CHAPTER 19. CLEAN SPACES

CLEAN SPACES are defined as areas in which particle concentration and environmental conditions are controlled at or within specified limits. Design of clean spaces (or cleanrooms) covers much more than traditional control of air temperature and humidity. Additional factors may include control of particle, microbial, electrostatic discharge (ESD), molecular, and gaseous contamination; airflow patterns; air pressurization; sound and vibration; environmental health; life safety; industrial engineering aspects; and manufacturing equipment layouts. The objective of good cleanroom design is to maintain effective contamination control while ensuring required levels of reliability, productivity, installation, and operating costs.

1. TERMINOLOGY

Acceptance Criteria. Upper and lower limits of a pharmaceutical critical parameter required for product or process integrity. If the measured conditions are not within the allowable limits, the pharmaceutical product may be considered adulterated.

ach. Air changes per hour.

Air Lock. A small transitional space between two adjacent spaces of different cleanliness classification and air pressure set points.

As-built Cleanroom. A cleanroom that is completely constructed, with all services connected and functional, but not containing production equipment, materials, or personnel in the space.

Aseptic Space. A space controlled such that bacterial growth is contained within acceptable limits. This is not a sterile space, in which absolutely no life exists.

At-rest Cleanroom. A cleanroom that is complete with production equipment and materials installed and operating, but without personnel in the room.

CFU (colony-forming unit). A measure of bacteria present in a pharmaceutical processing space, measured by sampling as part of performance qualification or routine operational testing.

Challenge. An airborne dispersion of particles of known sizes and concentration used to test filter integrity and filtration efficiency.

Cleanroom. A specially constructed enclosed space with environmental control of particulates, temperatures, humidity, air pressure, airflow patterns, air motion, vibration, noise, viable organisms, and lighting.

Clean Space. A defined area in which particle concentration and environmental conditions are controlled at or within specified limits.

Contamination. Any unwanted material, substance, or energy, including vibration, noise, lighting, radiation, etc.

Commissioning. A quality-oriented process for achieving, verifying, and documenting that the performance of facilities, systems, and assemblies meets defined objectives and criteria, usually beginning at the user requirements specification (URS) generation stage.

Conventional-flow Cleanroom. A cleanroom with non-unidirectional or mixed airflow patterns and velocities.

Critical Parameter. A space variable (e.g., temperature, humidity, air changes, space pressure, particulates, viable organisms) that, by law or per product development data, affects product strength, identity, safety, purity, or quality (SISPQ).

Critical Surface. The part of the work surface to be protected from particulate contamination.

Design conditions. The environmental conditions for which the clean space is designed.

DOP. Dioctyl phthalate: an aerosol formerly used for testing efficiency and integrity of HEPA filters.

ESD. Electrostatic discharge.

EU GMP. European Union guidelines for GMP (defined in following text) pharmaceutical manufacturing.

Electrically Enhanced Filtration (EEF). System that reduces fan energy requirements by using an electrical ionizing device to charge incoming particles and a high-voltage electrical field across the air filter to enhance filtration efficiency of the filter media.

Exfiltration. Air leakage from a space of higher pressurization to one of lower pressurization through material transfer openings; gaps between personnel/pass-through access doors and their respective jambs, window frame/glass interfaces; wall/ceiling and wall/floor interfaces; electrical/data outlets and other room boundary penetrations.

FDA. U.S. Food and Drug Administration.

First Air. Air supplied directly from the HEPA filter before it passes over any work location.

GMP. Good manufacturing practice, as defined by *Code of Federal Regulations* (CFR) 21 CFR 210, 211 (also, CGMP = current GMP).

High-efficiency Particulate Air (HEPA) Filter. A filter with a minimum efficiency of 99.97% of 0.3 µm particles.

IEST. Institute of Environmental Sciences and Technology.

Infiltration. Air leakage into a space from adjoining areas, such as interstitial spaces, of higher pressurization. Moisture leakage from a space of higher partial vapor pressure to one of lower partial vapor pressure may also be described as infiltration, even when one space is at a lower static pressure.

ISPE. International Society for Pharmaceutical Engineering.

ISO. International Organization for Standardization.

ISO 14644-1. Specifies classification of air cleanliness by particle concentration. Only particle populations having cumulative distributions based on threshold (lower limit) particle sizes ranging from 0.1µm to 5 µm are considered for classification purposes. ISO (International Organization for Standardization) *Standard* 14644-1 is an international standard for cleanrooms. Table 1 and Figure 1 summarize the ISO standard classes.

ISO 14644-1. Classification of air cleanliness by particle concentration. ANSI approved in 2015. Covers the classification of air cleanliness in cleanrooms and associated controlled environments.

Table 1 Airborne Particle Concentration Limits by Cleanliness Class per ISO *Standard* 14644-1 (2015)

	0.1 µm	0.2 µm	0.3 µm	0.5 µm	1.0 µm	5.0 µm
ISO 14644 Class	**Particles per m^3**					
1	10					
2	100	24	10			
3	1000	237	102	35		
4	10 000	2370	1020	352	83	
5	100 000	23 700	10 200	3520	832	
6	1 000 000	237 000	102 000	35 200	8320	293
7				352 000	83 200	2930
8				3 520 000	832 000	29 300
9				35 200 000	8 320 000	293 000

Note: Maximum concentration limits (particles/m^3 of air) for particles equal to and larger than considered sizes shown in table. All concentrations in table are cumulative (e.g., for ISO Class 5, the 10 200 particles shown at 0.3 µm include all particles equal to and greater than this size).

$C_n = 10^N(0.1/D)^{2.08}$ where C_n = concentration limits in particles/m^3, N = ISO class, and D = particle diameter in µm

ISO 14644-2. Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration. ANSI approved in 2015. Specifies requirements for monitoring and periodic testing of a cleanroom or clean zone to prove its continued compliance with ISO 14644-1.

ISO/ANS 14644-3. Test methods. ANSI approved in 2005. Specifies test methods for designated classification of airborne particulate cleanliness for characterizing the performance of cleanrooms and clean zones.

ISO 14644-3. Test methods. ISO standard in 2019. This ISO standard has not been approved as an American National Standard, and does not replace ANSI/IEST/ISO 14644-3:2005.

ISO/DIS 14644-4. Design, construction, and start-up. ANSI approved in 2001/DIS Ballot Oct. 2021. Specifies requirements for the design and construction of cleanroom installations.

ISO 14644-5. Operations. ANSI approved in Aug. 2004. Specifies basic requirements for cleanroom operations.

ISO 14644-7. Separative devices (clean air hoods, gloveboxes, isolators, minienvironments.) ANSI approved in Nov. 2004. Specifies the minimum requirements for the design, construction, installation, testing, and approval of separative devices.

ISO 14644-8. Classification of air cleanliness by chemical concentration (ACC). ANSI approved in 2013. Covers the classification of airborne molecular contamination (AMC) in cleanrooms and associated controlled environments.

ISO 14644-9. Classification of surface particle cleanliness. ANSI approved in 2012. Establishes the classification of cleanliness levels on solid surfaces by particle concentration in cleanrooms and associated controlled environments.

ISO 14644-10. Classification of surface cleanliness by chemical concentrations. ISO standard in 2013. Defines the classification system for cleanliness of surfaces in cleanrooms with regard to the presence of chemical compounds or elements.

ISO 14644-12. Specifications for monitoring air cleanliness by nanoscale particle concentration. ANSI approved in 2018. Covers the monitoring of air cleanliness by particles in terms of concentration of airborne nanoscale particles.

ISO 14644-13. Cleaning of surfaces to achieve defined levels of cleanliness in terms of particle and chemical classifications. ISO standard in 2017. Addresses the cleaning to a specified degree on cleanroom surfaces, surfaces of equipment in a cleanroom and surfaces of materials in a cleanroom.

ISO 14644-14. Assessment of suitability for use of equipment by airborne particle concentration. ISO standard in 2016. Specifies a methodology to assess the suitability of equipment for use in cleanrooms and associated controlled environments.

ISO 14644-15. Assessment of suitability for use of equipment and materials by airborne chemical concentration. ISO standard in 2017. Provides requirements and guidance for assessing the chemical airborne cleanliness of equipment and materials which are foreseen to be used in cleanrooms and associated controlled environments.

ISO 14644-16. Energy efficiency in cleanrooms and separative devices. ANSI approved in 2019. Provides guidance and recommendations for optimizing energy usage and maintaining energy efficiency in new and existing cleanrooms, clean zones and separative devices.

ISO 14644-17. Particle deposition rate applications. ISO standard in 2021. Provides guidance on the interpretation and application of the results of the measurement of particle deposition rate (PDR) on one, or more vulnerable surfaces in a cleanroom as part of a contamination control program.

Laminar Flow. Air flowing in parallel paths, without mixing between paths.

Leakage. The movement of air into or out of a space due to uncontrolled enclosure leaks and its pressure relationship to surrounding space(s).

Makeup Air. Outdoor air introduced to the air system for ventilation, pressurization, and replacement of exhaust air.

Minienvironment/Isolator. A barrier, enclosure, or glove box that isolates products from production personnel and other contamination sources to control or improve process consistency while reducing resource consumption.

Monodispersed Particles. An aerosol with a narrow band of particle sizes, generally used for challenging and rating HEPA and UPLA air filters.

Most Penetrating Particle Size (MPPS). The particle size that has the highest rate of filter penetration, or the particle size for which a filter has the least removal efficiency. Most penetrating article size is a function of the filter media, construction, aerosol density, and air velocity.

Non-unidirectional Flow Workstation. A workstation without unidirectional airflow patterns and velocities.

Offset Flow. The sum of all space leakage airflows; the net flow difference between supply airflow rate minus the exhaust and return airflow rates.

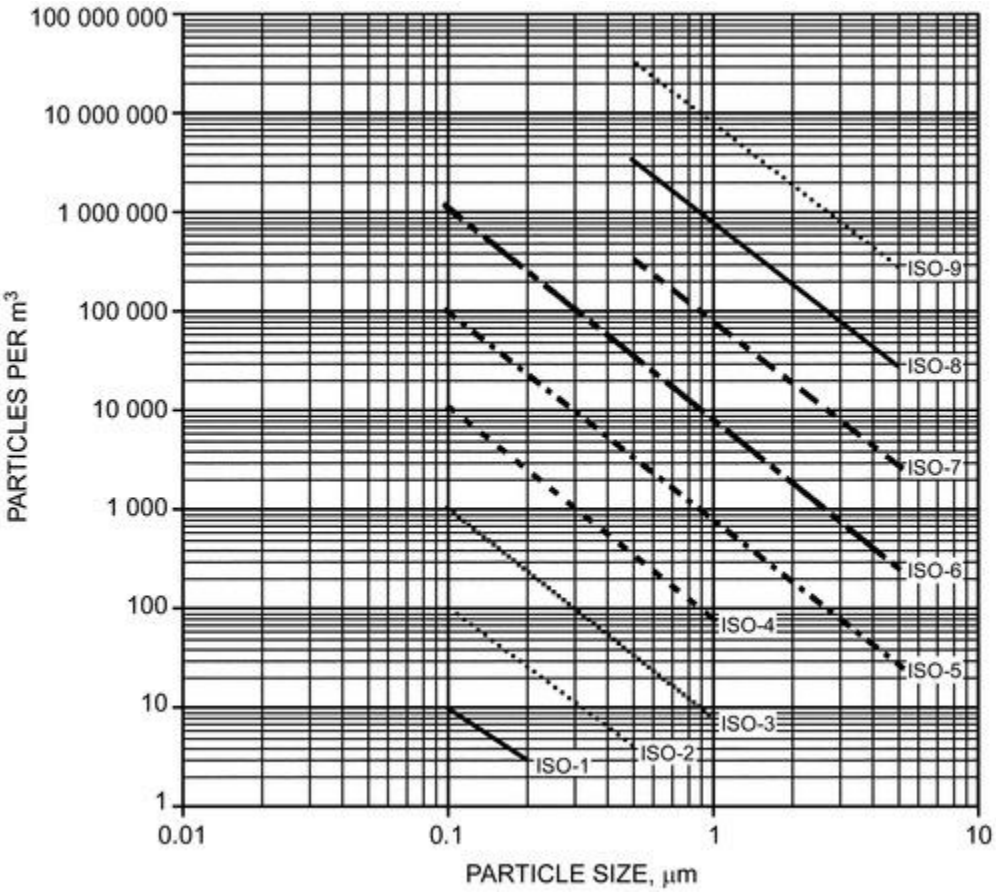


Figure 1. Air Cleanliness Classifications in ISO *Standard* 14644-1

Operational Cleanroom. A cleanroom in normal operation mode with all specified services, production equipment, materials, and personnel present and performing their normal work functions.

Oral Product. A pharmaceutical product to be taken by mouth by the patient.

OP. Operating parameter.

PAO. Polyalphaolefin, a substitute for DOP in testing HEPA filters.

Parenteral Product. A pharmaceutical product to be injected into the patient. Parenterals are manufactured under aseptic conditions or are terminally sterilized to destroy bacteria and meet aseptic requirements.

Particle Concentration. The number of individual particles per unit volume of air (e.g., number per cubic meter per ISO 14644 or number per cubic foot for non ISO).

Particle Size. The apparent maximum linear dimension of a particle in the plane of observation.

Polydispersed Particles. An aerosol with a broad band of particle sizes, generally used to leak-test filters and filter framing systems.

Qualification. Formal, quality-driven, thoroughly documented pharmaceutical commissioning activities undertaken to demonstrate that utilities and equipment are suitable for their intended use, and perform properly and consistently. These activities necessarily precede manufacturing drug products at the commercial scale, and usually consist of installation, operational, and performance testing procedures generated by engineering and quality teams.

Qualification Protocol (QP). A written description of activities necessary to qualify a specific cleanroom and its systems, with required approval signatures.

Room Classification. Room air cleanliness class (Figure 1, Table 1).

SOP. Standard operating procedure.

Topical Product. A pharmaceutical product to be applied to the skin or soft tissue as a liquid, cream, or ointment, which therefore does not need to be aseptic. Sterile ophthalmic products, though, are usually manufactured aseptically.

ULPA (Ultralow-penetration Air) Filter. A filter with a minimum of 99.999% efficiency at 0.12 µm particle size.

Unidirectional Flow. Air flowing in a constant direction uniformly over a defined space or region (different from laminar flow).

Validation. A systematic, quality-driven approach for verifying and documenting that a pharmaceutical process is designed, installed, functions, and is maintained properly, involving sequential executions of installation qualification, operational qualification, and performance qualification activities.

Workstation. An open or enclosed work surface with direct air supply.

2. CLEAN SPACES AND CLEANROOM APPLICATIONS

Use of clean space environments in manufacturing, packaging, and research continues to grow as technology advances and the need for control and containment of airborne particles in work environments increases. This chapter focuses on state-of-the-art facility design and operations to improve quality and resource efficiency in a worldwide industry that provides great benefits and consumes significant energy. The following major industries use clean spaces for their products:

- **Pharmaceuticals/Biotechnology.** Preparations of pharmaceutical, biological, and medical products require clean spaces to control viable (living) and nonviable particles that could impact product sterility.
- **Microelectronics/Semiconductors.** Advances in semiconductor microelectronics drive cleanroom design. Semiconductor facilities are a significant percentage of all cleanrooms in operation in the United States, with most newer semiconductor cleanrooms being ISO *Standard* 14644-1 Class 5 or cleaner.
- **Flat Panel Display.** FPD factories are some of the largest cleanrooms, with some cleanrooms greater than 200 000 m^2, requiring adherence to ISO 14644-1 Classes 5 to 8 throughout the factory. They typically change cleanliness requirements by process area and risk of exposure to the product. These facilities may produce liquid crystal, light-emitting diodes (LEDs), and organic light-emitting diodes based displays.
- **Aerospace.** Cleanrooms were first developed for aerospace applications to manufacture and assemble satellites, missiles, and aerospace electronics. Most applications involve large-volume spaces with cleanliness levels of ISO *Standard* 14644-1 Class 8 or cleaner.
- **Hospitals.** Operating rooms may be classified as cleanrooms, but their primary function is more to limit particular types of contamination than to control the quantity of particles present. Cleanrooms are used in patient isolation and surgery where risks of infection and cross contamination must be controlled, and in hospital pharmacies, where compounding sterile pharmaceuticals requires stringent control of the immediate and surrounding environments. For more information, see Chapter 9.
- **Miscellaneous Applications.** Cleanrooms are also used in aseptic food processing and packaging, microelectronic and nanotech applications, medical device manufacturing, automotive paint booths, crystal, laser/optic industries, and advanced materials research.

3. AIRBORNE PARTICLES AND PARTICLE CONTROL

Airborne particles occur in nature as pollen, bacteria, miscellaneous living and dead organisms, and windblown dust and sea spray. Industry generates particles from combustion, chemical vapors, manipulation of material, and friction in moving equipment. Personnel working in the cleanrooms are a prime source of particle generation (e.g., skin flakes, hair, clothing lint, cosmetics, respiratory emissions, bacteria from perspiration). Sizes of airborne particles vary from 0.001 to several hundred micrometres (μm). Although it is common for airborne particles of sizes larger than 5.0 μm to settle quickly due to gravity, it may take days for some forms of airborne particles smaller than 1.0 μm to settle (barring intervention and control mechanisms applied to the space). In many manufacturing processes, airborne particles are a source of contamination or facilitate spread of biological contaminants. Cleanroom designs must accommodate particulate sources and focus on particulate control to maintain acceptable environmental conditions. Locations and sizes of return and exhaust registers are important considerations, as are layouts of equipment and locations and sizes of supply registers.

Particle Sources in Clean Spaces

In general, the origins of cleanroom particles are described as either external or internal.

- **External Sources.** Externally sourced particles enter the clean space from the outside via infiltration through doors, windows, wall penetrations, surface contamination on personnel, material and equipment entering the space, and outdoor makeup air entering through the HVAC system. Air-handling equipment can also be a source of contamination from belt dust, particles flaking from ductwork fans, and manufacturing debris left in air-handling units. In a typical cleanroom, external particle sources normally have little effect on overall cleanroom particle concentration because HEPA filters remove particulates from the supply air and the cleanroom is operated at a higher pressure than surrounding spaces to prevent infiltration. However, the particle concentration in clean spaces at rest relates directly to ambient particle concentrations. Particles from external sources are controlled primarily by air filtration, room pressurization, and sealing space penetrations.
- **Internal Sources.** People, cleanroom surface shedding, process equipment, and the manufacturing process itself can generate particles in clean spaces. Cleanroom personnel, if not properly gowned, may be the largest source of internal particulate generation, generating several thousand to several million particles per minute. Personnel-generated particles are controlled with proper gowning procedures, including new cleanroom garments, and airflow designed to continually shower critical areas with clean air and direct less-clean airstreams toward the return/exhaust registers. As personnel work in the cleanroom, their movements may reentrain airborne particles from other sources by creating turbulent air movement, eddies, and vortexes. Other activities, such as writing, printing, or moving and bumping equipment may also cause higher particle concentrations. Door swings or equipment challenges can produce strong additional transient differential pressure excursions, which may lead to particle infiltration through crack and crevices.

Though particle concentrations in the cleanroom air may be used to define its cleanliness class, actual particle deposition on the product critical surface is of greater concern. In addition to the ISO 14644-1 standard covering classification by airborne particle concentration, ISO 14644-8 specifies classification of air cleanliness by chemical concentration (ACC), which is critical to many organic-based processes, and ISO 14644-9 and 14644-10 cover classification of surface cleanliness by particle and chemical concentration. The sciences of aerosols, filter theory, and fluid motions are the primary sources of understanding nonvolatile residue deposition and contamination control (IEST *Recommended Practice* RP CC016). Cleanroom designers may not be able to control or prevent internal particle generation completely, but they may anticipate internal sources and design control mechanisms, hoods and other source removal equipment, and airflow patterns to limit their effect on the product. Particle counters are used to measure particle counts and concentrations for selected locations in the cleanroom and provide control feedback. They should be well calibrated to ensure accuracy and reliability of contamination control (ISO 21501).

Table 2 Filter Classification, per ISO 29463, of High-Efficiency Filters and Filter Media for Removing Particles in Air

	Overall Value		
Filter Class and Group	**Efficiency, %**	**Penetration, %**	**Filter Application**
ISO 15 E	≥95	≤5	General
ISO 20 E	≥99	≤1	Industrial, hospital, food
ISO 25 E	≥99.5	≤0.5	
ISO 30 E	≥99.90	≤0.1	
ISO 35 H	≥99.95	≤0.05	

ISO 40 Hd	≥99.99	≤0.01	Unidirectional flow (semiconductor, pharmaceuticals)
ISO 45 Hd	≥99.995	≤0.005	Nanotechnology Applications
ISO 50 U	≥99.999	≤0.001	
ISO 55 U	≥99.9995	≤0.0005	
ISO 60 U	≥99.9999	≤0.0001	
ISO 65 U	≥99.99995	≤0.00005	
ISO 70 U	≥99.99999	≤0.00001	
ISO 75 U	≥99.999995	≤0.000005	

Fibrous Air Filters

Proper air filtration prevents most externally generated particles from entering the cleanroom via the HVAC system. High-efficiency air filters come in two types: high-efficiency particulate air (HEPA) filters and ultralow-penetration air (ULPA) filters. HEPA or Group H filters (ISO 29463) are individually tested, and their efficiency is between 99.95 and 99.995% at most penetrating particle size (MPPS), in accordance with ISO 29463-5. ULPA or Group U (ISO 29463) filters are individually tested, and their efficiency is between 99.999 and 99.999995% at MPPS, in accordance with ISO 29463-5. HEPA and ULPA filters use glass fiber paper technology; laminates and nonglass media for special applications also have been developed. HEPA and ULPA filters are usually constructed in a minipleat form with aluminum, coated string, filter paper, or hot-melt adhesives as pleating separators. Filters pleat depths are available from 25 to 300 mm; available filter media surface area increases with deeper-pleated filters and closer pleat spacing, which reduces filter pressure drop and increases dirt holding capacity.

There are four common mechanisms by which HEPA and ULPA filters capture particulate: (1) straining, (2) inertia, (3) interception, and (4) diffusion. In addition, some systems use electromagnetic forces to enhance HEPA and ULPA filter performance (see the section on Sustainability and Energy Conservation in Cleanrooms for details). In **straining** capture, sometimes called sieving, particles enter passages between two or more fibers that have dimensions less than the particle diameter (most of these particles are captured in prefilters). In **inertia** capture, particles traveling in airstream through fiber material have too much mass to stay in the airstream as it bends through the filter fibers; particles leave the airstream and attach to filter fibers. In **interception** capture, particles with mass small enough to stay in the airstream nevertheless touch the filter fiber and are attached. In **diffusion** capture, very small particles move randomly through Brownian motion; they touch and subsequently attach to filter fibers. Theories and models verified by empirical data indicate that interception and diffusion are the more effective capture mechanisms for smaller particles in HEPA and ULPA filters. In general, fibrous filters' lowest removal efficiency corresponds to the most penetrating particle size, which is determined by filter fiber diameter, volume fraction or packing density, and air velocity. For most HEPA and ULPA filters, the MPPS is between 0.1 to 0.3 μm. Group H (HEPA) and Group U (ULPA) filter efficiency is calculated using the MPPS per ISO 29463. Table 2 provides the ISO 29463 efficiency values and typical applications for Group H and U filters. NIOSH (2003) provides a detail illustration of filtration mechanisms in straining, inertial impaction, interception, diffusion, and electrostatic attraction.

4. AIR PATTERN CONTROL

Air turbulence in the clean space may be detrimental to environmental quality. Turbulence is strongly influenced by air supply and return configurations, air balancing adjustments, foot traffic, buoyancy effects from hot surfaces, and process equipment layout. Specifying and optimizing airflow patterns to meet operational requirements are the first steps of good cleanroom design. User requirements for cleanliness level, process equipment layout, available space for installing air pattern control device and systems (air handlers, clean workstations, environmental control components, types of recirculation air system, etc.), and project financial considerations all affect air pattern design selection.

Numerous airflow pattern configurations are possible, but they fall into two general categories: non-unidirectional airflow (commonly called turbulent or mixed flow), and unidirectional airflow (previously, often mistakenly, called laminar flow).

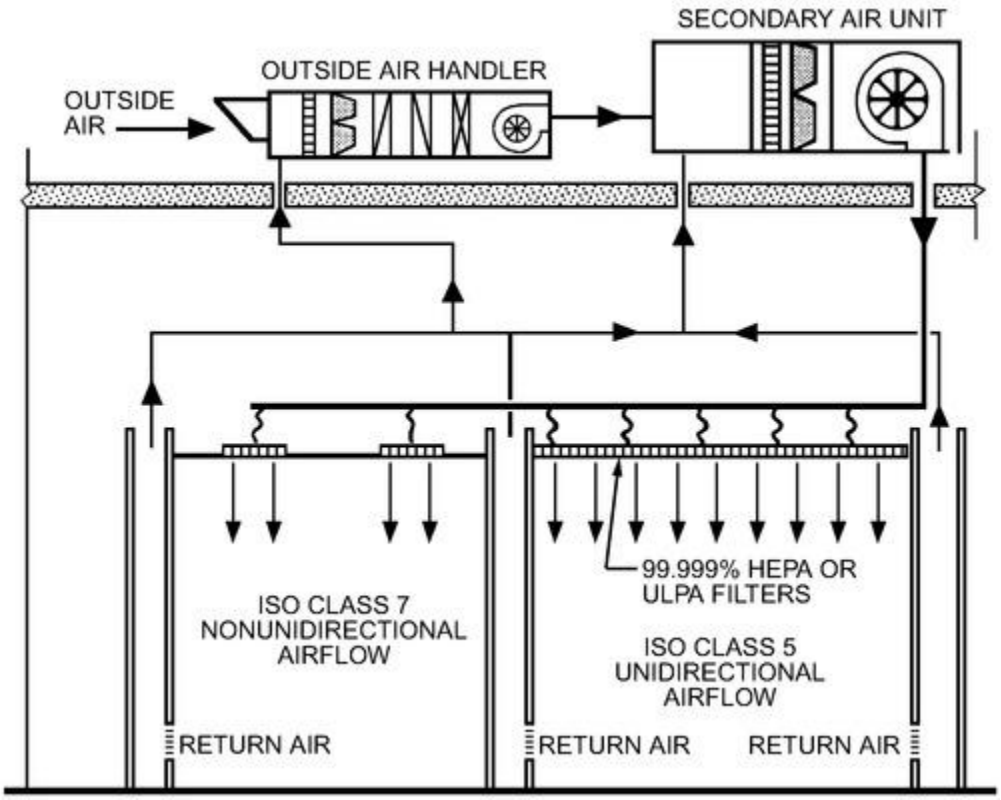


Figure 2. ISO Class 7 Non-unidirectional Cleanroom with Ducted HEPA Filter Supply Elements and ISO Class 5 Unidirectional Cleanroom with Ducted HEPA or ULPA Filter Ceiling

Non-unidirectional Airflow

Non-unidirectional airflow has either multiple-pass circulating characteristics or nonparallel flow streamlines. Variations are based primarily on the location of supply and return/exhaust air registers and the associated airflow rates. Examples of non-unidirectional airflow of cleanroom systems are shown in Figures 2, 3, and 4. Air is typically supplied to the space through supply diffusers with integral HEPA filters (Figure 2) or with HEPA filters in the supply diffuser ductwork or air handler (Figure 3). In a mixed flow configuration, air is prefiltered in the supply and then HEPA filtered at workstations in the clean space (see the left side of Figure 3).

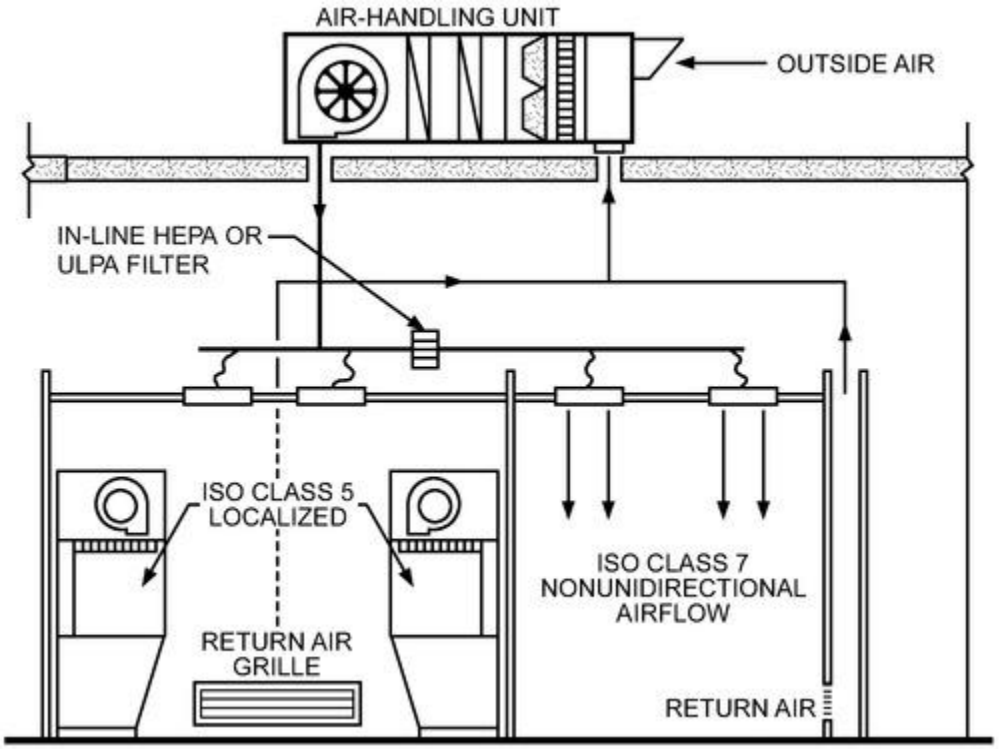


Figure 3. ISO Class 7 Non-unidirectional Cleanroom with HEPA Filters Located in Supply Duct and ISO Class 5 Local Workstations

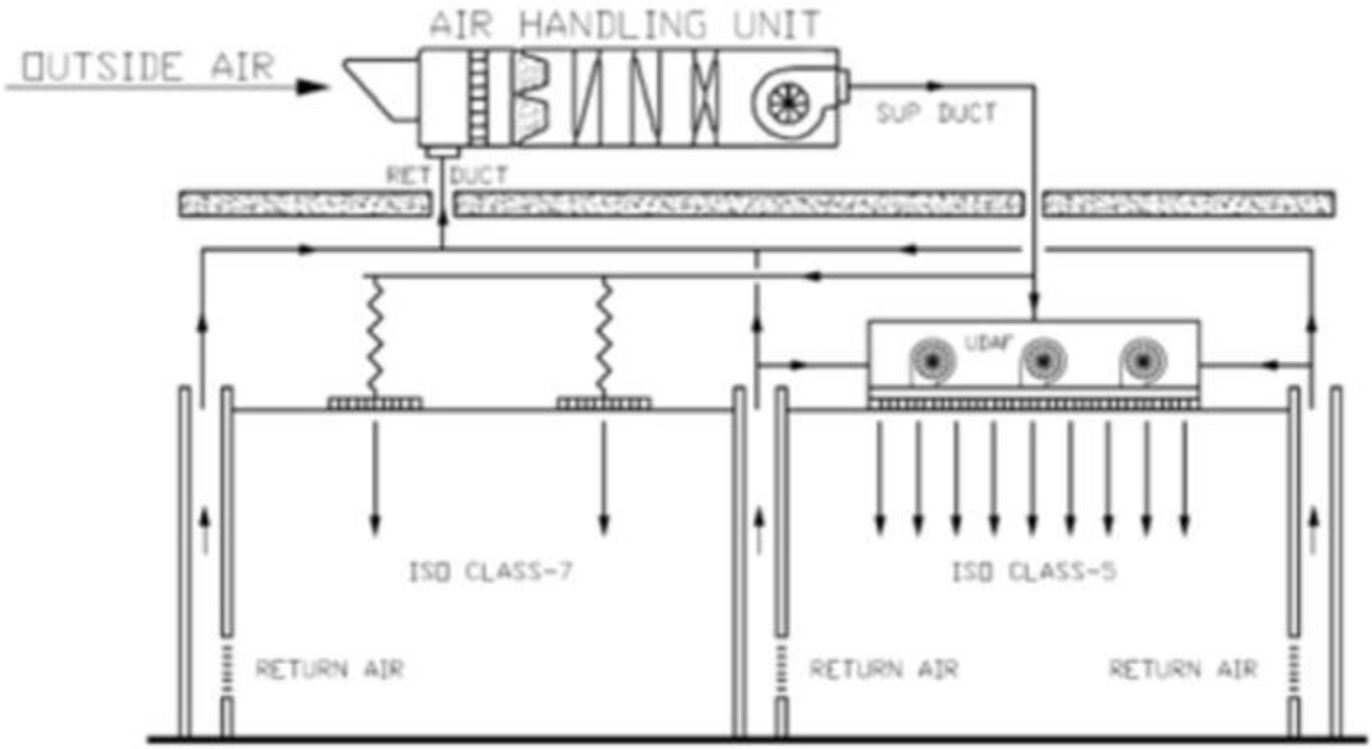


Figure 4. ISO Class 7 Non-Unidirectional Cleanroom with HEPA Filters Located in Supply Duct and ISO Class 5 Unidirectional Airflow Modules

Non-unidirectional airflow may provide satisfactory contamination control for ISO *Standard* 14644-1 Classes 6 to 8. Attaining desired cleanliness classes with designs similar to Figures 2 and 3 requires terminal or in-line mounted HEPA filters to remove airborne particulates from the supply air, which improves the interior particulate concentration levels through mixing. Selected air diffusers should introduce air with least amount of induction (to promote mixing) and maximize space flushing effect. Supply terminals with perforated sheet or low induction swirl diffusers are preferred, with low level extract or return for rooms with high process dust generation. When internally generated particles are of primary concern, clean workstations can be used effectively in the clean space.

Unidirectional Airflow

Unidirectional airflow, though not truly laminar, is characterized as air flowing in a single pass in a single direction through a cleanroom with generally parallel streamlines with lateral movement not exceeding 15° along an uninterrrupted flow. Ideally, flow streamlines would be uninterrupted; although personnel and equipment in the airstream distort the streamlines, a state of constant velocity is approximated. Most particles that encounter an obstruction in unidirectional airflow continue around it as the airstream reestablishes itself downstream of the obstruction. Hot surfaces and abrupt changes in flow streamlines may occur and create internal circulating paths. Identifying these phenomena during the design stage by using CFD modeling can help avoid high particle concentration areas.

Air patterns are optimized and air turbulence is minimized in unidirectional airflow. In a **unidirectional-flow space**, air is typically introduced through ceiling HEPA or ULPA filters and returned through a raised access floor or at the base of sidewalls. For pharmaceutical and life sciences applications, this method is not recommended because of the potential for biological growth under raised floors. Instead, judicial placement of supply filters and room returns allows unidirectional flow. Often, computational fluid dynamics (CFD) is used to determine these locations before construction; see Chapter 13 of the 2021 *ASHRAE Handbook—Fundamentals* for details on CFD. Because air enters from the entire ceiling area, this configuration produces nominally parallel airflow. In a horizontal-flow cleanroom, air enters one wall and returns on the opposite wall.

A **downflow cleanroom** has a ceiling with HEPA filters. As the space cleanliness classification becomes more stringent, the space air change rate and the number of HEPA filters may increase. Typically, for an ISO Class 5 or cleaner space, the ceiling has 70 to 100% HEPA filter coverage. Ideally, a grated or perforated floor serves as the air return/exhaust. In this configuration, clean air flows downward past a contamination source, sweeping away the contamination particles, and removes them directly down through the floor to prevent the particles from contacting the critical surface of a product. However, this type of floor is inappropriate for pharmaceutical cleanroom applications, which typically have solid floors and low-level wall returns. Raised-floor configurations may not be appropriate where there is concern for contamination under the floor.

Special attention should be given to ceiling HEPA and ULPA filter design, selection, and installation to ensure a leakproof ceiling system. Properly sealed filters in the ceiling can provide the cleanest air presently available in a cleanroom. HEPA and ULPA filters may be leak tested before installation, looking for filter defects, and again after

installation, looking for leaks in the system used to seal the filter into the ceiling system. Pharmaceutical cleanrooms have regulatory requirement that necessitate periodic testing. Provisions are normally made for in situ testing in the design of the filter assembly. Tubes included for introduction of the filter challenge cause a reduction in filter area and an increase in filter pressure drop. Filter quantity needed will therefore be affected.

In a **horizontal-flow cleanroom**, the supply wall consists entirely of HEPA or ULPA filters supplying air at approximately 0.45 m/s or less across the entire cross section of the space. Due to higher turbulence, the use of higher velocities may be necessary to address high particle generation rates, but note that 0.45 m/s may be too high for some applications, and velocities above 0.36 m/s may increase particle reentrainment and particle residence time. Return/exhaust air exits through the return wall at the opposite end of the space. As with the downflow cleanroom, the horizontal-flow cleanroom removes contamination generated in the space and minimizes cross contamination perpendicular to airflow. However, a major limitation is that downstream air particle concentration increases from entry plane to exit plane. Air leaving the filter wall is the cleanest; it then becomes contaminated by the process as it flows past the first workstation. Process activities should be arranged to have the most critical operations at the clean end of the space, with progressively less critical operations located toward the return or dirty end of the space.

ISO *Standard* 14644-1 does not specify velocity requirements, so the actual velocity is as specified by the owner or owner's agent. IEST published rule-of-thumb air change rates for various cleanliness classes (IEST RP CC012.3), which should be reviewed by the owner; however, the scientific basis for the ranges is unclear. Acceptable cleanliness class has been demonstrated with much lower air change rates (Xu 2003, 2004), suggesting that the actual particle concentration and cleanliness level may also depend on filter efficiency, filter coverage, and particle generation rates, in addition to air change rates. ISO *Standard* 14644-2 requires an owner to understand the risk to maintaining clean spaces' cleanliness and to prepare a monitoring plan to ensure cleanliness levels are maintained. Monitoring plans should take into account the level of air cleanliness required, critical locations, and performance attributes of the cleanroom that may affect performance of the space. These attributes should be identified during the risk assessment and may include room pressurization, room air velocity, HEPA filter leak testing, air change rates, etc. Any reduced air change rate design should be factored into risk assessment and monitoring plans. At this time, airflow rates in pharmaceuticals may be determined by regulatory requirements. Check with the client's regulatory officials prior to proposing reduced air flow rates.

Unidirectional airflow systems have a predictable airflow path that airborne particles tend to follow. Without good filtration practices, unidirectional airflow only indicates a predictable path for particles. However, superior cleanroom performance may be obtained with, in addition to other measures, a good understanding of unidirectional airflow, which remains parallel to below the normal work surface height of 760 to 915 mm, but deteriorates when it encounters obstacles (e.g., process equipment, work benches) or over excessive distances. Personnel movement also disturbs airflow patterns, resulting in a cleanroom with areas of good unidirectional airflow and areas of turbulent airflow.

Turbulent zones have countercurrents of air with high velocities, reverse flow, or no flow at all (stagnancy). Countercurrents can produce stagnant zones where small particles may cluster and settle onto surfaces or product; they may also lift particles from contaminated surfaces and deposit them on product surfaces.

Cleanroom mockups may help designers minimize and avoid turbulent airflow zones and countercurrents. Smoke, neutral-buoyancy helium-filled soap bubbles, and nitrogen vapor fogs can make air streamlines visible in the mockup.

Computational Fluid Dynamics (CFD)

Air is the primary carrier of heat, moisture, contaminants, and particles in cleanroom facilities. The distribution of supply air determines the resulting air velocities, temperatures, and concentration of particles at various locations in a cleanroom. Such distribution in turn determines thermal comfort and air quality. Satisfactory thermal comfort for occupants, higher energy efficiency, and maintaining the desired cleanliness are mutually competing goals. Obtaining these goals by optimizing various design and operating parameters of cleanroom air distribution systems is a daunting task.

Airflow patterns, temperature, and particle distribution in a cleanroom can depend on several interrelated factors, including location of supply diffusers, supply air flow rates (air change rates) and associated diffuser throws, supply air temperature, size and locations of room return, leakage areas and associated airflow rates, locations and strengths of various heat sources in a room, location and size of obstructions to airflow, and relative location and strength of particle-generating entities in a cleanroom. Physical testing and measurements to study the influence of all these factors on the thermal comfort, energy efficiency, and level of cleanliness are time consuming and labor intensive, if not impossible. In this situation, analysis of various realistic scenarios through computational fluid dynamics (CFD) simulations is an attractive alternative. In critical applications, it is good practice to verify the CFD predicted results.

Computational fluid dynamics analysis can predict airflow patterns, resulting temperature distribution, particle concentration, relative humidity distribution, and resulting thermal comfort of occupants in confined spaces such as cleanrooms. In addition, CFD is routinely used to predict wind patterns around buildings to evaluate impact of wind on environmental dispersion, wind pressure on building facade, and pedestrian comfort. In cleanroom design analysis, it is used to predict the effects of room pressurization (i.e., relative supply and return airflow rates, locations of supply and returns, particle generation rate on the distribution of cleanliness in a room). CFD analysis can help provide deep insight into real-life operation of cleanroom at the conceptual design stage, which in turn can help in optimizing the operating parameters and in reducing the first and operating costs of HVAC systems.

CFD involves solving and analyzing transport equations of fluid flow, heat transfer, mass transfer, and turbulence. The transport of mass, momentum, energy, and chemical species are governed by a generalized conservation principle that can be described in the form of a general differential equation. During this CFD procedure, the calculation domain (extent of space) is divided into a number of nonoverlapping control volumes, such that there is one control volume surrounding each grid point. Then, each governing differential equation is iteratively balanced over each control volume to conserve the mass, momentum, energy, and other similar physical entities. During iteration, the residual error for each governing equation is monitored and reduced. This process continues until the overall balance in the conservation of all the governing entities reaches the acceptable or desired level. Finally, such converged numerical solutions reveal a detailed distribution of pressure, velocities, turbulence parameters, temperature, concentration of chemical species, etc., in the calculation domain.

CFD results can be presented in color contour plots showing three-dimensional distributions of temperature and particle concentrations in cleanrooms. Flow path lines and vectors plots are used to reveal airflow patterns in a room. Flow animations also help in visualizing air and particle movement in a room.

CFD models of particle trajectories, transport mechanisms, and contamination propagation are commercially available. Flow analysis with computer models may compare flow fields associated with different process equipment, work benches, robots, building exterior envelope, personnel, and building structural design. Flow patterns and air streamlines are analyzed by computational fluid dynamics for laminar and turbulent flow where incompressibility and uniform thermophysical properties are assumed. Using CFD modeling in actual cleanroom design and layout planning, design parameters may be modified and optimized to determine the effect of airflow control and space or equipment layouts on particle transport, flow streamlines, and contamination concentrations, thus reducing or avoiding the cost of mockups (Tung et al. 2010; Yang et al. 2009).

Major features and benefits associated with most computer flow models are

- Two- or three-dimensional modeling of cleanroom configurations, including people and equipment
- Modeling of unidirectional airflows
- Multiple air inlets and outlets of varying sizes and velocities
- Allowances for varying boundary conditions associated with walls, floors, and ceilings
- Aerodynamic and buoyancy effects of process equipment, workbenches, and people
- Prediction of specific airflow patterns, velocities, and temperature gradients of all or part of a cleanroom
- Simulation of space pressures by arranging supply, return, exhaust, and planned exfiltration and infiltration airflows
- Reduced cost associated with new cleanroom design verification
- Identifying particle deposition risks to open wafers in some metrology tools
- Recognition of temperature hot spots
- Projection of particulate loading in the air spaces
- Calculation of flow fields and their effect on particulate control
- Use of chemical dispersion to aid airborne molecular contaminant (AMC) mitigation strategies
- Identification of recirculation zones and design features that may lead to detrimental airflow
- Raised-floor damper balancing
- Determining preliminary raised floor damper position settings
- Graphical representation of flow streamlines and velocity vectors to assist in flow analysis (Figures 5, 6, and 8)
- Graphical representation of simulated particle trajectories and propagation (Figures 7 and 9)

Research has shown good agreement between flow modeling by computer and physical experimentation done in simple mockups. However, computer flow modeling software should not be considered a panacea for cleanroom design because of the variability of individual project conditions.

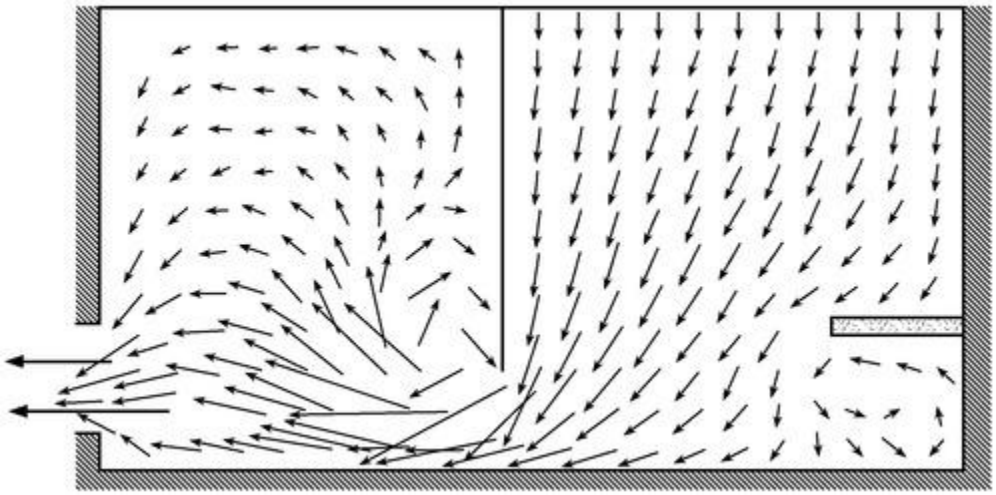


Figure 5. Cleanroom Airflow Velocity Vectors Generated by Computer Simulation

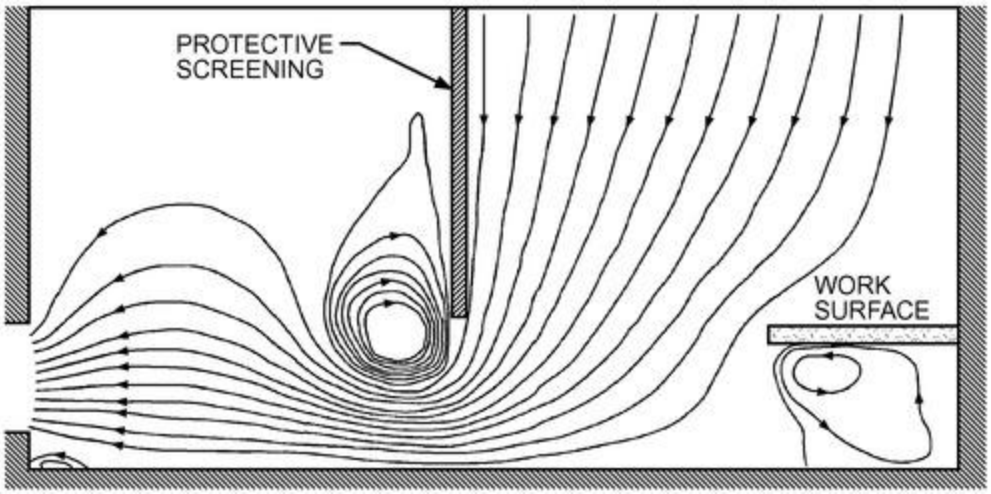


Figure 6. Computer Modeling of Cleanroom Airflow Streamlines

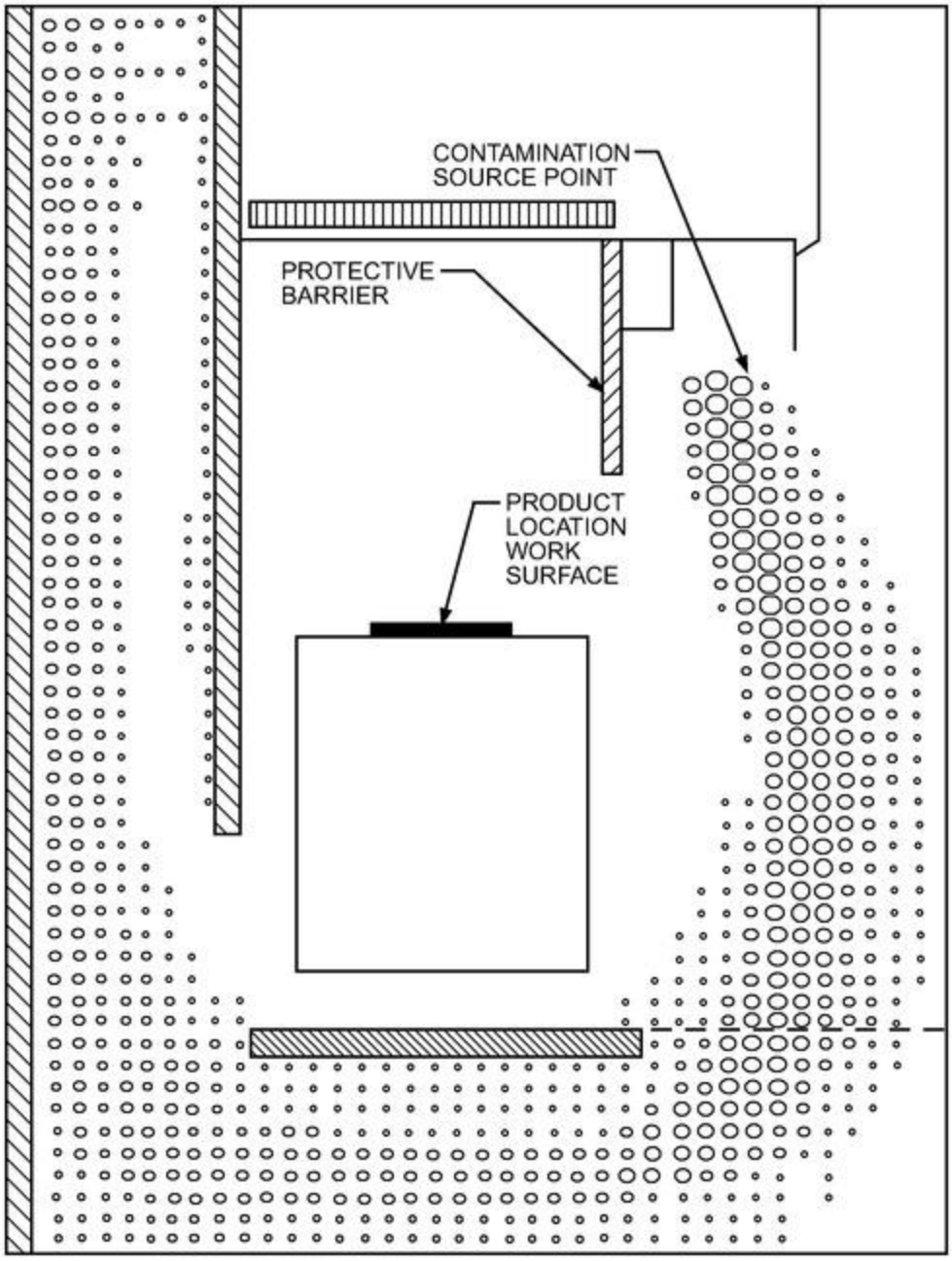


Figure 7. Computer Simulation of Particle Propagation in Cleanroom

For more information on CFD, see Chapter 13 of the 2021 *ASHRAE Handbook—Fundamentals*.

Air Change Rate Determination

Cleanroom HVAC systems are highly energy intensive (Lowell et al. 1999), and can have an energy use index of between 2543 kWh/m^2 and 3819 kWh/m^2 (Boyd 2011) for pharmaceutical factories and greater than 10 000 kWh/m^2 for semiconductor factories. Airflow rates in cleanrooms must meet not only the heating and cooling loads, but also the contaminant dilution requirements to reduce room particle concentration. It is critical to realize that particle contaminants generated in a cleanroom are not from HEPA-filtered supply air, but from activities inside the cleanroom. A very high air change rate is not typically needed for cooling, heating, or ventilation loads but mainly for controlling and diluting particle concentrations. There is a precedent of cleanroom design engineers using conservative, simplified rule-of-thumb values for air change rates published in IEST RP-12.3, supplier literature, or guidance documents from various government or industry sources. This approach uses the required room cleanliness class alone to suggest an air change per hour (ach) value, often arbitrarily, from a wide range specified in older documents and therefore ignores many critical variables that could significantly affect the room particle concentration in terms of air change rate requirements. Such variables include room internal particle size and generation rate, particle surface deposition, particle entry through filtered supply air, particle exit through return and exhaust air, air leakage (particle loss or gain) under pressurization or depressurization, layout of processes, and locations of supply, return, and exhaust registers. Intuitively, for example, activities that generate higher levels of particle concentration would need a higher air change rate to dilute particle concentration than those that generate lower levels of particle concentration, but existing practices use an oversimplified approach that ignores such differences. It is possible to create cleaner zones within an overall room classification. This

is frequently done in pharmaceutical where glassware is wrapped under ISO 5 hoods at autoclave glassware discharges. The room itself may be at ISO 7 or 8.

Each cleanroom facility is unique; its location, building construction, production or process activities, space configurations, HVAC systems, room cleanliness requirements, etc., can impact the air change requirement for each room. Using a rough, oversimplified approach without considering all these variables could cause either significant energy waste or poorly designed HVAC systems. Xu (2003, 2004) found that airflow rates or air velocities for cleanrooms in actual operation exhibited lower values than those described in IEST RP CC012.3.

In attempts to offset expected contamination generation rates, some operating cleanrooms may be overdesigned and may operate at higher airflow rates or airflow velocities than necessary, resulting in significant energy waste. To save fan and thermal energy in cleanroom HVAC systems, modeling technologies have been developed and published that provide more scientifically based, quantitative design tools (rather than rule-of-thumb values) (Sun 2008; Sun et al. 2010). Figure 10 shows the measured airflow rates and airflow velocities of actual ISO Class 5 and Class 6 cleanrooms in the United States in comparison with the typical ranges exhibited in IEST RP CC012.3.

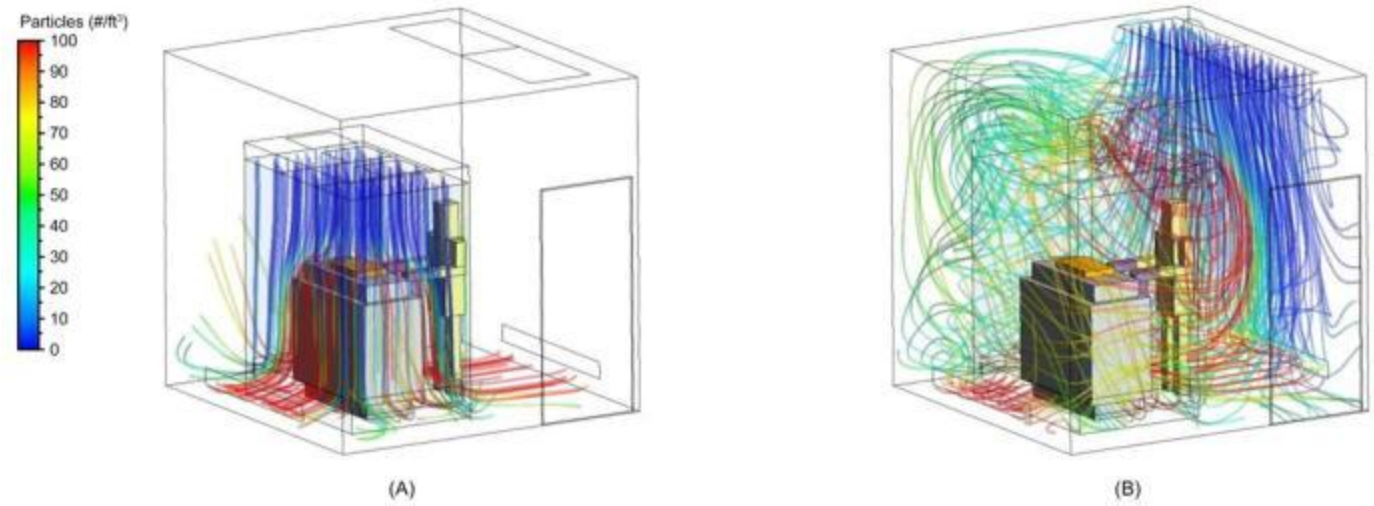


Figure 8. Computer Simulated Airflow Patterns in Minienvironment Cleanroom: (A) Unidirectional Flow and (B) Mixed Flow (CFD analysis provided by Kishor Khankari, Ph.D., President, AnSight LLC, Ann Arbor, MI)

Demand Control Airflow

Demand control is used in many applications such as variable-air-volume systems to control room temperature, variable water flow to control a coil's capacity, and demand control ventilation to decrease airflow to spaces during low occupancy. Additionally, demand-based control has been widely applied to research laboratory spaces to vary lab room air change rates in real time based on active sensing of both particulate and chemical containment levels. Extensive studies of lab room environmental conditions (Sharp 2010) have shown that the air quality in labs is typically acceptable over 98% of the time, which can allow significant savings in HVAC energy costs by reducing airflow to as low as 2 ach during these time periods. For the 1 or 2% of the time that chemical or particulate contaminants are sensed in the lab the air flow is raised to a high level to rapidly purge the lab of these contaminants.

Although less commonly used, this same technology and approach can also be applied to control cleanroom airflows. ASHRAE research project RP-1604, Demand Based Control for Cleanrooms (Sun [in progress]), is examining this concept and will provide qualitative data on the effectiveness of this approach. Lawrence Berkeley National Laboratory has also demonstrated the concept of demand based control in cleanrooms and shown its feasibility (Faulkner et al. 1996, 2008).

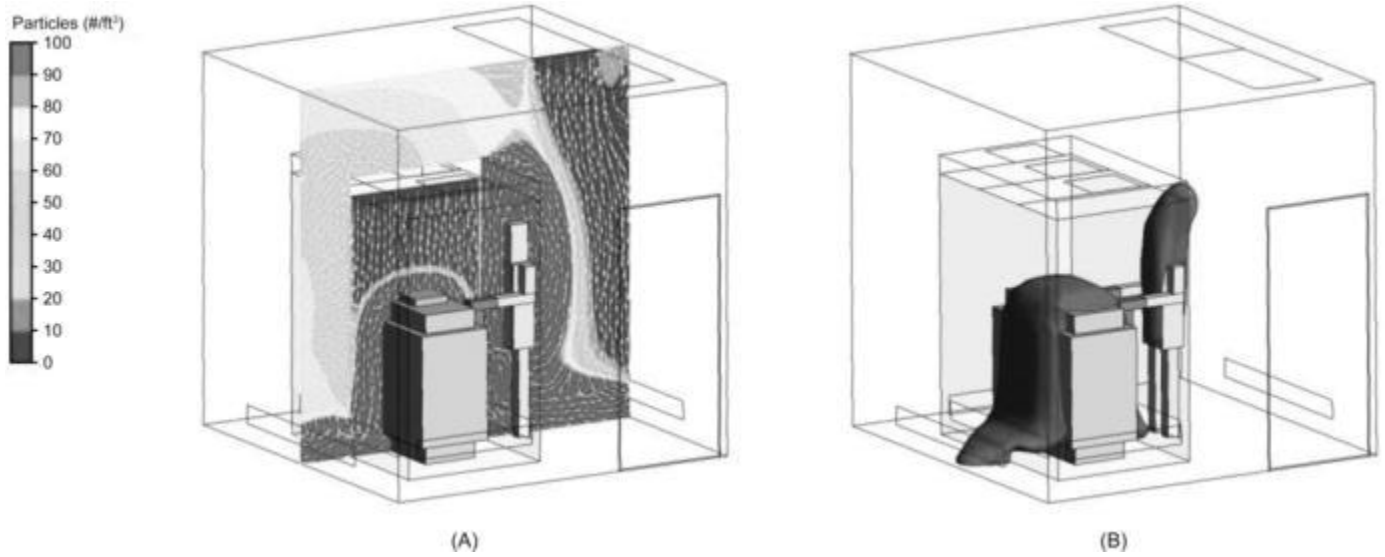


Figure 9. Computer Simulated Particle Concentration in Minienvironment Cleanroom Showing (A) Lower Particle Concentration in Minienvironment and Higher Concentration near Person because of Recirculation of Air around Occupant and (B) Particle Cloud of 35 311 particles/m^3 with Higher Particle Concentration near Occupant's Face (CFD analysis provided by Kishor Khankari, Ph.D., AnSight LLC)

The benefit of demand control in a cleanroom is a significant reduction in the average airflow rate and thus a large reduction in energy use. Typically, a room is actually challenged with particle emissions only for a small amount of time. Consequently, the best approach for controlling cleanroom air change rates is to vary the rate as needed based on the real-time quality of the cleanroom's air. When the cleanroom is clean of particles and other potential contaminants, the air change rate can be dropped significantly: perhaps one-half to one-quarter the nominal operating air change rate. When particles or other contaminants are detected, the air change rate can be increased to the nominal rates or beyond, to provide a faster purge of the contaminants.

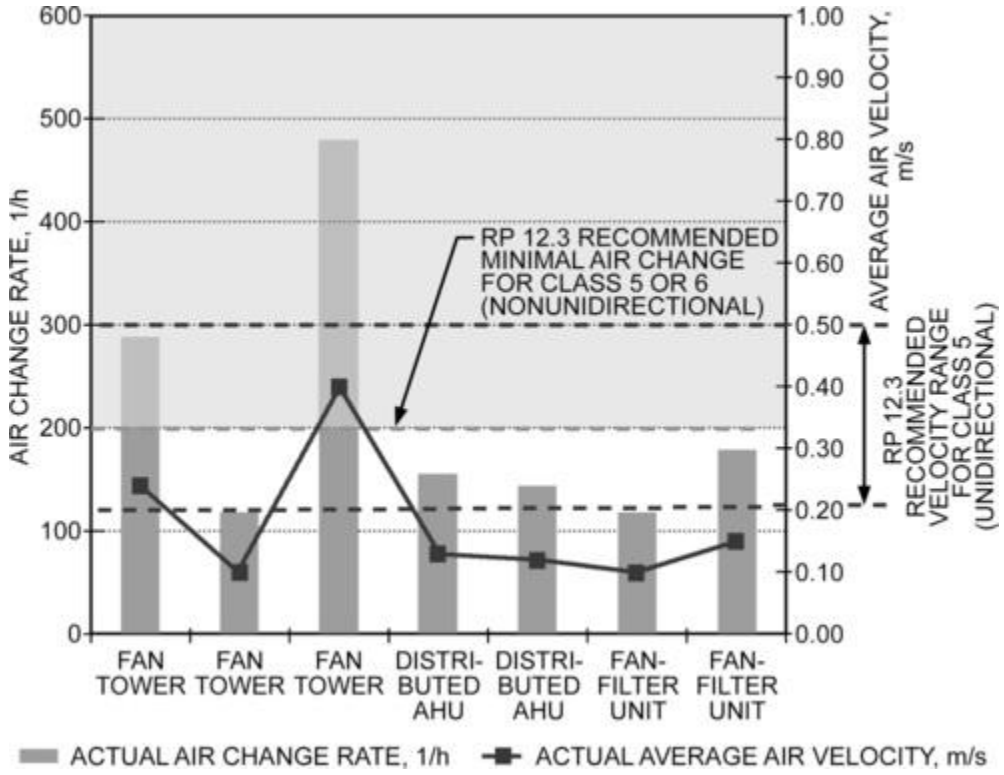


Figure 10. Actual versus Recommended Cleanroom Airflow Rates (Based on data from Xu 2004 and IEST RP CC012.3)

Implementing a dynamic approach to controlling minimum air change rates requires the ability to continuously measure particles in the cleanroom, but other parameters of interest (e.g., total volatile organic compounds [TVOCs], carbon dioxide, humidity) may be desirable as well. This information may then be integrated with the building management system for control purposes.

Different sensing approaches may be used to implement this concept. Individual sensors may be deployed in the cleanrooms of interest, or a manifolded sensing system may be used for a potentially more cost-effective deployment.

With this latter approach, one central set of sensors is used in a multiplexed fashion to sense not one, but many different rooms or areas. With this system, packets of air are sequentially drawn down to the central sensor for individual measurement on a periodic basis.

5. AIRFLOW DIRECTION CONTROL BETWEEN CLEAN SPACES

Airflow direction control between clean spaces having different cleanliness classifications is complex but critical to prevent airborne cross contamination. Particulate contaminants could infiltrate a cleanroom through doors, cracks, pass-throughs, and other penetrations for pipes, ducts, conduits, etc. An effective method of contamination control is control of space pressurization: air moves from spaces with higher pressures to adjacent spaces with lower pressures. Normally, the cleanest cleanroom(s) with the most critical operations should be designed with the highest pressure, having decreasing pressures correspond to lower cleanliness classifications. The desired flow path should be from the area of cleanest, most critical environmental requirements to less clean areas, progressively cascading down through less clean areas, and finally down to uncontrolled (dirty) areas.

Space Pressurization

Controlling contaminants in cleanrooms requires controlling the direction of airflow between adjacent spaces that have various levels of cleanliness classification(s). This is achieved by establishing and maintaining a pressure differential between the spaces. The pressurization set point for a space can be used to prevent contamination from entering the space by being positive relative to all surrounding spaces or to prevent contamination of other spaces by being negative relative to all surrounding spaces. Air pressure differences are created mechanically between spaces to introduce intentional air movement paths through space leakage or openings (Sun 2003, 2005). These openings could be designated (e.g., doorways, material transfer tunnel) or undesignated (e.g., air gaps around doorframes, other cracks). Pressurization resists infiltration of unfiltered external sources of contaminants. It can be achieved by arranging controlled flow rates of supply, return, and exhaust airstreams to each space based on the following rules:

- *Positive Pressurization*: entering (supply) airflow rate is higher than leaving (exhaust and/or return) airflow rate in the space.
- *Negative Pressurization*: entering (supply) airflow rate is lower than leaving (exhaust and/or return) airflow rate in the space.

Figure 11 illustrates three scenarios for pressurization, depressurization, and room in neutral pressure in respect to its surrounding spaces. Control of the airflow offset between the incoming air volume (typically supply air [SA]) and the departing air volume (typically exhaust air [EA] and return air [RA] combined) is the key. When the incoming air volume is more than the departing air volume, the room is pressurized and the flow offset is a surplus, which leaks out from the cleanroom; when departing air volume is more than the incoming air volume, then the cleanroom is depressurized and the flow offset is a deficit, which causes surrounding rooms' airs to leak into the cleanroom. Detailed information can be found in Sun (2008, 2020).

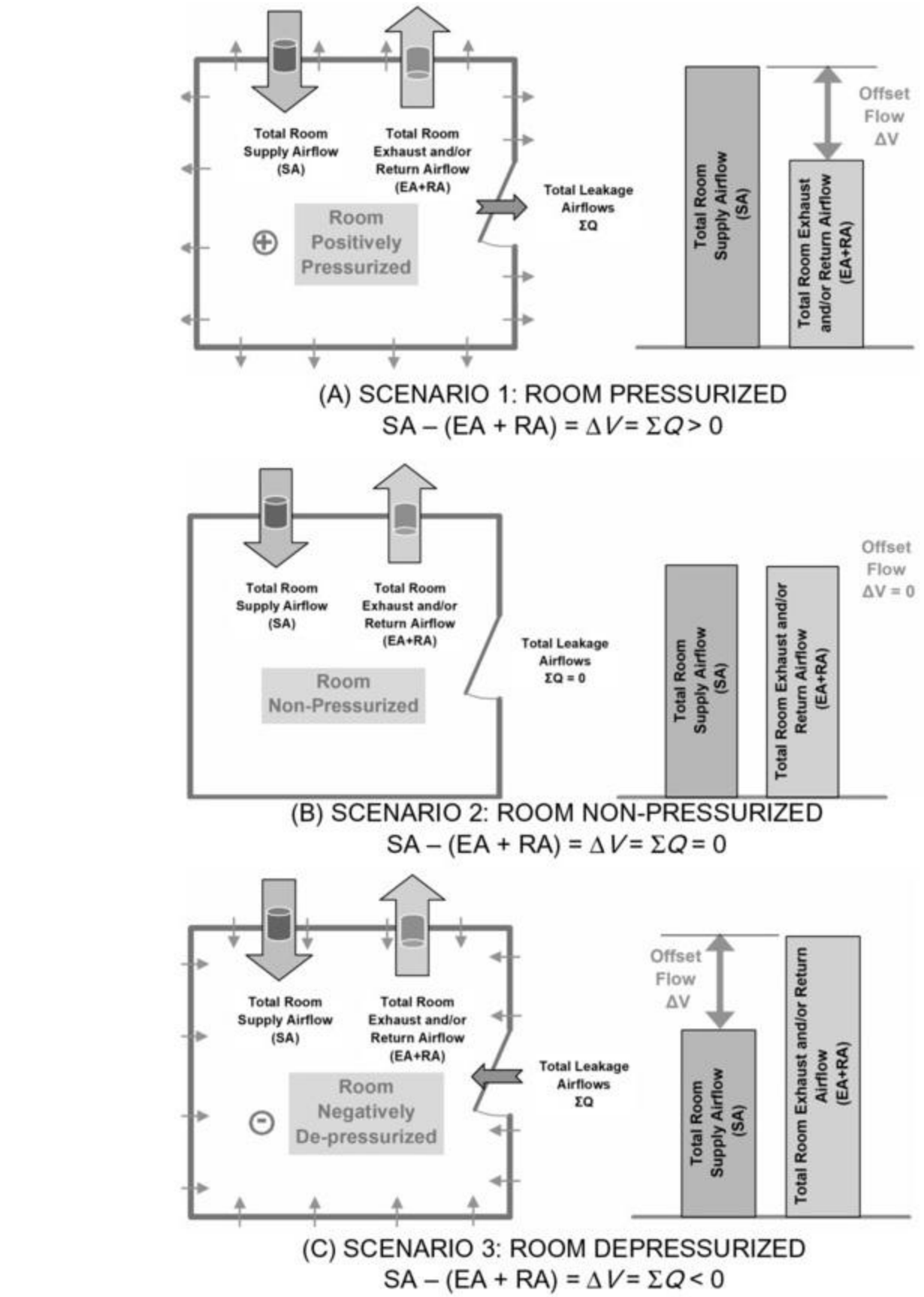


Figure 11. Room Airflow Offset (Either Surplus or Deficit) Is Required to Create Pressurization or Depressurization

A cleanroom envelope (including doors) is a natural barrier to contain airborne contaminants' (e.g., particle, microbial, chemical gas) migration. However, when a door is opened for traffic, the initial pressure differential across the door/envelope disappears much more quickly (typically in less than 0.25 s) than a door operation cycle (typically 6 to 10 s) closes the door, and is also much quicker than any airflow control devices (e.g., air valves) to modulate from prior flow positions to the new positions (1 to 2 s). The magnitude of particle migration is much higher at the door-in-operation (dynamic) condition than at the door-closed (static) condition. Additional treatment is required and associated design criteria need to be considered for the door-in-operation condition.

An effective mechanism to tackle this issue is to install a two-door airlock with a proper time delay. A time delay between two doors can allow the airlock room air to be fully or partially replaced by filtered clean air. Airlocks can reduce particle migration not only during door operations, but also in closed door conditions.

Recommended minimum pressure differentials ΔP across cleanroom envelopes are based on findings from ASHRAE research project RP-1431 (Sun et al. 2011). The static (door closed) ΔP requirement is the same for adjacent rooms of all class differences: 10 Pa ΔP across a cleanroom door in respect to adjacent areas is required to minimize particle migration. When an adjacent area across the door is two classes (or more) dirtier than the cleanliness class of the cleanroom, an airlock (see Figure 14) may be required to maintain acceptable pressurization when doors are opened/dynamic (depending on daily frequency of door operation). This requirement varies with the respective ISO class of adjacent rooms. For a difference of only one class between rooms, no airlock installation is required. For a two-class difference, airlock installation is required only when door operation is frequent (more than 30 times daily). For a difference of three classes (or more) and cleanrooms surrounded by noncleanroom areas, airlock installation is required regardless of door use frequency.

When airlock installation is necessary,

- A two-door airlock should replace a single door separating the two areas.
- A minimum pressure of 5 Pa is necessary across each door of the airlock.
- There should be a time delay between the two doors in the airlock.

Detailed information can be found in ASHRAE (2017).

Differential pressure between any two spaces is normally designed at 12.5 Pa or less.

A space's differential airflow rate is often called **offset flow**, which is the sum of all mechanically driven airflows (in or out, which correlates with space leakage). Figure 12 shows the relationship between leakage flow rates at a specific pressure differential across an opening. Each curve on the chart represents a different leakage area. Once a leakage area along a doorframe is estimated, then the air leakage rate through the door cracks while the door is closed can be calculated based on the pressure difference across the door.

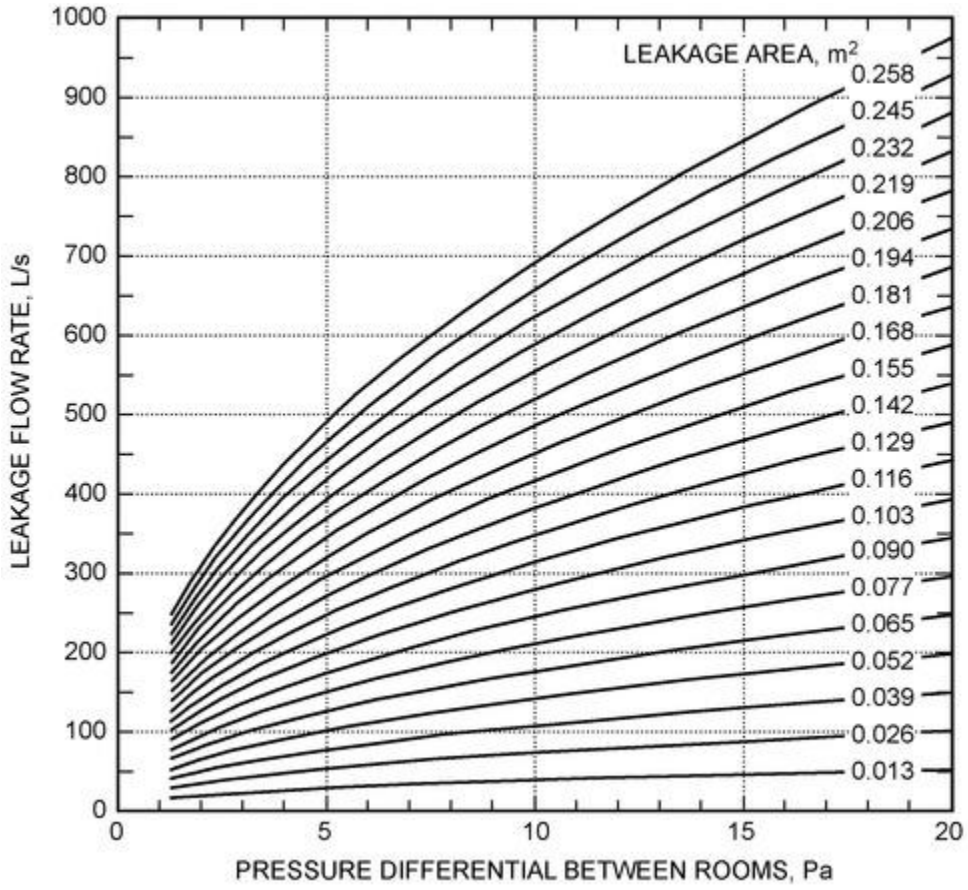


Figure 12. Flow Rate Through Leakage Area under Pressure Differential

Space airtightness (sealing condition of the cleanroom enclosure, joints, and penetrations) is the key element in the relationship between the space's flow offset value and the resulting pressure differential, and each space's airtightness is unique and unknown unless tested. Treatment of a space's offset value defines a pressurization control strategy. Typical pressurization control techniques include the following:

- **Direct pressure-differential control (DP)** uses a pressure differential sensor to measure the pressure difference between a controlled space and an adjacent space (e.g., a corridor). DP is suitable for a tightly constructed space with airlocks and/or limited traffic. It basically ignores the specific offset value as required; instead, it directly controls the airflow control devices to achieve the required pressure differential between the controlled space and an adjacent space. A door switch is recommended to trigger a reduced pressure-differential set point if the door opens or the DP control is based on average readings over a period of time (e.g., polling every 10 seconds and averaging over a minute).
- **Differential flow tracking control (DF)** assumes an offset value and refines it through commissioning; this value is then used as a volumetric or mass flow difference between supply and return/exhaust airflows through their airflow control devices. This method is suitable for open-style spaces or spaces with frequent traffic. DF normally maintains the same airflow offset value throughout operation to maintain constant space pressurization. A constant-percentage airflow offset value is sometimes used, but this creates a lower space pressurization at lower flow and may cause space pressurization reversal in facilities having multiple pressurization cascades.
- **Hybrid control (DF+DP)** (or **cascaded control**) combines the pressure accuracy of DP and the stability of DF. The offset value is resettable based on the pressure differential reading. The offset value reset schedule is predetermined, and the controller's parameters are adjusted or calibrated manually in the field.

Multiple-Space (Suite) Pressurization

Pressurization for a suite of clean manufacturing spaces is more complex. In practice, unforeseen air leakage interactions between spaces can lead to facility operational challenges. Because most of the air leaking out of one space leaks into another, adjusting one space's offset value often affects adjacent spaces' pressurization and can result in ripple effects. HVAC automation systems must provide stable control over supply, return, and exhaust to maintain the facility and environmental operational requirements. Careful facility designs and space layout arrangements are needed to minimize operational space pressurization challenges; overlooking this can cause difficulties in commissioning and operation. Properly designed facilities and control systems can avoid pressurization challenges such as sporadic, unstable, or unachievable pressurization requirements. For more information and procedures, consult the sources in the Bibliography.

A space pressure and flow (P&F) diagram for the controlled area (suite, zone, or floor) is often provided in design documents, and can be used as the basis of continuous quality control of cleanroom environmental parameters.

The system flow diagrams should indicate

- Airflow design settings (values) of all supply, return, and exhausts for each space inside the controlled area
- Desired space pressure value with an acceptable tolerance in each pressure-controlled space
- Resulting leakage flow directions (due to space pressure differentials) and their estimated leakage flow values through doors at closed-door conditions
- Room particulate classifications

The three traditional pressure-control methods (DP, DF, and DF+DP) require field adjustments of airflow offset values to achieve the differential pressurization values specified during design. A robust strategy is to control all spaces' pressures together as an optimized system, instead of independently. **Adaptive DF+DP** directly accounts for variable leakage flows between spaces, and actively adjusts each space's airflow offset to maintain required pressurizations continuously. It uses airflow and pressure differential measurements to estimate characteristics of leakage between spaces and adjust flow offsets automatically. This adaptive approach can be more effective for complex suite pressurization strategies. For design procedures and control strategies, see the related literature in the Bibliography.

6. TESTING CLEAN AIR AND CLEAN SPACES

The first standard written for a clean manufacturing room, or cleanroom, was published by the U.S. Air Force in March 1961. *Technical Order* (TO) 00-25-203 (USAF 1961) was the first standard with wide appeal to science and industry.

In 1963, a group of experts chaired by J. Gordon King created the first U.S. federal standard: U.S. General Services Administration (GSA) *Federal Standard* (FS) FED-STD-209, "Cleanroom and work station requirements, controlled environments." In 1966, it was released as FED-STD-209A, "Air-borne particulate cleanliness classes in cleanrooms and clean zones," and was revised several times over the years. Other cleanroom standards had been issued by many other countries, including Australia, France, Germany, Holland, Japan, and the United Kingdom. With the evolution of the global economy, the need for an international standard for cleanrooms became apparent. In 1993, International Organization for Standardization (ISO) Technical Committee TC 209 produced the first international cleanroom standard:

ISO 14644, "Cleanrooms and associated controlled environments." Finally, in 2001, FS 209 was canceled and superseded by the ISO 14644 standards, and other countries around the world followed suit.

Three basic test conditions are used to evaluate a facility: (1) as built, (2) at rest, and (3) operational. **As-built** condition is the stage in which the cleanroom is built, but with none of the equipment or fixtures installed. **At-rest** condition refers to the state of having equipment and fixtures installed and operational, but without personnel. **Operational** condition is where the equipment and fixtures are all installed and operational, and personnel are present. A cleanroom cannot be fully evaluated until it is tested in operational condition. Thus, techniques for conducting initial performance tests and operational monitoring must be similar.

Although cleanroom classification by particle concentration is the prevalent method of evaluation, additional cleanroom attributes may also be tested based on operations and products specific to a given clean space. ISO 14644 standards provide several different attribute testing methods and classification criteria. The test or tests applied are determined by the cleanliness attributes of interest. The following cleanliness attribute tests can be chosen:

- Air pressure difference test
- Airflow test
- Airflow direction test and visualization
- Recovery test
- Temperature test
- Humidity test
- Installed filter system leakage test
- Containment leak test
- Electrostatic and ion generator tests
- Particle deposition test
- Segregation test

The ISO 14644 standards also provide for certification by chemical concentration for those clean spaces concerned with chemicals in the air, such as organic light-emitting diode (OLED) display manufacturing or photolithographic areas in a semiconductor facility.

As noted previously, sources of contamination can be generated within the space or infiltrate into the space from an external source. The level of space contamination can be monitored using discrete particle counters or aerosol photometers, which use laser or light-scattering principles for detecting particles of 0.01 to 5 µm. For particles 5 µm and larger, microscopic counting can be used, with particles collected on a membrane filter through which a specific volume of sample air has been drawn.

HEPA filters in unidirectional flow and ISO *Standard* 14644-1 Class 5 (or cleaner) should be tested for pinhole leaks at the filter media, sealant between media and filter frame, filter frame gasket, and filter bank supporting frames. The filter frame interface with the wall or ceiling should also be tested. A filter bank pinhole leak can be extremely critical, because the leakage rate varies inversely as the square of the pressure drop across the hole (the industry term *pinhole* used to describe the leak site is a misnomer; the size is almost never that of a hole formed by a pin, but is actually many times smaller).

IEST testing procedures describe 12 tests for cleanrooms. The tests that are applicable to each specific cleanroom project must be determined based on the specific cleanroom's criteria.

7. PHARMACEUTICAL AND BIOMANUFACTURING CLEAN SPACES

Pharmaceutical product manufacturing facilities require careful assessment of many factors, including HVAC, controls, room finishes, process equipment, room operations, and utilities. Flow of equipment, personnel, and product must also be considered along with system flexibility, redundancy, and maintenance shutdown strategies. It is important to involve designers, operators, commissioning staff, quality control, quality assurance, maintenance, constructors, validation personnel, and the production representative during the conceptual stage of design. Critical variables for room environment and types of controls vary greatly with the clean space's intended purpose. It is particularly important to determine critical parameters with quality assurance to set limits and safety factors for temperature, humidity, room pressure, and other control requirements.

In the United States, regulatory requirements and specification documents such as current good manufacturing practice (CGMP) for finished pharmaceuticals (FDA 2008) and for sterile products (FDA 2004), ISPE guidelines (ISPE 2001, 2009, 2011), and National Fire Protection Association (NFPA) standards describe CGMP requirements. The goal of

CGMP is to achieve a proper and repeatable method of producing therapeutic, medical, and similar products free from microbial and particle contaminants.

One factor that differentiates pharmaceutical processing suites from other clean spaces (e.g., for electronic and aerospace) is the requirement to meet government regulations and inspection for product licensing (e.g., U.S. Food and Drug Administration [FDA]). It is important to include the appropriate regulatory arms, such as the FDA's Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER), early in the concept design process.

Design Process

It is important to develop a qualification plan (QP) early in the design process. Functional requirement specifications (FRS), critical parameters and acceptance criteria, installation qualification (IQ), operational qualification (OQ), and performance qualification (PQ) in the cleanroom suites are all required to ensure proper process performance and validation. IQ, OQ, and PQ protocols, in part, set the acceptance criteria and control limits for critical environmental parameters such as temperature, humidity, room pressurization, air change rates, and operating particle counts (or air classifications). These protocols must receive defined discipline approvals in compliance with the owner's quality policies. The qualification plan must also address master document updates, SOPs, preventive maintenance (PM), and operator and maintenance personnel training.

The quality of pharmaceutical products depends on the proper establishment of critical validation parameters and protocols. This ensures that the pharmaceutical manufacturing operations are executed properly and consistently, and maintained such that any deviations from the critical control parameters are identified, addressed, and mitigated. The pharmaceutical process must remain under control throughout the entire product life cycle, so it is important for engineers and designers to avoid including tangential or non-process-impacting parameters on the list of validated parameters. For example, while processing room temperature and relative humidity may be critical to a product's production, the associated air handler's chilled water flow rate and/or temperature are not, as long as the critical parameters are maintained within the requirements of the pharmaceutical process. The same logic often justifies not validating the facility's electrical supply or the drainage system if they do not have a direct impact on the product or process quality. Over validating can create a lot of additional paperwork in the original validation plan submittal, and a lot of unnecessary monitoring and reporting on deviations or excursions that don't impact the operations directly. It is wise to limit the systems, sequences, and equipment in the validation plan to only the essential items that impact the pharmaceutical product or process.

The technical design process often begins with **piping and instrumentation diagrams (P&IDs)** depicting the relationships between process equipment, utility systems, and control instrumentation. It is critical to document the physical sequence of equipment and systems throughout the design and installation processes, as well as how these systems interconnect, to ensure drug product quality and consistency. During design, these diagrams also provide the basis for developing system control schemes, process work and material flows, and further safety and operational investigations, such as the hazard and operability study (HAZOP).

Piping and instrument diagrams are necessary early in the facility design process to ensure design goals are achieved, with two types playing a central role in HVAC system design:

- **Room classification and pressurization diagrams** typically consist of a facility room layout plan drawing visually coded to indicate required pharmaceutical room classifications. Room pressurization values and directions often are shown on this diagram because differential pressure between rooms is critical to maintain required the environmental quality.
- **Air handler zoning layout diagrams** show the service area of each air handler system (or subsystem) on a plan view of the facility room layout. This diagram is used to optimize HVAC system layouts to minimize cross contamination issues, and to enhance facility operational responses to equipment failure and maintenance service outages. It is often necessary to segregate the exhaust and return HVAC system paths from other HVAC systems to prevent cross contamination.

System flow and room pressurization diagrams are used throughout the facility design process, and can be used as the basis of continuous quality control of cleanroom environmental parameters. It is critical to develop HVAC system layouts in conjunction with environmental quality requirements (room classifications) to minimize process contamination risks, promote stable facility pressurization strategies, and minimize facility operational challenges during equipment servicing.

Biomanufacturing and pharmaceutical aseptic clean spaces are typically arranged in operational suites based on specific process and formulation requirements. For example, common convention positions an aseptic core (ISO *Standard* 14644-1 Class 5) filling area in the innermost room, which is at the highest pressure, surrounded by areas of descending pressure and increasing particulate classes and bacterial levels (see Figure 13).

In aseptic processing facilities, the area of highest cleanliness is intentionally placed with lower-cleanliness areas surrounding it, separated by airlocks and room pressure differentials. A positive pressure difference of 10 to 15 Pa between air cleanliness classifications is common (FDA 2004), with the higher-cleanliness space having the higher

pressure. Lower pressure differences may be acceptable if they are proven effective. A pressure differential is generally accepted as good manufacturing practice to inhibit particles from entering a clean suite.

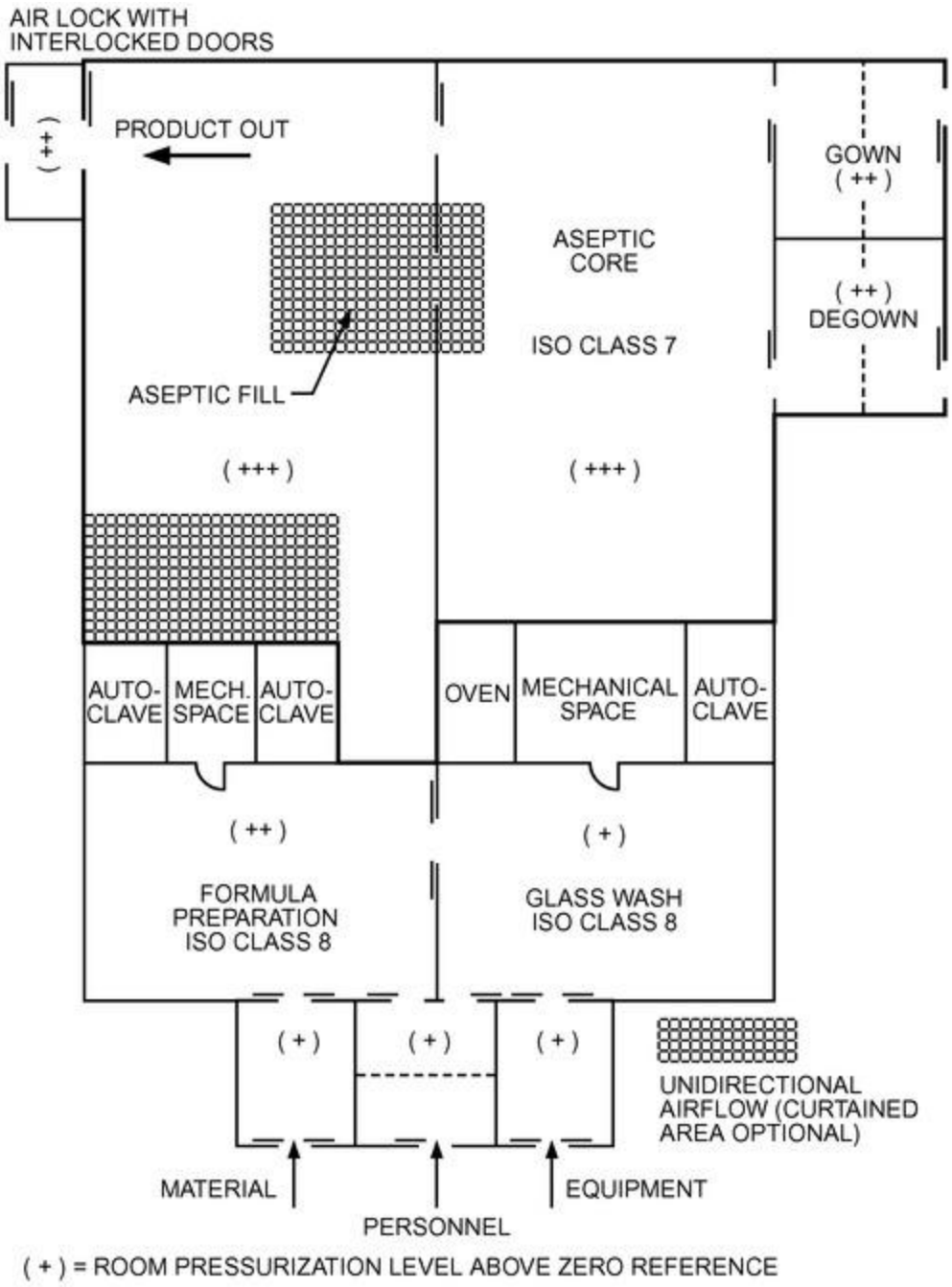


Figure 13. Typical Aseptic Suite

Where there are spaces adjoined in series that all have different cleanliness classifications, a multiple-step pressurization cascade should be implemented, which should have air flow from the cleanest spaces to the least clean spaces. Normally, three pressure steps are used for ISO Class 6, 7, or 8 applications; four pressure steps are desirable for Class 5 or cleaner applications. Air locks are effective at minimizing potential particle contamination from surrounding nonclassified or less-clean areas; selection depends on the type of cleanroom (Figure 14), because some that involve fume or biological agent operations may have a containment provision. For biological agent operations, the U.S. Centers for Disease Control and Prevention (CDC) and National Institutes of Health (NIH) define four biosafety levels (BSL-1 to BSL-4), discussed in more detail in Chapter 16.

An air lock is a transitional room between adjacent rooms to prevent airborne cross contamination. Based on relative space pressure levels, air locks can be classified as follows:

- **Cascading:** Air lock pressure is between pressures in cleanroom and corridor
- **Bubble:** Air lock pressure is above pressures in cleanroom and corridor
- **Sink:** Air lock pressure is below pressures in cleanroom and corridor

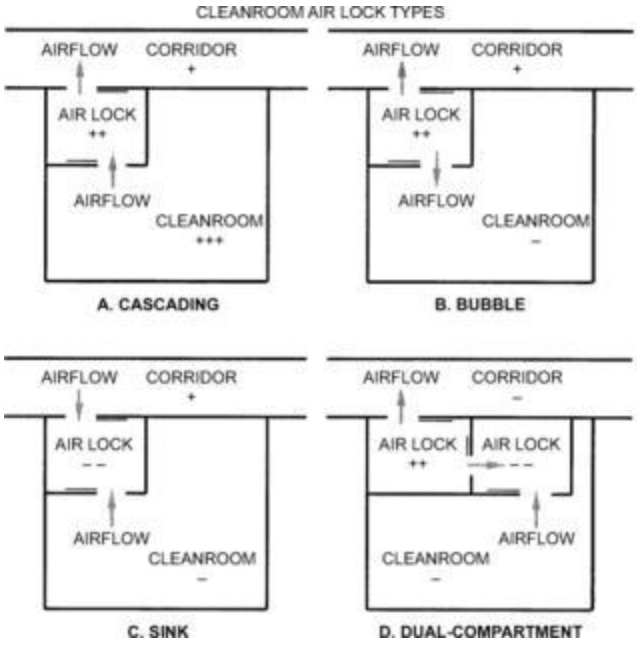
- **Dual-compartment:** A bubble and a sink air lock are connected

Double-door air locks are often used at cleanroom entrances and exits. A **required time delay (RTD)** needs to be specified between door openings, so both are not open simultaneously, to minimize possible contamination opportunities. The RTD should be long enough for HEPA-filtered clean supply air to partially or fully replace the entire air volume of the air lock room at least once before the second door is allowed to open. RTD operational procedures often use hard interlocks (i.e., the second door cannot be opened until after the required time delay) or soft interlocks, in which procedures are supplemented by lights or alarms.

Design Concerns for Pharmaceutical Cleanrooms

Proper design and qualification of a manufacturing facility is required under part 211, subpart C, of the CGMP regulations on Buildings and Facilities. Section 501(a)(2)(B) of the Act (21 U.S.C. 351[a][2][B]) states the following:

> A drug . . . shall be deemed to be adulterated . . . if . . . the methods used in, or the facilities or controls used for, its manufacture, processing, packing, or holding do not conform to or are not operated or administered in conformity with current good manufacturing practice to assure that such drug meets the requirements of this Act as to safety and has the identity and strength, and meets the quality and purity characteristics, which it purports or is represented to possess. . . . CGMP regulations require that manufacturing processes be designed and controlled to assure that in-process materials and the finished product meet predetermined quality requirements and do so consistently and reliably.



CLEANROOM AIR LOCK APPLICATION STRATEGIES

Type of Cleanroom	Air Lock Type	Purpose of Air Lock	Relative Pressure Relationship
• Positive pressure • No fume or bio agent • No containment needed	Cascading	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom being contaminated from surrounding spaces through cracks	Cleanroom: +++ Air lock: ++ Corridor: +
• Negative pressure • Has fume or bio agent contamination • Containment needed	Bubble	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom fume or bio agent releasing to corridor	Cleanroom: – Air lock: ++ Corridor: +
• Negative pressure • Has fume or bio agent contamination • Containment needed	Sink	• Provides containment • Prevent cleanroom fume or bio agent releasing to air lock. No personal protective equipment is needed.	Cleanroom: – Air lock: – – Corridor: +
• Negative pressure • Has toxic fume or hazardous bio agent contamination, or has potent compound substances • Containment needed • Personal protection needed	Dual-Compartment	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom fume or bio agent releasing to corridor • Personal protective equipment (such as pressurized suit and respirator) is required	Cleanroom: – Neg. Air lock: – – Pos. Air lock: ++ Corridor: –

Notes:
1. Excessive negative pressure in cleanroom is not recommended. If it is not surrounded by other clean spaces, untreated dirty air can infiltrate through cracks into cleanroom.
2. A cleanroom service corridor often must be designed slightly positive or neutral pressure. Do not design for negative pressure unless a dual-compartment lock is used.

Figure 14. Air Lock Types and Applications

Qualification of utilities and equipment is critical to demonstrate and document compliance with all requirements, and generally includes the following activities:

- Selecting utilities and equipment construction materials, operating principles, and performance characteristics based on whether they are appropriate for their specific uses.
- Verifying that utility systems and equipment are built as designed and installed in compliance with the design specifications, with proper materials, capacity, and functions, and properly connected and calibrated.
- Verifying that utility systems and equipment operate in accordance with the process requirements in all anticipated operating ranges. This should include challenging the equipment or system functions while under load comparable to that expected during routine production. It should also include the performance of interventions, stoppage, and start-up as is expected during routine production. Operating ranges should be shown capable of being held as long as would be necessary during routine production.

Before any batch from the process is commercially distributed for use by consumers, a manufacturer should have a high degree of confidence in the performance of the manufacturing process and that it will consistently produce APIs and drug products meeting requirements relating to identity, strength, quality, purity, and potency. Assurance should be obtained from objective information and data that demonstrates that the commercial manufacturing process is capable of consistently producing acceptable quality.

Manufacturers must establish control procedures that monitor the output and validate the performance of manufacturing processes to prevent variability in the in-process material and the drug product. Engineering responsibility includes identifying any and all variables that may foreseeably affect product or process quality, and assessing these potential problems during quality-driven risk analysis. Careful identification and control of variables that can affect product and process quality is necessary to ensure system performance and compliance. Utility system designs emphasizing performance stability and consistency through appropriate controls, alarms, and routine maintenance and inspections are required for compliance with pharmaceutical regulations. A lack of compensation for HEPA filter loading is a common HVAC system qualification challenge; if airflow or pressure controls are not used, appropriate alternative controls or alarms are required for documentation of continuous compliance. For most cleanroom applications, a routine environmental monitoring program verifies that the critical parameter of room cleanliness is being maintained. For holding rooms and other specialized applications, ensuring the stability of HVAC system performance through air filter loading compensation is usually the most effective way to support consistent facility operations.

The owner and designer must define the tolerable range of variable value (acceptance criterion) for each critical parameter. The product's safety, identity, strength, purity, and quality must be demonstrated to be unadulterated in that range. The owner should define **action alarm** points at the limits of acceptance criteria, beyond which exposed product may be adulterated. The designer should select tighter (but achievable) target design values for critical parameters (in the range of acceptance criteria), along with appropriate critical parameter monitoring strategies and values for warning alerts and actionable alarms.

Facilities manufacturing penicillin or similar antibiotics (e.g., cephalosporins) must be physically isolated from other manufacturing areas and served by a dedicated HVAC system. Other processes also require dedicated HVAC systems, including high-potency formulas and formulas that must have dedicated production facilities.

Facilities manufacturing aseptic/sterile products derived from chemical synthesis may have different requirements than those manufacturing biological or biotechnological products. The owner must define the inspecting agency's requirements.

The United States Pharmacopoeia (USP) limits temperatures to which finished pharmaceutical products may be exposed to 15 to 25°C. The production facility may need tighter limits than these, based on the owner's observed product data. Personnel comfort is also a factor in design. Personnel perspiring in their protective overgarments can increase particulate and microbial counts, so lower temperatures and tighter temperature control may be advantageous.

Relative humidity may be critical to the product's integrity. Some products are processed or packaged cold and need a low room dew point to prevent condensation on equipment and vials. Some products are hygroscopic and require lower humidity than a condensing coil can provide; in that case, consider desiccant dehumidification. Caution must be taken in designing low-humidity (i.e., low-vapor-pressure) spaces to ensure limited moisture migration through walls and ceilings bordering an unclean space. Low-humidity spaces should be provided with air locks to reduce moisture propagation into the low-humidity cleanroom. The importance of positive pressure increases when moisture infiltration potential becomes an element of the design process. Humidification is usually needed for personnel comfort but not usually for product needs; it may also be needed where dust might present an explosion hazard or where low humidity may hinder handling of dry materials. Clean steam (free of chemicals and other additives) is preferred for humidification because it is free of bacteria, but the humidification system should be free of amines or other contaminants if space air might contact the product. Humidification control systems often require careful sensor placement in critical areas and safety shutoff monitors to prevent overhumidification.

Although airborne particles and viable organisms may be minimized by dilution with high air change rates and by supplying filtered air, the most effective control is to minimize release of these contaminants in the space. Personnel and machinery are the most common sources of contamination, and can be isolated from the product by gowning, masks, and isolation barriers. Careful study of how each space operates should reveal the most probable sources of contaminants and help the HVAC designer determine dilution air quantities and locate supply air outlets and return air inlets. Avoid duct liners and silencers in supply air ductwork where contaminants can collect and bacterial and mold spores can accumulate. Ensure special attention is paid to cleaning and degreasing of metal sheeting and air ductwork before installation. Ensure the cleaning agent will not cause flaking of galvanized ductwork or leave residual soap. Factory-wrapped ducts and components with clean installation and inspection protocols promote cleanroom system cleanliness. To prevent contamination from entering the cleanroom, it is typically done by temporarily sealing off ductwork and using containment barriers with an airlock to isolate the cleanroom suite from the rest of the construction site. Once the cleanroom construction is completed, the ductwork can be connected and temporary barriers can be removed.

Airborne particle and microbe levels in aseptic processing areas are limited by government regulations, with lower limits for more critical spaces. European and FDA particle limits are for the space in full operational mode, and can also be used conservatively as limits for the space at rest.

Facilities complying with U.S. CGMPS for aseptic processing must meet particle levels with manufacturing under way. (An exception is aseptic powder processing, in which airborne particulate levels at powder filling heads will exceed limits.) There should be no microbial contaminants in the critical-zone airstream, where filling and other critical activities occur; this area should be ISO Class 5. The area immediately around the critical zone should be ISO Class 7. If the critical area is within an isolator, then the area outside the isolator may be ISO Class 8. Less critical support areas can be ISO Class 8. For more detail on facility design, see FDA requirements.

According to the FDA, 20 ach is usually sufficient for ISO Class 8 rooms; ISO Class 7 and 5 areas require significantly higher air change rates. Facility requirements for terminally sterilized products are not defined.

EU GMP (2008) also contains requirements for aseptic processing, and also addresses terminally sterilized products. Note that many facilities are constructed to meet both EU and U.S. GMPs (FDA 2008).

Restricted access barrier systems (RABS) are an alternative to a conventional cleanroom or isolator. Use of RABS should be approved by the manufacturer's quality unit during design.

Once the product is in containers, the need for particulate control and minimum air changes is reduced or eliminated, depending on the degree of protection provided by product packaging. The owner should determine the necessary critical environmental parameters and acceptance criteria for each space and processing step.

Return openings for space HVAC should be low on the walls, to promote downward airflow from supply to return, sweeping contaminants to the floor and away from the product. For ISO Class 8 and lower, ceiling return or exhaust register are common. Room air quality can be improved greatly by optimizing return and exhaust register locations to route air flows away from cleaner areas, which in many cases can resolve problems more effectively than changing supply register locations. In larger spaces, internal return air columns may be necessary. Perforated floors are discouraged because of the difficulty in cleaning them. It is good design practice to avoid returning air from one air-handling unit (AHU) system to another, unless special project considerations justify this decision. Mixing AHU zones through return air pathways may lead to cross-contamination concerns and operational challenges when HVAC maintenance shutdowns affect multiple operations. Combining noncontrolled and controlled areas through return or exhaust air pathways may also lead to operational challenges by expanding controlled-area boundaries into zones with activities that may negatively influence process or product integrity.

Aseptic product must be protected by pressurizing the space in which it is exposed, to about 12.5 Pa above the next lower cleanliness space classification. To keep the pressure differential from dropping to zero when a door is opened, air locks are often used between spaces of different air pressures, especially at the entrance to the aseptic fill space itself. Space pressure is a function of airflow resistance through cracks, openings, and permeable surfaces in the space shell. Consider all potential openings, slots, electrical outlets, annular spaces around pipe penetrations, and door leakage that could affect the amount of air needed to pressurize the space. Because space offset airflows and space pressure are closely related, outdoor or makeup air requirements are often dictated by space pressures rather than by the number of occupants. The HVAC system should be able to handle more makeup air than needed for commissioning, because door seals can deteriorate over time. Unintended leakage levels through cracks and openings at joints and penetrations can be identified and thus possibly reduced by the segregation test method, as indicated in ISO *Standard* 14644-3 (2022).

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ISO Class 5 unidirectional hoods are commonly used in process-critical applications for aseptic processes, consisting of banks of HEPA (or ULPA) filters, integrity-tested to be pinhole-free. Because it is difficult to maintain unidirectional flow for long distances or over large areas, the hood should be located as closely as possible to product critical surfaces (work surface). Hood-face velocity is usually 0.35 to 0.45 m/s, but the user should specify velocity and uniformity requirements. The velocity measurement is commonly taken at a distance of 150 to 300 mm from the filter face to demonstrate unidirectional airflow via airflow pattern testing. A unidirectional hood usually has clear sidewalls (curtains) to promote downward airflow and prevent entrainment of space particles into the hood's zone of protection. Curtains should extend below the product critical surface and be designed to prevent accidental disruption of airflow patterns by personnel. Many production facilities prefer rigid curtains for easier cleaning and sanitization.

Hood fan heat may become a problem, forcing the designer to overcool the space from which the hood draws its air or to provide sensible cooling air directly into the hood's circulating system.

Decontamination

Cleanrooms used for sterile operations are rarely built clean enough for their intended purpose. Before the initial use of the room or after a shutdown, the cleanroom must be decontaminated or disinfected to ensure bioburden and particulate levels are at or below acceptable limits. For some operations, such as compounding of sterile preparations, surface disinfection is considered adequate. However, larger-scale CGMP sterile manufacturing operations typically use some type of biological decontamination before final occupancy. Cleanrooms for sterile processing should be designed to accommodate decontamination or disinfection.

Having originated from small-volume spaces (i.e., sealed glove boxes), most early large-volume decontamination processes included using formaldehyde gas generated by heating paraformaldehyde in a frying pan or spraying with a mild peracetic acid and wiping all surfaces, which was very labor intensive. Today, most cleanrooms are decontaminated by using either chlorine dioxide (CD) or hydrogen peroxide. Regardless of the type of decontamination process used, the cleanroom should accommodate the process. Factors that should be considered include (1) leaktightness of the cleanroom shell, (2) compatibility of cleanroom finishes to the decontamination process, and ability to (3) remotely

control the process and recirculate the gas, (4) maintain appropriate humidity levels during the decontamination process, and (5) evacuate the gas after decontamination is complete.

Sometimes it is economically feasible to integrate the gas-generating equipment with the cleanroom air ducts. This decision is dictated by the intended gassing frequency, or by the need for automated recovery preparedness following any kind of bioevent. Strategically placed, airtight dampers, gas distribution nozzles, a means to agitate the gas within the cleanroom (or suite of rooms), and exhaust equipment for evacuation are some of the components necessary for automated decontamination. As with all decontamination procedures, protocols must be developed to demonstrate efficacy.

Barrier Technology

Cleanrooms designed to meet ISO Class 5 or better require considerable equipment, space, and maintenance. Operating such cleanrooms is expensive. Furthermore, cleanrooms typically need gowned operators inside to manipulate product and adjust machinery. Because the operator can be a major source of particle generation and contamination, it is better to separate the operator from the controlled environment; this allows the volume of the controlled space to be reduced significantly to a point where only the process equipment is enclosed. Using such a separative device can substantially reduce capital and operating costs while meeting required airflow patterns and cleanliness levels (IEST RP CC028.1; Xu 2007a, 2008). Separative devices, including microenvironments, isolators (glove boxes), and restricted access barrier systems (RABs), are thus becoming increasingly popular. These systems are also called **barrier technology** in pharmaceutical applications and **minienvironments** in semiconductor industries.

Barrier technology systems must be designed to fit the specific application and can be highly customized to allow the tasks required to accomplish the process needs. Applications vary widely based on product, process equipment, and throughput volume. Barrier technology systems are typically positive-pressure envelopes around the filling equipment with multiple glove ports for operator access, constructed of polished stainless steel with clear, rigid view ports. Systems can be fully sealed or leak into the support environment via "mouse holes" used to allow passage of vials in and out of the unit. Ancillary systems designed to prevent migration of contaminants are used for passing stoppers, containers, and tools in and out of the barrier systems. These can range from simple lock chambers to highly complex alpha/beta ports fitted with features to allow sanitization of the systems or contents. Important design concerns include accessibility, ergonomics, integration with mating equipment, decontamination or sterilization/sanitization procedures, access to service equipment, filter change, filter certification, process validation, and environmental control.

Extra attention must be paid to product filling, vial, and stopper protection; access to the barrier for sterilized stoppers; interface to the vial sterilization (depyrogenation) device; sterilizing product path, including pumps and tubing; and airflow patterns inside the barrier, especially at critical points. If a vapor-forming sanitizing agent such as hydrogen peroxide is to be used as a surface sanitizer, care must be taken to ensure good circulation and adequate concentration inside the barrier, as well as removal of residual vapor in the required time frame. In addition, because many of the sanitizing agents are strong oxidizers, care must also be taken in selecting construction materials to ensure compatibility and their ability to absorb and retain or potentially outgas the sanitizing agent at a later time.

Barrier technology systems may also be designed for applications requiring operator protection from high-potency and cytotoxic compounds (those that may have an inadvertent therapeutic effect on an operator), while maintaining a sterile internal environment. These tend to be total containment systems with totally contained product transfer ports. All internal surfaces are sealed from the external environment or potential operator exposure. Because of potential chamber leaks, its internal pressure may be kept negative compared to the ambient space via exhaust fans, posing an additional potential risk to the product that must be addressed by the owner.

Other systems, such as a nonsterile powder control booth, may incorporate more passive barrier designs. One such design incorporates a downflow sampling and weighing cubicle. This arrangement takes advantage of unidirectional airflow to wash particles down and away from the operator's breathing zone. Low-wall air returns at the rear of the cubicle capture fugitive dust. An arrangement of roughing and final filters allows air to return to the air handlers and back to the work zone through ceiling-mounted HEPA filters. Products involving noxious or solvent vapors require a once-through air design.

Barrier technology allows installation in environments that might require no special control or particulate classification. Isolators, RABs, and containment chambers are still relatively new to the pharmaceutical industry. As such, installations for sterile products should be in a controlled ambient room condition of ISO Class 8 or better.

Maintainability

A facility that considers maintainability (e.g., accessibility, frequency of maintenance, spare parts, rapid diagnostics and repair, reliability and facility uptime) in its design will be much more reliable and should have fewer operational and regulatory concerns. Many pharmaceutical facilities have been designed so that routine maintenance can be performed from outside the facility's clean space (except for unidirectional and terminal HEPA filters, which must be tested twice a year). Quality of materials is important to reliability, especially where failure can compromise a critical parameter or operation. Consider how much exposure and risk to product and personnel exist during maintenance (e.g., how to clean the inside of a glove box contaminated by a toxic product). Beyond cleanable room surfaces that must be sanitized, consider whether and how HVAC equipment may be decontaminated using the owner's procedures. Determine whether ductwork must be internally cleaned, and how. Reduced- or no-shutdown HVAC system designs require energy-efficient

and redundant components. When incorporating redundant components into systems, it is important to consider how both maintenance and removal/replacement of a component would be executed; the effect of redundancy is negated if there is no way to isolate equipment that needs to be replaced. Aligning HVAC system layouts with facility operational areas or suites can save significant operating costs and increase plant availability.

Controls, Monitors, and Alarms

Space pressure may be maintained by passive (fixed offset) HVAC systems if there are limited airflow variables. For example, the HVAC system for a few pressurized spaces may be statically balanced if there is a method of maintaining supply airflow volume to compensate for filter loading to ensure minimum supply, return, and exhaust air changes. More complex designs may require dynamic pressure control. Both filling lines with conveyors and slide gates between rooms where air moves from one room to another at varying rates usually require active pressure control to maintain room's pressures and their relationships at all times. It is important to avoid multiple pressurization loops controlled from the same or interrelated parameters, because this can lead to space pressurization instabilities. Complications can result from fans in series controlling similar or related properties. Improved system stability results from controlling to an airflow value at the room space level, and to duct air pressure at the branch or air handler level. Pressure controls should not overreact to doors opening and closing, because it is virtually impossible to pressurize a space to 12.5 Pa with a door standing open. A door switch is often used to send a signal to space pressure control to avoid overreaction. Architectural layout may affect dynamic room pressure control. It is a good practice to position such spaces away from exterior walls where wind loading exists and interior corridors, which typically do not have dynamic pressure control.

If space air humidity must be maintained to tolerances tighter than what normal comfort cooling can maintain, consider using active relative humidity control. If a desiccant dehumidifier is needed, unit operation over its range of flow must not adversely affect the ability of the HVAC to deliver a constant air supply volume to the facility.

Monitor and alarm critical parameters to prove they are under control. Log alarm data and parameter values during excursions. Logging may range from a local recorder to direct digital control (DDC) data storage with controlled access. Software source code should be traceable, with changes to software under the owner's control after qualification is complete. Commercial HVAC software is usually acceptable, but should be verified with regulatory agencies before detailed design begins. Also, keep complete calibration records for sensors, alarms, and recorders of critical parameter data.

When establishing alarm set points, consider that for systems serving regulated industries, alarms (or deviations from operational parameter [OP] acceptance limits) often require extensive documentation of the deviation, corrective actions taken, and any impact on critical processes and/or products. By setting up early warning alarm points, the operators can identify a system trending towards an operational deviation point and can intercede before the system hits its OP limits, precluding the need to prepare deviation or excursion reports.

Noise Concerns

HVAC noise is a common problem caused by attempts to overcome the pressure drop of additional air filtration. The noise level generated must be reduced in lieu of adding duct silencers, which may harbor bacteria and are difficult to clean. Separate supply and return fans running at lower tip speeds instead of a single-fan air handler may reduce generated noise levels. HVAC noise may not be an issue if production equipment is considerably noisier. For a more detailed discussion on noise and vibration issues, see Chapter 49.

Nonaseptic Products

Nonaseptic pharmaceutical facilities (e.g., for topical and oral products) are conceptually similar in design to those for aseptic product manufacturing (control of airborne particulate and microbial contaminations), but with fewer critical components to be qualified. However, critical parameters such as space humidity may be more important, and airborne particle counts are not considered in the United States. If the product is potent, barrier isolation may still be advisable. Space differential pressures or airflow directions and air changes are usually critical (needed to control cross contamination of products), but no regulatory minimum pressure or air change values apply.

8. START-UP AND QUALIFICATION OF PHARMACEUTICAL CLEANROOMS

Qualification of HVAC for Aseptic Pharmaceutical Manufacturing

Qualification is a systematic, quality-based approach to ensuring and documenting that the pharmaceutical facility, systems, equipment, and processes will deliver everything required for safe and repeatable drug products, including the facility design, installation, operation, maintenance, documentation, and pharmaceutical processing, filling, capping, holding, handling, and storage. Qualification of the pharmaceutical cleanroom HVAC is part of the overall qualification of the facility. Equipment affecting critical parameters and their control must also be qualified. Other groups in the

manufacturing company (e.g., safety or environmental groups) may require similar commissioning documentation for their areas of concern. The most important objectives in meeting the approving agency's requirements are to (1) state what procedures will be followed and verify that it was done, and (2) show that product is protected and space acceptance criteria are met.

Qualification Plan and Acceptance Criteria

Early in design, it should be determined who will be responsible for and how to produce as-built drawings, maintenance files, and training. They should create a qualification plan for the HVAC, including (1) a functional description of what the systems do along with specific process and room requirements; (2) maps of room classification and pressurizations, airflow diagrams, and cleanliness zones served by each air handler; (3) a list of critical components to be qualified, including the automation system controlling the HVAC; (4) a list of owner's procedures that must be followed for qualification of equipment and systems that affect critical parameters; (5) a list of qualification procedures (IQ/OQ/PQ protocols) written especially for the project; and (6) a list of equipment requiring commissioning, determined through a risk-based product and process impact analysis.

The approval procedure should be defined in the QP. It is important to measure and document critical variables of a system (e.g., space pressure), but it is also important to document and record performance requirements and results for components that affect the critical parameters (e.g., room pressure sensors, temperature sensors, airflow volume monitor) for GMP as well as business records. Documentation helps ensure that replacement parts (e.g., motors) can be specified, purchased, and installed to support critical operations.

It is important to determine all components and instruments that could affect critical parameters and could, through an undetected failure, lead to product adulteration. This may be accomplished by a joint effort between the mechanical engineer, owner, quality experts, and a qualified protocol writer. If performance data are in the qualification records, replacement parts of different manufacturers may be installed without major change control approvals, as long as they meet performance requirements. Owner approval for the qualification plan should be obtained during detailed design.

Qualification requires successfully completing the following activities for critical components and systems. The designer should understand the requirements for owner's approval of each protocol (usually, the owner approves the blank protocol form and the subsequently executed protocol).

The **installation qualification (IQ)** protocol documents construction inspection to verify compliance with contract documents, including completion of punch list work, for critical components. It may include material test reports, receipt verification forms, shop inspection reports, motor rotation tests, duct/equipment cleaning reports, duct leak testing, P&ID walkdowns for component installation inspections, and contractor-furnished testing and balancing. It also includes calibration records for instrumentation used in commissioning and for installed instrumentation (e.g., sensors, recorders, transmitters, controllers, and actuators) traceable to National Institute of Standards and Technology (NIST) instruments.

Control software should be bench tested, and preliminary (starting) tuning parameters should be entered. Control loops should be dry-loop checked to verify that subsystem installation, addressing, operation, and graphics are correct. Equipment and instruments should be tagged and wiring labeled, then field-verified against record drawings. Commissioning documentation must attest to completion of these activities and include as-built drawings and installation/operation/maintenance (IOM) manuals from contractors and vendors.

The **operational qualification (OQ)** protocol documents start-up, operation, and maintenance SOPs are correct and activated for critical systems and components. This includes individual performance testing of control loops under full operating pressure performed in a logical order (i.e., fan control before room pressure control). The commissioning agent must verify that operating parameters are within acceptance criteria.

The HVAC system may be challenged under extremes of design load (where possible) to verify operation of alarms and recorders, to determine (and correct, if significant) weak points, and to verify control and door interlocks. Based on observations, informal alert values of critical parameters that might signify abnormal operation may be set up. Even if the product would not be adulterated at these parameter values, staff may implement an alarm to require responses prior to encountering deviations from normal operation.

Documented smoke tests verify space pressure and airflow in critical spaces or inside containment hoods, and show airflow patterns and directions around critical parts of production equipment. Many smoke tests have been videotaped, especially when space pressure differentials are lower than acceptance criteria require and pressures cannot be corrected.

Files should include an updated description of the HVAC, describing how it operates, schematics, airflow diagrams, and space pressure maps that accompany it. Copies should be readily accessible and properly filed. Operating personnel should be familiar with the data in these records and be able to explain it to an agency inspector.

Other Documents. GMP documents should also include test reports for HEPA filters (efficiency or pinhole-scan integrity tests) at final operating velocities. If the filter installer performed the tests, the data should be part of the IQ package.

Documents should verify that instruments display, track, and store critical parameters and action alarms. Consider recording data by exception and routine documentation of data at minimal regular frequency.

Systems and equipment should be entered into the owner's maintenance program, including rough drafts of associated maintenance procedures (final drafts should reflect commissioning results).

Records should document the completion of these activities, including final as-built, system diagrams, facility pressurization diagrams, air change rate calculations, and air and water balance reports.

Performance qualification (PQ) is proof that the entire HVAC system performs as intended under actual production conditions. PQ is the beginning of ongoing verification (often called validation) that the system meets acceptance criteria of the product. This includes documentation of

- Maintenance record keeping and final operating and maintenance procedures in place, with recommended frequency of maintenance, and (at the owner's option) a procedure for periodic challenge of controls and alarms
- Logs of critical parameters that prove the system maintains acceptance criteria over a prescribed time
- Training records of operators and maintenance personnel
- Final loop tuning parameters

After accepting PQ, the owner's change control procedure should limit further modifications to critical components (as shown on IQ and OQ forms) that affect the product. Much of the facility's HVAC equipment should not need qualification, but records for the entire facility must be kept up to date through quality change control, and problems must be corrected before they become significant. Records of corrections should also be kept.

Once the system is operational, pharmaceutical product trial lots are run in the facility (process validation) and the owner should regularly monitor levels of viable (microbial) and nonviable particles, room pressurization, and other controlled parameters in the processing areas.

9. SEMICONDUCTOR CLEANROOMS

Semiconductor wafer fabrication cleanrooms (also called wafer fabs, fabs, or chip cleanrooms) have historically been some of the largest cleanrooms. Recently, mega and giga cleanrooms (i.e., those that produce megabyte and gigabyte memory chips) have been constructed that may exceed 40 000 m^2 of under-filter clean area and produce more than 200,000 wafers per month. A new fab today may cost 10 to 15 billion U.S. dollars, is expected to be built within 10 to 12 months, and is expected to recover capital investment in less than 3 years.

Wafer fabs seek to produce complicated products with extremely small feature sizes. Contamination at the wafer level can result in significant yield losses. Yield can be defined most basically as the proportion of successfully fabricated products (e.g., chips) compared to the total number of products that started the manufacturing process. Yield is often considered the most important financial factor in the manufacturing of semiconductor devices. It is inversely proportional to manufacturing cost: the higher the yield, the lower the cost.

Configuration

Semiconductor wafer fabs have traditionally been designed around common manufacturing processes (e.g., photolithography, metal deposition, etching, thin film deposition, implanting, diffusion, planarization) These process area layouts were coupled to the subfab utility distribution with some decoupling to allow for flexibility in equipment tool sets. Photolithography areas, with their tight vibration, temperature, and humidity control and susceptibility to molecular contamination, were always isolated from other process areas, allowing the building structure to be tailored to the specific needs of the photo areas and save costs for other process areas.

Semiconductor wafer fabs are extremely complex, with dozens of utility systems and many hazardous chemicals being used. In the absence of regulatory oversight of the manufacturing processes in pharmaceutical, medical device, and biotechnology facilities, building codes have been the most consistent regulator of semiconductor fab design and construction. The collaborative development of specific codes addressing semiconductors between code officials, owners, designers, and insurance industry has produced a set of codes that have attempted to meet the changing needs of the factories while still maintaining a safe working environment.

The unique multilevel building design and operation of wafer fabs led code officials to specifically identify semiconductor fabrication and the special needs involved. The various code sections (building, fire, and mechanical) have addressed the handling and storage of hazardous materials, fire resistance of materials of construction, conveyance of hazardous materials, egress paths, safe zones, fire protection, occupancy separations, etc.

Part of the justification of multiple levels is the need for extensive utility distribution; a typical semiconductor wafer fab can have in excess of 50 unique utilities. Fab complexity is best demonstrated by a visual of a typical multilevel wafer fab (Figure 15). Fab spaces are composed of process areas, subfabs (more than one), chases, return air plenums, and supply air plenums.

Referring to Figure 15, above the ceiling of the process area are the cleanroom supply air plenums, ductwork, fan filter units (FFUs) and, in some fabs, process utilities. The ceiling structure is designed to support cleanroom filters or FFUs, the wafer automated material handling system (AMHS), lighting, ionization system, maintenance personnel, and optional monitoring devices for temperature, humidity, and particles. The area where most wafer processing occurs is typically referred to as the **process area**. The process area is where most cleanroom operators work and contains the

process equipment main frames, wafer delivery equipment, metrology equipment, and other wafer-handling equipment. Below the process area is the subfab(s), where a hidden mass of equipment is located. Subfabs may be divided into clean and dirty subfabs, isolating potential contamination sources from the clean subfab, which in turn protects the process area.

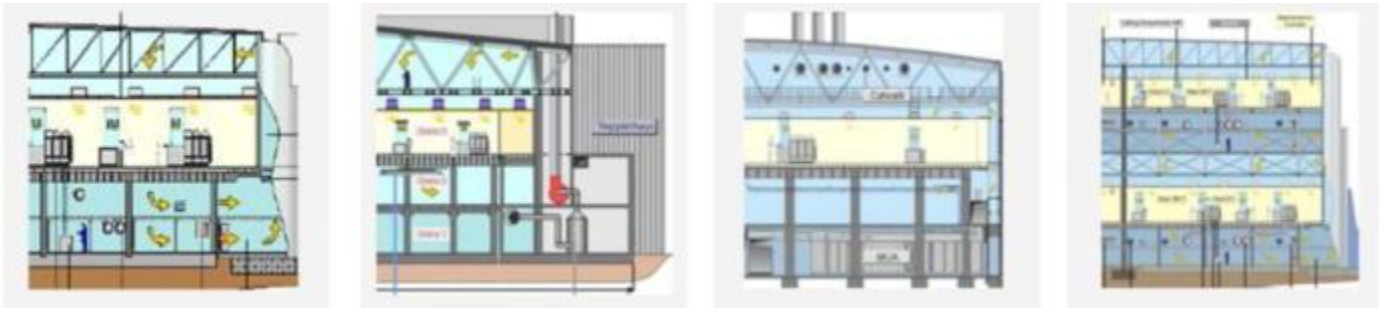

Figure 15. Multilevel Fabs (Courtesy of M+W Group)

The process area may have raised floors (most common) or a concrete slab (usually called a waffle floor due to the concrete casting shape) or other structural flooring materials supporting process equipment (heavy and vibration-sensitive tools sit on isolated pedestals and not directly on a raised floor). Some air management designs treat the space below the raised floor as an additional level, though most code authorities do not consider this a level when evaluating building height limitations. The space below the raised floor is considered an air plenum in most jurisdictions.

Contamination Control

In semiconductor cleanrooms, in addition to particle concentration, the most common contaminants impacting yield are airborne molecular contaminants, static charge and electromagnetic interference, and misprocessing due to electromagnetic interference with process control. Increasingly, more cleanrooms seek a controlled level of AMC concentration (i.e., chemical cleanliness class per ISO *Standard* 14644-8). Though not an explicit requirement, the airflow concepts used in a cleanroom have a direct impact on particle concentration and may also affect chemical cleanliness. Cleanroom designers have had to change airflow design concepts to meet the changing semiconductor process technology.

Airborne Molecular Contaminants (AMC). An increasing source of AMC in fabs is fugitive emissions associated with maintenance of local process exhaust scrubbers (e.g., for dopants). The fugitive emissions are exhausted to the building exterior and subsequently reentrained into the makeup air, and eventually back into the cleanroom. Including monitoring and mitigation of these fugitive emission sources is no longer optional for a good AMC protection plan; it is essential.

Wafer exposure to the chemicals in cleanroom environments presents another challenge. Deployment of fab-wide AMC filtration systems is becoming the rule rather than the exception for most process areas. Combining the fab-wide system with AMC filters at high-risk process tools helps to minimize exposure to hazardous particles.

Static Charge and Electromagnetic Interference

Electrostatic charge adversely impacts every phase of semiconductor manufacturing, causing three basic problems (SIA 2015a):

- **Electrostatic attraction (ESA)** contamination increases as particle size decreases. ESA is becoming particularly acute with photolithography masks, as the use of traditional pellicles is phased out.
- **Electrostatic discharge (ESD)** causes damage to both devices and photolithography masks. Decreasing device feature sizes means less energy is required for ESD to cause damage to a device or mask. Increased device operating speeds have decreased the effectiveness of on-chip ESD protection, and heightened device sensitivity to damage from ESD.
- Equipment malfunctions caused by ESD-related **electromagnetic interference (EMI)** decrease overall equipment efficiency and are becoming more frequent as equipment microprocessor operating speeds increase.

Trends in ESD sensitivity will have greater impacts on manufacturing process yields as the feature sizes of devices decrease (SIA 2015a). Cleanroom designers must understand the sources of ESD, and fab owners must verify that the installed ESD controls can handle these devices and must improve ESD control methods when necessary.

EMI Control. Electromagnetic interference is defined as "the degradation of the performance of an equipment, transmission channel, or system caused by an electromagnetic disturbance" (SEMI 2012). EMI causes a number of problems for semiconductor manufacturing, such as equipment lockup and malfunction, sensor misreading, metrology errors, and sensitive component damage. Sources of EMI in semiconductor environments include electromagnetic

emission from ESD; operation of equipment, especially high-energy tools; motors and actuators; and wireless communication. Colocation of sensitive equipment with high-energy tools, cabling, ground problems, improper maintenance of equipment, and other issues further aggravate EMI problems (SIA 2015a). Current practices for mitigating EMI impact are either passive-shielding the sensitive equipment or shielding the sources. Electrical transformers are a major source, and shielding of these in metrology areas is common practice.

Table 3 Process Area Environmental Conditions

	Temperature		Relative Humidity		Dew Point	
	Set Point Range	Tolerance	Set Point Range	Tolerance	Set Point Range	Tolerance
Critical Process Areas	18 to 23°C	±0.5 to ±1°C	35 to 50%	±2 to ±3%	2.3 to 12°C	±1 to ±2°C
Non-Critical Process Areas	18 to 26°C	±2°C	35 to 60%	±2 to ±5%	2.3 to 17°C	

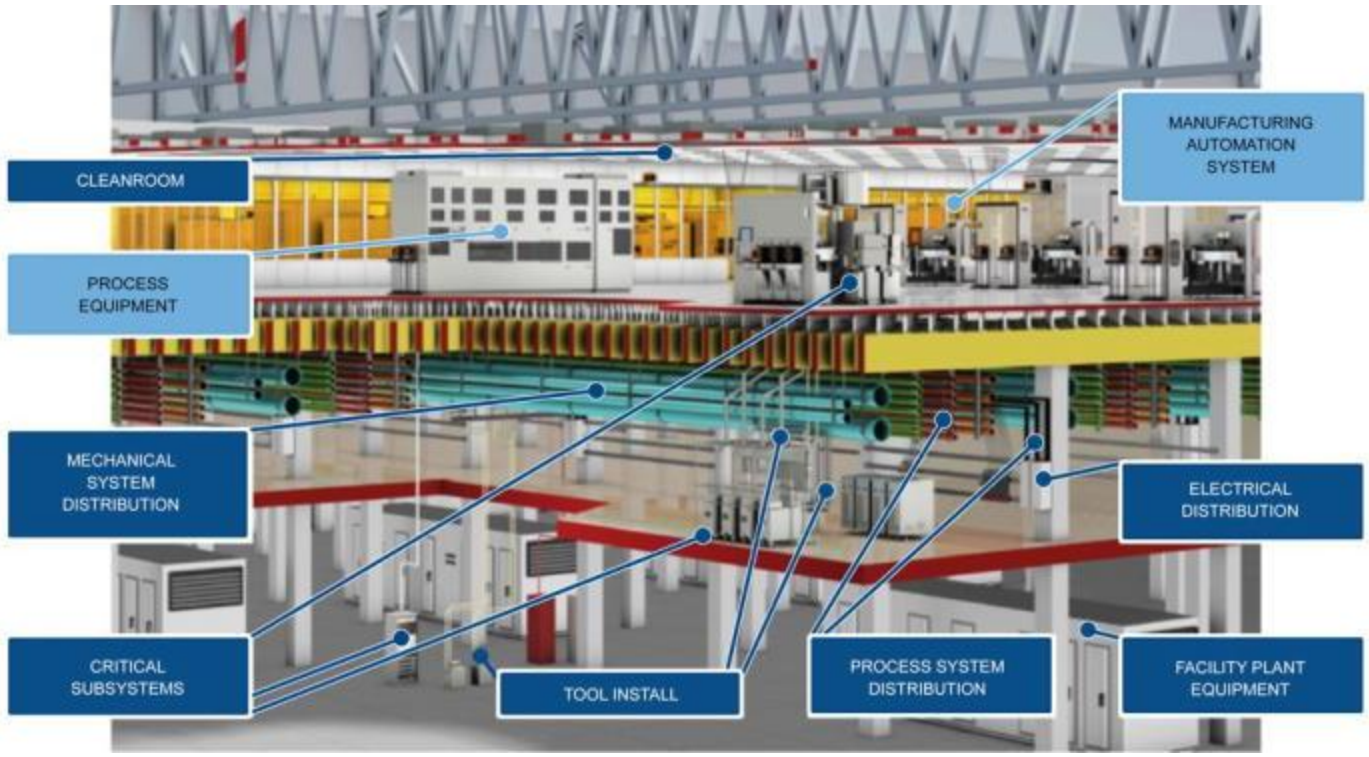

Figure 16. Fab Environment Figures (Courtesy of M+W Group)

Semiconductor Fab Conditions

Typical indoor design conditions are shown in Table 3. In the past, process requirements dictated the primary design criteria for temperature and humidity set points. To minimize changes in dimensions from expansion or contraction, temperature stability is needed in many atmospheric pressure processes that are exposed to the cleanroom ambient temperature. Good control of dry-bulb temperature is needed to provide stability in relative humidity. Relative humidity changes can affect the performance of many hygroscopic materials used in semiconductor manufacturing. Controlling dry-bulb temperature and dew point can provide uniform relative humidity.

Though there are hygroscopic processes in a semiconductor wafer fab, the hygroscopic forces are normally not enough to offset moisture gains or losses that can come from adjacent spaces with other dew points or from the introduction of makeup air. The sensible heat ratio for most wafer fabs is greater than 0.99 unless there is exposure to unconditioned spaces. Therefore, sensible cooling is the standard practice for wafer fabs. Latent cooling treatment of the entire fab recirculation air volume is normally not practical, and the adiabatic mixing of wetter or dryer air sources is a more energy-efficient method.

Cleanroom Cleanliness and Airflow Concepts

Design concepts are influenced by cleanroom size, building codes, process equipment footprints, cost control, energy optimization, and flexibility (among other things). Semiconductor wafer fab owners expect cleanrooms that cost little per square unit area to construct, yet provide improved performance, are faster to build, and are easily upgraded. As product technology and the process tools have changed, so have the basic design criteria.

The International Technology Roadmap for Semiconductors (ITRS) (SIA 2015b) currently recommends ISO Class 6 where operators are present and possibly ISO Class 7 in the future, though this practice is not uniformly adopted by all fab owners. ISO Class 6 does not necessarily warrant unidirectional airflow to support the cleanliness requirement. Wafer fabs continue to support unidirectional airflow because it makes sense in light of the multilevel layout of their facilities. Having air move in the same direction allows the spaces themselves to become transport conveyances. Therefore, cleanliness class does not always dictate classical unidirectional/non-unidirectional air management paths.

Options for process area air management with separate subfab airflow are (1) 100% unidirectional downflow and (2) unidirectional downflow for operator- and wafer-exposed areas, through the raised floor with return air upflow in service chases.

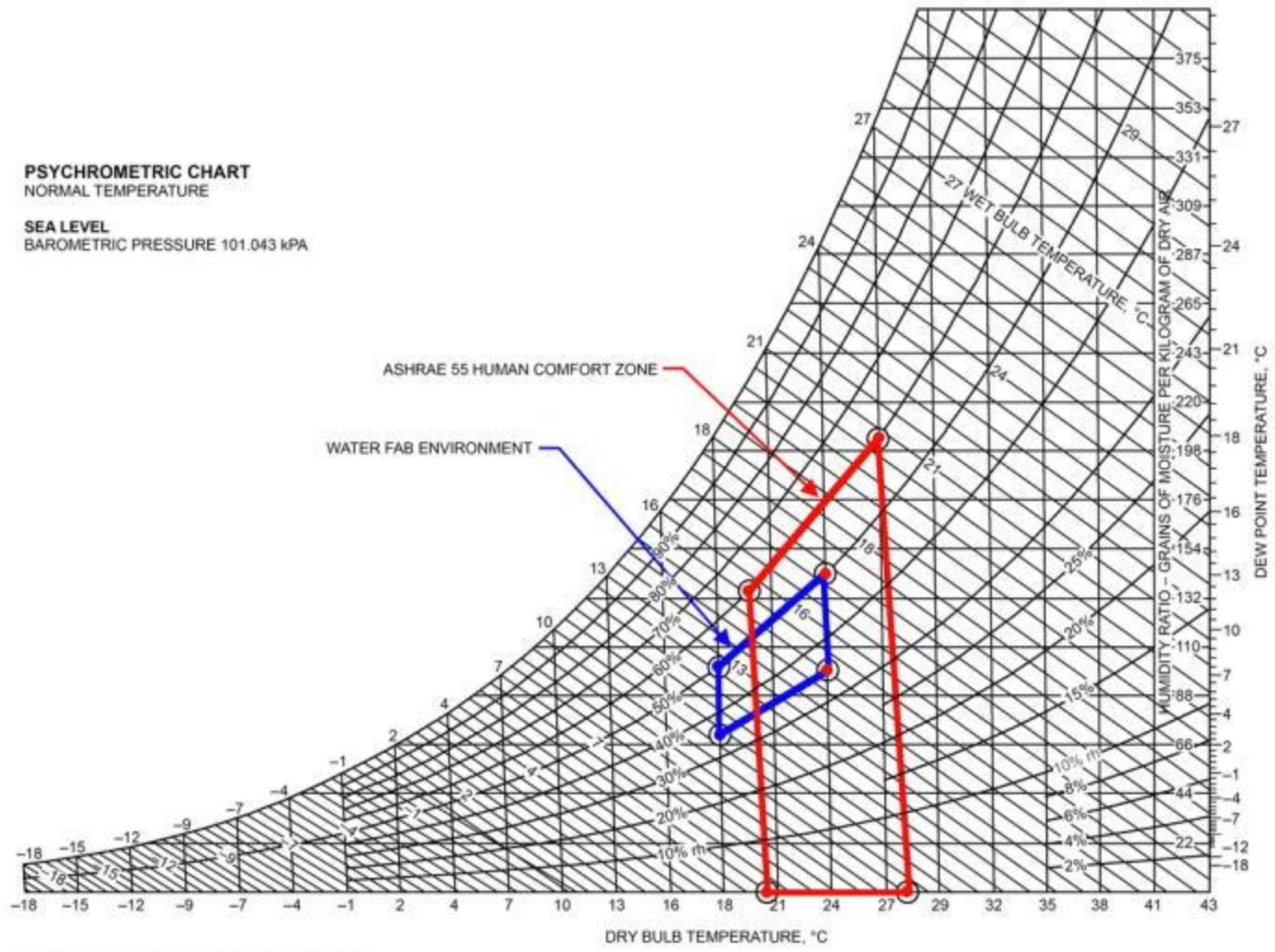

Figure 17. Wafer Fab Environment in Psychrometric Chart

Makeup Air. Makeup air plays a crucial role in the environmental conditions of a wafer fab by providing replacement air for the air exhausted for process requirements, providing excess air to create positive pressure in cleanrooms, and providing a source of wetter or dryer air to help control humidity levels inside the fab. Wafer fabs require a relatively large amount of makeup air due to the physical size of their factories, and depending on the local climate, makeup air may be 20 to 30% of the total fab chiller load. Although commercial facilities may consider ventilation rates per person, wafer fabs tend to use a design criteria based on the area of the cleanroom. Common rates for consumer semiconductor product based wafer fabs are 50 to 100 $m^3/(h \cdot m^2)$, whereas code requirements are 18.3 $m^3/(h \cdot m^2)$. There has been a trend toward lower ventilation rates due to changes in tool configurations with fewer liquid chemical ventilation hoods (e.g., wet chemical etchants) and more dry plasma-based processes. Treatment of makeup air before its addition to the cleanroom space includes moisture control (humidification or dehumidification) and filtration of external particles and airborne molecular contaminants.

Humidity. Makeup air provides a means of dehumidifying or humidifying air. The makeup air introduced into the fab environment is either below the space dew point, at the space dew point, or above the dew point. When it is below the space dew point, moisture must be added (humidification). When the makeup air dew point is above the space-required dew point, moisture must be removed (dehumidification).

Makeup air treatment schemes must be designed for the expected climate. Fabs located in tropical climates where outdoor dew points rarely go below 20°C may not need any humidification equipment, whereas fab locations in cold or temperate climates may need both humidification and dehumidification capabilities.

Control of dew point or relative humidity in a semiconductor wafer fab is also needed in many contamination control schemes. Humidity levels can affect ESD rates, particle adhesion, and corrosion of metal surfaces deposited on a wafer. Typically, the most critical need for precise humidity control is the sensitivity of photoresist chemicals used in photolithography. Relative humidity and temperature are both critical for precise dimensional control and resist chemical stability.

The typical semiconductor wafer fab space dew point is between 7 and 12°C, though it may be as low as –2°C or as high as 14°C to support some processes. Apart from very low dew points (less than 1.5°C), dehumidification by subcooling with chilled water is the most common method. Providing consistent dew-point control of the makeup air enables consistent moisture content of the makeup air when it is mixed with cleanroom recirculation air and can result in good relative humidity control (±2.5%) when combined with good dry-bulb temperature control. Some semiconductor wafer fabs may have process areas requiring better than ±2.0% rh. To achieve control of ±2.0% rh, the makeup air dew point must be controlled ±0.5°C.

Table 4 High-Bay Cleanroom Air Changes per Hour Versus Average Vertical Airflow Velocity, Space Height, and Cleanliness Class

		Air Changes per Hour for Ceiling Height, m							
ISO Class	**Velocity, m/s**	**12.2**	**15.2**	**18.4**	**24.4**	**30.5**	**36.6**	**42.7**	**48.8**
2	0.43 to 0.50	128 to 150	102 to 120	85 to 100	—	—	—	—	—
3	0.35 to 0.43	105 to 128	84 to 102	70 to 85	52 to 64	—	—	—	—
4	0.30 to 0.35	90 to 105	72 to 84	60 to 70	45 to 52	36 to 42	—	—	—
5	0.23 to 0.28	68 to 83	54 to 66	45 to 55	34 to 41	27 to 33	22 to 27	—	—
6	0.12 to 0.18	38 to 53	30 to 42	25 to 35	19 to 26	15 to 21	12 to 18	10 to 15	—
7	0.04 to 0.08	12 to 24	10 to 19	8 to 16	6 to 12	5 to 10	4 to 8	3 to 6	3 to 2
8	0.02 to 0.03	8 to 10	5 to 7	4 to 6	3 to 4	2 to 3	2 to 3	2	2
9	0.01 to 0.015	3 to 5	2 to 3	2 to 3	2	1 to 2	1 to 2	1	1

Filtration. Control of AMC is critical to maximizing yield by minimizing contamination of the photoresist and mitigating progressive defects forming on masks during exposure (Mueller 2013). For makeup air equipment, including AMC filters is commonplace for most semiconductor wafer fab locations due to local pollution and reentrainment of process exhaust. AMC filters typically involve a chemical adsorption process using activated carbon, sometimes doped with other activated chemicals (e.g., permanganate-embedded alumina) or ion-exchange resins. Most makeup air units integrate their AMC filters as part of a multistep particle and AMC filtration scheme. Some AMC filters are available with particle removal efficiencies of MERV 8 to as high as MERV 15, which can help reduce the overall air pressure drop through the makeup air equipment.

Air Velocity and Air Change Rate. For a given cleanroom, the supply airflow rate Q (cubic metres per second [m^3/s]) is

$$Q = LWv \tag{1}$$

$$\text{ACH} = \frac{3600Q}{LWH} \tag{2}$$

or

$$\text{ACH} = \frac{3600LWv}{LWH} = \frac{3600v}{H} \tag{3}$$

where

L = room length, m
W = room width, m
H = room height, m
v = average vertical air velocity, m/s through cleanroom horizontal plane L by W
ACH = air changes per hour

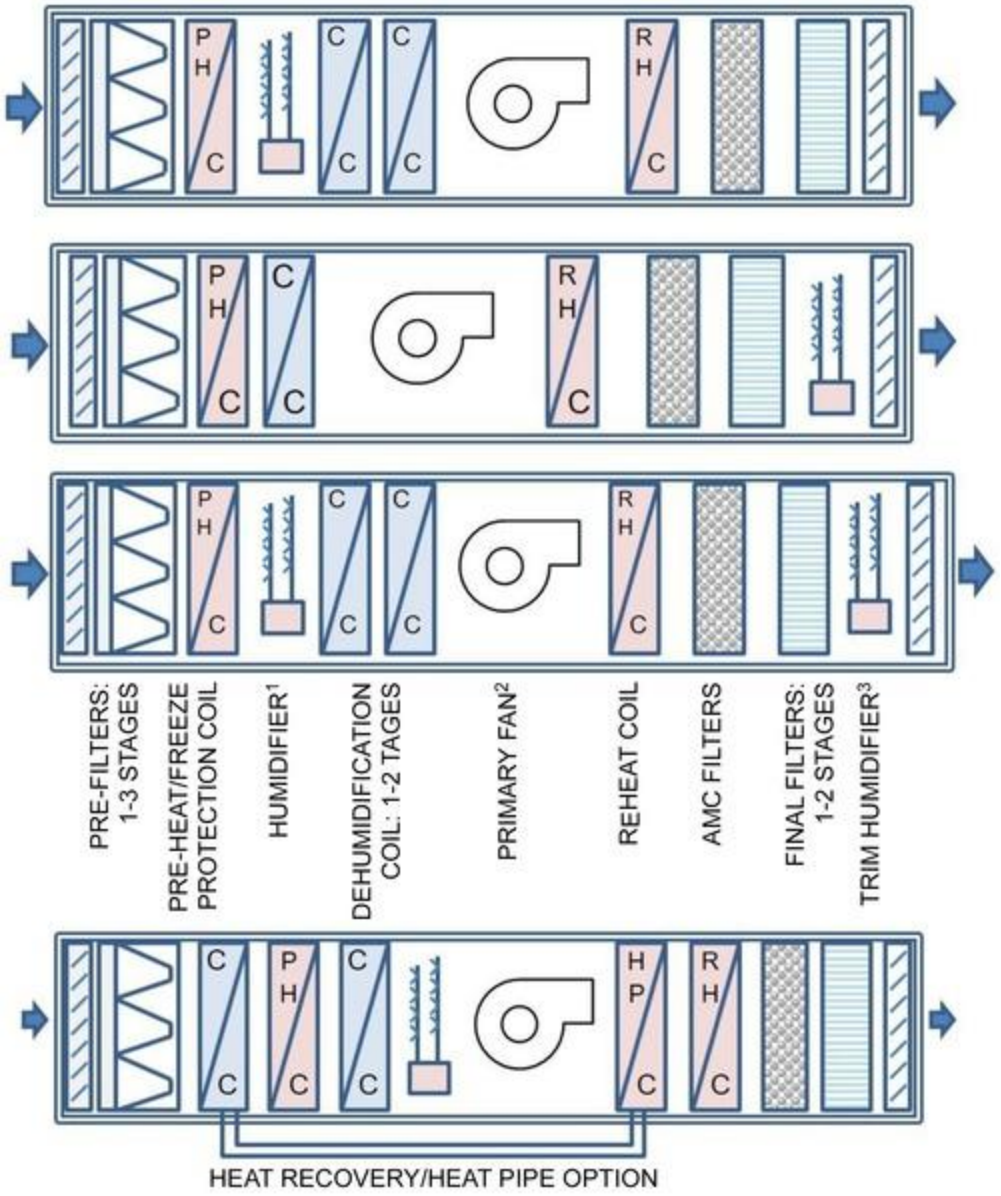

Figure 18. Makeup Air Configuration Schemes

From Equation (3), the number of air changes per hour is inversely proportional to the height of the room: the greater the height of the cleanroom, the fewer air changes per hour required, and vice versa. The exception is a clean space where contamination is generated at a considerable height above the finished floor. Examples include semiconductor and flat panel display transport systems and aerospace product assembly. In these situations, the velocity may need to remain high to sweep away particles, and ACH may be fixed regardless of the height of the space.

Air Ionization. In addition to cleanroom particle control with fiber filters, air ionization can be used to control particle attraction to product surfaces by eliminating electrostatic discharge and static charge build-up. However, the emitter tip material must be carefully selected to prevent depositing particles on the product.

10. HIGH-BAY CLEANROOMS

High-bay cleanrooms have ceiling heights between 12 and 50 m, with the higher ceilings used primarily in the aerospace industry for producing and testing missiles, launch vehicles, rocket engines, and communication and observation satellites, and lower ceilings primarily used in jet aircraft assembly, painting, and cleaning operations; flat panel display manufacturing; and in crystal-pulling areas in semiconductor chips manufacturing facilities.

Most high-bay cleanrooms are designed to meet ISO Class 7, Class 8 or higher as required by some U.S. Air Force and U.S. Navy specifications. Flat panel display factories may require ISO Class 5, 6, or 7. Crystal-pulling cleanrooms for semiconductor microchips are usually specified at Class 5 to Class 6 range.

Table 4 shows approximate ranges of ceiling-height-dependent airflow per minute and air changes per hour by cleanroom classes derived from Equation (3).

Downflow and Horizontal-Flow Designs

In **downflow designs**, air is delivered in a unidirectional (or simulated unidirectional) flow pattern from the ceiling and returned through floor return openings or low sidewall returns. The objective is to shower the object from above so that all particles are flushed to the returns. The supply air terminals may be HEPA-filter or high-volume air diffusers. Downflow spaces allow space flexibility because more than one device may be worked on in the space at the same air cleanliness level.

The disadvantage is the relative difficulty of balancing airflow. High-bay cleanrooms typically have concrete floors that may include trenches to return some of the air not taken in at low sidewall returns. Special care must be taken to ensure clean air at the object because the parallel flow starts to dissipate toward the floor. At the low velocities typical of unidirectional design, pathways may be created toward the returns, causing the clean air to miss the object. Any activity in the cleanroom that generates even a small amount of heat produces updrafts from buoyancy effects in downward-flowing supply air, resulting in the possibility of unforeseen turbulence.

Horizontal-flow designs are always unidirectional, with the cleanest air always available to wash the object in the space. Properly designed horizontal spaces are easier to balance than vertical-flow spaces because supply and return air volumes may be controlled at different horizontal levels in the space.

Downflow designs are most widely used, but certain projects such as the space telescope and space shuttle assembly spaces may require horizontal-airflow high-bay cleanrooms (Figure 19).

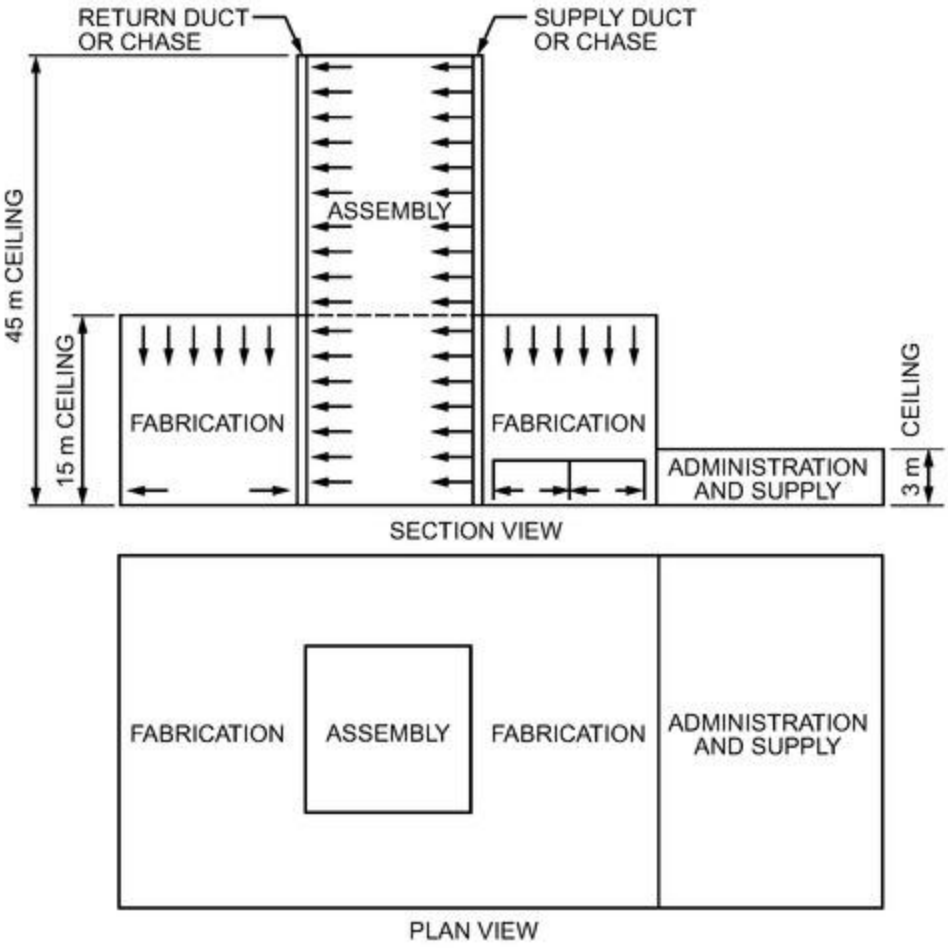

Figure 19. High-Bay Cleanroom Scheme

Air Handling

Because of the large volume of air in a high-bay cleanroom, central recirculating fan systems are commonly used with minimum heating and cooling capability. A separate injection air handler provides heating, cooling, and makeup air. The injection system must include volumetric controls to ensure proper building pressure. Flat panel display (FPD) factories deploy thousands of fan filter units (FFUs), allowing for flexibility and ease of adding additional airflow when needed.

Equipment and Filter Access

Air-handling equipment and prefilters should be accessible from outside the cleanroom. Adequate provision must be made for changing filters if air is distributed to the cleanroom with HEPA filters at the space envelope. In horizontal-flow cleanrooms, access should be from the upstream (pressure) side, and service scaffolds should be incorporated at least every 2.4 m in height of the filter bank. Downflow ceiling filters in T-bar or gel-seal ceilings must be accessed from below using an approved gantry crane with full mobility across the ceiling or from above the ceiling with a catwalk system built into the plenum. Prefilters in the main air supply should be placed in built-up frames with both upstream and downstream access. It is important to ensure that there are no possible air bypass pathways in filter frames and their seal to the filters or to the air handler walls since this reduces the effectiveness of the air filtration. A HEPA filter bank remote from the space air-distribution system should be installed in a built-up bank with a gel or clamp seal. Access doors must be installed up- and downstream for certification, scanning, and qualification testing.

Prefilter Selection

In any high-bay cleanroom cleanliness classification, air will pass through a final HEPA filter before entering the space; these final filters are usually protected by prefilters. HEPA filters for recirculating air should be protected with MERV 11 bag or rigid media filters with as few other prefilters as required. Makeup air should include minimum MERV 11 filters on the fan inlet and minimum MERV 16 filters on the fan discharge. Tight, leakproof sealing between the filters and frame/housing improves system cleanliness and reliability.

Design Criteria and Indoor Air Quality

The indoor design temperature range for aerospace and aircraft manufacturing cleanrooms is 23 ± 0.3°C, with the higher temperatures commonly used in summer, and the lower ones in winter. However, the user should provide guidance on specific required space temperature requirements. In FPD and semiconductor crystal-pulling cleanroom design, space temperature is usually required at a constant level of 22 ± 0.3°C, though FPD temperature tolerance is normally within ±1 K.

Another key parameter is relative humidity. For aerospace and aircraft manufacturing cleanrooms, relative humidity should not exceed 60%; FPD and semiconductor crystal-pulling cleanrooms usually require indoor relative humidity to be 50 ± 5% as design base.

Other issues include noise and vibration from process and HVAC equipment, and dusts, fumes, smoke, odors, vapors, moisture and gases generated during welding, sanding, painting, washdown, fuel filling, etc. See Chapters 8 to 12 of the 2021 *ASHRAE Handbook—Fundamentals* for additional information.

11. ENVIRONMENTAL SYSTEMS

Cooling Loads and Cooling Methods

Two major internal heat load components in cleanroom facilities are process equipment and HVAC system fans. Because most cleanrooms are located entirely within conditioned space, traditional heat sources of infiltration, fenestration, and heat conductance from adjoining spaces are typically less than 2 to 3% of the total load. Some cleanrooms have been built with windows to the outside, usually for daylight awareness, and a corridor separating the cleanroom window from the exterior window.

The major cooling sources designed to remove cleanroom heat and/or maintain environmental conditions are makeup air units, primary and secondary air units, and the process equipment cooling system. Some process heat, typically from electronic sources in computers and controllers, may be removed by process exhaust.

In many applications, cleanroom fan systems have their motors located in the airstream, resulting in significant heat from fan operation. This is especially true in ISO Class 4 or cleaner cleanrooms where recirculated airflows with air velocities of 0.45 m/s or air change rates around 500 per hour may be used. Xu (2003, 2004) found that many ISO Class 4 or 5 cleanrooms were operated with lower air velocities and lower air change rates than specified by the old or existing recommended practices, while achieving satisfactory contamination control for their specified cleanliness classes.

Latent loads are primarily associated with makeup air dehumidification. A low dry-bulb leaving air temperature, associated with de-humidified makeup air, supplements sensible cooling. Supplemental cooling by makeup air may account for as much as 950 W/m^2 of cleanroom.

Process cooling water (PCW) is used in process equipment heat exchangers, performing either simple heat transfer to cool internal heat sources, or process-specific heat transfer, in which the PCW contributes to the process reaction. Due to the superior energy efficiency of water cooling (versus air cooling), many process equipment manufacturers have redesigned their equipment to rely more on process cooling water. For many semiconductor and FPD factories, process equipment loads may be used for 50 to 75% of the process equipment heat transfer.

The diversity of manufacturing heat sources (the portion of total heat transferred to each cooling medium) should be well understood. When bulkhead or through-the-wall equipment is used, equipment heat loss to support chases versus to the production area affects the cooling design when the support chase is served by a different cooling system than the production area.

Makeup Air

Control of makeup air and cleanroom exhaust affects cleanroom pressurization, humidity, and room cleanliness. Makeup airflow requirements are dictated by the amounts required for (1) replacing process exhaust, (2) working personnel ventilation, and (3) meeting pressurization specifications. Makeup air volumes can be much greater than the total process exhaust volume to provide adequate pressurization and safe ventilation. Tsao et al. (2010) discusses how to optimize makeup air system design to improve its effectiveness and energy efficiency.

Makeup air is frequently introduced into the primary air path on the suction side of the primary fan(s) or into a negative pressure plenum system to enhance mixing. Makeup air volumes are adjusted with zone dampers and makeup fan controls using speed controllers, inlet vanes, etc. Opposed-blade dampers should have low leak characteristics and minimum hysteresis.

Makeup air should be filtered before injection into the cleanroom. If the makeup air is injected upstream of the cleanroom ceiling ULPA or HEPA filters, minimum MERV 16 filters (ASHRAE *Standard* 52.2) should be used to avoid high dust loading and reduced HEPA filter life.

In addition, MERV 8 efficient prefilters followed by MERV 11 filters may be used to prolong the life of the MERV 16 filter. When makeup air is injected downstream of the main HEPA filter, further HEPA filtering of the makeup air should be added to the prefilters. In addition to particle filtering, many makeup air handlers require filters to remove chemical contaminants (e.g., salts and pollutants from industries and automobiles) present in outside air. If the makeup air is from an internal conditioned space (i.e., outdoor air is conditioned by the main facility HVAC system), the same filtration level may still be required to prevent the entry of volatile organic compounds (VOCs). These VOCs may be present from another active process in the facility or from building maintenance items such as cleaning agents and paints. Chemical filtration may be accomplished with absorbers such as activated carbon or potassium permanganate impregnated with activated alumina or zeolite.

Process Exhaust

Process exhaust handles acids, bases, solvents, toxins, pyrophoric (self-igniting) fumes, and process heat exhaust. Process exhaust should be dedicated for each fume category, by process area, or by the chemical nature of the fume and its compatibility with exhaust duct material. Typically, process exhausts are segregated into corrosive fumes, which are ducted through plastic or fiberglass-reinforced plastic (FRP) ducts, and flammable (normally from solvents) gases and heat exhaust, which are ducted in metal ducts. Process exhaust may also be segregated by its need for pollution abatement due to air quality regulations. Care must be taken to ensure that gases cannot combine into hazardous compounds that can ignite or explode in the ductwork. Segregated heat exhausts are sometimes installed to recover heat, or hot uncontaminated air that may be exhausted into the suction side of the primary air path.

Required process exhaust airflow rates can vary from 5 L/s per square metre of cleanroom for photolithographic process areas, to 50 L/s per square metre for wet etch, diffusion, and implant process areas. With the advent of more vacuum-based processes and less use of ambient air or wet processes, the overall exhaust rates have trended downward. Many vacuum-based processes require additional abatement steps, with point-of-use (POU) abatement techniques being very common. These POU abatement processes may discharge directly to the atmosphere or into one of the central exhaust systems. When specific process layouts are not designated before exhaust design, an average of 25 L/s per square metre is normally acceptable for fan and abatement equipment sizing. Fume exhaust ductwork should be sized at low velocities (5 m/s) to allow for future needs.

For many airborne substances, the American Conference of Governmental Industrial Hygienists (ACGIH) established requirements to avoid excessive worker exposure. The U.S. Occupational Safety and Health Administration (OSHA) set specific standards for allowable concentrations of airborne substances. These limits are based on working experience, laboratory research, and medical data, and are subject to constant revision. See ACGIH (2007) to determine limits.

Fire Safety for Exhaust

International Building Code® (ICC 2021) designates semiconductor fabrication facilities as Group H occupancies. The Group H occupancy class should be reviewed even if the local jurisdiction does not use the IBC because it is currently the only major code in the United States specifically written for the semiconductor industry and, hence, can be considered usual practice. This review is particularly helpful if the local jurisdiction has few semiconductor facilities.

International Fire Code® (IFC; ICC 2021) addresses specific requirements for process exhaust relating to fire safety and minimum exhaust standards. Chapter 50 of the code, Hazardous Materials, is relevant to many semiconductor cleanroom projects because of the large quantities of hazardous materials stored in these areas. Areas covered include ventilation and exhaust standards for production and storage areas, control requirements, use of gas detectors, redundancy and emergency power, and duct fire protection.

Air Temperature and Humidity

Precise air temperature control is required in most cleanrooms. Specific chemical processes may change under different temperatures, or masking alignment errors may occur because of product dimensional changes as a result of

the coefficient of expansion. Temperature tolerances of ±0.6 K are common, and precision of ±0.06 to 0.3 K is likely in wafer or mask-writing process areas. Wafer reticle writing by electron beam technology requires ±0.06 K, whereas photolithographic projection printers require ±0.3 K tolerance. Specific process temperature control zones must be small enough to control the large air volume inertia in vertical laminar flow cleanrooms. Internal environmental controls, which allow space tolerances of ±0.6 K and larger temperature control zones, are used in many process areas.

Within temperature zones of the typical semiconductor factory, latent heat loads are normally small enough to be offset by incoming makeup air. Sensible temperature is controlled with either cooling coils in the primary air stream, or unitary sensible cooling units that bypass primary air through the sensible air handler and blend conditioned air with unconditioned primary air.

In most cleanrooms of ISO Class 6 or better, production personnel wear full-coverage protective smocks that require cleanroom temperatures of 20°C or less. If full-coverage smocks are not used, higher temperature set points are recommended for comfort. Process temperature set points may be higher as long as product tolerances are maintained.

In semiconductor cleanrooms, air humidity levels vary from 30 to 50% rh. Humidity control and precision are necessary for the specific process requirements, prevention of condensation on cold surfaces in the cleanroom, and control of static electric forces. Humidity tolerances vary from 0.5 to 5% rh, primarily dictated by process requirements. Photolithographic areas have more precise standards and lower set points. The exposure timing of photoresists (used in photolithography) can be affected by varying relative humidity. Negative resists typically require low (35 to 45%) relative humidity. Positive resists tend to be more stable, so the relative humidity can go up to 50% where there is less of a static electricity problem.

Independent makeup units should control the dew point in places where direct-expansion refrigeration, chilled-water/glycol cooling coils, or chemical dehumidification is used. Chemical dehumidification is rarely used in semiconductor facilities because of the high maintenance cost and potential for chemical contamination in the cleanroom. Although some cleanrooms may not require significant reheat, many systems are designed to provide heat to the space to support temperature control during normal operation and when production equipment is not operating. However, when relative humidity control is required, a large amount of energy may be lost when conditioning more air than necessary. Instead of bringing all the return air down to a low humidity level and then reheating, a system that optimizes the amount of return that goes through the air handler to avoid excesses is often significantly more energy efficient.

Makeup air and/or supply air humidification often uses steam humidifiers or atomizing equipment, with steam humidifiers being the most common. Good design practices include avoiding water treatment chemicals through clean steam generation. Stainless-steel unitary packaged boilers with high-purity water and stainless-steel piping have also been used. Water sprayers in the cleanroom return use air-operated water jet sprayers. Evaporative coolers can take advantage of the sensible cooling effect in dry climates.

Air Pressurization

Controlling air pressures in a cleanroom is an important part of effective contamination control, providing resistance to infiltration of external sources of contaminants. In nonpressurized spaces, or spaces with air pressures lower than that of the surrounding environment, nearby particulate contaminants enter the cleanroom by infiltration through doors, cracks, pass-throughs, and other penetrations for pipes, ducts, etc. A cleanroom with the most stringent cleanliness requirements should have the highest air pressure relative to its adjacent rooms, with decreasing room pressures corresponding to decreasing cleanliness levels.

For small cleanrooms or clean zones in ISO Classes 8 and 9, ceiling supply and low sidewall return is a typical airflow arrangement. The primary air system alone can handle the internal cooling load and the required room air change rate. Pressurization system designs are very similar to those in pharmaceutical facilities.

For semiconductor cleanrooms with ISO Class 7 or cleaner, primary/secondary air systems are common. The secondary (makeup) HVAC unit takes care of the outside air and internal cooling loads, and the primary (recirculating) unit delivers the required room air change rate, and additional cooling if needed. A raised, perforated floor return is common for these classes. During balancing, manual or automatic balance dampers are usually set at fixed positions at air supply, return, and exhaust systems.

In vertical- and unidirectional-flow cleanrooms, single-stage constant volume for supply and return flows is common. Because internal dust generation from people and process could be lower during nonoperating or unoccupied mode than operating or occupied mode, using multiple recirculating blowers to create two- or multiple-stage supply and return flow rates is feasible as long as the room cleanliness meets the designated classification at all times, validated through continuous particle count measurement. In nonoperating or unoccupied mode, reduced levels of supply and return airflow rates should also ensure maintaining proper room pressurization level.

Pressure level in the cleanroom is principally established by room airtightness and the **offset flow** value, which is the net flow rate difference between supply airflow rate and exhaust and return airflow rates. Process equipment exhaust rate is often determined by manufacturers' data, industrial hygienists, and codes. The design engineer should consult with the facility contamination control specialist to determine effective and efficient air change rates for each cleanroom.

One common method of cleanroom pressurization is to keep the supply airflow rate constant while adjusting the return airflow rate by volume dampers at return floor panels to create a specified positive space pressure. Return air to

underfloor plenum or subfloor basement through perforated panels floor grilles or grates (usually with a 15 to 35% free area) can be balanced to ensure a fixed flow differential (offset flow) in the space. An adjustable, lockable balance damper normally is attached beneath the perforated floor panel or grate. When the damper is fully open, it normally creates a minimal pressure drop of 5 to 20 Pa. Higher pressure drops can be achieved when the dampers are turning toward the closed positions. Note that the position of balance damper opening could affect parallelism of the room's unidirectional flow.

Another method uses variable-air-volume supply and return fans with volumetric airflow rates tracking to ensure the required room pressure. This method could be a reasonable choice for a single, large cleanroom, but is not flexible enough to serve a suite with different room pressure requirements. For some industries, variable-air-volume systems may not be favorable; design engineers should consult with facility contamination control specialists before specifying variable-volume systems for cleanrooms.

Air locks typically are used between uncontrolled personnel corridors, entrance foyers, and the protective-clothing gowning area. Air locks may also be used between the gowning room and the main cleanroom, and for process equipment staging areas before entering the cleanroom. Install air locks only when they are really necessary, because their use along traffic paths could restrict personnel access and increase evacuation time during emergencies.

Commercial pressure differential sensors can reach accuracy at 0.25 Pa or better, and significant progress has been made on precision room pressure control. Many processes affected by cleanroom pressure (e.g., glass deposition with saline gas) require process chamber pressure precision of 60 mPa.

Pressurization calculations can be performed by using the procedures detailed in either Pedersen et al. (1998) or Spitler (2009) in the chapters on infiltration:

- Using the provided charts, calculate the building exfiltration at designated room pressurization level.
- In accordance with ASHRAE *Standard* 62.1, with the actual number of occupancy, determine the required outdoor airflow rate.
- Determine the total airflow rate of exhaust from the building.

The sum of exfiltration airflow rate plus exhaust airflow rate, or plus the required outdoor airflow supply rate, whichever is greater, is the total ventilation rate under the designated building pressurization.

To ensure the designated pressurization level, a leak test must be performed for exterior walls, interior walls, partitions, doors and windows between two adjacent rooms with different pressurization levels, and for roof, exterior doors and windows, connections between wall and roof, and any building elements between two rooms with different pressurization levels. All major leaks must be eliminated before start-up of HVAC systems.

Sizing and Redundancy

Environmental HVAC design must consider future requirements of the factory. Products can become obsolete in as little as two years, and process equipment may be replaced as new product designs dictate. As new processes are added or old ones removed (e.g., wet etch versus dry etch), the function of one cleanroom may change from high-humidity requirements to low, or the heat load many increase or decrease substantially. Thus, the cleanroom designer must design for flexibility and growth. Unless specific process equipment layouts are available, maximum cooling capability should be provided in all process areas at the time of installation, along with provisions for future expansions.

Because cleanroom space relative humidity must be held to close tolerances and humidity excursions cannot be tolerated, the latent load removal capacity of the selected equipment should be based on high ambient dew points and not on the high mean coincident dry-bulb/wet-bulb data.

In addition to proper equipment sizing, redundancy is also desirable when economics dictate it. Many cleanroom facilities operate 24 h per day, seven days per week, and shut down only during holidays and scheduled nonworking times. Mechanical and electrical redundancy is required if loss of equipment would shut down critical and expensive manufacturing processes. For example, process exhaust fans must operate continuously for safety reasons, and particularly hazardous exhaust should have two fans, both running. Most process equipment is computer-controlled with interlocks to provide safety for personnel and products. Electrical redundancy or uninterruptible power supplies may be necessary to prevent costly downtime during power outages. Redundancy should be based on life-cycle economics and careful review of all foreseeable system failure and recovery scenarios. With the proper design focus, redundancy improvements can provide additional benefits; for example, operating redundant fans in parallel can reduce overall power consumption while improving system stability during failure recoveries.

Minienvironments

A minienvironment is a type of separate device mainly used in microelectronics industry to maintain a level of stringent cleanliness in a tightened volume of clean spaces (IEST RP CC028.1; ISO *Standard* 14644-7). It is a localized environment created by an enclosure to isolate or separate a product or process from the surrounding environment. A minienvironment is normally used to maintain a level of stringent, higher level of cleanliness by controlling particle concentrations within a tightened volume of clean spaces, often by maintaining desired pressure differential or supplying

unidirectional airflows. It is important to understand the characteristics of minienvironments' design, operation, and effectiveness in environmental control, and the impacts of integration with the cleanroom that houses the minienvironment or a group of minienvironments. Xu (2007a, 2008) found that pressure differentials under 0.0.2 Pa can be sufficient for achieving a high level of air cleanliness to meet environmental control expectation and requirements, suggesting that existing recommended practices or guidelines (e.g., IEST RP CC028.1) may be higher than necessary, at least in some minienvironment applications.

Advantages of using minienvironments include upgrading cleanliness classes, process integration, and maintaining better contamination control. Xu (2008) also suggested that, when appropriately integrated with a cleanroom, minienvironments may improve overall cleanroom energy efficiency and offer significant cost savings and reliability. The field investigations characterized energy performance of five different minienvironments (designated as ISO Cleanliness Class 3) operating and housed in a traditional, larger ISO Cleanliness Class 4 microelectronics cleanroom. The measured energy performance and associated metrics were compared to those of cleanrooms of various cleanliness classes, and indicated that potential energy savings up to 60 to 86% were achievable by integrating minienvironments in traditional cleanrooms, without losing effective contamination control. Other ways to increase energy savings in minienvironments include optimal design and operation, improving fan-filter unit operating efficiency, and space management in clean spaces.

Fan-Filter Units

A fan-filter unit (FFU) is a self-contained unit normally inserted and gasketed into cleanroom T-bar ceilings and is used to supply and clean airflows, which are fed to and then recirculated through the cleanroom space. An FFU usually consists of a small fan, a controller, and a HEPA or ULPA filter enclosed in a box, which fits into common cleanroom ceiling grids. Fan-filter units in air recirculating systems have become increasingly popular worldwide because of their specific contamination control, ease of installation, and adaptability in cleanroom construction, qualification, and operation.

Common ceiling grids typically carry FFUs with unit sizes ranging from 1220 by 1220 mm to 1220 by 610 mm or smaller. The small internal fans force air through the HEPA or ULPA filters. Coverage of a cleanroom ceiling normally ranges from 25 to 100% of the total ceiling area, and thus can require many FFUs. As a result, the large number of FFU fans constitutes considerable electric power demand and energy use (and noise generation) in providing air recirculation and cleaning (Xu et al. 2007). Appropriate applications of FFUs can generate unidirectional airflows desired for certain cleanroom activities or processes. New technologies able to control the airflow rate and uniformity through a networked feedback control system can improve the controllability and reliability of individual FFUs (Chen et al. 2007). Electrically commutated (EC) motors have replaced many of the older split capacitor motors, resulting in significantly improved motor efficiency.

Note that different FFUs' energy and aerodynamic performance can vary, even with similar components (Chen et al. 2007; Xu et al. 2007), and their performance may largely influence both energy efficiency and contamination control effectiveness in cleanroom design, qualifications, and operation. The energy efficiency level of the same unit may vary considerably, depending on actual operating conditions such as airflow speeds and pressure rise across the units; for instance, Xu et al. (2007) found that, when operating with the fan-wheel speed control dials at maximum, larger units tended to be more energy efficient than their smaller counterparts. To achieve sustainable development in cleanroom facilities, it is useful for designers and owners to have comparable information on FFU energy performance. This makes it feasible to select efficient units and to improve energy efficiency while maintaining or improving effectiveness in contamination control. Unfortunately, typical manufacturers' data sheets usually contain numbers that look similar but are not readily comparable because their approaches to reporting performance data are different from each other, and this can lead to confusion.

In recent years, the interest in understanding and improving fan-filter performance has increased among users, manufacturers, energy companies, professional organizations, and research institutes. Increasing energy costs in operating existing and future cleanrooms and mission-critical controlled environments have prompted end users to seek and select higher-efficiency FFUs in their cleanroom applications, and motivated suppliers to develop more energy-efficient FFUs for future cleanrooms. For example, manufacturers are increasingly interested in quantification of the energy performance of their fan-filter units, and in developing a method for systematically characterizing fan-filter performance as it is affected by fan-wheel design, air-path and size, unit size, motor type, availability of airflow control, and control schemes. Lawrence Berkeley National Laboratory has developed and published a standard test method to fully characterize energy and aerodynamic performance of individual FFUs in laboratory setting (Xu 2007b, 2007c).

12. SUSTAINABILITY AND ENERGY CONSERVATION

Cleanroom air systems may account for a significant portion of the HVAC energy use in cleanrooms. In cleanrooms, high electric power density for fans to deliver airflows, defined as the fan's electric power demand divided by the cleanroom floor area, would normally be expected because of large volume of airflows supplied, recirculated, and exhausted within a given time. Therefore, the design of cleanroom airflow systems may have a long-term impact on energy usage in that the amount of designed airflows significantly affects the operation costs associated with energy, initial equipment costs, and installation costs (Xu 2008).

The major operating costs associated with a cleanroom contamination control systems include conditioning the air, fan energy for air movement in the cleanroom, and process exhaust. The combination of environmental conditioning and control, contamination control, and process equipment electrical loads can be as much as 3 kW/m^2. Besides process equipment electrical loads, most energy is used for cooling, air movement, and process liquid transport (i.e., deionized water and process cooling water pumping), compressed air, vacuum systems, etc. A life-cycle cost analysis is useful to determine design choices and their total cost of ownership over time, as well as greenhouse gas contribution related to cleanroom design and operation.

Energy Metrics. The energy use required for operating wafer fabrication plants (fabs) is intensive and is one of the major concerns to production power reliability. Energy performance metrics to characterize the electric energy consumption and wafer production include production efficiency index (PEI), electrical utilization index (EUI), specific energy consumption such as annual electric power consumption normalized by annual produced wafer area, and annual electric power consumption normalized by units of production (UOP), which is defined as the product of annual produced wafer area and the average number of mask layers of a wafer (Chang et al. 2009; Hu et al. 2010, 2013).

To evaluate design options for HVAC systems in cleanrooms, it is convenient to compare overall efficiency using standard metrics. By using a metric such as airflow rate per kilowatt input, system efficiency for different schemes can be compared. The metric allows comparison of the amount of energy required to move a given quantity of air, and combines equipment efficiency as well as system effects. The owner can include this metric as a design criterion. Similarly, metrics for chilled-water system performance in terms of kilowatts per kilowatt of cooling can be established. Chiller performance and overall chilled-water system performance issues are well documented and should be consulted to set appropriate targets.

Fan Energy. Because supply airflow rates in cleanrooms can be very high, fan systems should be closely examined for right sizing and conservation of fan energy. Static air pressures and total airflow rate requirements should be designed to reduce fan power and its operating costs. Fan energy required to move recirculation air may be decreased by reducing airflow rates and/or static air pressures. Energy conservation operating modes should be verified during system qualification. If these modes are not part of the original design, the control procedure must be changed and the operational change validated.

Airflow rates may be lowered by decreasing recirculation airflow rate and minimizing cleanroom volumes in high-air-change-rate suites. A lower airflow rate could allow decreasing HEPA or ULPA filter coverage or reducing average air velocity. Reducing airflow rate can yield significant energy savings while enhancing space cleanliness through reduced turbulence. Based on a 0.45 m/s face velocity, each square metre reduction in filter coverage area in a room can save 250 to 500 W/m^2 in fan energy and cooling load. Reducing space average velocity from 0.45 to 0.40 m/s saves 50 W/m^2 in fan and cooling energy. If the amount of airflow rate supplied to the cleanroom cannot be lowered, reducing static pressure can also produce energy savings. With good fan selection and transport design, up to 150 W/m^2 can be saved per 250 Pa reduction in static pressure. Installing low-pressure-drop HEPA filters, pressurized plenums in lieu of ducted filters, and proper fan inlets and outlets may reduce static pressure. Many cleanrooms operate for only one shift. Airflow rate may be reduced during nonworking hours by using two-speed motors, variable-frequency drives, inverters, inlet vanes, and variable-pitch fans, or, in multifan systems, by using only some of the fans.

Additional fan energy may be saved by installing more efficient motors and electrical equipment, including transformers, UPS, and motor drives. Fan selection and inlet/discharge configuration also affects energy efficiency. The choice of forward-curved centrifugal fans versus backward-inclined, airfoil, or vaneaxial fans affects efficiency. The number of fans used in a pressurized plenum design influences redundancy as well as total energy use. Fan size changes affect power requirements as well. Sometimes lowering airflow velocities by operating more fans can improve a system's energy efficiency and reliability; investigate different options to ensure optimal designs and operation.

Makeup Air (MUA) and Exhaust Energy. Makeup air is required to replenish the lost air and to meet pressurization needs. The requirements for makeup airflow rates vary accordingly with an added amount for leakage and pressurization. The energy required to supply the conditioned makeup air can be significant. Optimizing MUA design by reducing or displacing mechanical cooling or electrical heating processes can improve energy efficiency, because cleanroom air-conditioning systems typically account for 30 to 65% of the total energy consumption in a high-tech facility. Different precooling and reheating/humidification schemes may result in difference in energy efficiency performance of MUA systems (Tsao et al. 2010). Careful attention to the layout and design of the makeup air system, especially minimizing system pressure drop and specifying efficient fans and motors, is important. The type of equipment installed normally determines the quantity of exhaust airflow rates in a given facility. Heat recovery has been used effectively in process exhaust; when heat recovery is used, the heat exchanger material must be selected carefully because of the potentially corrosive atmosphere; requirements for nonhazardous cleanrooms are not as significant. Also, heat recovery equipment has the potential to cross-contaminate products in pharmaceutical facilities. Pretreating makeup air using return water (either from process or building systems) is another way to reduce energy demands on primary systems serving a clean facility.

Makeup air cannot normally be reduced without decreasing process exhaust, which may be difficult to do because of safety and contamination control requirements. Therefore, design optimization of conditioning and delivering the makeup air should be explored and costs should be investigated. Conventional HVAC methods such as using high-efficiency chillers, good equipment selection, and precise control design can also save energy. One energy-saving method for large facilities uses multiple-temperature chillers to bring outdoor air temperature to a desired dew point in steps.

Cleanrooms and Resource Use: Opportunities to Improve Sustainability

Because of their highly specific and complex requirements, cleanrooms generally have high demands for energy and resources (Hu et al. 2013; Xu 2003). When possible, owners, designers, and operators should look for opportunities to reduce these demands, not only for reasons of environmental stewardship, but also for cost savings and avoidance of problems and complexity associated with larger power requirements and systems.

When developing a cleanroom-driven project, using integrated design and construction, under either the structured approach of integrated project delivery (IPD) or less formalized types of collaboration or partnering, can result in major rewards in cost, schedule, and operational efficiencies.

Some of the most promising areas for energy and resource use reductions include the following:

- **Optimizing air distribution and air change rates in clean areas.** Reducing space volumes and air change rates saves energy for environmental conditioning units and fans; and may reduce equipment and system sizing, filtration pressure drops, and equipment space requirements. Proper fan selection and duct layouts can eliminate the need for sound attenuators, thus saving space and energy. For spaces having the highest air change rate or airflow rate, enlarging duct sizing, increasing filter and coil area, careful fan inlet and discharge layouts, incorporating pressurized plenums, reducing overall duct path length, using transfer fans, and grouping spaces appropriately can reduce energy requirements and avoid extreme space differential pressure challenges. In addition, spot exhaust, cooling, or heating can improve overall system efficiencies. Implementing on-demand utility distribution, such as pressure and temperature reset control strategies, may provide further operational energy savings. Different system selections such as ducted distribution, fan-filter units, and pressurized plenum typically induce different levels of air delivery efficiency, as shown in Figure 20 (Tschudi et al. 2005; Xu 2003). Users of fan-filter units should have the FFU performance tested using a standard method, such as that developed by Xu (2007b, 2007c), so that optimal efficiency can be achieved within common ranges of operating airflow rates.

- Advanced control strategies including on-demand dynamic air flow control in response to real-time particle counts. This reduces power demand during occupied and unoccupied time, and requires testing at different operational levels to ensure consistent and reliable process performance (see the section on Air Pattern Control for details).

- Some high-performance applications use **electrically enhanced filtration (EEF)**, which uses high frequencies or other electrical methods of charging airborne particles for significant air filtration efficiency improvements, providing the required filtration effectiveness with lower resistance and less pressure drop, which reduces overall system fan power consumption (Jaisinghani et al. 2000). Typically, EEF reduces air filter penetration by at least one order of magnitude. Some EEFs use two separate fields; the field across the filter is electrostatic. Others apply one voltage to three or four electrodes to create an ionizing field to charge incoming particles, and another ionizing (not electrostatic) field to charge the filter media. This second kind also inhibits bacterial growth on the filter media and results in lower bioburden cleanrooms: in most cases, ISO Class 6 cleanrooms achieve the airborne bioburden requirements of an ISO 5 environment. This represents a significant savings in initial and operating costs for cleanroom applications that are primarily concerned with bioburden and have looser requirements for general particulate contamination.

- Analyze and evaluate process chemistry, including cleaning materials and methods. Reducing or eliminating VOC-based solvents, heavy metals, acids, etc., in processing reduces the need for dilution air, scrubbing, treatment of effluent, and other environmental and life safety issues. This step must be integrated with process developers, operators, and regulatory compliance personnel to ensure that changes do not compromise final product quality and acceptance.

- Process equipment specifications should include performance criteria for support utilities such as process water, compressed air, exhaust air, and electrical power. More efficient equipment saves operational and capital costs. This approach may also prove attractive where process equipment is leased and will be returned to the equipment vendor, as is common in microelectronics because of the processing technologies' rapid obsolescence. For equipment or tool manufacturers, higher efficiency may enhance the toolset's resale value.

The effects of these broad areas of resource use reduction and energy savings on building systems should be obvious; however, there are other tangible benefits that should be considered. Reducing the resource use or environmental footprint of the cleanroom extends the site infrastructure's carrying capacity. On developed sites in developed areas, this can save significant capital and operational costs by reducing the need to increase the site's capacity or infrastructure to handle an additional building or operation. Reducing use of hazardous, toxic, or noxious materials can reduce the owner's exposure to environmental health and safety risks and the need to treat discharge air and water streams. Improving HVAC energy efficiency can reduce equipment and penthouse space requirements, capital costs, and system-generated noise and vibrations.

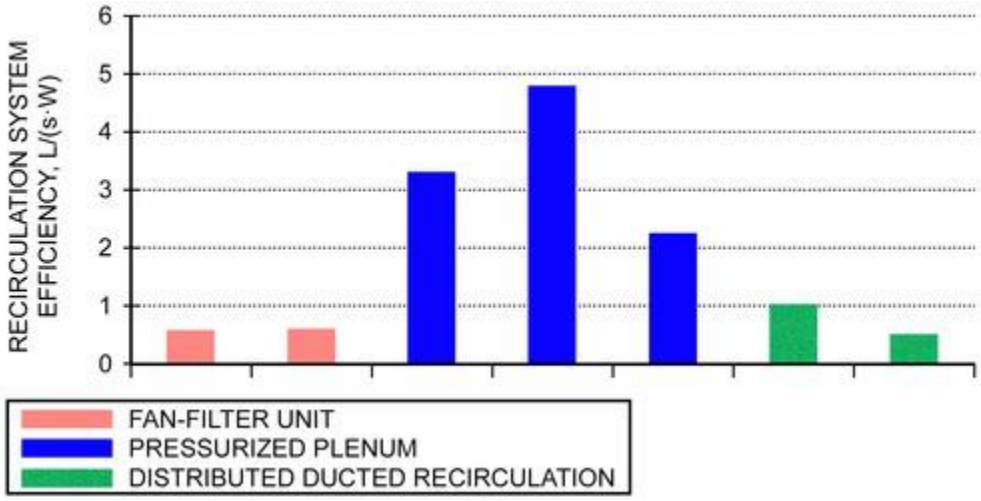

Figure 20. Energy Efficiency of Air Recirculation Systems (*Source*: Xu 2003)

13. NOISE AND VIBRATION CONTROL

Noise is difficult to control. Noise generated by contamination control equipment requires particular attention, although production equipment noise may be more significant than HVAC noise. Before beginning design, criteria for noise and vibration should be established. Chapter 49 provides more complete information on sound control.

In normal applications of microelectronics contamination control, equipment vibration displacement levels need not be dampened below 0.5 µm in the 1 to 50 Hz range. However, electron microscopes and other ultrasensitive microelectronics cleanroom instruments may require smaller deflections in different frequency ranges. Photolithographic areas may prohibit floor deflections greater than 0.075 µm. As a general rule, displacement should not exceed one-tenth the line width.

For highly critical areas, consider using vaneaxial fans. These fans generate less noise in lower frequencies, and can be dynamically balanced to displacements of less than 4 µm, which decreases the likelihood of transmitting vibration to sensitive areas in electronics cleanrooms. Energy-efficient features of cleanroom HVAC systems, such as straight, smooth duct layouts and elimination of sound attenuators, can exacerbate noise control issues. Instead of resorting to adding sound traps, acoustic problems can be mitigated through proper, energy-efficient duct layouts and efficient fan selections that avoid sound generation from excessive fan-blade tip speeds.

14. SPACE CONSTRUCTION AND OPERATION

Control of particulate contamination from sources other than the supply air depends on the classification of the space, the type of system, and the operation involved. Important documents published by IEST and ISO are available to guide the practices (e.g., IEST RPs CC003.2, CC004.2, CC005, CC018, CC026.1, and CC027.1; ISO *Standards* 14644-2, 14644-3, 14644-4, and 14644-5). The following illustrate some typical details that may vary with the room class.

Construction Finishes

- **General.** Smooth, monolithic, cleanable, and chip-resistant, with minimum seams, joints, and no crevices or moldings.
- **Floors.** Sheet vinyl, epoxy, or polyester coating with wall base carried up, or raised floor (where approved) with and without perforations using the previously mentioned materials.
- **Walls.** Plastic, epoxy-coated drywall, baked enamel, polyester, or porcelain with minimum projections.
- **Ceilings.** Gypsum wallboard or plaster, covered with plastic, epoxy, or polyester coating or with plastic-finished, clipped acoustical tiles (ceiling tiles are not common in ISO Class 5 or cleaner pharmaceutical processing cleanrooms, and tile edges should be sealed if used for less clean areas) when entire ceiling is not fully HEPA or ULPA filtered.
- **Lights.** Teardrop-shaped single lamp fixtures mounted between filters, sealed and installed in T-grid ceiling (gasket or gel seal) or flush-mounted and sealed.
- **Service penetrations.** All penetrations for pipes, ducts, conduit runs, etc., fully sealed or gasketed, then caulked in place. All conduits must have internal seals or pour stops to reduce infiltration/exfiltration through conduit.

- **Appurtenances.** All doors, vision panels, switches, clocks, etc., either flush-mounted or with sloped tops.
- **Windows.** All windows flush with wall; no ledges on cleanest side. Window gaskets must be closed cell and windows caulked.
- **Doors.** Sliding doors perform better than swinging doors in critical cleanrooms. All door movements must be controlled for gradual, smooth motion.

Personnel and Garments

- Hands and face cleaned before entering area
- Lotions and soap contain lanolin to lessen shedding of skin particles
- No cosmetics and skin medications
- No smoking or eating
- Lint-free smocks, coveralls, gloves, head covers, and shoe covers

Materials and Equipment

- Clean equipment and materials before entry, including the underside of rolling equipment and work surfaces, and wheels.
- Use nonshedding paper and ballpoint pens. Pencils and erasers are not allowed.
- Handle processing equipment and hardware with gloved hands, finger cots, tweezers, and other methods to avoid transfer of skin oils and particles.
- Sterile pharmaceutical product containers must be handled with sterilized tools only.

Particulate Producing Operations

- Electronics grinding, welding, cutting, sanding and soldering operations are shielded and exhausted.
- Use nonshedding containers and pallets for transfer and storage of materials.

Entries

- Air locks and pass-throughs maintain pressure differentials and reduce contamination.

15. CLEANROOM INSTALLATION AND TEST PROCEDURES

ISO, IEST, and the National Environmental Balancing Bureau (NEBB) have developed a set of standards for cleanroom installation and test procedures (IEST RP CC006.2; ISO *Standards* 14644-2, 14644-3, 14644-4, and 14644-5; NEBB 2009). This section provides some descriptions of the procedures based on field experience.

Installation

Space Preparation. Building envelope construction should be completed, its insulation thoroughly installed. Insulation materials should meet cleanroom requirements. All leaks must have been eliminated, construction debris removed, and floors cleaned, washed, and blow-dried.

Cleanroom Installation. After space preparation is completed, the HVAC, plumbing, process piping, and cleanroom elements are then ready to start installation in the following sequence:

1. Install cleanroom HVAC piping, ductwork, plumbing, and process piping (prior to hookup with process equipment). All open ends of duct and piping must be temporarily sealed at end of each workday.
2. Install cleanroom ceiling, floor, and wall systems.

3. Any process equipment package that is larger than the access doors must be moved into the cleanroom area before installing cleanroom wall access panels. All process equipment should be protected from construction damage and remain in shipping packaging, unopened.
4. Install cleanroom access doors, pass windows, wall access panels, floor and ceiling access panels. If hard ceiling is used, do not close ceiling access before test, balance, and acceptance by the responsible HVAC engineer.
5. After completing steps 1 to 4, check the tightness of all access doors, pass windows, and other cleanroom openings, as well as edges between (a) ceiling and walls and (b) walls and floors. Leaks must be completely eliminated.

Cleanroom Duct and HEPA Filters.

1. Thoroughly wash and clean air-handling unit (AHU) internals, including internals of AHU fans.
2. Use compressed air to blow dry (pressure high enough to dry, but not to damage internals of the AHU). Run the AHU at low speeds with no HEPA filters installed to blow out any loose dirt or debris before clean operation.
3. Shut down and inspect the AHU internals. If some dirt remains (especially on filter and edge areas), repeat steps 1 and 2.
4. Temporarily seal all openings on cleaned AHUs, including outdoor air (OA) intakes, return and supply openings, water, steam connections, humidifier control box tubes, drain openings, and doors.
5. Wash clean and blow dry all internal surfaces of duct sections and immediately seal. This will prepare the installation of duct system and HEPA filters.
6. Temporarily seal all open ends in the duct system at end of each workday during installation.
7. Temporarily seal the installed duct systems to wait for the finish of architectural internal work. Leave ceiling accesses open for ceiling HEPA filter installation and HVAC system test and balance.
8. Remove all construction debris from cleanroom. Wash and dry AHU external surfaces.
9. Wash and dry the cleanroom floor, walls, ceiling, and all materials and equipment thoroughly. After this step is completed, installation personnel should wear cleanroom shoe covers when entering the cleaned area to continue installation work.
10. Place the originally sealed HEPA filter packets at their installation locations (avoid any cardboard or particulate shedding packaging in cleanroom; remove such packaging materials outside of clean areas).
11. Unpack HEPA filters and install immediately. Do not open HEPA filter packets if not to be installed the same day.
12. Check HVAC control system installation and pretest to ensure the control system is functioning before HEPA filter installation.
13. Check installation of fire protection, life safety, and other HVAC-related systems to ensure the systems are properly functioning.

System Start-Up, Test, and Balance.

1. Read the major equipment and controls' installation, operation, and maintenance (IOM) manual thoroughly.
2. Walk through entire system to be started up.
3. Check that all mechanical systems have been installed. Replace covers, belts, gaskets, bolts, and screws if missing or damaged.
4. Check unit base concrete slabs, roof curbs, and structural supports. All units should be firmly installed on level plane.
5. Check that all equipment, devices, and fittings are installed correctly and in operating condition, including room pressurization monitoring systems.
6. Check that all dampers, louvers, and valves are set at the correct positions as shown on drawings and under the direction of test-and-balance engineer.
7. Remove all bolts and plates used for temporarily compressing internal spring isolators under AHU base during shipment.

8. Check chiller system. Ensure that the chilled-water supply and return are under operational condition.
9. If hot water is used, check the hot-water system. Check that hot-water supply and return temperature and pressure all meet HVAC system requirements.
10. If steam is used, check steam valve station. Check that the regulated steam pressure meets HVAC system required range.
11. If pneumatic control is used, check compressed air system, ensuring that the supply pressure meets control system requirement.
12. Electrical engineer should check the electric wiring and confirm that power source voltages conform to all equipment requirements.
13. Check and correct all motors' rotation.
14. Check that the controls system has been installed, energized, and pretested by the controls contractor.
15. Check that the fire-protection system is in place, with correct links verified by the fire protection contractor and electrical engineer.
16. General mechanical/HVAC contractor should coordinate with all disciplines for overall status of preparation for cleanroom HVAC, control, and fire-protection systems start-up. A written report stating the completion of all of the preceding listed items should be submitted to the responsible HVAC engineer at minimum two workdays before the scheduled system start-up date. The responsible HVAC engineer should determine a proper day to inform the on-site commissioning authority (CA) before start-up if commissioning is required by project scope.
17. Correct all problems that may have occurred during start-up; adjust systems to meet design conditions. Also, all system specific commissioning and qualification procedures must be finalized and accepted before placing new systems into operation.
18. Once HVAC system is running with all final filters, including HEPAs, all personnel entering clean spaces should be fully gowned to maintain the proper and clean operating state, and to ensure gowning procedures and personnel training are appropriate.
19. Initial test, balance, and adjustment work should be performed by a licensed test-and-balance contractor during system start-up. The engineering approval for the final configuration of mechanical systems must include a verification that all systems are appropriately configured to maintain correct and consistent operation throughout the life of the system, including correct and appropriate equipment, installations, system adjustments, controls, operation and maintenance procedures and training, AHU operating point on the fan curve, proper spare capacity for filter loading, system wear and tear, seasonal and ambient environmental impacts (wind, weather extremes), and all other foreseeable factors that may impact operations.
20. Check prefilters and final filters for cleanliness. Replace temporary construction filters with filters specified by design engineer. If the design filters have reached their pressure drop limit, change them.
21. Adjust supply, return, and exhaust fan airflows and room pressurizations to meet design rates.
22. Verify that operational testing of all system safeties (fire alarm, high-pressure limits, etc.) is completed before releasing system for automatic operational control.
23. Keep air system operating. Set room thermostat low enough to start cooling. Check chilled-water supply and return temperatures, control valves, and condensate drain. Check room temperature. Note that the cooling performance test is under the condition without process heat. The responsible HVAC engineer should determine if the HVAC and chiller systems are capable of satisfying the additional load with process running.
24. Keep air system operating. Set room thermostat at temperature high enough to start heating system. Check steam pressure and/or heating hot water system temperature, monitor served room temperature, and check control valves and condensate return and drain lines.
25. Keep supply air and heating system running. Set room humidistat at level high enough temporarily start humidifier. If steam humidifier is used, check steam pressure and all connections. Monitor relative humidity of served room and check control valves.
26. Clean the space for the last time using the operationally approved pharmaceutical cleaning procedures to prepare for final test. Cleanroom dress code enforcement begins before final test.
27. Perform final test. Attendees should include all contractors, subcontractors, the responsible HVAC engineer, the cleanroom facilities engineer, the future system lead operators, lead maintenance staff, and commissioning and

quality personnel, if appropriate.

28. All problems should be solved before the project completion, including the achievement of acceptable cleanroom pressurization, particulate and bioburden levels. Keep complete records of all problems and solutions during start-up, testing, adjusting, and balancing.

Pressurization Test and Map

Cleanroom pressurization must be verified before commissioning and engineering acceptance. An as-built space-to-space pressurization map should be submitted by the test-and-balance contractor to the responsible HVAC engineer for review and approval. The system must support acceptable room pressurizations within a narrow enough range to accommodate expected future system operational fluctuations; a retest may be performed if the HVAC engineer deems it necessary. Perform and document airflow pattern testing for final quality control verifications to demonstrate that particulates are being driven from the cleanest, most critical areas to less critical regions within and between rooms. Even when a room differential pressure is being maintained, it is important to find and correct counterintuitive airflow reversals through airflow pattern testing.

Operation Personnel Training Program

It is important that the operating and maintenance personnel responsible for systems on a particular project receive proper training. Usually, training is offered by the control contractor under the supervision of the responsible HVAC engineer, and should start during functional performance testing. It is important that the operating and maintenance personnel see the systems being set up, the issues encountered, and their resolution.

Cleanliness Verification Test

Empty (as-built) cleanroom cleanliness may be verified and determined by initial testing before process equipment installation and operation. Operational cleanroom cleanliness should be tested during formal process operation to gage the influence of emissions from process materials and products, as well as the performance of process exhaust systems together with cleanroom operation rules and operating personnel activities.

At-rest cleanroom status occurs after preparing the area for pharmaceutical manufacturing by installing process equipment and instrumentation, and the additional of properly gowned personnel creates **operational** cleanroom conditions. Space particulate levels measured at these different cleanroom operating states are important to meet processing space environmental requirements.

For ISO Class 3 and 4 cleanrooms, the owners will most likely prefer not to have commissioning personnel walking around the cleanroom facility during process in operation. They typically use their own professional staff to test and maintain the space cleanliness level. Therefore, as-built cleanroom cleanliness commissioning is the final step in most projects. Several publications by IEST and ISO address cleanroom testing and operation issues (IEST RP CC006.2; ISO *Standards* 14644-2, 14644-3, 14644-4, and 14644-5).

Commissioning

Participants in the commissioning process include personnel involved in the URS generation, design, start-up, test, and balance, in addition to process operators, the owner’s project authorities, and commissioning personnel.

Commissioning documents should include the following:

- Certificates and warranties of system completion with complete set of as-built drawings submitted from mechanical, electrical, plumbing, controls, and fire-protection contractors
- If available, all major equipment installation, operation, and maintenance (IOM) manuals, from the equipment manufacturers
- Complete records of all problems and solutions that occurred during start-up, and tests and adjustments submitted by every individual contractor
- A certified system test and balance report with verified major equipment models and capacities, and all tested performance numbers conforming to the system criteria from the licensed test-and-balance contractor. A complete space-to-space pressurization map submitted by the test-and-balance contractor
- A control system installation, operation, and maintenance (IOM) manual submitted from the control contractor
- A certificate of test for as-built cleanroom cleanliness (tested when cleanroom facility is complete, all services are connected and functional, but without equipment and operating personnel in the cleanroom)

- If the contract scope requires, a certificate of cleanroom cleanliness at the condition of process running with operating personnel in the facility
- Updated operating procedures, system drawings, facility flow diagrams, air handler service area diagrams, space classification, and pressurization drawings, as applicable.
- Commissioning protocol forms, signed and witnessed by all attendees

Process Equipment Installation (Tool Hook-up)

The process equipment installation (tool hook-up) work is covered by a separate, independent contract. It starts when the as-built cleanroom has been certified and accepted by the owner. The plant facility engineer is responsible for process equipment installation, and the project HVAC engineer monitors the cleanroom cleanliness while hook-up is in progress, offering consultation as needed. The following points apply to the cleanroom tool hook-up procedure:

- All cleanroom equipment installation personnel should attend a cleanroom orientation class before beginning work.
- All installation personnel must follow the dress code entering and working in the cleanroom area for process equipment installation, testing, adjusting, and operation.
- Do not unpack process equipment before the cleanroom has been cleaned, tested, certified, and is ready for installation of the equipment. Avoid unpacking equipment in clean areas; this should be done in a material airlock following proper procedures to minimize particulate introduction to the cleanroom.
- Do not unpack process equipment or open temporarily sealed pipe ends if not immediately installing or connecting to the equipment or pipe ends. Temporarily seal unfinished connection openings if not being connected immediately.
- Do not leave cleanroom doors or pass windows open anytime during installation or test operation.
- Establish a bimonthly cleanroom cleanliness retest timetable for monitoring and maintaining the cleanroom cleanliness level for the first six months. The frequency of retest can be modified according to the actual operating experience in future years.

16. INTEGRATION OF CLEANROOM DESIGN AND CONSTRUCTION

Integrated design and construction addresses all stages and aspects of cleanroom construction, to achieve better-quality, faster delivery; lower-cost, more optimized operation and maintenance; lower energy consumption; a cleaner environment; safer, more reliable, and more productive conditions; and longer service life. Integrated building design (IBD) is discussed in detail in Chapter 60.

A complete cleanroom project usually includes the following stages (see Figure 21): development of scope, budget, and overall project execution plan; predesign, conceptual, and schematic design; preliminary, final design, and construction documentation; and construction service.

One of the most important initial steps is to have a effective programming plan that involves all stakeholders: management, owners, users; designers (architects and engineers), process engineers, builders, and utility, maintenance and operation personnel.

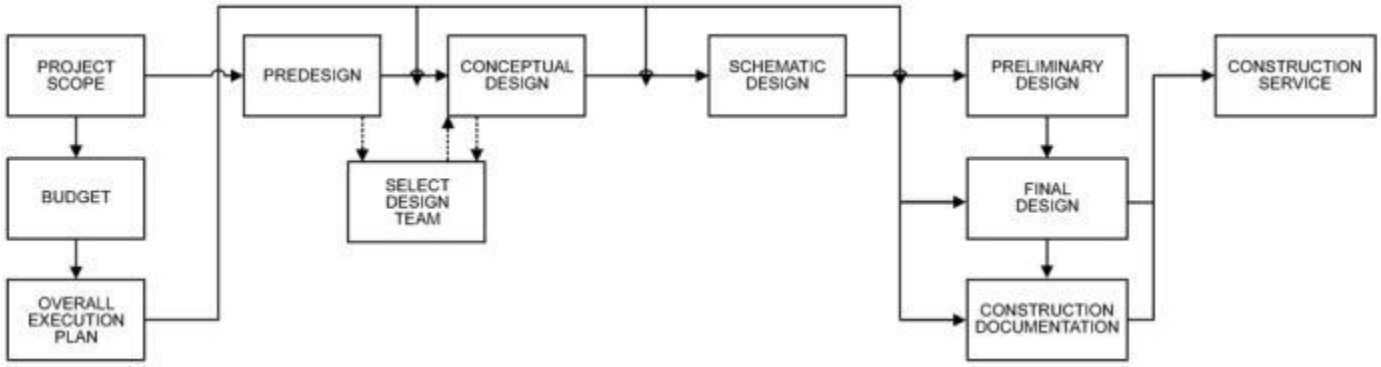

Figure 21. General Design and Construction Procedure

Although the entire cleanroom building project is a large and complex operation, it may be simplified if it is considered as an integrated system with a unified overall scope of work and timeline to be achieved by an integrated design and construction team (Shieh 1990, 2005). In an integrated approach, all individual systems and their

components are considered as subsystems of the overall integrated cleanroom building project, and optimizations are implemented at the component, system, and facility levels, including the following:

- **Site/utilities.** Overall site plan, entrances and gates, roads and transportation, landscape, electrical substations or electrical main connection, gas or other fuel main intake pressure regulation station, water, sewer, sanitary and storm drain piping and main connections, telephone, network, security and fire protection system main connections, outdoor lighting, etc.
- **Building.** Foundations, structure system, walls, roofs, ceilings, floors, elevators, electrical, gas, fuel, water, sewer, plumbing, sanitary, mechanical, HVAC, chiller, boiler, noise control, lighting, process systems, energy and process material recovery systems, exhaust air and wastewater treatment systems, hazard control systems, explosion- and corrosion-proofing, instrumentation and control systems, fire protection systems, etc.
- **Cleanroom.** Walls; roofs; ceilings; HEPA or ULPA filters; floors; mini-clean environment; clean tunnels; clean booths; recirculating air, makeup air, and exhaust air systems; lighting, process mechanical, chemical, electrical, and control systems; production lines; process conveyers; special gas supply systems; acoustics; operating personnel, material, and products access doors, windows, or openings; air showers; room temperature, humidity, static electricity, CO_2, pressurization, and cleanliness monitoring and control systems; fire protection and after-fire recovery systems; seismic design, emergency response facilities, etc.
- **Implementation.** Design documents, submittal approvals, receiving inspections, clean construction and installation work, field inspections, system start-up, test and adjustment, balancing, commissioning, and turnover.
- **Building management.** System operation and maintenance.

17. LIFE AND PROPERTY SAFETY

Human life and property safety must be thoroughly addressed in all types of new construction or renovation projects during cleanroom design, construction, installation, start-up, test, balance, operation, and maintenance. The American Conference of Governmental Industrial Hygienists (ACGIH) and National Fire Protection Association (NFPA) provide detailed regulations. The following are some of the essential categories to be carefully addressed during the entire cleanroom project design, construction, commissioning, operation, and maintenance process.

Hazards Generated on Cleanroom Property

When hazards are present on the project property, all safety issues must be carefully addressed; otherwise, the consequences could affect not only the occupancy personnel and the property, but also the surrounding communities. One of the duties for the design and commissioning authorities is to understand and successfully address the hazards generated in the property.

Different cleanrooms may be composed of many different operating systems, each with distinct equipment or operating processes that present unique hazards (e.g., fuel handling, chemical transport and emissions, airborne contaminants, heated lubrication and seal oil, oil-filled transformers, cable vaults, coal handling, electrical hazards, control rooms in industrial properties, active pharmaceutical ingredients [API], and medical gas supply and cross contamination in hospitals). Microelectronics manufacturing can also include extremely toxic, explosive, and pyrophoric gases and materials. These can create unique EHS hazards and special evacuation or containment emergency HVAC operational strategies.

Fume hoods are a design challenge when located in pharmaceutical processing rooms because they may have a small but measurable containment leakage rate. The processing room should be positively pressurized to promote product integrity, but fume hoods require a negatively pressurized environment to support containment of hazards. Architectural layout provides a primary solution to the issue of a processing space needing protection from inbound contamination, and addresses containment concerns to protect surrounding spaces. Anterooms and similar buffer zones allow the creation of *pressure doughnuts* or *pressure sinks* while limiting the amount of air needed to achieve appropriate control.

Implementing comprehensive human health and life protection requirements, as well as fire protection systems that include hazard detection, alarm, and suppression systems, can be a complex challenge that requires commissioning authorities' thorough understanding and experience of the intricacies of different type of individual projects.

Fire and Hazardous Gas Detection, Alarm, and Suppression Systems

Careful design, quality installations, continuous monitoring, and effective maintenance of explosion prevention and fire protection systems promote proper safety. Early, reliable fire and hazardous gas detection alerts personnel to the danger and initiates protective actions automatically or manually. Examples include but are not limited to the following:

- Gas detectors for oil and gas skids
- H_2 detectors for battery rooms
- Spark and flame detectors for coal conveyors and fuel oil tanks
- Heat detection for oil-filled transformers and lube oil and seal oil skids
- Linear heat detectors for cable galleries and fuel oil tanks
- Smoke and heat detection for plant and nonplant buildings

Active systems, such as pumping systems, can be automatically or manually activated for use in actual fire fighting. They network with fire and gas detection and alarm systems, deluge spray systems, foam systems, CO_2 detectors, clean agent systems, portable and mobile extinguishers, and fire station and fire tenders.

Homeland Security and Emergency Response Plan

Homeland security and emergency response have become more important in the United States since September 11, 2001. Awareness among first responders has raised the need to be prepared for extraordinary events. Emergency response plans need to include fire protection crews with scheduled routine training, exercise, and fire protection system testing, as well as in cooperation with homeland security and civil defense programs. Examples such as firefighter safety, first responders training, protective clothing, procedures, and equipment to deal with any predictable emergency are critical to good and sustainable operations. Refer to NFPA *Standard* 1600 for details.

IEST RECOMMENDED PRACTICES

All *Recommended Practices* are from the Institute of Environmental Sciences and Technology, Arlington Heights, IL.

RP-CC001.3	HEPA and ULPA filters
RP-CC002	Laminar flow clean-air devices
RP-CC003.2	Garment system considerations in cleanrooms and other controlled environments
RP-CC004.2	Evaluating wiping materials used in cleanrooms and other controlled environments
RP-CC005	Gloves and finger cots used in cleanrooms and other controlled environments
RP-CC006.2	Testing cleanrooms
RP-CC007.1	Testing ULPA filters
RP CC008	Gas-phase adsorber cells
RP-CC009.2	Compendium of standards, practices, methods, and similar documents relating to contamination control
RP-CC011.2	A glossary of terms and definitions relating to contamination control
RP-CC012.1	Considerations in cleanroom design
RP-CC012.2	Considerations in cleanroom design
RP-CC012.3	Considerations in cleanroom design
RP-CC013	Equipment calibration or validation procedures
RP-CC014	Calibrating particle counters
RP-CC015	Cleanroom production and support equipment
RP-CC016	The rate of deposition of nonvolatile residue in cleanrooms
RP-CC017	Ultrapure water: Contamination analysis and control
RP-CC018	Cleanroom housekeeping—Operating and monitoring procedures
RP-CC019	Qualifications for agencies and personnel engaged in the testing and certification of cleanrooms and clean air devices
RP-CC020	Substrates and forms for documentation in cleanrooms
RP-CC021	Testing HEPA and ULPA filter media
RP-CC022.1	Electrostatic charge in cleanrooms and other controlled environments
RP-CC023.1	Microorganisms in cleanrooms
RP-CC024.1	Measuring and reporting vibration in microelectronics facilities
RP-CC025	Evaluation of swabs used in cleanrooms
RP-CC026.1	Cleanroom operations
RP-CC027.1	Personnel practices and procedures in cleanrooms and controlled environments
RP-CC028.1	Minienvironments
RP-CC029	Automotive paint spray applications
G-CC035.1	Design considerations for AMC filtration systems in cleanrooms
STD-CC1246D	Products cleanliness levels and contamination control program

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