniformity of velocity is expected to be within 20% of the target value.

- HEPA filters should be integrity tested at accepted velocity. The casing of the hood also should be scanned for leaks at this time.
- Pressure drop across HEPA filters should be recorded at the accepted velocity.
- Airflow patterns at rest (no operators, production equipment not running) at the optimal average velocity. If not 90 ft/min (0.45 m/sec), it may be advisable to test at the lowest and highest velocities that create acceptable airflow patterns to justify a different velocity from 90 ft/min. Note that, if distance from the filter face is sufficiently large, there may be no measurable velocity at the working level, even with excellent airflow patterns. This is because of turbulence (see below); the air is moving, but its velocity is not measurable.
- Flow alarms should be tested. The alarm should not be a motor sensor, as the motor may continue to operate after the supply fan has failed.

The science of fluid dynamics says that air turbulence increases with velocity and with distance. Distance may be the “diameter” of the flow duct (i.e., the “face area” of the hood), the length of travel from the source (i.e., the distance below the filter outlet), or the diameter of an object obstructing the flow. For these reasons, optimal airflow patterns may occur at lower velocity and closer to the filter face. It is not uncommon, during the commissioning phase, to create temporary curtains and aerodynamic shields to improve airflow patterns at critical sites. These temporary structures can be converted to stainless forms or clear rigid curtains for permanent use.

5.3.14 Controls and Instrumentation

Instrumentation should be readily accessible for maintenance and replacement. Components should be calibrated prior to commissioning of the HVAC with calibration stickers applied. See ISPE GAMP® Good Practice Guide for Calibration Management (Reference 13, Appendix 12).

5.3.15 Building

Construction activities typically occur at a tightly coordinated and accelerated pace to meet schedule commitments. The owner should inspect the site on a regular schedule to verify design intent, construction quality, and integration of systems occur as planned. Ongoing site visits should be conducted during each phase of the building construction and the installation of equipment and services. Auditing can identify deficiencies that, if not corrected, will result in unacceptable performance of the HVAC system. Typical construction issues include:

- Air migration through the building caused by poorly sealed penetrations and finishes can lead to unacceptable control of space DPs, such that fumes and dirt can leak in and compromise room classification. Leak testing of room fabric is described in ISO 14644-3 (Reference 3, Appendix 12). The following penetrations and openings should be checked, noted, and resolved during walk throughs:
 - piping
 - ductwork
 - electrical conduit and receptacles
 - doors
 - diffusers and registers
 - architectural wall and ceiling joints
 - lighting fixtures

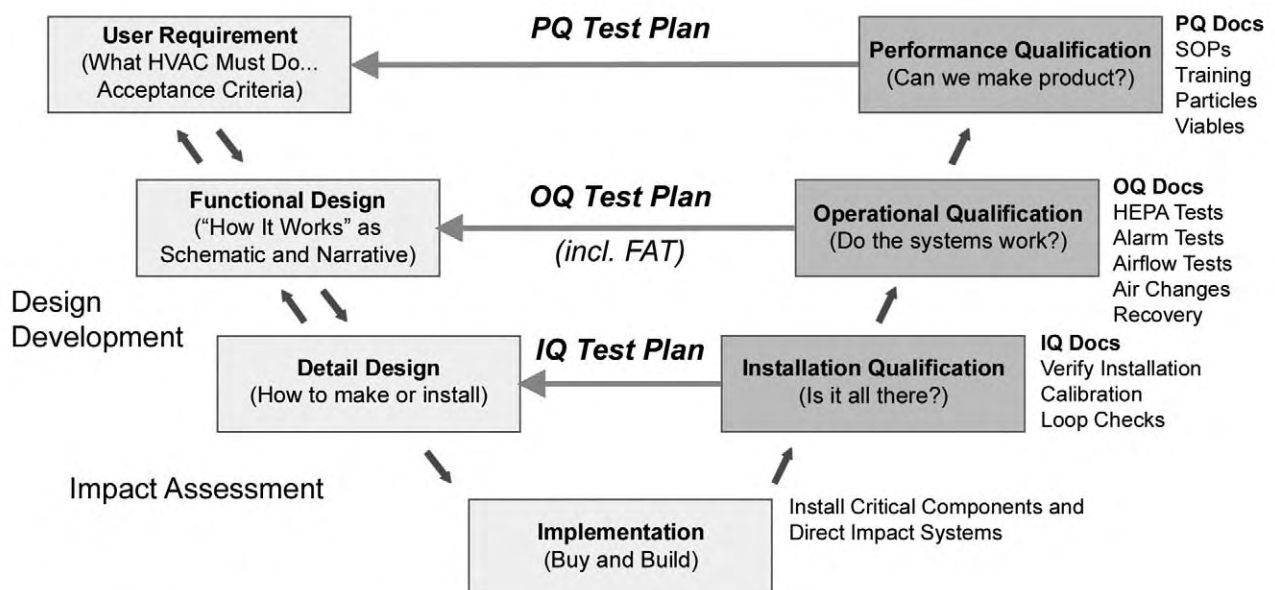
- During construction, cleaning procedures should minimize the accumulation of construction debris and dirt. If this is not controlled, extensive time for repetitive cleanup steps will be required, affecting the commissioning and qualification of the building and HVAC systems.
- Procedures should be in place for personnel to wear appropriate gowning (i.e., booties, smocks) to keep out dirt from areas which have been designated and substantially complete and cleaned). In addition, providing tacky floor mats and shoe cleaners can keep floors clean. Before HVAC startup, equipment, walls, and cleanroom floors should have been wiped down and floors swept and vacuumed.

5.4 Commissioning and Qualification

It is considered GEP for HVAC systems to be commissioned to verify that they perform as designed. Commissioning protocols typically are developed during design and executed during and after construction. HVAC engineers often are involved in Factory Acceptance Testing (FAT) and Site Acceptance Testing (SAT) of major HVAC equipment and systems.

Qualification should be performed for HVAC systems which have a direct impact on product quality and of components which are critical to product quality. Qualification may leverage documentation from earlier steps or may require extra testing.

Figure 5.9: Qualification V-Diagram for HVAC



Enhanced Design Review occurs all through design for Q7A facilities, this is "Design Qualification."

Note: the "what" that needs to be done to qualify the system is shown (user requirements and functional design requirements should be satisfied). For further detail, see ASHRAE Standard 1 on Commissioning, ISO 14644-3 (Reference 3, Appendix 12) on cleanroom commissioning, and various Recommended Practices (RP) from IEST (Reference 12, Appendix 12).

Direct impact, indirect impact, and no impact systems should be identified, followed by identification of the critical components within the direct impact systems. Critical systems and components should be qualified; the remainder of the systems and components should be commissioned. See the ISPE Baseline® Guide on Commissioning and Qualification (Reference 13, Appendix 12).

HVAC systems may be identified as direct impact systems with, e.g., the HEPA filters being critical components. An alternative approach may be to identify all the final HEPA filters as the “air quality system,” drawing a boundary around them as a direct impact system to be qualified with the air handler and its prefilters being indirect impact.

Similarly, direct impact system boundaries can be defined for pressure monitoring, temperature monitoring, etc., allowing qualification documents to focus on the components presenting the greatest risk to product quality and patient safety.

5.4.1 *Typical Commissioning and Qualification Activities*

Typical commissioning activities may include:

- ductwork leak testing
- layout and device location verification
- safety device testing (freezestats, firestats, smoke detectors, pressure switches, etc.)
- verification of filter installation
- AHU and duct cleaning
- motor rotation, speed, and amperage verification
- operational testing of all components (dampers, motors, switches, indicators, etc.)
- rotating equipment balancing
- vibration measurement
- lubrication
- static pressure setpoint adjustment
- temperature setpoint adjustment
- VFD adjustment
- air balancing
- coil performance verification (water and air side)
- startup

Typical qualification activities might include:

- air balancing
- filter integrity testing
- room classification testing
- room pressurization or airflow direction testing
- airflow visualization

- face velocity testing

5.4.1.1 Room Particle Counting

Setup for particle counting in a room is described in ISO 14644-2 (Reference 3, Appendix 12).

5.4.1.2 Room Recovery Test

Procedures using a smoke generator and multiple particle counters are outlined in ISO 14644-3 (Reference 3, Appendix 12).

For further information on recovery testing, see the ISPE HVAC COP Web site.

5.4.1.3 Room DP

Procedures for verifying DP are described in ISO 14644-3 (Reference 3, Appendix 12).

5.4.1.4 Time Delay on DP alarm

If a classified space is not separated from a space of a lower classification by an airlock, it may be necessary to verify the time delay on low DP alarms; a test may involve:

1. Raising particle levels in the space with lower classification with a smoke generator; monitoring these levels to assure that they do not drop on their own. They should be at the upper limit of the space's in-use air class.
2. Setting a particle counter in the cleaner space, between the doorway and the critical site. (If the critical site is under a UFH, locating the counter away from the hood.)
3. Opening the door and simulating normal traffic through the door. Measuring the time before particle counts start to increase beyond normal expected levels. This time period will be the maximum time delay permitted.
4. Setting the time delay set point at a time much less (e.g., 50%) than the measured time interval.

5.5 Training

Personnel who operate and maintain the HVAC system should be trained on its intended function (to satisfy the user requirements) and on the procedures needed to keep it running.

- What the system is expected to do (the user requirements): effect on product and patient. Operator or maintenance personnel should understand why an HVAC system and its maintenance are important.
- How do the HVAC systems maintain user requirements?
- Qualification activities and documentation – what components are under change control (as few as possible, based on criticality), as-built drawings?
- Operating SOPs: what are the access to set points, system startup, troubleshooting procedures?
- Maintenance SOPs: what activities are needed and when?
- Cleaning and precautions during maintenance activities
- Instrument calibration: procedures, frequency

- Where and how records are stored: records for GMP purposes may be stored separately. Who has access and control?

5.6 Equipment Operation and Maintenance

5.6.1 Introduction

The maintenance of systems is fundamental to achieving correct operation, appearance, longevity, and safety. Inadequate maintenance can lead to unexpected and extended shutdowns. It also could lead to underperformance in maintaining the various environmental parameters (temperature, humidity, air quality, air flow, and pressurization) required for GMP facilities.

Predictive Maintenance (PdM) encompasses a range of technologies to detect degradation of equipment performance at an early stage before it can become a problem. This allows maintenance personnel to order parts, schedule manpower, and plan multiple repairs during a scheduled shutdown. The goal of PdM is to proactively correct problems before significant deterioration occurs.

Traditional (scheduled) Preventive Maintenance (PM) practices often cannot identify mechanical equipment failures that could have been detected through changes in operating temperature, vibration signatures, and bearing wear indicators. Equipment is susceptible to unplanned catastrophic failure that can interrupt production operations, cause risk to product, and result in reactive repairs that can be more expensive than planned repairs.

Physical appearance of equipment and its surroundings reflects the quality of the maintenance performed upon the equipment. Spent materials, extra parts, and trash could give a regulatory inspector the impression of poor maintenance practices. Maintaining clean HVAC systems is important to acceptable IAQ. Contaminants in HVAC systems can take many forms. Common contaminants include:

- dust particles
- active bacterial or fungal growth
- debris from HVAC components (rust, belt shedding, grease)
- loose duct lining
- mold spores

Holes in the vapor barrier on exterior insulation can lead to condensation inside the insulation and eventual growth of mold and bacteria, as well as loss of insulating properties; good housekeeping practices should be followed.

Periodic walk downs of mechanical areas can ensure housekeeping is maintained at an acceptable level of quality. A new coat of paint may not improve HVAC performance, but it conveys a sense of attention to the state of the HVAC system.

5.6.2 Air Handling Units

The AHU should be inspected periodically for air leaks, rusting, condensate drainage problems, and dirt accumulation, and to verify the proper operation of doors, drives, dampers and actuators, and lighting and switches.

Periodic cleaning of the unit's interior is recommended, particularly for units serving classified spaces, such as aseptic operation. A cleanliness inspection should consider the components within the unit, such as:

- filters

- heating and cooling coils
- condensate pans
- condensate drain lines
- humidification systems
- acoustic insulation
- fans
- fan compartments
- dampers
- door gaskets
- general unit integrity

Prefilters do not remove all air contaminants inside an AHU. Dirt accumulation over time can lead to microbial growth. Typically, the units are washed down with a solution that will kill microorganisms, while at the same time, eliminating grease and oil that may have been dispersed from bearings and other lubricated joints.

It is recommended that visible rust is removed and surfaces repainted to return their appearance to new.

Pools of standing water in condensate drain pans can lead to microbial growth and rusting of ferrous parts. Drainage should be checked during hot and humid periods when condensate generation is high.

Lighting fixtures with failed fluorescent tubes or ballasts result in poor lighting levels, affecting maintenance of AHU components and personnel safety.

Defective electrical switches and receptacles can lead to electrical hazards, poor operation of the components they serve, and increased maintenance.

Door maintenance is significant to the air tightness of a space. Gaskets, frames, hinges and latching handles tend to loosen and wear, leading to lower air delivery from the unit, energy loss, sweating, and infiltration of dirt.

5.6.3 Fans

Maintaining desired fan airflow is critical to providing adequate conditioned supply air into a space. If not appropriately maintained, fan components can lead to diminished airflow and eventual failure; components include:

- fan housings
- wheels
- bearings
- belts
- guards
- motors

The fan wheel should be checked periodically for accumulation of dirt, mechanical fatigue, and imbalance that can result in increased vibration and noise, and ultimately catastrophic failure with life threatening potential (i.e., broken blades and housings). If these problems are not corrected, desired airflow volume may not be achieved.

Bearing failure is common, because of over- or under-lubrication and the use of lubricants that are not intended for the airstream environment. Personnel should have appropriate training from bearing manufacturers and lubrication suppliers. Vibration and temperature monitoring can assist in trending analysis to identify impending bearing failure.

Belt drives need extensive care and procedures for removing, installing, and starting-up equipment with belt drives. Improper belt tension is one of the most common root causes of premature failure; steps which should be followed include:

- Check belt tension, using a tension gauge or Sonic Tension Meter. Adjust the belt drive's center distance until the correct tension is measured.
- Rotate the belt drive by hand for a few revolutions. Re-check the belt tension and adjust as necessary.
- Start the drive, looking and listening for any unusual noise or vibration. If the motor or bearings are hot, the belt tension may be too high.
- V-belt Run-In Procedure: a run-in procedure is recommended for v-belt drives to optimize belt life. A run-in consists of starting the drive and letting it run under full load for up to 24 hours. After the belts have run-in, stop the belt drive and check the belt tension. Running the belts under full load for an extended period of time will then seat the v-belts into the sheave grooves. V-belt tension normally will drop after the initial run-in and seating process. Re-adjust the belt tension as necessary. Failure to check and re-tension the belt will result in low belt tension, belt slippage, reduction of airflow, and eventual premature belt failure.

Motors should be capable of operating for more than 10 years without major problems. Since motors are expensive to purchase and their operating costs are high (e.g., 25 hp motor $\times$ 8760 hrs/yr $\times$ \$0.075/kwh = \$12,250/yr) maintenance is essential to keep operating costs at a minimum. The following activities should be performed:

- Dirty motors run hot when thick dirt insulates the frame and clogs cooling air passages. Heat reduces insulation life and eventually causes motor failure. Motor exterior should be periodically cleaned to remove contaminants that can affect heat dissipation from the motor. Wipe, brush, vacuum, or blow accumulated dirt from the frame and air passages of the motor.
- Check for signs of corrosion. Serious corrosion may indicate internal deterioration and a need for external repainting.
- Lubricate the bearings only when scheduled or if they are noisy or running hot. Do not over-lubricate. Excessive grease and oil captures dirt and can damage bearings.
- Feel the motor frame and bearings for excessive heat or vibration. Listen for abnormal noise that may indicate a potential motor failure. Promptly identify and eliminate the source of the heat, noise, or vibration.
- Verify that belt and motor drive guards are securely fastened so as not to cause vibration and noise and possible damage to equipment and personnel.

5.6.4 Heating and Cooling Coils

Coils, whether for heating, cooling, or dehumidifying, should be clean both internally and externally, and the fins for heat transfer should be intact and undamaged. As cooling coils typically reduce both the sensible (cooling) and latent (de-humidify) heat of the air, they are more sensitive to loss in heat transfer capability (because of the higher heat load per area) than are heating coils. Cooling coils are more likely to accumulate dirt since they are usually wet.

Typically, coils (especially cooling coils) are externally cleaned once a year, as this side of the coil receives the most dirt (from the air stream). Internal cleaning typically is performed only when DPs of the heat transfer fluid (inlet versus outlet) increase beyond manufacturer recommendations for that which is acceptable for a particular operation. Coils may be periodically pressure tested for leaks. By treating heating steam and heat transfer water, tubes of coils should remain clean, and heat transfer capability should remain high for a number of years. When face and bypass heat coils are used, the damper mechanisms should be inspected annually to ensure they correctly operate smoothly over their entire range of motion.

Control valves wear out over time due to constant modulation. These valves should be included in a regularly scheduled maintenance program.

5.6.5 Steam Humidifiers

There are a number of components that make up the humidifier system; items that should be inspected and maintained include:

- the strainer screen: twice per year as a minimum (if fouled, steam flow will be reduced)
- the control valve: annually to ensure that:
 1. the steam valve closes tightly
 2. the stem packing is not leaking steam
 3. the diaphragm in the actuator is not leaking air
- the sealing and O-rings to assure that no steam leaks into the surrounding area with the possibility of personnel injury
- the nozzles for proper dispersion of steam into the airstream; if steam is not dispersing properly, capacity can be reduced or condensate can form downstream
- the silencer: annually as a minimum for cleanliness

5.6.6 Desiccant Dehumidifier

The maintenance of desiccant units includes:

- filters
- wheel drive assembly
- wheel support bearings
- seals between process and regeneration sections
- fans
- belts
- controls

Desiccant components should be maintained according to a recommended schedule.

As a desiccant system has incoming air on the supply side and a second air stream for reactivation, both sets of inlet air filters need regular replacement to prevent airflow being reduced. Clogged filters on the supply or process air will cause overheating because of reduced airflows, as well as wasted energy. Clogged filters on the reactivation side may cause problems, including insufficient airflow to remove the moisture from the desiccant wheel, reducing system performance. As filters load still further, there is insufficient airflow to safely absorb the heat from the reactivation heater, so the unit shuts down because the temperature of the reactivation air entering the wheel is too high. A large number of reported problems related to desiccant systems can be traced to clogged filters.

Seals between regeneration and process airflow sections should be inspected. Leakage will degrade performance.

Lithium chloride desiccant can absorb excess moisture, expanding and literally “exploding” out of the wheel. When not in use, LiCl wheels should be kept hot and rotating.

The drive belt around the desiccant wheel needs to be sufficiently tight to turn the wheel, but not so tight as to put an excessive load on the drive motor shaft bearings. Desiccant units are equipped with automatic tensioning devices, but belt tension should be checked at least twice a year or when the filters are changed to be assured that the belt is neither too slack nor too tight.

The desiccant wheel has bearings that should be inspected at the same time as the fan bearings, and should be greased based on the manufacturer’s recommendation. Typically, greasing is needed only once a year because of the wheel’s slow rotational speed.

Controls should be recalibrated regularly to assure a steady state of operation. Bypass dampers should be checked for proper operation and seating. Shut off damper seals should be checked.

5.6.7 Air Filtration

As filters load with particles, resistance to airflow increases (higher pressure drop) to a point where airflow could be reduced and the filters could collapse. Alternatively, as filters load with material, their efficiency increases. Ideally, filters should be replaced based on a predetermined DP drop and the cost of the filters. This optimizes the TCO for the filters. Higher energy costs typically require lower DP setpoints for change outs. Filters should be correctly installed to prevent air bypassing them. Filter manufacturers should be able to provide information to achieve the lowest TCO based on the operating conditions at a site.

5.6.7.1 ASHRAE Type Filters

ASHRAE type filters should be replaced after no more than two years of service, even if pressure differential change-out limits have not yet been reached. This eliminates potential microbial growth and filter degradation. Filters should be inspected twice per year as a minimum.

ASHRAE type filters (non-HEPA) should not be repaired nor require leak testing.

5.6.7.2 HEPA/ULPA

Depending on the testing method and product/process, leakage of the upstream aerosol concentration above an acceptable limit when tested in-situ may require that HEPA/ULPA filters be replaced or patched. The methods, equipment and materials used for in-situ filter leak testing are generally different from those used for determining the factory efficiency rating of the filters. Thus the two are generally not directly related. The most commonly recognized limit for defining a filter leak is a localized leak rate equal to or greater than 0.01% of the upstream aerosol concentration when tested via an in-situ filter face leak scan. More specific details regarding acceptance limits for localized leak rates in different applications can be found in ISO 14644-3, IEST-RP-CC034.2, and EN 1822, Parts 1 through 5 (Reference 3, 12, and 6, Appendix 12). In-situ leak testing normally is performed once a year for GMP operations, but aseptic manufacturing normally requires testing every six months for some areas. See the appropriate ISPE Baseline® Guide (Reference 13, Appendix 12).

HEPA/ULPA filter leaks can occur in several ways. Rough handling or touching with instruments, tools, or hands may easily damage the filter medium. Leaks also may occur along the interface where the medium is sealed to the frame. The adhesive material can sometimes crack or separate its bond from the frame. This usually occurs because of poor quality control manufacturing processes or adhesives that are incompatible with materials in the air stream. Another major leak source is at silicone gel seals, where the filter housing meets the knife-edge of the filter grid system. Over time, the gel can deteriorate because of exposure to aerosols used in the testing of filters (see Chapter 5 of this Guide).

When leaks are detected, the filter may be replaced or repaired. IEST has specific procedures that should be followed. The size and area of a patch over the leak is significant. If there is no owner's standard for filter repair, HEPA filters should be replaced when the patched area is more than 3 to 5% of the net face area of the filter as furnished from the factory or when a single patch has a lesser linear dimension exceeding 1.5 inches (3.8 cm) (IEST-RP-CC034.2) (Reference 12, Appendix 12). Patching material should be RTV silicone sealant caulk, which meets the FDA 21CFR 177.2600 (Reference 8, Appendix 12) and USDA for food grade applications. (It is not recommended to attempt to caulk a leak between silicone gel and the filter frame knife-edge, nor to repair a filter leak in a Grade 5 – Grade A hood where airflow patterns need to be uniform.)

Care should be taken when storing, handling, installing, and testing HEPA/ULPA filters. They should be stored in an environmentally controlled location within 40 to 100°F (4 to 38°C) and 25 to 75% RH. Filters should be stored in a manner that prevents damage or intrusion of foreign matter.

Care should be taken to follow manufacturer's handling recommendations to prevent damage by:

- dropping of cartons
- vibration
- excessive movement
- rough handling
- improper storage or stack height

Prior to installation, it is recommended that information on individual filters and filter housings is recorded (model number, serial number, performance, factory test data, etc.). This can resolve future questions regarding filter efficiency, replacement filters, or issues arising from a product recall.

5.6.8 Ductwork

Periodic inspection of HVAC ductwork can identify potential problems (dirt, debris, leaks, and corrosion) to be corrected before unexpected failure and extensive repairs are needed. Ductwork can lose its seal over time and can be a source of excessive leakage that can affect room pressurization. Ductwork that has been crushed leads to insufficient airflow, increased noise, and poor airflow control. Damaged or lost duct insulation should be quickly replaced so as to not cause sweating with the potential of condensation getting into work areas, surface rusting, and surface mold growth.

5.6.9 Dampers and Louvers

These should be checked for dirt accumulation and free movement without binding of the linkages over the full range of operation (full open to close). Linkages should not be loose. Dampers for low leakage applications should be replaced if gaskets have become hardened or do not provide a good seal. If these units are allowed to accumulate dirt or do not operate correctly, insufficient air distribution can result.

5.6.10 Diffusers and Registers

Dirt accumulation will result in insufficient air distribution and can be seen from a room. Registers and diffusers should be inspected and cleaned periodically.

5.6.11 Ultraviolet Lights

Maintenance required for ultra-violet lighting involves the replacement of the UV lamp or bulb. The bulbs typically last about 8,000 hours, but their life will be shortened by accumulation of dirt or fingerprints on them. Dirt limits the lamp's intensity and its ability to destroy microbes effectively.

UV lighting ballasts typically have a life of more than five years.

5.6.12 Fume Exhaust/Extraction Systems

Exhaust systems serving pharmaceutical operations need a high level of reliability, because of the impact on the process should they fail. Maintenance should ensure equipment up time, including:

- The system should be inspected to ensure it is free of debris and dirt that may reduce airflow volume.
- Control dampers should operate freely.
- Flexible duct connections should be checked to assure they are not leaking air, often because of deterioration or wear.

Fume hood performance should be tested in accordance with ASHRAE Standard 110.

Fans are the primary component in fume exhaust/extraction systems.

5.6.13 Building

As buildings age, leakage through the room fabric increases over time and can result in loss of room pressure relationships, requiring frequent readjustment of pressure dampers. Ultimately, the source of the leakage will need to be located; periodic inspection of penetrations and seals is recommended.

5.6.14 Air Balancing

Testing, Adjusting, and Balancing (TAB) for HVAC systems should be performed at regular intervals to ensure system compliance, as well as to verify that systems are operating as efficiently as possible. When changes to the room configurations or HVAC equipment occur, TAB should be performed. At a minimum, recalibration of monitoring instruments, verifying supply airflow to process spaces and recalculating air changes per hour (ACPH), and adjusting pressure relationships should occur at least annually for GMP spaces, or when terminal HEPA filters are tested. Full rebalancing should be considered every five years as a minimum and seven years for non-GMP spaces. A total rebalancing can uncover unsuspected increases in energy consumption and potential equipment failures. There is a risk in performing partial re-balancing; as a change in airflow to one zone may cause the opposite change in other zones (increasing air flow to one room may reduce airflow to all other rooms).

Note that typical airflow measurement accuracy is in the order of +/- 10%. This should cause no concern as long as room conditions (and recovery if measured) are achieved. Flow hoods used for air balancing should be calibrated periodically, usually annually. Adequate lead time should be factored into the re-balancing schedule for calibration.

Table 5.6: Suggested Maintenance Frequency

Room Type	Frequency
Aseptic Operation (Grades 5-7) – re-calibration of instruments, check ACPH and airflow; test HEPA filters	6 months
GMP Classified Operation (Grade 8) – re-calibration of instruments, check ACPH and airflow, test HEPA filters	1 year
Other GMP Spaces, Pilot Plants, Animal Facilities, Laboratory Space, R&D Space – full rebalancing	5 years
Non-GMP Spaces including electrical and mechanical rooms, auditoriums, utility spaces, central plant ventilation, kitchens and offices – full rebalancing	7 years

5.7 Spare Parts

GEP and the economics of keeping production on line require that spare parts are kept to minimize the effect of failures. A good PdM program should predict the need to replace parts before they fail, allowing time to order replacement parts. However, there are specific items that may be useful in case of sudden failure:

- A spare desiccant wheel: a desiccant wheel may fail because of remaining idle for months (as during cold winters when dehumidification is not needed), and not be ready for service the first humid day. This is particularly true for LiCl wheels, but silica wheels also have been known to become less effective over time.
- Sensors and transmitters for critical parameters. If all the temperature sensors in the system are the same specification, only one spare is needed; similarly for RH and DP sensors.
- Terminal HEPA filter or UFH HEPA filter: over-zealous cleaning may damage a HEPA filter exposed to the room. Rips and tears in UFH filters may have an effect on a critical zone. Sudden failure because of dirt loading of a terminal filter should not be a concern, particularly if a high efficiency filter in the AHU precedes the HEPA filter. Failed HEPA filters in an AHU have much less effect, and it may be possible to repair the filter while replacements are on order.
- High temperature HEPA filter: because of the gradual destruction of the binders in high temperature filters operated beyond their rated temperature, it is possible that the entire filter bank in a depyrogenation tunnel will need to be replaced at one time. Repairs are not possible.
- Fan belts: a good inspection program should notice belt wear; cost is relatively low.

6 Documentation Requirements

6.1 Introduction

On completion of qualification, the disposition of HVAC system documentation should be established. Documents may be used by maintenance and operations or required for periodic Chemistry Manufacturing Controls (CMC) filings, becoming critical master documents, i.e., engineering documents maintained as GMP records.

This section discusses documents which typically are required and provides guidance regarding classification and use of documents.

6.2 Engineering Document Life Cycle

6.2.1 *Planning Life Cycle*

The life cycle of project documents should be defined during conceptual design and no later than Functional/Schematic design to help to reduce ambiguity and prevent loss of data.

The planning document should define, which documents are required for construction, which documents will be part of an Engineering Turnover Package (ETOP) for maintenance and operations, which documents will be leveraged into qualifications, and which documents will be maintained as record documents for Maintenance and GMP use.

Defining the contents of the ETOP early in a project also allows the easy capture of design calculations and risk assessments as they are generated. Document management and collaboration software, which will apply the appropriate life cycle to documents as they are generated and approved, may be used to capture design and construction information into an ETOP.

A “Traceability Matrix,” (a documentation of the plan and progress of documentation and concepts through the sequence of design, construction, qualification, and eventually showing that the HVAC is fit for service through process validation) may be used for planning and updating of document life cycle. The traceability matrix shows this progress and maintains the chain of design intent, linking final documents to conceptual design documents (User Requirements and Functional Design).

6.2.2 *Typical Steps in the Document Life Cycle*

HVAC documents typically start their life cycle as conceptual documents, including:

- AFDs
- AF&IDs
- room/zoning layouts
- room condition tables (temperature, RH, area class, DP, etc.)
- load calculations
- design basis/assumption tables

These documents progress through the Engineering Process to:

- calculations

- plan drawings
- detail drawings
- specifications
- tables

Plans, details, and diagrams should be updated throughout (or after) the construction process to an “as-built” state (corrected after construction to match the actual final configuration). The update to “as-built status” is essential to maintenance and particularly important for systems that monitor or control critical environments. Specifications and designer’s calculations usually are augmented (or replaced) by manufacturer’s submittals, details, and calculations.

Some documents should be converted into master documents (engineering documents with construction notes removed) as a record of the ongoing state of systems and equipment and to allow capture of future construction changes. Those master documents that define the critical attributes of the HVAC system should be maintained as critical master documents (master documents that are maintained in a constant state of inspection readiness). The AF&ID, HVAC zoning layouts, and area classifications should be kept up to date, as a minimum.

6.3 Documents for Maintenance and Operations (Non-GMP)

A well-constructed (and concise) ETOP can save time during troubleshooting or when entering data into a Computerized Maintenance Management System (CMMS) and may be more beneficial to maintenance than a complete set of design and construction documents.

The list may contain items that have no GMP impact on laboratories, OSD, Packaging, API, etc. Typical Documents for an HVAC ETOP include:

- user requirements/FRS/functional design specification
- room condition tables – temperature, RH (and particle levels, DP, air changes, as required).
- as-built airflow and instrument diagram
- area classification diagrams
- pressure or airflow direction “maps”
- AHU zoning diagrams (what areas are served by each AHU)
- filter integrity testing (classified spaces, cross contamination in other facilities)
- air balance
- face velocity testing (HEPA filters in classified spaces)
- alarm testing
- pressure relationships
- equipment submittals
- ductwork shop drawings

- coordination drawings
- as-built ductwork, piping, and equipment plans
- control diagrams
- commissioning documents

The ISPE Baseline® Guides (Reference 13, Appendix 12) for each facility type define the critical parameters for the facility.

6.4 Master/Record Documents

Documents that typically are kept updated to become HVAC master documents (for maintenance and facility engineering) include:

- as-built AF&IDs
- area classification diagrams (if spaces are classified)
- pressure or airflow direction “maps”
- AHU zoning diagrams
- filter test data
- control diagrams and critical alarms calibration/test records
- sequence of operation
- equipment submittal drawings
- as-built ductwork, piping, and equipment plans

6.5 GMP HVAC Documents

It is important to align with the risk assessment performed in the design process to determine the HVAC documents to be leveraged into commissioning and qualification or become Critical Master Documents. Since the risk assessment varies by project, the following lists of typical documents should be reviewed against project/product needs. See the ISPE Baseline® Guides (Reference 13, Appendix 12).

6.5.1 Commissioning and Qualification Documents

Documents that typically are leveraged into commissioning and qualification include:

- as-built AF&IDs
- room environmental conditions – tables/schedules
- area classification diagrams (classified spaces)
- pressure or airflow direction “maps”

- GMP air filter location map
- AHU zoning diagrams
- control diagrams or functional design for direct impact systems
- critical instrument specifications
- commissioning documents:
 - filter integrity or overall penetration testing (HEPA/ULPA)
 - airflow patterns for Grade 5 (Grade A) hoods and Grade 7 (Grade B) rooms
 - air balance (air changes OK for classified spaces, airflow direction OK)
 - face velocity testing (HEPA/ULPA for Grade 5/Grade A)
 - pressure relationships (contamination control)
 - particle counts at rest
 - critical monitoring and alarm testing, including calibration and alarm delay verification
 - temperature
 - humidity (if deemed critical)
 - room DP or leakage air velocity (for contamination control)
 - supply airflow (classified spaces)
 - Grade A/Grade 5 hood air flow (DP, sail switch, velocity sensor)
 - temperature mapping (usually for warehouse) – see Appendix 2
 - test protocols and supporting information
 - evidence that acceptance criteria have been met

Documents that are typically produced during commissioning and qualification (or Process Validation) are:

- airflow visualization for Grade 5 (EU Grade A) or local protection areas in use
- total airborne particulate testing
- viable airborne particulate testing
- room recovery testing (classified spaces)
- test protocols and supporting information
- evidence that acceptance criteria have been met

6.5.2 ***Critical Master Documents***

Critical Master Documents provide HVAC information for the CMC section of a drug filing and are subject to regulatory review.

Documents that typically are maintained as critical master documents include:

- as-built AF&IDs
- risk assessments and traceability matrix
- room environmental conditions – tables and schedules
- area classification diagrams
- pressure or airflow direction “maps”
- AHU Zoning Diagrams
- qualification documents:
 - filter integrity testing (HEPA/ULPA)
 - air balance
 - air change calculations or recovery testing for classified spaces
 - face velocity testing (HEPA/ULPA in critical zones)
 - pressure relationships (continuous logging for classified spaces or spot-check?)
 - critical alarm and delay testing (temperature, RH, DP, airflow, etc.)
 - airflow visualization for Grade 5 (EU Grade A) or local protection areas
 - total airborne particulate testing (classified spaces)
 - viable airborne particulate testing (classified spaces)

Appendix 1

Fundamentals of HVAC

7 Appendix 1 – Fundamentals of HVAC

7.1 Introduction

This Appendix introduces the fundamentals of HVAC systems that control a GMP workplace environment.

HVAC aims to make personnel comfortable and to protect both workers inside a facility and the environment outside a facility from airborne materials that could be hazardous. In pharmaceutical manufacturing facilities, there also is a specific requirement to control the impact of the environment on the finished product (to assure product quality).

Three primary room environment variables may affect product and processes (at “critical locations,” i.e., locations where product is exposed or where cleaned product contact surfaces are exposed):

- air temperature
- RH
- airborne contamination (viable and non-viable particles)

Some of these variables, such as local airborne contaminants, depend on secondary HVAC factors, for example:

- room pressure
- air changes
- airflow volume
- airflow direction
- airflow pattern
- exhaust location and air velocity
- air filter efficiency

Tertiary HVAC variables, such as fan speed and duct pressure, may vary to satisfy these secondary HVAC factors, and therefore, have an effect on them.

This appendix explores these variables and how they affect product, patient, and personnel. It also introduces some basic HVAC terminology.

7.2 What Is Heating, Ventilation, and Air Conditioning?

Heating, Ventilation, and Air Conditioning (HVAC) is the generic name given to a system that conditions the environment through the control of temperature, RH, air movement, and air quality (including fresh air, airborne particles, and vapors). HVAC systems can:

- increase or decrease temperature
- increase or reduce the moisture or humidity of the air
- decrease the level of particulate or gaseous contaminants in the air

These capabilities are employed to protect personnel and product and for human comfort. HVAC systems also can protect the outdoor environment from hazardous material removed from a workplace environment via HVAC exhaust.

7.2.1 **Personnel Comfort**

The primary role of HVAC systems is to protect personnel and product. The most common role is to make personnel comfortable.

Four criteria usually are considered for personnel comfort and safety:

- Temperature
- Humidity
- Air quality (carbon dioxide (CO₂) levels and odors)
- Air movement (sense of air movement and unwanted “drafts”)

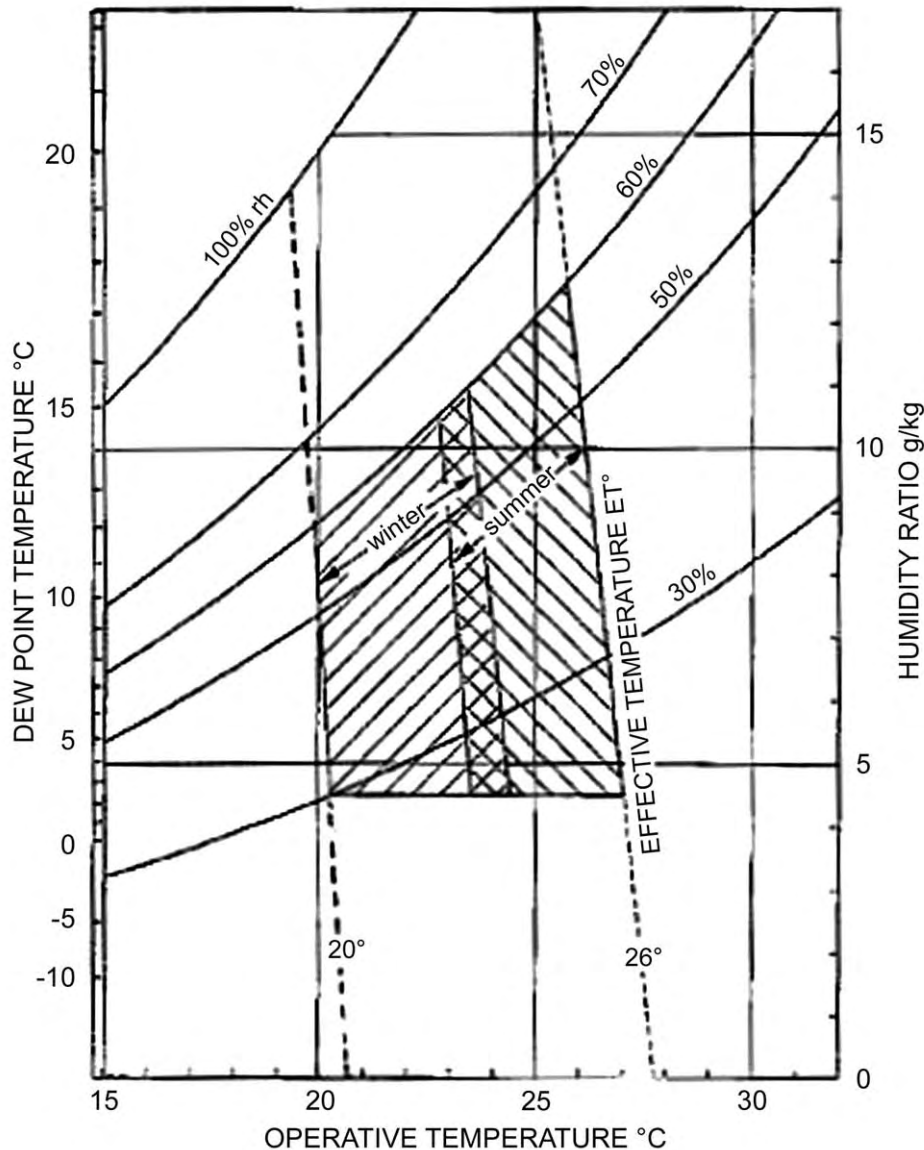
7.2.1.1 *Temperature and Humidity*

Figure 2.1 shows two boxes that define comfort conditions (temperature and humidity) that personnel in the US generally find comfortable in winter and summer (ASHRAE Handbook(Reference 19, Appendix 12). This standard varies across the world, e.g., in parts of the tropics, people prefer an office at 78°F (26°C) to one at 72°F (22°C).

Note: these are general guidelines; numerous factors affect these conditions, e.g., the type and variety of work being performed, the extent of personnel gowning, as well as individual preferences.

Generally, non-production areas should fall within the “comfort zone” shown in Figure 2.1.

Figure 7.1: Standard Effective Temperature and ASHRAE Comfort Zone for General Areas



Used with permission from ASHRAE, www.ashrae.org (source: ASHRAE Fundamentals 2001, Chapter 8)

Where gowning levels are heavier or where work is more intense, room conditions should be cooler and less humid than for office areas. Workers in industrial settings, especially those who are required to wear over-garments (gowning) in pharmaceutical facilities, could be uncomfortable working in office room conditions. Typically, room temperatures are cooler (about 20 to 21°C or 68 to 70°F) with room humidity below 60% to provide “comfort” conditions. In addition, the lower limit on comfort humidity often is set at 30% to minimize static charges and to avoid irritation of the throat that could lead to an increased risk of respiratory illness.

7.2.1.2 Air Movement

A sensation of gentle air movement often is preferable; a typical design figure of 0.1 m/s (0.3 ft/s) is used in an office environment. Greater air velocities (up to 1 m/s or 3.28 ft/s (200 ft/min)) usually are needed for product protection to capture airborne particles. In manufacturing environments, higher velocities may be needed where operators experience discomfort from heavier gowning.

7.2.1.3 Air Quality

Fresh air is required to dilute exhaled carbon dioxide, odors, and other environmental contaminants. The amount of fresh air required depends on personnel activities. Table 2.1 shows typical oxygen use for different levels of activity.

Table 7.1: Oxygen Consumption by Activity Level

Level of Exertion	Oxygen (Air) Consumed L/min
Light Work	Less Than 0.5 (< 2.5)
Moderate Work	0.5 to 1.0 (2.5 – 5)
Heavy Work	1.0 to 1.5 (5 – 7.5)
Very Heavy Work	1.5 to 2.0 (7.5 – 10)
Extremely Heavy Work	Greater Than 2.0 (> 10)

Used with permission from ASHRAE, www.ashrae.org (source: ASHRAE Fundamentals 2009)

ASHRAE 62 (Reference 22, Appendix 12) states the amount of fresh air required to provide adequate IAQ in a non-contaminated workspace should be 15 to 20 cubic feet/min (CFM) or 24 to 32 cubic meters per hour per person; unless a complex ASHRAE analysis is performed. Local building codes may require different quantities.

7.2.2 Product and Process Considerations

Products may be sensitive to temperature, humidity, and airborne contamination from outside sources or cross-contamination between products.

Process operators may need protection from exposure to hazardous airborne materials.

When considered critical, product environmental requirements normally are listed in a New Drug Application (NDA). Data from process development of a new drug may be available. The affects of conditions outside these ranges will depend on the duration of exposure; prolonged exposure time may affect product quality. Safety requirements for personnel exposure normally are found in Material Safety Data Sheets (MSDSs).

Control of airborne contamination should be considered and frequently is associated with temperature and humidity, e.g., the effect of temperature:

- Comfortable personnel work more efficiently and are more productive. They also produce fewer environmental contaminants: a typical worker will discharge 100,000 particles a minute doing relatively sedentary work (particles sized 0.3 μm and larger (a human hair is approximately 100 μm in diameter)). A worker who is hot and uncomfortable may shed several million particles per minute in the size range, including a greater number of bacteria.

Additional ways in which environmental conditions inside a building can influence the product include, e.g., high humidity may increase microbial and mold growth rates on surfaces.

If environmental conditions inside are significantly different from environmental conditions outside a building and the fabric of the building has insufficient integrity, condensation can occur in interstitial spaces and can lead to microbial contamination problems and deterioration of the building.

In addition, protection of personnel depends on airflow direction both within and between rooms. Airflow can entrain particles of product or other hazardous materials harmful to operators. DP and the airflow it produces frequently are used to control the migration of airborne particulate between two rooms (to prevent cross-contamination between products).

7.2.3 *Control of Parameters by HVAC Systems*

7.2.3.1 *Temperature and Humidity*

HVAC systems control the temperature and humidity in a room by supplying that room with air in a condition that produces the desired temperature and humidity when mixed with the room air.

Thermal heat gains and losses to and from a space occur through three types of heat transfer:

1. radiant
2. conductive
3. convective

These may occur as a result of the temperature from sunlight outside the facility and internal heat gains resulting from the process, equipment, lighting, and personnel.

Changes in humidity may arise because of processes, personnel, and the environment. Moisture migration through openings or porous walls into a controlled space from surrounding areas is governed by the difference in vapor pressure (as defined by Dalton's law) and may migrate against an air pressure differential.

7.2.3.2 *Air Velocity*

Air velocity in manufacturing spaces usually is higher than recommended for human comfort. Adequate velocity is vital to correct mixing (dilution) of air within the room and for the removal of airborne contaminants. The direction of airflow should protect operators as well as product. Air velocity that is too high can create eddies and vortices near operators and increase the risk of exposure to hazardous material.

7.2.3.3 *Particulate, Fume, and Vapor Control*

Filtration in HVAC systems usually is capable of removing almost the entire mass of particles. Filters vary in efficiency:

- Low efficiency filters may remove much of the **mass** of particles, but this represents only 20 to 30% of the **number** of particles.
- High Efficiency Particulate Air (HEPA) and Ultra Low Particulate Air (ULPA) filters remove almost the entire **number** of particles, but a very small number of nearly "massless" particles may pass through.

The majority of airborne particles are non-viable. A fraction (< 1%) of airborne particles are viable, e.g., bacteria and viruses; however, these can multiply. Viable particles travel with non-viable particles; therefore, controlling the total number of airborne particles also controls the number of viable particles.

Airflow patterns have a significant effect on the control of airborne contaminants, which may be removed by dilution or displacement (see Section 2.8), reducing contaminant levels through the use of exhaust and replacement (makeup) fresh air where necessary.

7.2.4 *Limitations of HVAC Systems*

HVAC systems are not a substitute for good process, facilities, and equipment design or for good operating procedures. HVAC systems are not able to:

- clean surfaces that are already contaminated

- adequately control processes that generate excessive contaminants
- compensate for improperly designed or maintained facilities

As viable particles, such as bacteria and viruses, travel with non-viable particles, HVAC systems can only help control biocontamination in a room by delivering clean air to that room. Where an HVAC system has been properly designed, constructed, and maintained, that system is unlikely to be either the cause or the solution for persistent contamination problems.

7.3 Air Quality Fundamentals

7.3.1 Introduction

Pharmaceutical HVAC should control airborne contamination and needs to help to ensure the "...purity, identity and quality..." of the product (21 CFR Part 211) (Reference 8, Appendix 12). By introducing conditioned clean air, HVAC can help control temperature, humidity, and airborne particulates in a space within the requirements for a product. In order to determine the equipment needed at the HVAC system level, the purpose of air supplied to a room needs to be predefined.

Both the quality (temperature, humidity, cleanliness) and quantity of air introduced into a room affect its ability to maintain environmental conditions. The effects of physical layout (geometry), air velocity, and air volume should be considered to ensure effective ventilation.

7.3.2 Fundamentals of Ventilation

Ventilation is the movement and replacement of air for the purpose of maintaining a desired environmental quality within a space. The term "Ventilation" has two common uses:

- It may refer to the movement or exchange of air through a space, which is responsible for the transport of airborne particles, the mixing or displacement of masses of hot or cold air, and the removal of airborne contaminants (e.g., vapors and fumes). In this use, ventilation may supply all outdoor ("fresh") air or may recirculate air from the building combined with some fresh air.
- It may refer to the supply of "fresh" oxygen-rich air.

This Guide uses the definition only for movement or exchange of air through a space.

For pharmaceutical spaces, both "air change rates" and "ventilation rate" may be used. Appropriate filtration and attention to the physical airflow patterns in a space tends to be successful where pharmaceutical HVAC design.

The locations of air inlets and outlets relative to the location of sources of contamination/heat and to expected airflow obstructions are crucial to controlling contamination. The relationship between these factors is expressed in the "effective ventilation rate" for a space. This measure expresses the efficiency of the dilution air supply at removing contaminants expressed as a percentage of the theoretical performance with perfect (complete) dilution. For further information and calculations, see Appendix 9.

A comparison of the ventilation rates of various designs indicates that good air supply layout, good return/exhaust layout, and effective supply filtration may produce desired airborne particulate levels and recovery rates with less air change rates than used traditionally. The importance of room level airflow patterns in the control of contamination and the performance of classified spaces has led to the application of computer modeling (Computational Fluid Dynamics (CFD)) and testing to assure effective design. The WHO guidance 937 Annex 2 (Reference 2, Appendix 12) suggest that this be performed for oral dosage spaces, but the practice is common only for the most potent products.

7.3.3 Contamination Control

Pharmaceutical HVAC should help to:

- prevent unwanted environmental contaminants from adversely affecting product
- prevent products from contaminating each other
- limit operator exposure to hazardous pharmaceutical compounds, ingredients, or reagent vapors
- prevent hazardous materials being spread to the outdoor environment

Room contamination control generally is achieved by filtering the incoming air to ensure that it does not carry unwanted particles, and then introducing the air to the work space to mix with ambient air and dilute any contaminants. Contaminants may be removed more rapidly using displacement airflow of adequate velocity and direction (e.g., in a UFH, local extraction vent, or via non-aspirating diffusers) than with dilution ventilation.

The number and intensity of contamination sources in a room should be considered; if low, a displacement airstream may be more useful in controlling airborne contaminants than dilution.

The orientation of airflows can be aligned to protect product or personnel by sweeping across one or the other (or both) between the supply terminal and the extract point. Local (usually high level) supply or extraction, or complete enclosure of the process also can create a local environment that excludes or removes particulates. Local supply or extraction is considered most effective when located near the point of contaminant generation.

Pharmaceutical HVAC can help control contaminants within a space, but facilities should be designed with physical architectural features, such as airlocks, which limit the migration of contaminants.

7.3.4 Classified Space

The concentration of total airborne particles and microbial contamination within the space is a key measurement of room environmental conditions for pharmaceutical operations, particularly for sterile products and some biopharmaceutical APIs. The target maximum reading for these measurements is referred to as the “classification” of the space.

Several similar systems have been communicated for the classification of space; however, there is no consensus between international regulators on a single terminology for classification:

- the EMEA uses “Grades A to D”
- the FDA refers to ISO levels (5, 7 and 8), but only “in-use” (there are no “at-rest” limits), and further adds bioburden limits for each ISO class

It would be cumbersome to apply EU and FDA GMP nomenclature to facilities and to explicitly state “ISO X, in-use with colony forming unit (CFU) limits of Y per cubic meter.”

This Guide uses the term “Grade” followed by an ISO level number. Therefore, “Grade 7” meets ISO 7 (10,000 0.5 micron particles per cubic foot or 352,000 per cubic meter) in use only with bioburden limits of 10 per cubic meter. By comparison, a Grade 7 space looks much like a European Grade B space, but the European Grade (A, B, C, D) also has at-rest limits.

Table 7.2: Comparison of Classified Spaces

Reference	Description	Classification
ISPE Sterile Baseline® Guide	Environmental Classification	Grade 5 Grade 7 Grade 8 Controlled Not Classified (with local monitoring) Controlled Not Classified (CNC)
European Commission EU GMP, Annex 1, Vol. IV, Manufacture of Sterile Medicinal Products (effective 1 March 2009) (similar to PIC/S GMP Annex 1 2007) (References 4 and 7 Appendix 12)	Descriptive Grade	A B C D Not Defined
	At Rest	Maximum no. particles permitted per m ³ ≥ the stated size 0.5 µm 3,520 3,520 3,520,000 -
	In Operation	Maximum no. particles permitted per m ³ ≥ the stated size 5 µm 29 2,900 29,000 -
		Maximum permitted number of viable organisms cfu/m ³ 0.5 µm 3 520 3,520,000 Not stated -
		5 µm 20 2 900 Not stated -
		< 1 < 10 < 100 < 200 -
FDA, October 2004, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing (Reference 9, Appendix 12)	In Operation	ISO 5 (Class 100) ISO 7 (Class 10,000) ISO 8 (Class 100,000) Not Defined See ISPE Biopharm or Sterile Baseline® Guides
	Action level number of viable <u>airborne</u> organisms cfu/m ³	1 10 100 Not Defined -
Notes:		
- There are small differences in numerical values between the US and European air classes. - The US particle levels are for the ‘in operation’ state only, but it is considered GEP to measure periodic at rest particle levels to monitor the overall health of a facility. - The US has no equivalent to EU Grade D although the term Controlled Not Classified (CNC) has been used in the pharmaceutical industry and is discussed in the ISPE Baseline® Guides for Sterile and Biopharmaceuticals (Reference 13, Appendix 12). A CNC space may meet ISO 8 at rest without the use of HEPA filters if the airborne challenge is low. For further information on air filters, see Chapter 3 of this Guide. Therefore, a “CNC with monitoring” space could look and perform similarly to a European Grade D space. - Air quality for facilities that do not require classified spaces, (e.g., oral dosage, packaging, warehousing, closed biopharmaceutical, most APIs (except aseptic processing), and API intermediates) is described in the relevant ISPE Baseline® Guide (Reference 13, Appendix 12).		

7.3.5 Total Airflow Volume and Ventilation Rate

The relationship between air change rate, ventilation rate, the air particle concentration in the space, and recovery rates from in-use to at-rest conditions should be considered.

The process that will be operated in a given space should be understood in order to determine the air flow rate (not air change rate) required to meet the stated room air classification (see Chapter 5 of this Guide).

Arbitrary air changes may be either excessive or insufficient. The airborne particle level depends on several factors. After a facility is commissioned, particle levels and room recovery should be sufficiently below specified limits, rather than having an arbitrary number of air changes.

7.3.5.1 Air Change or Air Flow?

Arbitrarily set air change rates often drive decisions regarding room size and airflows. This can have significant cost implications, but does not relate directly to the particle count in a room. Air change rates are more related to a room's ability to recover from an upset, **not** the room classification. The following is an explanation of this difference:

- Assume a 1 cubic foot room containing an aseptic process that generates 10,000 particles per minute. If the room is purged with 1 CFM of clean air, the steady state (equilibrium) airborne particle level will be 10,000 particles per cubic foot (PCF) (see Appendix 17 for equations) (Appendix 12). This 1 CFM creates an air change every 1 minute or 60 air changes per hour. This value (60/hr) is often assumed to be more than enough to keep a space well below 10,000 PCF.

Now put the same process into a 100 cubic foot volume and keep the airflow at 1 CFM, assuming good mixing occurs inside the room. Now the room sees an air change every 100 minutes or about 0.67 ac/hr. However, when the dilution is calculated, the equilibrium airborne particle counts are still 10,000 PCF (10,000 particles per minute/1 cubic foot per minute = 10,000 particles per cubic foot). Hence, average airborne particle counts are not determined by the air changes, but by the three factors (assuming perfect mixing, see Appendix 9):

1. particles generated inside a space (PGR)
2. quantity of dilution air supplied to a space (cubic volume per time) assuming adequate mixing in the room
3. cleanliness of dilution air (assumed to be negligible in aseptic processing based on HEPA filtration)

A room receiving only 1 air change per hour will take several hours to recover from in-use to at-rest conditions. With a clean air supply of 20 air changes per hour, a 100-fold reduction in airborne particle levels can occur with less than 20 minutes recovery time, satisfying the European GMP requirement. See the ISPE Sterile Manufacturing Facilities Baseline® Guide (Reference 13, Appendix 12).

For **recovery**, **air changes** are important; a rate of 20/hr often is used as the minimum for classified spaces. (See the Appendix 9).

For applicable oral dosage facilities, the WHO 40th report (Reference 2, Appendix 12) suggests 6 to 20 AC/hr with recovery of 20 minutes from in-use to at-rest conditions (to be defined by the User and verified at building commissioning).

Although "air change rate" is important, for pharmaceutical HVAC system design, greater benefit may be obtained from correct air filtration and attention to the airflow patterns in a space.

7.3.5.2 Particle Generation Rate

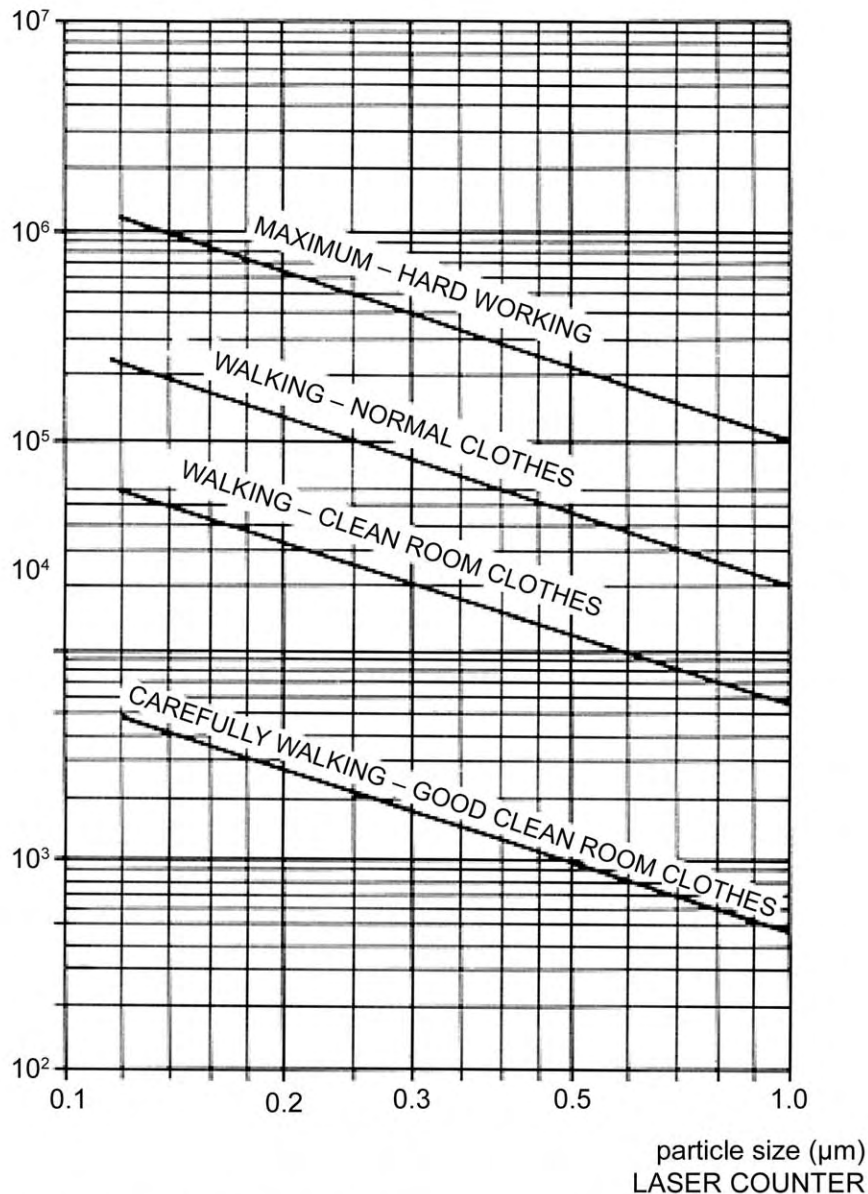
The PGR for an existing process may be calculated if the steady-state room particle count, the room supply airflow, and the supply airflow particle level are known (see Appendix 9). The calculated value of PGR can then be used for the same process in a new facility.

However, equipment manufacturers may not know the PGR of their equipment, necessitating HVAC designers to make conservative estimates and over-design room airflow. Data gathered during “water batching” (process simulation), but before actual production, may offer an opportunity to reduce airflow rates where in-operation airborne particle levels appear to be low (because of over-design).

When using empirical data for airborne particulate monitoring, it should be taken into consideration that particulate of the product being processed is not a contaminant. This is of particular interest in aseptic powder filling operations, where high particle counts may be associated with the filling process, but do not indicate failure of a cleanroom design. If an air volume reduction appears to be feasible, other critical HVAC parameters (temperature, RH, room DP (DP), recovery, and at-rest levels) should be maintained.

Figure 7.2 gives an indication of particulates generated by personnel within a cleanroom. Although equipment in operation can generate many times more particles per minute, personnel are a primary source of viable contamination. Increased control of total particles released from personnel leads to an increased control of viable particles in a room.

Figure 7.2: Number of Particles Generated per Second per Person
(particles/second)



Note: Even lower particle release numbers may be possible with the latest generation of cleanroom gowning.

Used with permission from Camfil Farr, www.camfilfarr.com

7.3.5.3 Impact of Unidirectional Airflow Hoods on Air Change Rates

Air leaving the processing space inside a hood is often significantly cleaner than the air of the room into which it moves. The relatively clean air from the hood may help, along with the supply air from the HVAC system to dilute airborne particles in the room.

In addition to reducing airborne particles, air flow from a hood may accelerate the recovery time of a room from in-use to at-rest conditions. The entire air flow from a hood may not be available to include in air change calculations because:

- Short-circuiting of the air leaving the hood zone back (upward) to the hood inlet; the added dilution will affect only areas near the airflow path. If the hood inlet is near a room air supply outlet, that air could also short circuit into the hood without helping to mix air in the room.
- Hood air may not be as clean as HVAC supply air. Even though the critical location under the hood might be rated as ISO 5, the air leaving the Grade 5 work space has collected additional contaminants from equipment and personnel outside the critical zone before passing back into the hood inlet.
- Similar increases in room air cleanliness and recovery can be accomplished with HEPA-equipped FFUs operating inside a room. Short circuiting of filtered air back to the air intake may create only localized “super-clean” areas, as with UFHs.

7.3.6 Room Air Distribution and Quality of Incoming Air

Optimal layout for air inlet and outlet, and adequate filtration, can produce desired airborne particulate levels and recovery rates using lower air change rates than those used traditionally.

Using the recovery example in Section 2.3.5.1 of this Guide, faster recovery can be accomplished in a classified room where clean air supply is distributed over a high percentage of the ceiling (or via multiple non-aspirating diffusers) than by supplying the same total supply volume from one conventional air outlet. It is not necessary to create a “laminar flow ceiling.” Numerous air outlets equally spaced, with equal flow rates, can create a “plug flow,” a situation where air generally moves downward from ceiling to floor, but not at constant velocity. This can lead to faster recovery (often less than 10 minutes for 20 ac/hr) and also prevent “hot spots” of high particle count in a room. The resultant downward velocities are much less than those used in a unidirectional flow (Grade 5) area, and activity in the room may cause undesirable airflow patterns that should be investigated during commissioning. Numerous well-located low wall air returns can help prevent “dead zones” near the floor. (Generally, pharmaceutical facilities do not use perforated floors for air returns.)

7.3.7 Airflow Direction and Pressurization

Constructing a space that is absolutely airtight is considered impractical using normal construction techniques; therefore, alternative approaches are required to prevent airborne particulate migrating into or out of a space. A continuous flow of air in the desired direction through the cracks in building construction (door gaps, wall penetrations, conduits, etc.) can reduce transport of airborne particulates. A velocity of 100 to 200 FPM (0.5 to 1.0 m/sec) usually will capture and transport light powders and bioburden, assuming there are no strong drafts nearby (such as a worker passing quickly in front of a laboratory hood).

One method to control the direction of airflow is to control the relative pressurization of adjacent spaces, i.e., the DP between the spaces.

A simplified method (neglecting the orifice coefficient for the opening) to calculate the expected velocity of airflow through a “crack” (e.g., around a closed door) resulting from a given pressure differential is:

Where:

- 4005 is a conversion factor
- V is velocity in ft/min
- VP is velocity pressure, here assumed to be the room DP in inches wg
- A is area of the opening in square feet
- Q is airflow in Cubic Feet per Minute

$$V = 4005 (\text{sqrt VP}) \text{ or } VP = (V/4005)^2$$

Velocity (V) can be broken down to volume divided by area, giving $V = Q/A$:

For SI units: $VP = (Q/4005A)^2$

For metric units: $VP \text{ (Pascals)} = (Q/110A)^2$, (where Q is in cuM/hr and A is in square meters)

Assuming room DP converts fully to VP through an opening (a conservative assumption), calculating the opening area, such as the crack area around a closed door between rooms, allows calculation of the airflow (CFM) required to create a pressure across that door, or the velocity that results from a known DP.

For A=1 sq foot (0.1 sq m) opening, 890 CFM (about 1500 cuM/hr or 0.45 cuM/sec) will create 0.05 inch wg (12.5 Pa) DP ($V = Q/A = 890 \text{ FPM} = 4.5 \text{ M/s}$)

(For further information, see Appendix 9.)

Other “cracks” in the fabric separating a pressurized room from lower pressure spaces may not be accounted for using this calculation. This often leads to a requirement for more airflow to the room than predicted by the calculation to satisfy DP requirements. A common method which accounts for this additional airflow is to allocate 0.05 to 0.5 CFM per square foot of room surface, depending on construction and DP. This airflow can be minimized by constructing rooms tightly and testing for (and correcting) leaks during commissioning.

7.3.8 Control of Operator Exposure to Potent and Hazardous Compound

Modern pharmaceutical processing increasingly requires handling of potent active ingredients, requiring small dosages to produce a pharmacological effect, and may require the handling of other materials that can be hazardous to human health. The prevalence of these challenges creates a burden on the HVAC system and process engineers to control operator exposure and possible environmental discharge. Worker protection standards vary by jurisdiction, but Control of Substances Hazardous to Human Health (COSHH) regulations (this is a terminology coined in the UK, but common in the industry) are ubiquitous. These standards may specify 8 hour Operator Exposure Limits (OELs) for commonly used substances and require that manufacturers specify OELs for proprietary compounds. A hierarchy of control is expected; with substitution and control at the source being considered before Local Exhaust Ventilation (LEV) and other HVAC methods, followed by Personal Protective Equipment (PPE) and administrative controls.

7.4 Psychrometrics

7.4.1 Introduction

Psychrometrics is the science involving the properties of moist air (a mixture of dry air and water vapor) and the process in which the temperature or the water vapor content of the mixture are changed. A psychrometric chart is used to identify conditions of air and to illustrate the process of achieving the desired state of the controlled space. For further information, see Appendix 1. See sources such as the ASHRAE Fundamentals Handbook (Reference 22, Appendix 12) for a detailed discussion. This section contains a high level overview of psychrometrics.

7.4.2 Basic Properties of Air

Dry air is normally comprised of 78.1% nitrogen, 21% oxygen, and has trace amounts of 10 additional elements totaling 0.9%. Air is normally a mixture of dry air and water vapor. When moist air reaches a level at which it cannot hold more moisture, it is said to be, “saturated.” The colder the air, the less moisture it can hold. Warmer air can hold larger quantities of moisture.

The moisture in air (its specific humidity) is measured in:

- grains of moisture per pound of air (7,000 grains equal 1 pound)
- grams of moisture per kg of air (SI units)

Air at 75°F (24°C) and 60% RH has a specific humidity of 78 grains of water per pound (7000 grains) of dry air (11g/kg).

A psychrometric chart (see Appendix 3) provides an overview of thermodynamic properties of air-water mixtures. If any two properties of the air mixture are known, the chart allows an engineer to determine its remaining properties. Air-water vapor mixtures have interrelated psychrometric properties that can be plotted on the chart. The values on the chart are for a given barometric pressure (usually assumed to be at sea level); the values will be different at substantially different elevations.

Sensible (dry) heat causes a change in the temperature of a substance. Sensible heat can be “sensed” or felt and quantified by measurement with a dry bulb thermometer. Addition or removal of sensible heat will cause the measured air temperature to rise or fall.

On the psychrometric chart, sensible heat shows as temperature, as a horizontal line with a scale increasing from left to right. As mixed air is heated with only sensible heat, there is no resulting change in the **amount** of water vapor in the air.

Latent heat is the heat of vaporization carried by the moisture in the air/water mixture. Changes in latent heat are not detected with a dry bulb thermometer. The addition of water vapor to air may increase the humidity of the air without changing the temperature of the air, for example:

- If sufficient latent heat is added to water in its liquid state, it will change state into a vapor (or steam) by evaporation:
 - The change of state caused by heating a liquid to steam is called the latent heat of vaporization.
 - The change of state caused by cooling from a steam to a liquid is called the latent heat of condensation.
 - The change of state from a liquid to a solid (ice) is called the latent heat of fusion.
 - The change of state from a solid to liquid is called the latent heat of melting.

Latent heat (mass of water per mass of dry air) appears on the psychrometric chart as horizontal lines on a vertical scale.

RH is the amount of moisture in the air versus the air’s capacity to hold moisture. As warmer air can hold more moisture, sensible heating of air reduces the RH, and vice versa. Generally, at room temperature, it is assumed that each degree Fahrenheit change in temperature will yield a 2% change in RH. RH is a useful measure as it is related to the vapor pressure of water in the air, and therefore, reflects the tendency of water (in its liquid state) or moist surfaces to lose moisture to the air. Human comfort is more closely associated with RH than specific humidity, because of this drying effect on skin and mucus membranes.

7.4.3 *Psychrometric Properties of Air*

See Appendix 3 for a discussion of the terms used in Psychrometrics and for an explanation of the Psychrometric Chart.

Appendix 2

HVAC Applications and Equipment

8 Appendix 2 – HVAC Applications and Equipment

8.1 Equipment

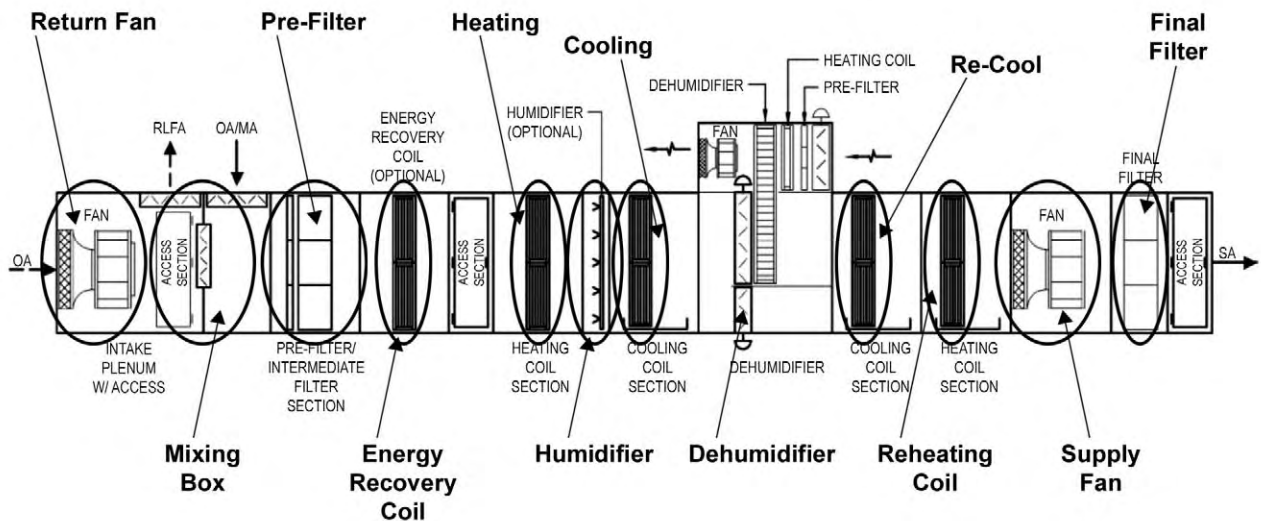
8.1.1 Introduction

HVAC equipment helps to meet the user requirements for room environmental conditions. HVAC equipment serving GMP areas is intended to work in conjunction with associated controls and sequences of operation systems to:

- maintain room temperature
- maintain room pressurization and DP relationships; therefore, assisting in the prevention of contamination and cross-contamination
- minimize airborne contamination delivered to the conditioned space by HVAC systems
- provide make-up air for ventilation and room pressurization
- maintain RH by adding to or removing from the moisture content of the air
- provide required air flow volumes to maintain room cleanliness classification and recovery rate, when required

Figure 8.1 illustrates the possible arrangement of components in an HVAC system for a draw-through, recirculating air handler (draw-through theory is discussed in Appendix 1) with nearly all possible components. (Note that the arrangement is not considered preferable; it is for illustration only.)

Figure 8.1: Air Handler Unit Components



8.1.2 Air Handling Unit

An Air Handling Unit (AHU) is an equipment package that includes a casing box (usually metal), a fan or blower, heating and cooling coils, air filtration, etc. to provide HVAC to duct systems and then to a building. Access doors or panels are usually provided for maintenance of each component (not shown in Figure 8.1).

8.1.3 Fan

A fan is a driven air moving device used to supply, return, or exhaust/extract air to or from a room through ductwork to move air in sufficient amounts to provide ventilation, heating, or cooling or to overcome room air pressure losses.

8.1.3.1 Supply Fan

Air handlers have a supply fan to provide the motive force to distribute air throughout an HVAC system.

8.1.3.2 Return Fan

Most large recirculating air systems use a return air fan. This fan allows return duct pressure and flow to be managed independently from the supply. This is particularly important if the duct system has volume controllers on both the supply and return (such as for controlled supply air volume and room pressure control). It also allows the return air to be diverted to exhaust when outside air conditions are closer to desired discharge conditions than return air (economizer cycle) or when return air contains flammables. An “economizer” generally is employed only in offices, some laboratories and warehouses, or other spaces that are not pressure controlled.

8.1.4 Mixing Box

Common in recirculating air systems, the return air is mixed with outside air for pressurization and fresh air ventilation. The resulting air stream is referred to as mixed air. In very cold environments, the mixed air may “stratify” and not mix well with return air, leading to errors in temperature readings and potential for partial freeze-up of heating coils (even a steam heating coil can freeze). An internal turbulence-inducing device (air blender) can assure thorough mixing and avoid temperature stratification.

8.1.5 Energy Recovery Coil

Once-through air systems, or other systems with high amounts of expensive exhausted air, may employ an energy recovery coil to return a portion of the energy lost in the exhausted air to the incoming air. These coils typically are upstream of other supply air conditioning coils, and may be placed upstream of the intake air filters to melt snow in cold climates. These systems also may employ a bypass damper to decrease pressure drop caused by the coil when energy recovery is not advantageous.

8.1.6 Fume Exhaust/Extraction System

This is a system made up of ductwork, fans, and possibly air cleaners (filters, dust collectors, scrubbers, carbon adsorbers, etc.) that discharges unwanted or contaminated air to the outside atmosphere to a safe distance to avoid re-entrainment of exhausted materials in other HVAC systems, and to avoid exposure to people.

8.1.7 Heating Coil

A Heating Coil is a heat transfer device consisting of a coil of piping, covered with heat-transfer fins, which increases the sensible heat transfer into an air stream, using steam, hot water, glycol, or sometimes hot refrigerant gas as the heating medium. An electric air-heating element also can be called a “heating coil.”

8.1.7.1 Preheat Coil

Once-through air systems or other systems with high amounts of cold outside air may employ a preheat coil to condition the incoming or mixed air. These coils are positioned upstream of cooling coils to protect them from freezing and may be placed upstream of the filters to melt airborne snow. As these coils do not typically impose a large pressure drop, a bypass damper is not common. Care should be taken to avoid freezing preheat coils if the temperature of the air mixture entering them is below freezing. In warm weather, the coil’s heating is turned off.

8.1.7.2 *Reheat Coil*

Systems that require over-cooling for humidity control (in place of desiccant dehumidification) also may employ a reheat coil to avoid overcooling of the space. By heating air leaving cooling coils, reheat coils decrease the RH of air leaving the AHU to avoid condensation in air filters or in the ductwork.

8.1.8 *Cooling Coil*

A cooling coil is a heat transfer device consisting of a coil of piping, covered with heat-transfer fins, which reduces the sensible heat and possibly latent heat (via condensation of water vapor) in the air stream using chilled liquid or refrigeration gas as the cooling medium. Cooling to maintain environmental conditions is common in pharmaceutical applications. Cooling coils may be located upstream or downstream of the fan (draw-through versus blow-through). A cooling coil is a common method of lowering air humidity; therefore, air velocity and drainage from these coils are key design issues. Mist eliminators may be employed to eliminate carryover of liquid water droplets that condense on the coil. These coils impose a large pressure drop, but a bypass damper (used when cooling is not needed) can add a risk of unconditioned air leakage around the coil when maximum cooling is needed.

8.1.8.1 *Re-cool Coil (Post-cooling Coil)*

These coils may be installed downstream of desiccant dehumidifiers to eliminate excess sensible heat in the supply air. They may provide additional dehumidification downstream of a condensing cooling coil, operating below chilled water temperature using a refrigerant or a low temperature brine (typically water and glycol (ethylene or propylene)). Mist eliminators may be employed on these coils. Coils operating at sub-freezing internal temperatures can eventually ice over, and an alternation bypass/de-icing scheme is normally needed.

8.1.9 *Humidifier*

Humidifiers increase the humidity within a controlled space by the discharge of water vapor (steam or water mist) into a supply air stream or directly into a room. Systems in cold or arid climates may employ a humidifier to inject water vapor to increase the moisture level of the air supply. These devices typically are downstream of the preheating coil, and may be mounted in ductwork where air turbulence and high velocity promote absorption of water vapor. When employed in an AHU, mounting upstream of a cooling coil provides a natural baffle to prevent carryover of liquid water droplets, as it is unlikely that both humidifier and dehumidification through cooling will be in use at the same time.

Generally, the water source is steam, potable water, or demineralized water (produced via reverse osmosis (RO), ion exchange resins, or distillation) that will not introduce objectionable contaminants into a room. It is common practice to use steam that is free of volatile additives in pharmaceutical manufacturing HVAC systems. Volatile additives that meet USP (Reference 31, Appendix 12) requirements can be considered, allowing direct use of plant steam in pharmaceutical manufacturing HVAC systems. Plant steam (which may contain amines or other volatile additives, necessary to prevent corrosion in steam piping) frequently is used for non-production spaces.

Facilities may use clean steam, generated from USP purified water or Water For Injection (WFI) (also called pure steam) for humidification. This practice is considered wasteful, as steam of adequate cleanliness for classified spaces may be obtained from copper, brass, or stainless steel re-boilers fed with water of adequate quality and heated by higher pressure plant steam. However, it may make sense to use clean steam if it is the most readily available form of steam. Maintenance should be considered, as purified steam or steam free from additives can corrode piping. Softened or demineralized water are commonly used for this service, as minerals in potable water can be left behind in the steam generator.

Water mist humidifiers are usually fed with deionized or purified water to prevent the carryover of dissolved mineral solids into an air stream. When a humidifier is not in use, additional care is required to prevent growth of bacteria in an unprotected water system.

It is common practice to install a length of welded, liquid tight stainless steel (or other corrosion resistant) ducting downstream of in-duct humidifiers to prevent damage and rust from condensation. Generally, duct humidity should be kept significantly below saturation level; 80% RH is a common upper limit.

8.1.10 Dehumidifier

A dehumidifier is a device that removes water vapor from the air to reduce humidity, either by condensation of water vapor from the air using a cooling coil or by absorption or adsorption using a desiccant (when room RH below 30 to 40% is required). Desiccant dehumidifiers often are located downstream of a cooling coil that removes much of the moisture challenge at lower energy cost and increases RH to increase desiccant efficiency. However, care should be taken to assure saturation or carryover of liquid water droplets does not damage the desiccant.

The choice of desiccant depends on the application. Desiccants are regenerated using heat; therefore, air leaving the dehumidifier is both drier and hotter than upon entering. A re-cooling coil may be needed. It may be necessary to keep the wheel regenerated even when dehumidification is not needed to prevent damage to some desiccants. Appropriate expertise is required to design and commission the control of desiccant dehumidifiers. Manufacturers should be consulted before attempting a dehumidification control scheme.

8.1.11 Air Filtration

Air filters remove particulate material from an airstream by means of various media types. Pre-filters typically are provided upstream of coils in an air handler to protect the coils from fouling with dirt or debris. Pre-filters use low efficiency dust stop filters followed by a medium or high efficiency intermediate filter. For further information, see Chapter 2 of this Guide.

Air filters of activated carbon or other materials may be used to absorb some vapors. This is common where objectionable aromas or small quantities of volatile organics need to be decreased.

8.1.11.1 Final Filter

Filters may be provided as the last air treatment step in an air handler. The use of high efficiency filters (typically 95% DOP or HEPA) can assure air quality (with reference to particles) inside supply air ductwork and can protect terminal (ceiling mounted) filters from fouling with dirt or debris; therefore, extending the life of the terminal filters and preventing differential blinding. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).

In systems without terminal filtration, final filters in AHUs can provide adequate filtration, perhaps for some classified spaces, as long as ductwork is clean. High efficiency final filters are more commonly used in systems that employ fan drive belts that shed particulate into the airstream.

8.1.12 Ductwork

This is a network of air conduits distributed throughout a building, connected to a fan or AHU to supply, return, or exhaust/extract air to or from zones and rooms in a building. These ducts may be constructed of metal, plastic, building construction materials, fiberglass boards, or a combination of these materials. Metal ductwork is recommended for most pharmaceutical applications.

8.1.13 Damper and Louver

8.1.13.1 Damper

A damper is a valve for controlling airflow in ductwork, which consists of a movable element plate, plunger, or bladder that opens and closes to regulate airflow. Dampers may be used to regulate airflow to and from specific rooms (to "balance" airflow) and to control fresh air or return air to the AHU.

8.1.13.2 Louver

A louver is an assembly of sloping vanes, usually fixed in position, intended to permit air to pass through, while inhibiting passage of water droplets from outdoors into air systems. A louver also may be found in return air ductwork at room interfaces.

8.1.14 Diffuser, Register, and Grille

Air distribution inlet or outlet grilles are composed of a combination of blades, plates, or vanes intended to direct airflow entering or leaving a space in a desired pattern. Grilles generally are characterized by their pattern of distribution from 1 to 4 directions (single or double 'deflection' grilles are common) and projection distance at a given airflow (the throw).

Registers are grilles with an added airflow control damper close coupled to the concealed side.

Diffusers are air outlets, assembled from a series of vanes and plates, generally designed to mix supply air with room air to minimize drafts and maximize dilution. An exception is the non-aspirating diffuser, which is designed to provide equal velocity of discharge in all directions with minimal mixing. Diffusers, like grilles and registers are characterized by their discharge pattern, which can be from 1 to 4 directions (1 to 4 way blow). Air diffusers are usually found at ceilings and located to distribute the air as uniformly as possible throughout a space.

8.1.15 Ultraviolet Light

Ultraviolet (UV) lights (a form of ionizing radiation) at 254 nm may be employed in an airstream to disrupt microorganisms. The energy flux required to achieve destruction at typical duct or AHU velocities is prohibitively high, because of the relationship between the energy level and exposure time needed for this purpose. UV lights may be mounted in conjunction with filters to increase exposure time; however, this is considered of little value in pharmaceutical HVAC systems.

Table 8.1: System Components and Their Influence on Environmental Parameters

Equipment	Temperature	Humidity	Room Static Pressure	Airflow Rate	Air Cleanliness
Air Handler	X	X	X	X	X
Fan (Supply and Return Air)			X	X	
Fume Exhaust/Extract Systems				X	X
Heating Coil	X				
Cooling Coil	X	X			
Air Filter					X
Humidifier		X			
Dehumidifier		X			
Ductwork			X	X	
Damper and Louver				X	
Diffuser and Register				X	
UV Light					X

8.2 HVAC System Configuration

8.2.1 Introduction

This section gives a brief overview of the key factors to consider, the options available in HVAC system design, and the factors influencing decisions to choose a particular system type.

This section should be read in conjunction with Chapter 3 of this Guide.

8.2.2 Number of Air Handling Units

A manufacturing area often is into zones with a separate AHU is used for each zone. In the pharmaceutical industry, a zone is usually considered to be an area with one type of manufacturing process or area cleanliness classification, e.g., a tablet compression suite in an oral solid dosage facility or all classified areas for aseptic product. When dividing a facility into zones, advantages include:

- Use of multiple AHUs improves reliability of the total area; it would be unusual for all zone units to fail. If one unit fails, other zones may continue to operate.
- The use of multiple smaller AHUs may make air balancing (commissioning) easier and reduce the need for automated balance or pressure controls.
- Total energy costs may be lower, as each zone uses only what it needs and may be turned down to use much less energy if idle, without the use of automated balancing controls.
- The use of multiple smaller AHUs allows the main distribution ducts to be smaller, and therefore, easier to route in smaller ceiling voids.
- Modifications to parts of a facility should be easier. Upgrades to a small AHU serving a single zone should be easier than changing a large single AHU, which serves many zones, without automated balancing controls.
- The use of multiple AHUs allows easier separation of areas within a multi-product concurrent manufacturing plant. The potential for cross contamination of products via the HVAC system is minimized, hazardous materials can be isolated, and upstream processes for a single product can be isolated from those downstream. Air filtration also can address this issue.

Disadvantages include:

- If once-through air is desired for all zones, there is less justification for more zoning of AHUs to reduce risk of cross-contamination between products. A single large system may be sufficient (see Figure 8.2).
- If an automated air balancing control system is employed, most of the advantages are offset by the ability of the control system to manage system changes.
- Increased initial cost, (more of the same controls for more systems).
- Increased maintenance (more labor, more parts, more protocols)

The decisions regarding AHU system zoning are important factors in subsequent facility commissioning, qualification, and related documentation. The decisions for zoning should be based on risk to product and to operators, taking into account the preferred air filtration and monitoring technology.

8.2.3 Basic System Types

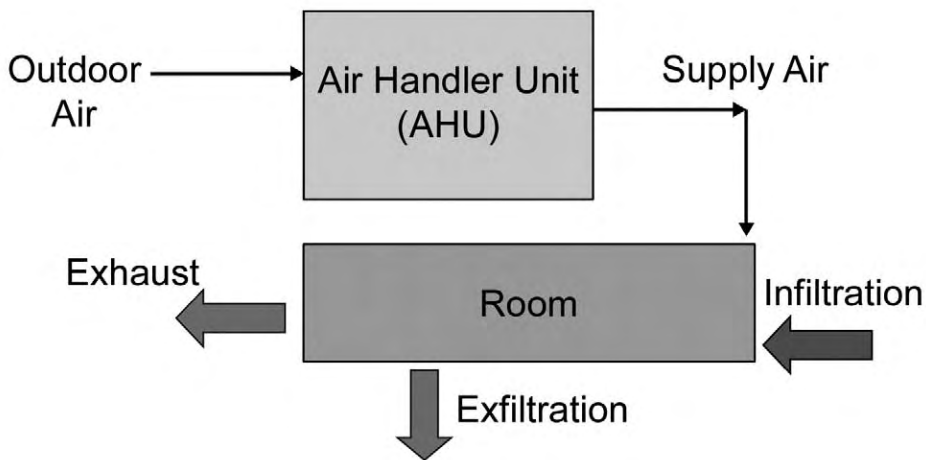
There are three basic categories of HVAC system:

1. once-through
2. recirculated
3. exhaust/extract systems

8.2.3.1 Once-Through HVAC Systems

Once-through HVAC systems supply treated outside air to satisfy the design conditions for a space. This air is then extracted from the space and exhausted to the atmosphere.

Figure 8.2: Once-Through HVAC



Advantages of this system:

- This system provides an abundance of oxygen rich fresh air to dilute contaminants and assure the health of personnel.
- The system can handle hazardous materials without recirculation into supply air; however, the extracted air may need treatment before it is discharged to the atmosphere.
- Lower risk of cross contamination of products from another room, via HVAC system ducting
- Exhaust fans may be located remote from the AHU making exhaust duct routing simpler.
- As there are fewer concerns about noise in the extract ductwork, it can usually be sized for a high velocity and smaller diameter, making it easier to route. Higher velocity also may be necessary to convey powder materials to an air cleaner device before discharge to the atmosphere; however, higher velocity requires disproportionately more energy to achieve.

Disadvantages of this system:

- More expensive to operate than an equivalent recirculating system, particularly when cooling and heating. Energy recovery often is justifiable.

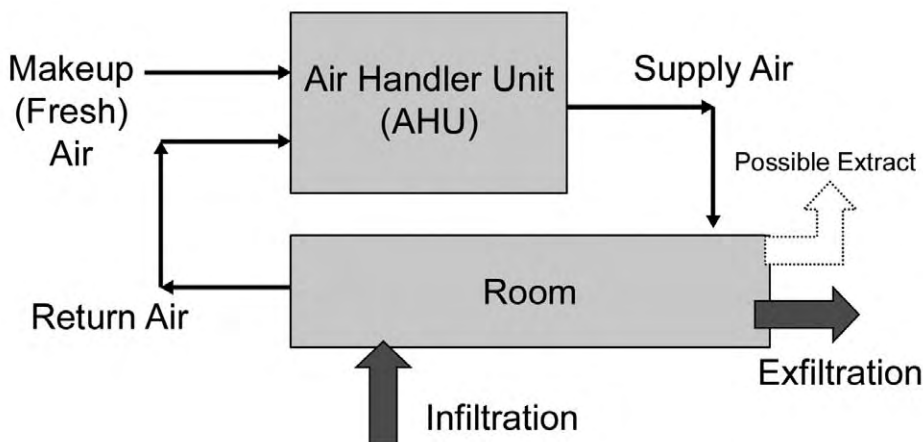
- Air Filter loading will be very high leading to frequent replacement.
- Potential need for air treatment (e.g., scrubbers, dust collectors, filters) for exhausted air contaminated by the process.
- Room conditions may be more difficult to control as the system needs to be sized to handle extreme outdoor air conditions, but may operate most of the time under much less load.

8.2.3.2 Recirculating Systems

This system type is widespread; the room supply air is made up of a portion of treated outside air mixed with some of the air returned from the space. An equivalent portion of the air supplied to the room is either discarded (e.g., exhaust from a containment isolator) or lost through leakage to adjacent areas, due to local area pressurization. The amount of outside air is driven by:

- IAQ requirements (see ASHRAE 62) (Reference 22, Appendix 12), about 20 CFM (35cuM/hr) per occupant
- the need to offset exhaust from the area
- the need to provide excess air to pressurize the area

Figure 8.3: Recirculated HVAC



Advantages of this system:

- A smaller range of challenge to HVAC systems may result in better control of parameters (e.g., temperature or RH), as heating/cooling equipment may be smaller and may not need to handle as large a heat range as a once-through system.
- Usually, less AHU air filter loading is required; therefore, less filter maintenance is required, and there is an opportunity for higher grade air filtration at a lower replacement cost.
- Usually, lower heating/cooling energy cost than once-through air systems.
- A single once-through AHU may pre-treat outdoor air for numerous individual recirculated systems, concentrating pre-heating and humidity control in one unit, with potential energy savings.

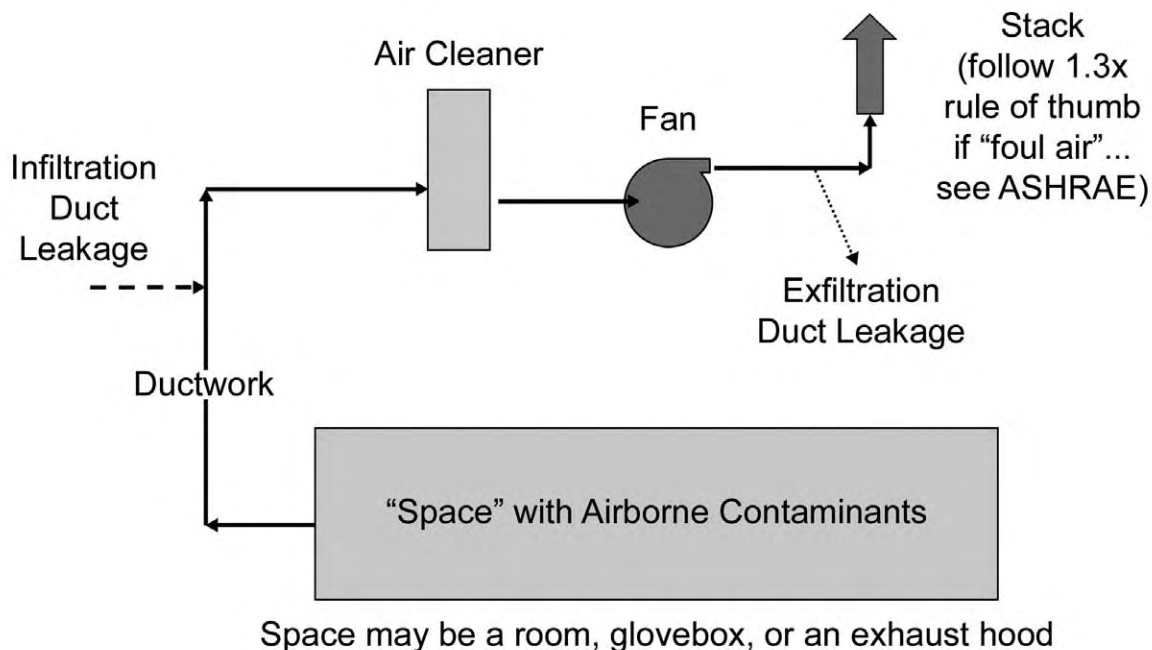
Disadvantages of this system:

- Return air ductwork routing back to the AHU may complicate congestion above ceiling and make duct chases larger.
- Potential for cross contamination, via the HVAC system. Requires adequate supply air filtration (and sometimes return air filtration to prevent contamination of the AHU).
- Potential for recirculation of odors and vapors. Poor design may result in inadequate fresh air supply for the health of personnel and room pressurization.

8.2.3.3 Exhaust (Extract) system

Exhaust systems may be stand-alone systems that remove airborne contaminants, either solid particles or gasses/vapors, from a work space. They may be interlinked to a once-through or recirculated air supply system. Used alone, the extract/exhaust system will create a negative DP in a room or space, drawing in air from the surroundings.

Figure 8.4: Exhaust System



Advantages of this system:

- Simple to operate. Makeup air for the fan is pulled from surrounding spaces.
- It can be used to draw fresh air into an unventilated building, such as a warehouse, that does not require heating or cooling.

Disadvantages of this system:

- If used to capture large quantities of contaminants, such as from open processes, high energy costs will be associated with conditioned air being discarded (see once-through system above). Exhaust system energy is greatly reduced if emissions from processes are contained within process enclosures.

- If exhaust air is not adequately cleaned, stack height and velocity should be adequate to prevent re-entrainment in HVAC systems and to prevent personnel hazards. See ASHRAE Fundamentals Handbook. (Reference 22, Appendix 12).
- Temperature and humidity are influenced by the surrounding area.

Detail about design of operation of exhaust and dust collection systems is provided in Chapter 5 of this Guide.

8.2.3.4 *Use of Air Handling Units in Parallel or Series*

AHUs may be placed in series, e.g., if a higher air pressure is required to offset the pressure drop through HEPA filters in ductwork to just one area served by the primary HVAC system. Normally, the boost is accomplished just with an inline fan. A common series configuration uses an AHU to precondition outdoor air as makeup air to one or more 'local' AHUs downstream. This minimizes or eliminates condensation at local AHUs, simplifies installation, and saves energy at the local AHU(s). Controls are needed to balance 'over-feeding' preconditioned air to downstream units.

The use of parallel AHUs is common practice where large areas are being conditioned, e.g., warehouses and large research laboratories. This approach increases reliability allowing acceptable conditions in the area to be maintained if one unit fails or when the load on the system is light. A parallel configuration may permit the use of multiple "package" AHUs instead of one large "custom" AHU, a common practice when the project must proceed quickly or at low cost.

Parallel fan installations may be configured for 100% or reduced redundancy. In a 100% redundant installation, multiple fans are installed in parallel, the fans are sized to be capable of meeting the entire load with one fan out of service. These fans commonly are alternated or run at reduced capacity.

In a reduced redundancy system, the multiple fans are capable of less than full capacity with one fan out of service.

As duct pressure drops with a reduction in flow, each fan in a reduced redundancy system will deliver more airflow with one fan out of service than with all fans running.

Example

A system with 2 fans each capable of delivering 50% of flow at design pressure may deliver as much as 70% of design capacity with one fan out of service because of a reduction in static pressure. When configuring units in parallel serving one duct system, care should be taken to assure that the fans can be isolated and started independently and that air does not flow backward through the idle unit. Automatic isolation dampers and variable fan drives assist in managing these factors.

8.2.3.5 *Series Configuration for Outside Air Pretreatment*

In recirculating air systems, a separate, series air handler may be used to pre-treat incoming outside air rather than overcooling or chemical dehumidification of an entire recirculated air stream. This is a common configuration, particularly where the outside air condition represent all or most of the latent load addressed by a system (e.g., in the tropics). In its most economical application, a central pre-conditioning unit may serve multiple recirculation systems.

This configuration has limitations and it may not be suitable for all applications. For further information, see Chapter 2 of this Guide.

8.2.4 **Air Handling Unit Configurations**

There are two basic types of AHU configuration:

1. blow-through

2. draw-through

The term describes the relationship of the fan to the coils inside an AHU. The two configurations have distinct characteristics.

8.2.4.1 Blow-Through Units

In blow-through units, air is drawn into the AHU, typically through a set of pre-filters, which are used to reduce the dirt load on the (usually more expensive) final filters, and to prevent build up of dirt on the heating and cooling coils, which would rapidly reduce their efficiency.

Advantages:

- It allows the AHU discharge temperature to be at the cooling coil discharge air temperature, because the fan heat is removed in the cooling coil. This is particularly useful when heat loads are particularly high. Supply air temperature should be as cold as possible. It is not advisable to follow a blow-through AHU immediately with a set of HEPA filters, unless special precautions are included to prevent moisture carryover from the cooling coil to the HEPA filters.
- If the drain trap on the cooling coil runs dry, then some treated air will blow out through the trap, but not allow contaminants to enter the AHU through the trap.

Disadvantages:

- The unit typically needs to be longer to allow a diffuser (that has some pressure drop) to be installed after the fan to ensure that the airflow is spread over the entire face area of coils and downstream filters, and not concentrated on the middle, which would cause a drop in coil and final filter performance.
- Air leaving the cooling coil may be saturated with moisture that could collect on final filters is a potential disadvantage. The draw-through fan of an AHU provides some 'reheating,' reducing the airflow humidity.

8.2.4.2 Draw-Through Units

Draw-through units typically are arranged with the pre-filters and coils before the fan.

Advantages:

- The unit is often smaller, and the motor and fan provide a small amount of reheat (usually 1 to 2°F, 1°C) to the air coming off the cooling coil. This lowers the RH of the air and prevents the problems with wetting final AHU HEPA filter banks.

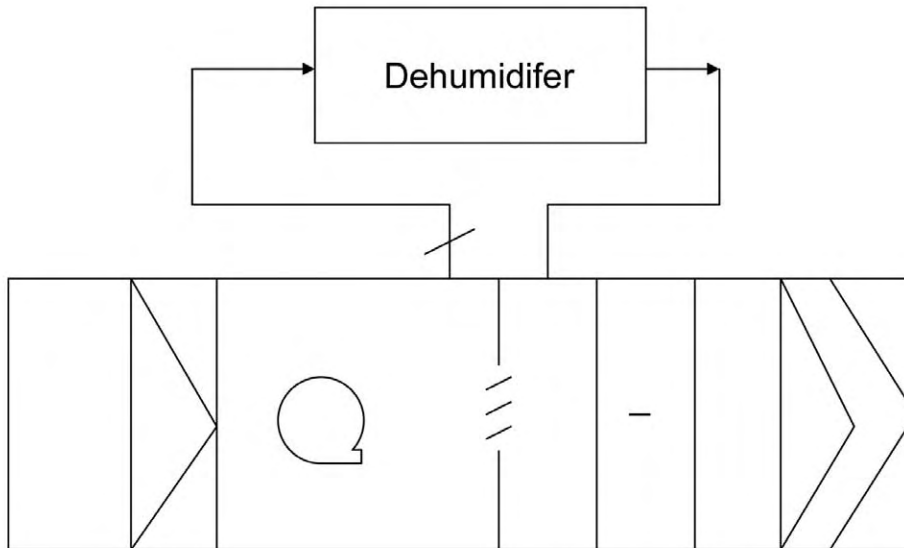
Disadvantages:

- If the drain trap is dry, then untreated air can be drawn into the unit through the trap. The cooling condensate trap design should include provision for charging and maintaining a wetted drain trap, which can be several inches in height; therefore, raising the AHU above the floor.

8.2.4.3 Air Handling Unit Design Variations

A face and bypass damper to direct a portion of the air stream for further treatment should be considered. The concept is shown in Figure 8.5, using a desiccant dehumidifier and varying the bypass volume to vary the condition of the resulting re-mixed air. This approach helps to achieve more precise control of a parameter, particularly when it is not easily controllable. It can be used in either blow-through or draw-through AHU configurations. When using a face and bypass system, care should be taken in the design of airflow controls to assure the desired flow from the system to the process rooms.

Figure 8.5: Face and Bypass Control with a Packaged Dehumidifier and Cooling Coil



A similar concept often is employed in the first mixing box of the AHU when “enthalpy control” is used. Careful selection and sizing of the dampers is necessary to achieve the correct operation of these systems, both to ensure adequate control and to maintain constant system volume as the proportions of the air streams are varied.

8.3 Pressure Control Strategies

8.3.1 Airflow Direction or Measurable DP?

GMPs for classified spaces, such as EMEA Grade B or FDA ISO7/Grade 7, require a measurable DP between cleanrooms and adjacent less clean spaces, in the order of 10 to 15 Pa (0.04 to 0.06 inch wg) DP between air classes. Airlocks can prevent DP between air classes from dropping to zero when doors are opened between the classes.

Products in rooms that are not classified may be protected by measurable DP or by airflow velocity and direction that cannot be measured with traditional DP instrumentation.

Oral solid dosage facilities and laboratories often are protected by airflow patterns between rooms that can be verified by “smoke testing” or by calculating the offset between supply and return/exhaust airflow, taking into account the measurement accuracy.

When DP sensors and airlocks are used, satisfactory protection can be achieved at the lowest range of current DP sensor technology. An outward airflow of 100 to 200 ft/min (0.5 to 1 m/sec) can keep airborne particles from passing through an opening. The DP needed to create this velocity (< 1 Pa) is lower than current DP sensor accuracy (in the range of +/- 0.005 inch or +/- 1.2 Pa). If a DP sensor is used for non-classified spaces; therefore, a DP reading of greater than the instrument accuracy is justified (usually 2 Pa minimum DP or more commonly 5 Pa, which also satisfies recommendations in WHO 937) (Reference 2, Appendix 12).

8.3.2 Automated Differential Pressure Control

There is no GMP requirement that DP or airflow direction be automatically controlled (such as by using actuated dampers or CV devices). Satisfactory designs using “static” air balance to achieve desired DP values are common in the pharmaceutical industry and are successful because:

- Airflow to the room is constant:
 - Terminal HEPA filters do not load very quickly, because they are preceded by a protective (GEP) high efficiency filter in the air handler.
 - If CV devices can also keep airflow to each zone constant; however, this adds a level of complexity.
- There are no significant variable flows for air leaving the room:
 - There are no on/off extract systems.
 - Door seals and pass-throughs are diligently maintained so leakage through them is constant and pressure degrades very slowly (within scheduled HVAC maintenance intervals).

For further information, see the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).

8.3.3 Airlocks

The primary role of airlocks is to provide an effective obstacle to airborne contamination.

In order to minimize the amount of air that is needed to maintain airborne particle transport velocities (usually greater than 100 fpm or 0.5 m/s), the doors of a contamination controlled space should remain closed. An open door of 21 square feet (2 square meters) area would need a very high airflow through it (i.e., 2100 CFM, 3500 CuM/hr) to contain airborne particles. A closed door of 21 square feet (2 square meters) area may need less than 100 CFM (160 CuM/hr) leaking through only its cracks to keep particles out. One way to reduce the need for high velocity flow through the open door is to provide airlocks or 'ante rooms.' These rooms control traffic into and out of a space through a series of doors.

An interlocking system or a visual or audible warning system is recommended to prevent the opening of more than one door at a time, (required for sterile facilities by EU GMP Annex 1) (Reference 4, Appendix 12). The closed door provides a very small area for airborne particle passage and therefore, needs a smaller airflow to keep particles out.

Airlocks also may:

- maintain a DP between the two areas, avoiding low DP alarms
- Provide a location for gowning or de-gowning prior to entering or upon exiting a classified space (the EU GMP Annex 1 (Reference 4, Appendix 12) refers to changing rooms as airlocks). (Two or more airlocks in series may be used for "staged gowning." See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Be designed with a small volume. They may have a modest airflow, but still have a high air change rate to allow them to recover quickly from high airborne particulate levels; therefore, minimizing the contamination introduced into the clean space when a door is opened. This principle is exemplified by the EU GMP Annex 1 Manufacture of Sterile Medicinal Products (Reference 4, Appendix 12) requirement that: "The final stage of the changing room should, in the at-rest state, be the same grade as the area into which it leads." The basic concept seems clear; the airlock should recover to particle counts low enough that, when the door to the cleaner room is opened, airborne contamination carried from the airlock does not affect airborne contamination levels in the cleanroom. See the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- Provide a location for sanitizing/decontamination of incoming or outgoing materials and equipment (material or equipment pass-through, Material Air Lock (MAL). Generally, material airlocks are larger, but may have lower air change rates as the equipment may sit inside the airlock for extended time and particle counts can gradually decrease.

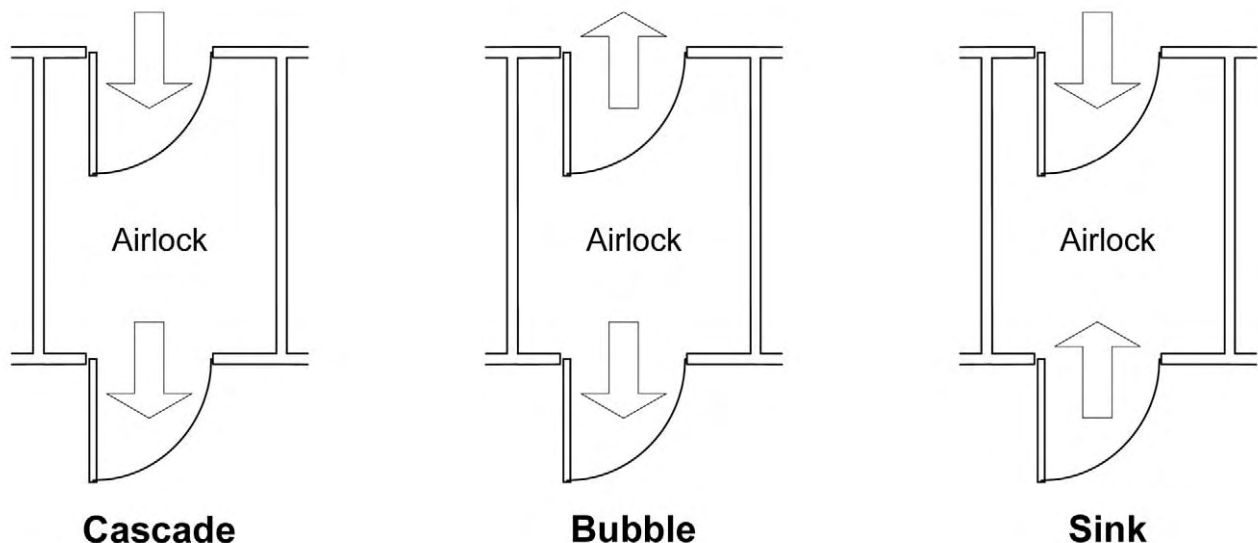
- Act as a high pressure or low-pressure buffer (anteroom) to control the ingress and egress of contaminants for special processes (usually oral dosage or hazardous materials).

Specific small material airlocks, called 'pass-throughs,' are too small for personnel use, but can experience high air change rates just from leakage through their access doors. For very clean rooms (Grade 7 or cleaner), pass-throughs should be ventilated with HEPA filtered air.

Many non-aseptic facilities have bi-directional airlocks, i.e., they are used for passage in, as well as passage out. HVAC system design should be similar to that for one-way airlocks, but more frequent air changes may be necessary if in and out activities are close together in time. For further information see the ISPE Baseline® Guide on Sterile Manufacturing Facilities. (Reference 13, Appendix 12).

Three types of airlock pressure arrangements are indicated in Figure 8.6:

Figure 8.6: Airlock Configurations



8.3.3.1 Cascade

The "cascade" pressurization scheme should be used when:

- there are area cleanliness classification requirements, but few containment issues
- there are containment issues, but no cleanliness classification requirements

(That is, cascade outward from the room for aseptic operations, but cascade into the room for hazardous early intermediates. The normal differential from one air class to the next (**across** the airlock) and from classified space to unclassified space is 10 to 15 Pa (0.04 to 0.06 inch wg). The pressure **inside** the airlock is somewhere between the two adjoining spaces, depending on which door is open. It is not necessary to have 10 to 15 Pa between a room and its airlock (see "Not required" in Figure 8.7). The pressure differential of a cascade airlock is measured across the airlock, not across each door. Therefore, when only one door of an airlock is opened, a measurable DP between the air classes persists.

Airlocks should have their own ducted air supply and/or return. (Unventilated airlocks are no longer used.) Airflow into a cascade airlock usually is equal to the return airflow leaving it, such that leakage through the doors creates the desired DP relationships. Supply air is introduced high at the 'clean' end of the airlock and returned low at the 'dirty' end. Air changes may be added with local fan-HEPA units at the cleaner end of the room, providing an "air shower"

effect over the operator passing into the cleanroom. Airlocks are common between Grade B and C (Grade 7 and 8) and are recommended for Grade C (Grade 8) to next lower class (Grade D, CNC, or unclassified).

8.3.3.2 Special Airlocks/Anterooms

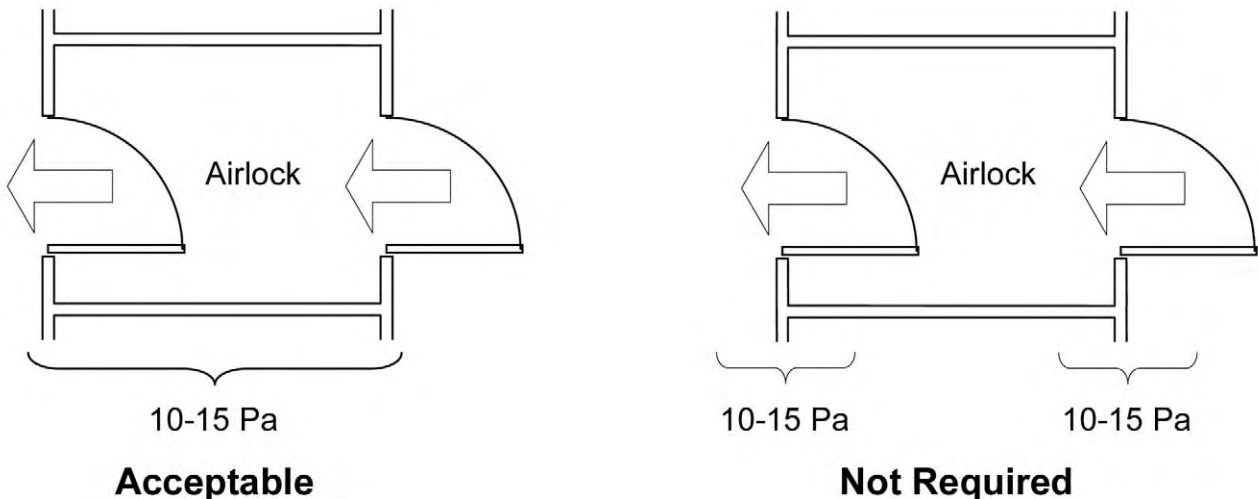
If there are requirements for both area cleanliness classification and product containment, the use of pressure sinks and bubbles (Figure 8.6) may be required. Pressure bubbles usually are used for 'uncontaminated operations' (e.g., gowning or material entry airlock) if used to contain a hazardous product. Pressure bubbles should meet the air classification of the cleaner room which they serve, as their air leaks into that room.

Product facilities that do not require measurable pressure differentials, such as oral dosage, some API, and laboratories, often do not have airlocks. Rooms with exposed hazardous materials could be isolated from the building by a bubble or sink. In terms of humidity control, low humidity areas could benefit from a low humidity pressure bubble anteroom.

Pressure sinks usually are used for 'contaminated operations' (e.g., de-gowning, material decontamination/exit airlock). The pressure differential in bubble and sink airlocks will drop momentarily while one door is opened; alarms and controls should be designed to take account of this. The pressure differential should not reverse.

For unclassified areas there is no requirement for DP, but if DP measurement is desired the minimum suggested pressure differential should be greater than the minimum reliably detectable by current pressure sensor technologies.

Figure 8.7: Example of Cascade Pressure Relationships



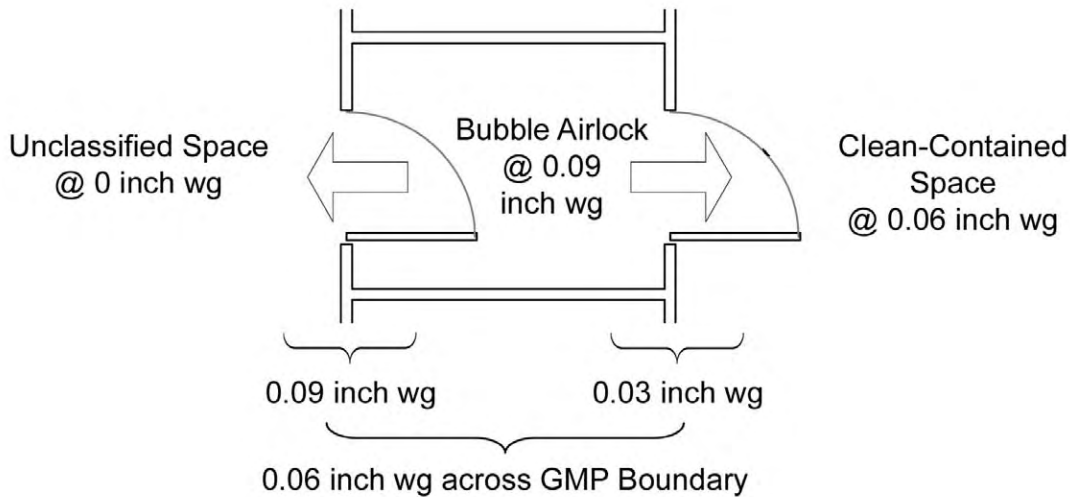
8.3.3.3 Positive Pressure Bubble

The normal design pressure target for a 'bubble' pressurization scheme, with doors closed, between room classifications should be 0.04 to 0.06 inch wg (10 to 15 Pa). The bubble should be at the same in-operation air class as the cleaner room it serves, because air exfiltrates to the classified room. There may be different pressure drops across each door because of building tolerances or adjacent room conditions, but this is not considered a problem.

If protecting unclassified spaces, a lower pressure difference is acceptable, but should be measurable. The pressure of the 'bubble' is usually designed to be about 0.02 to 0.03 inch wg (5 to 8 Pa (approx.)) above the higher of the two room pressures. Supply airflow to the bubble should be much greater than return airflow, which may be zero if there is sufficient leakage from the airlock to adjoining spaces.

The positive pressure airlock provides a robust means of segregating areas using positive airflow, as the velocity pattern of air passing through the crack extends farther from the crack than the velocity profile of air being pulled into the crack (see Figure 8.8).

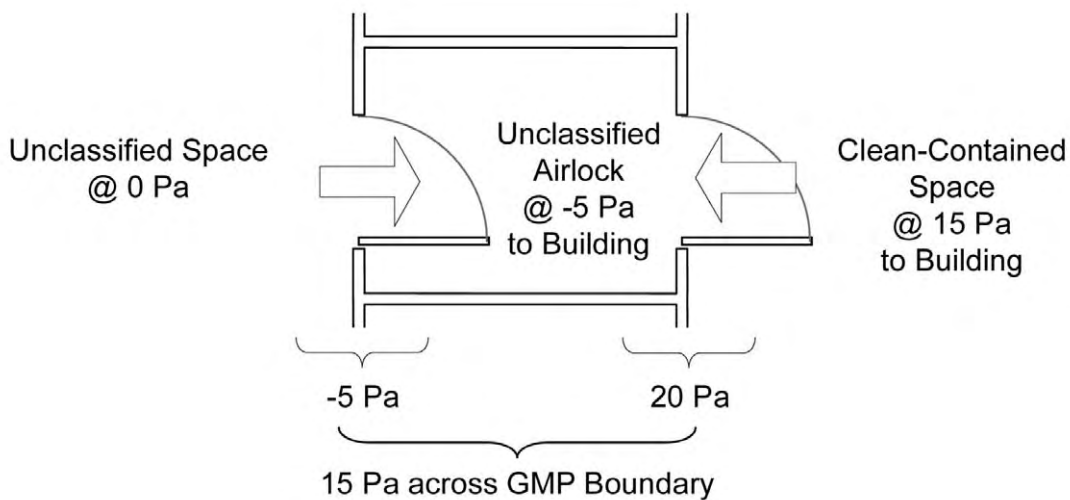
Figure 8.8: Example of “Bubble” Pressure Relationship for Sterile Product with Containment



8.3.3.4 Negative Pressure Sink

With the “sink” pressurization scheme, the normal design pressure between classifications should be 0.04 to 0.06 inch wg (10 to 15 Pa) with doors closed. As with a ‘pressure bubble,’ there may be different pressure drops across each door. The pressure of the contaminated airlock ‘sink’ usually is designed to be about 0.02 to 0.03 inch wg (5 to 8 Pa) below the lesser of the two room pressures. Although more air needs to be removed from the airlock than is supplied, supplying some airflow to the sink is recommended to facilitate quicker recovery from the contaminated state.

Figure 8.9: Pressure “Sink” Relationships



8.3.3.5 *Pass-Through Boxes*

A pass-through box is a very small airlock used for material transfer from one zone to another, such as from a Grade 7 area to Grade 5 or from a general area to a contained oral dosage area. Pressure cascades should follow the product requirements; for classified spaces, there should be a cascade from cleanest area downward. If high degrees of cleanliness or fast recovery are needed, ventilation (often with HEPA filtered air) is common.

8.3.4 **Determining DP and Air Leakage**

For operational reasons, it often is necessary to have pressure differentials between rooms within the same air class area. The minimum operational differential between areas of the same classification (where required) is suggested to be 0.006 inch wg (1.5 Pa) with a design target of 0.02 inch (5 Pa) as a minimum, because of limits of sensor technology. Directional air flows may be needed for operational reasons, without a measurable pressure differential, e.g., as found in non-classified areas, such as oral dosage manufacture.

Pressure relationships usually are not possible across open doors between air classes when no airlocks are present. Without the added protection (buffer) provided by the airlock, excessive airflow volumes would be required to maintain measurable DPs. When airlocks are not feasible, some airflow velocity through the open door is achievable (see Appendix 9).

Doors preferably should operate, such that the DP tends to keep them closed; however, area ergonomics and emergency egress requirements will influence this choice.

The airflow leakage rate should be calculated for each room. This calculation should be based on the known architecture and the design pressure differential established in the project documents. It should not be based on an arbitrary method, e.g., percentage of supply air.

The door perimeter (especially if silencers are employed without door gaskets) is the primary path of room air leakage; therefore, doors and door frames are critical components of the facility construction, as more leakage air would need to be designed into the system to obtain desired DP for doors with poor seals. The facility architect should be consulted to assure specifications are adequate and robust for the for pressurization requirements.

Door frames may include continuous seals to reduce the leakage, to maintain the desired pressure, as well as provide isolation in case of airflow failure. Doors may include a provision for operable floor sweeps that drop down as the door closes, but these may present cleaning problems.

Where double doors are used in the facility, gasketed astragals are suggested to minimize air leakage. Door grilles should be avoided, unless these are part of a pressure scheme without airlocks (see Appendix 9).

In Appendix 1, the method for calculating airflow to produce a desired pressure differential is discussed. A more detailed discussion can be found in Figure 14, Chapter 27 of the 2005 ASHRAE Handbook – Fundamentals (Reference 22, Appendix 12). Common practice is to design for a 1/8 inch (3 mm) average crack between the door and frame on sides and top, and .25 inch to .5 inch (7 mm to 15 mm) on the bottom. Note that corrections are to be applied for design pressure differentials using the formula contained in Figure 14. For further information, see the *Pharmaceutical Engineering* article by Manuel del Valle, “Airlocks for Biopharmaceutical Plants,” (Reference 15, Appendix 12) and the NFPA Smoke Control Handbook (Reference 29, Appendix 12).

The calculated room leakage may exceed the design air change rate for small rooms, e.g., airlocks. In these instances the total supply air to the space should match the calculated leakage. The design should allow for some return air from the space, in case the actual leakage is less than calculated. To avoid under-sizing return ducts, the return is often sized for 50% to 80% the supply airflow into the room. In applying this approach, care should be taken in sizing volume control (manual or automatic pressure damper, or CV box, if used) on the return air duct to ensure that the actual flow rate is within the operable range of the control device. A secondary manual balancing damper may be needed to allow the control damper to function within a greater proportion of its operating range.

It is considered GEP to put a tighter specification on the supply air volume (which is more critical to maintain the room conditions) and a broader design range on the return air flow; the value needed to maintain desired DPs.

8.3.5 DP Measurement

Two methods of measurement are commonly used to monitor room pressure relationships;

- room-to-room
- room-to-common reference point

Larger facilities needing to record numerous pressure differentials usually use the common reference point method to minimize the number of pressure sensors and to minimize compounded error from a number of pressure readings added together. One port of the DP transmitter (often the “High” side) is piped to the room being monitored and the other side (often the “Low” side) is piped to a common reference in (or via a header connection to) a pressure-stable location not under the influence of outdoor wind.

The size of the pressure reference piping can be small, because the flows are very small; the only effect of pipe sizing is to slow the progress of pressure waves.

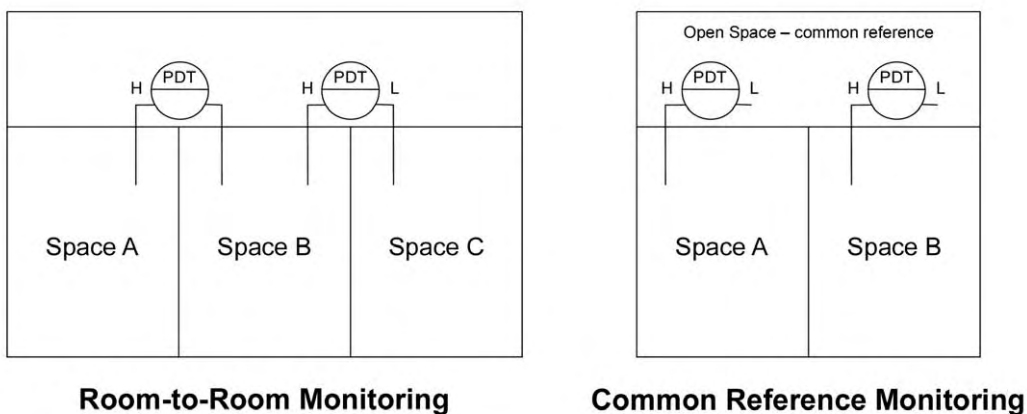
The ideal pressure reference location has a large volume, few openings, and an unvarying or slowly changing pressure relationship to the outdoors, for example:

- mechanical equipment rooms
- the interstitial space above all the pressurized rooms (without thermostatically controlled ventilation)
- an open general building space that adjoins the pressurized suite (such as a large hallway with few doors to create pressure differentials in the hallway)

Areas that experience changes in pressure due to HVAC flow changes or due to weather are less desirable reference points. Outdoor pressure references, while intuitively desirable, are difficult to achieve because of the effects of weather. In the event that the reference (interstitial) space is partitioned by firewalls or by other means, it may be necessary to provide multiple common reference points by building a ‘zone.’ The pressure relationship across a ‘zone’ should be room-to-room or involve the use of two DP transmitters, one to each reference point.

Small or simple facilities with just a few DP sensors may prefer to read pressures from area class to area class (or from room to room if there are no airlocks). This option also verifies the most critical room pressure relative to its adjoining room without calculations.

Figure 8.10: DP Sensor Locations



Where room to room monitoring is used, it is a good practice to confirm through the system balancing that net airflow into the facility is greater than the extract/exhaust (i.e., some air is leaking out the building for positive pressure operations).

8.4 Ventilation Strategies

8.4.1 Room Air Supply Distribution

There are two basic types of room air supply distribution:

1. dilution air supply distribution
2. displacement air supply distribution

8.4.1.1 Dilution Air Distribution

In a dilution air supply distribution design, room air is mixed continuously with supply air to help achieve uniform air temperatures within a room. In areas where temperature uniformity is the only factor, aspirating-type diffusers allow turbulent mixing of room air with supply air. From a particulates perspective, this dilution also can mix 'less clean' room air with clean supply air; non-aspirating-type diffusers are preferred in clean classified rooms.

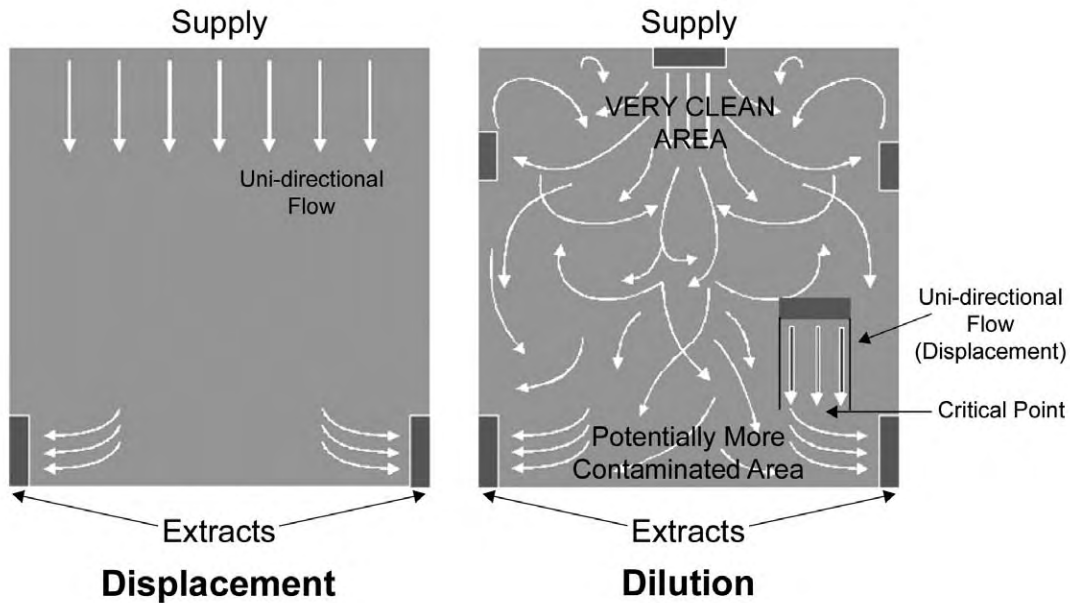
Non-aspirating diffusers reduce undesirable mixing effects, but do not eliminate turbulent air patterns in a room. The overall particulate level in a room can be reduced through dilution by increasing the flow of the clean air supply).

Dilution air supply distribution with non-aspirating diffusers (typically perforated face plate covering the terminal HEPA face) is acceptable to clean classified areas up to Grade 7 (EU Grade B). This method is also preferred where powders are handled and may become airborne.

8.4.1.2 Displacement Air Distribution

In a displacement air supply distribution design, such as for Grade 5 areas, airborne particles in a room are displaced by clean terminal HEPA filtered air flowing in one direction. This design requires nearly continuous HEPA coverage at the ceiling and properly sized and located low level returns or exhaust grilles. Rooms of lesser classification (Grade 6 or 7) may have a number of ceiling supply outlets, but with much less than 100% coverage to create a downflow air pattern (plug flow).

Figure 8.11: Types of Airflow Patterns



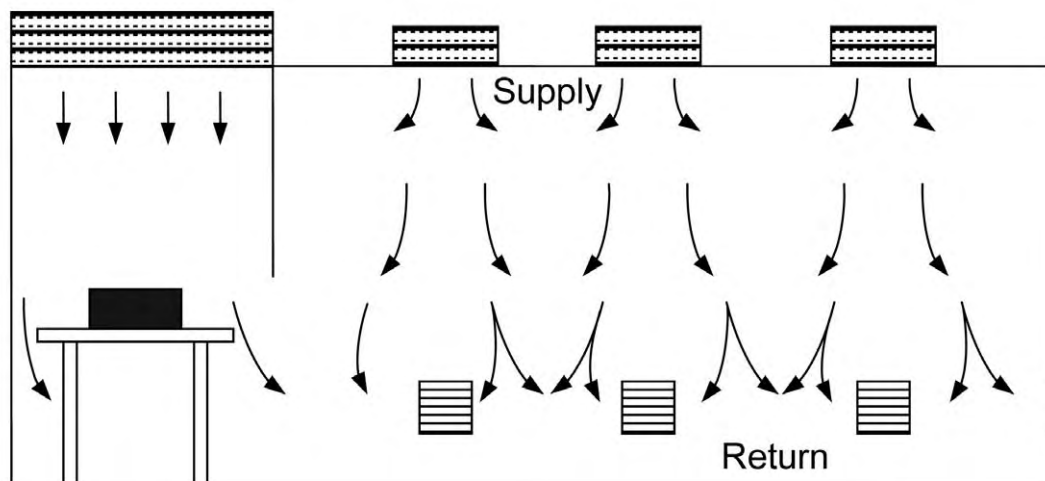
8.4.1.3 Room Air Supply Distribution Options

Conventional air distribution techniques generally are acceptable for administrative, warehouse, and unclassified spaces. However, large warehouse spaces may see hot and cold spots with poor air distribution. Aspirating diffusers are commonly used.

GMP spaces and cleanrooms require more stringent methods. For classified spaces, supply air should be introduced at the ceiling level and return/general exhaust air should be extracted near the floor (process exhaust should be extracted as close to the point of emission as possible). The use of non-aspirating diffusers on the face on terminal HEPA filters may improve room airflow patterns, but may decrease the degree of uniform mixing and dilution of airborne particles.

Within mixed airflow rooms, airflow patterns should be from the clean side of a space to the less clean. For example, within a space that contains an ISO 5 micro-environment/zone with an ISO 7 background, air should flow from the cleaner zone into the less clean background area.

Figure 8.12: Mixed Airflow Space

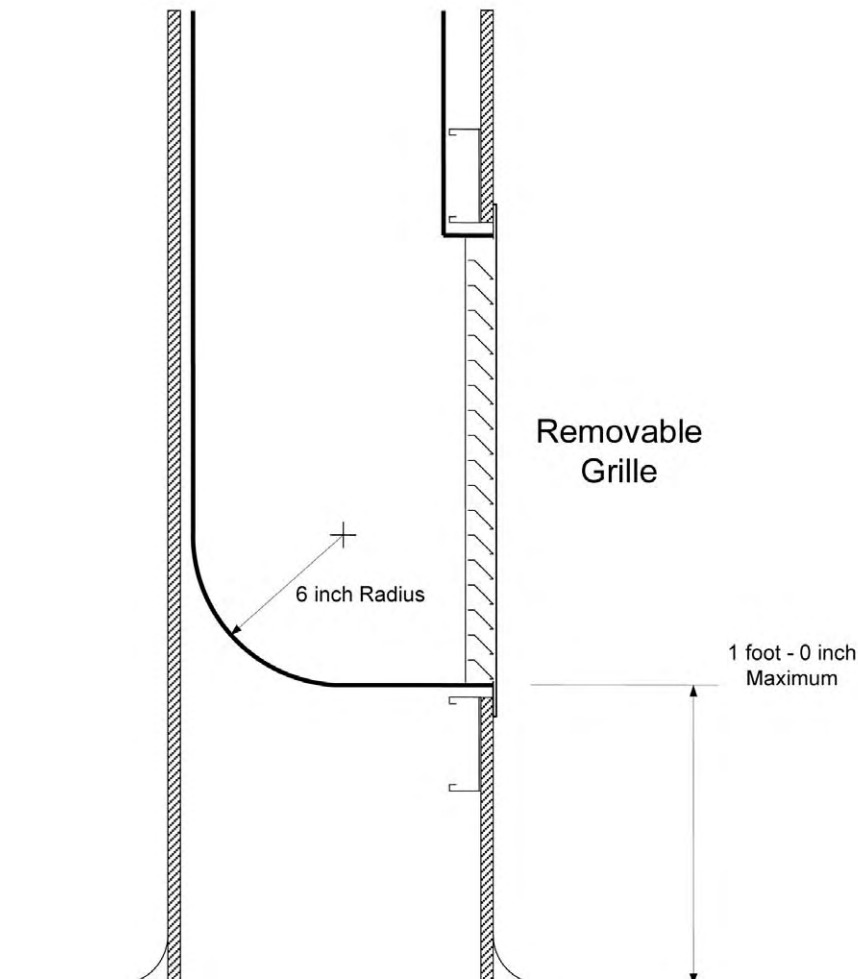


Some process operations, e.g., tableting or capsule filling, are inherently particle generating. Airflow patterns within the spaces that contain these processes should take this into account by locating returns/exhausts near the particle generating operation. Enclosed processes generally require much less exhaust volume and provide a physical separation between the product and operator. For classified rooms, returns should be distributed evenly and located on as many walls as possible, and not behind cabinets and other equipment against the wall.

Airlocks and gown rooms are usually divided, often by a physical line on the floor, into “clean” and “dirty” zones in accordance with the flow of personnel, material, and equipment. Within such rooms, air should flow from the clean side to the ‘dirty’ side of the airlock. HEPA air supplies should be located on the clean side and low wall returns should be located on the opposite side of the room. This also applies if gowning is divided into two separate airlocks in series (pre-gown and final gown). This helps to minimize the effect of opening of the airlock door on the clean space.

Low wall returns can help keep contamination below the height of working surfaces and should, therefore, be located below the working level, preferably about 12 inch (30 cm) above the floor. Return openings and ducts should be sized generously and well distributed around the room, but not within 2 feet (0.6 m) of door openings where they can induce flow through the door. Unless low level exhaust ducts need to convey powders, return and exhaust ductwork velocities should be low to minimize noise. The heel of the connecting elbow should have a broad radius to facilitate cleaning. If cleaning is required, the elbow and first section of connecting ductwork may be Type 316L stainless steel to prevent corrosion from cleaning agents. A removable perforated grille can facilitate cleaning and prevent room items from being drawn into the air system. Fewer choices may be available if a cleanroom panel system is used, as the return duct and grille are integral to the panel.

Figure 8.13: Typical Low Wall Return



Return air ducts located in stud wall spaces need not be insulated within the walls. Insulation should terminate at the top of the wall. The facility architect should be consulted to assure that, where needed, wall cavities are adequate to contain low wall returns.

8.4.1.4 Air Walls

An “air wall” is a vertical duct chase constructed by placing a “false wall” that spans from the ceiling to near the floor within the room, adjacent to the room walls. It is used to convey large quantities of return airflow to the AHU, typical plenum depths of 12 inches (30 cm). The opening is about 12 to 20 inches (30 to 51 cm) above finished floor and protected with a wire screen having a large free open area. Placement of an air wall on only one side of a clean space is **not** recommended and can drastically affect uniformity of downward airflow in clean spaces.

8.4.2 Extract (Exhaust/Return) Strategies

There are three approaches to dealing with the capture and removal of hazardous materials:

1. Release and dilution: used for mildly offensive non-hazardous materials. Contaminants are diluted with room air supply to acceptable levels (not captured at the source), e.g., sugar coatings for oral dosage. Generally, extract grilles should be located at a high level (for gasses and hot air) or low (for heavy vapors and large particles), as close to the point of emission as possible.
2. Capture at the source: used for hazardous materials that, if allowed to pervade room air, could lead to health, safety, or flammability issues. An LEV hood, e.g., a capture hood for ethanol fumes in an open granulator, typically operating at high velocity to enhance capture, is placed near the source,
3. Containment and exhaust: used for very hazardous materials that can cause health or safety problems at very low levels in the air and for less hazardous materials to enhance housekeeping. The process is contained and the enclosure exhausted, e.g., a glove box for viruses, high potency oral dosage API.

For information on methods of capture see the Industrial Ventilation Manual published by the American Council of Government Industrial Hygienists. (Reference 19, Appendix 12) Containment techniques constantly change; see the ISPE Containment COP for current information (www.ispe.org) (Reference 17, Appendix 12).

Point capture and containment also may be used to prevent particles and heat generated within a room from dispersing in the room (e.g., from a motor in a Grade 7 room).

Many materials captured at the process require rigorous control, usually through:

- scrubbing
- dust collection
- high efficiency (or HEPA) filtration
- carbon adsorption

Some materials may be exhausted to the outdoor atmosphere via a tall/high velocity stack. For further information on abatement system design see the ASHRAE Handbooks (Reference 22, Appendix 12).

8.4.3 Ductwork Design

Design concepts for ductwork distribution systems, e.g., equal velocity, equal friction, and static regain are covered in the ASHRAE and SMACNA Handbooks (References 22 and 30, Appendix 12). These calculations should be performed by appropriately qualified HVAC professionals, who understand HVAC system design, using manual or computerized methods.

In general, good ductwork designs:

- are reasonably symmetrical
- have the minimum number of offsets and turns
- reduce in size as the flow decreases
- are equipped with balancing dampers to control non-plenum divergences or convergences of flow
- have balancing dampers, but do not depend solely on them to regulate flow

8.5 HVAC Controls and Monitoring

8.5.1 Introduction

This section gives a brief overview of the options available for controlling and monitoring HVAC systems and the environments that they provide. The section also provides guidance on the points to consider when designing a new system or reviewing an existing installation.

Early in the design process, decisions should be made regarding whether an HVAC control system (or multi-use system such as a Building Management System/Building Automation System (BMS/BAS) will also act as the quality 'system of record' to provide alarm functionality, operator response management, and electronic data records proving that critical environments are maintained within specified limits. This system also can capture data from critical HVAC equipment, as well as direct environmental monitoring data that may be used to support product release or other GMP processes.

A common alternative approach is to employ an independent system for alarming and managing critical data, such as a data logger, process control system, or LIMS. The HVAC control system is limited to control and maintenance information required to manage a facility.

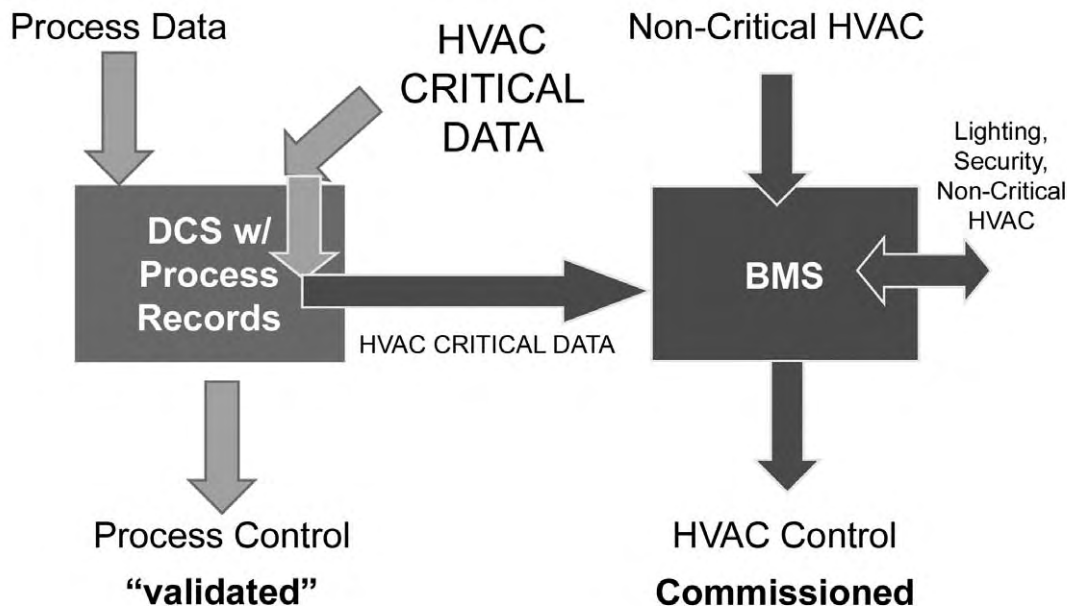
A BMS/BAS could be used as a data source interface to equipment and instruments, transmitting information to the monitoring system, which is responsible for all other data management and backup/archiving functionality. The maintenance of separate parallel systems, without validation of the control loop, can be challenged if not carefully undertaken and is not preferred.

In smaller facilities needing to monitor just a few HVAC parameters, the data management and the control of **all** HVAC points can be included in the process control system (Distributed Control System (DCS), Direct Digital Control (DDC), PLC, etc.). On a cost per point basis, this is likely the most expensive plan, as software often needs to be written to handle HVAC functions, including basic functions, as opposed to pre-programmed HVAC software that is included with BMS systems. In addition, with both critical and non-critical HVAC points in the same system, the extent of computer system qualification expands significantly. A hybrid plan, with DCS for critical points and standalone controls for non-critical points, differentiates the maintenance and record-keeping roles, and therefore, may be less expensive to qualify, but may be more costly to maintain.

Where critical parameter logging, indication, recording, and alarming take place, critical field data may be collected by a separate standalone process computer (e.g., DCS or PLC), instead of 'validating' a BMS for process HVAC recording and alarming. The critical parameter data may originate from a common device and be relayed to the BMS/BAS or the output may go to both systems. The BMS is commissioned to perform the actual control function and to deal with non-critical data and control.

Using a common device has the advantage of common data being provided to both systems with one device to calibrate. Systems using two parallel sensors are likely to suffer from different readings because of, e.g., sensor calibration/location. See the GAMP® Forum position paper on use of BMS systems in *Pharmaceutical Engineering* (Reference 16, Appendix 12).

Figure 8.14: BMS and Process Control/Logging Relationship



BMS/BAS systems may control and monitor a range of systems and equipment, from critical utilities and environmental stores (e.g., cooling and humidity for product/intermediates), to building lighting and security. Commissioning and qualification plans for testing the system in association with HVAC systems should be designed to isolate non-critical HVAC functions from higher-level requirements related to product-critical functions. This approach to verifying systems in the manufacturing domain is based on a functional-level assessment of risk. (A non-HVAC example would be Enterprise Resource Planning (ERP), where risk factors associated with functionality are graded from non-GMP (financial/GEP) to GMP (master data and product genealogy)). The various functionalities, as well as critical versus non-critical parameters handled in the BMS, can be assessed for risk and tested and documented accordingly.

If a part of the system requires commissioning and qualification to meet regulatory requirements, functionality for specific common attributes, such as data integrity, may need to be tested to a higher standard.

Each approach can help mitigate the efforts needed for verifying, operating, and maintaining a BMS and associated HVAC System. In addition to GMP, monitoring of safety requirements and parameters should be considered, using methods, such as HACCP to determine risks and appropriate mitigation approaches. These decisions affect the overall controls and monitoring designs and affect the number and scope of items that need to be included in a GMP commissioning and qualification plan.

8.5.2 Controls

Many types of equipment can be used to monitor and control an HVAC system, each with advantages and disadvantages. Three of the more common are:

1. Single Loop Controls
2. DDC/BMS

3. DCS with Intelligent Field Devices

8.5.2.1 Single Loop Controls

A traditional basic system may use packaged stand-alone controllers ranging from 'proportional' only (such as a thermostat) to Proportional and Integral (PI) or Proportional Integral and Derivative (PID) electronic controls for each of the controlled variables. There may be independent control units, e.g., temperature, humidity, or a single combined temperature/RH unit with the sensors and controlled items, e.g., dampers or valves, connected to the controller. The controller also may provide alarms and send data to a central data collection system.

This option usually has low purchase and installation costs. Control panels in a large installation can be standardized and complete panels can be held as spares.

As the controller is not able to monitor or analyze the system performance trends or component performance significantly; however, this type of controller is usually used in simple systems or where local technology cannot support more complex PLC/SCADA or computer-based systems. A typical control unit is shown in Figure 8.15.

Figure 8.15: Typical Single Loop Control



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8.5.2.2 Direct Digital Control/Building Management System

The most common monitoring/control system found in the HVAC industry is the DDC/BMS (BAS); a proprietary packaged system typically comprised of a number of local independent controllers and accessories panels, field panels, or outstations with the software/control logic installed. The panel may control one or more HVAC systems or other building systems (e.g., fire, security, and lighting).

The field panels are connected by a network to one or several "supervisors." These are computer terminals that allow a user to see the input and output signals and to setup the system to record data and alarms. The terminals allow users to review plant performance data and trends, change setpoints, and have alarms reported/printed in a central location.

This type of system is more expensive, but allows HVAC system performance to be monitored remotely with adjustments made to set points from a central location if required. A hierarchy of alarms and security also can be setup easily. The large-scale use of these systems has reduced the cost significantly, leading to wider application and ease of commissioning. Although the use of BMS/BAS is not required, manufacturers have developed methods to qualify BMS/BAS systems for pharmaceutical HVAC applications.

8.5.2.3 *Distributed Control System with Intelligent Field Devices*

DCSs are similar to those used for process control. These may employ advanced features, such as redundant processors and “intelligent” components (sensors and valves) connected via networks to the control system (e.g., “Fieldbus,” profibus, arcnet, and Echelon).

There are a number of industry standard communication protocols.

The software is held within the control system that communicates with the devices; devices can self diagnose faults. Automated components also can self-calibrate to the control signals.

This type of system is the most expensive to install, but should be more reliable and simple to maintain, as controllers are self-checking. The cost typically limits the use of this type of system to process operations, but this may change as the costs reduce.

8.5.3 **Actuation Methods**

There are two common means of actuating control components:

1. electric motors
2. pneumatic actuators

8.5.3.1 *Electric Actuators*

Electric actuators vary in sophistication from small low voltage motors controlled by low resolution positioning circuits to servo motors and line voltage motors controlled by sophisticated positioners. The speed of actuation of electric or electronic actuators typically is slower than that for pneumatic actuators, because of the prevalence of low torque motors and high gear ratios in units sold for HVAC devices. They are well suited for slowly changing parameters, such as temperature and humidity control. The speed of the best electronic actuators rivals that of pneumatic actuators.

8.5.3.2 *Pneumatic Actuators*

Pneumatic actuation uses compressed air as the motive force for actuation, instead of electricity. These are prevalent in industrial HVAC systems. Pneumatic actuators typically respond quickly and are well suited for fast changing control loops, such as airflow control for Variable Air Volume (VAV) laboratories. These units typically have a faster response time than an electric or electronic unit. The all-pneumatic system also is ideal for hazardous areas requiring intrinsically safe installations. Typical applications would include active pressure control.

For further information on actuators and the control of liquids, see Appendix 9.

For HVAC applications, response time of controls may not be critical, as the response time of the overall system is slow, e.g., even if the full room heat load is added instantaneously, the room temperature will rise slowly, not instantaneously. Similarly the rate of change of outdoor conditions typically is slow. If the design requires dynamic control of room pressure; however, actuators for pressure control may require response times in the range of seconds. Generally, this is feasible if all controllers respond quickly to changes in parameters.

8.5.4 **Critical Parameter Control**

The requirements for instrumentation should be considered in regard to selecting the most cost effective type and to define the appropriate calibration regime. Industrial grade instruments/sensors usually are employed, as they usually are more reliable, more robust, but more expensive.

For some instruments, accuracy and repeatability are important, e.g., measuring room temperature. For others, accuracy is not as important as repeatability, e.g., measuring a system's flow rate in order to maintain constant flow using a variable speed fan.

Three point calibration may be required, but single point calibration may be justifiable.

Commonly monitored environmental parameters include:

- airflow (affects the dilution of airborne particles in a room and room recovery from in-use to at-rest conditions)
- DP between rooms (affects the migration of contaminants into a room from adjoining spaces)
- temperature (may affect exposed product quality)
- RH (may affect exposed product quality)

8.5.4.1 Airflow Measurement

Measurement of supply airflow from the AHU and in ducts typically is coupled with the control of constant supply airflow in a system to:

- offset flow decay because of an increasing pressure drop in air filters
- offset changes in variable exhausts (known as "airflow tracking")

For classified spaces, supply airflow should be kept constant to ensure that particle counts, recovery, and room pressure are controlled.

Air velocity may be measured using a grid (array) of measuring devices in a duct, arranged to compensate for the non-uniform nature of velocities within the duct.

Pitot tubes commonly are used this purpose. Pitot tubes normally employ small holes facing upstream to sense total air pressure or have holes facing perpendicular to the direction of flow (or downstream) to sense throat sub-static pressure. The difference in pressure signal between the two sets of tubes is proportional to the square of the mean velocity in the duct. By connecting the output tubes to a suitable instrument, the pressure difference, and therefore, the velocity can be measured easily. To get total flow, velocity is multiplied by the area of the duct. DP flow measurements have a limited turndown capability, because of the square-root calculation of flow.

A similar grid system uses a hot wire anemometer. Anemometers indicate velocity, but are more properly considered a mass flow measurement device, as they measure the ability of the airflow to affect the temperature, and therefore, the resistance and current flow through a heated wire or thermister. The cooling effect of the mass of air is linearly proportional to the mass flow, and therefore, the velocity. Improved accuracy is possible at low flows or where sufficient straight duct length is not possible, because flow sensing is not dependent on the square root of pressure.

The vortex shedding flowmeter also is a linear response device that is employed in airflow measuring arrays. This device works on the principle that an obstruction in a fluid flow stream produces low pressure vortices on the downstream side of the body. These vortices originate on alternating sides of the body at a frequency that is linearly related to the flowrate.

To achieve a degree of accuracy, an in-duct airflow monitor should be installed in a straight section of ductwork, usually a minimum 5 duct diameters upstream and 3 duct diameters downstream; the monitor manufacturer may provide alternative installation requirements. HVAC System designs may include flow straighteners upstream of airflow monitor grids. These devices remove turbulence, but (like the monitor itself) if installed too close to elbows, fan outlets, or other direction changes, will not help to improve accuracy.

Fan venturi meters (piezometer rings) provide the advantage of reading total air volume with greater accuracy. They can either be retrofitted to or be an integral part of the system fan inlet. Performance is independent of the ductwork design (the fan is inside the AHU), and can be a useful commissioning aid. The wiring and tubing are all local to the fan/AHU, simplifying installation.

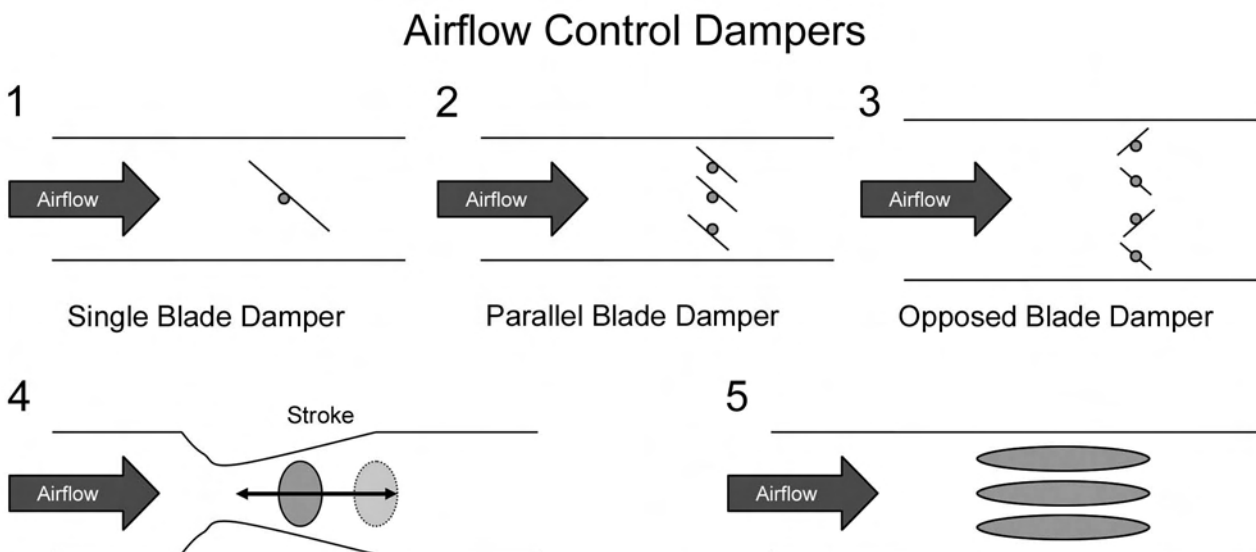
The principal function of the grid is to maintain the desired conditions determined during system commissioning, whether reading actual flow or not, rather than to obtain an accurate reading.

For specialized applications, such as the monitoring of low velocity unidirectional air flow devices (UFH or laminar flow hoods), hot wire anemometers are used. Vane anemometers commonly are used for air velocity measurement in commissioning, as they tend to have an averaging affect over the sample area compared to the spot reading from the hot wire unit.

8.5.4.2 Airflow Control

The most common form of airflow control is the damper, which can be manually adjusted or actuated, and can use a single blade, or be multi blade parallel or opposed blade. Fan airflow volume may be controlled using a discharge damper, an inlet damper (or “guide vanes”), or variable frequency motor speed control. VFDs have become an accepted method for fan airflow control in terms of energy savings and cost. The use of a fan discharge damper wastes energy and is not recommended.

Figure 8.16: Common Damper Types



Dampers usually are basic; the relationship between airflow and position is non-linear. Care should be taken when using motorized blade type dampers for varying air flow control; correct sizing is critical to provide good control across a damper. Improved airflow control is possible using more expensive devices, such as a pneumatic ‘bladder’ damper, which uses a bladder inflated with low pressure compressed air to open aerodynamically shaped blades. These provide more linear control with better pressure recovery and turndown.

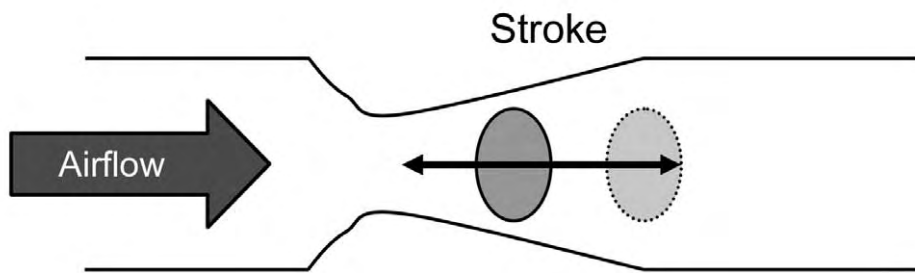
Figure 8.17: Pneumatic (“Bladder”) Damper



Used with permission from Waddell Engineering Co., www.waddellengineering.net

A variable orifice, also called a venturi damper, may provide better control. A venturi orifice commonly is used for laboratory hood flow control and room pressure control.

Figure 8.18: Variable Orifice (Venturi) Damper



8.5.4.3 Fluid Control Valves

The correct selection of a fluid (liquids, compressed air, or steam) control valve is critical for good system performance, together with tuning of the control loop.

There are two types of control valve:

1. the three port valve, which can be used as a mixing or diverting valve to supply the controlled equipment
2. the two port valve, which directly controls flow to the equipment

For further information on control valves, see Appendix 9.

8.5.4.4 DP

There are three applications for the measurement of DP:

1. the use of a DP monitor to interpret the readings from an airflow-measuring device (pitot tube)
2. the use of a pressure switch to detect:
 - flow failure of a fan (usually not necessary if the system has flow monitoring)
 - detection of high pressure across a filter or filter set to provide an indication that the filters require changing (not necessary unless filters load quickly)

3. The detection of low DP between rooms to provide an indication of incorrect airflow direction (non sterile areas) or failure of a design DP (sterile areas). A pressure switch is not needed if the pressure sensor and monitor system can provide an alarm.

There are several options for DP sensing and indication:

- The inclined manometer is acceptable for local DP measurements, such as the pressure drop across an air filter or from the inside of an isolator to its room.
- A basic instrument is the Magnehelic™ gauge: a robust device that measures the deflection of a metal diaphragm due to air pressure and provides a visual indication of DP. This gauge also is available with an adjustable electrical contact switch (high and low alarm, the Photohelic™ gauge) or a variable output. Mounting position affects whether accurate readings are obtained. These gauges often are used to monitor room DP, but resolution of readings may be marginal and the gauges can be only single point calibrated (the zero is adjustable, the span is not). These gauges are excellent airflow direction indicators for locations where the exact pressure is not critical, but are not suitable for precise DP measurement. It may be possible to obtain silk screening of the faces of these gauges to indicate the desired conditions with a green quadrant and the out of range conditions with red quadrants.
- A simple device using a colored ball mounted in a clear inclined tube provides an alternative direction of airflow indicator; see Figure 8.19. This type of unit is very simple and does not require calibration, but has the disadvantage that there is airflow through the unit so it requires routine cleaning. In addition, it indicates only relative DP and not an absolute value of DP so it finds better use in non-classified spaces (oral dosage, etc.)

Figure 8.19: Visual DP indicator



Used with permission from Airflow Direction Inc., www.airflowdirection.com

Where greater sensitivity is required or a control function is needed based on a DP, electronic pressure transducers can be used. These are available with or without indicator readouts to allow operators to see the measured value. The most sophisticated DP sensors are pressure diaphragms with an accuracy of ± 0.005 inch (± 1.25 Pa). Output is commonly 4-20 mA.

When specifying DP units, the operating pressure range should be considered and the device should be sufficiently robust to handle the occasional pressure spike.

Pressure transducers are located where they can be calibrated with tubing connecting them to the rooms where DP is to be measured. The exterior of the sensor tube should be cleanable where tubing penetrates into the room.

8.5.4.5 Temperature Sensor

The Resistance Temperature Device (RTD) is an industrial sensors used to monitor temperature. 100-Ohm RTDs are available with different accuracy standards and response curves, e.g., accurate to $\pm 0.2^{\circ}\text{F}$ (approx. $\pm 0.1^{\circ}\text{C}$). Industrial standards require the use of a transmitter to offset accuracy losses because of resistance in the system wiring. Some HVAC systems may use 1000-Ohm sensors to minimize the effect of wiring resistance without the use of a transmitter. Thermocouples also may be used. Self-contained liquid and gas expansion systems are used for actuation of self-acting controllers and switches. Temperature sensors may not be capable of being calibrated in the field and should be replaced if found to be out of specification.

8.5.4.6 Humidity Sensor

RH in a room usually is monitored, though there are applications where it may be advantageous to monitor a room's absolute humidity or dew point. For example, in a system used to supply multiple areas, each room's supply duct has a local temperature control re-heater, and the HVAC control system would "reset" the supply temperatures to be able to turn off one re-heater to save energy. If an RH sensor at the AHU controls supply moisture, the change in supply temperature would change the RH in air leaving the AHU. This would cause a change in room RH. Where there are many rooms with moisture sources, it is possible to monitor room RH, while controlling dew point (absolute humidity) leaving the AHU. It also is common (in smaller systems) to use RH sensors in critical rooms and to control humidity in the AHU by reading the **average** RH in the return duct before it enters the AHU.

The sensors used to monitor RH industrially usually are units that measure the change in capacitance between two plates due to the variation in humidity. Accuracy usually is in the range of $\pm 2\%$. Commercial grade RH sensors may have lower accuracy. Semiannual or more frequent calibration may be justified.

8.5.5 Setpoints

Controls setpoints should be selected to assure that errors (drift, hysteresis, accuracy) do not combine to allow a condition outside operating or acceptance criteria. This is particularly important in systems where multiple instrument signals are used to calculate a control response (e.g., airflow tracking, multi-point pressure control).

8.5.6 Monitoring of Critical HVAC Parameters

8.5.6.1 Critical HVAC Parameters

Critical HVAC parameters are particular to individual products and processes. Typical critical parameters may not apply to facility areas or equipment where the HVAC parameters have little or no impact. For example, closed processes and processes with clean environments maintained inside product containers or equipment may see little or no impact from HVAC systems, unless normal operations require opening the process or changing process connections.

It is common practice to qualify monitoring systems (sensors, transmitters, indicators, recorders, alarms, etc.) for those parameters defined as critical (usually handled in the process monitoring computer system) and to use GEP to ensure the development and maintenance of a robust control system (via the HVAC control system, see Figure 8.14).

This approach provides the quality unit with a record from a validated system of room conditions during process operations, without the need for a formal change control process for the HVAC control system (an engineering change control system is still required, which typically is more manageable and less extensive in its scope, e.g., it may include only some set points and some hardware in the system).

Main factors to consider for a monitoring system:

- accuracy and repeatability required

- long term stability and failure modes
- sensor location/locations
- alarm requirements
- record requirements
- ease of maintenance and calibration

8.5.6.2 Accuracy Required

The potential error of any single loop in a monitoring system should be subtracted from the defined limits to ensure that the product requirements are met. It may be cost effective to use a reliable high accuracy sensor, allowing maximum latitude for the control system.

For example, if the acceptance criteria are 18 to 25°C (64 to 77°F) and the monitoring system has an accuracy of +/- 0.5°C, the action limits should be set at 18.5 to 24.5°C; if the monitoring sensor has an accuracy of +/- 2°C, the limits should be set between 20°C and 23°C.

8.5.6.3 Long Term Stability and Failure Modes

Some instruments are prone to drift out of calibration more than others, e.g., liquid pH probes. Humidity sensors may require more frequent calibration than temperature or pressure sensors. Maintenance procedures and frequencies should be based on manufacturers' recommendations.

Failure modes should be considered by system designers:

- If an instrument (sensor/transmitter, indicator, recorder, alarm) were to fail, in what mode should it fail?
 - Generally, an unusual reading should trigger an alarm.
- If an actuated field device (control valve or damper) fails, should it fail open, closed, or in its last position?
 - A failure mode should be chosen that is safest for the product and personnel and maximizes the probability of detection of the failure.

8.5.6.4 Sensor Location – General

The following should be considered when selecting where to mount a sensor:

- Instrument should be mounted to be easily accessible and easy to calibrate and replace. Local indicators should **not** be obscured.
- Local cleaning required should be considered in the instrument specification and mounting.
- Pneumatic control lines should be kept as short as possible.
- Sensor elements in negative pressure duct and mechanical spaces should be appropriately sealed to avoid the influence of unconditioned air.
- Contaminated locations should be avoided, particularly where hazardous materials are handled to avoid calibration problems and exposure to personnel.

- Sensors should be located in well-mixed air (e.g., not in an AHU mixing box where outdoor air can stratify).
- Potential interference to electronic devices from nearby electrical devices, especially motors should be considered.

8.5.6.5 *Temperature and Relative Humidity Sensor Locations*

Potential lack of uniformity throughout a room should be considered for mounting of temperature and humidity (typically RH) sensors (see Appendix 11).

Temperature and RH monitoring sensors often are mounted in the common return air duct, giving an average of the conditions in a space, assuming that the supply diffusers are mixing the supply air with the room air adequately.

An RH sensor (or temperature sensor) in a negative pressure (return) air duct should be located upstream of duct access doors and should be sealed thoroughly to prevent the ingress of warm or humid air that would corrupt the sensor reading, causing the control system to over-react and push a critical parameter out of its normal operating range.

It may still be necessary to study the relationship between worst-case conditions in the room and the mixed condition in the return duct to see if the average reading agrees with the readings near the critical sites. Assumptions regarding sensor location can be verified during commissioning.

If there are significant heat or humidity sources, the local conditions near the source will be different.

When considering sensor locations, the process in regard to the product should be considered. For example, for a typical tablet compression room:

- The raw material sits in a hopper typically near a supply register so that the hopper is flushed with clean air. It is then fed into the tableting dies, where it is compressed, generating a significant amount of heat and dust. The compressed tablet is then released into a de-duster/metal detector, then into a collection bin, where it cools and is exposed to room conditions. The local RH will be lower at the bin because of the localized heat although the moisture content (dew point) is the same throughout the room.
- Since the equipment generates a significant amount of heat, the airflow rate or air mixing in the room may need to be high to keep the room air temperature variation within product limits. The difference between the temperature at the product and the temperature as indicated on the room temperature sensor can be “mapped” during performance qualification, if, potentially, the temperature is critical.
- The most critical area is the feed hopper, which is washed by supply air. If temperature or humidity are critical parameters and could be out of range within normal room variations (sometimes as much as +/- 5°F), it is appropriate to monitor near the feed hopper to indicate the condition of the material within it. Since this site may be dusty, it also is acceptable to monitor at a more convenient location in the room and verify (during commissioning) the offset in temperature between the sensor and the area near the hopper.

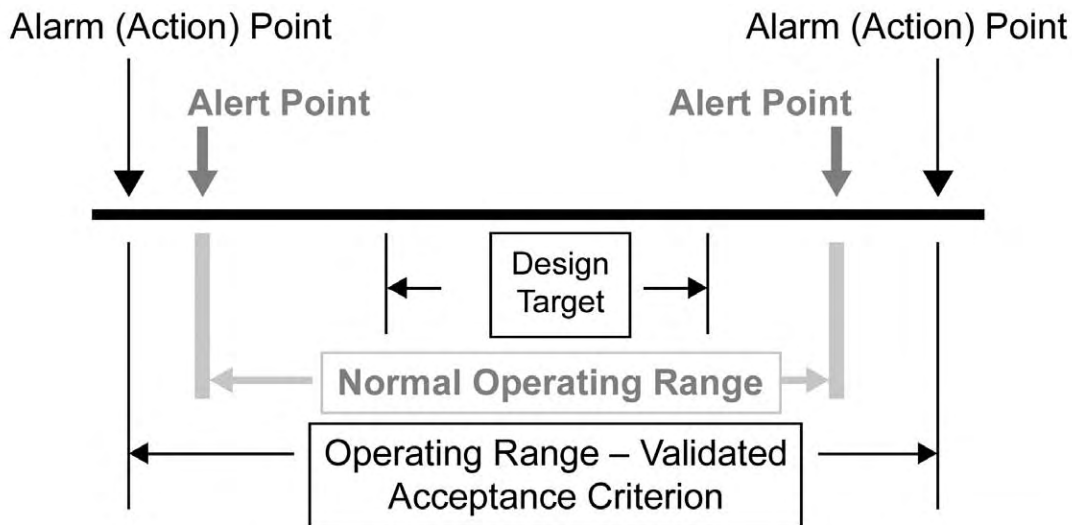
8.5.6.6 *Alarm Requirements*

Alarms may provide an audible or visual indication, e.g., a horn and flashing light mounted in a common area of the production suite, where they can be seen or heard from the entire suite. The choice of alarm type should consider noise levels during operations and locations of personnel.

It is considered good practice to set the action alarm at the extreme acceptance conditions and have an engineering “alert” alarm at conditions just outside the normal (observed) operating range to alert engineering personnel of a potentially unusual condition (e.g., a loss of a water chiller causes room temperature to drift upward) as soon as possible, so that steps may be taken to prevent an action alarm.

This engineering alarm may come from a validated monitoring system or a GEP control system (see Figure 8.15 and Appendix 2).

Figure 8.20: Action Alarms, Alert Alarms, Operating Range, and Design Targets



Unless there are extremes in weather, investigate values outside the NORMAL range.

Alarm Time Delays

Parameters may change slowly or rapidly. Room pressure can change very quickly, and therefore, has potential to create a low-pressure (nuisance) alarm whenever a door is opened. DP alarms often have time delays, particularly where airlocks are not employed to keep DP between air classifications above zero. The duration of the time delay should be sufficient to permit normal passage through a door and be verified during commissioning by particle counting in the cleaner space. For DP across airlocks, the set point should be above zero (just below the normal DP with a door open). When the DP across an airlock is zero (meaning more than one airlock door is opened), a low DP alarm with no delay may be used. For areas with no airlock, the DP alarm set point should be zero with acceptable delay to permit passage through an open door.

Time Weighted Averaging

Measurements with “noisy” (rapidly changing) signals, such as airflow measurements, may require filtering to avoid nuisance alarms. A commonly used filter is to use a rolling time weighted average signal, rather than an instantaneous signal for recording and alarming. A rolling average of readings from 4 to 10 seconds typically is capable of smoothing out signal noise without missing significant failure events.

8.5.6.7 Alarm Response

The desired response to an alarm state should be considered.

An alert alarm should provide early warning to facility engineering personnel of an unusual state requiring attention or adjustment, but not an indication of a deviation outside the required operating conditions for a product or process (acceptance criteria).

Action alarms for a variable may indicate that operating conditions have exceeded the specified acceptance criteria and that action is required to ensure that product quality is not compromised. These alarms should be relayed to the appropriate business and quality unit.

The regulatory requirement is for a local alarm, notifying the operator when the conditions are outside the acceptance criteria limits. However, there should be a written course of action defined for each action alarm:

- Who sees it?
- Who responds to it?
- Where is it recorded?
- What action will be taken?
- Where the information on the action will be stored?

If no action is needed, justification for the action alarm may be questionable.

8.5.6.8 Record Requirements

The frequency of data collection is dependent on the parameter being measured.

There is no regulatory guidance regarding frequency of monitoring although the USP (in the general chapters <1118>) (Reference 31, Appendix 12) states that the user must consider how rapidly the monitored condition is likely to change, suggesting that for storage conditions, a response time of 15 minutes may be appropriate, whereas for transport of product a more rapid response time of 5 minutes may be required.

In a manufacturing area, there are unlikely to be sources of heat energy or humidity that can create instant changes, considering the thermal mass and sizes of the monitored areas. Therefore, temperature and humidity will change very slowly and could be recorded on two or three minute intervals (or longer) and still provide an accurate record of the environmental conditions. Room pressure changes quickly so data intervals may be very short, perhaps seconds, during an out-of-specification state. For classified spaces without airlocks, DP will drop to zero soon after the door is opened. This drop should be recorded, but the alarm should be on a time delay to permit the door to close within a validated time.

It may be acceptable to have a record of alarms (or lack thereof) only during manufacturing, recorded on the batch record sheet.

It may be preferable to have an actual record of measured values.

Data logging may be in the form of a continuous chart or a daily printout of minimum, maximum, average, standard deviation.

8.5.6.9 Airborne Particle Monitoring

The 2004 FDA Guidance for Industry, "Sterile Products Produced by Aseptic Processing – Current Good Manufacturing Practice" (Reference 9, Appendix 12) states "Regular monitoring should be performed during each production shift."

EU GMP Volume 4 Annex 1 (Reference 4, Appendix 12) makes the following statement:

"A continuous measurement system should be used for monitoring the concentration of particles in the grade A zone and is recommended for the surrounding grade B areas. For routine testing the total sample volume should not be less than 1 m³ for grade A and B areas and preferably also in grade C areas."

These requirements have been interpreted as requiring a minimum of one test per day (during the periods that production is taking place) with re-qualification of the aseptic process areas of a facility every 6 months.

The version of EU GMP Volume 4 Annex 1 (Reference 4, Appendix 12) that came into force on 1 March 2009 gives much more specific information – it states that “for Grade A zones, a minimum sample of 1 m³ should be taken per sample location” (it defines Grade A as ISO 4.8 as dictated by the limit for particles ≥ 5.0 µm, and allows the use of ISO14644-1 to determine the number of sample locations).

“Portable counters with a short length of sample tubing should be used for classification purposes because of the relatively high rate of precipitation of particles ≥ 5.0 µm in remote sampling systems with long lengths of tubing.”

“For Grade A zones, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter...”

The requirement for a 1 m³ sample with a standard particle counter means that a single test will generally take between 20 and 35 minutes depending on the sampling rate of the equipment being used.

ISO 14644 (Reference 3, Appendix 12) provides the following guidance:

This Standard provides a formula to calculate the sample size to be used to classify a clean-room or clean air device. The sample volume must be based on the class limit of the largest considered particle size. When considering ≥ 5 micron particle size, this would require a sample volume of approximately 0.7 m³. The standard also provides guidance on test frequencies; it suggests that an ISO 5 clean room that has continuous particle monitoring installed should be re-qualified at least every 24 months.

Based on this guidance, there is a trend toward the installation of continuous monitoring systems since they provide a better understanding of the process, and the data can be used to support a reduced frequency of testing, while assuring continued levels of control.

There are three methods that can be used to obtain continuous data:

1. a manifold system
2. individual particle counters
3. a combination of a manifold system and individual particle counters

Description of Continuous Monitoring Systems

Manifold System

Manifold systems are composed of a network of sampling lines fed to a single particle counter. This may be the lowest cost option for some applications, but does not provide true continuous sampling. The settling of particles in the sampling lines and manifold may render the information unreliable, making this technique unsuitable for some applications (especially Grade 5/Grade A), where larger particle sizes need to be evaluated. The operation of manifold systems requires that the monitoring point be switched sequentially to cover all of the installed points. Systems are usually configured to have more frequent sampling for those points that are deemed to be more critical (or representative of the area where product is exposed). Sample size is less than cited in the EU GMP, because of the need to continually switch points. Manifold systems may require identical lengths of tubing from each area. Manufacturers should be consulted before designing a real-time particle monitoring system.

Individual Particle Counters

A particle counter should be used for each location; networked electronically to a data acquisition and evaluation system. This configuration can provide continuous data and also the flexibility to modify sampling locations and the sampling frequency. It is likely to be the most expensive option.

Combination System

A combination of the manifold systems and particle counters with dedicated particle counters in higher risk areas and manifold system sampling for less critical locations.

Considerations

The following should be considered when selecting a system for a specific application:

- the selection of sample locations, using a risk-based approach to assess the process
- The affect of particle loss in sample tubing. Long tubes can lead to attenuation of particle concentration, particularly at larger particle sizes. This may invalidate such systems where consideration of larger particles is a requirement.
- The potential for static charge of sample tubing. Suitable smooth tubing using materials, such as stainless steel or specialist antistatic plastics should be chosen to reduce particle loss and accumulation in tubing systems. Static charges also can lead to intermittent “clump” release of particles, creating false readings.
- the smoothness and long radius of bends in the sample tubing installation
- the maintenance of appropriate turbulent transport velocities in sample tubing
- the sampling frequency at each location
- the sample time at each location and the potential to detect contaminant release from an operator intervention or other contamination event
- when manifold systems are used, the adverse affect of no-flow conditions that may occur between sample acquisitions at the same location

Sample Locations

ISO 14644-2 (Reference 3, Appendix 12) provides guidance on determining the number of particle monitoring points. There is a regulatory (EU) expectation that at least one location be the most likely to experience high counts (such as near the product where the operator can interfere with protective air flow patterns).

8.5.7 Equipment Monitoring/Maintenance

There are several ways that HVAC equipment can be monitored; e.g., considering a fan motor:

- the control contactor can be wired so that an alarm is given if the unit goes into overload
- the motor current can be monitored
- the motor temperature can be monitored
- vibration or acoustic output may be monitored

- the airflow from the fan can be monitored using an in-duct device or an in-fan device

The unit that measures the flow is the unit that can detect all of the fan failure modes, but does not provide any predictive information. Other units have potential limitations, depending on the fan drive arrangement. Airflow measurement also is likely to be the most sensitive. In addition, for a system requiring fixed airflow to the spaces (e.g., for classified rooms), the flow monitor provides a continuous indication of acceptable air quantity delivery. Current monitoring is less sensitive than flow measurement, provides information on common failure modes, and can give predictive information regarding filter loading, incipient bearing, or drive coupling failure. Current monitoring is most effective as a maintenance measurement when the system has airflow control on the AHU or individual use points.

Vibration-sensing accelerometers may make it cost effective to monitor the performance of rotating equipment to diagnose system wear or predict incipient failure. The sensors can be wired to a BMS or be wireless, transmitting data to a base station for monitoring.

Other equipment parameters also may be monitored as part of GEP to ensure lowest life cycle cost:

- supply duct pressure (to permit energy setback)
- damper actuator positions (to predict need for re-balancing of the HVAC system or filter change out)
- Filter pressure drop. AHU and in-duct filters should be outfitted with manometers, as a minimum, for visual pressure drop indication
- cooling coil leaving air temperature (may be reset upward when humidity is satisfied)
- return static pressure
- casing high and low pressure safeties
- freezestat, firestat and smoke detector safeties
- coil entering and leaving temperature
- coil pressure drop (where bypass dampers are employed)
- outside air filter pressure drop and rate of rise (rate of rise identifies snow accumulation on filters)
- outside air quantity
- outside air enthalpy (temperature and RH)
- mixed air temperature
- exhaust air volume

Appendix 3

Psychrometrics

9 Appendix 3 – Psychrometrics

9.1 Introduction

This section augments the discussion on psychrometrics in Appendix 1, see Figure 9.1.

Figure 9.1: A Typical Psychrometric Chart (SI units)

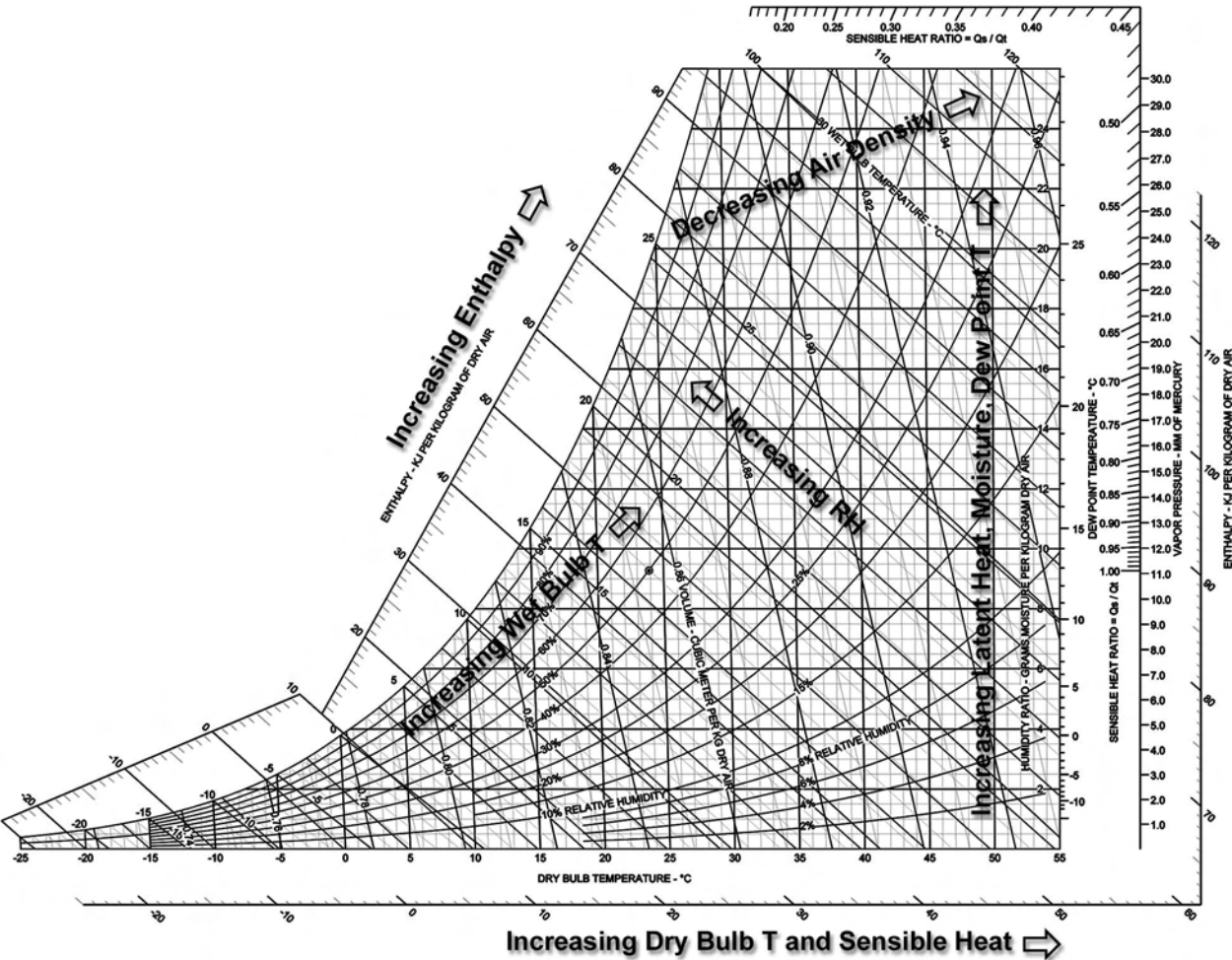


Table 9.1: Psychrometric Terminologies

Measurable Psychrometric Properties		Calculable Psychrometric Properties	
Dry-bulb Temperature	t_{DB}	Specific Enthalpy	h
Wet-bulb Temperature	t_{WB}	Specific Volume	v
Dew-point Temperature	t_{DP}	Humidity Ratio	W
Relative Humidity	RH	Water Vapor Pressure	p_w
Barometric Pressure	P_{BAR}		

9.2 Dry-Bulb Temperature

Dry bulb temperature can be read with an ordinary thermometer, RTD, or temperature sensor that has no moisture on its surface. The process of changing the dry bulb temperature is referred to as “sensible heating” or “sensible cooling.”

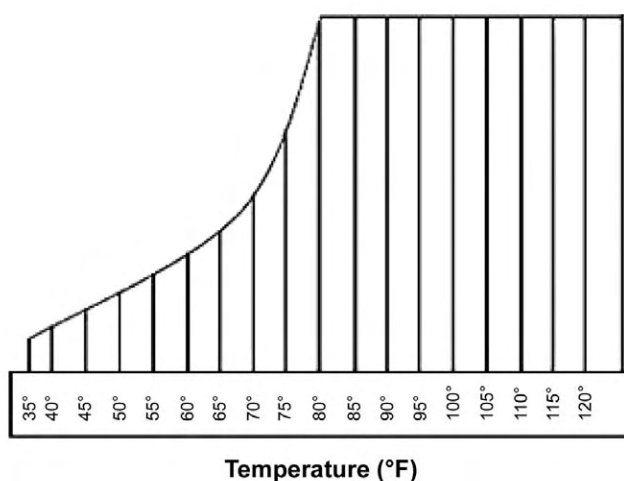
Symbol: t_{DB}

Units: °F (°C)

Example: 70°F_{DB} (21°C_{DB})

The dry bulb temperature of the air is represented as vertical lines, increasing in temperature from left to right on the psychrometric chart, Figure 9.2.

Figure 9.2: Dry Bulb Temperature



9.3 Wet-Bulb Temperature

Wet bulb temperature is indicated by an ordinary thermometer having its sensor (bulb) covered with a sleeve wetted with (distilled) water in rapidly moving air, measuring the reading as the water evaporates. Evaporation removes heat from the thermometer bulb, cooling the thermometer in proportion to the amount of evaporation. This cooling lowers the temperature of the “wet bulb” thermometer. How much the wetted sleeve cools depends on the rate at which the water on the wick evaporates, which depends on the dry bulb temperature of the air and the moisture content of the air. If the air is very dry, the water on the wet bulb wick evaporates very quickly and the temperature drops sharply. If the air already contains a lot of moisture, very little moisture will be able to evaporate from the wick and the temperature will change very little. When the air is saturated with moisture (100% RH), no water will evaporate to cool the thermometer bulb and the wet bulb temperature will be the same as the dry bulb temperature.

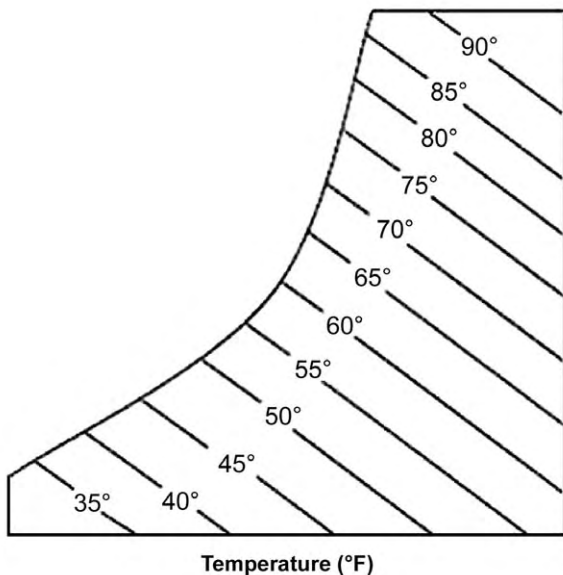
Symbol: t_{WB}

Units: °F (°C)

Example: 65°F_{WB} (18°C_{WB})

The wet bulb temperature of air is represented as downward slanting lines from top-left to bottom-right on the psychrometric chart, Figure 9.3.

Figure 9.3: Wet Bulb Temperature



9.4 Dew-Point Temperature

The temperature at which water vapor leaves the air and collects on cool objects in the form of fine water droplets or bands together and becomes fog is called the saturation or dew point (t_{DP}) temperature. The higher the amount of moisture in the air; the higher the dew point temperature.

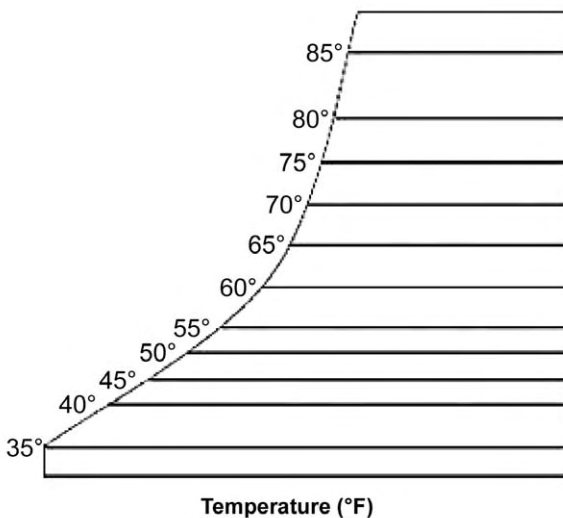
Symbol: t_{DP}

Units: °F (°C)

Example: 62°F_{DP} (16°C_{DP})

Dew point temperature is represented by horizontal lines extending across the chart and intersecting the saturation line, the left boundary of the chart (see Figure 9.4).

Figure 9.4: Saturation/Dew Point Temperature



9.5 Relative Humidity (Percent of Saturation)

RH is the ratio of the amount of water vapor in the air compared to the maximum amount of water vapor the air can hold at the same dry bulb temperature and pressure, expressed as a percentage. Air's ability to hold moisture increases as the temperature of the air increases. The dry bulb temperature of the air should be defined when using RH, as it is relative to a specific dry bulb temperature.

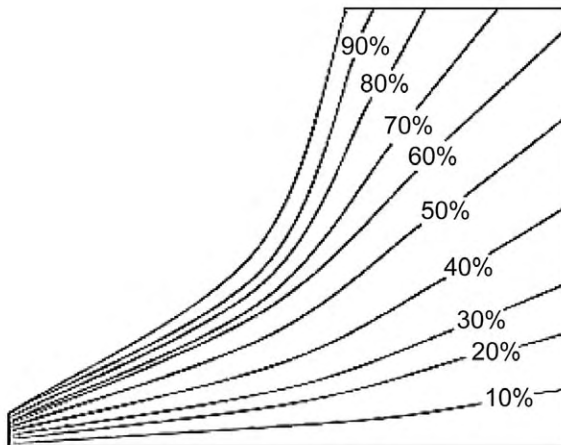
Symbol: RH

Units: %

Example: 77% RH at 68°F_{DB} (77% RH at 20°C_{DB})

RH is displayed as a series of upward curved lines on the psychrometric chart (see Figure 9.5). The uppermost curve that runs from the left axis to left side of the top is 100% humidity line, representing totally saturated air. The bottom axis (horizontal line) of the chart is the 0% humidity line and represents totally dry air.

Figure 9.5: Relative Humidity



9.6 Barometric or Total Pressure

Pressure is the force per unit area exerted by gravity on an air mass. Barometric pressure is measured with a barometer, often filled with mercury. Unless stated otherwise, the properties of moist air/water mixtures represented on a psychrometric chart are those of air at standard sea level barometric pressure (29.92 inch Hg or 101.325 kPa); therefore, there is no scale on the chart for barometric pressure.

Symbol: P_{BAR}

Units: inch Hg (Pa)

Example: 29.92 inch Hg or 101.3 kPa

9.7 Specific Enthalpy

Enthalpy is a measure of both latent heat (moisture) and sensible heat (dry heat only). Enthalpy difference is used to quantify the total amount of heat energy (BTU or Joules) added to or removed from air in a given HVAC process. When air is hot or contains moisture, the enthalpy value is higher than air that is cold or contains lower quantities of moisture.

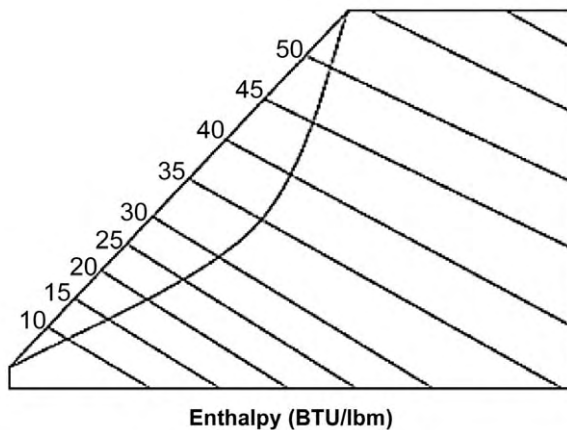
Symbol: h

Units: BTU/lb (kJ/kg) of air

Example: 30.02 BTU/lb

Enthalpy is represented by slanted lines that travel from top-left of the psychrometric chart (see Figure 9.6), extending downward to bottom-right of the psychrometric chart to the bottom axis, almost parallel to t_{wb} lines.

Figure 9.6: Enthalpy



9.8 Specific Volume

Specific volume is the amount of space 1 lb of air occupies at specific atmospheric conditions, expressed as cubic feet per pound of dry air. It is the inverse of density.

When a cubic foot of air is heated, it will expand to more than a cubic foot of space although its original weight will not change. A cubic foot of the heated air will weigh less than a cubic foot of the original air. Since the heated air weighs less than the original (now cooler) air, the heated air will “rise” higher and the cooler air will “sink” lower.

When working in altitudes above 2,000 feet (600 m), calculations should be adjusted for specific volume and density. With increasing elevations, the air becomes “thinner” so a greater volume of air needs to be moved in order to move the required mass of air needed to meet design criteria.

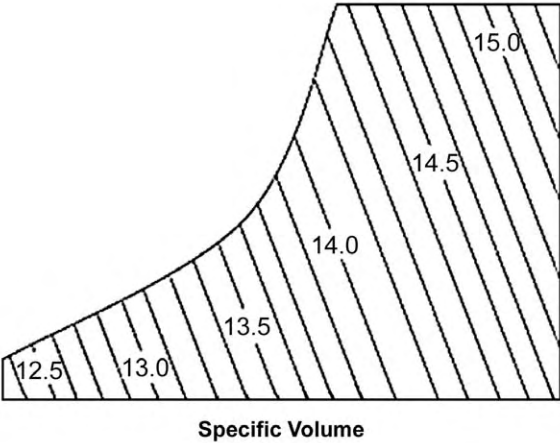
Symbol: v

Units: ft^3/lb (m^3/kg) of dry air

Example: 13.61 ft^3/lb

Specific volume is represented as steep downward sloping lines traveling from the top of the psychrometric chart, Figure 9.7 to the bottom axis.

Figure 9.7: Specific Volume



9.9 Humidity Ratio or Specific Humidity

Humidity ratio is a measurement of the actual amount of water in the air and is independent of the air's temperature. It is measured in either lbs/lbs or in grains/lb dry air. The weight of the moisture in the air is compared to the weight of the air.

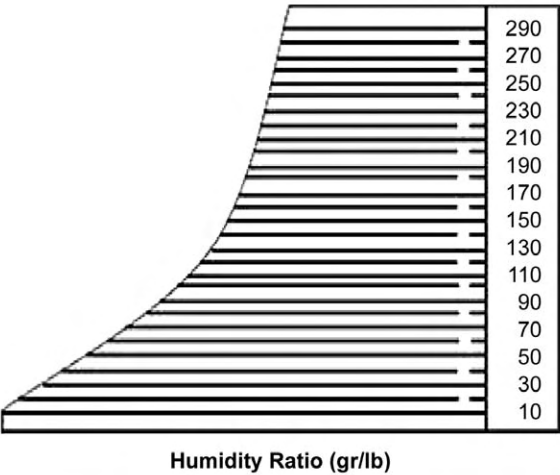
Symbol: W

Units: lbs of water vapor/lbs of dry air or grains/lb ($\text{kg}_{\text{WV}}/\text{kg}_{\text{DA}}$ or grams water/kg dry air)

Example: 85 grains/lb or 0.012 lb/lb or 12 g/kg

Humidity ratio can be read by tracing a horizontal line from an established condition on the psychrometric chart, Figure 9.8 to the chart's right edge, where the scale indicates the weight of the moisture in mass/mass. If the scale is expressed in grains of moisture per pound (gr/lb) of air and there is a need to convert the scale to pounds of moisture per pound of air, divide the number of grains by 7,000. If the scale is expressed in pounds of moisture per pound of air and there is a need to convert the scale to grains of moisture per pound of air (or kg/kg), multiply the W number by 7,000.

Figure 9.8: Humidity Ratio



9.10 Vapor Pressure

Water vapor pressure is the pressure exerted by the water vapor molecules in the air/water mixture, the higher the specific humidity the higher the vapor pressure.

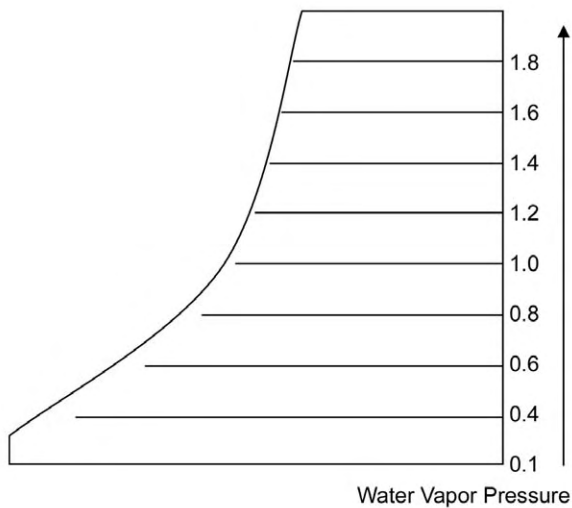
Symbol: p_{wv}

Units: inches Hg (Pa) or inches Hg

Example: 0.5691 inch Hg

The vapor pressure scale is sometimes found on the right side of the psychrometric chart, Figure 9.9, increasing linearly from the bottom of chart to the top of chart.

Figure 9.9: Vapor Pressure

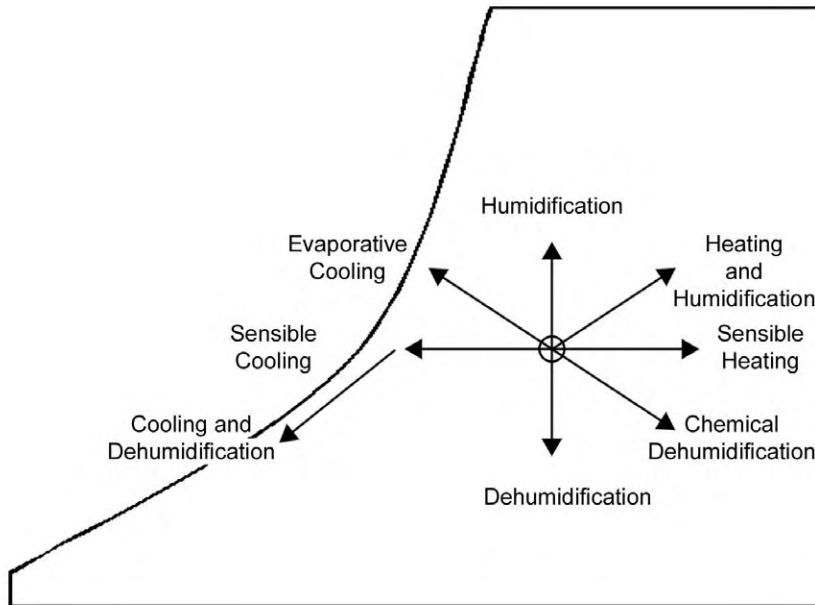


9.11 Eight Fundamental Vectors

There are eight (8) fundamental vectors or processes that can be represented on a psychrometric chart (see Figure 9.1).

1. Humidification
2. Heating and Humidification
3. Sensible Heating
4. Chemical Dehumidification
5. Dehumidification
6. Sensible Cooling
7. Cooling and Dehumidification
8. Evaporative Cooling

Figure 9.10: Eight Fundamental Vectors

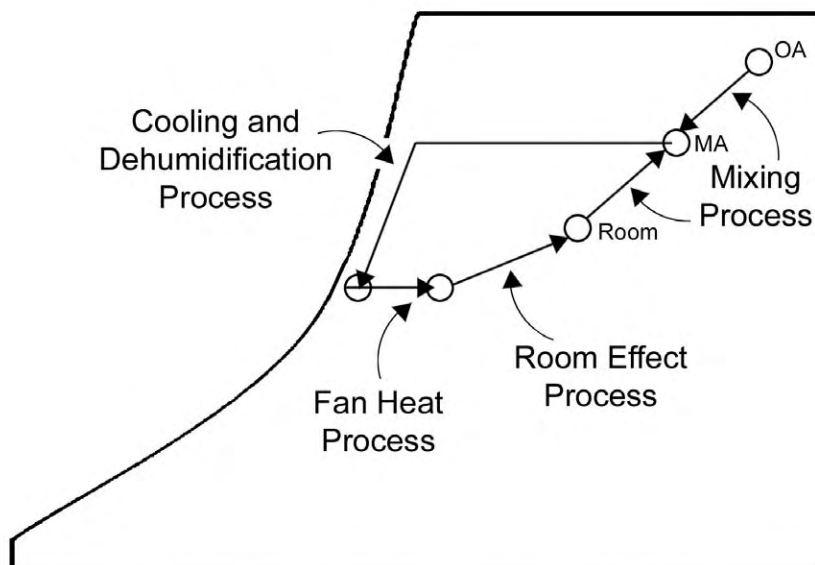


9.12 System Mapping

The treatment of supply air to a room can be “mapped” on a psychrometric chart. Each segment of the map represents a specific operation (e.g., heating, cooling) being performed on the air. See Figure 9.11.

Room air and outdoor air are mixed to create mixed air. The mixed air is then cooled to the dewpoint of the mixture (the line extending to the left) and with further cooling, the saturated mixture is dehumidified. The air then passes through the draw-through fan, which adds sensible (dry) heat. As the air is introduced into the room, it is mixed with air heated by the room’s heat sources to reach the desired temperature and humidity conditions.

Figure 9.11: Typical HVAC Cooling/Dehumidification Process with a Draw-Through AHU



A Four-Process Air Conditioning Cycle

Appendix 4

Science-Based Quality Risk Management

10 Appendix 4 – Science-Based Quality Risk Management

Risk management is a systematic application of management policies, procedures, and practices to the task of identifying, assessing, controlling, and monitoring risks. It is typically an iterative process.

Risk management should be based on good science and product and process understanding, e.g., an understanding of CQAs, which is based upon and ultimately traceable back to the relevant regulatory submission.

Qualitative or quantitative techniques may be used. The focus should be on the risk posed to patient safety and product quality.

Risk management should reduce risks to an acceptable level. Complete elimination of risk is neither practical nor necessary.

For a given organization, a framework for making risk management decisions should be defined to ensure consistency of application across functions. Such a framework is most effectively implemented when it is incorporated into the overall Quality Management System.

10.1 ICH Q9 Quality Risk Management Approach

The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guideline ICH Q9 (Reference 1, Appendix 12) describes a systematic approach to quality risk management. ICH Q9 is used as the basis of the Quality Risk Management approach described in the Guide.

ICH Q9 defines two primary principles of quality risk management:

The evaluation of the risk to quality should be based on scientific knowledge and ultimately, link to the protection of the patient.

The level of effort, formality, and documentation of the quality risk management process should be commensurate with the level of risk.

ICH Q9 is intended for general application within the pharmaceutical industry.

This Guide uses the following key terms taken from ICH Q9.

Harm: damage to health, including the damage that can occur from loss of product quality or availability.

Hazard: the potential source of harm.

Risk: the combination of the probability of occurrence of harm and the severity of that harm.

Severity: a measure of the possible consequences of a hazard.

This Guide applies the general principles of ICH Q9 to describe a general process for quality risk management consisting of the following elements:

- Risk Assessment
- Risk Identification
- Risk Analysis

- Risk Evaluation
- Risk Control
- Risk Reduction
- Risk Acceptance
- Risk Communication
- Risk Review

The process is described in more detail in the following sections.

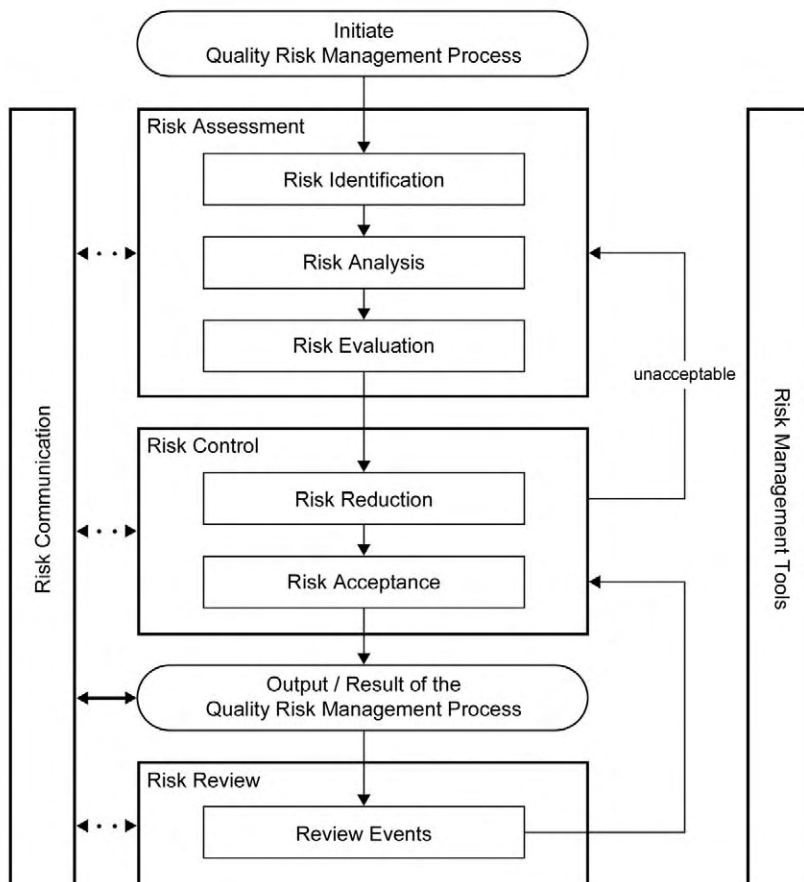
10.2 Overview of the Quality Risk Management Process

Quality risk management is a systematic process for the assessment, control, communication, and review of risks to the quality of the drug (medicinal) product across the product lifecycle.

A model for quality risk management is outlined in Figure 10.1, which is taken from ICH Q9.

The emphasis on each component of the framework might differ from case to case, but a robust process will incorporate consideration of all the elements at a level of detail that is commensurate with the specific risk.

Figure 10.1: Overview of a Typical Quality Risk Management Process – from ICH Q9



10.3 Initiating Quality Risk Management

Quality risk management should include systematic processes designed to coordinate, facilitate, and improve science-based decision making with respect to risk.

The following steps should be considered when initiating and planning a quality risk management process:

- Define the problem and/or risk question, including pertinent assumptions.
- Identify the potential for risk.
- Assemble background information and/or data on the potential hazard, harm, or human health impact relevant to the risk assessment.
- Identify a leader and necessary resources.
- Specify a timeline, deliverables, and appropriate level of decision making for the risk management process.

Determining the risks associated with maintenance requires a common and shared understanding of factors such as:

- impact of operational tolerances on patient safety and product quality
- impact of design of facilities and equipment on maintenance activities
- impact of methods and materials used during maintenance activities
- maintenance programs and maintenance plans
- training

10.4 Risk Assessment

Risk assessment consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards, and consists of identification, analysis, and evaluation activities.

Risk assessment addresses the following questions:

- What might go wrong?
- What is the likelihood (probability) it will go wrong?
- What are the consequences (severity)?

Risk identification is a systematic use of information to identify hazards referring to the risk question or problem description. Information can include historical data, theoretical analysis, informed opinions, and the concerns of stakeholders. Risk identification addresses “What might go wrong?” including identifying the possible consequences. This provides the basis for further steps in the quality risk management process.

Examples of CGMP risks include:

- contamination of product caused by maintenance practices, e.g., use of inappropriate spare parts that contaminate product

- facilities or equipment design that does not facilitate appropriate levels of maintenance
- lack of CGMP training for maintenance technicians
- maintenance activities causes (critical) equipment to be (unknown to production) out of service

Systems or equipment that may impact product quality or patient safety (CGMP systems or equipment) should be identified as part of the commissioning process.

Risk analysis is the estimation of the risk associated with the identified hazards. It is the qualitative or quantitative process of linking the likelihood of occurrence and severity of harms. The ability to detect the harm also should be considered in the estimation of risk.

Risk evaluation compares the identified and analyzed risk against given risk criteria. Risk evaluations consider the strength of evidence for all three of the fundamental questions.

Typically, the outcome of the risk assessment will be expressed using qualitative descriptors, such as “high,” “medium,” or “low.” These terms and how they are used should be defined in as much detail as possible.

10.5 Risk Control

Risk control includes decision making either to reduce risks or accept them, or both. The purpose of risk control is to reduce the risk to an acceptable level. The amount of effort applied to risk control should be proportional to the significance of the risk.

Risk control addresses the following questions:

- Is the risk above an acceptable level?
- What can be done to reduce or eliminate risks?
- What is the appropriate balance among benefits, risks, and resources?
- Are new risks introduced as a result of the identified risks being controlled?

Risk reduction focuses on processes for mitigation or avoidance of quality risk when it exceeds a specified (acceptable) level. Risk reduction might include actions taken to mitigate the severity and probability of harm. Processes that improve the detectability of hazards and quality risks also might be used as part of a risk control strategy. The use of PdM technologies can increase the detectability of an equipment failure and might be implemented where the associated risk warrants such an approach.

The implementation of risk reduction measures can introduce new risks into the system or increase the significance of other existing risks. For example, frequent maintenance on equipment increases the probability of error in disassembly or reassembly. Hence, the results of risk assessment should be revisited to identify and evaluate any possible change in risk after implementing a risk reduction process.

Risk acceptance is a decision to accept risk. Risk acceptance can be a formal decision to accept the residual risk or it can be a passive decision in which residual risks are not specified.

For some types of harms, even the best quality risk management practices might not entirely eliminate risk. In these circumstances, it might be agreed that an appropriate quality risk management strategy has been applied and that quality risk is reduced to a specified (acceptable) level. This (specified) acceptable level will depend on many parameters and should be decided on a case-by-case basis.

Procedural and technical controls available to reduce risks to an acceptable level include:

- Establishing a Maintenance Program, including:
 - system inventory and risk assessments
 - maintenance plans
 - change management
 - clearly defined roles and responsibilities
 - documentation requirements
 - spare parts
 - training

10.6 Risk Communication

Risk communication is the sharing of information about risk and risk management between the decision makers and others. Parties can communicate at any stage of the risk management process.

The output and result of the quality risk management process should be appropriately documented, and communicated, e.g., to regulators, to the patient, within a company.

The relationship between the Maintenance Unit and Operations should be a partnership with mutual accountability for asset care. Each department should communicate with the other to ensure errors are avoided. For example, operating departments need to provide detailed information about equipment when in need of repair rather than indicating "it is not working." Similarly, the Maintenance Unit should inform the operating department that they can resume use of the asset following completion of a repair to avoid partially repaired equipment from being placed into service.

10.7 Risk Review

Risk management should be an ongoing part of the quality management process. A mechanism to review or monitor events should be implemented.

The output and results of the risk management process should be reviewed to take into account of new knowledge and experience. Once a quality risk management process has been initiated, that process should continue to be utilized for events that might impact the original quality risk management decision, whether these events are planned (e.g., results of product review, inspections, audits, change control) or unplanned (e.g., root cause from failure investigations, recall).

Use the data gathered by the quality system to find opportunities to further minimize the CGMP risks.

10.8 Quality Risk Management Tools

No one tool or set of tools is applicable to every situation in which a quality risk management process as described is applied. ICH Q9 provides a general overview of and references for some of the primary tools used in quality risk management by industry and regulators:

- Predictive Maintenance (PdM)
- Reliability Centered Maintenance (RCM) Analysis
- Failure Modes and Effects Analysis (FMEA)
- Root Cause Failure Analysis (RCFA)

Typically, the Maintenance Unit is involved in these types of processes and analysis.

Appendix 5

HVAC Risk Assessment Examples

11 Appendix 5 – HVAC Risk Assessment Examples

11.1 Examples – Risk Assessment for HVAC

These examples describe an approach to risk assessment and countermeasures for HVAC systems serving product handling spaces.

To perform a successful risk evaluation, the SME should consider:

- risk description
- risk probability
- risk impact on product/patient
- ability to detect
- risk reduction steps

11.1.1 Example One – Classified Space

- **Risk** – upset of room air balance due to failure of CV box on air supply.
- **Risk probability** – medium: it does happen.
- **Risk impact** – medium: changes in airflow will change room particle counts and room pressures. Adverse pressure relationships may follow.
- **Ability to detect** – high: DP alarms will detect change in room DP due to airflow change if there are no DP controls in the room to mask the problem. Daily in-operation particle monitoring should detect room count changes due to changed airflow.
- **Risk reduction** – risk to patient is low: for GEP, to avoid having the problem cause a loss of product; however, the use of low-quality CV boxes should be avoided. If air supply is held constant and double HEPA filters are used (primary HEPA in AHU and terminal filters), CV boxes should not be needed. Airflow to each room will follow airflow from HVAC AHU (which is monitored for fan control); alarm low AHU airflow. Summary: risk to patient is low 'as-is.' However, changing the design (e.g., replacing CV devices with terminal HEPA) may increase confidence in the air filtration, while eliminating the potential for CV failure.

11.1.2 Example Two – Classified Space

- **Risk** – failure of UFH over Grade 5 (EU Grade A) area.
- **Risk probability** – medium: either the fan must fail to run (medium probability) or a HEPA filter must fail (low probability).
- **Risk to product/patient** – high: product is exposed under the hood.
- **Ability to detect** – medium: operators may not notice a change in hood status.

- **Risk mitigation** – airflow switch on fan (not a motor current switch) or airflow velocity monitoring (hot wire) at the hood filter face, but not in the path to critical sites. Periodic scan testing of HEPA filters should include velocity check. Summary: a hood flow monitor should reduce the risk and increase ability to detect. Periodic HEPA integrity and velocity checks also are advised.

11.1.3 Example Three – Pressure Controlled Space

- **Risk** – pressure reversals due to improper action of room pressure control damper.
- **Risk probability** – medium: usually a small system can be tuned such that active pressure control will not adversely affect pressure relationships, but large systems may be more difficult to maintain in control. In addition, controls may reset wind up because of doors being open too long: when doors close pressure relationships reverse.
- **Risk to product/patient** – high: pressure reversal may upset air balance in depyrogenation equipment or introduce large quantities of contamination from room to room.
- **Ability to detect** – high: pressure monitoring and alarm.
- **Risk mitigation** – calibrate and challenge DP monitoring periodically and ignore momentary DP changes because of doors opening and closing (validate acceptable time delay). No further action will be needed, unless economics require minimal product loss due to upsets. If further action is needed to avoid loss of product (GEP), use airlocks between air classes. Alarm if DP = zero through an airlock (two doors are open). Choose which DP control dampers should be “fast” and which “slow.” Consider eliminating automated pressure control by simplifying the air balance (no variable exhausts, constant supply, etc). Summary: if pressure monitoring can be trusted, no unacceptable product should result because of pressure control malfunction.

11.1.4 Example Four – Multi-Product Campaigned OSD Facility with One AHU

- **Risk** – cross-contamination potential because of backflow in HVAC or residue from earlier product in air ducts or from other rooms running different product.
- **Risk probability** – medium: power/HVAC failures are infrequent. Product contamination in air ducts is likely, but large amounts are not expected as each room has local process exhaust to keep airborne levels low.
- **Risk impact** – could be high if sufficient quantities of deposited material break loose and contaminate another product.
- **Ability to detect** – low.
- **Risk mitigation** – 1. put processes under protective hood or (better) inside pressurized containment device. If product is potent, consider a double wall barrier to also protect operator. Do not recirculate process exhaust from isolator. 2. Terminal HEPA filters will capture in-duct material and keep cross-contaminants from entering the room via HVAC, even if air supply power fails. Filters should be tested periodically. 3. Rooms should be held negative to building to help prevent airborne cross-contamination from other concurrent processes. 4. Optional: a central return air duct filter bank will keep AHU clean and capture airborne product closer to the room. An alternative would be return air filters at each room with volume controls (possibly DP control) to compensate for air filter loading. Summary: process containment and terminal HEPAs will do the most to reduce the risk to low, probability to low.

Appendix 6

Impact Relationships Example

12 Appendix 6 – Impact Relationships Example

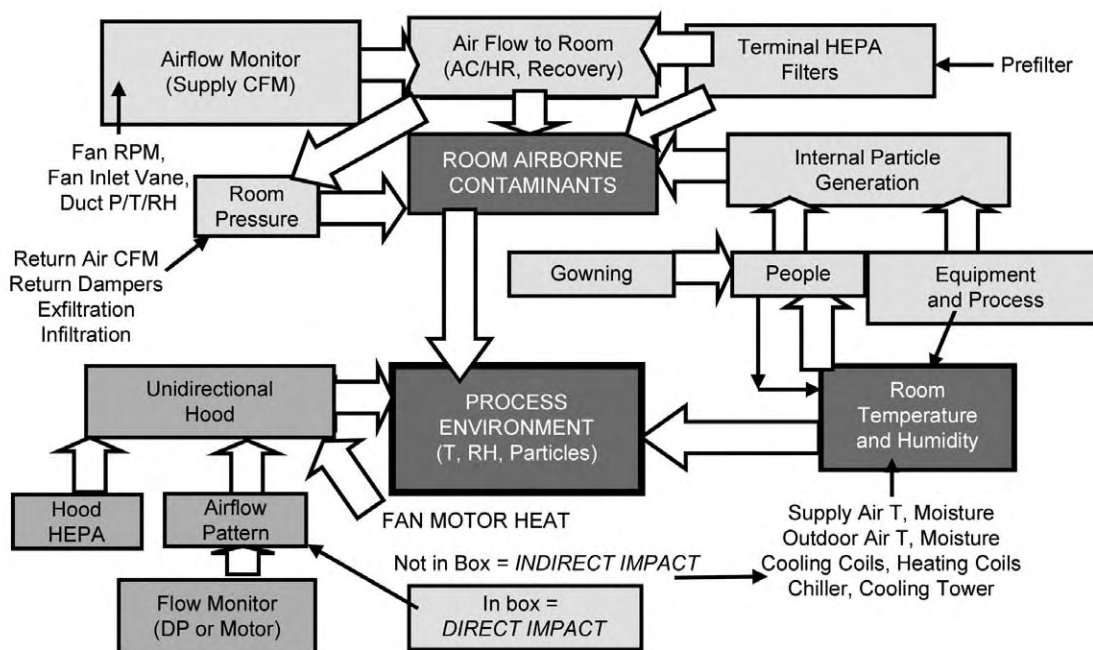
Figure 12.1 addresses the inter-relationships between critical HVAC parameters for Aseptic Processing (a classified space) and the HVAC components. Items in shaded boxes are more critical (i.e., direct impact) as determined by the Baseline® Guide on Commissioning and Qualification (Reference 13, Appendix 12). The three boxes showing the actual HVAC critical parameters are temperature/RH, room airborne contaminants, and process environment. Monitoring systems for temperature, RH, and particles should be qualified.

Secondary parameters (that can affect the HVAC critical parameters) are also usually included in HVAC qualification:

- airflow to the room, affecting particle counts and recovery, monitored at the AHU
- recovery (periodic test)
- terminal HEPA filters (note that HEPAs in the air handler are for GEP to extend terminal filter life)
- internal particle generation (requires control of people and process, outside the HVAC qualification scope, but may depend on local exhaust for particle removal)
- room pressure (to keep contaminants out)
- UFH airflow patterns
- UFH HEPA filters
- UFH airflow monitor

An HVAC system serving a non-classified area (oral dosage, non-sterile drug substance, packaging, etc.) would have fewer or different direct impact systems and critical components. Understanding the impact of components on product quality allows qualification efforts to focus on critical components (e.g., monitoring systems, HEPA filters).

Figure 12.1: Impact Relationships for Aseptic HVAC



Appendix 7

ISO 14644-3 – A Qualification Document

13 Appendix 7 – ISO 14644-3 – A Qualification Document

The ISPE Baseline® Guide on Commissioning and Qualification (Reference 13, Appendix 12) suggests qualifying, while commissioning, without repetition of commissioning tests for qualification.

International Standard ISO 14644-3, Cleanrooms and Associated Controlled Environments – Part 3, Test Methods, (Reference 3, Appendix 12) outlines procedures for testing the performance of clean spaces, whether the space is a classified (such as ISO 7, Euro Grade B) cleanroom or a non-classified processing space (such as for oral dosage products). Incorporating ISO 14644-3 may help to create documents to qualify the performance of a cleanroom.

Procedures covered by Annex B of 14644-3 include methods and equipment for testing:

- airborne particle counting for room classification (classified pharma spaces)
- airborne particle counting, ultrafine particles (smaller than 0.1 micron) – not normally used in pharma
- airborne particle counting, macroparticles (larger than 5 micron) – not a normal pharmaceutical test
- airflow – velocity and uniformity – for unidirectional airflow spaces, airflow supply from filters and in ducts; also airflow to non-unidirectional spaces
- air DP – may be used for classified and other process spaces. For classified space (as in sterile product manufacture), verify GMP DP values of 10 to 15 Pa between air classes.
- installed filter leakage – total leakage, scan test, choice of aerosols (may be used for non-classified space, such as where hazardous products are processed). The sterile processing guidances may require a specific performance for HEPA filters serving classified spaces.
- Airflow visualization (smoke testing) – common in Grade A (ISO 5) unidirectional spaces, but may be used where process containment is used. The “tracer thread” method is not commonly used in pharmaceutical environments, and videos are expected for most UFHs.
- Temperature – usually a critical parameter where product is stored, may be critical to personnel comfort (and subsequent generation of bioburden) in classified spaces.
- Humidity – not usually an issue for liquid products, and may be a personnel comfort issue. See the appropriate ISPE Baseline® Guide (Reference 13, Appendix 12) for the pharmaceutical dosage form.
- electrostatic and ion generators – usually used for electronics manufacture, not pharmaceutical environments
- particle deposition – electronics; pharma uses settling plates for CFU counting instead
- room recovery – common test in European pharmaceutical cleanrooms, a good indicator of HVAC robustness; in the US recovery testing can justify as-built air changes. See ISPE Baseline® Guide for Sterile Manufacturing Facilities (Reference 13, Appendix 12).
- containment leakage – to check integrity of the room “fabric,” sometimes done in pharmaceutical environments, particularly where potent materials are exposed to the room environment

Appendix 8

Science- and Risk-Based Specification and Verification Approach

14 Appendix 8 – Science- and Risk-Based Specification and Verification Approach

14.1 Introduction

This chapter describes an enhanced science- and risk-based approach to verifying that a system is fit for intended use, based on recent regulatory and industry trends, and published guidance, specifically ICH documents, such as Q8 Pharmaceutical Development, Q9 Quality Risk Management, and Q10 Pharmaceutical Quality System, and various supporting industry consensus standards, such as the *ASTM E2500 Standard Guide for Specification, Design, and Verification of Pharmaceutical and Biopharmaceutical Manufacturing Systems and Equipment* (Reference 10, Appendix 12).

This approach is based on:

- a thorough understanding of the product and process and the role of science
- use of risk assessments to determine the scope and extent of required verification in the overall risk management process, which is related to patient safety
- focusing on parameters that affect product quality and patient safety
- focusing on practices that lead to achieving fitness for intended use

Key principles that provide the basis for developing engineering requirements include:

- The assessment and designation of criticality should be primarily based on impact on the safety and efficacy of the drug product to the patient.
- CQAs should drive the focus of the risk assessment along with CPPs.
- The installation and verification process should focus on value added activities and should remove activities that are wasteful or do not add value.
- Verification practices performed solely for regulatory compliance should be avoided.⁴

Well planned commissioning activities and documentation that follow GEP can contribute to meeting installation and verification requirements.

Acceptance of this approach by individual regulators (or even individual operating organizations) will likely vary. The operating company may wish to discuss the approach with appropriate regulators before defining detailed activities and documents for facility acceptance.

The appropriate ISPE Baseline® Guide (Reference 13, Appendix 12) covers regulatory expectations for HVAC performance. The extent of verification documentation may depend on the level of risk identified.

14.2 Key Concepts of the Approach

This section addresses the application of the key concepts described in ASTM E2500 (Reference 10, Appendix 12) to the specification, installation, and verification of HVAC Systems.

⁴ If a practice adds to the assurance that the equipment or system will work as intended, then that practice should be performed whether or not the system is part of GMP manufacturing operations. If it does not, then that practice should not be performed unless specifically required for compliance.

The goal of this approach is to improve patient safety while controlling costs and reducing non-value adding effort.

It should be noted that these key concepts focus on patient safety and product quality (GMP). The verification of the specification and design impacts on worker safety, health, environmental, and other non-GMP concerns also should be considered.

14.2.1 Risk-Based and Science-Based Approach

The level of risk to product quality should be based on scientific knowledge that leads to protection of the patient. The level of effort expended in the quality risk management process should reflect the level of risk. Product and process information related to product quality and patient safety should be the basis of the science- and risk-based decision to ensure that manufacturing systems are designed and verified fit for their intended use.

Considerations include CQAs, CPPs, process control strategy, and prior production experience.

For HVAC Systems, the risks of system failures and interruptions should be addressed during the specification and design part of the process.

14.2.2 Critical Aspects of Manufacturing Systems

Critical aspects of manufacturing systems typically are functions, features, abilities, and performance characteristics necessary for the manufacturing process and systems to ensure consistent product quality and patient safety. HVAC systems may affect the manufacturing system and the critical aspects. Verification activities should focus on the critical aspects of the HVAC system's effect.

14.2.3 Quality by Design

Quality by design concepts should be applied to the manufacturing system throughout its life cycle.

14.2.4 Good Engineering Practice

GEP is a set of established engineering methods and standards that are applied throughout the facility life cycle to deliver appropriate and effective solutions. For HVAC systems, GMP requirements, code requirements, including sustainability requirements and energy efficiency, safety, health environmental, ergonomic operational, and maintenance, should be addressed.

GEP covers all engineering activities and documentation and encompasses the following:

- Design and installation that takes account of GMP, safety, health, environmental, ergonomic, operational, maintenance, recognized industry guidance, and statutory requirements.
- Professional and competent project management, engineering design, procurement, construction, installation, and commissioning that demonstrates functionality in accordance with design specifications.
- Appropriate documentation, including design concepts, design schematic drawings, as-installed drawings, test records, maintenance and operations manuals, statutory inspection certificates, etc.

14.2.5 Subject Matter Experts

SMEs have specific expertise and responsibility in a particular area or field. For HVAC systems, this could include the HVAC engineer, quality unit, automation experts, or operations.

14.2.6 Use of Supplier Documentation

Supplier documentation may be used in the verification process if a vendor with an acceptable quality system produces it. A risk- and science- based approach can be used to determine if the supplier's practices are aligned to manage the risks associated with the selected equipment or system.

14.2.7 Continual Improvement

Continual improvement can happen as information is gained from operations. Improvements can be based on periodic reviews and evaluation, operational data, and root-cause analysis of failures. Typically, for HVAC systems, energy optimization is reviewed.

14.3 Design, Specification, Verification, and Acceptance Process

This section addresses the verification process as they relate to the overall specification, design, and verification process for the manufacturing system as well as the HVAC subsystem. For a more detailed description of the HVAC design process, see Chapters 2 to 4 of this Guide.

14.3.1 Requirements Definition

Product knowledge, process knowledge, regulatory requirements, and company quality requirements should be considered when determining the requirements for the HVAC system. The requirements definition should be driven by patient safety.

14.3.2 Specification and Design

For HVAC Systems, the design process should follow the process described in this Guide.

14.3.3 Verification

The verification process uses a multidisciplinary team focused on product and patient safety. Team members include process, product, and SMEs who may ask "What are the elements of this system that are critical to product quality and patient safety, and how can the team appropriately manage risks associated with those elements to maintain or improve our overall product quality?"

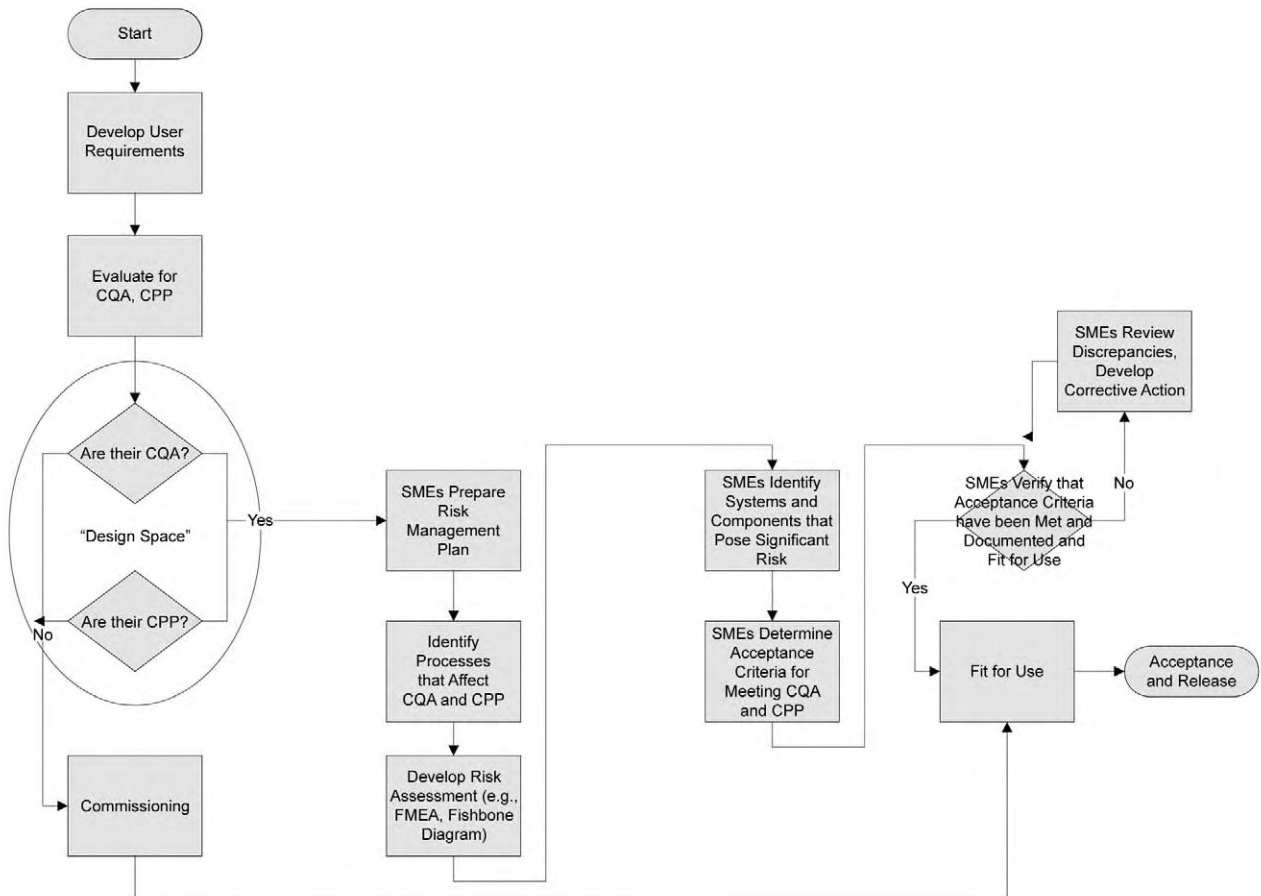
The interdisciplinary expert team forms the foundation for developing a risk management plan. Team members should decide on methodologies to determine acceptable levels of risk and appropriate tools to evaluate risk (e.g., FMEA) after establishing the User Requirements. User Requirements should identify the CPPs, CQAs, and other aspects related to product quality and patient safety.

Once the critical aspects have been identified and documented by the interdisciplinary team, this document becomes the basis for the Verification Plan to be developed. Engineers should know what acceptance tests the quality unit expects to be performed after the verification process is complete in order to prepare systems to pass these tests.

Verification covers the activities, testing, and documentation to confirm that systems, equipment, and environments are fit for their intended use. It is based on GEP coupled with the risk management plan developed in the risk assessment phase. The types of checks and tests to be performed are developed by the SME. For example, the HVAC SME would design a plan to verify the acceptance criteria that meet the critical aspects within the framework of the risk management plan.

For an overview of the verification process, refer to Figure 14.1.

Figure 14.1: Overview of Verification Process



14.3.4 Acceptance and Release

The acceptance and release phase confirms that the manufacturing system and supporting HVAC system are fit for their intended use. This is the last check before initial operation.

14.4 Supporting Processes

The activities described here support the specification, design, and verification process. They occur throughout the process.

14.4.1 Quality Risk Management (QRM)

Quality Risk Management is the high level concept applied to all systems, including HVAC systems. QRM defines the risk assessment process for the manufacturer. Risk Assessment for the HVAC system should be addressed as part of the overall Risk Assessment activity.

14.4.2 Design Review

Design Reviews are planned systematic reviews of specifications, design, design development, and continuous improvement changes performed throughout the life cycle of the manufacturing system. For HVAC systems in the design phase, reviews typically occur at the BOD, schematic design, design development, and construction document phases. HVAC equipment specifications are often not available until the construction document phase, but their review is critical to system quality.

14.4.3 Change Management

Change Management controls changes that affect critical aspects of the manufacturing system, both before and after acceptance for use. After acceptance, changes that affect GMP critical parameters are usually approved by the quality unit prior to implementation. With continual improvement as a goal of the FDA initiative, it is expected that systems that have been verified and accepted for intended use will be later modified to achieve improved patient safety or to reduce operating costs as opportunities arise during the system's life cycle.

14.5 Example Verification Report

The approach described is not prescriptive. One possible approach to the process for an OSD facility, intended as a basis for discussion, is presented.

14.5.1 Design Verification

The company has a single system for reviewing design proposals covering both GEP and GMP aspects. Once the company is satisfied that its comments have been either incorporated or responded to, they issue a memo to the design authority affirming that the drawings may be issued for construction. This document is the written confirmation that the design is, in the companies' opinion, fit for its intended purpose.

Concept: a design review quality system is in place and used in support of GEP – no additional requirements have been added to make this a “quality documentation” exercise. The formal communication to the designer is a contract requirement, not a GMP requirement.

14.5.2 Construction

In this example, the Construction Manager is responsible for getting the project built and commissioned to predefined robust specifications. The CM verifies that work has been completed to specification.

14.5.3 Risk Assessment

The company has identified two quality systems that affect the facility:

- 1. The environmental monitoring program, including:*
 - HEPA leakage testing*
 - area airborne particle and microbiological monitoring*
 - confirmation of the area monitoring system alarm history - temperature, humidity, and “critical” room DPs*
- 2. The HVAC calibration and maintenance system, to verify that monitors are correct*

The system verification summary report covers both of these systems. It is supported by a review that releases the area and the supporting systems for use, incorporating a company quality, environmental impact, and EHS review.

For example, a company has completed a risk assessment of the HVAC system for a new OSD facility, and the following are considered to be critical aspects to allow operation:

- *installation of the correct grade of and leak testing of the AHU mounted HEPA filter (cross-contamination control)*
- *the construction, testing, and verification of the environmental monitoring system*
- *maintenance and calibration of monitoring systems for critical parameters*
- *supporting procedures*

14.5.4 The GEP Documentation Package from the CM should include the following:

14.5.4.1 Installation Verification

The installation documentation confirms that the HVAC system is installed to specification. In this example, it also is used to gather the information needed to populate a CMMS and is a check of the major components. As this document is also used to release the system for use, it will include:

- *verification of the key components*
- *verification of the specified system construction quality checks, e.g., ductwork leakage testing, installation quality, HEPA certification*
- *control system point-to-point cable testing, instrument calibration checking, and controlled component functional testing (e.g., control valves operate in the correct direction and over their entire range)*

14.5.4.2 Automation Check Out/Functional and Performance Testing

Industry practice is inclined toward ACO and FPT:

Automation Check Out (ACO) – checking the BMS sequence of operation, alarms, and interlocks.

Functional and Performance Testing (FPT) - setting up the system for balance, tuning the control loops and setting system alarm points based on the performance achieved by the installed system. For a critical system, a simulated load test also may be carried out.

In the example, company practice is not to produce a “commissioning summary report,” but a system installation and operation verification report that releases the system for use. In this case, the HVAC system release is a part of the requirements for the area release, together with the verification report for the facility and monitoring system.

The project team then checks that this documentation is adequate to confirm correct installation and performance and follows with a Verification Report.

14.5.5 Verification Report

The verification report for this example is less than 15 pages. It contains the following sections:

- **Summary**
- **Purpose and Scope**
- **System Description**

- **Summary of Verifications Performed** – confirming that installation, ACO, and FPT have been satisfactorily completed.
- **Risk Assessment Qualification Requirement Summary** – confirming that requirements identified in the Risk Assessment have specifically been addressed in the commissioning; in this example, the correct grade of HEPA has been installed with certification (from installation) and has been leak tested, and the area has been able to maintain the specified conditions over a representative test period (FPT). (It should be noted that the pre-defined acceptance criteria are derived from the design specification, which is derived from User Requirements.)
- **System Operational Requirements** – confirming the SOPs required to operate the system have been identified.
- **System Maintenance and Calibration** – confirming the SOPs required to maintain the system have been identified.
- **Engineering Change Management Review** – confirming that change of the design from the accepted “issue for construction” drawings has been managed and that the installed design remains acceptable.

Acronyms used in the Example Verification Report

ACO	Automation Check Out
CM	Change Management
EHS	Environmental Health and Safety
FPT	Functional and Performance Testing

Appendix 9

Economics and Sustainability

15 Appendix 9 – Economics and Sustainability

15.1 HVAC System Economics

In addition to protecting the product and patient, production facilities need to consider economics (i.e., making a profit) to continue in business. Overall cost is a major factor in deciding which options to implement for an HVAC system. Life cycle cost usually is much greater than the initial (capital) cost of an HVAC system.

It is common practice to use methods, such as net present value or the rate of return to evaluate different design options. These concepts often are unfamiliar to engineers who strive for the most robust design regardless of cost. Organizations usually have internal accounting systems to facilitate the evaluation of different design concepts, evaluating payback against capital cost, (investment analysis) over the expected life of a facility. Typical systems include net present value and investment rate of return. A cost model should be developed early in a project to estimate the final maintenance, consumables, and energy usage of the facility. It should be the basis against which life cycle cost decisions are evaluated and can be used to challenge User Requirement decisions.

Cost models should be holistic and consider the impact of HVAC on production costs, down time, product or productivity losses, and other costs of doing business.

15.1.1 Risk to Product and Associated Costs

The production-related considerations described are additional to conventional economical considerations balancing capital and operating costs. See Appendix 2.

15.1.1.1 Impact of Failure

The impact of an HVAC system failure could be financially significant in the pharmaceutical industry, possibly causing loss of a batch of product or the loss of control of the conditions in a research laboratory and potentially invalidating the results of a long term test. The risk assessment of a system's failure should include product quality issues, as well as potential business issues. A clear definition of the potential impact of system failure can influence and justify the budget for a system.

The potential impact of a system failure on the area being conditioned and adjacent areas should be reviewed and consider potential modes of failure, such as:

- airflow failure
- air filter failure
- failure of temperature control
- failure of humidity control

15.1.1.2 Redundancy

If the cost and likelihood of failure are high, duplication of systems/equipment may be justified. Redesign the system or process to reduce the risk may be considered a better option. The potential impact of redundancy complicates HVAC system design, startup, and maintenance, along with design requirements for the supporting utilities. For example, duplex air handling systems may require duplex chillers and circulating pumps to decrease risk appropriately.

15.1.1.3 Aesthetics

Materials and systems that do not add functionality, but are provided for aesthetic reasons (e.g., screen walls, high cost materials) should be considered in the cost evaluation. For example, stainless steel and similar duct materials may provide lower life cycle costs when exposed to a rigorous cleaning regimen, but may not be justified in most applications.

15.1.1.4 Defining User Requirements

Range of internal conditions:

- What are the critical parameters?
- What are their Acceptance Criteria?
- How much variation is acceptable?

A wider operating range may mean a lower cost system, both to install and operate. Specifying closer tolerances, may not provide a “better”, (i.e., more robust) system. In order to maintain closer tolerances, a facility may be designed with greater capacity and faster responding sensors and actuators, which are more sensitive and require careful tuning and increased maintenance. Having specified closer tolerances, the larger and more complex system will need to be commissioned to operate to meet these specifications. The capital and operating costs of this more complex system are likely to be higher than a simpler smaller system, with no benefit to the product.

Design value for external conditions:

- If a facility needs to be operable 365 days a year, it should be sized to handle extreme external design conditions. If it is acceptable to have a small percentage down time during peak seasons, the HVAC system and supporting utilities can be significantly downsized. Load shedding may be incorporated into the design of the support utilities, such as reduction of chilled water for office cooling, with only the process HVAC system components being sized to suit the extremes.
- Area classification, air change rates, and DPs should not be over-specified, as this will result in higher life cycle cost with no extra value to the product. For further information, see the applicable ISPE Baseline® Guide and Chapter 2 of this Guide.

15.1.1.5 Other Factors

Other factors can affect the system economics, for example:

- Internal layout/design: this should keep the influence of major heat loads outside the conditioned area or use other systems to minimize the internal loads. For example, a dust extract unit also can remove heat from a motor in the room, reducing space heat gains. There may be benefits to grouping environmentally critical areas within a building, keeping them away from external walls to reduce external heat load variations.
- The use of Computational Fluid Dynamics (computer airflow modeling) may be considered for optimizing air distribution design.
- Sustainability (see Appendix 7)
- Availability/uptime of HVAC systems: demanding high availability (little shut down or maintenance time) drives costs up.

- Other Regulations: requirements of Building and Fire Codes, local zoning, worker protection (OSHA), environmental (EPA), and numerous other requirements must be met, in addition to GMP product/process requirements. These requirements may affect HVAC system design (transport of hazardous powders via HVAC systems to other rooms or outdoors, smoke ventilation, etc.).

15.1.2 Life Cycle Cost Considerations

Numerous factors influence the life cycle cost of a facility and should be considered in the design process to financially assess a project properly.

15.1.2.1 First Cost versus Life Cycle Cost

There is an optimal balance between first cost and operating cost that is unique for each organization and time period. Increased capital investment that yields reduced operating costs may not be the optimal solution, depending on cash flow issues. Additional factors that should be considered include:

- the system design life
- energy costs and trends
- costs of consumables
- ongoing reliability and maintenance costs

15.1.2.2 System Design Life

If the facility has a short life, it may be possible to save money on the equipment and not invest in plant of the quality that would be optimum for a facility with a long predicted operating life. Maintenance costs (as discussed below) extend over the entire facility life, becoming more cost-significant as the facility life increases.

15.1.2.3 Energy Costs and Trends

The type and cost trend of energy supply has a significant impact on HVAC system design choices. Where supply costs are high or expected to rise, systems can be configured to minimize demand and the “total cost of ownership.”

Air Filtration

A low average filter pressure drop translates into reduced fan energy usage. Higher filtration efficiency also results in cleaner coils and equipment, optimizing heat transfer and reducing frequency of equipment cleaning. Lower velocities through the filter medium may translate into better capture efficiency. The optimum selection of pre-filtration systems will balance:

- labor cost
- filter cost
- the contaminants to be captured
- the capacity of the filter
- energy costs and the cost of cleaning the AHU during changing of the filter: this may be a conventional panel/bag or a bag-in/bag-out filter combination.

Drive Belts

Up to 7% efficiency can be lost with traditional v-belt drives because of slippage by worn belts and improper tensioning. This can be reduced dramatically by using direct driven fans, where possible. Cogged or synchronous belt drives could improve the drive efficiency by 2% over v-belts. In addition to saving energy, synchronous belts and flat belts run cooler and tend to last longer than v-belts.

Makeup Air Pretreatment

Rather than cool the entire mixed air quantity to the desired dew point, it may be more economical (when outside air quantities are relatively high) to treat only the outdoor air (preheat or dehumidify for RH control) in a smaller AHU. This treated air, when later mixed with return air in the second AHU, may be of sufficiently low moisture content that further condensing cooling is not required, leading to savings in cooling and reheating energy. It also is possible to pre-treat outdoor air in a large AHU and send the pretreated makeup air to a number of AHUs serving separate areas. These pretreatment schemes are common in sterile facilities and in many OSD facilities with high levels of exhaust. In addition, when coupled with an exhaust air heat recovery system, better energy efficiency may be possible.

Economizer

An outside air economizer is a collection of air dampers and controls that allows more outside air and less return air to be drawn into the air handler. Some designs have incorporated a “blended” approach, attempting to create the ideal supply air temperature by mixing outdoor air and return air. Non-linearity of control dampers can lead to higher airflows than expected, requiring more fan control.

Some spaces (e.g., offices, laboratories, and warehouses) may have less rigid airflow requirements and will not be affected by variable airflow. An outside air economizer saves on cooling energy when outside ambient conditions (sensible and latent heat) are favorable (typically in the more temperate months of a year), rather than using warmer return air to reduce the load on the cooling section. When the outside ambient temperature conditions are lower than the inside space temperature, increased usage of the cooler and less humid outside air will reduce cooling energy that would come from mechanical cooling.

The supply, return, outside, and exhaust air quantities can change during the economizer cycle, leading to changes in facility room pressurization. If another AHU serves an adjacent area, it is possible for unwanted room pressure excursions to occur because of the changing air quantities resulting from varying positions of dampers in an HVAC system. The use of the economizer in areas that require pressurization control is not recommended. Additionally, the increased use of less clean outside air can shorten air filter life and consume more energy to overcome filter pressure. Outside air dampers should have a minimum stop position to assure adequate fresh air for personnel. The guidelines established in “ASHRAE 62.1, Ventilation for Acceptable Indoor Air Quality” (Reference 22, Appendix 12) should be followed to ensure a healthy indoor environment.

Energy Recovery: General

Wherever a significant amount of energy is lost as exhaust, the possibility of energy recovery should be explored. There are some limitations on energy recovery, such as excessive powders in the air stream, the use of scrubbers for pre-treatment, or the presence of significant quantities of condensable hazardous materials in the airstream. Many pharmaceutical facilities may benefit from some sort of recovery.

When evaluating energy recovery options, all costs (pumping, air pressure drops, etc.) on both sides of the equation should be considered. It is recommended that the efficiency of the system, with some level of performance degradation due to fouling, is included in the calculation.

In climates with high humidity during the summer months, energy recovery can be enhanced by employing evaporative cooling in the exhaust air stream; therefore, recovering a portion of the latent heat. Evaporative cooling may be achieved using an evaporative pad or by direct spray on the energy recovery coil.

Energy Recovery – Enthalpy Wheel

Similar in construction to a desiccant dehumidifier wheel, an “enthalpy” heat recovery wheel recovers total energy (sensible, as well as latent heat). Supply and exhaust ducting configuration should be adjacent at the heat recovery device. Purge section and labyrinth sealing system can limit cross contamination to 0.04% of the exhaust air concentration by volume. Specific contaminants in the exhaust stream may be retained in the wheel to be released into entering fresh air. Generally, such recovery units are used only rarely in pharmaceutical HVAC systems.

Energy Recovery – Air-to-Air Plate Exchangers

Air-to-air plate exchangers normally are used to recover only sensible heat from general and toilet exhausts, transferring it to the incoming outside air. Supply and exhaust ducting configuration needs to be adjacent. The reduced heating demand will reduce mechanical heating equipment sizing and operating costs. If recovery efficiency is too high, it could cause icing of the exhaust air in extremely cold weather, requiring a bypass around the unit. Additional fan energy is needed to overcome airside pressure drop.

Energy Recovery – Run Around Coil

Run around coils are normally used on 100% outside air units by transferring only sensible heat from an exhaust air stream to a makeup air stream, via coils and piping normally filled with a glycol solution to avoid freezing. They should be applied where exhaust and supply air handlers are separated by a suitable distance and usually perform best when heating requirements are more dominant than cooling requirements (greater temperature difference between the two air streams). The recovered heat can reduce demand from mechanical heating equipment, resulting in possible downsizing and reduced operating costs. Additional fan power is required because of increased airside static pressure drop through the coils. Refrigerant filled loops also may be employed; these are a hybrid of this system and a static refrigeration device. In these systems, the preload pressure is adjusted to allow the condensation of refrigerant at the temperature of the cooler airstream. These systems are not common and should be attempted only by experienced refrigeration engineers.

Energy Recovery – Refrigerant Coils

Similar in layout to air-to-air exchangers, requiring both air streams to be adjacent, a coil using passive refrigeration (no compressor) can transfer a high percentage of sensible heat from exhaust stream to outdoor (makeup) air. Precautions required are similar to those for air-air exchangers, but also close attention should be given to mounting details.

Component Selection

The cost of energy should be considered from both the system design concepts and the perspective of component selection, for example:

- AHU housing: low cost (off the shelf) units may be made of pre-finished steel and have minimal insulation. The unit may suffer from high leakage of conditioned air, causing increased operating costs, and suffer from external sweating, leading to corrosion and a shorter working life. Custom units may cost appreciably more, but may incur lower energy losses and maintenance costs.
- High-efficiency motors: these reduce energy usage. With proper installation, high-efficiency motors can run cooler than standard motors, and consequently, can have higher service factors, longer bearing life, longer insulation life, and less vibration. NEMA rated Premium Efficient motors have a slightly higher initial cost, but should pay for themselves because of reduced electrical consumption.
- Building envelope: a low cost poorly insulated facility will mean a corresponding increase in the operating cost and capital cost of the HVAC system for a given set of internal conditions. Similarly, a review of the facility construction/insulation may be beneficial, e.g., improving the insulation may allow a warehouse facility to require only a heating system and no air conditioning.

Night Time or Off Hours (Unoccupied) Setback of HVAC

Typical pharmaceutical manufacturing spaces operate as at a constant airflow (CV and reheat system) to:

- ensure adequate airflow to offset particle generation in-operation
- maintain the space “cleanliness” or room classification

In the case of sterile filling areas, this also satisfies regulatory requirements for 20 AC/hr or 15 to 20 minute recovery time (in non-sterile filling these requirements do not apply, but are common in the industry). This approach results in high energy usage, particularly during periods when the space is not in use.

Designs may allow reduced airflow in manufacturing spaces during idle periods. This normally is achieved with airflow controls (dampers or boxes) with flow measurement and a trigger mechanism (push button, time of day function, timer, light switch, etc.) to change airflow to the space. Pressure relationships should be maintained during the setback period, regardless of flow. The time required take for the desired conditions to be achieved (typically 3 to 4 cycles of dilution) should be understood. Setback airflows should be designed to maintain critical conditions in the space as mandated by stored materials, equipment, closed product, etc. It is common to reduce flow to 6 AC/hr in a setback scheme.

Room temperatures and humidity levels may be set back (raised or lowered) periodically to save energy, but should be within the operating acceptance criteria for a room if:

- closed product is present
- corrosion is an issue
- bioburden control is an issue

15.1.2.4 Consumables Costs

The life and cost of each consumable component should be considered. For example, air filters; the optimum selection of pre-filtration systems balances:

- labor cost (for the replacement and the cleanup required)
- filter cost
- particle capture required
- the capacity of the filter
- rate of change of pressure drop
- energy costs

The optimum may be a conventional panel/bag arrangement or may be a bag/bag filter combination to be more cost effective. More expensive, high capacity filters can last longer in service, and over time, require less replacement labor, while providing improved air filtration efficiency as they become dirty. The cost of ULPA filters or “scanned” HEPA filters, rather than ordinary HEPA filters, may be offset by less potential for “bleed-through” issues during routine testing, leading to fewer out-of-specification reports.

An additional example is a fan's drive belt; v-belts have a significantly shorter life than flat belts, but cost less. They are not as energy efficient as flat belts; therefore, the savings in maintaining a stock of spare belts, energy savings, and saving in labor costs to replace the belts and re-tension them, may make flat belts cheaper over the operating life of a facility.

15.1.2.5 Reliability/Maintenance Costs

The decision to invest in labor-saving features, such as performance monitoring and centralized lubrication systems, should consider the anticipated facility life and trends in the cost of labor.

The life cycle cost analysis also should consider reliability/maintenance aspects.

Examples

- Consider the lowest cost material used for a cooling coil: aluminum fins on copper tube. In a poor environment (such as in drug substance facilities), there will be corrosion on the fin material, reducing the heat transfer efficiency of the unit with the fins eventually corroding to the extent that the unit will not perform adequately. Optional coil materials, e.g., copper tube with polyester coated aluminum fins or copper tube with electro tinned copper fins, will increase the first cost, but also will extend the operating life.
- A fan specification with a long-life bearing design will allow for extended operating periods without maintenance. Grouped lubrication points will minimize costs and allow lubrication, while the facility is in operation.
- The cost of routinely calibrating instrumentation should be considered; it may be cost effective to have one calibrated high DP switch across a bank of filters with un-calibrated "engineering information" manometers or pressure gauges across each filter. It also may be economical to install only pressure taps, using a portable calibrated gauge to take readings.

Robust HVAC equipment is more likely to perform reliably from the start and continue beyond its normal anticipated life when properly maintained. Good maintenance procedures performed in a timely manner will, over the life of the equipment, reduce total costs and have a positive effect on the uptime of the production process. For example, vivariums are extremely sensitive operations with long-term animal studies that require reliable and redundant systems to achieve steady environmental conditions. The loss of room conditions could mean the loss of years of data and delay of product introduction.

Reliability and maintenance items that should be considered include:

- redundant fans (if 100% uptime is needed)
- direct driven fans (no belt breakage/slippage, less adjustment needed)
- vibration monitoring of blower and motor bearings (predicts failures, extends up time)
- automated lubrication (reliability and labor cost savings)
- bearing life of ABMA L₁₀ 200,000 hours (reliability)
- lower rotation speeds of motors and fan wheels (extend life, lower noise, suggest 1800 RPM maximum)
- high efficiency air filters (keep the HVAC system clean)

15.1.2.6 Other Factors

Factors to consider, which may vary the ratio of direct (capital) versus indirect (operating) cost include:

- availability grants to assist with capital costs
- incentives from utility providers to make a system more energy efficient
- tax rates

15.2 Sustainable Design for HVAC Systems

15.2.1 Introduction

For a facility that is aiming to be considered as 'green' or sustainable, HVAC systems are an important component. Many pharmaceutical HVAC SMEs may be asked to follow sustainable design and construction guidelines or standards. The requirements may come from a company standard, industry guideline, a design and construction regulation, or a regulation imposed on an already operating facility. Compliance with sustainability guidelines has been optional and considered progressive, and provided market differentiation for the building owner. Compliance with sustainability guidelines and standards may be required in some regions.

15.2.2 Basics – Personnel, Planet, Profit

Many products, technologies, and buildings have claimed to be “green” and many facility owners and personnel want to be considered in line with this concept:

- The first goal is to make the facility and its impact good for society and the people that are affected.
- The second is that the environment should not be disturbed in a way that would cause change, such as global warming or toxic pollution that would affect nearby inhabitants or the plant and animal environment.
- The third goal is that this should all be done in a way that allows the economic system to thrive and return a profit to shareholders.

In an effort to meet these goals, a number of groups have formed to develop guidelines and standards.

There have been claims that green buildings also increase the productivity of personnel. This is beyond the scope of this Guide, but may be a key driver of the movement toward sustainability.

15.2.3 Rating Systems – Project Based

New buildings and large renovation projects can be graded through the use of third party ratings systems. These rating systems are prepared by green building groups. The largest umbrella organization is currently the World Green Building Council (WGBC), represented in the United States by the United States Green Building Council (USGBC). There are equivalent groups throughout the world. There are other organizations that also are developing standards for sustainable construction.

The USGBC produces the Leadership in Environmental and Energy Design (LEED) rating systems. In addition, in the US, the Green Building Initiative (GBI) is a group referenced by many local jurisdictions. The GBI manages the “Green Globes” rating system. There is a move to make either or both of these systems part of a sustainability building code, and some jurisdictions have adopted these guides as regulations.

Both groups are actively working on code language versions (USGBC with ASHRAE and GBI internally) and there is likely to be wider acceptance as time progresses. For pharmaceutical facilities, there may be exceptions for specific spaces, such as cleanrooms. These spaces are important as they consume a lot of energy per unit area.

Each rating system gives points or credits for going beyond the norm compared to similar facilities. There is no credit given for more profit. There are prerequisites that must be met by every building that strives to be considered a green building.

The USGBC has developed an internet-based tool to help teams submit information to achieve certification, using third party reviewers of each building certification application. This review will be run by a separate entity and provides an independent review of prerequisite and credit submissions. The prerequisites and credits needed to achieve the building rating cover a wide variety of green building issues. The overall green building submission and approval process is usually not managed by the HVAC SME. The HVAC SME's involvement is important, but the HVAC SME cannot deliver a building rating alone.

The USGBC also has established a professional credential, the LEED Accredited Professional (LEED AP) based on passing a test related to the sustainable building design and construction process.

15.2.4 Building Energy-Labeling

There are also building energy-labeling systems to address the efficiency of existing building stock. These energy-labeling programs also may be applied to new construction.

Global plans are being developed to label each existing building. Directive 2002/91/EC (EPBD, 2003) (Reference 5, Appendix 12) of the European Parliament and Council on energy efficiency of buildings is being implemented; ultimately, all buildings in the EU will have an energy rating that can be compared to other buildings. In the UK, each building will be required to post a placard with a letter rating of A to G at the main entry. In the US, the rating system is in development by ASHRAE. One optional label available to buildings is from the US EPA Energy Star Program. (Reference 25, Appendix 16). The Energy Star program identifies top performing buildings and provides guidance on how to design and operate an "Energy Star building." The Energy Star program also provides additional guidance on designing a green building.

15.2.5 New Project Design Process and Considerations

15.2.5.1 Sustainable Design Process

For new projects, the sustainable design process starts with an event called the Design Charette. The project team members (including HVAC SMEs, architects, other designers, owner, and builder) participate in selecting the sustainable features of a facility. Team members are assigned specific prerequisites and credits to review and provide feedback to the team on cost, schedule, and impact to occupants. A goal is then established and the team prepares materials for submission.

The design team completes the design in an accepted manner. A submission can be made at the end of the design process using LEED to give the team feedback on how many credits can be achieved. After the design is released for the construction, the team constructs and commissions the facility in preparation for occupancy.

Once prerequisites and an adequate number of credits have been achieved, the building can be considered a green building with a specific level. The LEED program identifies certified, silver, gold, and platinum levels of building certification.

15.2.5.2 Energy Consumption

Rating systems for new projects have a major focus on Energy Consumption with much effort placed on selecting the right system and on selecting design criteria (either occupied space or outdoor conditions) that do not require excessive capital and energy to achieve the desired conditions. Building HVAC systems are normally designed to comply with the local energy sub-code that are usually developed by HVAC centered organizations (such as ASHRAE) and require a minimum level of energy performance. Energy performance can be proven through modeling or prescriptive methods. The level of energy consumption allowed by code is being progressively lowered as technology progresses. The building rating systems expect superior performance for a building to be classified as green. For further information, see Section 3.6.3 of this Guide.

15.2.5.3 Day Lighting – Impact on HVAC

One element of sustainable design is for a building to have natural lighting and views for personnel to see outside. This generally results in larger window areas and potentially the need to increase heating and cooling capacities. In pharmaceutical clean space design, this may require that a series of windows permit a view from a clean space through less clean adjoining spaces to the outside.

Commissioning

Commissioning for sustainable buildings is focused on HVAC, lighting controls, on-site renewable power generation, and domestic hot water systems. Pharmaceutical projects focus on patient safety and product quality and include HVAC systems, as well as critical utility and processing equipment. Pharmaceutical plants normally are commissioned using a process that covers HVAC systems in a GMP manner that complements the sustainable approach.

Sustainable commissioning practices include the development of an Owner's Project Requirements (OPR) document, a commissioning plan, and a summary commissioning report, similar in practice (if not in name) to pharmaceutical commissioning and qualification. The use of the user requirements document in manufacturing systems is similar to the owner project requirements document in sustainable commissioning practices.

Several useful documents, which may be used as a basis for creating commissioning protocols for a specific project or referenced in project protocols without re-writing are listed in the references (References 3, 6, 22, 26, 28, and 30, Appendix 12).

The ASHRAE Guidelines may be used to define the commissioning process activities and scope; they do not describe how to perform hands-on activities.

15.2.6 Indoor Air Quality during Construction and Prior to Occupancy

It is considered a sustainable practice to monitor the interior of buildings to ensure that there is proper ventilation during construction to avoid the buildup of toxic materials in the building that could affect construction workers and occupants. There also is concern for mold growth if materials are moist and promote growth. An IAQ Management Plan for the construction phase can assist with:

- keeping ductwork sealed
- installing temporary filters to reduce dust in equipment and systems
- isolating work areas
- keeping the construction site clean

At the end of construction, buildings can be tested for contamination or flushed out to prepare for move-in of the building occupants.

15.2.7 Measurement and Verification of Utility Services

It is considered a sustainable practice to install metering equipment on utility services, including steam and chilled water on large sites. This data is considered useful in understanding peak demand and identifying options that can lower energy consumption.

15.2.8 On-site Renewable Energy Sources

Certain on-site energy sources can be considered part of the HVAC system, such as solar power water heating and geothermal energy. Local jurisdictions may provide financial incentives to use these systems. The project team should look for these opportunities during the design charrette.

15.2.9 Materials

Some rating systems consider the use of materials made locally or from recycled materials a sustainable practice. However, this is limited to non-mechanical/electrical/plumbing materials in the LEED rating system. HVAC system materials often are considered recyclable and most metal products have some recycled content.

15.2.10 Refrigerants

Refrigerants are regulated to reduce the destruction to the ozone layer and their contribution to green house gases that are identified as contributors to global warming. The use of refrigerants with low Ozone Depletion Potential (ODP) and low Global Warming Potential (GWP) is considered a sustainable design practice. The phase out of ChloroFluorocarbons (CFCs) has been regulated as a result of the Montreal Protocol of 1987 and amendment in 1992 to eliminate HCFCs as well as the Kyoto Protocol of 1997 for reduction of gasses with high GWP where applicable.

15.2.11 Indoor Environmental Quality

The concept of off gassing of Volatile Organic Compounds (VOCs) from materials installed inside buildings, including HVAC system components, should be understood. VOCs have been shown to cause cancer and other diseases in humans, and specific limits have been set to reduce exposure to building occupants. Materials used inside a building must meet specific requirements, including VOCs for field applied HVAC system adhesives and caulks (including fire caulks).

Monitoring of outdoor air and use of carbon dioxide sensors in occupied space are also common elements of design in sustainable projects. Many pharmaceutical facilities use large amounts of outside air and do not permit a high CO₂ condition under normal operation, as typically there is more air introduced than needed by IAQ code.

Exhausting of potentially toxic materials is a requirement in some rating programs.

Rating systems may include credits for walk-off mats and enhanced filtration in AHU systems. Most particulates in non-pharmaceutical buildings come from personnel's shoes, and grates to catch the particles often are installed at building entrances. While the added filtration used in pharmaceutical facilities reduces airborne particulate, it also requires more energy to accomplish the particulate removal.

Smoking is allowed in a green building, within specific strict constraints, as meeting a human want or need; however, most pharmaceutical facilities do not allow smoking.

15.2.12 Increased Ventilation

The building can obtain a greener rating by increasing ventilation to provide more outdoor air to a space. While this may increase energy use, the concept of added “fresh air” is seen to have a positive impact on building occupants.

15.2.13 Controllability of Systems – Thermal Comfort

One way to improve occupant comfort is to give building occupants greater control of their environment. In pharmaceutical facilities, this would have to be within the parameters of the product being handled, but facilities may look at this feature when products are not affected by changes in temperature or humidity.

15.2.14 Summary

Many aspects of the HVAC system design are important to the sustainability of a facility. HVAC engineers are critical to the successful creation of a “green building,” they should be engaged and understand rating systems for each project in order for the design team to be effective.

Appendix 10

Medical Devices

16 Appendix 10 – Medical Devices

16.1 Introduction

The regulations regarding medical devices provide opportunity for risk assessment to define different requirements for the associated HVAC systems.

There are three classifications of device according to the FDA:

- Class I – those subject to the least regulatory control, as they present minimal potential for harm to the user, hence are subject to “general controls.” Class I devices include elastic bandages, examination gloves, and hand held surgical instruments. They are subject to 21 CFR Part 820.
- Class II – Class II devices are devices subject to special controls, i.e., those for which general controls alone are insufficient to assure safety and effectiveness, and existing methods are available to provide such assurances. Examples of such products include powered wheelchairs, infusion pumps, and surgical drapes. Again, HVAC requirements are relatively simple
- Class III – this is the most stringent regulatory category. Class III devices are those for which insufficient information exists to assure safety and effectiveness solely through general or special controls. Class III devices are usually those that support or sustain human life, including heart valves, silicone gel filled breast implants, and implanted cerebella stimulators.

The FDA Medical Device Quality Systems Manual makes the following statements “A controlled environment is, to various degrees, an integral part of most production facilities. Some environmental factors to be considered are lighting, ventilation, temperature, humidity, pressure, particulates, and static electricity. Section 820.70 (c), Environmental Control, of the QS regulation, is considered by the FDA as a “discretionary” requirement: that is, the degree of environmental control to be maintained should be consistent with the intended use of the device and details of how to achieve this control are left to the manufacturer to decide.”

It also makes the statement that “General air conditioning is not normally regarded as an environmental control; however, changes in temperature and lighting can have an adverse effect on employee performance and, in turn, on assuring that the device is properly assembled, inspected, and tested.”

This Guide suggests that for each operation, the manufacturer should analyze the operations to identify the controls needed for the finished device to meet the specifications and be fit for use. Many Class I and Class II devices may require only comfort HVAC or at best, CNC. Although the manufacture of some Class III devices may start in an environment similar to a machine shop (with comfort HVAC at best), at some point, they become functionally implantable, requiring CNC or classified spaces, depending on sterility of the device.

The guidance provided in the FDA “Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice” often is used as an environmental specification in the absence of any specific guidance for Medical Devices.

16.2 Clean Workstations for Medical Devices

As medical devices commonly do not include potent compounds (with the exception of combination devices) horizontal flow clean workstations may be employed to protect product without endangering operators. Horizontal flow workstations are preferred as they present the lowest risk of operator contamination of components which are being assembled for implantation.

Appendix 11

Miscellaneous Information

17 Appendix 11 – Miscellaneous Information

17.1 Equations Used in HVAC and their Derivation

The equations provided are intended as a foundation and do not address all situations that may affect a HVAC system in a pharmaceutical facility.

17.1.1 Room DP

Air, like any gas, expands as it is heated and contracts (become more dense) as it is cooled. For every 5°F (3°C) that air is heated, it expands (becomes less dense) by approximately 1%.

The **ideal gas law** states that the pressure (P) and the volume (V) of a gas are proportional to its temperature (T). If a gas (in HVAC, the gas is air) is heated, it wants to expand to a larger volume, but if it is constrained in a fixed volume container, its pressure will increase and the air becomes more dense.

$$PV = N R_u T$$

Where R_u is the universal gas constant and N the mass of the gas in moles. Since R_u is constant, and N is usually fixed for a particular situation, the equation reduces to:

PV is proportional to T

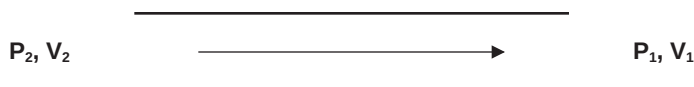
Bernoulli's Equation for fluid dynamics also plays a role in HVAC.

$$P/\rho + V^2/2 + gh = \text{constant}$$

Where g is the Earth's gravitational constant, h is elevation, and ρ (rho) is the density of air. In HVAC, air density is affected by altitude above sea level, but for practical HVAC applications (assuming the manufacturing building is less than 10 stories high), air density and elevation are essentially constant. Thus, Bernoulli's Equation applied to HVAC is:

$$P/\rho + V^2/2 = \text{constant} \quad \text{or} \quad (P/\rho + V^2/2)_1 = (P/\rho + V^2/2)_2$$

Where the subscripts 1 and 2 imply two different points along an airflow path, such as in a duct:



Therefore: **$(P_2 - P_1)$ is proportional to $(V_1)^2 - (V_2)^2$**

From this, it can be deduced that pressure is proportional to the **square** of the airflow velocity, i.e., to double the velocity of airflow between two points along a fixed path, the pressure difference between them must be quadrupled. In HVAC, V_2 often is zero (it is the air inside a space at zero velocity (effectively)). If zero velocity air is to be accelerated into an opening to move it to another location or under a door to pressurize a room, according to Bernoulli:

$P_2 - P_1$ is proportional to $(V_1)^2$

This can be used in calculating the velocity of air flowing through the cracks around a door at a given DP between two rooms. Further manipulation yields the somewhat imperfect, but very simple and useful method described in the *Pharmaceutical Engineering* article by Manual del Valle, "Airlocks for Biopharmaceutical Plants" (Reference 15, Appendix 12).

VP ~ P2 – P1

Where VP is the velocity pressure of the airflow **within** the door crack (i.e., where the air is moving faster, creating a pressure drop).

This equation also can be used to calculate the velocity inside the crack (from ASHRAE):

$$V = 4005 \times \sqrt{VP} \text{ (square root of VP)}$$

Where:

- V is in feet/minute
- VP is in inches water gauge (1 inch wg = 254 Pascals)

4005 is a constant derived for air at roughly standard temperature (68°F) and at sea level.

(If calculating for, e.g., Denver Colorado, where air is about 15% less dense, this constant (4005) will change a little.)

This method ignores “duct” entry loss and the pressure recovery that offsets it, such that the resultant calculated air velocity will be more than is required to create a pressure differential between two rooms. Since rooms are rarely as tight or well constructed as desired, this method provides a small surplus airflow quantity for adjustments during commissioning. In this case, VP can be replaced with DP (the DP between the two spaces, inches wg).

$$V = 4005 \times \sqrt{DP} \text{ (square root of DP)}$$

For example, the VP of air flowing at 890 feet per minute is 0.05 inches wg or 12.5 Pa. The above equation implies that the air flowing through the cracks between two rooms at 0.05 inch DP has a velocity of 890 feet per minute. In reality, because of geometry where the air enters the crack, and the length of the path of travel, velocity may be much less (therefore, the air volume leaking through is less) and would still provide a DP of 0.05 inch. However, where the area of the crack is large as for an open door and the DP required is significant (as for a classified room needing 0.05 inch or more), excessive quantities of airflow will be needed. Using the equation

$$Q = V \times A$$

Where:

- Q is cubic volume per time, usually cubic feet/minute (CFM)
- V is velocity in feet/minute
- A is area in square feet

An open 20 square foot door with air flowing through it at 890 ft/min (to maintain 0.05 inch DP) requires airflow of 17,800 CFM. This may be more than the capacity of the entire HVAC system and could provide a robust justification for airlocks, as stated in the del Valle article from *Pharmaceutical Engineering* (Reference 15, Appendix 12).

A closed “pharmaceutical grade” door typically has a crack area of 0.3 square feet or less, needing less than 300 CFM to maintain 0.05 inch wg across the closed door. A specific leakage rate should not be assumed without knowing about the type of door to be used, e.g., a tight sterile room door with seals (leaking as little as 50 CFM at 10 Pascals) or a warehouse sliding door leaking over 1000 CFM closed. Small details, such as door seals, can have a significant impact on air balance.

17.1.2 Fans

A useful equation for fan power is:

HP is proportional to $\eta \times P \times Q$

Where:

- HP is horsepower,
- η is fan efficiency at the operating point
- P is fan pressure
- Q is fan airflow in cubic volume per time (such as CFM)

From the pressure equations, if airflow in an existing duct system needs to be doubled, the fan's delivery pressure will need to be **quadrupled**, as well as having its airflow doubled; therefore, needing **eight** times the horsepower. It is considered better to slightly oversize an HVAC system's fan and ductwork and not need all the horsepower installed, rather than run out of horsepower when the system cannot supply sufficient air to meet required room particulate levels. When this happens, additional filtered airflow will need to be provided from the HVAC system at considerable cost and construction time, or by adding local filtered air supply units serving only the areas needing more air.

17.1.3 Room Air Balance

A basic **air balance** equation is:

Air Volume in = Air Volume out or **Q in = Q out** or

Supply + Infiltration = Return + Exhaust + Exfiltration

For a fixed volume (i.e., not a balloon), any air that enters the room has to leave the room. In a cleanroom, exfiltration is difficult to measure (it is the air flowing under the door and out the cracks in the wall), but it can be calculated. An air balance check should be performed on **each** fixed volume, including air handlers.

Note that air handled only **inside** a room, such as with a ceiling mounted FFU or local class 100 hood, does not actually leave the room or enter it; therefore, it does not affect the room's air balance relative to the building. However, the FFU unit **does** add its air changes as well as filtered air supply volume to the room HVAC supply, and it will contribute to faster room recovery time and help reduce room airborne particle levels.

17.1.4 Airborne Particle Levels

Another simplified equation deals with air particles per unit volume (C):

$C_{avg} = C_s + PGR/Q$

Where:

- C_{avg} is average particles per cubic foot in the pressurized room
- C_s is the particle concentration in the air supply (often negligible)
- PGR is the **steady state** internal particle generation rate in particles per minute

- Q is the supply airflow in cubic feet/minute, including contributions from in-room fan-HEPA units

With little air mixing (turbulence) in the room, localized values of C may be orders of magnitude more or less than C_{avg} . When a room is at rest and PGR approaches zero (assuming that there are no particles leaking into the room), the equation above indicates that room counts will eventually approach the particle counts in the supply air.

Note that this equation ignores air changes and room volume. The value of C_{avg} will be the same regardless of room volume as long as the airflow (Q) and particle generation (PGR) are constant. Hence, the particle counts in a big room running a specific process will be the same as the particle counts in a small room running that identical process, as long as the Q and particle counts of the supply airflow are the same.

17.1.5 Recovery

Room volume is an element of the measurement of **air changes** in a room. The formula for air changes is:

$$AC/hr = 60 \times Q/Volume$$

Where:

- AC/hr is room air changes per hour
- Q is CFM supply in cubic feet per minute*
- Volume is the volume of the room in cubic feet

*For a containment room, such as where flammable materials are handled, building and fire codes use **exhaust** flow (Q) to calculate air changes.

From the two equations above it appears that AC/hr is merely an indicator of air change rates in the room and not directly associated with air quality (it is CFM that most determines steady state air quality). However, air changes per hour play two critical roles.

1. Air changes need to be sufficiently high to assure sufficient turbulence in a room to achieve thorough mixing and dilution, such that particles counts are relatively the same throughout the room (except under local unidirectional hoods). This may require more than 10 (and usually more than 20) air changes per hour.

It also implies that the term “air changes per hour” does not apply to UFHs, which are unidirectional flow zones, not turbulent; however, a hood or FFU operating in the room does contribute to the total air changes per hour in the room.

2. Air changes per hour affect how quickly a room can recover from its in-use state to its at-rest state. European GMPs require this recovery to be 15 to 20 minutes.

The appendix of the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12) uses the formula:

$$C \text{ (at rest)} = (C_{op} - C_s)^{(-Nt)} + C_s$$

Where:

- C_{op} is in-operation particle count
- N is number of air changes
- t is time

- C_s is supply air particle counts (usually close to zero)

From the room recovery graph in the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12), a 100-fold recovery (from say $C = 10,000/\text{volume}$ to $C = 100/\text{volume}$, typical of an EU Grade B room) would occur in less than 15 minutes with 20 air changes per hour. So, for cleaner classified rooms (EU grades B and C), a minimum starting point would be an HVAC supply CFM that creates 20 AC/hr although more Q may be necessary if internal PGR is high (common to a small room with high equipment or people activity).

In addition to air changes, the thoroughness (or uniformity) of airborne particle counts throughout a room depends on the configuration of air supply and return openings. A single supply outlet near a single return inlet would lead to cleaner air in the path between the two with poor mixing (and higher particle counts) in other parts of the room. Such a room would show a slower recovery (with the same number of air changes) than a room with multiple well-distributed air supply outlets and low level returns.

17.1.6 Cascaded HEPA Filters

A HEPA filter passes a percentage of upstream particles of the MPPS (traditionally, particles at 0.3 microns). The MPPS of a modern HEPA may be closer to 0.15 to 0.25 micron. In other filters (e.g., a ULPA), the MPPS is in the range of 0.10 to 0.15 microns. For a given particle size, the overall leakage of a series of HEPA filters in a supply air path is the product of the leakages for each of the filters. If L is the leakage as a percent of upstream concentration, two HEPA filters in series will have a total leakage L_{tot} of:

$$L_{\text{tot}} = L_1 \times L_2$$

Where:

- L_{tot} is the resultant leakage
- L_1 is the leakage of the first HEPA filter
- L_2 is the leakage of the second HEPA filter

For a pair of standard 99.97% HEPA filters (assuming 0.03% leakage at MPPS):

$$L_{\text{tot}} = 0.03 \times 0.03 = 0.0009 \text{ \% leakage at MPPS}$$

Therefore, placing two 99.97% HEPA filters in series with no particle sources between them creates a virtual 99.9991% HEPA filter at the MPPS. If the filter's **worst** penetration (such as at a pinhole) is 0.03%, then combined results will be improved. In addition to the advantages in particle removal, there is an engineering advantage if the primary HEPA is at the air handler and the second HEPA filter is at the room (a terminal HEPA). The terminal filter will receive very little challenge, and therefore, its pressure drop increases so slowly that its flow is not reduced significantly (if at all) over months or maybe years of service. Air balance of the system is easier, requiring less in-duct hardware, such as CV devices, and room pressure deviations because of decay of supply airflow are less likely. For further information on cascaded HEPA filters, see the ISPE Baseline® Guide on Sterile Manufacturing Facilities (Reference 13, Appendix 12).

Note: (according to EN1822 (Reference 6, Appendix 12)) HEPA filters may be rated at **MPPS**. A HEPA rated 99.97% at 0.3 micron has **less** leakage for larger particles; it also should have less leakage for **smaller** particles.⁵ As bacteria and spores usually are much larger than 0.3 micron, and viruses are smaller than 0.3 micron, a 99.97% filter with MPPS at 0.3 micron is considered a suitable filter for pharmaceutical applications. Other filters, such as 99.99% HEPA, ULPA, or Teflon, could perform better, but at a higher cost.

⁵ Although HEPA filters capture 99.97% or better of particles at 0.3 micron, their true MPPS may be somewhat smaller with a capture rate lower than 99.97%. A HEPA filter rated at 99.97% at 0.3 micron may actually be as low as 99.9% at 0.1 to 0.2 micron MPPS. If viruses are a concern, the HEPA may be scanned to 99.99% or better using a smaller aerosol (such as thermally generated PAO); ULPA filters may be advisable.

17.1.7 Summary of Useful Cleanroom Equations

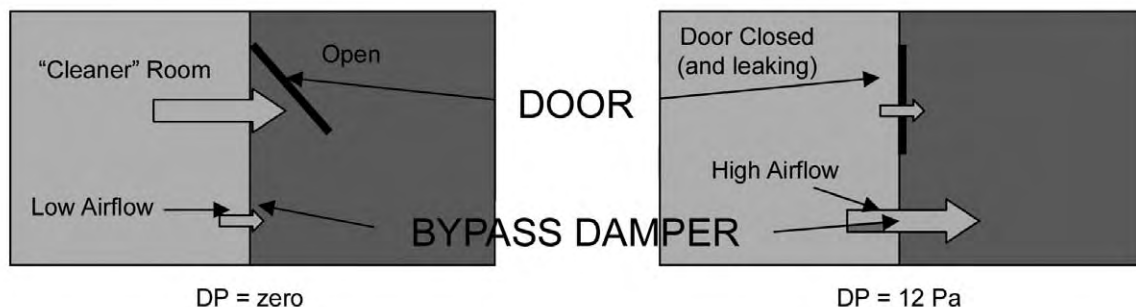
Ideal Gas Law	$PV = N R_u T$
Flow due to DP	$VP \sim P2 - P1$
Airflow through an Opening	$Q = V \times A$
Fan Horsepower	$HP = \eta \times P \times Q$
Air Balance	Supply + Infiltration = Return + Exhaust + Exfiltration
Average Airborne Particle Level	$C_{avg} = C_s + PGR/Q$
Air Changes	$AC/hr = 60 \times Q/Volume$
Room Recovery	$C \text{ (at rest)} = (C_{op} - C_s)^{(-Nt)} + C_s$
Cascaded HEPA Filters	$L_{tot} = L1 \times L2$

(See text for symbols.)

17.2 Pressure Control When Airlocks are not Possible

New facilities, particularly those with classified rooms, should have cascaded airlocks between air classes, but it may not be possible to retrofit airlocks into older facilities. The FDA Sterile Drug Products GMP (Reference 9, Appendix 12) suggests a measurable DP between rooms of different classes and air velocity through open doors sufficient to keep airborne contaminants out. Sufficient air velocity often leads to airflow volumes that are too great to pass around the cracks of a closed door and may prevent the door from closing against the very high pressure the airflow would create. For separations without airlocks, an alternative design (see Figure 17.1) can permit high airflows through open doors, while keeping DP below 15 Pa when the door is closed.

Figure 17.1: DP without an Airlock



To get observable airflow pattern from the clean room to the "dirtier" room with the door open, we need a transport velocity of at least 100 ft/min (0.5 m/sec). For a 2 sq meter (20 sq ft) door, the leakage has to be about 2000 CFM (3200 cum/hr). When the door closes we need about 300 CFM (500 cum/hr) to create 12 Pa DP. The remaining air passes through the "bypass" opening (damper).

An automated bypass damper can do the job, but a fixed orifice damper or a "gravity" damper will, too.

A fixed orifice damper will require a little more airflow

Total airflow with door closed = Total airflow with door open

17.3 HEPA Filter Arrangements

17.3.1 Air Filtration Arrangements

It is common practice for aseptic manufacturing facilities to recirculate air back to the air handler unit. Generally, this is good practice as it limits the particle load on the filters, reduces the cost of conditioning outdoor air, and optimizes control. However, there are other factors to account for:

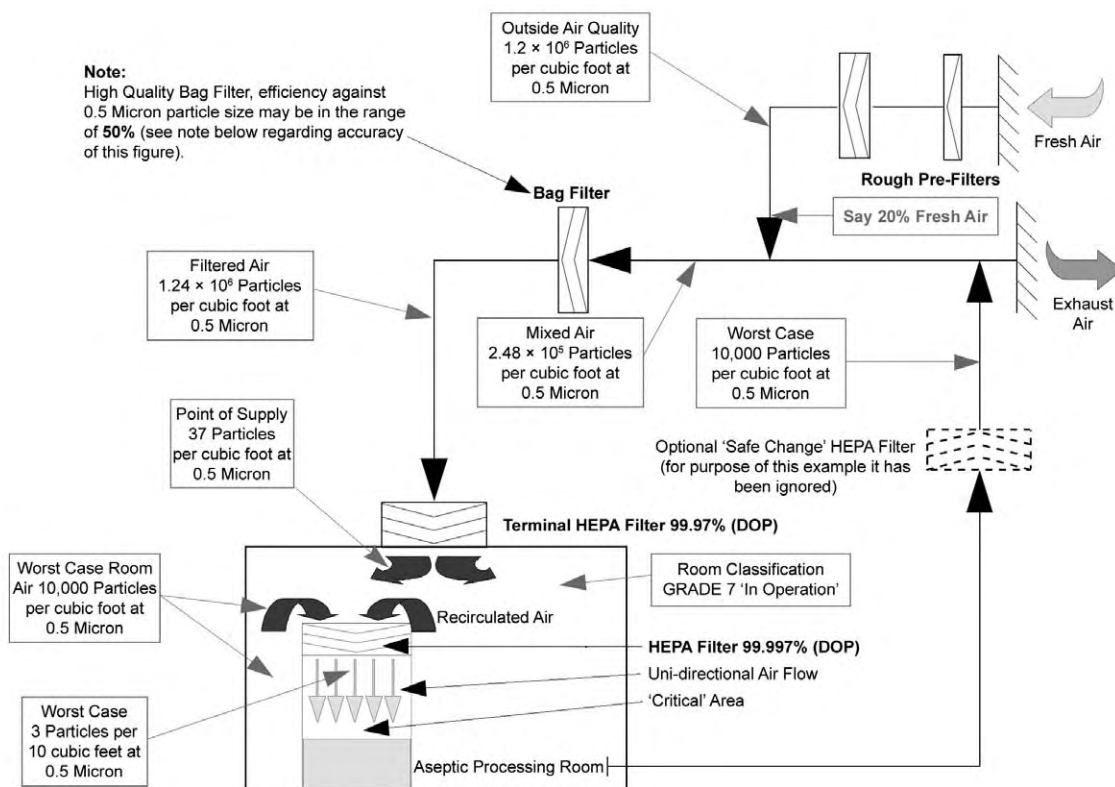
- potential for cross-contamination in multi-purpose facilities
- accidental recirculation of product-contaminated air affecting operators or plant maintenance staff

These factors may be overcome by the use of return air filters. If the logic is that these are to capture airborne contamination; however, they need to be of the “safe change” type to protect maintenance personnel.

The environmental standards in the FDA Sterile Drug Products GMP (Reference 9, Appendix 12) identify a 0.5 μm particle size as the reference point. As a result of standard filter test methods, only HEPA and ULPA filters have quantified performance ratings against a most penetrating particle size, usually sizes smaller than 0.5 μm . Although other filters, such as bag filters, provide some reduction against a 0.5 μm challenge, there is no reliable way to test performance in situ. When looking at sub-micron particle reduction by filtration; therefore, only HEPA and ULPA filters should be considered as effective. ULPA filters are not commonly used, as HEPA filters can remove contaminants to acceptable levels. Good engineering design stipulates the use of highly effective pre-filters to prolong HEPA filter life.

The location of HEPA filters within a system should be at points such that there is no opportunity for the air to become re-contaminated. The use of terminal supply (ceiling) HEPA filters is recommended for classification of Grade 7 and cleaner. They also have the additional advantage of maintaining the sealed envelope of the processing area should the supply fan fail.

Figure 17.2: A Possible Aseptic Area Filter Arrangement



DOP and PAO (and Sodium Flame) penetration tests use a high concentration of particles of a known spectrum (usually in the range of $0.3\ \mu\text{m}$ diameter). Efficiency results then can be related to specific size of airborne particle. Only filters that are tested by such methods have any reliable data for this size of particle. Filters grades lower than HEPA are tested by averaging methods in which specific particle size efficiencies are not identified. However, some suppliers have claimed to have particle data available, but it should be treated with care, as these are not recognized standard tests. This data should not be relied upon when designing the HVAC air filtration arrangement.

Note: European H14 air filters can pass a penetration scan test, but the purchaser must request that H13 filters do so.

17.3.2 Prefiltration for Terminal HEPA's

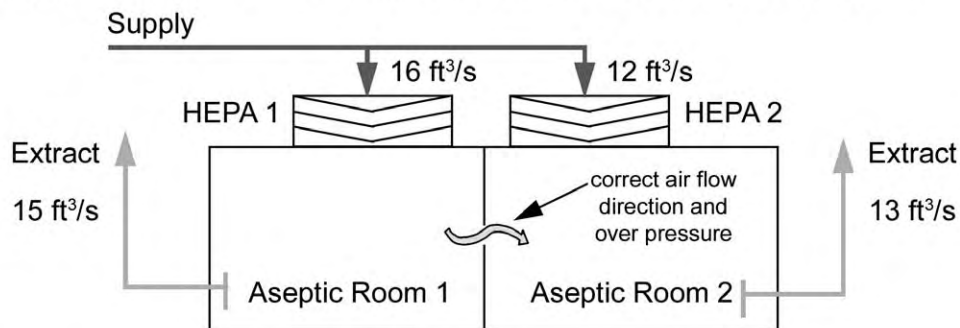
As Figure 12.2 demonstrates, a single HEPA filter bank in normal circumstances is adequate to reduce supply particulate concentration below that of a reasonable “at rest” design classification, for example, 100 PCF. An important consequence of using a single HEPA bank is that the supply air $0.5\ \mu\text{m}$ particle count is unlikely to be near zero. This could affect the calculations of air change volume flow rate to offset particulate gains, and in particular, recovery periods.

Another potential problem to be addressed if only terminal HEPA filters are used, is that of filter blinding that can result in reversed DPs putting environmental conditions at risk.

Figure 17.3: Example of the Effects of Terminal Filter Differential Blinding

a. Initial Conditions

Supply air is CV controlled, and has a concentration of 40 particles (at $0.5\ \mu\text{m}$) per ft^3 .

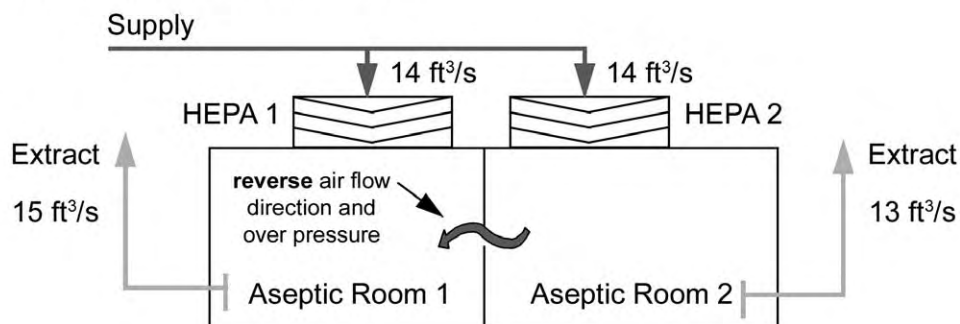


Note: With time, filters get dirty (blind) and the pressure drops increase. HEPA 1 is getting dirtier more quickly than HEPA 2, due to greater supplied volume; therefore, more air is diverted to HEPA 2 as the system dynamic balance is maintained. This will continue until supply air volume through both filters is equal. (See below).

Note: Extract volumes remain constant.

b. After a Period of Operation

Unacceptable reversal of DP occurs.



As Figure 12.3 demonstrates, terminal filter blinding can result in design DPs being reversed. There are a number of possible solutions:

- Install a main bank of HEPA filters.
- Install a main bank of high efficiency non-HEPA filters (minimum MERV 13/F7 or better – which do not have the maintenance cost of regular integrity testing) in the AHU.
- Employ active pressure or constant air volume control.
- Frequently replace terminal HEPA filters.
- Install airflow or pressure drop indicators to indicate filter performance.

The last three options above can result in higher capital or maintenance costs.

The option to use high efficiency pre-filters in series with the HEPA will use more energy than a single HEPA filter, but has a number of advantages:

- The air flow rates differ to individual terminals, the effects of differential blinding will be minimized. Hence, the performance of the terminal filters will be maintained constant for years longer, balancing the ratio between supply and extracts, and in turn, DPs, without the use of expensive active pressure or supply air flow controls.
- Secondly, because the bank of filters handles the main particulate load and acts as a prefilter in the AHU, only these will require regular replacement. Typically, there are more terminal filters to give good air distribution than are needed in the main AHU so this practice reduces replacement maintenance costs and maintenance downtime.

It is recommended that high efficiency non-HEPA pre-filtration be installed in all new or renovated facilities employing HEPA terminal filtration.

17.4 Recovery Period versus Air Change Rates

If a minimum recovery period is required, this factor may be the deciding criterion for the air change rate. Figure 17.4 is a simplified model for calculating the relationship between air change rate and recovery period. This model is based on two major assumptions (good mixing efficiency with clean supply air).

For further information, see the ISPE Baseline® Guide for Sterile Manufacturing Facilities (Reference 13, Appendix 13).

Figure 17.4: Recovery Period versus Air Change Rates

(note that the curves and equation are merely basic exponential decay expressions)

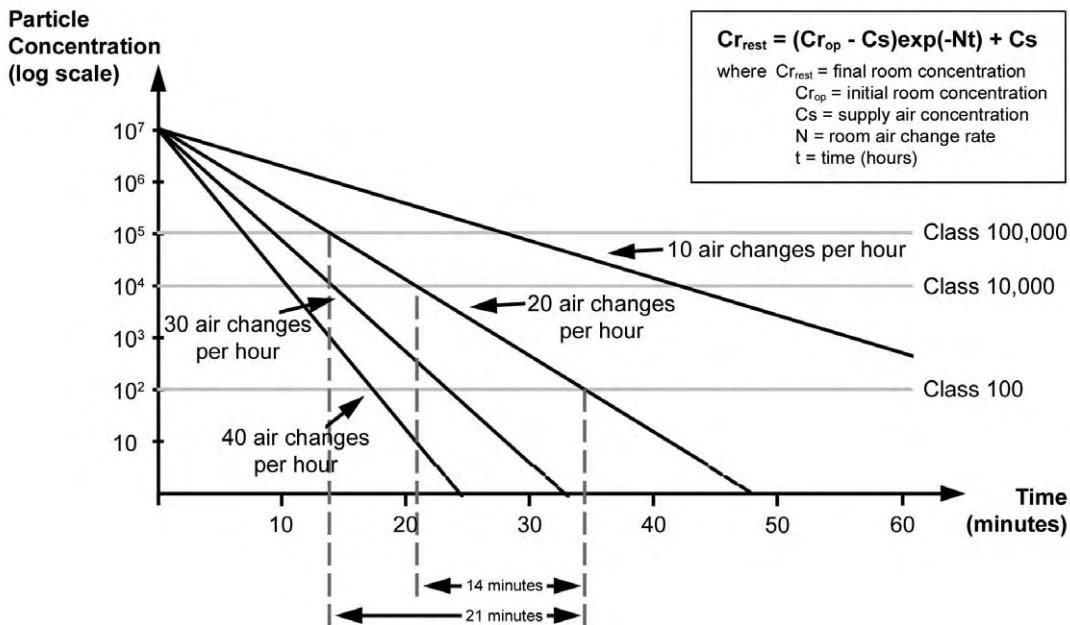


Figure 17.4 shows how by assuming a simple exponential decay, the “recovery period” changes greatly with air change rate: a 100-fold recovery, from ISO 7 to ISO 5, with 20 air changes per hour, takes approximately 14 minutes; with 30 air changes per hour, it takes approximately 9 minutes.

In general, it is considered more important to achieve target recovery than to achieve target air change rate.

17.5 Additional Controls Information

17.5.1 Electrical/Electronic Actuators

The actuator uses a low voltage control signal to drive an electric motor; the units can be on/off or proportional.

These systems are used where the speed of actuation can be slower, typical times for a valve to go from fully open to fully closed are in the range of 1 to 2 minutes.

Installation is simple, as all signals are by cable, e.g., control signal, power supply, and feedback, such as valve position or open/closed signals.

The actuators can be supplied as fail open, fail closed, or with a manual override.

17.5.2 Pneumatic Actuators

An electronic control signal (from a stand-alone controller, BMS, or Process Controller) varies the output air pressure from a pneumatic controller, which is fed to a pneumatic actuator on the controlled component.

The system requires the use of an I/P (control signal to pneumatic) converter, an instrument quality air supply, and local tubing to the actuator. In order to get the best response time, the converter should be as close as possible to the actuator. Fully pneumatic controllers (no electronics) are available, but rarely used with large installations and BMSs.

The units use air pressure in one direction with an opposing spring to return the controlled item to the fail position. The system is proportionally controlled, i.e., the controlled item's position is proportional to the control signal.

These units typically have a faster response time than an electric or electronic unit. The all-pneumatic system also is ideal for hazardous areas requiring intrinsically safe installations.

17.5.3 Control Valves for Liquids

There are two types of control valve; the three port valve, which can be used as a mixing or diverting valve to supply the controlled equipment, or the two port valve, which directly controls flow to the equipment. The three-port valve was the industry standard; however, the use of two port valves with variable flow rate systems is becoming more common. A well designed system is as effective with a much lower capital and operating cost.

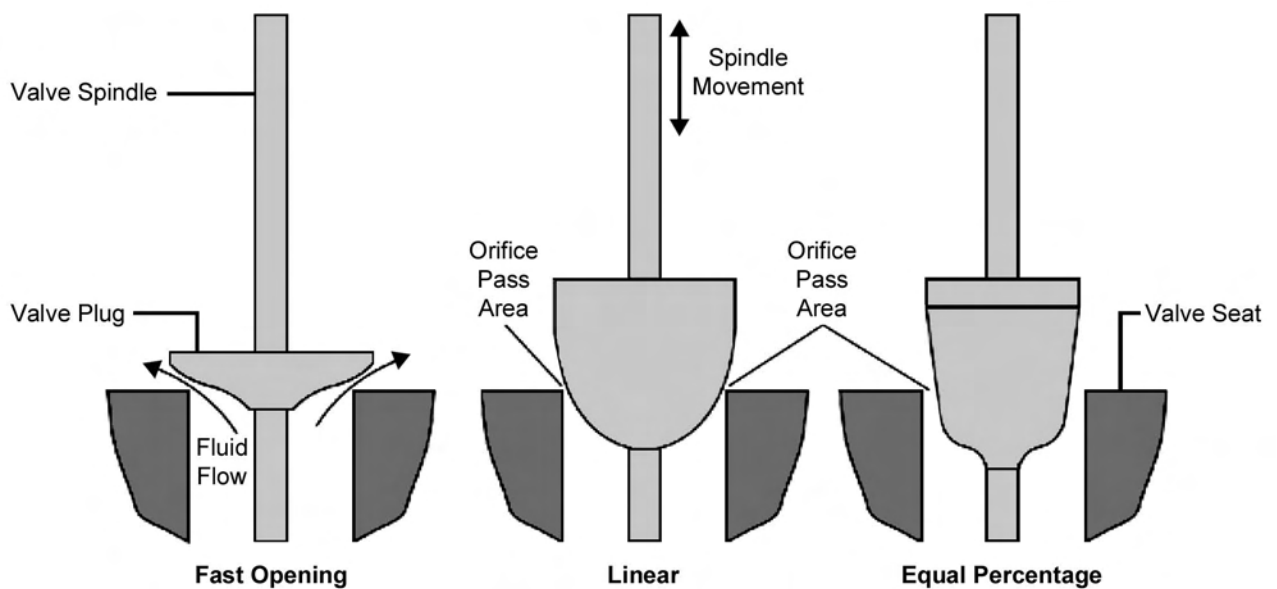
Correct valve selection is important for the correct operation of a system. A summary of the selection process is provided.

17.5.3.1 Valve Characteristic

The valve characteristic is the ratio of flow through the valve to the valve lift (opening) at a constant DP across the valve (inlet to outlet).

There are three main types of valve characteristics:

Figure 17.5: Valve Characteristics



Used with permission from Spirax Sarco, www.spiraxsarco.com/resources/steam-engineering-tutorials.asp

These characteristics are shown graphically with vertical stroke (as seen in a globe valve):

- the fast opening valve typically is used for only on/off control
- the linear valve has a flow rate directly proportional to the amount it is open and is commonly used for diverting applications, such as supplying water to heating or cooling coils

- the flow rate in an equal percentage valve has a logarithmic relation to the amount it is open; it is more commonly used in water flow applications

The characteristic should be chosen with respect to the application of the valve. The installed characteristic is the relationship between the flow and valve lift in the system where it is installed. Where the pressure drop across the valve decreases with increasing flow, the Equal Percentage valve produces a more desirable linear characteristic and is often selected for use in steam control applications.

17.5.3.2 Flow Coefficient

A simple flow coefficient calculation that may be used for C_v for liquids (C_v – the flow capacity in gallons per minute (GPM) of 60°F water with a pressure drop of 1 psi)

$$C_v = \text{design flow rate (gpm)} \times \sqrt{\text{Specific Gravity of the fluid/ Allowable pressure drop}}^6$$

$$\text{In English Units: } C_v = \text{gpm (SG/dp)}^{1/2}$$

Where gpm = water flow (US gallons per minute), SG = specific gravity (1 for water), dp = pressure drop (psi)

$$\text{In SI Units: } C_v = 11.7 \text{ CMH (SG/dp)}^{1/2}$$

Where CMH = water flow (Cu.Meter/hour), SG = specific gravity (1 for water), dp = pressure drop (KPa)

Select a valve where the required C_v is in the 30 to 80% range of the stroke – use of a valve that is too small (typically less than half the line size) or too large (line size or greater) would be wrong – the valve will not have the ability to control the flow accurately, i.e., will not have adequate “authority.” If the valve normal operating condition results in operation in a near closed condition, control can be erratic, particularly if installed where flow tends to close the valve. Almost all control valves are not meant for full shut-off service. Control valves should be located in a position where they can be tested and maintained easily

17.5.3.3 Valve Authority

Valve Authority is the percentage of total system pressure drop assigned to the valve, i.e., in a circulation system, the pump will deliver some head to overcome pipe and heat exchanger losses and some to overcome valve resistance. If the latter is small in comparison to the former, the valve will have less ability to control effectively.

⁶ Calculation should be based on the allowable pressure drop to determine the C_v needed. Selected valve should have that C_v at 90% opening or less.

17.6 Sample Controls Description

The following is a sample description of the controls operation for one HVAC system. It should be used only as a guide.

HVAC Control System Typical Description System One

Contents

1. Control Description
2. Design Notes
3. I/O Outputs
4. System Schematic Layout
5. Psychrometric Chart

1. Control Description

1.1 Plant Operation

- On plant startup, the fresh air damper (MD 1) and the recirculation damper (MD 2) should be fully opened.
- On normal plant shutdown, the supply fan should be stopped and all dampers fully closed.
- In the event that the mixed air temperature (TX 1) falls below 5°C, an alarm should be raised and the plant stopped.
- All control valves should be closed on plant shut down.

1.2 Temperature Control

- The supply air temperature (TX 2) should be maintained by modulation in series of the cooling coil control valve (CVM 1) and the heating coil control valve (CVM 2).
- The supply air temperature set point (TX 2) should be adjusted (min 12°C) to ensure that the reheat control valve output is minimized.

1.3 Humidity Control

- The return air humidity (HX 1 and HX 2) should be maintained at the required set point (60% maximum) by providing override control of the cooling coil control valve.
- (CVM-1) to achieve dehumidification.

1.4 Fan Speed Control

- The supply fan speed (SCM 1) should be modulated to maintain a constant supply airflow rate to the dictates of the fan mounted flow airflow measuring device (AFD 1).
- When required to operate, the supply fan (SF 1) run status should be confirmed to start and run at a variable speed as dictated by the fan speed control loop.

1.5 Monitoring/Alarm

- A general alarm should be raised at the central supervisor for all conditions as shown on the HVAC point schedule.

3. I/O Point Schedule

4. System Schematic Layout – not included in this example

5. Psychrometric Chart – not included in this example

17.7 Temperature Mapping

The purpose of temperature mapping helps confirm that the area as a whole remains within its defined limits and determine the locations representing temperature extremes within the area.

The second objective defines the locations for permanently installed sensors that provide data for the quality system of record for the area, the information from which the MKT is calculated (if required).

There are benefits to a smaller number of sensors for this purpose, while it is necessary to use a sufficient number of sensors to ensure that the mapping study is robust.

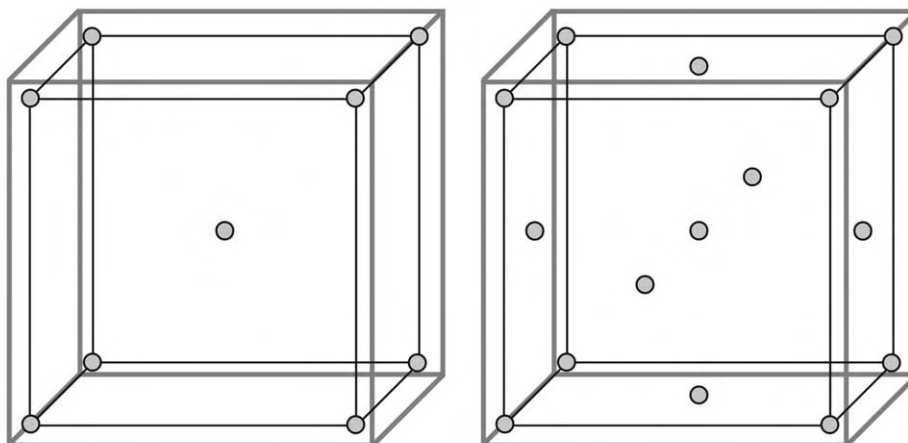
There is very little guidance on temperature mapping, the French Standard, (NF X15-140 October 2002 “Measurement of Air Moisture – Climatic and thermostatic Chambers – Characterisation and Verification”) (Reference 11, Appendix 12) provides some guidance on sensor locations to be used for mapping of environmental chambers, as summarized below.

The method is based on the size of the chamber and the area potentially occupied by product. For chambers over 700 cubic feet (20 cubic meters), the standard suggests considering the factors that may affect the specific installation, including:

- door openings
- location of the cooling system
- position of the control sensor

Figure 17.6 is based on the French Standard (Reference 11, Appendix 12). The drawing on the left shows the minimum number and suggested location of sensor locations mounted in the working area for a chamber up to approximately 70 cubic feet (2 cubic meters). For bigger areas, up to 700 cubic feet (20 cubic meters), the standard suggests using as a minimum the number and location of sensors shown on the right hand drawing. The number of sensor locations suggested should be increased as necessary to monitor, for example, conditions for product located near a conditioned air discharge or the door, as well a sensor located near the temperature control sensor.

Figure 17.6: Temperature Mapping for Chambers up to 2 m³ and up to 20 m³

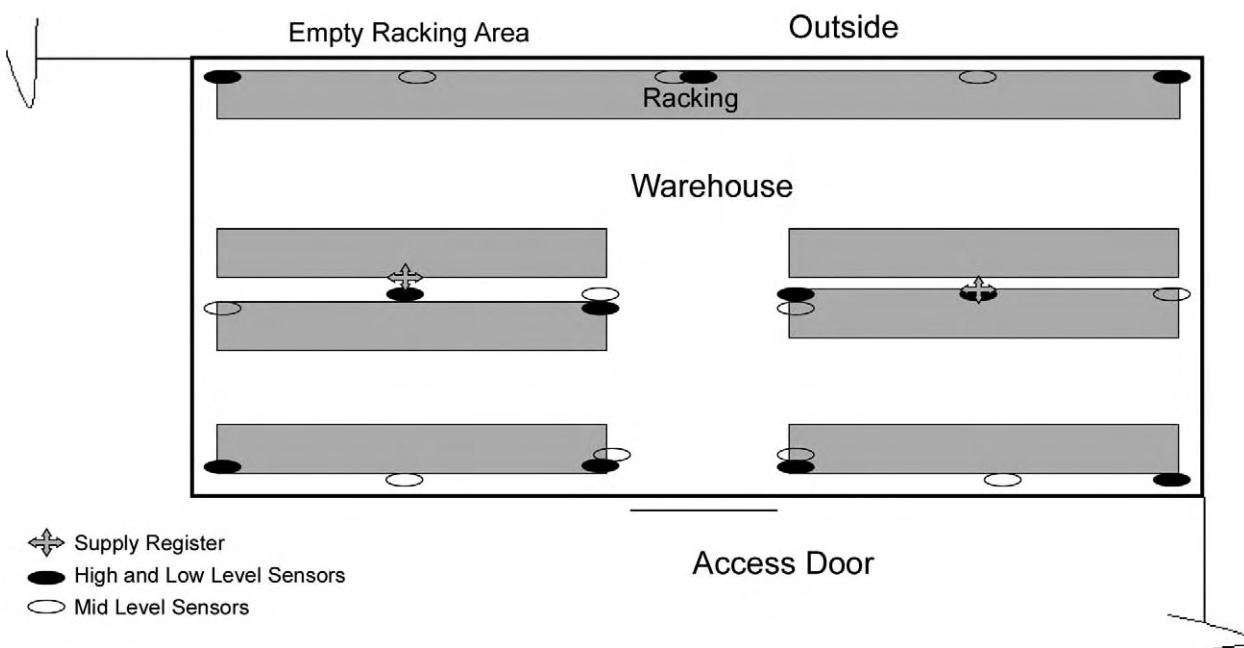


Note: The inner box represents the working area (where product is stored); the dots represent the sensor locations.

While not directly relevant, the guidance provided should prove helpful – distances between sensors depend on the local conditions and influences, such as racking layout, positions of the HVAC outlets, doors, internal and external walls, etc. An approach that has been used with some success is to consider the area around each HVAC outlet as a zone and apply the logic suggested in the right hand drawing shown above with a sensor adjacent to the temperature control sensor as well as others monitoring the supply and return temperatures.

For an area bounded by an external wall, the area requires mapping in the seasonal extremes in order to determine the influences of heating and cooling supply temperatures from the HVAC system, and the heating or cooling effect of the external walls and roof adjacent to the racking. The strategy developed for this seasonal testing should consider the effects, because of empty and full racking, the effects of the thermal mass/insulation/airflow changes. As an example, Figure 17.7 shows a potential mapping layout with one part of the room full of product and one part empty – a simple approach in this instance as the layout is symmetrical.

Figure 17.7: Warehouse Temperature Mapping Layout Plan



Other factors that should be defined before testing include:

- Product temperatures – if upon delivery these are significantly different from the defined storage conditions, the product may require monitoring to determine how long it remains outside the defined storage conditions.
- Loading and unloading – will the product be at a different temperature, how much is loaded/unloaded at any one time, will there be a significant ingress/egress of conditioned air, replaced by unconditioned outside air from outside?
- Is there an outside door that can be left open or is it monitored to a defined maximum time that it could be open?
- storage locations nearest the heating/cooling system inlet/outlet
- internal loads – lighting, equipment. and personnel
- conditions during minimum (empty) and full storage capacity

Ideally these factors will be reviewed and considered with a representative test method defined. An example is included below:

Example Plan:

External Heat Gains and Losses

The major heat gains and losses to the cold room are due to the influences of the external environment with the most significant being through the walls and ceiling.

Internal Heat Gains and Losses

Lighting – the lighting is from low energy fluorescent lamps that are left on during the working day.

Product – the product stored in the room is supplied at the storage temperature and will not represent additional load to the room.

Equipment – the equipment used in the room is a stacking fork truck - a relatively small intermittent load.

People – there are 2 people occasionally working in the area; therefore, the heat gains are small and transient.

HVAC – the room is conditioned through two registers mounted as shown with a common return air grille located at high level in the center of the room.

Mapping Sensor Placement

The areas considered during the mapping are only the areas where product will be stored.

The proposed sensor locations are based on the following:

- *The chamber may be considered as two zones with each zone supplied by a register.*
- *As a minimum, a temperature sensor will be placed in the location of the lowest and highest storage point that product could be stored at each corner of the room on the racking nearest the perimeter.*
- *One temperature sensor will be located in the center of these locations at the midpoint level between these sensors.*

Monitoring Sensor Placement

The mapping data will be used to define the sensor locations that indicate the typical positions where of minimum and maximum temperatures, considering the results of the tests represent normal usage.

Load Testing

The unit will be mapped during the peak summer and winter seasons, considering two “load” scenarios:

- *empty chamber*
- *One half of the warehouse will be kept empty*

Note that the HVAC has constant flow rate and with the room empty, there are no constraints on the airflow direction, hence, the airspeed will be low. When the room is not empty, the airflow will be at a higher speed, as the same volume of air must travel through a smaller area.

- “full” sections

One half of the warehouse will be filled with full boxes of product simulating the largest stored full pallet (40 inches × 48 inches × 46 inches tall). This scenario will give minimum thermal mass, but maximum interruption of airflow, allowing the effect of a full room to be seen in the filled zones. Note that the area selected is based on the fact that the room is symmetrical.

Appendix 12

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Appendix 13

Glossary

19 Appendix 13 – Glossary

19.1 Abbreviations

AAALAC	Association for the Assessment and Accreditation of Laboratory Animal Care
ABMA	American Bearing Manufacturers Association
ACGIH	American Council of Government Industrial Hygienists
AIHA	American Industrial Hygiene Association
AMCA	Air Movement and Control Association (International)
ANSI	American National Standards Institute
ARI	Air Conditioning and Refrigeration Institute (US)
ASHRAE	American Society of Heating, Refrigeration and Air Conditioning Engineers
ASTM	American Society for Testing and Materials (International)
CIBSE	Chartered Institute of Building Service Engineers (UK)
COP	Community of Practice
COSHH	Control of Substances Hazardous to Human Health
CSA	Canadian Standards Association
EC	European Commission
EMA	European Medicines Agency
EPA	Environmental Protection Agency
EPBD	Energy Performance of Buildings Directive (EU)
EU	European Union
EU-OSHA (EASHW)	European Union – Occupational Safety and Health Administration (European Agency for Safety and Health at Work)
FDA	Food and Drug Administration (US)
HSE	Health and Safety Executive (UK)
HVCA	Heating and Ventilating Contractors Association (UK)
ICC	International Code Council
ICH	International Conference on Harmonisation

IENT	Institute of Environmental Sciences and Technology (US)
ISA	International Society of Automation
ISO	International Standards Organisation
ISPE	International Society for Pharmaceutical Engineering
NEBB	National Environmental Balancing Bureau – NEBB (US)
NEC	National Electrical Code (US)
NEMA	National Electrical Manufacturers Association (US)
NFPA	National Fire Protection Association (US)
OSHA	Occupational Safety and Health Administration (US)
PIC/S	Pharmaceutical Inspection Convention and Pharmaceutical Inspection Co-operation Scheme
SI	International System of Units
SMACNA	Sheet Metal and Air Conditioning Contractors National Association (North America)
US FDA	United States Food and Drug Administration
USDA	United States Department of Agriculture
USGBC	United States Green Building Council
WGBC	World Green Building Council
WHO	World Health Organization

19.2 Acronyms

AF&ID	Airflow and Instrument Diagram
AFD	Air Flow Diagram
AHU	Air Handling Unit
API	Active Pharmaceutical Ingredient
BAS	Building Automation System
BL	Biosafety Level
BMS	Building Management System
BOD	Basis Of Design
BSC	Bio Safety Cabinet

BV	Balance and Vibration
CD	Construction Document
CDR	Conceptual Design Report
CE	Conformite Europeenne
CFCs	ChloroFluorocarbons
CFD	Computational Fluid Dynamics
CFU	Colony Forming Unit
CGMP	Current Good Manufacturing Process
CIP	Clean In Place
CMC	Chemistry Manufacturing Control
CMMS	Computerized Maintenance Management System
CNC	Controlled Not Classified
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CV	Constant Volume
CVD	Constant Volume Damper
DCS	Distributed Control System
DDC	Direct Digital Control
DOP	Diocetyl Phthalate
DP	Differential Pressure
EMS	Environmental Monitoring System
EN	European Norm
ENEC	European Norms Electrical Certification
ERP	Enterprise Resource Planning
ETOP	Engineering Turnover Package
FAT	Factory Acceptance Testing
FDS	Functional Design Specification

FFU	Fan-Filter Unit
FMEA	Failure Modes and Effects Analysis
FRP	Fiberglass Reinforced Panels
GBI	Green Building Initiative
GEP	Good Engineering Practice
GMP	Good Manufacturing Practice
GWP	Global Warming Potential
HACCP	Hazard Analysis and Critical Control Points
HCFC	Hydrochlorofluorocarbon
HEPA	High Efficiency Particulate Air
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome
HVAC	Heating Ventilation and Air Conditioning
IAQ	Indoor Air Quality
IFB	Internal Face and Bypass
IMC	International Mechanical Code
LEED	Leadership in Environmental and Energy Design
LEED AP	Leadership in Environmental and Energy Design (LEED) Accredited Professional
LEL	Lower Explosive Limit
LEV	Local Exhaust Ventilation
LiCl	Lithium Chloride
LIMS	Laboratory Information Management System
MAL	Material Air Lock
MERV	Minimum Efficiency Reporting Value
MKT	Mean Kinetic Temperature
MMD	Mass Median Diameter
MPPS	Most Penetrating Particle Size
MSDS	Material Safety Data Sheet

NaCl	Sodium Chloride
NDA	New Drug Application
Non-XP	Non-Explosion Proof (type of fan motor)
ODP	Ozone Depletion Potential
OEL	Operator Exposure Limit
OPR	Owner's Project Requirements
OSD	Oral Solid Dosage
P&ID	Piping and Instrumentation Diagram
PAO	Polyalphaolefin
PdM	Predictive Maintenance
PGR	Particle Generation Rate
PI	Proportional and Integral
PID	Proportional and Integral and Derivative
PLC	Programmable Logic Controller
PM	Preventive Maintenance
PPE	Personal Protective Equipment
QA	Quality Assurance
QRM	Quality Risk Management
R&D	Research and Development
RABS	Restricted Access Barrier System
RCFA	Root Cause Failure Analysis
RH	Relative Humidity
RHC	Reheat Coil
RO	Reverse Osmosis
ROI	Return On Investment
RP	Recommended Practice
RTD	Resistance Temperature Device

SAT	Site Acceptance Testing
SCADA	Supervisory Control And Data Acquisition
SF	Supply Fan
SME	Subject Matter Expert
SOP	Standard Operating Procedure
SS	Stainless Steel
TAB	Testing Adjusting and Balancing
TCO	Total Cost of Ownership
TE	Temperature Sensing Element
UDAF	Unidirectional Airflow
UFH	Unidirectional Flow Hood
UL	Underwriters Laboratories
ULPA	Ultra Low Penetration Air
UPS	Uninterruptible Power Supply
UV	Ultraviolet
VAV	Variable Air Volume
VFD	Variable Frequency Drive
VOC	Volatile Organic Compound
VP	Velocity Pressure
VPHP	Vapor Phase Hydrogen Peroxide
WFI	Water For Injection

19.3 Definitions

Acceptance Criteria

The limits of conditions of critical parameters that may affect the product quality. These conditions may include temperature, humidity, and room air quality. For example, if humidity or particulates are not critical parameters affecting product quality they are not included in acceptance criteria.

Action Limit

Criteria established based on possible impact to product quality, outside the operating range (acceptance criteria). A documented response is usually required.

Air Change Rate

The number of times the total air volume of a defined space is replaced in a given unit of time. This is computed by dividing the total volume of the subject space (in cubic volume) into the total volume of air exhausted from (or supplied to) the space per unit of time.

Airflow and Instrument Diagram (AF&ID)

Based on the AFD, it shows HVAC instrumentation and controls, with critical GMP components highlighted.

Air Flow Diagram (AFD)

Schematically shows rooms and zones served by an air handler, with air balance requirements, and often room pressures.

Alert Limit

Criteria established with the intent of notification and possible corrective action prior to exceeding action limits; alert when a parameter is drifting toward extremes of the operating range.

Arrestance

A measure of the ability of an air filter to remove synthetic dust from the air when tested as described in ASHRAE Standard 52.2-2008, *Method of Testing General Ventilation Air Cleaning Devices for Removal Efficiency by Particle Size*. Arrestance test results typically relate to larger size particles.

As-Built Drawings

Construction drawings that represent the physical condition of the plant or system at turnover from the designer or installer at satisfactory operation. These documents supplement and complement the system manuals and protocols.

Building Management System (BMS)

A computerized system that controls, monitors, and optimizes environmental conditions, through functions and facilities such as heating, air-conditioning, lighting, and security.

Change Control

A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes which might affect validated status. The intent is to determine the need for action which would ensure that the system is maintained in a validated state.

Closed

Not exposed to the room, capable of holding some pressure or purge. PDA TR-28 provides a rigid definition of closed.

Closed Process

A process condition when the product, materials, critical components or container/closure surfaces are contained and separated from the immediate process environment within closed/sealed process equipment. A process step (or system) in which the product and product contact surfaces are not exposed to the immediate room environment.

Commissioning

Commissioning is a quality oriented process for verifying and documenting that the performance of facilities, systems and assemblies meets defined objectives and criteria.

Critical Component

A component within a system where the operation, contact, data, control, alarm, or failure may have a direct impact on product quality or the ability to know product quality.

Critical Location

The location where product is exposed; the location where a cleaned product contact surface is exposed.

Critical Parameter

A processing parameter (temperature, pressure, pH, etc.) which directly influences the drug substance characterization or impurity profile in or after a critical step.

Critical Process Parameter

A process parameter whose variability impacts a quality attribute and therefore needs to be controlled to ensure the process produces the desired quality. A critical process parameter remains critical even if it is controlled.

Critical Quality Attribute

A physical, chemical, biological or microbiological property or characteristic that needs to be controlled (directly or indirectly) to ensure product quality.

Design For Impact

The practice of making design decisions related to the impact of the system in operation, at the beginning of design development.

Design Point

Provided in the basis of design as the nominal set point around which the parameter is expected to be controlled, +/- a given tolerance value (the Design Tolerance) to provide the Design Target.

Design Qualification (DQ)

Documented verification that the proposed design of the facilities, equipment, or systems is suitable for the intended purpose.

Design Target

A value for a critical parameter that is more conservative than its acceptance criterion, used by designers to assure that the system is capable of meeting the acceptance criterion. Design Targets should not be used for system qualification; they are “wishful” values that may not be achieved in reality.

Design Tolerance

The expected (design) upper and lower points of the normal operating range.

Direct Impact System

A system that is expected to have a direct impact on product quality. These systems are designed and commissioned in line with Good Engineering Practice and also are subject to Qualification Practices that incorporate the enhanced review, control and testing against specifications or other requirements necessary for GMP compliance.

DOP (Diocetyl Phthalate)

Material used in the past to generate aerosols comprising particles in the 0.1 to 0.7 micron range (typically with an average size of 0.3 micron) used to test HEPA and ULPA filters. This chemical is believed to have carcinogenic properties and has been generally replaced by a mineral oil, e.g. Emery 3004/ Durasyn 164, or Shell Ondina EL.

The smoke generated from this has very similar characteristics and the term DOP testing remains, although it is now understood to mean 'Dispersed Oil Particulate.'

Dust Spot Efficiency

The measure of a the ability of a filter to remove synthetic dust when tested as described in ASHRAE Standard 52.2-2008, Method of Testing General Ventilation Air Cleaning Devices for Removal Efficiency by Particle Size.

Enhanced Design Review (EDR)

A documented review of the engineering design, at an appropriate stage in a project, for conformance to operational and regulatory expectations.

Exfiltration

Leakage of air out of a room through cracks in doors and pass-throughs through material transfer openings, etc. due to a difference in room pressures.

Exhaust air

Air removed mechanically from the space and discarded

Functional Design Specification

Description of acceptance criteria, in terms of ranges and logic of system operation, etc. In HVAC, a description of HOW the HVAC will meet the acceptance criteria (room air class, DP, airflow, recovery time, level of air filtration, etc.).

Good Engineering Practice (GEP)

Established engineering methods and standards that are applied throughout the project life cycle to deliver appropriate, cost-effective solutions.

Grade

Applied to air cleanliness, "grade" implies airborne particle count limits in operation, with associated bioburden limits. The number of the grade is the upper limit in operation as defined by ISO 14644 -1 (i.e., Grade 5 has 0.5 micron upper particle limit of 3500/cubic meters). In the European GMP, Grades A through D also involve particle limits at rest.

High Efficiency Particulate Air (HEPA) Filter

High efficiency particulate air filter, a filter with DOP efficiency in excess of 99.97% on 0.3 µm particles.

Indirect Impact System

A system that is not expected to have a direct impact on product quality, but typically will support a Direct Impact system. These systems are designed and commissioned following Good Engineering Practice only.

Infiltration

The entry of air from an adjoining room or from outdoors through wall and ceiling openings due to a difference in air pressure between the two areas.

Laminar Flow – see Unidirectional Flow

Latent Heat

Latent heat refers to the amount of energy released or absorbed by a chemical substance during a change of state, meaning a phase transition such as the melting of ice (latent heat of fusion) or the boiling of water (latent heat of vaporization). In an HVAC application typically used to condense water from humid air.

“Nearly Massless” Particles

Particles smaller than 0.5 μm , which typically constitute less than 1% of the total mass of particles typically found in outside air, but represents a large percentage of the total number of particles in a typical sample of air. (Due to the exponential increase in the mass of a particle caused by an increase in the diameter, very small particles typically represent a small fraction of the total mass of particles in an airstream.)

Normal Operating Range

The actual observed values of the critical parameter during operations, collected over time. This range may be larger than the design tolerance, but should be well within Action Limits.

Operating Range

The validated acceptance criteria within which a control parameter must remain, wherein acceptable product is being manufactured.

PAO (Polyalphaolefin)

A synthetic oil used in lieu of DOP for HEPA filter testing.

Particle Count

Airborne particle count of both viable (living) organisms and non-viable (inert) particles. [Measured in PCF (particles per cubic foot) (multiply by ~35.3 to obtain particles per cubic meter)].

Particles Generation Rate (PGR)

Particles generated within a space by a process and occupants per unit time.

Plenum

An enclosed space used for HVAC airflow, typically at low velocity. A plenum may be constructed of duct materials (e.g., sheet metal) or may utilize interstitial spaces in building construction such as below floors, above ceilings, or in vertical chase-ways. A plenum accomplishes air distribution via static pressure difference between the plenum and surroundings, rather than using velocity and associated diversion/distribution devices, as in ductwork.

Process Validation

Establishing documented evidence that provides a high degree of assurance that a specific process will consistently produce a product meeting its predetermined specifications and quality attributes.

Psychrometry

Determination of the properties of gas-vapor mixtures. The air-water vapor system is the most commonly encountered.

Requirement Specifications

A detailed document used to specify the requirements of the client for individual aspects of the facility, item of equipment, utility, and systems in terms of function, throughput, operability, and applicable local standards.

Return Air

Air removed mechanically from the space and returned to the air handling system serving that space for recirculation

Supply Air

Conditioned air supplied mechanically to the space (room), measured here in cubic feet per minute (CFM) (Divide by 0.6 to get cubic meters per hour CMH).

Ultra Low Penetration Air (ULPA) Filters

Extended media dry filters in a rigid frame that have a minimum particle-collection efficiency of 99.999% for particles greater than or equal to 0.12 μm in size.

Unidirectional Airflow

Controlled airflow through the entire cross-section of a clean zone with a steady velocity and approximately parallel streamlines.

Ventilation Rate

The number of times in an hour that the air volume of a room is replaced; see Air Change Rate.



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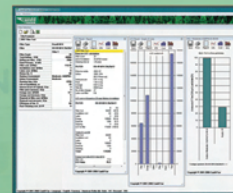
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