



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 GMP 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).

Table 1.1: Comparison of Classified Spaces

Reference	Description	Classification					
ISPE Sterile Baseline® Guide	Environmental Classification						
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	At Rest		Maximum no. particles permitted per m ³ ≥ the stated size		Grade 5	
		In Operation		Maximum no. particles permitted per m ³ ≥ the stated size		Grade 7	
	In Operation	0.5 µm		3 520		Grade 8	
		5 µm		29		Controlled Not Classified (with local monitoring)	
		Maximum permitted number of viable organisms cfu/m ³		< 1		Controlled Not Classified (CNC)	
FDA, October 2004, Guidance for Industry Sterile Drug Products Produced by Aseptic Processing (Reference 9, Appendix 12)	In Operation	0.5 µm		ISO 5 (Class 100)		See ISPE Biopharm or Sterile Baseline® Guides	
		Action level number of viable airborne organisms cfu/m ³		1		Not Defined	
		100		ISO 8 (Class 100,000)		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).

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.

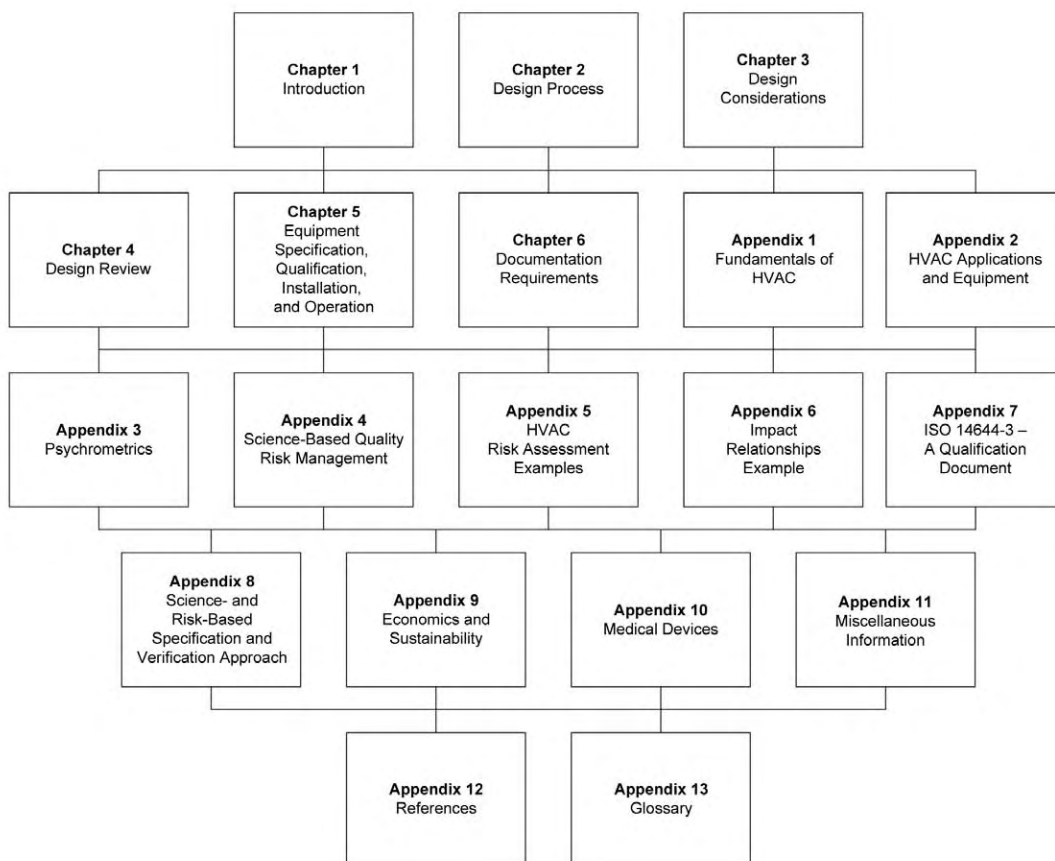
This Guide uses terms as defined in the online ISPE Glossary of Pharmaceutical Engineering Terminology (Reference 17, Appendix 12). New terms or terms specific to the content of this Guide are defined in the Glossary.

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

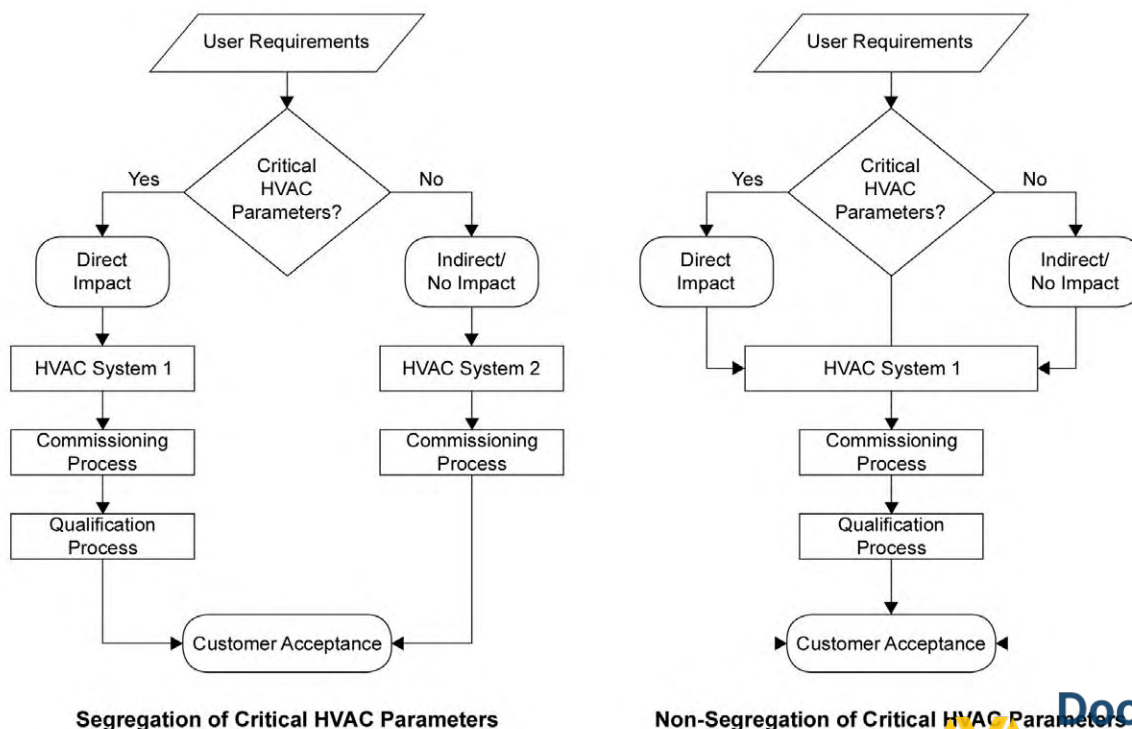


Figure 2.1 reflects a traditional approach, as described in the ISPE Baseline® Guide on Commissioning and Qualification, (Reference 13, Appendix 12) where two systems, one direct impact and one indirect or no impact, can serve a facility. The second approach is a single system that is qualified to serve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

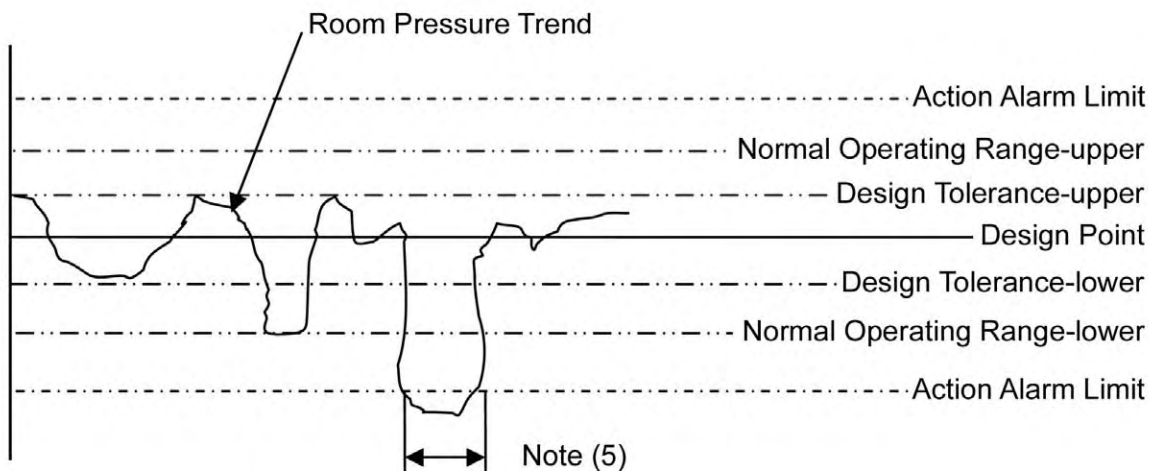
Specific terms should be understood in context (for definitions see Appendix 13):

- 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

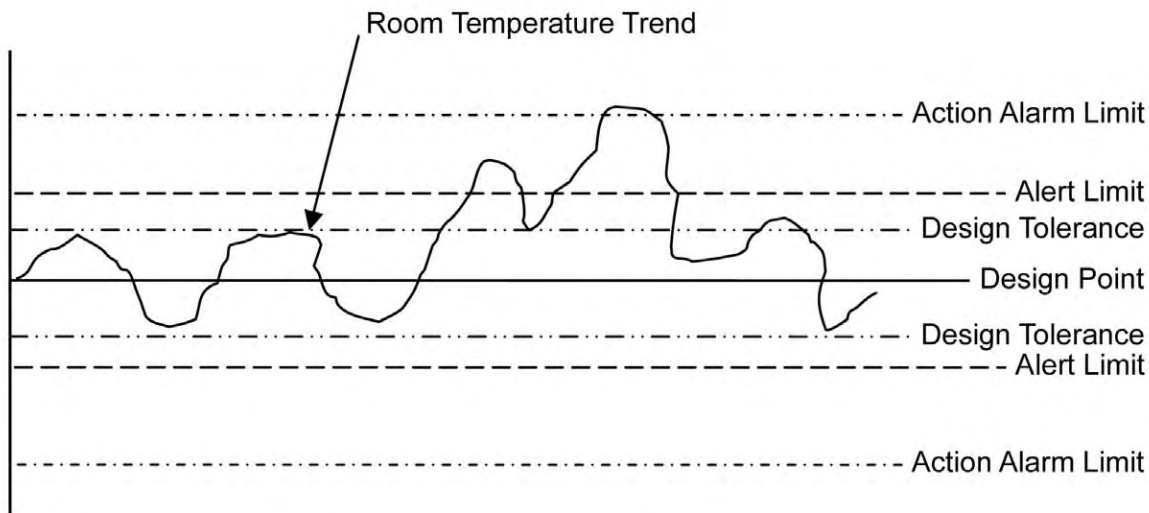


Notes:

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.*

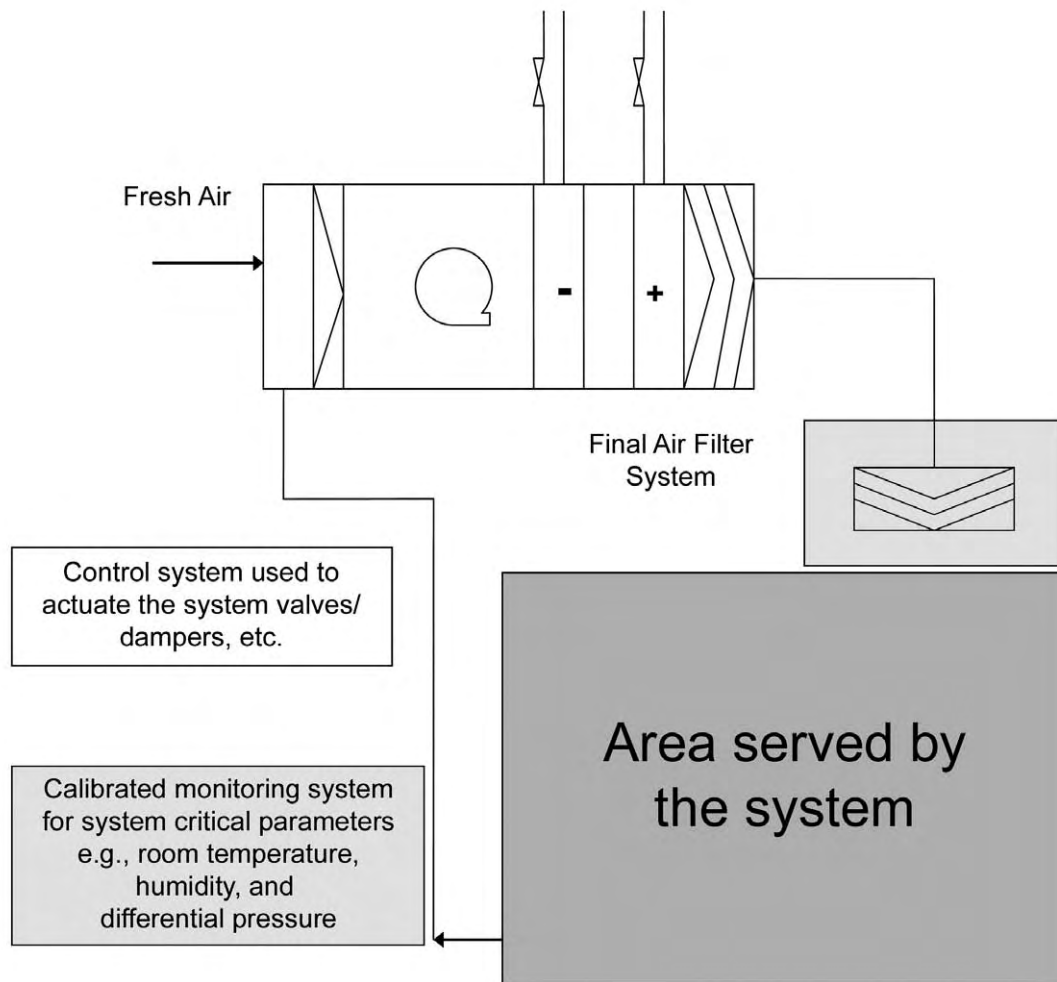
STEP 4.0 Define how the CPPs are achieved, and any associated equipment risks of failure and the probability of detection of those failures. Some examples may be:

- *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.