CHAPTER 18

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 these limits are exceeded, the pharmaceutical product may be considered adulterated.

ach. Air changes per hour.

Air lock. A small transitional room between two adjacent rooms 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 and is 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 nonunidirectional or mixed airflow patterns and velocities.

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

Critical surface. The surface of the work part 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 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 room 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. The air leakage results from differential pressure across gaps in walls or barriers.

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) 21CFR210, 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 space(s) or areas, such as interstitial spaces.

ISPE. International Society for Pharmaceutical Engineering.

ISO. International Organization for Standardization.

ISO 14644-1. Specifies airborne particulate cleanliness classes in cleanrooms and clean zones. ISO (International Organization for Standardization) *Standard* 14644-1 is an international standard for cleanrooms. Table 1 and Figure 1 summarize the ISO standard classes.

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).

The preparation of this chapter is assigned to TC 9.11, Clean Spaces.

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

ISO 14644 Class	0.1 μm	0.2 μm	0.3 μm	0.5 μm	1.0 μm	5.0 μm
	Particles per m^3					
1	10	2				
2	100	24	10	4		
3	1000	237	102	35	8	
4	10 000	2370	1020	352	83	
5	100 000	23 700	10 200	3520	832	29
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

Source: ISO *Standard* 14644-1.
Note: Values shown are the concentration limits for particles equal to and larger than the sizes shown.
$C_n = 10^N(0.1/D)^{2.08}$ where C_n = concentration limits in particles/m^3, N = ISO class, and D = particle diameter in μm

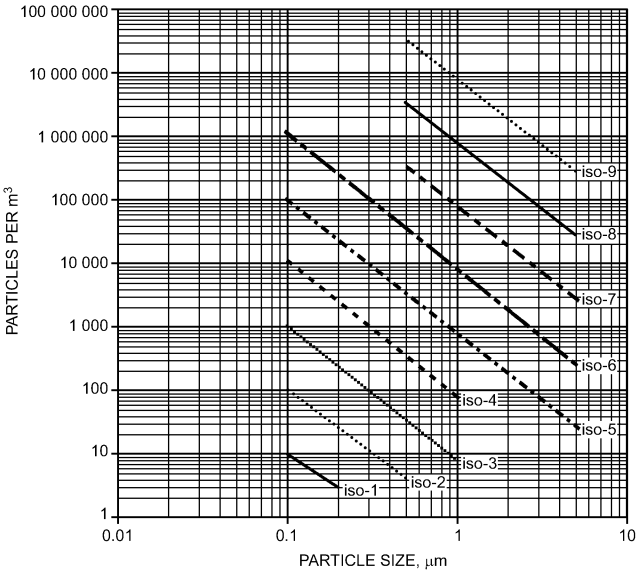


Fig. 1 Air Cleanliness Classifications in ISO *Standard* 14644-1

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.

Nonunidirectional 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 and exhaust and return airflow rates.

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.

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.

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. 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 cleaner 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) 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.
- **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 8.
- **Miscellaneous Applications.** Cleanrooms are also used in aseptic food processing and packaging, microelectronic and nanotech applications, manufacture of artificial limbs and joints, 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 are a prime source of particle generation (e.g., skin flakes, hair, clothing lint, cosmetics, respiratory emissions, bacteria from perspiration). These airborne particles vary from 0.001 μm to several hundred micrometers. Particles larger than 5.0 μm tend to settle quickly by gravity, whereas those smaller than 1.0 μm can take days to settle. In many manufacturing processes, these airborne particles are viewed as a source of contamination and can provide a pathway for 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 well as 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 and 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. 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 particles, 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 may be used to define its cleanliness class, actual particle deposition on the product critical surface is of greater concern. 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 and airflow patterns to limit their effect on the product Particle counters are used to measure and 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 (IEST RP CC014).

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 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 mechanisms by which HEPA and ULPA filters capture particulate: (1) straining, (2) inertia, (3) interception, and (4) diffusion. Also, some systems use electromagnetic forces to enhance HEPA and ULPA filter performance (see the section on Sustainability and Energy Conservation in Cleanrooms for details). Straining, sometimes called sieving, occurs in a filter when the 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, particles with mass small enough to stay in the airstream nevertheless touch the filter fiber and are attached. Diffusion captures very small particles that 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 dominant capture mechanisms for HEPA and ULPA filters. Fibrous filters have their lowest removal efficiency at the most penetrating particle size (MPPS), 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. Thus, HEPA and ULPA filters have rated efficiencies based on 0.3 and 0.12 μm particle sizes, respectively. Different types of filter media

are produced to meet various cleanroom applications. See Table 2 for the different types of filter media, their filter efficiency, and their typical applications. IEST publishes recommended practices for HEPA and ULPA filters and testing of filter media (IEST RPs CC001.3, CC007.1, and CC021).

4. AIR PATTERN CONTROL

Air turbulence in the clean space, which can be detrimental to environmental quality, is strongly influenced by air supply and return configurations, air balancing adjustments, foot traffic, 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: nonunidirectional airflow (commonly called turbulent), and unidirectional airflow (previously, often mistakenly called laminar flow).

Nonunidirectional Airflow

Nonunidirectional airflow has either multiple-pass circulating characteristics or nonparallel flow. Variations are based primarily on the location of supply and return/exhaust air registers and the associated airflow rates. Examples of unidirectional and nonunidirectional airflow of cleanroom systems are shown in Figures 2 and 3. 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 unidirectional and nonunidirectional system, outdoor air is prefiltered in the supply and then HEPA filtered at workstations in the clean space (see the left side of Figure 3).

Nonunidirectional 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 levels through dilution. When internally generated particles are of primary concern, clean workstations can be used effectively in the clean space.

Table 2 Filter Media Types, Efficiencies, and Applications

Filter Type	Filter Efficiency, %, at Particle Size, μm	Filter Application
A	99.97% at 0.3	Industrial, hospital, food
B	99.97% at 0.3	Nuclear
C	99.99% at 0.3	Unidirectional flow (semiconductor, pharmaceuticals)
D	99.999% at 0.3	Semiconductor, pharmaceutical
E	99.97% at 0.3	Hazardous biological
F	99.97% at 0.12	Semiconductor

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. 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.

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 2013 *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 100% HEPA filter coverage. Ideally, a grated or perforated floor serves as

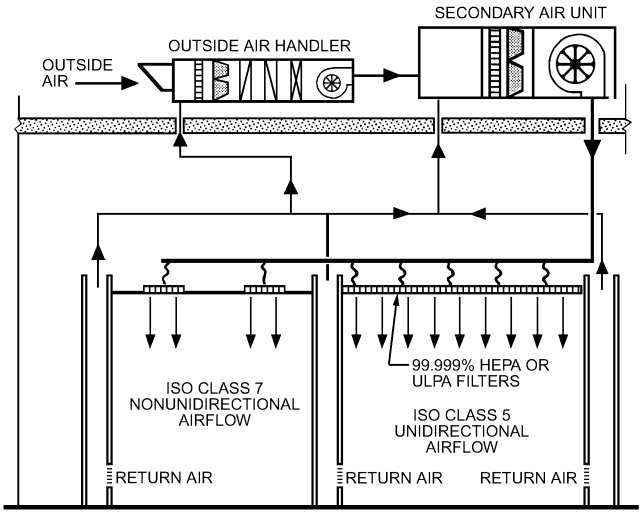


Fig. 2 ISO Class 7 Nonunidirectional Cleanroom with Ducted HEPA Filter Supply Elements and ISO Class 5 Unidirectional Cleanroom with Ducted HEPA or ULPA Filter Ceiling

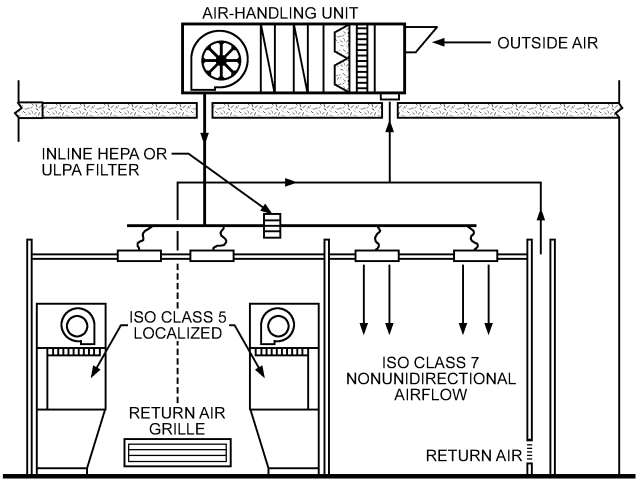


Fig. 3 ISO Class 7 Nonunidirectional Cleanroom with HEPA Filters Located in Supply Duct and ISO Class 5 Local Workstations

the air return/exhaust. In this configuration, clean air flows downward past a contamination source, picks up the contamination particle, and removes it directly down through the floor to prevent the particle 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.

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.

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 section of the space. (Note that 0.45 m/s can be too high for optimum cleanroom performance: velocities above 0.36 m/s tend to increase turbulence, reentrainment, and particle residence time, but may be necessary to address high particle generation rates). 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 becomes contaminated. 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 recommended 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 not known. 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 and filter coverage in addition to air change rates. Perform careful testing to ensure that required cleanliness levels are maintained. Other reduced-air-volume designs may use a mixture of high- and low-pressure-drop HEPA filters, reduced coverage in high-traffic areas, or lower velocities in personnel corridor areas.

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 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 also 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 becomes an attractive alternative.

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 the buildings to evaluate impact of wind on environmental dispersion, wind pressure on building façade, 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 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, first 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 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
- Graphical representation of flow streamlines and velocity vectors to assist in flow analysis (Figures 4, 5, and 7)
- Graphical representation of simulated particle trajectories and propagation (Figures 6 and 8)

Research has shown good correlation 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.

For more information on CFD, see Chapter 13 of the 2013 *ASHRAE Handbook—Fundamentals*.

Air Change Rate Determination

Cleanroom HVAC systems are highly energy intensive (Lowell et al. 1999), and may consume up to 50 times more energy than those used in commercial spaces of the same size. 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 are from inside the cleanroom activities. A very high air change rate is not typically needed for cooling, heating, or ventilation loads but mainly for controlling and diluting particle concentrations. Cleanroom design engineers have traditionally used conservative, simplified rule-of-thumb values published in *Federal Standard* FS-209 and IEST RP-12.1. This approach solely used the required room cleanliness class to determine an air change per hour (ach) value, often arbitrarily, from a wide range specified in older documents. However, this practice ignores many critical variables that could significantly affect the room particle concentration in terms of air change rate requirements, such as 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 the existing recommended table uses an oversimplified approach that ignores such differences.

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 underdesigned HVAC systems. Xu (2003, 2004) found that airflow rates or air velocities for cleanrooms

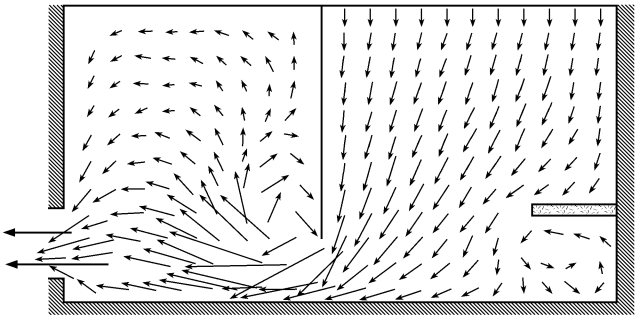


Fig. 4 Cleanroom Airflow Velocity Vectors Generated by Computer Simulation

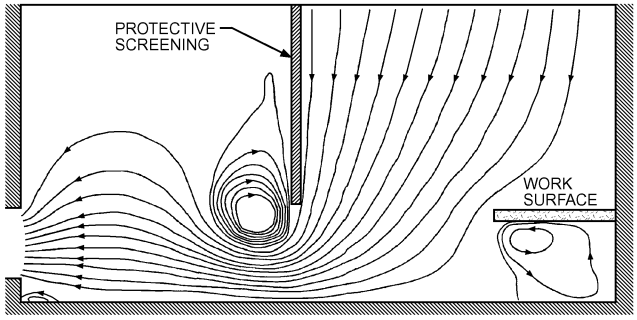


Fig. 5 Computer Modeling of Cleanroom Airflow Streamlines

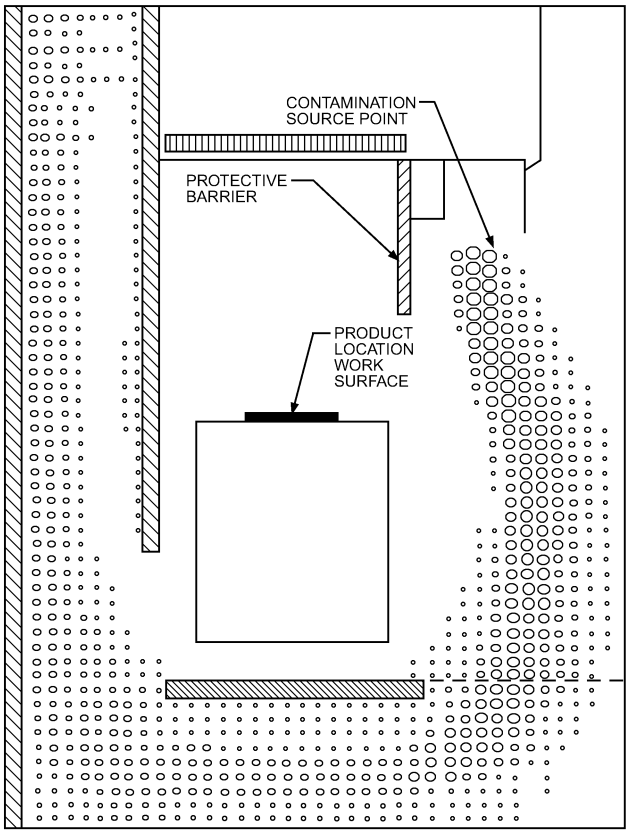


Fig. 6 Computer Simulation of Particle Propagation in Cleanroom

in actual operation exhibited lower values than those specified in IEST RP CC012.1.

Some operating cleanrooms avoid higher airflow rates or airflow velocities than necessary, many cleanrooms may be overdesigned, 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). As a part of this trend, IEST RP CC012.2 has replaced the previous RP 12.1's "recommended" air change table with a more loosely defined "typical" air change rate table as an interim step. Although there is room for the improvement in these recommendations, IEST RP CC012.3 also presents the same table and provides more clarifications about the limitations of the recommended ranges. Figure 9 shows the measured airflow rates and airflow velocities of actual ISO Class 5 cleanrooms in the United States in comparison with the typical ranges exhibited in IEST RP CC012.3.

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 allowing 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

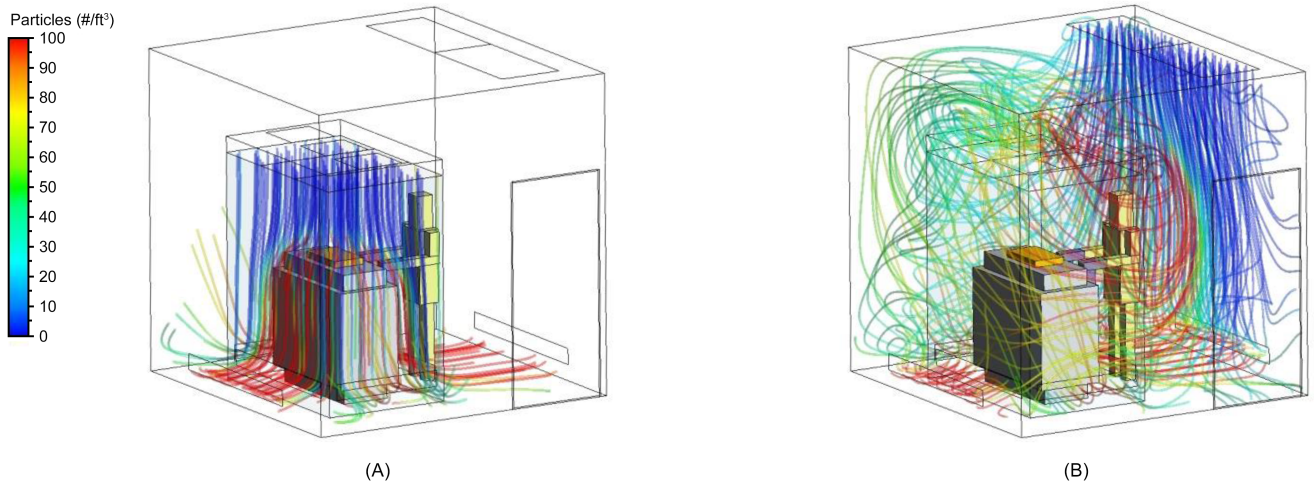


Fig. 7 Airflow Patterns in Minienvironment Cleanroom: (A) Unidirectional Flow and (B) Mixed Flow
(CFD analysis provided by Kishor Khankari, PhD, President, AnSight LLC, Ann Arbor, MI.)

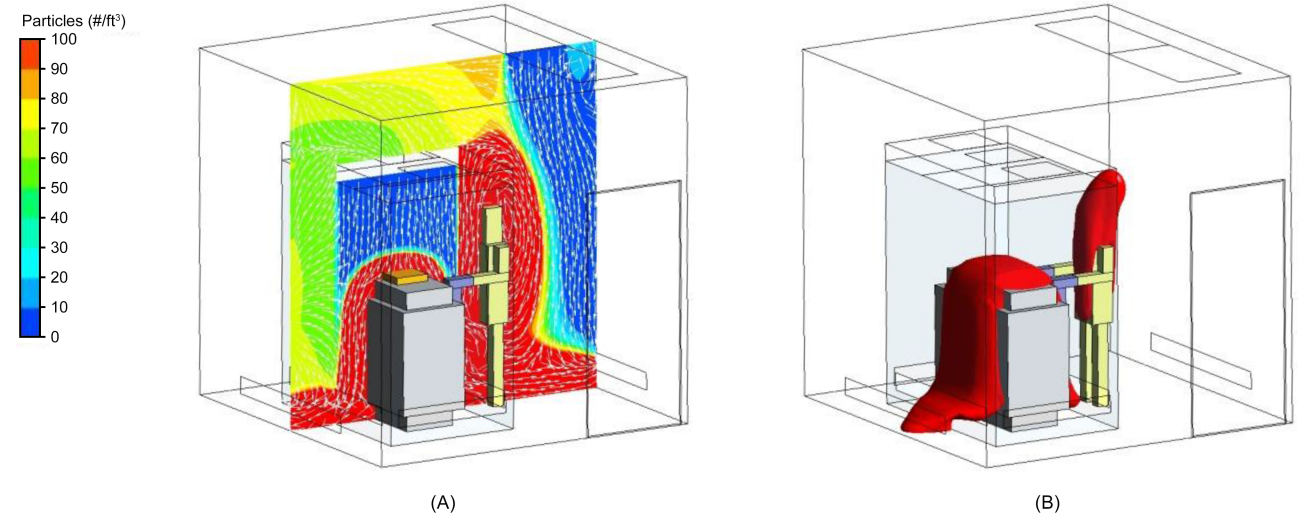


Fig. 8 Particle Concentration in Minienvironment Cleanroom Showing (A) Lower Particle Concentration in Minienvironment and Higher Concentration near Person because of Recirculation of Air around Occupant and (B) Particle Cloud of 35 311 particles/m³ with Higher Particle Concentration near Occupant's Face
(CFD analysis provided by Kishor Khankari, PhD, President, AnSight LLC, Ann Arbor, MI.)

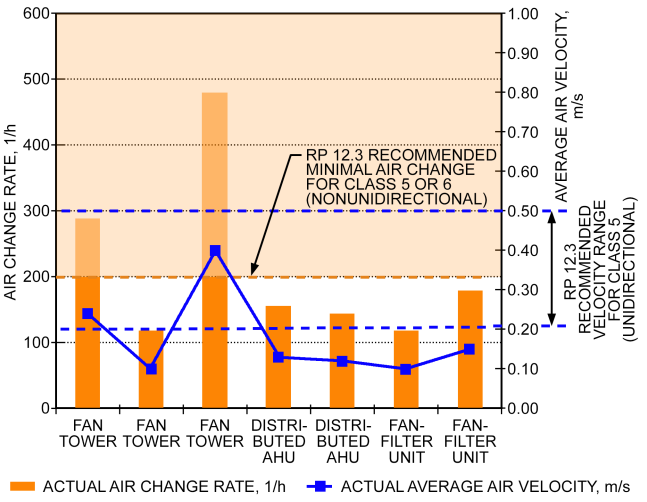


Fig. 9 Actual versus Recommended Cleanroom Airflow Rates
(Based on data from Xu 2004 and IEST RP CC012.3)

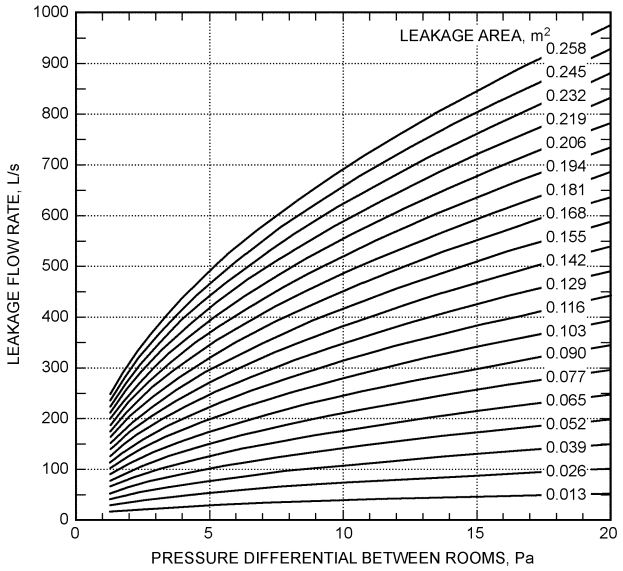


Fig. 10 Flow Rate Through Leakage Area under Pressure Differential

research project 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 showed its feasibility (Faulkner et al. 1996, 2008).

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. This is because the amount of time that the room is challenged with particle emissions is typically a relatively small amount of time. Consequently, the best approach for controlling cleanroom air change rates is to determine or vary the rate as needed based on the real-time quality of the cleanroom's air. When the cleanroom is clean of particles or potentially other contaminants, the air change rate can be dropped significantly, to 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.

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 may be desirable as well such as total volatile organic compounds (TVOCs), carbon dioxide, and humidity. This information may then be integrated with the building management system for this or other 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) having the most critical operations should be designed with the highest pressure, with decreasing pressures corresponding to lower cleanliness classifications. The desired flow path should be from the area of cleanest, most critical environmental requirements to less clean areas, then 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:

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

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 10 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.

Space airtightness (sealing of the facility, fixtures, 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 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.
- **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' room 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 room layout arrangements are needed to minimize operational room pressurization challenges; overlooking this fact 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 room 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

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

Because early cleanrooms were largely for governmental use, testing procedures were set by government standards. U.S. *Federal Standard* 209 was widely accepted and defined air cleanliness levels for clean spaces around the world, but it was formally withdrawn in 2001. ISO standards now govern. Standardized testing methods and practices have been published by the Institute of Environmental Sciences and Technology (IEST RP CC006.2; ISO *Standards* 14644-2, 14644-3, and 14644-4).

Three basic test modes are used to evaluate a facility: (1) as built, (2) at rest, and (3) operational. A cleanroom cannot be fully evaluated until it is operated in operational test mode, which includes all equipment operating and personnel present. Thus, techniques for conducting initial performance tests and operational monitoring must be similar.

As noted previously, contamination sources 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, 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 ceilings 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, 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 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 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 system 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.

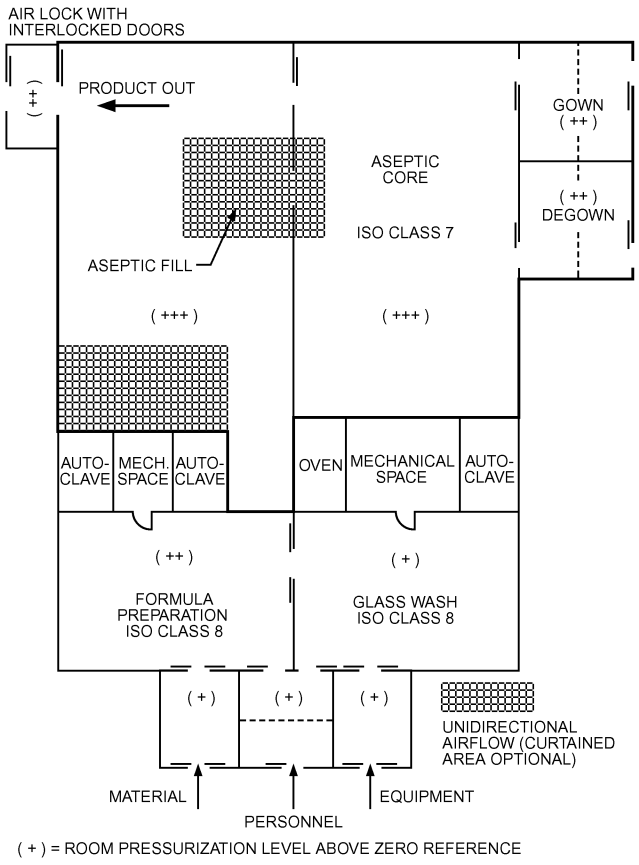
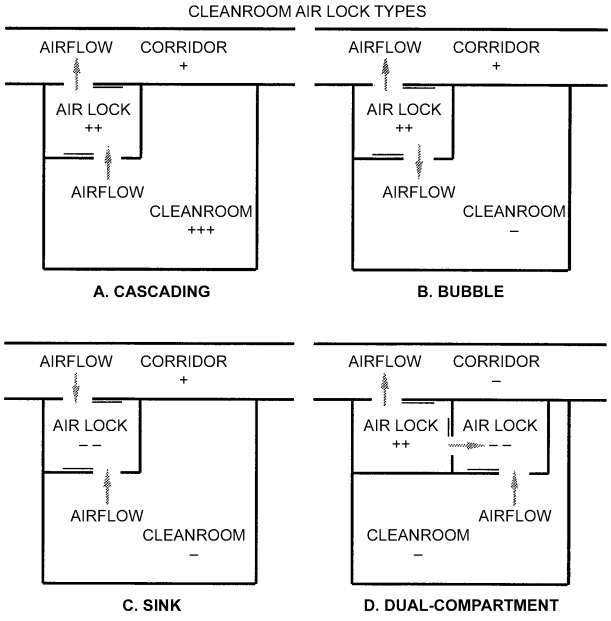


Fig. 11 Typical Aseptic Suite

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 11).

In aseptic processing facilities, the highest-cleanliness area is intentionally placed within lower-cleanliness areas, separated by air locks and room pressure differentials. A common pressure difference is about 12.5 Pa or less between air cleanliness classifications, 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.

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 biosafety level (BSL) 3 and ISO Class 6, 7, or 8 applications; four pressure steps are desirable for BSL-4, 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 12), 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.



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.

Fig. 12 Air Lock Types and Applications

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, to minimize possible contamination during 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.

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 assurance in the performance of the manufacturing process such that it will consistently produce APIs and drug products meeting those attributes relating to identity, strength, quality, purity, and potency. The 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 foreseeable variables that may 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. In that range, the product's safety, identity, strength, purity, and quality must be demonstrated to be unadulterated. 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 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. Factory-wrapped ducts and components with clean installation and inspection protocols promote cleanroom system cleanliness.

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 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 registers 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 difficulty 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 facilities usually require pinhole-scanned (integrity-tested) HEPA filters (not ULPA) on supply air. Many facilities install HEPA filters in the supply air to nonaseptic production facilities to minimize cross contamination from other manufacturing areas served by the HVAC system. To increase the life of terminal HEPA filters in aseptic facilities, and to minimize the need to rebalance the supply system because of differential loading of

terminal HEPA filters, many designers install a high-capacity HEPA bank downstream of the supply air fan, with constant-volume control to compensate for primary filter pressure changes and any dehumidifier airflow. The final HEPA filter is usually in a sealed gel frame or of a one-piece lay-in design that can be caulked to the ceiling frame, maintaining the integrity of the room envelope.

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, and door leakage that can 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.

ISO Class 5 unidirectional hoods are commonly banks of HEPA 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 0.45 m/s or less, but the user should specify velocity and uniformity requirements. 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 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 roots in 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 this equipment is expensive. Furthermore, cleanrooms typically need gowned operators inside to manipulate product and adjust machinery. Because the operator is the source of the majority of the 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-risk 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, 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. Consider how much exposure and risk to product and personnel are required 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 sanitized using the owner's procedures. Determine whether ductwork must be internally cleaned, and how. Reduced- or no-shutdown HVAC system designs require energy-efficient components. 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 (statically balanced) HVAC if there are few 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. 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 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.

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.

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.

Nonaseptic Products

Nonaseptic pharmaceutical facilities (e.g., for topical and oral products) are similar in design to those for aseptic product manufacturing, 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, the owner and designer should discuss who will be responsible for as-built drawings, setting up 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 also 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 HVAC 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 approvals 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 startup, 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 building'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

Advances in Process Technology

Since the mid-1990s, most microelectronic facilities manufacturing semiconductors have required cleanrooms providing ISO Class 3 and cleaner for wafer fabs and Class 5 to 8 for auxiliary manufacturing rooms. This state-of-the-art cleanroom technology has been driven by the decreasing size of microelectronic circuitry and larger wafer sizes (Chang et al. 2009; Hu et al. 2010, 2013). A deposited particle with a diameter of 10% of the circuit width may cause a circuit to fail. Many facilities are designed to meet as-built air cleanliness of less than 35 particles at 0.5 μm and larger per cubic metre of air.

Currently, semiconductor manufacturing cleanroom integration is important in semiconductor facilities design. Larger wafers require larger processing equipment. Cleanroom structures are now integrated into the process and mechanical systems to reduce overall building height and construction cost, and to shorten construction duration. In addition, particle control has advanced to the level of molecular contamination control. Product contamination control also includes internal contaminations such as chemical, ionic, and static electricity control, and fire resistance performance.

Semiconductor Cleanroom Configuration

Semiconductor cleanrooms today are of two major configurations: clean tunnel or open-bay (ballroom). The **clean tunnel** is composed of narrow modular cleanrooms that may be completely isolated from each other. Fully HEPA- or ULPA-filtered pressurized plenums, ducted HEPA or ULPA filters, or individual fan modules are used. Production equipment may be located in the tunnel or

installed through the wall where a lower-cleanliness (nominally ISO Class 7 or cleaner) service chase is adjacent to the clean tunnel. The service chase is used in conjunction with sidewall return or a raised floor, possibly with a basement return.

The primary advantage of the tunnel is reduced HEPA- or ULPA-filter coverage and ease of expanding additional tunnel modules into unfiltered areas. The tunnel is typically 2.5 to 4.3 m wide. If the tunnel is narrower, production equipment cannot be placed on both sides; if wider, flow becomes too turbulent and tends to break toward the walls before it leaves the work plane. Figure 13 shows a clean tunnel.

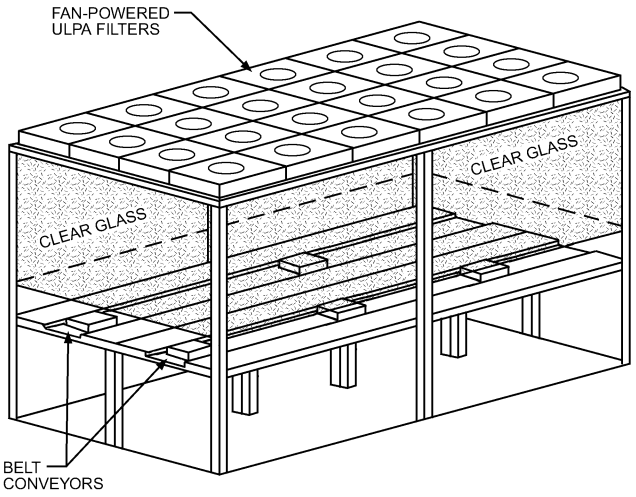


Fig. 13 Elements of a Clean Tunnel

The tunnel design has the drawback of restricting new equipment layouts. Cleanroom flexibility is valuable to semiconductor manufacturing. As processes change and new equipment is installed, the clean tunnel may restrict equipment location to the point that a new module must be added. The tunnel approach may complicate moving product from one type of equipment to another.

Fan/filter clean tunnels have a wide range of applications. However, the noise generated by fans is directly distributed to the tunnel, and the unit's efficiency is lower than in central station recirculating systems. Life-cycle cost analysis can be used (among other considerations) to determine the appropriate configuration.

Ballroom or **open-bay design** involves large (up to 10 000 m^2) open-construction cleanrooms. Interior walls may be placed wherever manufacturing logistics dictate, providing maximum equipment layout flexibility. Replacing process equipment with newer equipment is an ongoing process for most wafer fabrication facilities; support services must be designed to handle different process equipment layouts and even changes in process function. Often, a manufacturer may completely redo equipment layout if a new product is being made.

Open-bay designs can use either a pressurized plenum or ducted filter modules, although pressurized plenums are becoming more common. Pressurized plenums usually are recirculating air plenums, in which makeup air mixes with recirculating air or is ducted to the recirculating units (Figure 14). Either one large plenum with multiple supply fans or small adjacent plenums are acceptable. Small plenums allow shutting down areas of the cleanroom without disturbing other clean areas, and may also include one or more supply fans.

In the past decade, silicon wafer diameter has increased threefold. Along with the requirement for larger process equipment, the demand for larger space sizes has also become increasingly significant. Major semiconductor facilities, with total manufacturing

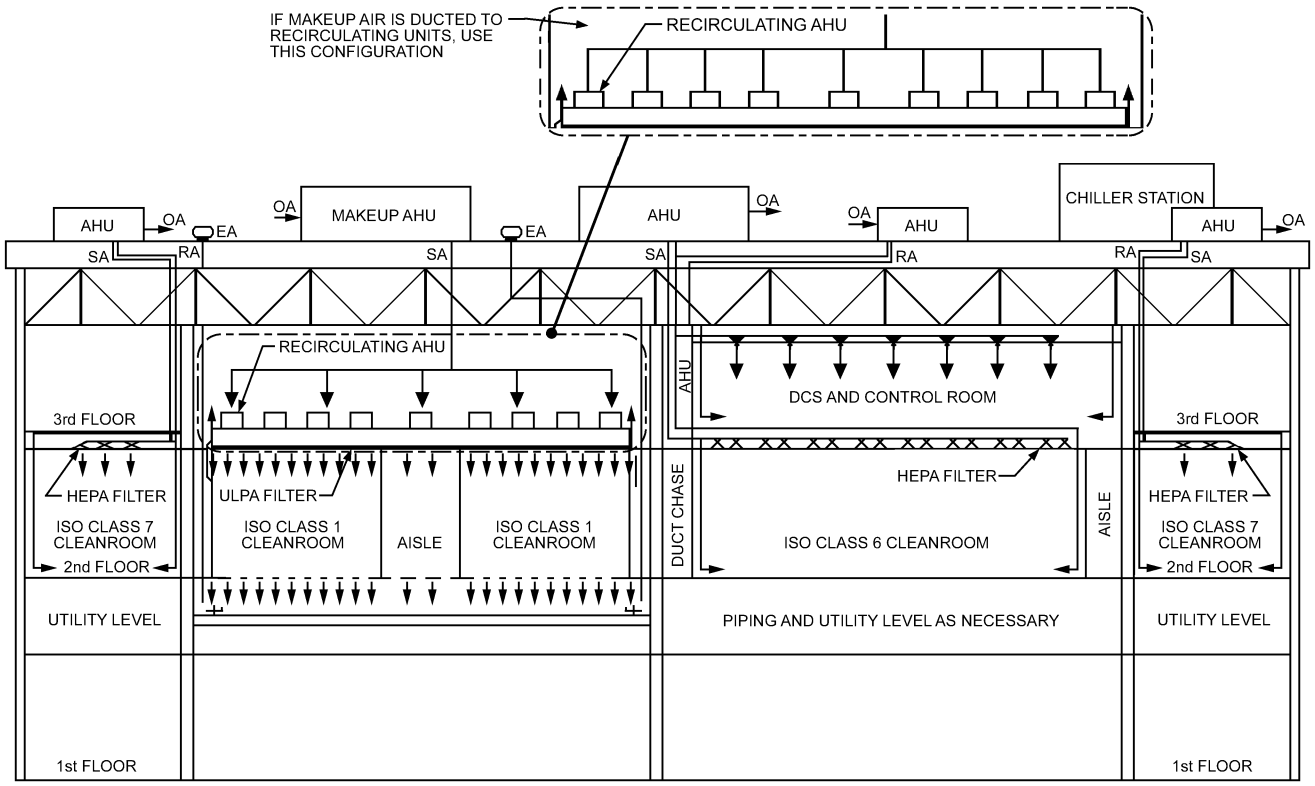


Fig. 14 Typical Semiconductor Manufacturing Plant Section View

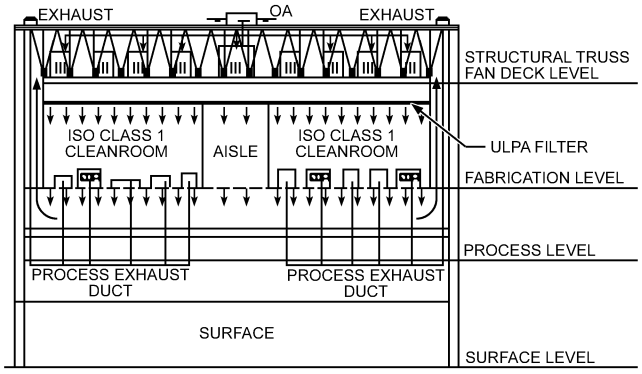


Fig. 15 Building Truss Level Arranged as Fan Deck and Air Plenum

areas of 2800 m^2 and larger, may use both open-bay and tunnel design configurations. Flexibility to allow equipment layout revisions warrants the open-bay design. Process equipment suitable for through-the-wall installation such as diffusion furnaces, may use either design. Equipment such as lithographic steppers and coaters must be located entirely in laminar flow; thus, open-bay designs are more suitable. Which method to use should be discussed among the cleanroom designer, production personnel, and contamination control specialist.

Building structure areas are sometimes used as recirculating and makeup air units, fan deck, and plenum. Some structures perform as very large cabinets of makeup air units or recirculating units. Figure 15 shows a building truss level arranged as a fan deck and air plenum. Coordination between architects, engineers (structural, process, and mechanical), semiconductor facilities personnel, and construction industries must continue to minimize building size and to satisfy ever-evolving process requirements.

Many semiconductor facilities contain separate cleanrooms for process equipment ingress into the main factory. These ingress areas are staged levels of cleanliness. For instance, the equipment receiving and vacating area may be ISO Class 8, and the preliminary equipment setup and inspection area may be ISO Class 7. The final stage, where equipment is cleaned and final installation preparations are made before the fabrication entrance, is ISO Class 6. Some staged cleanrooms must have adequate clear heights to allow forklift access for equipment subassemblies.

Airflow in Semiconductor Cleanrooms

Current semiconductor industry cleanrooms commonly use vertical unidirectional airflow, which produces a uniform shower of clean air throughout the entire cleanroom. Particles are swept from personnel and process equipment, with contaminated air leaving at floor level; this produces clean air for all space above the work surface.

In vertical unidirectional airflow, the cleanroom ceiling area consists of HEPA or ULPA filters set in a nominal grid size of 0.6 by 1.2 m, T-bar-style grid with gasketed or caulked seals for many ISO Class 5 systems; Class 3 and Class 4 systems often use either low-vapor-pressure petrolatum fluid or silicone dielectric gel to seal the filters into a channel-shaped ceiling grid. Whether T-bar or channel-shaped grids are used, the HEPA or ULPA filters normally cover 85 to 95% of the ceiling area, with the rest of the ceiling area composed of grid work, lighting, and fire protection sprinkler panels.

HEPA or ULPA filters in vertical unidirectional airflow designs are installed (1) with a pressurized plenum above the filters, (2) through individually ducted filters, or (3) with individually fan-filter units or modules. A system with a plenum must provide even pressurization to maintain uniform airflow through each filter. Ducted HVAC typically has higher static pressure loss from the ducting and balance dampers, resulting in higher fan energy and higher operating cost. Maintenance costs may also be higher because of the balance method involved with ducted HVAC.

An individual fan-filter unit (i.e., fan-powered filter module) uses one or more small fans (e.g., usually forward-curved fans) that provide airflows through one filter assembly. This configuration allows airflow from each unit to be individually controlled throughout the cleanroom and requires less space for mechanical components (Chen et al. 2007; Xu et al. 2004, 2007). Potential disadvantages are lower fan and motor efficiencies because of the small sizes, potentially higher fan noises, and higher operation and maintenance costs. Energy performance and controllability of fan-filter units on the market vary significantly within common operational ranges. Standard testing of such units is recommended before final product selection for cleanroom recirculation (Xu 2007b; Xu and Jeng 2004).

When through-the-floor return grating is used, a basement return is normally included to provide a more uniform return as well as floor space for dirty production support equipment.

Sidewall returns are an alternative to through-the-floor returns; however, airflow may not be uniform throughout the work area. These returns are most applicable for ISO Class 5 to 8 cleanrooms.

Prefiltration is an economical way to increase ULPA filter life. Prefilters are located in recirculation airflow, in either the return basement or air handler, to allow replacement without disrupting production.

Cleanroom Air Velocity and Air Change Rate

For a given cleanroom, the supply airflow rate Q (m^3/s) is

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

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

or

$$\text{ACH} = \frac{3600LWv}{LWH}$$

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

where

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

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.

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

Table 3 Air Changes per Hour Versus Vertical Airflow Velocities, Room Heights, and Cleanliness Classes

ISO Class	Velocity, m/s	Air Changes per Hour for Ceiling Height, m							
		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

ceilings primarily used in jet aircraft assembly, painting, and cleaning operations; 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. Crystal-pulling cleanrooms for semiconductor microchips are usually specified at Class 5 to Class 6 range.

Table 3 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 laminar flow of the air disintegrates. 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 in downward-flowing supply air.

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 rooms because supply and return air volumes may be controlled at different horizontal levels in the space.

The main disadvantage of horizontal-flow high-bay spaces is that they provide clean air for only one object, or at best, several objects in the same plane. Once past the object, air cleanliness degrades to the extent that the process generates particles.

Downflow designs are most widely used, but certain projects such as the space telescope and space shuttle assembly room may require horizontal-airflow high-bay cleanrooms (Figure 16).

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.

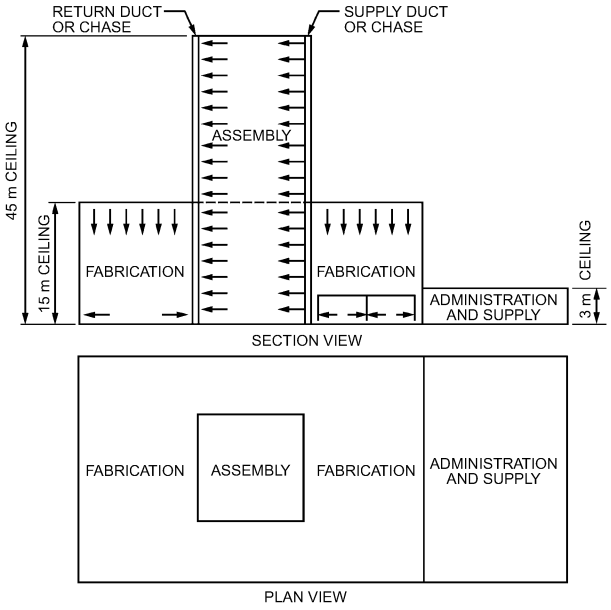


Fig. 16 High-Bay Cleanroom Scheme

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 entry. 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. 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 must be protected by prefilters. HEPA filters for recirculating air should be protected with 85% rated bag or rigid media

filters with as few other prefilters as required. Makeup air should include minimum 85% ASHRAE filters on the fan inlet and minimum 95% 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°C ± 0.3 K, 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 semiconductor crystal-pulling cleanroom design, space temperature is usually required at a constant level of 22°C ± 0.3 K.

Another key parameter is relative humidity. For aerospace and aircraft manufacturing cleanrooms, relative humidity should not exceed 60%; 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, moistures and gaseous generated during welding, sanding, painting, washdown, fuel filling, etc. See Chapters 8 to 12 of the 2013 *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 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.

Heat from fan operation can be significant in ISO Class 4 or cleaner cleanrooms. Designed recirculated airflows with air velocities of 0.45 m/s or air change rates around 500 per hour are commonly specified for these facilities (IEST RP CC012.1). Studies performed by Lawrence Berkeley National Laboratory found that many ISO Class 4 or 5 cleanrooms operated with lower air velocities and lower air change rates than specified by the old or existing recommended practices (IEST RPs CC012.1 and CC012.2), but achieved satisfactory contamination control for their specified cleanliness classes (Xu 2003, 2004).

Latent loads are primarily associated with makeup air dehumidification. A low dry-bulb leaving air temperature, associated with dehumidified 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.

The diversity of manufacturing heat sources (i.e., 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) 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 95% efficient filters (ASHRAE *Standard* 52.2) should be used to avoid high dust loading and reduced HEPA filter life.

In addition, 30% efficient prefilters followed by 85% filters may be used to prolong the life of the 95% 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 exhausts for semiconductor facilities handle acids, 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. 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. 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

ICC's (2009a) *International Building Code*® (IBC) 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.

Chapter 18 in ICC's *International Fire Code*® (IFC, ICC 2009b) addresses specific requirements for process exhaust relating to fire safety and minimum exhaust standards. Chapter 27, 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 semiconductor 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 functions of 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 semiconductor 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. The cleanest cleanroom should have the highest pressure, with decreasing pressure corresponding to decreasing cleanliness. A differential pressure around 12.5 Pa is often used.

For small semiconductor 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 cleaner (ISO Class 7 and cleaner) semiconductor cleanrooms, 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 wafer fabrication area, and for process equipment staging areas before entering the wafer fabrication area. 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 semiconductor 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 areas with different pressurization levels, and for roof, exterior doors and windows, connections between wall and roof, and any building elements between two areas 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. Semiconductor 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 semiconductor wafer 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 0.2 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 cost savings. 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 attached to 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 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).

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 not readily comparable and can be confusing, because their approaches to reporting performance data are different from each other.

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). IEST also has formed a working group to develop recommended practices for FFU testing.

12. SUSTAINABILITY AND ENERGY CONSERVATION

Cleanroom air recirculation systems may account for a significant portion (e.g., 50%) 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 that is supplied, recirculated, and exhausted within a given time. Therefore, 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 in many cleanroom facilities. 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). A life-cycle cost analysis is useful to determine design choices and their total cost of ownership over time, as well as global warming potential 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, 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 much greater than those in conventional office buildings with the same floor area (e.g., by up to 100 times), 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 room 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 room 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. Process exhaust requirements in the typical semiconductor facility can vary from 5 to 50 L/s per square metre. 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 fabrication plant. 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.

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, many cleanrooms have high demand 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 health, 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 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 room 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 areas with 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 rooms appropriately can reduce energy requirements and avoid extreme room 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 17 (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.

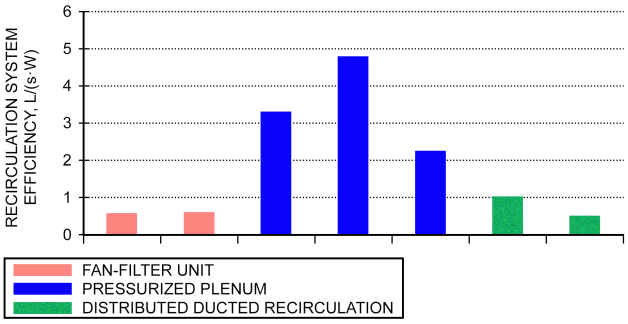


Fig. 17 Energy Efficiency of Air Recirculation Systems
(Source: Xu 2003)

- 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.

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 48 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. ROOM 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, 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 oversee 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 determines 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. Room particulate levels measured at these different cleanroom operating states are important to meet processing room environmental requirements.

For ISO Class 3 and 4 cleanrooms, the owners will most likely prefer not to having commissioning personnel walking around the clean 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 warrantees 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, room 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 58.

A complete cleanroom project usually includes the following stages (see Figure 18): 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.

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.

Figure 15 shows an example of an HVAC fan deck and related electrical and control systems integrated into the building structure level. In a recent semiconductor plan, the mechanical room was used as the housing for makeup air units.

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. ACGIH (2012) and the National Fire Protection Association (NFPA 2012) 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. Therefore one of the duties for the design and commissioning authorities is to understand and successfully address the hazards generated in the property.

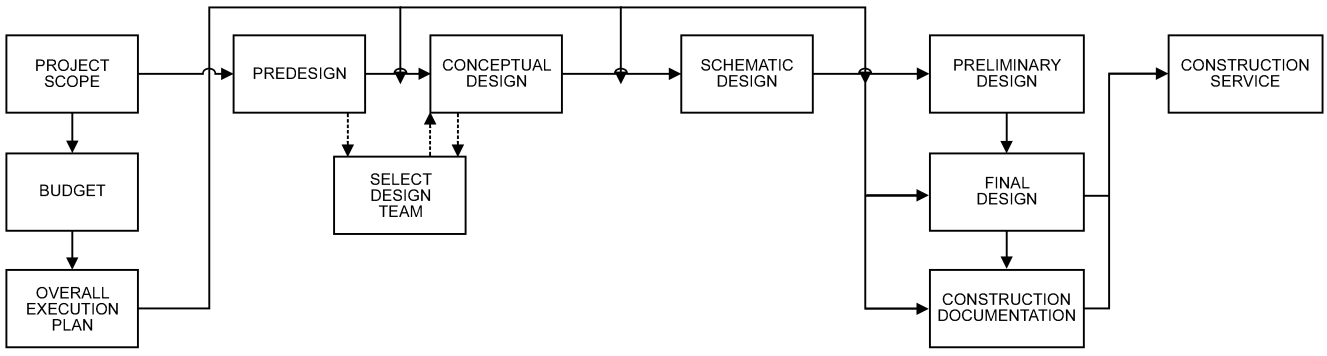


Fig. 18 General Design and Construction Procedure

Different cleanrooms may be composed of many different operating systems, each with distinct equipment or operating processes that presents unique hazards such as 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, etc.

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. This conflict can be resolved by locating the fume hood at the end of an alcove, with air supply registers arranged to support a strong room-level airflow toward the fume hood (0.2 m/s or greater is a common design parameter).

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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