CHAPTER 16

CLEAN SPACES

DESIGN of clean spaces or cleanrooms covers much more than traditional temperature and humidity control. Other factors may include control of particle, microbial, electrostatic discharge (ESD), molecular, and gaseous contamination; airflow pattern control; pressurization; sound and vibration control; industrial engineering aspects; and manufacturing equipment layout. The objective of good cleanroom design is to control these variables while maintaining reasonable installation and operating costs.

TERMINOLOGY

Acceptance criteria. The upper and lower limits of a pharmaceutical critical parameter (in this case, the room environment). If these limits are exceeded, the pharmaceutical product may be considered adulterated.

Air lock. A small room between two rooms of different air pressure, with interlocked doors to prevent loss of pressure in the higher-pressure room.

As-built cleanroom. A cleanroom that is complete, and ready for operation, with all services connected and functional, but without production equipment or personnel in the room.

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 installed and operating, but without personnel in the room.

CFU (colony forming unit). A measure of bacteria present in a pharmaceutical processing room measured by sampling as part of performance qualification.

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

Cleanroom. A specially constructed enclosed area environmentally controlled with respect to particulate, temperature, humidity, air pressure, air pressure flow 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 below specified limits.

Contamination. Any unwanted material, substance, or energy.

Conventional-flow cleanroom. A cleanroom with nonunidirectional or mixed airflow patterns and velocities.

Critical parameter. A room 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.

E.U. European Union guidelines for GMP pharmaceutical manufacturing.

ESD. Electrostatic discharge.

Exfiltration. Air leakage from a room through cracks in doors and pass-throughs or through material transfer openings, etc., because of differences in space pressures.

First air. Air that issues directly from the HEPA filter before it passes over any work location.

FS 209. A former U.S. *Federal Standard* (canceled in November 2001) that specified airborne particulate cleanliness classes in cleanrooms and clean zones. ISO (International Organization for Standardization) *Standard* 14644-1 is a comparable international standard for cleanrooms. Table 1 and Figure 1 compare and summarize the Federal and ISO standard classes. Typical FS 209 classes were as follows:

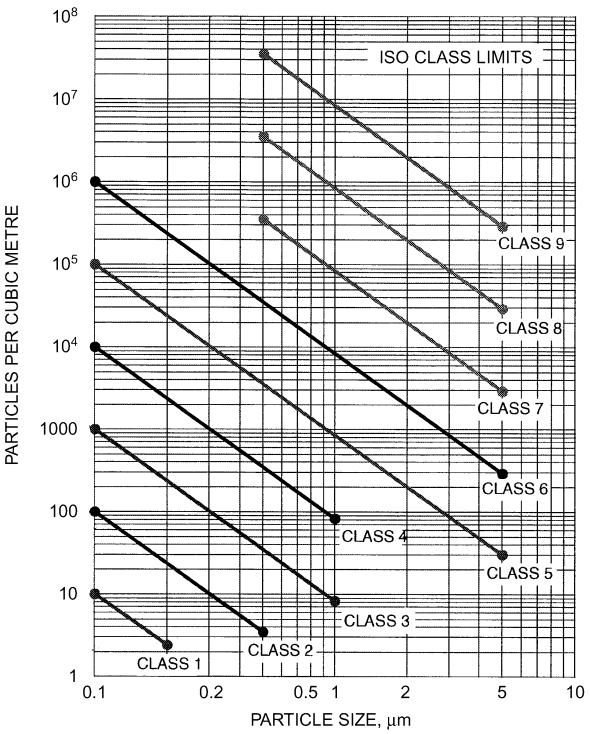

Fig. 1 ISO Air Cleanliness Class Limits

[Adapted with permission from ISO/FDIS *Standard* 14644-1:1999, Cleanrooms and Associated Controlled Environments, Figure A.1, Graphical Representation of ISO-Class Concentration Limits for Selected ISO Classes, copyright International Organization for Standardization (ISO), www.iso.org]

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

- **FS 209 Class 1.** Particle count not to exceed 35 particles per cubic metre of a size 0.5 µm (or appropriate other size, in accordance with Figure 1) and larger. This criterion should be based on sampling of counts.
- **FS 209 Class 10.** Particle count not to exceed 353 particles per cubic metre of a size 0.5 µm and larger, with no particle exceeding 5.0 µm.
- **FS 209 Class 100.** Particle count not to exceed 3530 particles per cubic metre of a size 0.5 µm and larger.
- **FS 209 Class 1,000.** Particle count not to exceed 35 300 particles per cubic metre of a size 0.5 µm and larger.
- **FS 209 Class 10,000.** Particle count not to exceed 353 000 particles per cubic metre of a size 0.5 µm and larger or 2300 particles per cubic metre of a size 5.0 µm and larger.
- **FS 209 Class 100,000.** Particle count not to exceed 3 530 000 particles per cubic metre of a size 0.5 µm and larger or 24 700 particles per cubic metre of a size 5.0 µm and larger.

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

High-efficiency particulate air (HEPA) filter. A filter with an efficiency in excess of 99.97% of 0.3 µm particles.

IEST. Institute of Environmental Sciences and Technology.

Infiltration. Uncontrolled air that exfiltrates from spaces surrounding the cleaner space.

ISPE. International Society for Pharmaceutical Engineering.

ISO. International Organization for Standardization.

ISO 14644-1 Class 3. Particle count not to exceed 35 particles per cubic metre of a size 0.5 µm (or appropriate other size, in accordance with Figure 1) and larger. This criterion should be based on sampling of counts.

ISO 14644-1 Class 4. Particle count not to exceed 352 particles per cubic metre of a size 0.5 µm and larger, with no particle exceeding 5.0 µm.

ISO 14644-1 Class 5. Particle count not to exceed 3520 particles per cubic metre of a size 0.5 µm and larger.

ISO 14644-1 Class 6. Particle count not to exceed 35 200 particles per cubic metre of a size 0.5 µm and larger.

ISO 14644-1 Class 7. Particle count not to exceed 352 000 particles per cubic metre of a size 0.5 µm and larger or 2930 particles per cubic metre of a size 5.0 µm and larger.

ISO 14644-1 Class 8. Particle count not to exceed 3 520 000 particles per cubic metre of a size 0.5 µm and larger or 29 300 particles per cubic metre of a size 5.0 µm and larger.

Laminar flow. See Unidirectional flow.

Leakage. See Exfiltration.

Makeup air. 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 workers and other contamination sources.

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

Nonunidirectional flow workstation. A workstation without uniform airflow patterns and velocities.

Operational cleanroom. A cleanroom in normal operation with all services functioning and with production equipment and personnel present and performing their normal work functions.

Oral product. A pharmaceutical product to be taken by mouth by the patient. They are usually not manufactured in aseptic spaces.

PAO. Polyalphaolefin, a substitute for DOP in the testing of 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 commissioning and operating of a system through established installation, operational, and performance qualification procedures (with approvals).

Qualification protocol. A written description of activities necessary to qualify a pharmaceutical facility, with required approval signatures.

Room classification. Room air quality class (Figure 1, Table 1).

SOP. Standard operating procedure.

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

ULPA (ultra low penetration air) filter. A filter with a minimum of 99.999% efficiency at 0.12 µm particle size.

Unidirectional flow. Formerly called laminar flow. Air flowing at constant and uniform velocity in the same direction.

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

CLEAN SPACES AND CLEANROOM APPLICATIONS

The use of clean space environments in manufacturing, packaging, and research continues to grow as technology advances and the-

Table 1 Comparison of Airborne Particle Concentration Limits from FS 209 and ISO/FDIS 14644-1

FS 209 Class	ISO Class	0.1 µm			0.5 µm			5.0 µm		
		Federal *Standard* 209		ISO	Federal *Standard* 209		ISO	Federal *Standard* 209		ISO
		Particles/ft^3	Particles/m^3	Particles/m^3	Particles/ft^3	Particles/m^3	Particles/m^3	Particles/ft^3	Particles/m^3	Particles/m^3
	1			10						
	2			100			4			
1	3	35	1230	1000	1	35	35			
10	4	345	12 200	10 000	10	353	352			
100	5	3450	122 000	100 000	100	3530	3520			29
1000	6	34 500	1 220 000	1 000 000	1000	35 300	35 200	7	247	293
10,000	7	345 000	1.22×10^7		10 000	353 000	352 000	65	2300	2930
100,000	8	3450 000	1.22×10^8		100 000	3 530 000	3 520 000	700	24700	29 300
	9	3.45×10^7	1.22×10^9				35 200 000			293 000

Note: Values shown are the concentration limits for particles equal to and larger than the sizes shown.

$C_n = N(0.5/D)^{2.2}$ where C_n = concentration limits in particles/ft^3, N = FS 209 class, and D = particle diameter in µm

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

need for cleaner work environments increases. The following major industries use clean spaces for their products:

Pharmaceuticals/Biotechnology. Preparation of pharmaceutical, biological, and medical products requires clean spaces to control viable (living) particles that would produce undesirable bacterial growth and other contaminants.

Microelectronics/Semiconductor. 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 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 14644-1 Class 8 or cleaner.

Miscellaneous Applications. Cleanrooms are also used in aseptic food processing and packaging; manufacture of artificial limbs and joints; automotive paint booths; crystal; laser/optic industries; and advanced materials research.

Hospital operating rooms may be classified as cleanrooms, but their primary function is to limit particular types of contamination rather than the quantity of particles present. Cleanrooms are used in patient isolation and surgery where risks of infection exist. For more information, see Chapter 7, Health Care Facilities.

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, and friction in manufacturing equipment. People in the workspace are a prime source of particles (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 µm tend to settle by gravity. In many manufacturing processes, these airborne particles are viewed as a source of contamination.

Particle Sources in Clean Spaces

In general, particle sources, with respect to the clean space, are grouped into two categories: external and internal.

External Sources. Externally sourced particles enter the clean space from the outside, normally via infiltration through doors, windows, and wall penetrations for pipes, ducts, etc. The largest external source is usually outside makeup air entering through the air conditioning.

In an operating cleanroom, external particle sources normally have little effect on overall cleanroom particle concentration because HEPA filters clean the supply air. However, the particle concentration in clean spaces at rest relates directly to ambient particle concentrations. 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 generate particles in the clean space. Cleanroom personnel can be the largest source of internal particles, generating several thousand to several million particles per minute in a cleanroom. Personnel-generated particles are controlled with new cleanroom garments, proper gowning procedures, and airflow designed to continually shower workers with clean air. As personnel work in the cleanroom, their movements may re-entrain airborne particles from other sources. Other activities, such as writing, may also cause higher particle concentrations.

Particle concentrations in the cleanroom may be used to define cleanroom class, but actual particle deposition on the product is of greater concern. The sciences of aerosols, filter theory, and fluid motions are the primary sources of understanding contamination control. 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.

Fibrous Air Filters

Proper air filtration prevents most externally generated particles from entering the cleanroom. 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 either aluminum, coated string, filter paper, or hot-melt adhesives as pleating separators. Filters may vary from 25 to 300 mm in depth; available media area increases with deeper filters and closer pleat spacing.

Theories and models verified by empirical data indicate that interception and diffusion are the dominant capture mechanisms for HEPA 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 filters, the MPPS is 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.

AIR PATTERN CONTROL

Air turbulence in the clean space is strongly influenced by air supply and return configurations, foot traffic, and process equipment layout. Selecting air pattern configurations is the first step of good cleanroom design. User requirements for cleanliness level, process equipment layout, available space for installation of air pattern control equipment (i.e., air handlers, clean workstations, environmental control components, etc.), and project financial considerations all influence the final air pattern design selection.

Numerous air pattern configurations are used, but they fall into two general categories: unidirectional airflow (often mistakenly called laminar flow) and nonunidirectional airflow (commonly called turbulent).

Nonunidirectional Airflow

Nonunidirectional airflow has either multiple-pass circulating characteristics or nonparallel flow. Variations are based primarily on the location of supply air inlets and outlets and air filter locations. Examples of unidirectional and nonunidirectional airflow of pharmaceutical cleanroom systems are shown in Figures 2 and 3. Airflow is typically supplied to the space through supply diffusers with HEPA filters (Figure 2) or through supply diffusers with HEPA filters in the ductwork or air handler (Figure 3). In a mixed unidirectional and nonunidirectional system, outside 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 cleanliness levels of ISO 14644-1 Classes 6 through 8. Attaining desired cleanliness classes with designs similar to Figures 2 and 3 presupposes that the major space contamination is from makeup air and that contamination is removed in air-handler or ductwork filter housings or through HEPA filter supply devices. When internally generated particles are of primary concern, clean workstations are provided in the clean space.

Unidirectional Airflow

Unidirectional airflow, though not truly laminar, is characterized as air flowing in a single pass in a single direction through a cleanroom with generally parallel streamlines. Ideally, flow streamlines would be uninterrupted; although personnel and equipment in

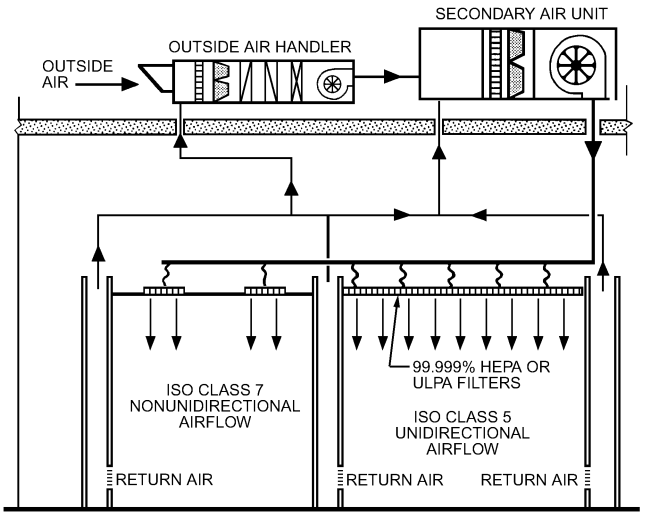

Fig. 2 ISO Class 7 Nonunidirectional Cleanroom with Ducted HEPA Filter Supply Elements and ISO Class 5 Unidirectional Cleanroom with Ducted HEPA or ULPA Filter Ceiling

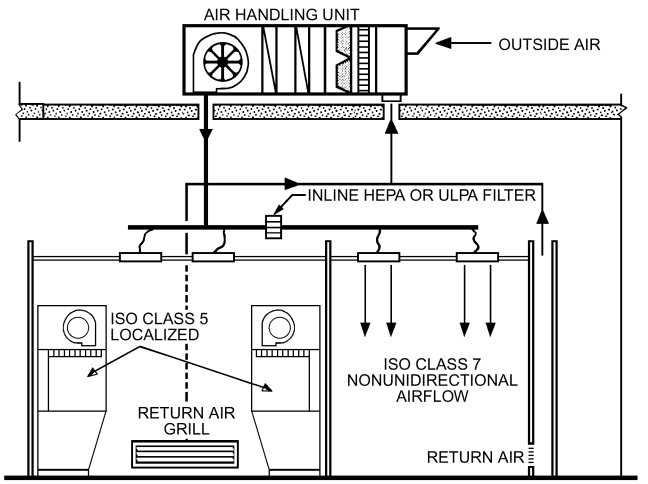

Fig. 3 ISO Class 7 Nonunidirectional Cleanroom with HEPA Filters Located in Supply Duct and ISO Class 5 Local Workstations

the 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 room**, air is typically introduced through the ceiling HEPA or ULPA filters and returned through a raised access floor or at the base of sidewalls. 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. A lower class number requires more HEPA filters; for an ISO Class 5 or better room, the entire ceiling usually requires HEPA filtration. Ideally, a grated or perforated floor serves as the exhaust. This type of floor is inappropriate in pharmaceutical cleanrooms, which typically have solid floors and low-level wall returns.

In a downflow cleanroom, a uniform shower of air bathes the entire room in a downward flow of ultraclean air. Contamination generated in the space will not move laterally against the downward flow of air (it is swept down and out through the floor) or contribute to a buildup of contamination in the room.

Care must be taken in design, selection, and installation to seal a HEPA or ULPA filter ceiling. Properly sealed filters in the ceiling can provide the cleanest air presently available in a workroom.

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 room. The air then exits through the return wall at the opposite end of the room and recirculates. As with the downflow room, this design removes contamination generated in the space and minimizes cross-contamination perpendicular to the airflow. However, a major limitation to this design is that downstream air becomes contaminated. The air leaving the filter wall is the cleanest; it then becomes contaminated by the process as it flows past the first workstation. The process activities can be oriented to have the most critical operations at the clean end of the room, with progressively less critical operations located toward the return air, or dirty end of the room.

ISO 14644-1 does not specify velocity requirements, so the actual velocity is as specified by the owner or the owner's agent. The Institute of Environmental Sciences and Technology (IEST) published recommended air change rates for various cleanliness classes. These recommended ranges should be reviewed by the owner; however, the basis for the ranges is not known. Acceptable cleanliness has been demonstrated at lower air change rates, suggesting that results are depend more on filter efficiency and coverage than on air changes. Careful testing should be performed 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. This airflow remains parallel to below the normal work surface height of 760 to 915 mm. However, flow deteriorates when it encounters obstacles such as process equipment and work benches, or over excessive distances. Personnel movement also degrades flow, 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 avoid turbulent airflow zones and countercurrents. Smoke, neutral-buoyancy helium-filled soap bubbles, and nitrogen vapor fogs can make air streamlines visible within the cleanroom mockup.

Computer-Aided Flow Modeling

Computer 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, and building structural design. Airflow analysis of flow patterns and air streamlines is performed by computational fluid dynamics for laminar and turbulent flow where incompressibility and uniform thermophysical properties are assumed. Design parameters may be modified to determine the effect of airflow on particle transport and flow streamlines, thus avoiding the cost of mockups.

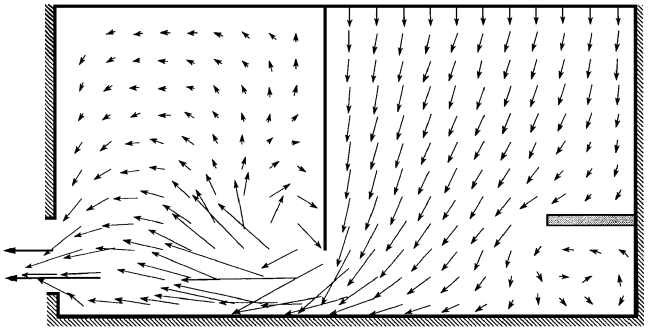

Fig. 4 Cleanroom Airflow Velocity Vectors Generated by Computer Simulation

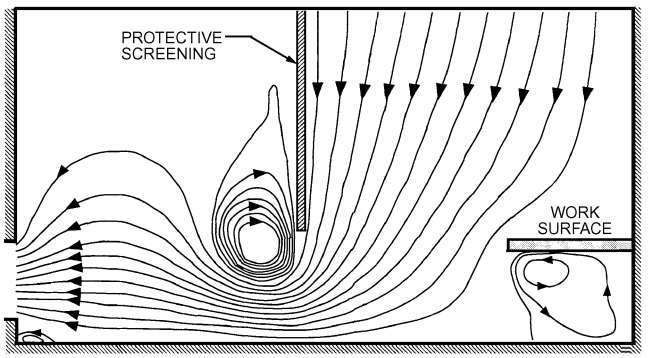

Fig. 5 Computer Modeling of Cleanroom Airflow Streamlines

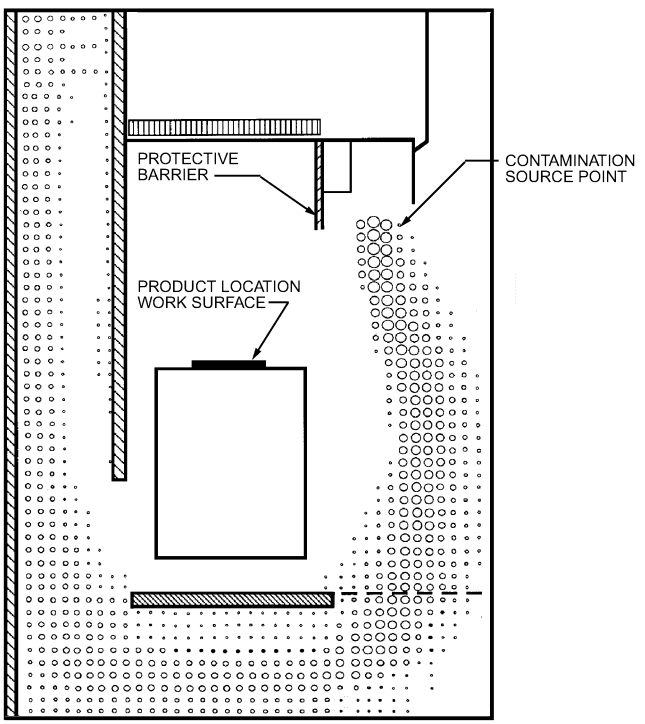

Fig. 6 Computer Simulation of Particle Propagation in a Cleanroom

Major features and benefits associated with most computer flow models are

- Two- or three-dimensional modeling of simple 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, work benches, and people
- Prediction of specific airflow patterns, velocities, and temperature gradients of all or part of a cleanroom
- Reduced cost associated with new cleanroom design verification
- Graphical representation of flow streamlines and velocity vectors to assist in flow analysis (Figures 4 and 5)
- Graphical representation of simulated particle trajectories and propagation (Figure 6)

Research has shown good correlation between flow modeling by computer and that 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.

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, because it 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 developed and published by the Institute of Environmental Sciences and Technology (IEST), the American Society for Testing and Materials (ASTM), and others.

Three basic test modes for cleanrooms are used to evaluate a facility: (1) as built, (2) at rest, and (3) operational. A cleanroom cannot be fully evaluated until it has performed under full occupancy, and the process to be performed in it is operational. Thus, the techniques for conducting initial performance tests and operational monitoring must be similar.

Sources of contamination are both external and internal for both unidirectional and nonunidirectional flow cleanrooms. The primary air loop is the major source of external contamination. Discrete particle counters using laser or light-scattering principles may be used to detect 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 sample of air has been drawn.

HEPA filters in unidirectional flow and ISO 14644-1 Class 5 ceilings should be tested for pinhole leaks at the filter media, the sealant between the media and the filter frame, the filter frame gasket, and the filter bank supporting frames. The area between the wall or ceiling and the frame should also be tested. A pinhole leak at the filter bank 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. Which tests are applicable to each specific cleanroom project must be determined.

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. It is

important to involve designers, operators, commissioning staff, quality control, maintenance, constructors, 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 for temperature, humidity, room pressure, and other control requirements.

In the United States, regulatory requirements and specification documents such as CFR 210 and 211, ISPE Guides, and National Fire Protection Association (NFPA) standards describe GMP. The goal of GMP is to achieve a proper and repeatable method of producing sterile products free from microbial and particle contaminants.

In the United States, the one factor that makes pharmaceutical processing suites most different from other clean spaces (e.g., for electronic and aerospace) is the requirement to pass U.S. Food and Drug Administration (FDA) inspection for product licensing. It is important to include the FDA's regulatory arms, the Center for Biologics Evaluation and Research (CBER) or the Center for Drug Evaluation and Research (CDER) for design early in the concept design process.

In addition, early in the design process, a qualification plan (QP) must be considered. 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 for process validation. lQ, OQ, and PQ protocols, in part, set the acceptance criteria and control limits for critical parameters such as temperature, humidity, room pressurization, air change rates, and operating particle counts (or air classifications). These protocols must receive defined approvals in compliance with the owner's guidelines. The qualification plan must also address SOPs, preventive maintenance (PM), and operator and maintenance personnel training.

Biomanufacturing and pharmaceutical aseptic clean spaces are typically arranged in suites, with clearly defined operations in each suite. For example, common convention positions an aseptic core (ISO 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 7).

In aseptic processing facilities, the highest-quality area is intentionally placed within the lower-quality areas and separated by room air classification and air pressure differences via air locks. A commonly used pressure difference is 12 to 15 Pa between air classifications, with the higher-quality room 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 product containment is an issue (e.g., pathogens or toxic materials), the suite requires a lower pressure than adjacent rooms, but may still require a higher air quality. In this case, the air lock may be designed to maintain one pressure level higher than the adjacent room, and also higher than the contained suite (Figure 8). Biological containment requirements are addressed by the U.S. National Institutes of Health, which groups potentially hazardous organisms in biosafety levels BL-1 to BL-4.

Design Concerns for Pharmaceutical Cleanrooms

The owner and designer must define the maximum range of variable value (**acceptance criterion**) for each critical parameter. In that range, the product's safety, identity, strength, purity, and quality will not be affected. The owner should define **action alarm** points at the limits of acceptance criteria, such that product exposed to conditions outside these action limits may have been adulterated. The designer should select tighter (but achievable) target design values for critical parameters (in the range of acceptance criteria) and for noncritical parameters.

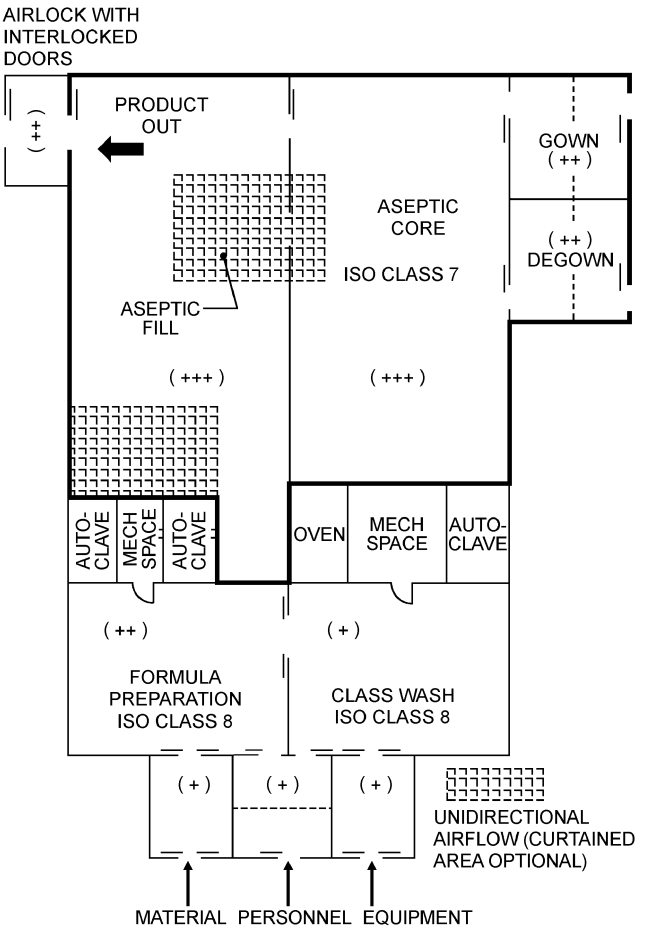

Fig. 7 Typical Aseptic Suite

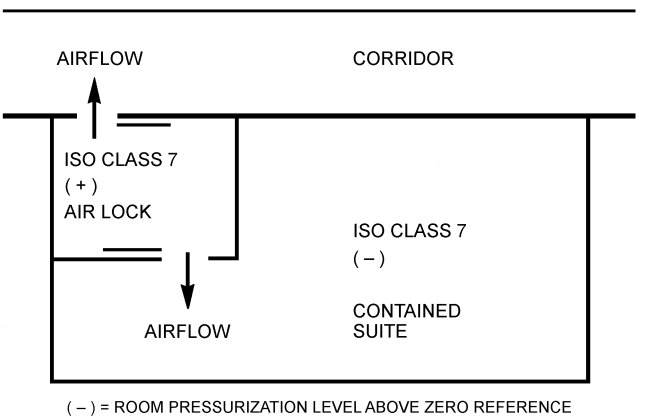

Fig. 8 Contained Suite Arrangement

Facilities manufacturing penicillin or similar antibiotics (such as cephalosporins) must be physically isolated from other manufacturing areas and served by their own HVAC system. Certain other products may require similar separation.

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 the 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 will be a factor in design. Personnel perspiring in their protective overgarments can cause particulate and microbial counts to increase, so lower temperatures and tighter temperature control may be necessary.

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. Certain products are hygroscopic and require lower humidity than a condensing coil can provide; desiccant dehumidification should be considered. 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 the 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 room air might contact the product.

Although airborne particles and viable organisms may be minimized by dilution (high air changes) and by supplying high-quality HVAC air, the most effective control is to minimize release of these contaminants within the room. Personnel and machinery are the most common sources of contamination, and can be isolated from the product by gowning, masks, and isolation barriers. A careful study of how each room operates should reveal the most probable sources of contaminants and help the HVAC designer determine dilution air quantities and locate air supply outlets and returns. 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.

Airborne particle and microbe levels in aseptic processing areas are limited by government regulations, with lower limits for more critical rooms. European and FDA particle limits are for the room in operation, but may also define limits for the room at rest.

Facilities meeting U.S. GMPs must meet particle levels with manufacturing under way (an exception is aseptic powder processing, where airborne particulate levels at powder filling heads will exceed limits. These rooms are tested with production running but no product present). GMPs suggest a minimum of 20 air changes per hour (ACH) for rooms with an air particulate classification, with exposed sterile product under a unidirectional flow hood or inside an ISO 14644-1 Class 5 barrier enclosure. U.S. GMPs currently require only two classes: ISO 14644-1 Class 5 for sterile product exposure, and ISO 14644-1 Class 8 for adjoining spaces. However, common practice places exposed products in an ISO 14644-1 Class 5 unidirectional flow zone inside an ISO 14644-1 Class 7 room. Where isolation barriers and containment or spot exhaust are not practical, airborne contaminants may be minimized by increased room air changes. There are no minimum air change requirements for facilities manufacturing nonaseptic products.

Once product is in containers, the need for particulate control and minimal 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 room and processing step.

Return openings for room HVAC should be low on the walls, to promote a downward flow of air from supply to return, sweeping contaminants to the floor and away from the product. In larger rooms, internal return air columns may be necessary. Perforated floors are discouraged because of difficulty cleaning them.

Aseptic facilities usually require pinhole-scanned (integrity-tested) HEPA filters (not ULPA) on supply air. Many operations install HEPA filters in the supply air to nonaseptic production facilities to minimize cross-contamination from other manufacturing areas served by the HVAC. 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 room in which it is exposed, to 15 Pa above the next lower cleanliness room classification. To keep pressure differential from dropping to zero when a door is opened, air locks are often used between rooms of different air pressure, especially at the entrance to the aseptic production room itself. Room pressure is a function of airflow resistance through cracks, openings, and permeable surfaces in the room shell. Consider all potential openings, slots, and door leakage that can affect the amount of air needed to pressurize the space. Because net room airflow and room pressure are closely related, outdoor or makeup air requirements are often dictated by room 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 basically 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 exposure sites (the 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 room particles into the hood's zone of protection. Curtains should extend below the product exposure site and be designed to prevent accidental disruption of airflow patterns by personnel. Many production facilities prefer rigid curtains to facilitate cleaning and sanitization.

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

Barrier Technology

Cleanrooms designed to meet ISO 14644-1 Class 5 or better require considerable equipment, space, and maintenance. Operating this equipment is expensive. Furthermore, cleanrooms typically need gowned operators inside to manipulate the product and adjust the machinery. Because the operator generates much of the contamination, it would be better to place the operator outside the controlled environment; the volume of the controlled space can then be reduced, leading to substantially reduced capital and operating cost. Barrier technology or isolators are thus becoming increasingly popular.

Each isolator is designed to fit a specific application and is customized for its tasks. Applications vary widely based on product, process equipment, and throughput volume. Sterile barriers 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.

"Mouse holes" allow passage of vials in and out of the unit. Special transfer ports are used for stoppers and tools. Important design concerns include accessibility, ergonomics, interference with mating equipment, decontamination or sterilization 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 hydrogen peroxide is to be used as a surface sterilant, care must be taken to ensure good circu-

lation and adequate concentration inside the barrier, as well as removal of residual vapor in the required time frame.

Other barrier applications offer operator protection from potent compounds while maintaining a sterile internal environment. These tend to be total containment isolators with totally contained product transfer ports. All internal surfaces are sealed from the external environment or 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.

Nonsterile powder control may incorporate more passive barrier designs such as a downflow sample weighing hood. 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 back of the cubicle capture the dust. An arrangement of roughing and final filters permits the air to return to the air handlers and back to the work zone through the ceiling. 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. Because isolators and containment chambers are still relatively new to the pharmaceutical industry, installations for sterile product must be in a controlled ambient room condition of ISO 14644-1 Class 8.

Maintainability

A facility that considers maintainability (e.g., accessibility, frequency of maintenance, spare parts) 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 is required during maintenance activities (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 if and how HVAC equipment may be sanitized using the owner's procedures. Determine whether ductwork must be internally cleaned, and how.

Controls, Monitors, and Alarms

Room pressure may be maintained by passive (statically balanced) HVAC if there are few airflow variables. For example, the HVAC system for a few pressurized rooms may be statically balanced if there is a method of maintaining supply airflow volume to compensate for filter loading to ensure minimum room air changes. More complex designs may require active room pressure control, usually by controlling exhaust or return air volume in a control loop that senses and controls room pressure, not airflow differentials. Pressure controls should not overreact to doors opening and closing, because it is virtually impossible to pressurize a room to 12 Pa with a door standing open. Some time delay is advisable in pressure controls and pressure alarms to allow time for doors to close. Length of the delay can be determined by observing actual processes, but should be as short as possible.

If room humidity must be maintained to tolerances tighter than the broad range that normal comfort cooling can maintain, active relative humidity control should be considered. 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 verify this 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 because fans must overcome the pressure drop of additional air filtration. The amount of noise generated must be reduced instead 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 can reduce the noise. HVAC noise may not be an issue if production equipment is considerably noisier.

Nonaseptic Products

Nonaseptic pharmaceutical facilities (such as 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 room 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. Room 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.

START-UP AND QUALIFICATION OF PHARMACEUTICAL CLEANROOMS

Qualification of HVAC for Aseptic Pharmaceutical Manufacturing

Qualification of the pharmaceutical cleanroom HVAC is part of the overall commissioning of the building and its equipment, except that documentation is more rigorous. The qualification covers equipment affecting critical parameters and their control. 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 requirements of the approving agency are to (1) state what procedures will be followed and verify that it was done, and (2) show that product is protected and room 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 will do; (2) maps of room pressures, airflow diagrams, and cleanliness zones served by each air handler; (3) a list of critical components to be qualified, including the computer controlling the HVAC; (4) a list of owner's procedures that must be followed for qualification of equipment and systems that affect critical variables; (5) a list of qualification procedures (IQ/OQ/PQ protocols) written especially for the project; and (6) a list of needed commissioning equipment.

The approval procedure should also be defined in the QP. It is important to measure and document the critical variables of a system (such as room pressure), but it is also important to document performance of components that affect that critical variables (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 satisfy critical variables.

It is important to determine what the critical components are (including 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 engi-

neer, owner, and a qualified protocol writer. If performance data are in the qualification records, replacement parts of different manufacture can be installed without major change control approvals, as long as they meet performance requirements. Owner approvals for the qualification plan should be obtained while proceeding with 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 records 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, 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 (NlST) 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 installation is correct. Equipment and instruments should be tagged and wiring labeled. Commissioning documentation must attest to the completion of these activities and include as-built drawings and installation-operation-maintenance (lOM) manuals from contractors and vendors.

The **operational qualification (OQ)** protocol documents startup, including critical 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 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, which might signify abnormal operation, may be considered. Although product would not be adulterated at these parameter values, staff could assess an alarm and react to it before further deviations from normal operation occurred.

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

Files should include an updated description of the HVAC, describing how it operates, schematics, airflow diagrams, and room 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 have been 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, with rough drafts of new maintenance procedures (final drafts should reflect commissioning experience).

Records should attest to the completion of these activities, including final as-built and air and water balance reports.

Performance qualification (PQ) is proof that the entire HVAC performs as intended under actual production conditions. PQ is the beginning of the ongoing verification that the system meets acceptance criteria of the product (often called validation). 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 the 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 should be kept and problems 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 viable (microbial) and nonviable particles in the room.

SEMICONDUCTOR CLEANROOMS

Cleanroom Advances with Modern 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. 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 one particle 0.1 μm and larger per cubic foot 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 moleculate contamination control. Product contamination control has also extended to include 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 within the tunnel or installed through the wall where a lower cleanliness level (nominally ISO 14644-1 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, the flow becomes too turbulent and tends to break toward the walls before it leaves the work plane. Figure 9 shows 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

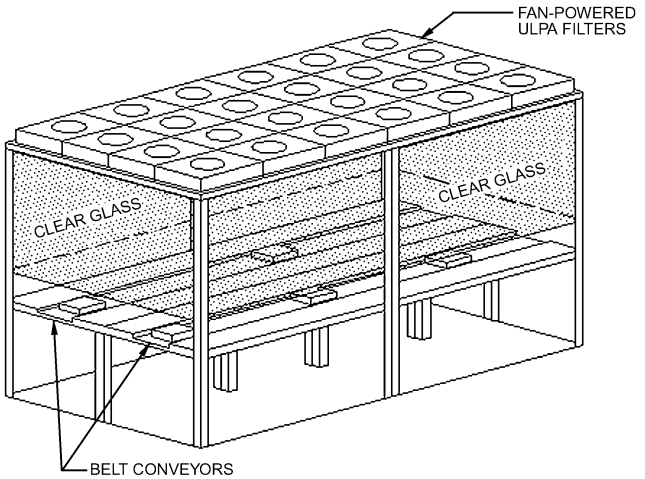

Fig. 9 Elements of a Clean Tunnel

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 10). Either one large plenum with multiple supply fans or small adjacent plenums are acceptable. Small plenums provide the ability to shut 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 room sizes has also become increasingly significant. Major semiconductor facilities, with total manufacturing 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 the tunnel design or open bay. 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.

Recently, building structure areas have been 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 11 shows a building truss level arranged as a fan deck and air plenum. In the future, architects; structural, process, and mechanical engineers; semiconductor facilities personnel; and construction industries must continue to work as an integrated team 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 (Class 100,000), and the preliminary equipment setup and inspection area may be ISO Class 7 (Class 10,000). The final stage, where equipment is cleaned and final installation preparations are made before the fabrication entrance, is ISO Class 6 (Class 1000). In some cases, these staged cleanrooms must have adequate clear heights to allow forklift access for equipment subassemblies.

Airflow in Semiconductor Cleanrooms

Current semiconductor industry cleanrooms 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 14644-1 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-powered filter 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. Higher maintenance costs may also be incurred because of the balance method involved with ducted HVAC.

Individual fan-powered filter modules use fractional horsepower fans (usually forward-curved fans) that provide airflow through one filter assembly. This method allows airflow to be varied throughout the cleanroom and requires less space for mechanical components. The disadvantages of this method are the large number of fans involved, low fan and motor efficiencies because of the small sizes, potentially higher fan noises, and higher operation and maintenance costs.

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. As previously stated, these returns are most applicable for ISO Class 5 to 8 (Class 100 to 100,000) cleanrooms.

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

Cleanroom Air Velocity and Air Changes

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

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

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

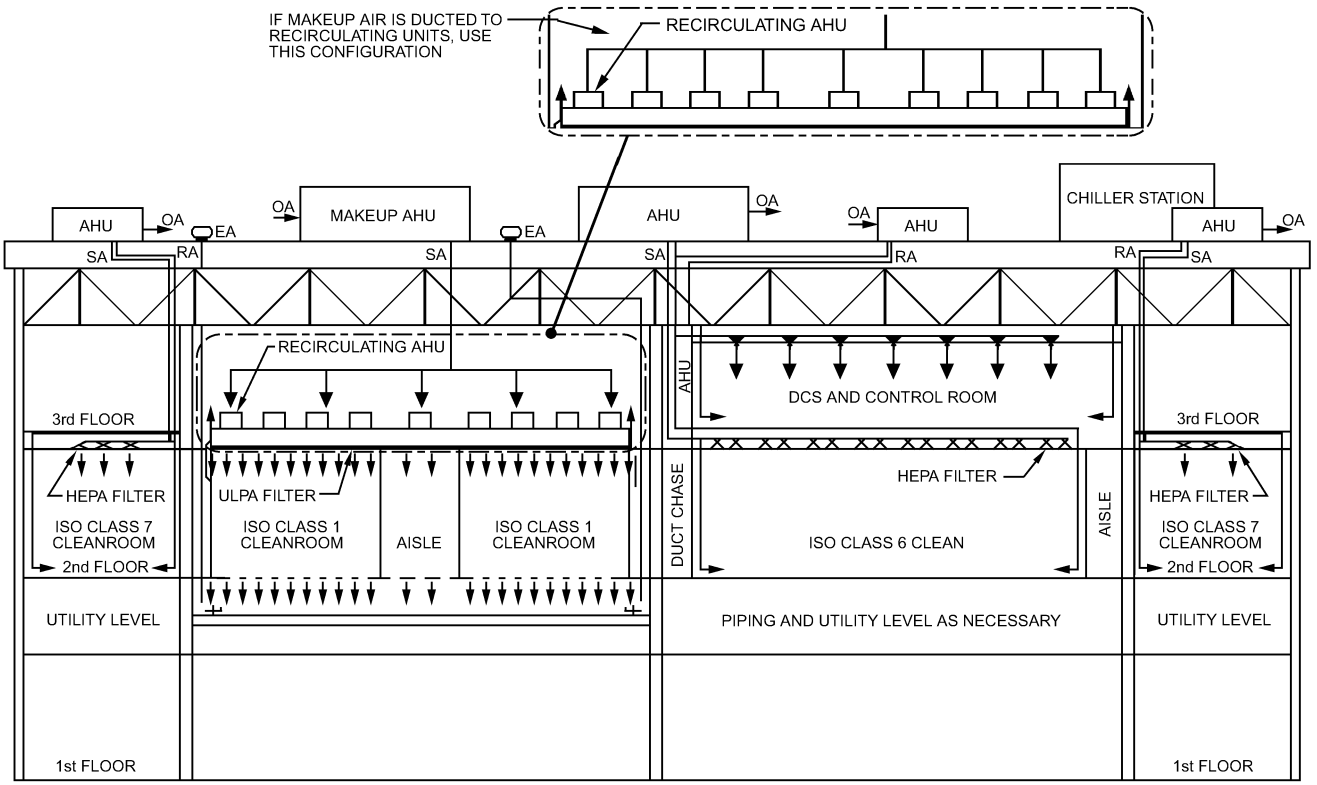

Fig. 10 Typical Semiconductor Manufacturing Plant Section View

Table 2 Vertical Airflow Velocities and Air Change Rates Versus Cleanroom Classes

Class ISO 209	Average Room Velocity, m/s	Air Changes per Hour					
		2.5 m Ceiling	3 m Ceiling	6 m Ceiling	9 m Ceiling	12 m Ceiling	18 m Ceiling
2	0.43 to 0.51	638 to 750	510 to 500	255 to 300	170 to 200	128 to 150	85 to 100
3 Class 1	0.36 to 0.43	525 to 838	420 to 510	210 to 244	140 to 170	105 to 128	70 to 85
4 Class 10	0.30 to 0.36	450 to 525	360 to 420	180 to 210	120 to 140	90 to 105	60 to 79
5 Class 100	0.23 to 0.28	338 to 413	270 to 330	135 to 165	90 to 110	68 to 83	45 to 55
6 Class 1000	0.13 to 0.18	166 to 263	150 to 210	75 to 105	50 to 70	28 to 53	25 to 35
7 Class 10,000	0.04 to 0.09	60 to 120	50 to100	24 to 48	15 to 30	12 to 24	8 to 16
8 Class 100,000	0.02 to 0.04	30 to 45	25 to 35	12 to 16	8 to 12	8 to 9	4 to 6
9 Class 1,000,000	0.010 to 0.015	15 to 23	12 to 18	6 to 9	4 to 6	3 to 5	2 to 3

or

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

$$\text{ACH} = \frac{3600v}{H} \quad (3)$$

where

L = room length, m
W = room width, m
H = room height, m
v = room air velocity, m/s
ACH = air changes per hour

Equation (3) shows that, under a certain velocity, the room ACH varies with the inverse ratio of room height H. Table 2 lists room air velocities versus cleanliness class and the correlation between room air velocity and ACH.

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 buildup. However, the emitter tip material must be carefully selected to prevent depositing particles on the product.

HIGH-BAY CLEANROOMS

High-bay cleanrooms have ceiling heights between 12 and 35 m. They are used primarily in the aerospace industry for producing and testing missiles, launch vehicles, rocket engines, communication and observation satellites, and jet aircraft assembly, painting, and cleaning operations. Crystal-pulling areas in semiconductor manufacturing facilities labs also use high-bay designs.

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.

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

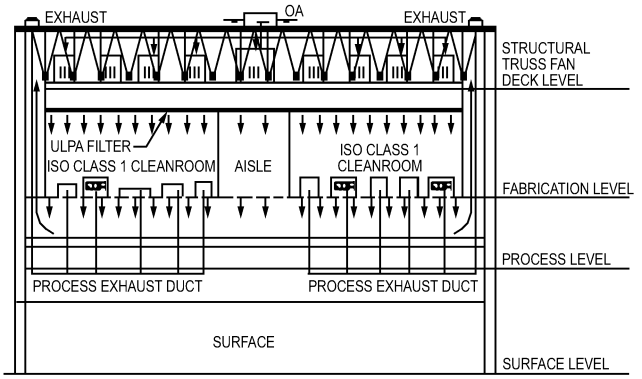

Fig. 11 Building Truss Level is Arranged as Fan Deck and Air Plenum

the returns. The supply air terminals may be HEPA-filter or high-volume air diffusers. Downflow rooms allow space flexibility because more than one device may be worked on in the room 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 the downward-flowing supply air.

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

The principal disadvantage of horizontal-flow high-bay rooms 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 (see Figure 12).

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.

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 room 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. A HEPA filter bank remote from the room 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.

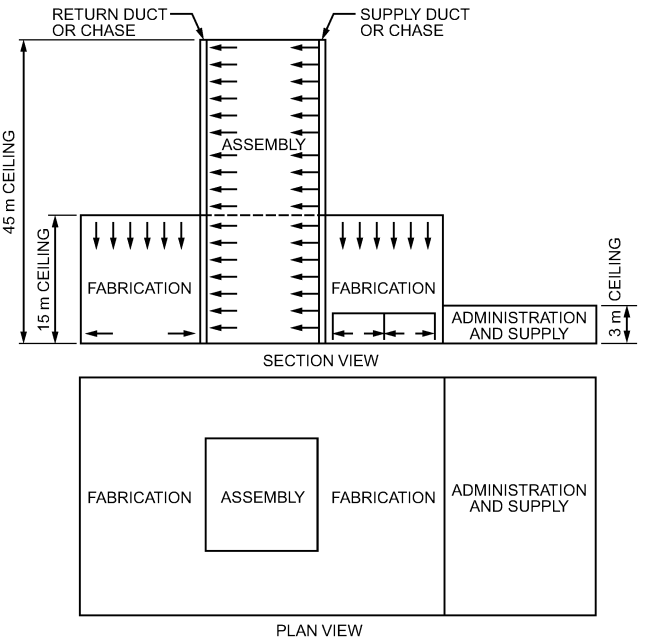

Fig. 12 High-Bay Cleanroom Scheme

Prefilter Selection

In any high-bay cleanroom class, air will pass through a final HEPA filter before entering the room; 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 no other prefilters present than required. Makeup air should include minimum 85% ASHRAE filters on the fan inlet and minimum 95% dispersed oil particulate (DOP) filters on the fan discharge.

Design Criteria and Indoor Air Quality

The indoor design temperature range for aerospace and aircraft manufacturing cleanrooms is 23°C ± 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 room temperature requirements. In semiconductor crystal-pulling cleanroom design, room 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, wash-down, fuel filling, etc. See Chapters 7, 8, 9, 12, and 13 of the *ASHRAE Handbook—Fundamentals* for additional information.

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 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 the process exhaust.

Fan energy is a very large heat source in ISO 14644-1 Class 4 or better cleanrooms. Recirculated room airflow rates of 0.45 m/s or less (500+ ACH) are typical for these facilities.

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, the equipment heat loss to support chases versus to the production area will affect 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. The flow requirements of makeup air are dictated by the amount required to replace process exhaust and by air volumes for pressurization. Makeup air volumes can be much greater than the total process exhaust volume to provide adequate pressurization and safe ventilation.

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* 52.1) 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 present in outside air. These contaminants include salts and pollutants from industries and automobiles. 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 acid, solvent, toxic, 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 volumes 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 *Industrial Ventilation: A Manual of Recommended Practices* (ACGIH 1998) to determine limits.

Fire Safety for Exhaust

The *Uniform Building Code* (UBC) designates semiconductor fabrication facilities as Group H, Division 6 occupancies. The H-6 occupancy class should be reviewed even if the local jurisdiction does not use the UBC because it is currently the only major code in the United States specially 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.

Article 51 in the *Uniform Fire Code* (UFC) addresses specific requirements for process exhaust relating to fire safety and minimum exhaust standards. Article 80, 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.

Temperature and Humidity

Precise 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 room 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 (1) cooling coils in the primary air stream, or (2) 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, lower temperature set points are recommended for comfort. Process temperature set points may be higher as long as product tolerances are maintained.

Semiconductor humidity levels vary from 30 to 50% rh. Humidity control and precision are functions of process requirements, prevention of condensation on cold surfaces within 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 are used. Chemical dehumidification is rarely used in semiconductor facilities because of the high maintenance cost and the potential for chemical contamination in the cleanroom. Although an operating cleanroom generally does not require reheat, systems are typically designed to provide heat to the space when new cleanrooms are being built and no production equipment has been installed.

Makeup air is humidified by steam humidifiers or atomizing equipment. Steam humidifiers are most commonly used. Care should be taken to avoid releasing water treatment chemicals. 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.

Pressurization

Pressurizing of semiconductor cleanrooms is another method of contamination control, providing resistance to infiltration of external sources of contaminants. Outside particulate contaminants enter the cleanroom by infiltration through doors, cracks, pass-throughs, and other penetrations for pipes, ducts, etc. Positive pressure in the cleanroom (compared to any less clean space) ensures that air flows from the cleanest space to the less clean space. Positive differential pressure in the cleanroom inhibits the entrance of unfiltered external particulate contamination.

A differential pressure of 15 Pa is a widely used standard. The cleanest cleanroom should have the highest pressure, with decreasing pressure corresponding to decreasing cleanliness.

Pressure in the cleanroom is principally established by the balance between process exhaust, leakage, makeup air volumes, and supply and return air volumes. Process equipment vendors, codes, and industrial hygienists dictate process exhaust requirements, which cannot be changed without safety risks. Cleanroom supply air volumes are set by contamination control specialists. Makeup air and return air volumes are the primary means for pressure control. Pressure differences should be kept as low as possible while still creating the proper flow direction. Large pressure differences can create eddy currents at wall openings and cause vibration problems.

Static or active control methods are normally used in cleanroom pressure control. One method is used in lieu of the other based on pressure control tolerance. Pressure control precision is typically ±2 to 8 Pa; the owner's contamination control specialist specifies the degree of precision required. Many semiconductor processes affected by cleanroom pressure (e.g., glass deposition with saline gas) require process chamber pressure precision of ±600 mPa.

Static pressure control methods are suited for unchanging cleanroom environments, where the primary pressure control parameters (process exhaust and supply air volumes) either do not change or change slowly over weeks or months at a time. Static controls provide initial room pressure, and monthly or quarterly maintenance adjusts makeup and return volumes if the pressure level has changed. Static systems may include differential pressure gages for visual monitoring by maintenance personnel.

Active systems provide closed-loop control where pressure control is critical. Standard controls normally cannot maintain differential pressure when doors without an air lock are opened. The need for active systems should be evaluated, however.

Air locks may be used to segregate pressures in the factory, but are typically 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. In the main portion of the factory, air locks are rarely used because they restrict personnel access, evacuation routes, and traffic control.

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. 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, or space should be provided for future installations.

Because cleanroom space relative humidity must be held to close tolerances and humidity excursions cannot be tolerated, the latent load removal 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 nonwork times. Mechanical and electrical redundancy is required if loss of the 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.

ENERGY CONSERVATION IN CLEANROOMS

The major operating costs associated with a cleanroom include conditioning makeup air, air movement in the cleanroom, and process exhaust. Environmental control, contamination control, and process equipment electrical loads can be as much as 3 kW/m^2. Besides process equipment electrical loads, most energy is used for cooling, air movement, and process liquid transport (i.e., deionized water and process cooling water pumping). A life-cycle cost analysis should be performed to determine design choices and their total cost of ownership over time.

Energy Metrics. 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 per kilowatt input, it is possible to compare system efficiency for different schemes. This is a good metric for air systems because it compares 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.

These data highlights the wide variation in performance and the need to establish goals for system performance.

Similarly, metrics for chilled-water system performance in terms of kilowatts per kilowatts 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 flow rates in typical semiconductor facilities are 90 to 100 times greater than in conventional HVAC, and very high in other cleanrooms, the fan system should be closely examined for ways to conserve energy. Static pressures and total airflow requirements should be designed to reduce operating costs.

The fan energy required to move recirculation air may be decreased by reducing the air volume and/or static pressure. 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.

Air volumes may be lowered by decreasing recirculation airflow. This could allow decreasing HEPA or ULPA filter coverage or reducing cleanroom average air velocity. With reduced air volumes, each square metre of reduced HEPA coverage saves 250 to 500 W/m^2 in fan energy and in cooling load. Reducing room average velocity from 0.45 to 0.40 m/s saves 50 W/m^2 in fan energy and in cooling energy. If the amount of air supplied to the cleanroom cannot be lowered, reductions in static pressure can produce significant 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. Air volume 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 energy may be saved by installing high-efficiency motors on fans instead of standard-efficiency motors. Fan selection also affects energy cost. 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 power requirements as well. Different options should be investigated.

Makeup and Exhaust Energy. Process exhaust requirements in the typical semiconductor facility vary from 5 to 50 L/s per square metre. Makeup air requirements vary correspondingly, with an added amount for leakage and pressurization. The energy required to supply the conditioned makeup air can be quite large. 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 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, the costs of conditioning the makeup air 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.

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, noise and vibration criteria should be established. Chapter 47 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, vaneaxial fans may be considered. These fans generate less noise in the 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.

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. Typical details that may vary with the room class include the following:

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.** Plaster covered with plastic, epoxy, or polyester coating or with plastic-finished clipped acoustical tiles (no tiles in pharmaceutical cleanrooms) when entire ceiling is not fully HEPA- or ULPA-filtered
- **Lights.** Teardrop-shaped single lamp fixtures mounted between filters, or flush-mounted and sealed
- **Service penetrations.** All penetrations for pipes, ducts, conduit runs, etc., fully sealed or gasketed
- **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

Personnel and Garments

- Hands and face cleaned before entering area
- Lotions and soap containing 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

- Equipment and materials are cleaned before entry.
- Nonshedding paper and ballpoint pens are used. Pencils and erasers are not permitted.
- Work parts are handled 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, and soldering operations are shielded and exhausted.
- Nonshedding containers and pallets are used for transfer and storage of materials.

Entries

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

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IEST-RP-CC005 Gloves and finger cots used in cleanrooms and other controlled environments
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IEST-RP-CC011.2 A glossary of terms and definitions relating to contamination control
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IEST-RP-CC014 Calibrating particle counters
IEST-RP-CC015 Cleanroom production and support equipment
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