ASHRAE DESIGN GUIDE for CLEANROOMS

Fundamentals, Systems, and Performance

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Preface

Cleanrooms and associated technologies are commonly used in modern microelectronics, semiconductor, pharmaceutical, biotechnology, nanotechnology, medical device, life science, aerospace, optics, automotive, health care, biosafety laboratory, and food processing industries, virtually covering all the major high-tech sectors where indoor airborne or surface-borne contaminants can adversely affect the manufacturing process or scientific research. Such contaminants include particles, viable microbes, chemical vapors, and unwanted gases. Cleanrooms demand much lower levels of contaminants than commercial spaces, and though noncontamination cannot be completely achieved, cleanrooms *can* be designed, operated, and controlled with ultralow concentrations of these contaminants to meet specific process requirements for indoor air cleanliness.

For the cleanroom design industry worldwide, currently ISO 14644-4 is a condensed standard that covers basic cleanroom design requirements, Institute of Environmental Sciences and Technology's Recommended Practice 12.3 provides cleanroom design considerations, and Chapter 18 of *ASHRAE Handbook—HVAC Applications* provides a brief discussion of cleanroom design elements. Of course, there are also a few reference books on the market drafted from the academic sector. However, there is an urgent need from the global cleanroom design industry for a more practical, comprehensive, and technical book that covers not only the HVAC systems of cleanrooms but also cleanroom theories, fundamentals, performance, control, testing, and industrial applications.

ASHRAE Technical Committee (TC) 9.11 is concerned with HVAC&R systems for cleanrooms and clean spaces, including process, product, and facility air conditioning and related process ventilation for research and development, manufacturing, assembly, test, and clean medical areas. This includes cleanrooms associated with electronic, microelectronic, pharmaceutical, and aerospace facilities as well as operating rooms. In conjunction with ASHRAE's overall goal of supporting the design of energy-efficient HVAC&R systems, TC 9.11 members are committed to raising such awareness in cleanroom design and operation and to developing proactive solutions to support ASHRAE's position.

In 2011, TC 9.11 formed a Design Guide subcommittee, led by Wei Sun as the principal author of the book, who was also the TC 9.11 chair from 2011 to 2014. The subcommittee took lead of a multiyear effort to develop a comprehensive design guide for cleanrooms. The Basic Requirements document was initiated and drafted; it defined the book's structure and style, each chapter's content subheadings and coverage, and the approximate word count for each chapter to have a balanced structure. The intention was to provide a technical reference book to assist cleanroom design engineers, university students in cleanroom study, cleanroom facility managers in various industries, and profes-

sionals in cleanroom control, automation, performance testing, certification, qualification, and commissioning.

After the public announcement to develop the book, more than 50 highly recognized experts agreed or volunteered to participate, including university professors, cleanroom design engineers, researchers, facilities and operation managers, and testing and certification engineers. Over 30 individuals were selected as coauthors, and another 20-plus people served as contributors and reviewers. Since 2012, this book has become a truly multidisciplinary effort that included the top experts not only from the United States but also globally.

This design guide was developed in the technical book category—it is neither an encyclopedia nor a high-level normative standard. It uses easily understood language and simple descriptions to explain complex cleanroom information to readers who may only have basic knowledge about cleanrooms or are new to the industry. It does not use the rigid language and structure of a code, and it is not like conference proceedings that have various structures and are less consistent in style. This book was developed instead to have balanced technical perspectives from many experts with various expertise and experiences and from different market sectors. It was intended to provide mature technologies and techniques with the latest information. Our goal was to make this single-volume guide one of the most-used technical books in cleanroom design today.

This design guide is divided into four parts, each containing multiple chapters: Cleanroom Fundamentals; Cleanroom Design and Environmental Control Systems; Cleanroom Testing, Certification, Commissioning, and Qualification; and Cleanroom Design In Select Industries. It is the work of many authors over many years; the editors have attempted to blend the various writing styles to meet ASHRAE publication guidelines and improve the overall readability of the book. It is the hope of the editors that *ASHRAE Design Guide for Cleanrooms* will be an indispensable resource to designers, builders, owners, and operators of cleanrooms and advance HVAC engineering practices, providing the guidance needed for designers of successful cleanroom projects.

This first edition took countless hours; a great deal of energy from the coauthors, contributors, and reviewers; and especially the diligent efforts from ASHRAE Special Publications staff. Although many highly renowned experts served as coauthors, we eagerly look forward to readers' comments and suggestions to help us improve the content for a future revision.

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Acknowledgments

Throughout its development, many past and present members of ASHRAE TC 9.11 and other experts have contributed to this design guide. In particular, Wei Sun was the driving force behind this book.

There are several categories of participants—coauthors, contributors, and reviewers. Coauthors are those responsible for major contributions to the book in writing, editing, and responding to reviewers' comments. Contributors are those who partially contributed by adding or modifying paragraphs of the book. Reviewers are those who provided review comments in writing and/or editing on the draft manuscript of the book, not necessarily substantial writing.

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Abbreviations and Acronyms

ACH, ach	air changes per hour
ACR	air changes rate
A/E	architect/engineer
AHJ	authority having jurisdiction
AHU	air-handling unit
AMC	airborne molecular contamination
AMHS	automated material handling system
API	active pharmaceutical ingredient
BAS	building automation system
CFD	computational fluid dynamics
cfm	cubic feet per minute
CGMP	Current Good Manufacturing Practice
CPC	condensation particle counter
CR	contamination rate
Cx	commissioning
DCS	distributed control system
DDC	direct digital control
DPC	discrete particle counter
EMA	European Medicines Agency
EMI	electromagnetic interference
EU	European Union
FDA	U.S. Food and Drug Administration
FFU	fan filter unit
FOUP	front-opening unified pod
GMP	Good Manufacturing Practice
HACCP	Hazard Analysis Critical Control Point
HEPA	high-efficiency particulate air
HF	hydrofluoric acid
HMI	human-machine interface
IBC	*International Building Code*®
ICC	International Code Council
I/O	input/output
MPPS	most penetrating particle size
µm	micrometre, micron
nm	nanometre

NVR	nonvolatile residue
OEL	occupational exposure limit
OPC	optical particle counter
PAL	personnel air lock
PAPR	positive air-purifying respirator
PFD	process flow diagram
PLC	programmable logic controller
PLC/HMI	programmable logic controller/human machine interface
POU	point of use
PTFE	polytetrafluoroethylene
QA	quality assurance
RFU	recirculation fan unit
SME	subject matter expert
ULPA	ultralow particulate air
UPS	uninterruptible power supply
UPW	ultrapure water
UR	user requirement
URS	user requirements specification
VFD	variable-frequency drive
VOC	volatile organic compound

Part 1

Cleanroom Fundamentals

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1

Introduction

1.1 HISTORY OF CLEANROOMS AND CLEANROOM STANDARDS

Clean spaces are used for patient care in hospitals and for the testing and manufacture of products in such industries as microelectronics, pharmaceuticals, biotechnology, aerospace, medical devices, and food and beverages. A cleanroom is an enclosed space that can "provide for the control of airborne particulate contamination to levels appropriate for accomplishing contamination-sensitive activities" (ISO 2015a, p. 4). The contamination may be viable, such as bacteria, microbes, or viruses, or it may be in the form of nonviable particles such as metals, organic or inorganic compounds, pollution, or dust.

Hospitals were the first spaces to attempt to control the air where patients were located. Controlling the ventilation of hospital spaces was seen in first-century Roman military hospitals. Over the centuries, hospitals were large, open halls that were well heated and ventilated. Florence Nightingale made dramatic improvements in the mortality rates of wounded soldiers by insisting on scrupulously clean, well-ventilated hospital rooms (Thompson and Goldin 1975). While bacteria were first discovered in the fifteenth century, it was not until the late nineteenth century that the connection between bacteria and germs was proposed and proven by Pasteur and Koch (Wikipedia 2017). This led to a need for improved clean, ventilated spaces for patients.

In 1861 a report from the American Sanitary Commission recommended that hospitals be specially constructed to provide the needed heating and ventilation for patient wards. The development of formal hospital ventilation standards did not occur until the mid-twentieth century, when the United States passed the *Hospital Survey and Construction Act* (or the *Hill-Burton Act*) in 1946, which called for the construction of hospitals and related health care facilities. In the 1950s, experiments performed by Bourdillon and Colebrook (1946) in the United Kingdom showed that supplying clean air through the ceiling and exhausting at floor level further reduced contamination in a hospital. They concluded that ventilation of the whole room was required to offset "the great variability of the sources of contamination" (Bourdillon and Colebrook 1946). Sufficient under-standing of ventilation and airflow direction resulted in the publication of a comprehensive design guide in 1962 by the United Kingdom Medical Research Council (Blowers et al. 1962).

In industrial applications, reducing contamination can be dated back to the nineteenth century, when watchmakers Aaron Dennison and Edward Howard moved their watch factory from downtown Roxbury in Boston to the suburbs of Waltham because "the city streets in Roxbury were not paved, and the dust thrown up by traffic wreaked havoc on

the small mechanisms" (Holbrook 2009, p. 175). The drive to reduce military component sizes required cleanrooms for high-precision manufacturing in support of this miniaturization (Shadewald 1963).

The watershed in the history of the cleanroom was the invention of the first "laminar flow" or unidirectional concept of ventilation in 1961 by physicist W.J. Whitfield at Sandia Laboratories (Whitfield 1962). Soon thereafter, other Sandia technicians developed the first clean bench. The success of the laminar flow cleanroom and clean bench quickly spread, with Dr. Randy Lovelace, MD, using a cleanroom during operating procedures, and NASA seeking proposals to have cleanrooms used in the space program. By the end of 1962, more than 20 companies had been licensed to construct and build cleanrooms and clean benches for various projects.

1.2 EVOLUTION OF INTERNATIONAL STANDARDS FOR CLEANROOM DESIGN

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

By 1963, the lack of a set of cleanroom standards was evident, and in April 1963 Sandia Laboratories, the U.S. General Services Administration (GSA), the U.S. Air Force, the United States Atomic Energy Commission, and other experts from across the United States gathered in Albuquerque, New Mexico, with the mission to create the first federal standard on cleanrooms (Bice 1963; Whitfield 1963; Casberg 1963). A group chaired by J. Gordon King was formed, and together they created the first federal standard, entitled *Cleanroom and Work Station Requirements, Controlled Environments*. It was issued by the GSA and assigned the code FED-STD-209. In 1966 it was released as FED-STD-209A, *Air-borne Particulate Cleanliness Classes in Cleanrooms and Clean Zones* (GSA 1966). U.S. Federal Standard (FS) 209 was revised several times over the years (see Table 1.1. Until it was superseded by the ISO 14644 standards in 2001, FS 209 was the benchmark for cleanroom cleanliness. It defined a cleanroom as an enclosed area with control over the particulate matter in the air as well as control of temperature, humidity, and pressure as required, and it established standard classes of air cleanliness for airborne particulate levels in cleanrooms and clean zones.

Other cleanroom standards have been issued by many countries, including Australia, France, Germany, Holland, Japan, and the United Kingdom (see Table 1.2). With the evolution of the global economy the need for an international standard for cleanrooms became apparent. In 1993 an international group, International Organization for Standardization (ISO) TC 209, was assembled to produce the first international cleanroom standards: ISO 14644, *Cleanrooms and Associated Controlled Environments.*

As of the time of this writing, the ISO 14644 standards (ISO 2016) consist of the following parts:

- *Part 1: Classification of Air Cleanliness by Particle Concentration*
- *Part 2: Monitoring to Provide Evidence of Cleanroom Performance Related to Air Cleanliness by Particle Concentration*
- *Part 3: Test Methods*
- *Part 4: Design, Construction and Start-up*
- *Part 5: Operations*
- *Part 7: Separative Devices (Clean Air Hoods, Gloveboxes, Isolators and Mini-Environments)*

Table 1.1 History of FS 209

FS 209, 1963
FS 209A, December 1966
FS 209B, April 1973; amended May 1976
FS 209C, October 27, 1987
FS 209D, June 15, 1988
FS 209E, September 11, 1992
Canceled, November 29, 2001

Table 1.2 Cleanroom Standards Timeline

1960s	1970s	1980s	1990s	2000s	2010s
U.S. Air Force TO 00-25-203	FS 209B	FS 209C	FS 209E	ISO 14644-3	ISO 14644-1
US-MIL-STD-1246	Australia AS 1386	FS 209D	ISO 14644-1	ISO 14644-4	ISO 14644-2
FS 209	Britain BS 5295		Russia GOST R 50766	ISO 14644-5	ISO 14644-12
FS209A	Japan JIS B 9920			ISO 14644-6	ISO 14644-13
	France AFNOR X44101			ISO 14644-7	ISO 14644-14
	Germany VDI 2083:3			ISO 14644-8	
	Holland VCCN 1			ISO 14644-9	

- *Part 8: Classification of Air Cleanliness by Chemical Concentration (ACC)*
- *Part 9: Classification of Surface Cleanliness by Particle Concentration*
- *Part 10: Classification of Surface Cleanliness by Chemical Concentration*
- *Part 12: Specifications for Monitoring Air Cleanliness by Nanoscale Particle Concentration (Draft International Standard, DIS)*
- *Part 13: Cleaning of Surfaces to Achieve Defined Levels of Cleanliness in Terms of Particle and Chemical Classifications*
- *Part 14: Assessment of Suitability for Use of Equipment by Airborne Particle Concentration*

Additional parts of ISO 14644 are under development.

1.3 CLASSIFICATION OF CLEANROOMS

Cleanrooms are classified according to the number and size of particles permitted per volume of air. Table 1.3 shows the particle concentration values for various classes from various standards. Since the development of the ISO 14644 family of standards (ISO 2016), contamination levels for chemicals and surface contamination have also been developed.

FS 209 was developed using hybrid Systéme International and Inch-Pound units of measure, with particle sizes being metric and concentrations in particles per cubic foot. Starting with the FS 209E revision (GSA 1992), volumetric measures using cubic metres were introduced to be more aligned with standards outside the United States. In the

Table 1.3
Comparison of Various International Cleanroom Classifications
(Naughton 2016)

ISO 14644-1 (ISO 2015a)	FS 209D (GSA 1988)	FS 209E (GSA 1992)	Britain BS 5295 (BSI 1989)	Australia AS 1386 (SA 1989)	France AFNOR X44101 (AFNOR 1989)	Germany VDI 2083? (DIN 1990)	Japan JIS B 9920 (JSA 1989)	*EU Guidelines to GMP* (EC 2010)
ISO Class 1							1	
ISO Class 2					—	0	2	
ISO Class 3	1	M1.5	C	0.035	—	1	3	—
ISO Class 4	10	M2.5	D	0.35	—	2	4	—
ISO Class 5	100	M3.5	E or F	3.5	4 000	3	5	A/B
ISO Class 6	1 000	M4.5	G or H	35	—	4	6	—
ISO Class 7	10 000	M5.5	J	350	400 000	5	7	C
ISO Class 8	100 000	M6.5	K	3500	4 000 000	6		D
ISO Class 9								

FS 209 formula for cleanliness classes, “Class 100” or “Class 1000” referred to the number of particles of size 0.5 µm or larger permitted per cubic foot of air.

Table 1.4 provides a comparison of classifications between ISO 14644-1 and FS 209E. Because 1 m^3 is approximately 35 ft^3, the two standards are mostly equivalent when measuring 0.5 µm particles, although the testing standards differ. Ordinary room air is approximately ISO Class 9, or Class 1,000,000.

1.4 CLEANROOMS REQUIRED BY VARIOUS INDUSTRIES

Today, cleanrooms have grown from Whitfield’s laboratory (Whitfield 1962) to a global industry of an estimated 125 million ft^2 (12 million m^2), up 5% from 2013. It is estimated that the cleanroom market will continue to grow at a compound annual growth rate of 5% until at least 2018 (Technavio 2014). Figure 1.1 demonstrates the cleanroom market by application in 2013.

1.5 CLEANROOM AIRFLOW

During Whitfield’s work in the early 1960s, the concept of clean air entering from one plane and exiting at the floor was developed. Whitfield had identified the primary problem with earlier cleanrooms: they were not self-cleaning. In other words, the dirt in the room stayed in the room unless taken out by the janitor (Whitfield 1963). Whitfield and his team addressed this problem by having all air within the room leave at the floor to be captured by a prefilter outside the cleanroom. Whitfield described this design in his patent application as using a laminar airflow concept (Whitfield 1963). While the flow streamlines are intended to be parallel, the room air velocity was not technically laminar flow. The 1988 edition of FS 209, FS 209D, corrected this and introduced the terms *unidirectional* and *nonunidirectional* (Naughton 2016).

Since the issue of FS 209D, air pattern configurations in cleanrooms generally fall into two categories: unidirectional airflow and nonunidirectional airflow. Unidirectional airflow is controlled airflow through the entire cross section of a cleanroom or a clean

Table 1.4 Classification of Air Cleanliness by Particle Concentration

ISO Classification (ISO 2015a)	Maximum Concentration Limits (particles/m^3) Equal to and Greater Than the Considered Sizes Shown Below						FS 209 Cleanliness Class (GSA 1992)
	0.1 µm particle	0.2 µm particle	0.3 µm particle	0.5 µm particle	1.0 µm particle	5.0 µm particle	
ISO Class 1	10	Note 3	Note 3	Note 3	Note 3	Note 4	
ISO Class 2	100	24	10	Note 3	Note 3	Note 4	
ISO Class 3	1000	237	102	35	Note 3	Note 4	Class 1
ISO Class 4	10,000	2,370	1,020	352	83	Note 4	Class 10
ISO Class 5	100,000	23,700	10,200	3520	832	Notes 3,4	Class 100
ISO Class 6	1,000,000	237,000	102,000	35,200	8,320	293	Class 1,000
ISO Class 7	Note 2	Note 2	Note 2	352,000	83,200	2,930	Class 10,000
ISO Class 8	Note 2	Note 2	Note 2	3,520,000	832,000	29,300	Class 100,000
ISO Class 9	Note 2	Note 2	Note 2	35,200,000	8,320,000	293,000	

Notes:
1. All concentrations in the table are cumulative.
2. Concentration limits are not applicable in this region of the table due to very high particle concentrations.
3. Sampling and statistical limitations for particles in low concentrations make classification inappropriate.
4. Sample collection limitations for both particles in low concentrations and sizes greater than 1 µm make classification at this particle size inappropriate, due to potential particle losses in the sampling system.
5. Conversion to alternative units of measure is not recommend or allowed for ISO classes.

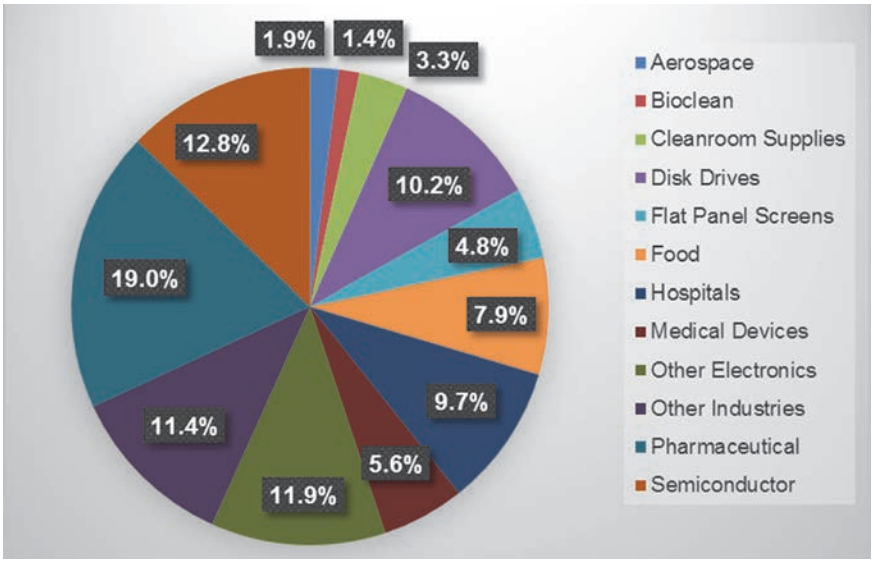

Figure 1.1 Estimated Global Cleanroom Area by Industrial Sector

zone with a steady velocity and airstreams that are considered to be parallel. Ideally, the flow streamlines are uninterrupted, and although personnel and equipment in the airstream do distort the streamlines, a state of constant velocity is approximated. Nonunidirectional air distribution is where the supply air entering the cleanroom or clean zone mixes with the internal air by means of induction.

Some examples of unidirectional and nonunidirectional airflow systems are shown in Figures 1.2 and 1.3. Airflow is typically supplied to the space through supply diffusers containing high-efficiency particulate air (HEPA) filters (Figure 1.2) or through supply diffusers with HEPA filters located in the ductwork or air handler (Figure 1.3). In a mixed-flow (nonunidirectional) room, air is prefiltered in the supply and then HEPA-filtered at the workstations located in the clean space (see the left side of Figure 1.3) (ASHRAE 2015).

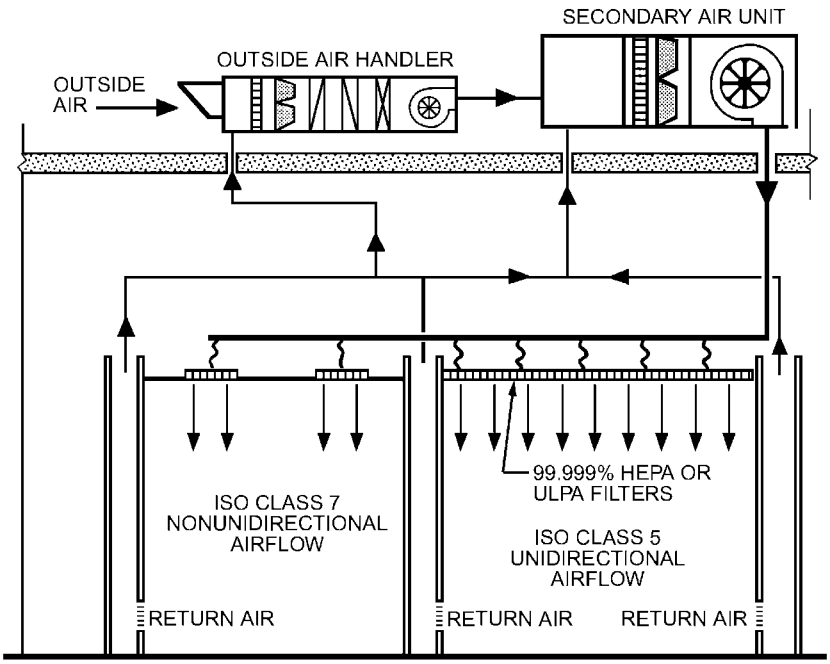

Figure 1.2 ISO Class 7 Nonunidirectional Cleanroom with Ducted HEPA Filter Supply Elements and ISO Class 5 Unidirectional Cleanroom with Ducted HEPA or ULPA Filter Ceiling

(ASHRAE 2015)

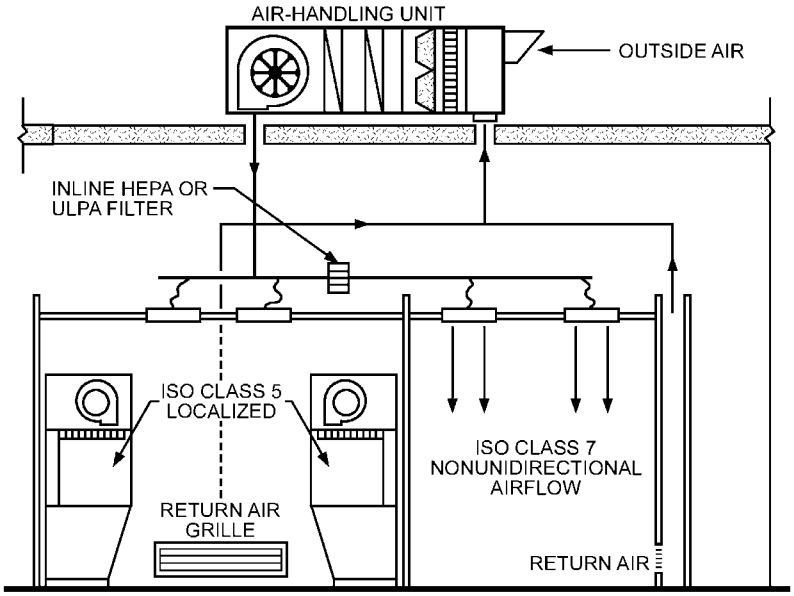

Figure 1.3 ISO 14644-1 Class 7 Nonunidirectional Cleanroom with HEPA Filters Located in Supply Duct and ISO 14644-1 Class 5 Local Workstations

(ASHRAE 2015)

1.5.1 UNIDIRECTIONAL AIRFLOW

In unidirectional airflow, air patterns are optimized and air turbulence is minimized. In a vertical laminar flow (VLF) room, typically air is introduced through ceiling HEPA or ultralow particulate air (ULPA) filters and returned at the base of sidewalls or through a raised-access floor. The air enters from the entire ceiling area, so this configuration produces nominally parallel airflow. In a horizontal flow, air enters from one wall and returns on the opposite wall (ASHRAE 2015).

A downflow cleanroom has a ceiling with HEPA filters, but air flows from only a portion of the ceiling. In a cleanroom with a low class number the greater part of the ceiling requires HEPA filters. For an ISO Class 5 (ISO 2015a) or better room, the entire ceiling

may require HEPA filtration, though more common practice is that only a high percentage of the ceiling need contain filters—enough to provide good uniform velocity. ISO Class 3 to ISO Class 5 cleanrooms may warrant only 90% to 70% filter coverage (Naughton 2003). Ideally, the air return is a grated or perforated floor; however, this type of floor is inappropriate for several types of cleanrooms, including pharmaceutical cleanrooms, which require solid floors and low-level wall returns. In a vertical downflow cleanroom, the entire room is bathed in a uniform shower of downward-flowing ultraclean air. With this design, contamination that is generated in the space is swept down and out through the floor and will not move laterally against the downward flow of air or contribute to contamination buildup in the room. To seal a HEPA or ULPA filter ceiling, care must be taken in design, selection, and installation. Properly sealed HEPA or ULPA filters installed in the ceiling can provide the cleanest air currently available in a workroom environment (ASHRAE 2015).

In a horizontal-flow cleanroom, the supply wall consists entirely of HEPA or ULPA filters supplying air at approximately 90 fpm (0.45 m/s) across the room. The air exits at the opposite side of the room through the return wall and recirculates. As with the vertical downflow room, this design minimizes cross-contamination perpendicular to the airflow and removes contamination generated in the space. However, this design is limited because the downstream air becomes contaminated: the air that leaves the filter wall is the cleanest, and it is contaminated by the process in the room as it flows past the first workstation. Ideally the process activities should be oriented so that the most critical operations are at the cleanest end of the room, progressing with less critical operations, with the least critical operations located at the return air end of the room. Unidirectional airflow systems have a predictable airflow path that airborne particles tend to follow. However, unidirectional airflow only indicates a predictable path for particles to follow if no good filtration practices accompany it. With a good understanding of unidirectional airflow, though, superior cleanroom performance can be achieved. This airflow is designed to remain parallel (or within 18° of parallel) to below the normal work surface height of 30 to 35 in. (760 to 900 mm). The result is a cleanroom with areas of good unidirectional airflow. However, this flow deteriorates when the air encounters obstacles (for example, work benches or process equipment) or if the air must travel excessive distances. The movement of personnel also degrades the flow. Turbulent zones have countercurrents of air with no flow at all (stagnancy), reverse flow, or high velocity. These countercurrents can produce stagnant zones where particles cluster and settle on surfaces or may lift particles from already contaminated surfaces. Once lifted, these particles may deposit on product surfaces (ASHRAE 2015).

1.5.2 NONUNIDIRECTIONAL AIRFLOW

Variations of nonunidirectional airflow are typically based on the locations of supply inlets and outlets and air filters. Satisfactory contamination control results for cleanliness levels of ISO Classes 6 through 8 (ISO 2015a) may be achieved with nonunidirectional airflow. Attainment of desired cleanliness classes with designs similar to those in Figures 1.1 and 1.2 assumes that makeup air is the major source of space contamination and that this contamination is removed in the filter housings of air handlers or ductwork or through supply HEPA filters. When particles generated within the cleanroom are the highest concern, clean workstations should be provided in the clean space (ASHRAE 2015).

1.6 SOURCES OF CONTAMINANTS INSIDE CLEANROOMS

Contamination is a process that causes surfaces to be soiled with contaminating substances. The two broad categories of surface contaminants are particulates and film type.

These contaminants can produce what's known as a "killer defect" in a miniature circuit manufactured in a semiconductor cleanroom. Film contaminants of only 10 nm, for example, can drastically reduce the adhesion of a coating on a wafer or chip. Though particles of 0.5 μm or larger are typically the target, some industries are now targeting even smaller particles (McFadden n.d.).

A partial list of contaminants is found in the following subsection. Any of these can be the source of a defect that may damage a product beyond repair. The objective is preventing these contaminants from entering the cleanroom, and succeeding requires commitment of everyone who enters the cleanroom, including professional cleaning personnel. Whenever personnel enter or clean a cleanroom, strict procedures must be followed. Compromise is not acceptable when cleaning in a cleanroom (McFadden n.d.).

1.6.1 CONTAMINATION SOURCES

Some of the commonly known contaminants that can cause problems in various cleanroom environments are included here. Research has found that many of these contaminants are generated from five basic sources—facilities, people, tools, fluids, and the products being manufactured (McFadden n.d.):

- Facilities
  - Walls, floors, and ceilings
  - Paint and coatings
  - Construction materials (gypsum wallboard, saw dust, etc.)
  - Air-conditioning debris
  - Room air and vapors
  - Spills and leaks
- People
  - Skin flakes, oil, and perspiration
  - Cosmetics and perfumes
  - Spittle
  - Clothing debris (lint, fibers, etc.)
  - Hair
- Tools and supplies
  - Noncleanroom writing materials and supply bags
  - Friction and wear particles
  - Machinery vibration
  - Lubricants and emissions
  - Brooms, mops, and dusters
  - Raw-material bags and containers
- Fluids
  - Particulates floating in air
  - Bacteria, organics, and moisture
  - Floor finishes or coatings
  - Cleaning chemicals
  - Plasticizers (off-gasses)
  - Deionized water
- Products
  - Silicon chips
  - Quartz flakes
  - Cleanroom debris
  - Metal particles

Table 1.5 Number of Particles Produced per Minute During Various Activities

(McFadden n.d.)

Activity	Particles/min (0.3 μm and larger)
Motionless (standing or seated)	100,000
Walking about 2 mph (3 km/h)	5,000,000
Walking about 3.5 mph (5.5 km/h)	7,000,000
Walking about 5 mph (8 km/h)	10,000,000
Horseplay	100,000,000

1.7 EFFECT OF HUMAN INTERFERENCE

When personnel are present in cleanrooms there are both physical and psychological concerns. Physical behavior such as sneezing, coughing, fast motion, and horseplay can increase contamination. Psychological concerns such as claustrophobia, odors, room temperature and humidity, and workplace attitude are important. People are a major source of contamination in cleanrooms. They produce contamination in several ways (McFadden n.d.):

- Body processes and products, such as hair, skin flakes, perspiration, and oils
- Behavior such as sneezing, coughing, and other types of movement
- Attitudes such as communication between workers and work habits

Table 1.5 shows the number of particles produced per minute during the activities listed.

1.7.1 GENERAL CLEANROOM GUIDELINES

The following are actions that are typically prohibited in cleanrooms of all types (McFadden n.d.):

- Fast motions such as walking fast, running, or horseplay
- Leaning or sitting on work surfaces or equipment
- Writing on cleanroom garments or equipment
- Removing items from beneath cleanroom garments
- Wearing cleanroom garments outside the cleanroom
- Wearing torn or soiled cleanroom garments
- Reentering a cleanroom wearing previously used cleanroom garments

Personnel entering a cleanroom—including operators, supervisors, cleaning personnel, and the like—need to be trained and at all times be aware of and follow the regulations of the cleanroom. According to McFadden (n.d.), general regulations recommended as a minimum for successful cleanroom operation are as follows:

- Personal items such as keys, watches, rings, matches, lighters, and cigarettes should be stored in personal lockers outside the gowning room.
- Valuable personal items such as wallets may be permitted in the cleanroom provided they are never removed from beneath the cleanroom garments.
- Eating, smoking, and gum chewing are not allowed inside the cleanroom.
- Only garments approved for the cleanroom should be worn when entering.
- Cosmetics are not to be worn in the cleanroom. This includes rouge, lipstick, eye shadow, eyebrow pencil, mascara, eye liner, false eye lashes, fingernail pol-

ish, hair spray, mousse, and the heavy use of aerosols, aftershaves, and perfumes.
- Only approved cleanroom paper is allowed in the cleanroom.
- Approved ball point pens are the only writing tool allowed for use.
- Use of paper or fabric towels is prohibited. Use of hand dryers equipped with HEPA filters is suggested.
- Only approved gloves, finger cots (powder-free), pliers, or tweezers should be used to handle products. Fingerprints can be a major source of contamination on some products.
- Gloves or finger cots should not be allowed to touch any item or surface that has not been thoroughly cleaned.
- Solvent contact with bare skin should be avoided. Solvents can remove skin oils and increase skin flaking.
- Approved skin lotions or lanolin-based soaps are sometimes allowed. These can reduce skin flaking.
- Tools, containers, and fixtures used in the cleaning process should be cleaned to the same degree as the cleanroom surfaces. All of these items are sources of contamination.
- No tool should be allowed to rest on the surface of a bench or table; it should be placed on a cleanroom wipe.
- Only cleanroom-approved wipes are allowed to be used. The wipes must be approved for the class of cleanroom being cleaned.
- Equipment, materials and containers introduced into a sterile facility must be subjected to stringent sterilization prior to entrance.
- No one who is physically ill, especially with respiratory or stomach disorders, should enter a sterile room. This is a good practice in any cleanroom environment.

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2 Airborne Particulate Contaminants

2.1 AIRBORNE PARTICLES AND THEIR PROPERTIES OF RELEVANCE TO CLEANROOMS

Airborne particles are one of two primary sources of contamination in cleanroom air (gaseous or molecular contamination being the other). This chapter primarily discusses airborne particles with particular relevance to cleanroom design. Particles of interest in cleanrooms can be liquids, solids, or those formed by the reaction of materials used and emitted during the operation of the cleanroom. These particles have many shapes, structures, and chemistry. Not all of them are spherical with standard properties such as unit density or perfect light-scattering properties. Hence, it is just customary convenience that we use particle diameter to refer to particle size. Implied in this reference to size is the equivalence of the measured property of the particle to that of a sphere with the same response. For example, a particle with eight times the density will settle at the same rate as a unit density particle with twice the diameter if the settling velocity or volume is used to measure particle size. Although this is an important consideration in particle measurements, it is often ignored in practice, mainly because most of the measurements are made with similar methods, such as optical particle counting, and hence the measurements are equivalent regardless of the nature or shape of the particles, relatively speaking.

The size and chemistry of particles are arguably the most important properties of direct relevance to the processes in cleanrooms. The size determines the ability of particles to be transported to products, processes, and operators of cleanrooms, as well as the ability of cleanroom systems to remove them. For example, as seen by the settling velocities of particles of different sizes in Table 2.1, whereas the larger particles will most likely settle reasonably quickly, the submicron-sized particles will stay airborne for long time periods, remaining a threat to the cleanliness of the cleanroom. For this reason, all the discussions on particle contamination are made in the context of small particles. Larger particles are assumed either to have settled or to have been captured completely by the cleanroom filtration systems. The behavior of submicron particles is less influenced by their intrinsic chemical properties and more by other properties such as induced surface charge and their mobility and transport.

The chemistry of the particles determines their reactivity to the products and processes in cleanrooms. The particle chemistry and whether they are solid or liquid depends on their source. They are introduced either by the air supplied to the cleanroom or by the processes in the cleanroom. Thus, particle properties are specific to each cleanroom. For

Table 2.1 Settling Velocities

Particle Diameter, μm	Velocity, ft/min (M/s)
0.1	0.00016 (8.128e-07)
1.0	0.007 (3.5568e-05)
10.0	0.59 (0.00299)
100	59.2 (0.3007)

Table 2.2 Relaxation Times

Particle Diameter, μm	Relaxation Time, ms
0.05	0.05
100	0.1
500	0.7
1000	5

example, the properties of particles generated in a pharmaceutical cleanroom will be quite different than those generated in a microelectronic cleanroom. Other properties of particles that are of interest include the optical properties and the charge or charge distribution on the particles. Optical properties, or more specifically the refractive index, are important because most common particle detection devices specified for cleanroom testing and certification are optical particle counters (OPCs) that depend on the light-scattering property of the particle. Charge on a particle affects its transport and deposition. A negatively charged particle will be more readily deposited on a surface at a negative potential.

2.2 DISPERSION OF AIRBORNE CONTAMINANTS

Particles in a cleanroom are transported within the cleanroom, to the surfaces, and through the airflow systems by molecular diffusion, convective transport, or Brownian motion. Of these, molecular diffusion is relevant to gaseous contaminant transport and is addressed in Section 4.1.1 of Chapter 4.

Convective transport occurs when particles are carried with the airflow in and around the cleanroom. How readily a particle assumes the motion of the air can be explained by the concept of relaxation time. This is a measure of the time a particle takes to decelerate to 0.368 (or 1/*e*) of its initial velocity. Or in other words, it is also a measure of how readily the particle will follow the airflows. The smaller the particle, the shorter the relaxation time and the more readily the particle follows the air movement. Relaxation times for selected particle sizes are given in Table 2.2. As seen in the table, small particles are carried around the cleanroom more readily with the airflow pattern and velocities as the air flows within the cleanroom.

In cleanroom design this is both a problem and a convenience. A problem because particles will follow airstreams and contaminate wherever air flows. A convenience because, with proper designs, airflow patterns can be made to ensure that any particle is scavenged away from its source and filtered. The ability for airflow to readily scavenge particles is the key reason lower-ISO-class (ISO 2015a) cleanrooms are designed for unidirectional flows. This is shown in Figure 2.1. When a particle is generated by any means within the cleanroom and reaches the streamlines in a unidirectional flow (commonly referred to as *laminar flow*), the particle is scavenged and removed by the airflow (Figure 2.1a).

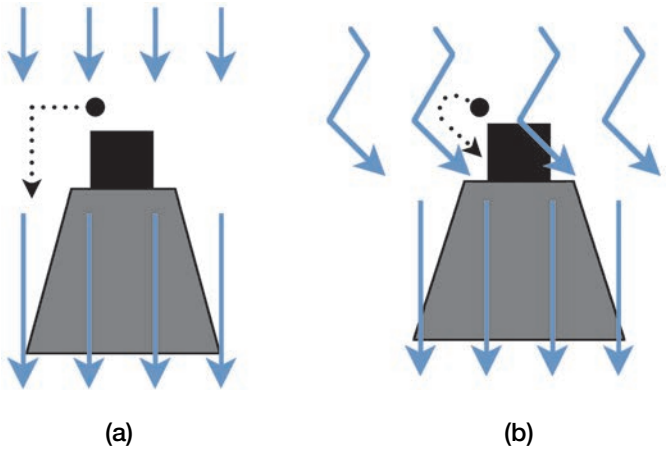

Figure 2.1 Particle Scavenging in Cleanroom Airflows: (a) Unidirectional Flow and (b) Nonunidirectional Flow

(Courtesy R. Vijayakumar of AERFIL)

On the other hand, when the airflow is nonunidirectional (sometimes called *turbulent* or *mixed airflow*) (Figure 2.1b), with mixed airflow patterns, a particle generated in a cleanroom will likely be recirculated into the work area as shown in Figure 2.1b. Hence, for cleaner classes (< ISO Class 5) of cleanrooms, unidirectional airflow will ensure that the submicron particles are effectively removed. Discussions on the choices of airflow velocities and cleanliness classes are discussed in Section 2.8. Also see Section 8.1 of Chapter 8.

2.3 PARTICLE SIZE DISTRIBUTION

Although it is common for all design considerations in cleanrooms (or for that matter wherever particles are involved) to treat particle size in the singular, particles are seldom present singly or in one size. Particles in the real world are generally distributed over a range of particle sizes. Particle size distributions are best represented by a geometric standard distribution:

$$F(X) = \frac{1}{(2\pi)^{1/2}\ln\sigma}\int e^{-(\ln x - \ln x_m)^2/2(\ln\sigma)^2}dx \qquad (2.1)$$

where x_m is the geometric mean and σ is the geometric standard deviation, also commonly notated as σ_g. Examining the distribution function, one can notice the similarity to the traditional standard normal distribution function, but with the distributed variable transformed to its logarithm (i.e., $X = \log x$). All the analyses common in normal statistics can be used for geometric standard distributions using this transformation. There are two points of interest. First, on a logarithmic scale, sums become products and differences become ratios. Second, unlike the standard normal distribution, the geometric standard distribution does not have negative values. Hence, it fits particle distributions quite well, since negative particle sizes are not realistic. This is shown in Figure 2.2, with the distribution originating at zero.

In dealing with particle size distributions in contamination control, it is customary to differentiate the distribution as monodisperse or polydisperse. Although in the strict sense *monodisperse* implies one size of particles (or σ_g =1), it is common practice to refer to particle size distributions with σ_g ~ 1.3 as monodisperse. The mean size is used in all design considerations and other computations. It is useful to keep in mind that even with

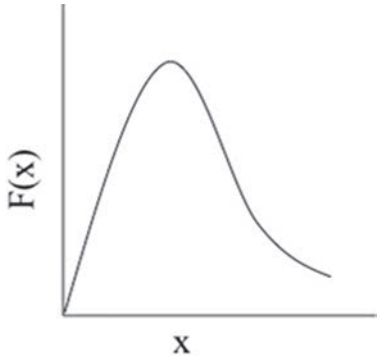

Figure 2.2 Geometric Standard Distribution

this practical monodisperse aerosol ($\sigma_g \sim 1.3$), 95% of the particles can be within ±60% of the mean size and still be considered monodisperse at the mean size.

2.4 CONTAMINATION RISKS AND ASSESSMENT

In a traditional risk characterization of human health, the major components to obtain the risk value are hazard identification, exposure assessment, and dose-response assessment. Generally, the higher the exposure, the higher the risk observed. Similar to human health, the contamination risk of products in a cleanroom mainly results from the exposure of products to contaminants. The exposure dose of the products to contaminants can be the amount of adhesion particles presented in both airborne and liquid-borne contaminants. Deposition could be the major mechanism for the particles to attach and contaminate products based on Stokes' law. The rate of deposition, or the deposition velocity, is much lower for particles of an intermediate size (1000 to 10,000 μm). Large particles (>1000 μm) will settle quickly through settling or impaction processes. However, the deposition velocity for 10,000 μm (0.11811024 in./s) (0.3 cm/s) particles is still much less than that of air in a unidirectional flow (11.811023 in./s [~30 cm/s]) cleanroom.

The risk of contaminants depends not only on their concentration, which is of critical importance, but also on the motion of the contaminants in a cleanroom (Ljungqvist and Reinmüller 1997). If particulate contaminants are being considered, the rate of incidence of the particles characterizes the risk. When this is considered mathematically, the term flux vector *K*, or impact vector, is used, which can be calculated as follows (Ljungqvist and Reinmüller 1997):

$$K = -D\ grad\ c + v \cdot c \tag{2.2}$$

where *D* is the diffusion coefficient, *c* is the particle concentration, and *v* is the velocity vector. In principle, the numerical value of *K* indicates the number of particles passing a supposed unit area, placed perpendicular to the direction of particle flow, per unit time.

Considering there is no motion of the air and no diffusion, a chamber of height *H* containing at time 0 a specified initial concentration c_0 of uniformly distributed monodisperse particles, particles will be settling with the same constant settling velocity v_s and the particle flux becomes $v_s \cdot c_0$. The particle concentration is equal to zero everywhere in the chamber after a time of H/v_s has passed. However, at the other extreme condition, when the air is completely turbulently mixed, a uniform concentration throughout the chamber at all times is assumed. In addition, diffusion and deposition on the chamber wall are assumed to be negligible. The particle settling velocity will be superimposed on

the vertical components of convective velocity. Because the up and down convective velocities are equal, every particle will have, as average, a net velocity equal to v_s. Then the concentration decays exponentially with time and as such never reaches zero. The concentration becomes $1/e$ (or 37%) of c_0 in the same time (H/v_s) that is required for complete removal in the above case with no motion of the air case (Ljungqvist and Reinmüller 1997). The expression for the particle settling flux K_s at time t in this case with monodisperse aerosol is as follows:

$$K_s = v_s \cdot c_0 \cdot e^{-\frac{v_s t}{H}} \tag{2.3}$$

The number of particles of a monodisperse aerosol settling (N_s) in a time t on the unit area of the bottom of chamber becomes

$$N_s = \int_0^t K_s dt = c_0 H\left(1 - e^{-\frac{v_s t}{H}}\right) \tag{2.4}$$

Ljungqvist and Reinmüller (1997) found that the risk of contamination was more intimately associated with the flux vector than with concentration. It is important to have knowledge about the interaction between air movements and dispersion of contaminants when contamination risks are assessed.

The main sources of cleanroom contaminants are people and machinery. Risk situations are created by the interactions among air patterns, the dispersion of airborne contaminants, and people. These situations are difficult to predict using computer simulations and monitoring methods (Ljungqvist and Reinmüller 2004).

Assessment of airborne contamination of aseptic products produced in classified clean zones and cleanrooms can be done by applying any of several commonly accepted risk assessment methods (Ljungqvist and Reinmüller 2004). This is in agreement with the International Organization for Standardization (ISO) standard regarding biocontamination in cleanrooms (ISO 2003) and with both European Union (EU) and U.S. Food and Drug Administration (FDA) good management practices (FDA 2004). Risk analysis should be based on a documented system that checks and evaluates several parameters of the process and takes into account their potential effects on product quality. The key to understanding the risks is understanding the process, including the manufacturing process and its vulnerability to airborne contamination, as well as, in this case, the cleanroom and the clean zone and their performance. Airborne contamination risks result from entrainment of air from a lower-classification adjoining area, contaminant accumulation in turbulent and stagnant regions, and unfiltered air leakage (Ljungqvist and Reinmüller 2004).

2.4.1 THE LIMITATION OF RISKS METHOD

For designing and evaluating manual interventions, the limitation of risks (LR) method combines airflow visualization, a challenge test, and risk factor calculation to provide a reliable procedure for systematically assessing the microbiological risks of airborne contamination in cleanrooms; Ljungqvist and Reinmüller (2004) describe the method in detail. In brief, there are three steps to the LR method. The first is visualizing (e.g., with smoke) main air movements and identifying critical vortices and turbulent regions, which can accumulate or disperse contaminants unpredictably. The second step is to conduct a particle challenge test to identify potential risk scenarios. To conduct this test, a particle counter probe is placed in a critical area where the product is exposed, and

continuous total particle counts are taken as particles are generated in the surrounding air (e.g., using air current test tubes) to a challenge level of >300,000/ft^3 particles of ≥0.5 μm (~107 particles/m^3). Production activity should be simulated to take these measurements. The third step is evaluating the risk scenario by calculating the risk factor, which is defined as the ratio between measured particle concentration (number of particles per cubic foot [metre]) in the critical region and the challenge level in the surrounding air. Because measurement accuracy is limited at high concentrations, a value of 300,000/ft^3 (~107 particles/m^3) is used as a challenge level in such calculations. When the risk factor is 10^{-4} (0.01%) during the challenge test, it is expected that, during typical operating conditions, there will be no microbiological contamination from the air. These results have been verified by final media fills showing no contaminated units (Ljungqvist and Reinmüller 2004).

2.5 SAMPLING TECHNIQUES

Appropriate sampling techniques for airborne particles should be applied to certify or verify the performance of cleanrooms and clean zones for designated classification in any of three defined occupancy states: as-built, at-rest, and operational (ISO 2005). Samplings are typically focused on particle concentrations with size distributions having a threshold size between 0.1 and 5 μm. For particles outside the specified size range, ultra-fine particles (particles smaller than 0.1 μm), and macroparticles (particles larger than 5 μm), ISO 14644-1 (ISO 2015a) used U descriptors and M descriptors, respectively, to quantify these populations. These descriptors are discussed in Sections 2.12.4 and 2.13.2, respectively.

The characteristics of particles presented in cleanrooms or clean zones, such as size distribution, number concentration, physicochemical property, and biological or nonbiological properties, could be the major consideration for the selection of measurement methods. In general, there are two categories of particle measurement methods. The first one is collection by filtration or inertial impaction (a cascade impactor), followed by microscopic measurements of the number and size of or gravimetric analysis for the mass of collected particles. The second is in situ measurement of the concentration and size of particles using a particle counter, such as a time-of-flight particle counter, a discrete particle counter (DPC) (e.g., an optical particle counter), or a condensation particle counter (CPC) (ISO 2005). It is worth mentioning that the sample probe velocity should not differ from the sampled air velocity by more than 20% to meet the isokinetic sampling for unidirectional flow present (ISO 2015a). However, in areas where nonunidirectional flow exists, the sampling instruments should be located with the sample inlet facing vertically upward (ISO 2005). The basic principles of the aforementioned instruments are discussed in the following paragraphs.

A DPC, a light-scattering instrument, has a means of displaying or recording the count and size of discrete particles of sampled air. According to the design feature of commercial DPCs, 3 to about 10 size discriminations of particle count are normally reported. The time-of-flight particle counter measures aerodynamic particle diameter determined by the time required for traveling the distance of two fixed planes and reports the concentration and size of micron-sized particles. The CPC counts all droplets formed by condensation of supersaturated vapor on sampled aerosol particles. Accumulative particle concentrations are produced for particles larger than or equal to the minimum size sensitivity of the CPC. For ultrafine particle measurement, a particle size cutoff device should be attached to the sample inlet of the DPC or CPC. A wide variety of sizes and configurations of particle size cutoff devices are available and acceptable, provided that they produce the required penetration characteristics. Diffusion battery elements and vir-

tual impactors both are suitable particle size cutoff devices (ISO 2005). Detailed descriptions of principles and applications of the time-of-flight particle counter, DPC, and CPC are provided in the following section.

Techniques used to collect particles for subsequent analysis or for particle classification are inertial classification, gravitational sedimentation, centrifugation, and thermal precipitation. Inertial classifiers, including cyclines, impactors, and virtual impactors, are widely used for particle sampling. Cascade impactors are the instrument of choice and have extensively been used for determining aerosol mass size distributions, which collect aerosol particles using impaction upon a series of collector surfaces. The particle samples allow for further microscopic and chemical analyses.

A culturable sampling is usually collected to verify and quantify the presence of bioaerosols (viable aerosols) to identify their sources for control or to monitor the effectiveness of control measures (Baron and Willeke 2001). Up to now, none of the presently available samplers can be considered as a reference method. Impingers and cascade impactors have been suggested for that purpose, and Table 24-1 in the Baron and Willeke (2001) source shows the existing commercial bioaerosol samplers. More detailed descriptions of the sampling devices and methods are provided in Section 6.2 of Chapter 6.

2.6 PARTICLE COUNTERS

2.6.1 LIGHT-SCATTERING-BASED TECHNIQUE

Optical particle size (or size parameter), α, defined as $\pi D_p/\lambda$ (where D_p is the physical particle size and λ the wavelength of the light source), is the key parameter for "seeing" particles (i.e., their size and morphology) using the light-scattering-based technique. As a rule of thumb, the scattering is in the Rayleigh regime if α is less than 0.15. In this regime, the intensity of scattered light is proportional to D_p^6/λ^4. The scattering is in the Lorenz-Mie regime if α is greater than 0.15 but less than 15, and it is in the geometric scattering regime if α is greater than 15. In order to "see" particles, the light-scattering instruments have to be operated in the Lorenz-Mie and geometric scattering regimes. In general, lights of short wavelengths are needed to detect nanoparticles. In addition to the optical particle size, the intensity of scattered light is also dependent on the refractive index of the particles being measured. Conducting particles in general scatter more photons than absorbing ones.

2.6.2 OPTICAL PARTICLE COUNTER (OPC)

An optical particle counter (OPC) is widely used for measurement of size distribution in both indoor and outdoor environments. Figure 2.3 shows the operating principle of the OPC (Chen and Pui 2008) used in three commercial OPCs. In this instrument, an airstream carries single, individual particles through an illuminated viewing volume that cause light to be scattered to a photodetector, which generates a voltage pulse for each particle that passes through the viewing volume. The pulse amplitude is considered a measure of particle size, and the pulse is counted and processed electronically to give a pulse-height histogram; a calibration curve is used to convert this histogram to a particle size distribution histogram. Many commercial counters with incandescent light sources have been developed for measurement of particle size distribution in the range of 0.3 μm to approximately 10 μm, and advancements using laser illumination have achieved detection limits down to 0.05 μm (Pui and Liu1988).

OPCs differ greatly in their design and performance characteristics. Some use the scattered light in the near forward direction; some gather the scattered light over a wide

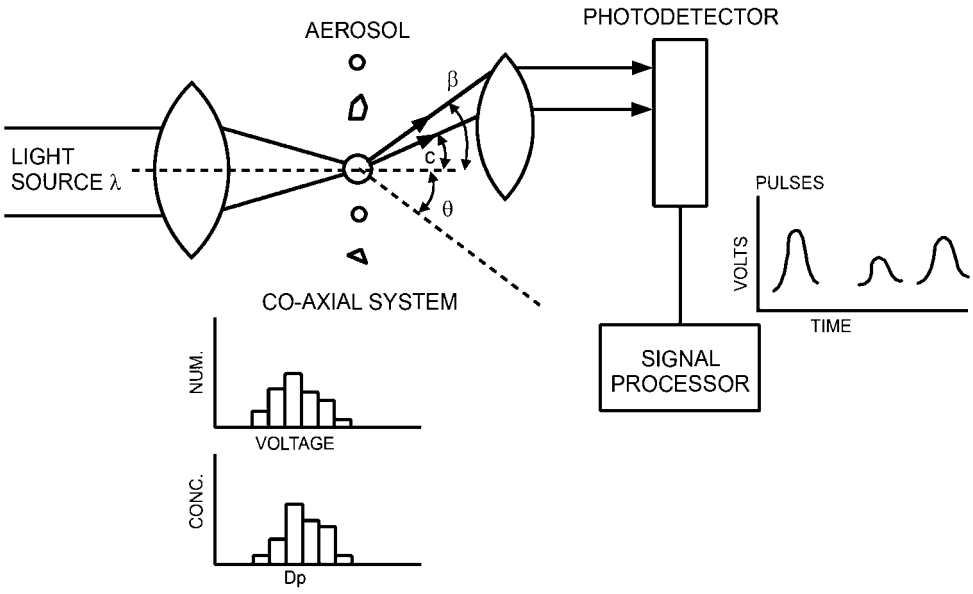

Figure 2.3 Operating Principle of an OPC

(Reproduced from Chen and Pui [2008] with permission of ACGIH®)

angle; some implement the intracavity scattering technique, in which the particles are passed through the resonant cavity of a laser; and some include the use of intracavity scattering and a sensor array for particle detection, as discussed by Chen and Pui (2008). In contrast, some instruments use a solid-state laser diode so that they have a small, portable, lightweight sensor. Table 2.3 provides a selected list of OPCs available commercially, revised from Table 4 of Chen and Pui (2008). OPCs can be differentiated by the number of channels of data provided, their sampling flow rate, their light source (white light, laser, or laser diode), and other distinguishing characteristics, such as their interfacing ability and their portability. Generally, an OPC with a laser source, especially for "active scattering" types, can detect smaller particles than one with an incandescent light source because the laser has a higher illuminating intensity. Active scattering laser counters can detect particles 0.07 µm and smaller, whereas white-light and laser diode counters typically have a lower detection limit of around 0.3 µm. An OPC with a higher sampling flow rate can count more particles in a time period than one with a lower flow rate. However, high-sampling-flow-rate OPCs typically have low particle coincidence levels. This type of OPC is especially important for particle counting in environments with low concentrations, such as cleanrooms. An OPC with a low sampling flow rate has higher resolution than a counter with a high flow rate and can also detect smaller particles. A sampling flow rate of 0.01 cfm is usually considered low and a flow rate of 1 cfm is usually considered high (Chen and Pui 2008).

The response of the OPC provides a relationship between the particle size and the pulse height, and it depends on the properties of both the particle and the instrument. The former includes the refractive index, particle size and shape, and the orientation of nonspherical particles with the incident beam, and the latter includes illumination source, optical design, and electronics gain (Chen and Pui 2008). The OPC response as a function of particle size can be calculated using the Mie theory of electromagnetic scattering (Yushanov et al. 2013). Calculations for some white-light counters were reported by Cooke and Kerker (1975), and other studies concentrated on laser particle counters (Liu et al. 1986).

For an OPC with near forward direction and narrow angle ($\alpha < \beta < 30°$) and an axisymmetric scattering geometry ($\theta = 0°$), the simple geometry is relatively insensitive to variations in both imaginary and real parts of the refractive index and provides strong

Table 2.3 Selected OPCs, Updated from Table 4 of Chen and Pui (2008)

Manufacturer	Model No.	Flow Rate, lpm	Size Range, μm	No. of Size Channel	Illumination Source
Climet Instrument Co., Redland, CA, USA	CI-20	2.83	0.5–5	2	Laser diode
	CI-40	50	0.5–5	2	Laser diode
	CI-90	100	0.5–5.0	2	Laser diode
	CI-450t	50	0.3–5.0	4	Laser diode
	CI-750t	75	0.3–5.0	4	Laser diode
	CI-1054	100	0.5–5.0	4	Laser diode
HACH Ultra, Grants Pass, OR, USA	3400 series	50/28.3	0.3/0.5–25	6	Laser diode
	237A/237B	2.83	0.3/0.5–5.0	2–6	Laser diode
	237H	2.83	0.1–1.0	2–6	He-Ne laser
	2400/2408	28.3	0.3/0.5–5.0/10.0	2–6	Laser diode
	2100C/2200C	28.3	0.1/0.2–1.0/5.0	6	He-Ne laser
Met One Grants Pass, OR, USA	GT-521	2.83	0.3–5.0	2	Laser diode
	GT-526S	2.83	0.3–5.0	6	Laser diode
	Model 804	2.83	0.3–10.0	7	Laser diode
	BT-610	2.83	0.3–10	6	Laser diode
Particle Measurement System, Inc., Boulder, CO, USA	LASAIR III 110	28.3	0.1–5.0	8	Laser diode
	LASAIR III 310B/C	28.3	0.3–10/0.3–25	6	Laser diode
	LASAIR III 350L/5100	50/100	0.3–25/0.5–25	6	Laser diode
	LASAIR II 110	28.3	0.1–5.0	6	Laser diode
Lighthouse, Fremont, CA, USA	SOLAIR 1100LD	28.3	0.1–1.0	8	Laser diode
	2016	2.83	0.2–2.0	6	Laser diode
	5016	2.83	0.5–25	6	Laser diode
TOPAS GmbH, Dresden, Germany	LAP 340	28.3	0.3–10	16	Laser diode
	LAP 322	3	0.2–40	128	He-Ne laser
RION, Tokyo, Japan	KC-32	50	0.3–10.0	2	Laser diode
	KC-52	2.83	0.3–5.0	5	Laser diode
	KA-03	2.83	0.3–5.0	5	Laser diode
	KC-22A	2.83	0.1–0.5	5	Solid-state laser
	KC-22B	0.3	0.08–0.5	5	Solid-state laser
	KC-24	28.3	0.1–0.5	5	Solid-state laser
	KM-27	28.3	0.3–10	6	Laser diode

signals but with higher background noises. This type of OPC is also prone to strong multivalued response (i.e., the same pulse height given by different particle sizes) (Pui 1996). Figure 2.4 gives the response of a near forward light-scattering instrument (PMS-ASAS-300X; angular range: 4° to 22°) (Liu et al. 1986). For a wide-angle counter (Climet CI-7300; angular range: 15° to 150°), the response is more sensitive to changes in both imaginary and real parts of the refractive index but much less susceptible to multivalued response, particularly for white-light illumination (Pui 1996). Figure 2.5 shows the calculated response of the Climet CI-7300 counter (Cooke and Kerker 1975).

Experimental studies are generally required to determine instrument characteristics of OPCs such as the absolute voltage-size response, response to irregular particles, resolu-

tion, count coincidence, and inlet efficiency (Chen and Pui 2008). Liu et al. (1974a) evaluated several commercial white-light counters using monodisperse spherical particles, and Wen and Kasper (1986) and Liu and Szymanski (1987) evaluated several commercial OPCs' counting efficiencies. Liu et al. (1974b) developed a technique for determining OPC response to irregular coal dust particles, and Marple and Rubow (1976) obtained aerodynamic particle size calibration of OPCs using inertial impactors. Other works mostly evaluated laser OPCs (Hinds and Kraske1986; van der Meulen and van Elzakker 1986; Kim and Boatman 1990; Yamada et al. 1986; Chen et al. 1984; Szymanski and Liu 1986). Comprehensive discussions of the principles and applications of OPCs can be found in the papers by Willeke and Liu (1976), Knollenberg and Luehr (1976), and Gebhart et al. (1976).

Other developments on OPCs include increasing the count coincidence level while keeping a high sampling flow rate, measuring particle refraction indices (Dick et al. 1994), and determining particle shape using scattering intensity from multiangle light scattering (Sachweh et al. 1995, 1998; Szymanski and Schindler 1998).

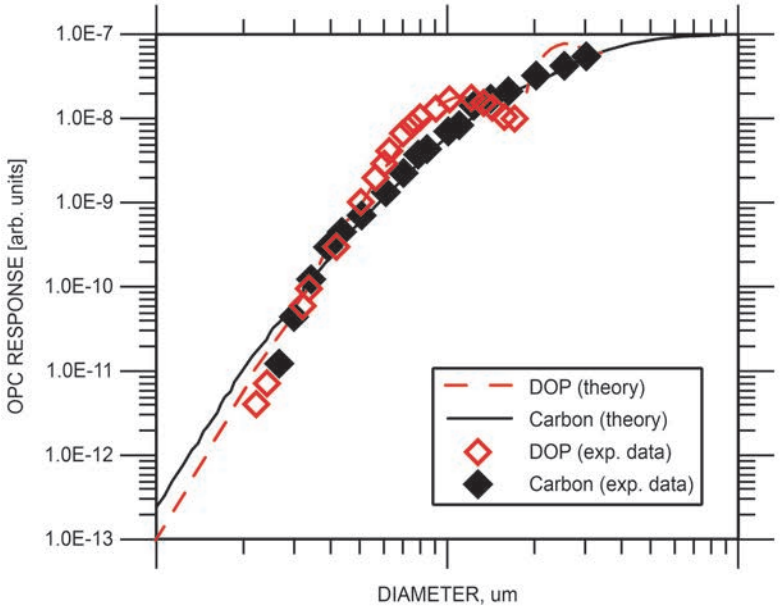

Figure 2.4 Theoretical and Experimental Responses for a Near Forward Light-Scattering Sensor (PMS-ASAS, Angular Range: 4° to 22°)

(Reproduced from Chen and Pui [2008] with permission of ACGIH®)

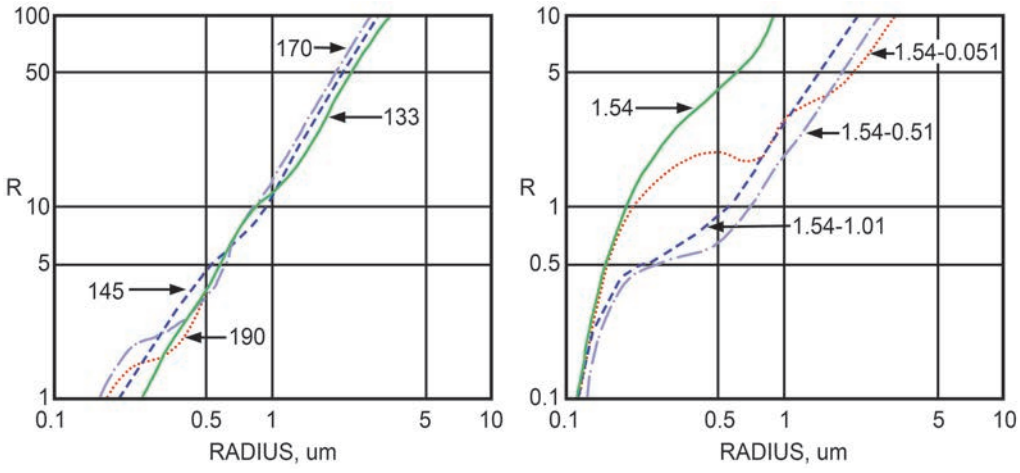

Figure 2.5 Theoretical Response Curves for a Wide-Angle Optical Counter (Climet-226, Angular Range: 15° to 150°)

(Reproduced from Chen and Pui [2008] with permission of ACGIH®)

2.6.3 CONDENSATION PARTICLE COUNTER (CPC)

A condensation particle counter (CPC), or condensation nucleus counter (CNC), is frequently used to measure particles in the range of approximately 0.005 to 1.0 µm diameter. The device passes an aerosol stream through a vapor-supersaturated region produced by either direct contact cooling or adiabatic expansion to cause vapor condensation on the particles, which are grown to a size that can be optically detected by light scattering (Chen and Pui 2008). Developments of CPCs include a direct-contact, continuous flow type (Bricard et al. 1976; Sinclair and Yue 1982) and the mixing of a cool aerosol stream and a hot vapor stream to achieve a supersaturation condition (Kousaka et al. 1982).

Figure 2.6 shows a schematic diagram of a commercially available, continuous-flow CPC (Agarwal and Sem 1980). In this device, an airstream is saturated with the working fluid, butyl alcohol, in a saturator kept at 95°F (35°C) (Chen and Pui 2008). Additional cooling of this airstream in a condenser tube that is thermoelectrically cooled and kept at 50°F (10°C) produces the supersaturation required for vapor condensation on the particles. Particles exiting the condenser tube at approximately 12 µm size are optically detected by light scattering. In low particle concentrations, individual particles are counted (Pui and Liu 1988), and in particle concentrations of above 1000 particles/cm^3, a photometric mode is used to detect the total light scattering from the droplet cloud for total particle concentration measurement (Chen and Pui 2008). This CPC has a concentration range from less than 0.01 particles/cm^3 to more than 10^6 particles/cm^3.

Water-based CPCs have been made commercially available in recent years (Biswas et al. 2005; Hering and Stolzenburg 2005; Hering et al. 2005). Figure 2.7 shows a schematic diagram of such a water-based CPC. To condense water vapor on particles, the instrument operates by first cooling the sampled aerosol and delivering the heated aerosol stream into a moisture-saturated and heated "condenser." In this heated condenser, the water vapor is moved from the water-saturated porous wall to the core region of the tube. When the cooled aerosol stream is introduced in the tube, water vapor condenses on particles and grows the particle size. The detection-of-particles event is the same as that used in CPCs using butanol. Switching working fluid from butanol/isopropyl alcohol to water opens the CPC to applications in critical situations where the ethanol-based chemical vapor is not allowed. Special attention must be paid when using such a CPC. The calibration of the CPC reveals that when detecting particles containing slightly hydrophilic materials, this

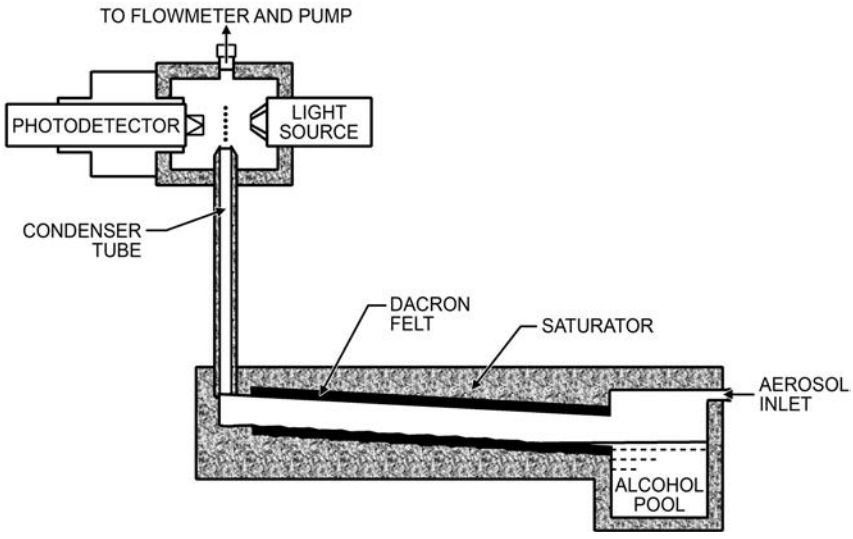

Figure 2.6 Schematic Diagram of Commercially Available, Continuous-Flow CPC

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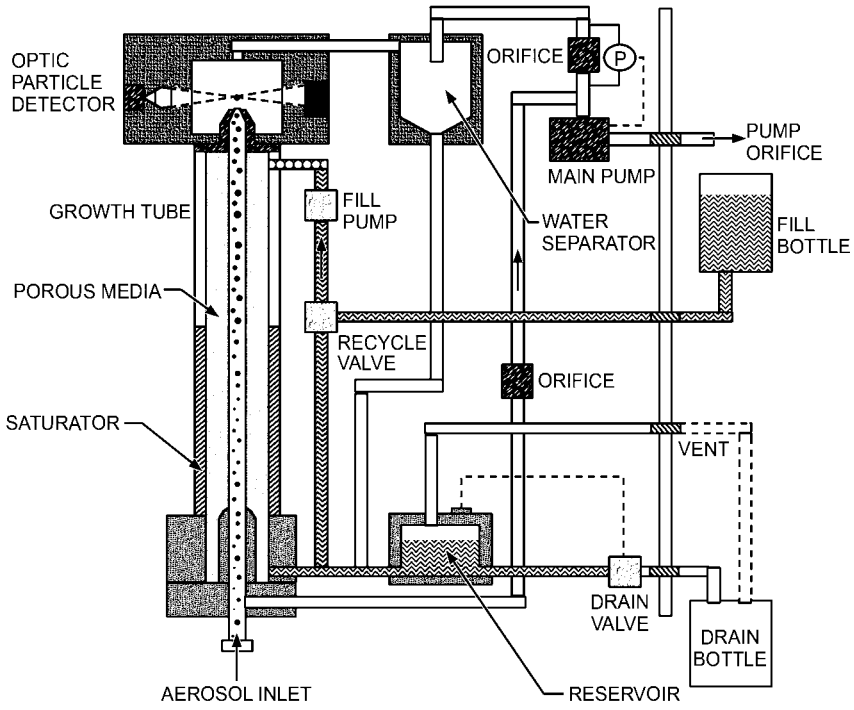

Figure 2.7 Schematic Diagram of Commercially Available, Water-Based CPC

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CPC's lower detection limit can be as good as that of butanol-based CPCs. When detecting highly hydrophobic particles, the lower detection limit can be as large as 20 to 30 nm (Chen and Pui 2013).

CPCs of the mixing type have also been commercialized recently. This type of CPC mixes a hot vapor stream and a cool aerosol stream to achieve a supersaturation condition (Fuchs and Sutugin 1965; Kousaka et al. 1982; Okuyama et al. 1984; Kim et al. 2003; Gamera-Castaño and de la Mora 2000; Sgro and Juan Fernández de la Mora 2004; Kim et al. 2002). The detection of individual particles after they are grown is the same as that in CPCs of other types. Fuchs and Sutugin (1965) were the first to propose a CPC of this type. The development of such a CPC had remained primarily in academic institutes until the recent commercial development. The turbulent mixing of aerosol- and vapor-saturated streams is typically used to enhance the mixing process and to maintain the fast response of the CPC (i.e., fast growth of particles) (Kim et al. 2003; Gamera-Castaño and Fernández de la Mora 2000; Sgro and de la Mora 2004). With the careful control of temperatures of aerosol- and vapor-saturated streams, it is claimed that particles with sizes of 1 nm and below can be activated and detected.

2.6.4 TIME-OF-FLIGHT PARTICLE COUNTER

Another particle counter is an accelerating nozzle combined with light-scattering measurement. Figure 2.8 shows a schematic diagram of the commercially available aerodynamic particle sizer (APS) described by Agarwal and Sem (1980). In this device, particles are accelerated to different speeds through a small nozzle. Due to particle inertia, the larger the particle size, the lower the speed of the particle. To provide a measure of particle size, the particle velocity at the particle's exit from the nozzle is measured by detecting the time it takes for the particle to pass through two laser beams with a fixed separate distance. This enables measurement of the "aerodynamic size" of the particles in the size range of 0.5 to 30 μm, which is related to particle deposition in the lung and to the settling

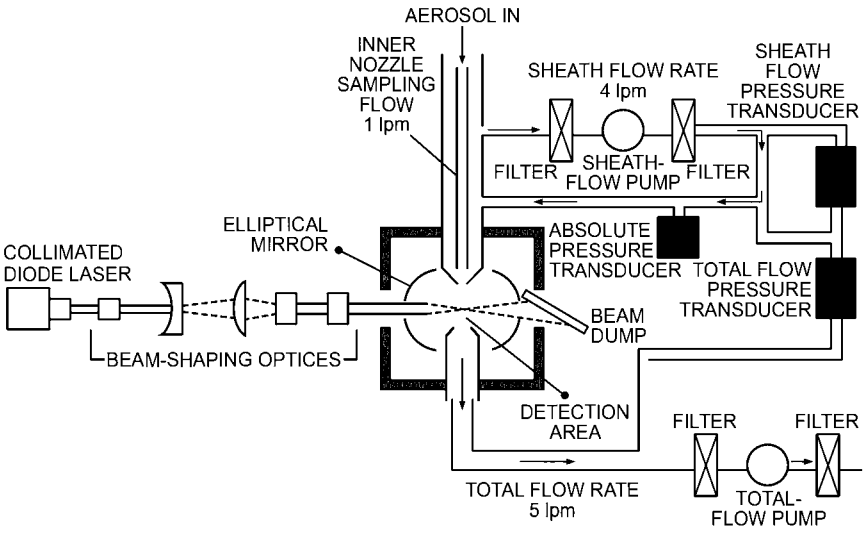


Figure 2.8 Schematic Diagram of APS

(Reproduced from Chen and Pui [2008] with permission of ACGIH®)

speed of the aerosol (Chen and Pui 2008). Calibration studies on the APS were reported by Chen et al. (1985) and Baron (1986). Recent APS developments include the incorporation of an ultraviolet pulse laser to detect the viability of bioaerosol and of a high-energy laser (Hairstone et al. 1997) and using mass spectrometry for measurement of in-situ particle composition (Noble and Prather 1996; Sylvia and Prather 1998; Salt et al. 1996; Silva and Prather 1997).

The aerosizer is another commercial aerodynamic sizing instrument and operates under the same principle of time of flight as the APS. One significant difference between the APS and the aerosizer is that in an aerosizer, particles are accelerated through a critical nozzle at sonic flow, whereas in an APS they are subjected to a moderate acceleration at subsonic flow. An aerosizer is capable of measuring a wider size range of particles, from 0.5 to 2000 μm and higher, which is up to 1100 particles/cm^3 more than the APS. The aerosizer's calibration curve, however, is strongly dependent on particle density (Chen and Pui 2008). Cheng et al. (1993) calibrated two aerosizers, one using uniform-sized spherical polystyrene latex (PSL) particles and glass beads and one with nonspherical natrojarosite particles.

2.7 FIBROUS FILTERS

High-efficiency filters are usually the last element in controlling the cleanliness of air supplied to a cleanroom. Regardless of filter efficiency, virtually all air filters used for filtering supplied air to cleanrooms are made from fibrous filter media. That is, these are filter media made with multiple layers of fibers, which are then manufactured into filters of various configurations. Although most filter media are manufactured from fibers, expanded polymeric membranes or polytetrafluoroethylene (PTFE) are also fibrous filters. In this case, fibrous dendrites are formed during the process of expanding the polymer in the manufacture of PTFE. The dimensions and the properties of the fibers determine the filter performance. In general, the finer the fibers, the higher the efficiency as well as the cost of the filter media.

2.7.1 FIBERS IN CLEANROOM FILTER MEDIA

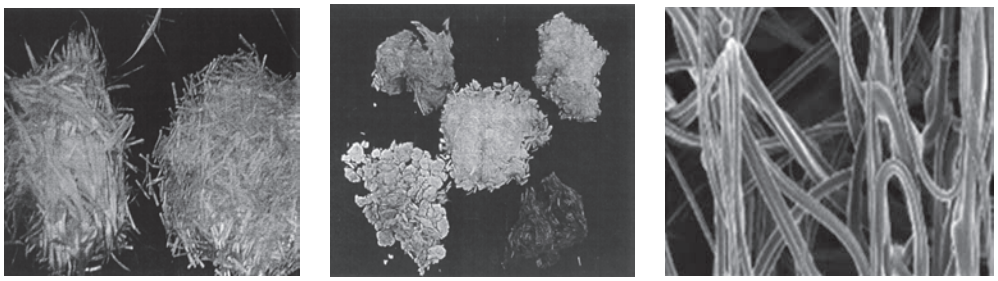
The most common fiber used in cleanroom filters is microfiber glass with diameters from nano sizes to several microns (see Figure 2.9).

High-efficiency filters in cleanrooms are seldom used by themselves. It is common practice to use prefilters with lower efficiency and cost, mainly to improve the overall performance of the filter system at a lower cost and resistance. These prefilters also protect the high-efficiency filters from premature dust loading. Most of the prefilters are made either with coarser glass fibers, glass or polymeric filaments, or in some cases cellulosic fibers. These are shown in Figure 2.10. Because cellulosic fibers are similar to those used for conventional paper products and many cleanroom filter media are made on paper machines, filter media from any material are often colloquially referred to as *filter paper*.

Microfiber glass is mostly used in filters with minimum efficiency reporting values (MERVs) (ASHRAE 2017) from MERV 8 to high-efficiency particulate air (HEPA) and ultralow particulate air (ULPA) filters. For cleanrooms, the latter can also be considered finishing filters since they are the last filter element in the air supply to a cleanroom. Almost always these glass fibers are made into filter media by a wet-laid process on a paper machine. Filament fibers can be either polymeric or glass. These are mainly made into filter media using dry-laid or blown techniques. Unlike the short cellulose or microfiber glass fibers, filament fibers are continuous, as shown in Figure 2.9. These filament fiber media are primarily used for prefiltration in cleanrooms. Cellulosic fibers are seldom used by themselves for cleanroom filter media; however, they may be used as part of a blend of fibers in some cases. Regardless of the material used, fiber size is key to the performance of the filter media and hence the filter. Higher efficiencies require finer fibers, sometimes down to 100 nm in size, but these are not only more expensive but also lead to higher resistance and costs.

2.7.2 HIGH-EFFICIENCY CLEANROOM FILTER MEDIA

It is commonly assumed that reference to cleanroom filters implies HEPA or ULPA filters. As noted previously, these are mostly made with microfiber glass. A typical media



Microfiber glass | Cellulose | Polymeric, filament fiber

Figure 2.9 Fibers in Filter Media

(Courtesy R. Vijayakumar of AERFIL)

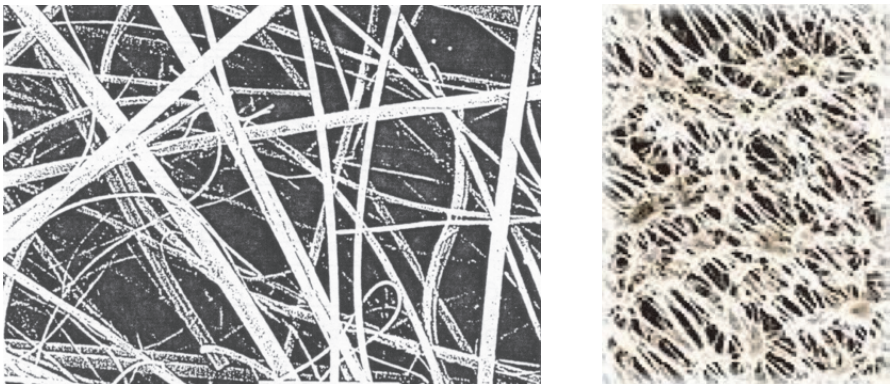


Figure 2.10 Microfiber Glass and PTFE Media

(Courtesy R. Vijayakumar of AERFIL)

is almost 0.5 μm thick and has several hundred layers of loosely formed fibers held in place by a small amount of polymeric binder. As seen in Figure 2.10, although each layer appears to have large openings, the media as a whole provides a sufficiently tortuous path for the airflow to allow effective removal of particles. In addition to microfiber glass media, PTFE membranes are also used for cleanroom filters. These membranes are made by stretching a slurry of polymer and binder into a sheet and flashing off the binder to form a dendrite structure (see Figure 2.10). Unlike glass media, these membranes are made in single layers. Hence, in practice, they are used in double or multiple layers to avoid problems due to nonuniformity in the individual layers.

2.8 FILTRATION MECHANISMS

The mechanisms by which particles are removed by fibrous filters are sieving (straining), interception, inertial impaction, and diffusion. These are schematically shown in Figure 2.11, where the multiple layers of fibers are shown as gray circles perpendicular to the page. In addition, electrostatic attraction (ESA) enhances particle capture due to the electric force between particles and charged fibers. Charged fibers are increasingly common in polymeric media used in lower-efficiency filters. Because the performance of these charged filters may decrease with time due to charge dissipation due to dust loading, these types of filters are not common for cleanroom HEPA and ULPA filters, except as prefilters in the central air handlers.

Sieving (straining) is the common intuitive mechanism of particle removal. Particles larger than the gap between fibers are trapped (see Figure 2.11). Since particles of concern in cleanrooms are submicron and the gaps between fibers in most media are often larger than this size, sieving is not a dominant mechanism of particle removal for cleanrooms.

Interception, as the name implies, occurs when a particle in the airstream collides with the fiber and is collected (see Figure 2.11). Although interception can occur for all particle sizes, in cleanroom filters it mainly affects larger particles, because smaller particles are affected more readily by diffusion capture.

Inertial impaction occurs when particles in the airstream are unable to stay with the airstream as air flows around fibers and separate from it, impacting the fiber. That is, the particle continues to move towards the fiber even as the airstream bends around it, as

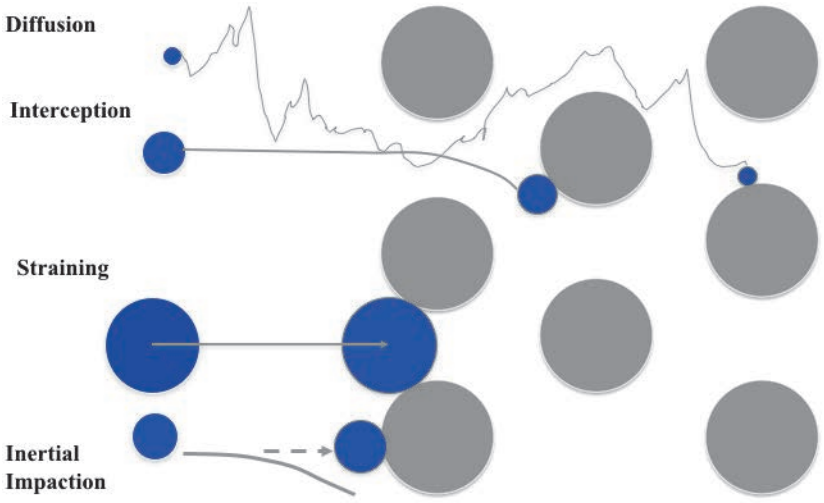


Figure 2.11 Particle Capture Mechanism

(Courtesy R. Vijayakumar of AERFIL)

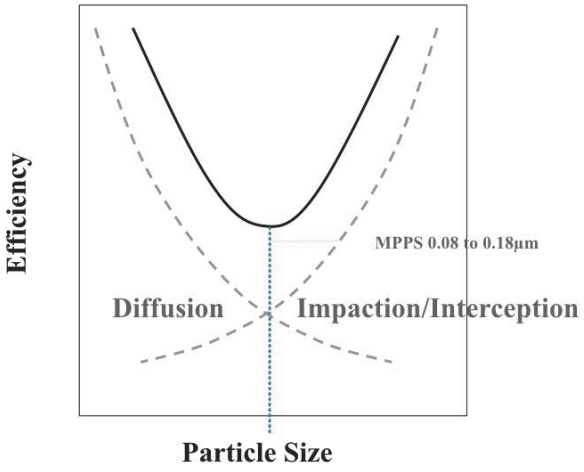


Figure 2.12 Filtration Mechanisms and MPPS

(Courtesy R. Vijayakumar of AERFIL)

shown in Figure 2.11. Because inertia increases with particle size, inertial impaction favors larger particles and is aided by higher flow velocities.

Diffusion capture occurs as a result of the rapid and random motion of small particles due to their internal thermal energies, also known as *Brownian motion*. As these small particles flow with the airstream, their rapid random motion can bring them in contact with the fiber and they are collected. This random motion increases with decreasing particle sizes. Since submicron particles are of main concern in cleanrooms, particle removal is considered to be diffusion-dominated in cleanroom filters. Further, changes in airflow velocities alter diffusion capture by changing the time available for airflow through the filter and hence the diffusion transport of particles to the fiber.

The combined effect of all the mechanisms of filter capture results in filter efficiency with a distinct minimum efficiency (see Figure 2.12), which is unique to fibrous filters. The particle size at which the minimum efficiency occurs is called the most penetrating particle size (MPPS) (Lee and Liu 1980). While it is intuitively obvious that the filter will have a higher efficiency at larger sizes, it is somewhat counterintuitive that the filter has higher efficiencies even for particles smaller than the MPPS. The MPPS also increases with lower velocities, as shown in Figure 2.13, since a lower velocity enhances diffusion capture and diminishes inertial impaction. For cleanroom HEPA and ULPA filter media, as an approximate rule of thumb, reducing the velocity by half will result in nearly an order of magnitude increase in efficiency and also result in about half the resistance. The changes will be somewhat less but still substantial for complete filters. So it is always advisable to aim for the lowest operating velocities through the filter to take advantage of this property of fibrous filters. This is discussed further in Section 2.10.

2.9 MEMBRANE FILTERS

Membranes are webs with a complex pore structure that are created by forming, casting, or stretching polymers. In cleanrooms, most applications for membrane filters are for process liquids or for high-purity compressed gases.

Among membranes, only PTFE is used for cleanroom air filters. Because PTFE is resistant to acids and several other chemicals, filters made with PTFE are finding favor where these chemicals are used, for example, hydrofluoric etch baths in microelectronics. Because they are also more robust than traditional microfiber glass media, they are also finding uses where handling or cleaning may be required, such as in minienvironments, hazardous material laboratories, and the like. PTFE is usually more expensive and sealing

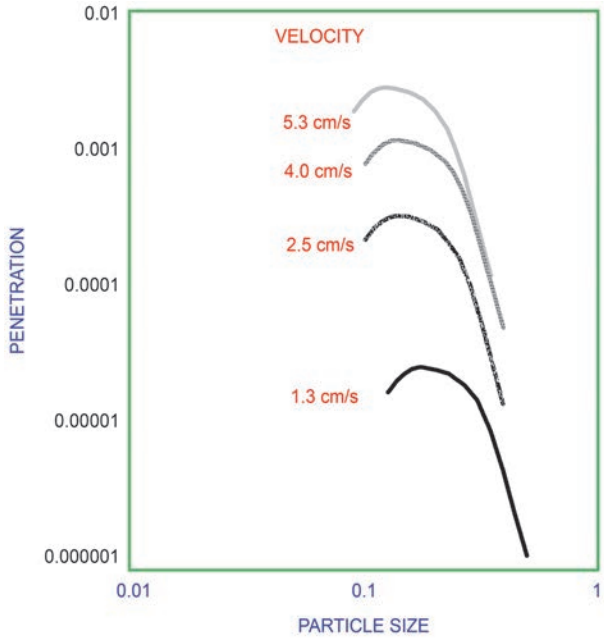


Figure 2.13
Filter Efficiency and Velocity

(Courtesy R. Vijayakumar of AERFIL)

leaks in PTFE filters is more difficult. Thus, in spite of their advantages their use is somewhat limited in cleanroom filters.

2.10 TYPE AND CONSTRUCTION OF HIGH-EFFICIENCY FILTERS FOR CLEANROOMS

High-efficiency filters for cleanrooms are usually made by pleating one of the media discussed previously and encasing the pleated filter pack in a suitable frame. In general, the performance of a filter depends on the velocity of air through the media and not on the total airflow through the filter. That is, in a 24 × 24 in. filter (4 ft^2) (610 × 610 mm [0.37m^2]) with 40 ft^2 (3.72 m^2) of filter media, the velocity through the media will be a tenth of the mean velocity through the face of the filter. Hence, the more media one can pack into a filter element the lower the pressure drop across it (up to a point) and the higher its efficiency. Commercial filters achieve this by one of three main styles of pleating: pleating with corrugated separators of aluminum, paper board, or other material (Figure 2.14); pleating with beads of adhesive or with strings or ribbons of media, also called *minipleat* style (Figure 2.15); or by separating pleats by means of embossing the media (Figure 2.16). The minipleat style of filter is currently available as a flat panel filter or assembled in a V formation from individual thin pleated panels, as shown in Figure 2.17. This type of construction, also known as a *V bank filter*, is common for prefilters in the air-handling systems of cleanrooms. It allows for compact filters with large amounts of media.

Because the minipleat and embossed construction allow for denser pleats, these types of filters can be constructed more compactly and thinner for the same amount of media than the corrugated separator construction. Due to the numerous airflow channels provided by the corrugations, the corrugated style of filter may result in more uniform velocity variations across the face of the filter that may be an important consideration for certain applications. Currently, minipleat filters with about the same amount of filter

Figure 2.14
Separator Style Filter

(Courtesy Yantair Co. Ltd.)

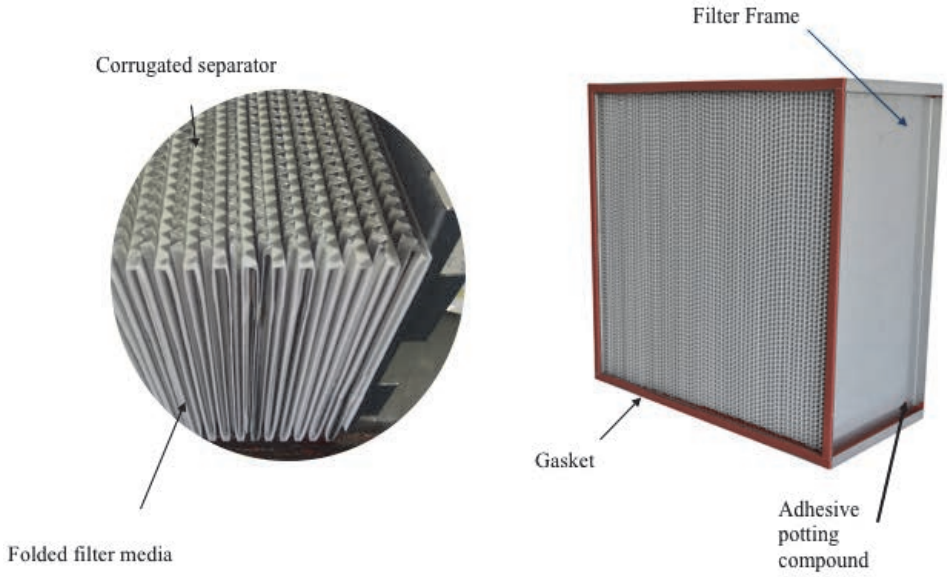


Figure 2.15
Minipleat Filter

(Courtesy Yantair Co. Ltd.)

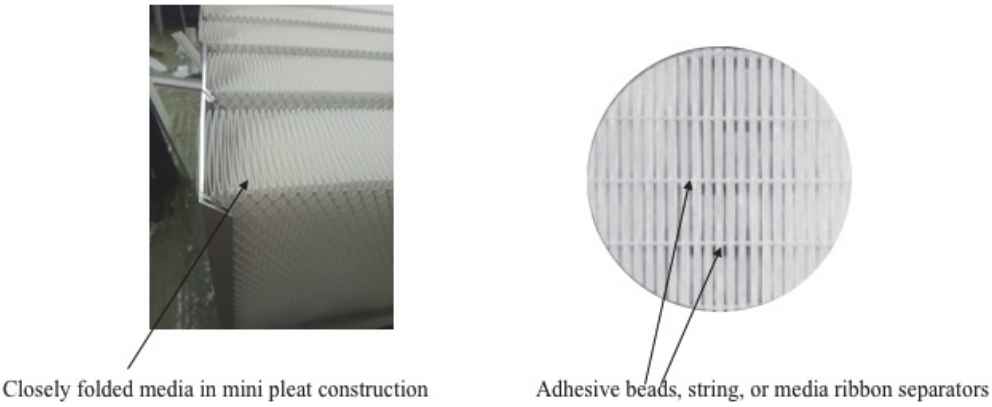
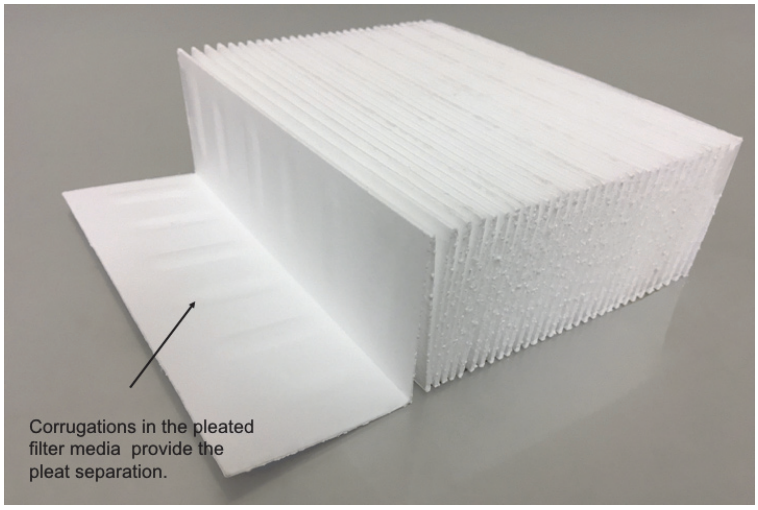


Figure 2.16
Embossed Pleat Filter

(Courtesy AAF FLanders)



media and equivalent performance as filters with corrugations are about a third the depth, i.e, 4 in. (101 mm) as opposed to the typical 12 in. (305 mm) for the traditional corrugated separator HEPA filter.

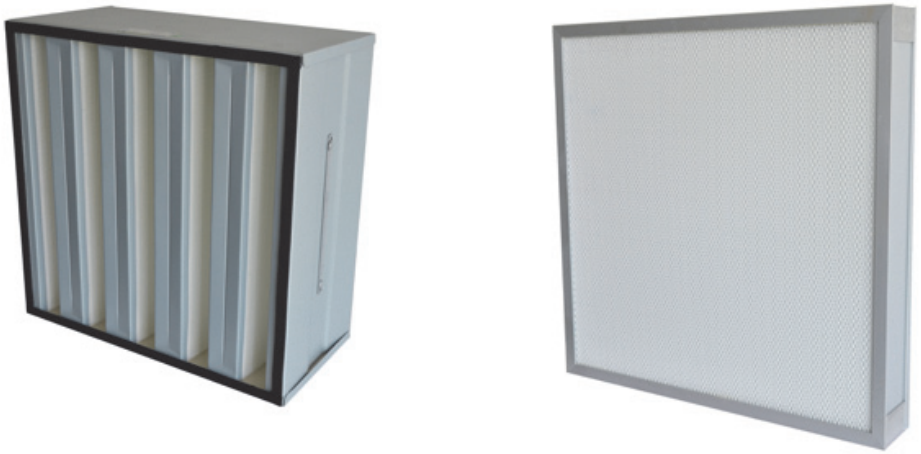
In modern filter manufacturing operations, the filter packs of any of the three styles are first made on automated pleating machines. Then these packs are assembled in a filter frame and held in place by adhesives or potting compound, as shown in Figures 2.14 to 2.16. The faces of these filters may also be provided with mesh screens, partly as protection during handling and partly as an aid to developing uniform velocities. Standards such as IEST-RP-CC001 (IEST 2016a) provide minimum requirements for filter construction.

A typical modern cleanroom panel filter is made with metal frames, often extruded or powder coated (see Figure 2.17). These filters are provided with gaskets to seal them to the support framing on which they are mounted. These gaskets may also be formed seamlessly in situ using appropriate polymers. Alternatively, especially in microelectronic cleanrooms, gaskets are replaced by a very soft gel material and sealed against a knife edge. Figure 2.18 shows a filter with the gel in its frame. In Figure 2.19, the gel is in the supporting ceiling grid and the edge in the filter frame seals against it. In both cases, it is crucial that the edge does not bottom out on the holding frame, because this will result in an improper seal, leading to leaks in the filter ceiling or housing.

Panel filters are the preferred filter construction for flooded plenum or ballroom cleanrooms. An alternative filter construction in vogue is shown in Figure 2.20. In this construction, the filter is provided with a "hood" with an attachment for a flexible duct. The use of ducts and ducted filters can simplify construction of the cleanroom by elimi-

Figure 2.17
V Bank and Panel Minipleat Filters

(Courtesy Yantair Co. Ltd.)

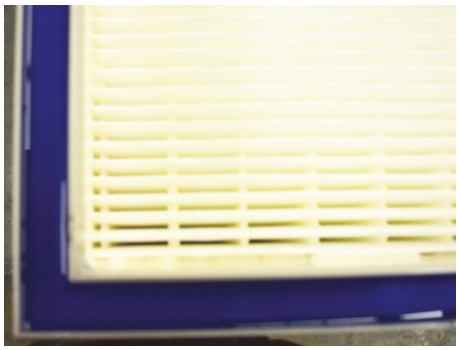


V Bank minipleat filter

Cleanroom panel minipleat filter

Figure 2.18
Filter with Blue Gel Instead of Gasket

(Courtesy R. Vijayakumar of AERFIL)



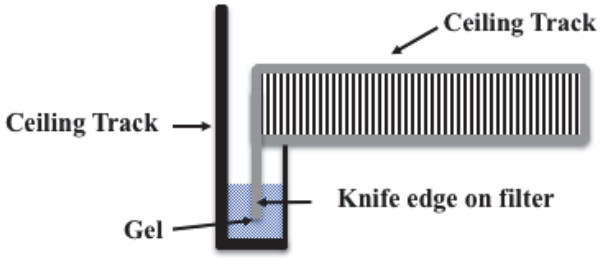


Figure 2.19
Filter with Knife Edge in Gel Poured in Support Grid

(Courtesy R. Vijayakumar of AERFIL)

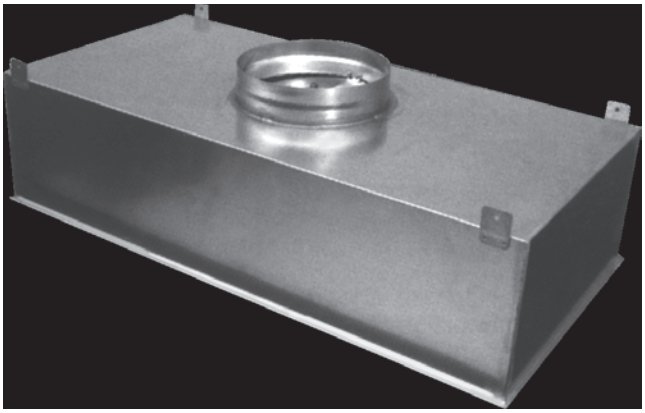


Figure 2.20
Ducted Filter

(Courtesy AAF FLanders)

nating the need for an airtight plenum. It also makes repairs and replacement of single filters less disruptive to the entire cleanroom, since each filter may be isolated. In a variant of the ducted filter, a fan is added to the duct opening, resulting in a self-contained filter with its own air supply. These units are also called *fan filter units* (FFUs). FFUs afford a convenient means of constructing a clean space without elaborate ductwork or structures as in formal cleanrooms. For this reason, FFUs are more common for portable cleanrooms or workstations than for large facilities.

2.11 TESTING OF HIGH-EFFICIENCY FILTERS

Unlike most other air filters, all cleanroom filters are tested and individually certified. Not only are they tested to determine their efficiency, but they are also tested for leaks (i.e., integrity). Further, in many instances, especially in regulated industries, these filters are periodically tested for leaks as installed.

Filter efficiency is a measure of its overall performance to remove particles in the airstream. For example, when we specify a filter with 99.99% efficiency at 0.12 µm, we expect the filter to remove 99.99% of 0.12 µm particles in the airstream and allow just 0.01% to pass downstream of the filter. One may also think of this filter allowing 100 particles of this size to pass through it for every million upstream. The efficiency does not take into account any variability of the performance across the filter. Thus, areas with worse performance than the desired are balanced by better-than-desired performance elsewhere in the filter to result in the overall desired mean value.

The efficiency of filters is determined by challenging the filter with particles and computing the efficiency from the measured concentrations of particles upstream and downstream of the filter:

$$\text{Efficiency} = 1 - (\text{Downstream Concentration}/\text{Upstream Concentration}) \qquad (2.5)$$

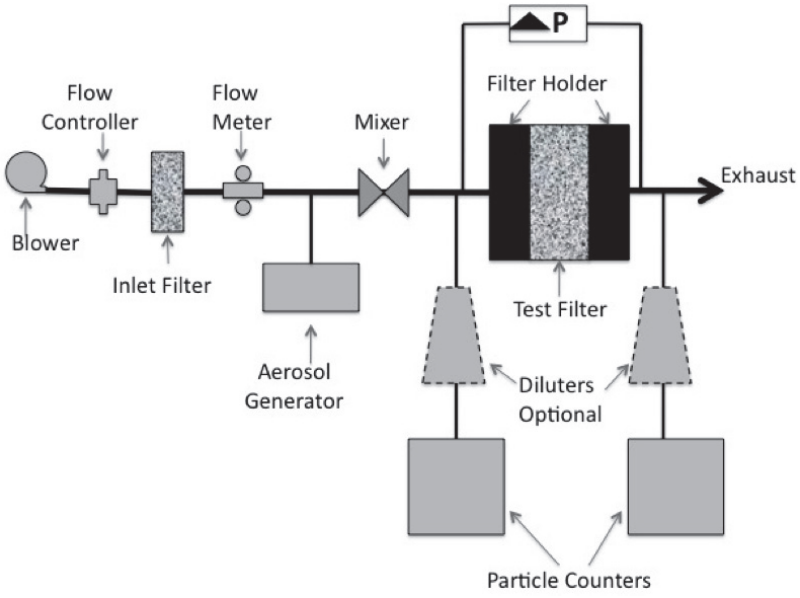


Figure 2.21
Schematic of Filter Efficiency Test Setup

(Courtesy R. Vijayakumar of AERFIL)

A schematic of a typical filter efficiency test setup is shown in Figure 2.21. Particle concentrations are usually measured in series by one particle detection instrument or simultaneously using two devices in parallel, as shown. Bear in mind that either technique yields valid test results and neither is superior to the other.

Because the filter efficiency varies substantially with particle size as discussed previously, it is good practice to specify filter efficiency at a specific particle size, usually the size critical to the process in the cleanroom. Current practice is that most cleanroom filters are specified and tested at or near their MPPS to ensure that they are tested at their worst condition. For most cleanroom HEPA and ULPA filters, the MPPS varies between 0.1 and 0.25 µm. Because filter performance is also closely linked to airflow rate, it is also good practice to test filters at the design flow rate, or at least at a flow rate somewhat higher than the design flow rate so that the filter will be equal to or better than the tested efficiency. Guidelines for efficiency testing are available in many national and international standards such as IEST-RP-CC001 (IEST 2016a), IEST-RP-CC007 (IEST 2016b), EN 1822 (CEN 2009), Japanese Industrial Standards, etc. All of these require testing at or close to MPPS and at rated airflow.

A leak in a filter is a local phenomenon, usually caused by mechanical defects or blemishes in the filter. In this case, the efficiency of the filter at this location will be substantially worse than the desired value. It is common practice to consider a filter to have a leak when the penetration (i.e., 1 – Efficiency) at any location is 5 to 10 times higher than the overall penetration. For the HEPA and ULPA filters previously discussed, a local penetration of 500 particles or 0.05% is considered a leak. Institute of Environmental Sciences and Technology (IEST) and International Organization for Standardization (ISO) standards specify a leak when the photometer-measured penetration is equal to or is five times higher than, respectively, the overall penetration tested at MPPS. Since most cleanrooms operate with unidirectional flows, any leak in a filter will introduce unacceptable levels of particles that will be carried by the unidirectional flow stream to areas of the work surfaces. Thus, leak-free filters are almost always required for cleanrooms.

Filter leaks are determined by scanning the surface of the filter with a probe (see Figure 2.22). Particle concentrations are measured by detection instruments connected to the scan probe. When the scan head passes over a leak, the concentrations downstream are

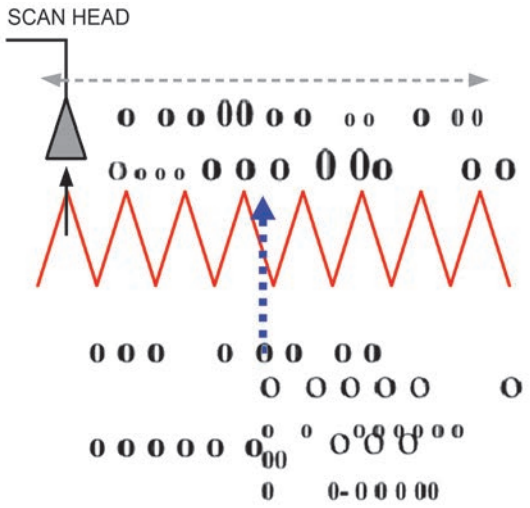


Figure 2.22
Filter Scanning for Leak Detection

(Courtesy R. Vijayakumar of AERFIL)

high and may even approach the upstream concentrations for large leaks, as shown in Figure 2.22. This location is then considered a leak. Scanning for leaks is usually accomplished by automated systems in the factory and by trained operators when hand scanning is required for testing installed filters. Guidelines for leak testing are provided in standards such as IEST-RP-CC034 (IEST 2016c), EN 1822 (CEN 2009), and ISO 14644-3 (ISO 2005). Generally, most standards recommend particles larger than MPPS for leak testing, since at the larger sizes the mean efficiency of a filter is much higher, permitting the ready detection of leaks. These standards also provide guidance and limitations on repairing leaks.

2.11.1 AEROSOL CHALLENGE

Efficiency and leak testing of cleanroom filters require a challenge aerosol. Without a controlled challenge, filter performance and leaks cannot be determined. The challenge aerosol materials in common use include poly-alpha-olefin (PAO), dioctyl phthalate (DOP), dioctyl sebacate (DOS), sodium chloride (NaCl), mineral oils, fused silica, and polystyrene latex (PSL) spheres of a specific particle size. Either polydisperse or monodisperse challenge aerosols may be used in filter testing. Polydisperse aerosols of the material of choice are used when a particle counter is used for measurements, since the device can size and count the particles in the sample. That is, the device will provide a size-specific concentration from which the efficiency for any particle size can be computed. A monodisperse aerosol of known distribution is used when a photometer is used for measurements, since this device measures the total aerosol concentration and cannot distinguish particle size. Because the photometer measures the total concentration, the measurements tend to be more stable and hence preferred for much in situ leak testing. When filter performance at a specific particle size is required, it is customary to test the filter using PSL spheres of the desired size. PSL spheres are available in sizes traceable to national standards bodies.

2.11.2 NOTE OF CAUTION ON FILTER SPECIFICATIONS

In cleanrooms, filters are the last stage in filtering air. Hence, it is important for the cleanroom designer to recognize that although filters tested to any national or international test standards will be good filters, not all of them are equivalent. It is especially important to note the continued erroneous specification of HEPA filter efficiency at

0.3 μm. The original HEPA filters were developed during the 1950s and the test specification is given in MIL-STD-282 (DOD 1956). This method uses a hot DOP challenge aerosol with a mass mean diameter of 0.3 μm and a geometric standard deviation around 1.35. The test specifies photometers to measure the particle concentrations for determining the efficiency. There are two subtle but important details in the method that lead to two common misconceptions. Failure to understand them may result in inferior performance to those specified for the cleanroom.

First, the count or number mean diameter of the hot DOP challenge aerosol used in MIL-STD-282 is somewhat smaller than the mass mean diameter of 0.3 μm and closer to the typical MPPS for HEPA filters. Hence it is erroneous to specify HEPA filters at 0.3 μm if the requirement is for efficiency at MPPS. Filters tested with 0.3 μm particles will be inferior to filters of the same efficiency tested according to MIL-STD-282. Historically, results of 99.99% efficiency filters tested by the MIL-STD-282 method have compared well with those tested at MPPS using particle counters.

Further, the response of a photometer varies nearly linearly with the cube of the particle diameter in the submicron size range of interest to cleanrooms. Since the mass of a particle is proportional to the cube of its diameter, it is also sometimes assumed that HEPA filters are tested by gravimetric measurements by photometers.

Thus, for good cleanroom design, it is important that the designer take into account these subtle but real differences in test standards. This becomes important because different filter suppliers follow different test standards, depending on their preference.

2.12 AIRBORNE ULTRAFINE PARTICLES AND MEASUREMENT

2.12.1 PARTICLE MATTER (PM) RATINGS, ULTRAFINE PARTICLES, AND NANOPARTICLES

If contamination risks in a cleanroom are caused by particles smaller than 0.1 μm, which are not within the size range in cleanroom classification, adequate sampling devices and measurement procedures to specify characteristics of these nanosized particles should be employed. The customer and the supplier should decide the maximum permitted concentration of such particles and the test method to be used to verify compliance (ISO 2015a). Currently, quite a large number of instruments are available, as discussed in Section 2.6, to conduct ultrafine particle measurement.

2.12.2 DEFINITIONS OF NANOPARTICLES AND ULTRAFINE AEROSOLS

Environmental nanoparticles are those that are formed spontaneously in the atmosphere. They are emitted from manufacturing processes, transportation systems, and power plants. Engineered nanoparticles are those formed from liquid-phase route or gas-phase synthesis. They are important building blocks for nanoscale materials and devices. Compared with micron-sized particles of the same composition, nanoparticles typically have special biological, chemical, or physical properties (Chen and Pui 2013). Particles with a diameter of 1 to 100 nm are considered nanoparticles. The weight of particles that have a diameter smaller than 100 nm micrometer is often identified by particle matter (PM) ratings as $PM_{0.1}$. It is important to note that the term *nanoparticle* was clearly defined in a workshop on Nanotechnology (IWGN 2000) as particles with at least one dimension less than 100 nm. In other words, nanoparticles can be particles, nanowires, or films in nanometer thickness. The "size" determined by an aerosol process may not be completely correlated with other properties (such as magnetic structure or catalytic activ-

ity). However, biological molecules, stable molecular clusters, and fullerene and oligonucleotides molecules may serve as examples of nanoparticles near the lower size limit (Pui and Chen 1997).

The terms *ultrafine particles* and *ultrafine aerosols* were used by atmospheric aerosol scientists who participated in a 1979 Workshop on Ultrafine Aerosols (WUFA) in Vienna (Liu et al. 1982). The purpose of the workshop was to evaluate the counting efficiencies of a number of condensation nuclei counters then available. At the time, ultrafine aerosols were defined as those characterized by particle diameters less than 0.1 µm (D_p < 100 nm) (Pui and Chen 1997). Previously, Fuchs and Sutugin (1971) had defined aerodisperse systems with particle diameters less than 100 nm with the term *highly dispersed aerosol*. More than 20 years later, the U.S. Environmental Protection Agency (EPA) used the term *ultrafine particles in a biological context* to characterize particle size distributions with mass median diameter (MMD) below about 0.1 µm (EPA 1996).

2.12.3 MEASUREMENT METHODS FOR ULTRAFINE PARTICLES

Although a large number of particle-counting techniques and commercial particle counters exist, not all of them are adequate for cleanroom application. In a cleanroom, a particle counter must be able to count individual particles. For the integral moment measurement, commercial instruments (i.e., CPCs) are capable of measuring nanoparticles as small as 3 nm. With respect to the number concentration level, nanoparticle concentration can be detected up to 3×10^5 particles/cm^3 in the single particle counting mode. The current status in detecting nanoparticle mass is, however, far from satisfactory. The lower limit in particle mass detection is 100 pg in practice (i.e., particle swarm optimization [PSO]), although the theoretical value is 10 pg.

The electrical-mobility-based technique (i.e., using differential mobility analyzers [DMAs]) has made significant progress for size distribution measurements. The technique measures the electrical mobility distribution of particles and converts the measured mobility distribution to the particle size distribution. With the recent development of DMAs, particles as small as 2 nm can be classified and sized. Significant progress has also been made in the response time of the instruments. Switched-mode power supply (SMPS) reduces the cycle time to 2 min, and differential mobility spectrometry (DMS) further reduces the time to a fraction of a millisecond (using sensitive electrometers as the particle concentration detectors). Despite these improvements, the challenge of the electrical-mobility-based technology remains: to conduct fast measurement of the nanoparticle size distribution at low concentration.

The separation of nanoparticles based on particle inertia is quite feasible. Most of the solid-stage impactors include stages with cutoff sizes less than 100 nm. Low-pressure impactors and nano-impactors (microorifice uniform deposit impactors, or MOUDIs) are specially designed to separate particles in submicron and nanometer size ranges. When these are combined with other particle concentration detectors, rapid measurement of particle size distributions has been made possible (i.e., using electrical low-pressure impactors [ELPIs]). The general issue with using impactor technology to measure nanoparticles is its low sizing resolution. The bounce of nanoparticles when they are impacted on solid or coated-solid stages could bias the size distribution measurement if the mass distributions were to be measured.

The shorter the wavelength of the light sources, the smaller the particles that can be detected. For light-scattering-based technology, some of the laser-based particle counters have lowered size detection limits to particle sizes smaller than 100 nm using He-Ne lasers. But, these are mostly used for particles ranging from 50 to 1000 nm. Using the technique of polarized lights, the lower size limit can be further reduced to 25 nm.

Dynamic light scattering (DLS) is the most popular technique used in commercial light-scattering instruments, with the claim of measuring particles down to 2 or 1 nm. The technique detects the broadening of the laser beam energy spectrum due to light interaction with nanoparticles. The broadening of laser beams refers to the mean diffusivity of nanoparticles. The size distribution of nanoparticles is recovered by matching the mean diffusivity with that calculated from the preassumed size distribution forms. Although the technique can be applied to aerosol measurement, most commercial instruments measure nanoparticles in liquid suspensions.

Finally, the old but mature technology of using the diffusion battery technique for nanoparticle measurement is still a viable option for budget-conscious users. The technology removes particles based on the particle diffusivity. By measuring the penetration through screens or capillary tubes, one can recover the size distribution of nanoparticles to be measured. Low size resolution and sophisticated data reduction schemes are the concerns of using devices of this type.

ISO 14644-3 (ISO 2005) presents a general sampling procedure to examine the ultrafine particle contamination in a cleanroom or clean zone. The first step is setting up the sample inlet probe of the DPC or CPC (with a particle size cutoff device, if required). Next is sampling the required air volume at each sample point and making replicate measurements as required in accordance with Annex B of ISO 14644-1 or with ISO 14644-2 (ISO 2015a, 2015b). Sampling ultrafine particles with a long sampling tube and a small sampling flow rate can cause a significant diffusion loss. Care must be taken to ensure that the sampling error due to ultrafine particle loss by diffusion is no greater than 5%. Next is calculation of the U descriptor concentrations in the ultrafine particle size ranges defined by the customer and the supplier and reporting of the data. When ultrafine particle concentration stability information is required, three or more measurements at selected locations are required at time intervals agreed upon by the customer and the supplier (ISO 2005).

2.12.4 U DESCRIPTORS

ISO 14644-3 (ISO 2005) reports the U descriptor method to present the measurement results for ultrafine particle concentration in a cleanroom or clean zone. The descriptor serves as the upper limit for the location averages or as an upper confidence limit (UCL), or both, as appropriate. It is independent of airborne particulate cleanliness classes but might be specified alone or in conjunction with one or more of the classes. U descriptors are expressed using the format "U (x; y)", where x is the maximum allowable concentration (number of particles per cubic metre of air) of ultrafine particles and y is the size in micrometers at which the applicable DPC counts such particles with 50% counting efficiency. For example, U (100,000; 0.01 μm) describes air with no more than 100,000 particles/m^3 at a particle size of 0.01 μm (ISO 2005). Note that if the U descriptor is used to supplement an airborne particulate cleanliness class, x should be no less than the particle concentration limit applicable to the considered size of 0.1 μm for the specified ISO class (ISO 2015a). The sampling system used to measure a U descriptor should have a counting efficiency within 50% at the ultrafine particle size defined (U). It includes a tolerance band of ±10% of the ultrafine particle size, shown as sizes 1.1U and 0.9U. For particles above and below the 10% size tolerance band, acceptable minimum and maximum counting efficiencies are based on the penetration of a diffusion element calculated to have at least 40% penetration efficiency for particles 10% larger than U and at least 60% penetration efficiency for particles 10% smaller than U. If the DPC or CPC has a counting efficiency curve that falls to the right of the designated region, it should not be used to measure or verify the U descriptor. If the curve falls to the left of the designated region,

modify the counting efficiency with a particle size cutoff device to decrease it. These cutoff devices remove particles smaller than a defined size, which reduces penetration in a well-defined and reproducible manner. Particle size cutoff devices are available in a variety of sizes and configurations, all of which are acceptable provided they produce the penetration characteristics required. Diffusion battery elements and virtual impactors are suitable particle size cutoff devices that can be used (ISO 2005).

2.13 AIRBORNE MACROPARTICLES AND MEASUREMENT

Similar to contamination risks caused by ultrafine particles, if contamination risks are caused by macroparticles, appropriate sampling devices and measurement procedures to specify the characteristics of these large particles should be used. In the measurement, it is important to minimize losses of macroparticles to obtain an accurate sample. As was mentioned in Section 2.5, two methods could be applied to obtain the size distribution and mass concentration of macroparticles. There are many existing instruments for conducting macroparticle measurements, such as time-of-flight particle counters, DPCs, and cascade impactors.

2.13.1 MEASUREMENT METHODS FOR MACROPARTICLES

The measurement methods for macroparticles with and without particle collection were mentioned in Section 2.5. For particle collection measurement cascade impactors are mostly used, and DPCs and time-of-flight particle counters are usually used for measurements without collection. Microorifice uniform deposit impactors (MOUDIs) and electrical low-pressure impactors (ELPIs) are widely used to collect both nanosized and macrosized particle samples. In stages 1 to 3 of MOUDI, macroparticles are collected with size intervals of $PM_{10–18}$, $PM_{5.6–10}$, and $PM_{2.5–5.6}$, respectively. The ELPI can be used for both particle collection and number count. The first three stages of ELPI collect macroparticles with $PM_{6.8–10}$, $PM_{4.4–6.8}$, and $PM_{2.5–6.8}$, respectively. The collected macroparticle samples from both MOUDI and ELPI allow for further microscopic observation and gravimetric analysis. The mass concentration of macroparticles is then defined as the total weight or number on the 1 to 3 impactor stages divided by the total airflow which was passed through the impactor. Measurements made for individual particles with a light microscope or for particle composition using an electron microscope are also allowed, presenting shape and number of macroparticles (ISO 2005).

As was previously mentioned, many in situ direct-reading instruments are now available for reporting size and concentration of macroparticles. DPCs and time-of-flight particle counters are often used. The aerodynamic particle sizer (APS) is a time-of-flight particle counter that provides a measure for particles between sizes of 0.5 and 30 μm. Another commercial instrument operated under the same time-of-flight principle as the APS is the aerosizer. This instrument is capable of measuring particles in a wider size range of 0.5 to 2000 μm and in higher concentrations up to 1100 particles/cm^3.

Similar to measurement for ultrafine particles, ISO 14644-3 (2005) describes the following procedure for macroparticle measurement: Set up the sample inlet probe of the selected apparatus such as an APS or MOUDI. Sample the air volume required for collecting at least 20 macroparticles at each sample point and making measurements as specified in ISO 14644-1 or ISO 14644-2 (ISO 2015a, 2015b). Calculate the M descriptor concentration in the particle size ranges agreed upon by the customer and the supplier, and report the data. If macroparticle concentration stability information is required, make

three or more measurements at selected locations at time intervals agreed upon by the customer and the supplier (ISO 2005).

2.13.2 M DESCRIPTORS

ISO 14644-3 (ISO 2005) reports the M descriptor method to present the measurement results for ultrafine particle concentrations in a cleanroom or clean zone. The M descriptor may be specified independently or as a supplement to airborne particulate cleanliness classes (ISO 2015a). The M descriptor is expressed in the format "M (*a*; *b*); *c*", where *a* is the maximum permitted concentration of macroparticles (expressed as macroparticles per cubic metre of air), *b* is the equivalent diameter (or diameters) associated with the specified method for measuring macroparticles (expressed in micrometers), and *c* is the specified measurement method (ISO 2005). Note that if the sampled airborne particle population contains fibers, the M descriptor may have to be supplemented with a separate descriptor for fibers, having the format "M_{fiber} (*a*; *b*); *c*". For example, to express an airborne particle concentration of 10,000 particles/m^3 in the particle size range of >5 μm using a time-of-flight aerosol particle counter to determine the aerodynamic diameter of the particles, the designation would be "M (10,000; >5 μm); time-of-flight aerosol particle counter". To express an airborne particle concentration of 1000 particles/m^3 in the particle size range of 10 to 20 μm using a cascade impactor and microscopic sizing and counting, the designation would be "M (1000; 10 μm to 20 μm); cascade impactor followed by microscopic sizing and counting". Note that if the M descriptor supplements an airborne particulate cleanliness class, the macroparticle concentration *a* should be no greater than the particle concentration limit (particles per cubic metre) applicable to the considered size of 5 μm for the specified ISO class (ISO 2005).

2.14 STATISTICAL ANALYSIS

ISO 14644-1 (ISO 2015a) reports the statistical analysis method for the treatment of particle concentration data obtained in a cleanroom or clean zone. A brief description follows.

2.14.1 AIRBORNE PARTICLE CONCENTRATION LIMITS

The air in a cleanroom or clean zone meets the airborne particulate cleanliness class acceptance criteria when the averages of the concentrations measured at each location fall at or below the class limit. In addition, if the number of locations sampled is less than 10, the mean of these averages must fall at or below the class limit or U descriptor (please refer to Section 2.12.4) with a 95% UCL (ISO 2015a). The average particle concentrations and the 95% UCL are to be calculated using the equations in the following sections.

2.14.2 AVERAGE PARTICLE CONCENTRATION AT A LOCATION

Calculation of the average particle concentration should be performed for each sampling location at which two or more samples were taken. The average particle concentration *A* at a location is the sum of the individual sample particle concentrations *C* divided by the number of samples taken at the location *n* as shown in Equation 2.6. If only one sample is taken, it is the average particle concentration (ISO 2015a).

$$A = (C_1 + C_2 + \ldots + C_n)/n \tag{2.6}$$

Table 2.4 UCL Factors for 95% UCL

Number of Individual Averages (l)	2	3	4	5	6	7	8	9
95% ULC Factor	6.31	2.92	2.35	2.13	2.02	1.94	1.90	1.86

2.14.3 MEAN OF THE AVERAGES

The mean of the averages M is the sum of the individual averages A divided by the number of locations l as shown in Equation 2.7. All locations are weighted equally, regardless of the number of samples taken (ISO 2015a).

$$M = (A_1 + A_2 + \ldots + A_l)/l \tag{2.7}$$

2.14.4 STANDARD DEVIATION OF THE AVERAGES

The standard deviation of the averages SD is the square root of the sum of the squares of differences between each of the individual averages and the mean of the averages, $(A_l - M)^2$, divided by the number of locations l minus 1, as shown in Equation 2.8 (ISO 2015a):

$$\mathrm{SD} = \sqrt{\frac{(A_1 - M)^2 + (A_2 - M)^2 + \ldots + (A_l - M)^2}{l - 1}} \tag{2.8}$$

2.14.5 UPPER CONFIDENCE LIMIT (UCL)

The 95% UCL of the mean of averages M is determined by adding to the mean the product of the appropriate UCL factor and the standard error SE as shown in Equation 2.9 (ISO 2015a):

$$95\%UCL = M + t_{0.95}\left(\frac{SD}{\sqrt{l}}\right) \tag{2.9}$$

The variable $t_{0.95}$ represents the 95th percentile (quantile) of the t distribution, with $l - 1$ degrees of freedom. Values of the Student's t distribution ($t_{0.95}$) for the 95% UCL are given in Table 2.4. Alternatively, Student's t distributions provided in a statistical computer program are also acceptable (ISO 2015a).

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3 Surface Particulate Contaminants

Surface particulate contamination is a major problem in cleanrooms in semiconductor and electronics industries. Particle deposition on sensitive mechanical or electrical parts or wafer surfaces can lead to device failure, causing yield losses. In the manufacture of precision electrical or mechanical components such as integrated circuits, particulate contamination control is of vital importance.

3.1 SURFACE PARTICLE DEPOSITION

In aerosol physics, deposition is the process of aerosol particles collecting or depositing on solid surfaces. It can be divided into two subprocesses: dry deposition and wet deposition. The deposition velocity, or the rate of deposition, is slowest for intermediate-sized particles. Very small particles are greatly influenced by Brownian diffusion, and very large particles settle quickly through sedimentation or impaction.

If there is no motion of the air and the diffusion is neglected, particles will settle with the same constant settling velocity v due to gravity and drag, and the flux density F is calculated as $v \cdot c$, where c is particle concentration. Whether a particle will impact with a certain obstacle or not is often studied. This can be predicted with the Stokes number $\mathrm{Stk} = S/d$, where S is the stopping distance and depends on particle size, velocity, and drag forces and d is the characteristic size, often the diameter, of the obstacle. If Stk is greater than 1, the particle will collide with the obstacle; if less than 1, it will not.

Deposition due to Brownian motion obeys Fick's first and second laws. The resulting deposition flux is defined as $J = n \cdot (D/\pi t)^{1/2}$, where J is deposition flux, n is the initial concentration, D is the diffusion constant, and t is time. This can be integrated to determine the concentration at each moment of time. This deposition flux was derived based on a stationary air condition; for real air in a cleanroom, the calculation of flux is shown in Section 2.4 of Chapter 2.

Dry deposition is caused by any one of the following processes:

- Gravitational sedimentation, where particles fall down due to gravitation.
- Interception, where small particles follow airstream lines but may collide with an obstacle if they flow too close to it.
- Impaction, where small particles near larger obstacles are unable to follow the curved airstream lines due to inertia, resulting in the small particles hitting the bigger obstacle. The larger the mass of the small particle, the greater its displacement from the airstream line.

- Diffusion (or Brownian motion), where aerosol particles move randomly due to collisions with gas molecules. These collisions may lead to additional collisions with obstacles or surfaces. There is a net flux towards lower concentrations.
- Turbulence, where turbulent eddies in the air transfer particles that can collide. Again, there is a net flux towards lower concentrations.
- Other processes, such as diffusiophoresis, thermophoresis, and electrophoresis.

In wet deposition, atmospheric hydrometeors scavenge aerosol particles, meaning dry deposition is gravitational coagulation with water droplets. However, wet deposition seldom occurs in a cleanroom.

3.2 PARTICLE ADHESION TO SURFACES

The primary forces that influence the adherence of small particles to dry surfaces are the intermolecular London-van der Waals forces (attractive forces between adjacent molecules attributable to electron cloud interactions). These forces vary as the first power of particle diameter.

Because cleaning-related forces, such as drag or acceleration, vary as higher powers of particle diameter, small particles are more difficult to remove than larger particles; that is, while both adhesion and cleaning forces decrease with decreasing particle size, the London-van der Waals forces decrease much more slowly. The net effect is that the ratio of London-van der Waals adhesion force to cleaning force increases as particle size decreases. This relationship is illustrated by the data shown in Table 3.1.

Electrostatic forces can also create attractive adhesion forces between an electrically charged particle and a surface (or between an electrically charged surface and a particle). These forces should be minimal in a cleanroom that incorporates advanced electrostatic protection; otherwise, under some conditions, electrostatic forces could be important as a capture mechanism and, to a lesser degree, as a retention force.

Another particle adhesion consideration is the phenomenon of capillary condensation. This phenomenon is the formation of a liquid meniscus, or a bridge in the gap between the particle and an adjacent surface, which, because of surface tension, holds the particle on the surface. Such condensation can occur with air humidity well below the dew point of the ambient air, and it reflects the properties and geometry of the constricted airspace between the particle and the surface (see Figure 3.1).

Removing surface particles requires overcoming the adhesive force holding the particles to the surface. For purposes of this discussion, electrical retention forces are assumed negligible for cleanroom particles; only London-van der Waals forces and liquid bridge adhesion are considered. Immersing the surface in a liquid, and thereby surrounding the adhering particle in a solution, eliminates the liquid bridge adhesion force as a factor.

In addition, by careful selection of the liquid medium, the London-van der Waals attractive force can be reduced or eliminated, although present understanding does not allow accurate prediction of the magnitude of this effect. The choice of cleaning agent usually is determined empirically.

Using a liquid solution, however, introduces the possibility of ionic charges and their electrical forces. *Electrostatic double layer* is the term used to describe the charge distribution surrounding a charged particle immersed in a liquid electrolyte.

A negatively charged spherical particle is covered and adhered to by a layer of adsorbed, mostly positively charged ions. In the solution through which the particle and its ion sheath pass, an encircling ring of negative space charge always exists whereby the net charge of the enclosed volume remains zero.

Table 3.1 Effect of Particle Size on Adhesion Force

(IEST 2007)

Particle Size, µm	Particle Mass, g	Adhesion Force, dynes	Acceleration Required for Removal (Adhesion Force Expressed in Terms of its Gravity Equivalent), Gs
10	2×10^{-9}	9×10^{-2}	4.5×10^{4}
1	2×10^{-12}	9×10^{-3}	4.5×10^{6}
0.1	2×10^{-15}	9×10^{-4}	4.5×10^{8}

Materials: Al2O3 particles on an Al2O3 surface in air.

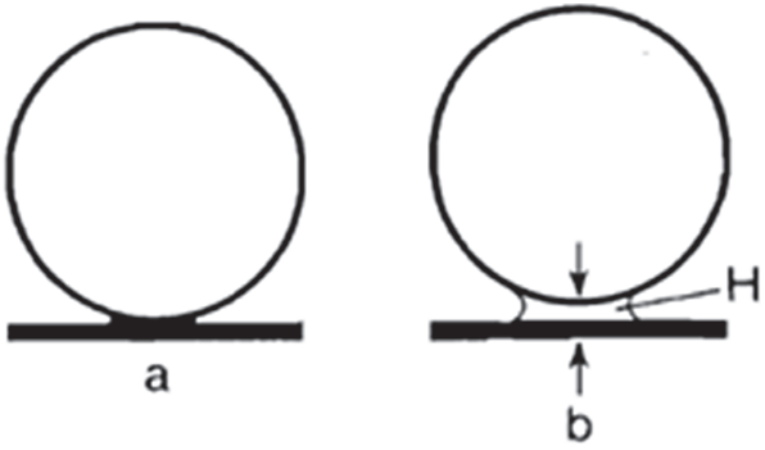


Figure 3.1 Capillary Condensation Associated with the Contact of a Particle with a Surface: (a) without an Intermediate Layer, (b) with an Intermediate Layer of Thickness *H* in the Contact Zone

The positively charged adsorbed layer and the negatively charged diffuse layer together constitute an electrostatic double layer surrounding the particle. The permanent presence of the adsorbed ion layer, the magnitude of which is measured by the zeta potential, represents an additional source for creating repulsive forces between a particle and a surface. The proper choice of surfactants in cleaning solutions maximizes this repulsive force.

Liquids also can dissolve soluble particles (e.g., many salt particles are soluble in aqueous solutions) and create greater drag forces during cleaning. Liquids have much higher viscosities than gases, so for a given fluid velocity, the drag forces exerted on an attached particle are much greater in a liquid than in a gas.

3.3 RATE OF DEPOSITION OF NONVOLATILE RESIDUE

Nonvolatile residue (NVR) refers to the matter that remains after the solvent containing such matter has been filtered and evaporated at a specified temperature. NVR normally occurs either as a film, a solid, or droplets of liquid, and it is generally expressed as mass per unit area of surface.

Cleanrooms are designed to protect products from contaminants that affect the performance of those products. Cleanrooms in the pharmaceutical industry are also designed to protect the operator. In any type of cleanroom, particles are of primary concern, but NVR can also be detrimental. NVR, introduced by the air that enters the cleanroom or by

Table 3.2 Maximum Average Rates of Deposition of NVR

(IEST 2002)

NVR Rate Level	Maximum Average Deposition Rate, mg/0.1 m^2·month (mg/ft^2·month)
I	0.10
II	0.30
III	1.0
IV	3.0
V	10.

emissions from items within the cleanroom, condenses or falls onto surfaces as thin film or droplets.

MIL-STD-1246C (DOD 1994) is frequently used to establish the maximum allowable level of NVR that a product can have when it is removed from a cleanroom. Since that maximum amount represents the sum of the NVR that was on the product when it was brought into the cleanroom plus the amount of NVR that was added while it was in the cleanroom, the maximum allowable deposition rate within the cleanroom is determined by the following equation:

$$NVR_d/t = (NVR_f - NVR_i)/t$$

where

NVR_d = NVR deposited on the product while in the cleanroom, mg/ft^2 (mg/0.1 m^2)
t = time product was in cleanroom, months (based on 28-day month)
NVR_f = maximum allowable NVR allowed on final product when removed from cleanroom, mg/ft^2 (mg/0.1 m^2)
NVR_i = amount of NVR on product when brought into cleanroom, mg/ft^2 (mg/0.1 m^2)

Thus, NVR_d/t, in mg/ft^2·month (mg/0.1 m^2·month), is the maximum average rate of deposition of NVR that can be allowed if the product is to meet the requirement of NVR_f after an exposure of time t.

Several different maximum average rates of deposition of NVR, which may be used as bases for specifying or determining conformance to requirements for cleanliness, are listed in Table 3.2.

3.3.1 TECHNIQUES FOR MEASURING NVR

Three techniques for measuring NVR are suggested: the gravimetric method, the multiple internal reflectance spectroscopy (MIRS) method, and the temperature-controlled quartz crystal microbalance (TQCM) method. The selection of a method depends upon the requirements that must be met and the sensitivity of the method. Each of these methods is discussed in more detail in the following subsections.

3.3.1.1 Gravimetric Method

In the gravimetric method described in ASTM E1235 (ASTM 2012b), witness plates made of stainless steel are placed strategically in the cleanroom. The NVR that deposits on the plate is flushed from the plate using a solvent (methylene chloride). The solvent is collected and evaporated, and the residue (the NVR) is weighed. The sensitivity of this method is approximately 0.2 mg/ft^2 (0.2 mg/0.1 m^2).

3.3.1.2 Multiple Internal Reflectance Spectroscopy (MIRS) Method

In multiple internal reflectance spectroscopy (MIRS), infrared plates designed to allow multiple internal reflections of light are used. These plates, often made of germa-

nium, are also known as *attenuated total reflectance* (ATR) plates. ASTM E573 (ASTM 2013b) identifies contaminants by the analytical technique of MIRS.

The mass of NVR can be determined by calibration, that is, by measuring the absorbance of typical or known materials. This method is more sensitive than the gravimetric method if the NVR is in the form of a uniform film on the ATR plate. If the NVR forms droplets, the sensitivity depends upon the contact area of the droplets with the ATR plate surface. Sensitivities can range from 0.02 mg/ft^2 (0.02 mg/0.1 m^2) to that of the gravimetric method.

3.3.1.3 Temperature-Controlled Quartz Crystal Microbalance (TQCM) Method

The temperature-controlled quartz crystal microbalance (TQCM) method can be used to provide continuous, real-time measurements of NVR deposition. Measurement sensitivities of 0.01 mg/ft^2 (0.01 mg/0.1 m^2) can be achieved. This technique is especially useful as an early-warning indication of increasing NVR deposition rates.

3.4 PARTICLE DEPOSITION VELOCITY

The rate of deposition of aerosol particles on a wafer or some other surface governs the rate with which the surface becomes contaminated by airborne particles. The two major mechanisms responsible for particle deposition on surfaces are sedimentation and diffusion. Sedimentation is important for large particles (those above 1.0 µm in diameter), while diffusion is important for small particles below 0.1 µm. In the intermediate size range, both sedimentation and diffusion are important and must be considered. When the particle and/or the surface are electrically charged, enhanced deposition due to electrostatic effects can also occur and must also be considered.

Figure 3.2 shows the settling speed of unit density (0.8 oz/in.^{3} [1.0 g/cm^3]) spheres in air at a temperature of 68°F (20°C) and 1 atmospheric pressure calculated from the Stokes law with the correction for particle slip:

$$V_s = \rho_p D_p^2 C g / 18\mu \tag{3.1}$$

where

V_s	=	settling speed, cm/s
ρ_p	=	particle density, g/cm^3
D_p	=	particle diameter, cm
μ	=	gas viscosity, poise
g	=	acceleration of gravity

In Equation 3.1, C is the slip correction given by

$$C = 1 + 2.592\lambda / D_p + 0.84\lambda / D_p + e^{-0.435 D_p / \lambda} \tag{3.2}$$

The slip correction is important when the particle diameter is of the same order of magnitude as the mean free path λ of the surrounding air. For air under normal temperature and pressure conditions, λ is equal to 0.0652×10^{-4} cm.

The rate of diffusion of a small aerosol particle to a surface is governed by its diffusion coefficient, which is given by

$$D = kTC / 3\pi\mu D_p \tag{3.3}$$

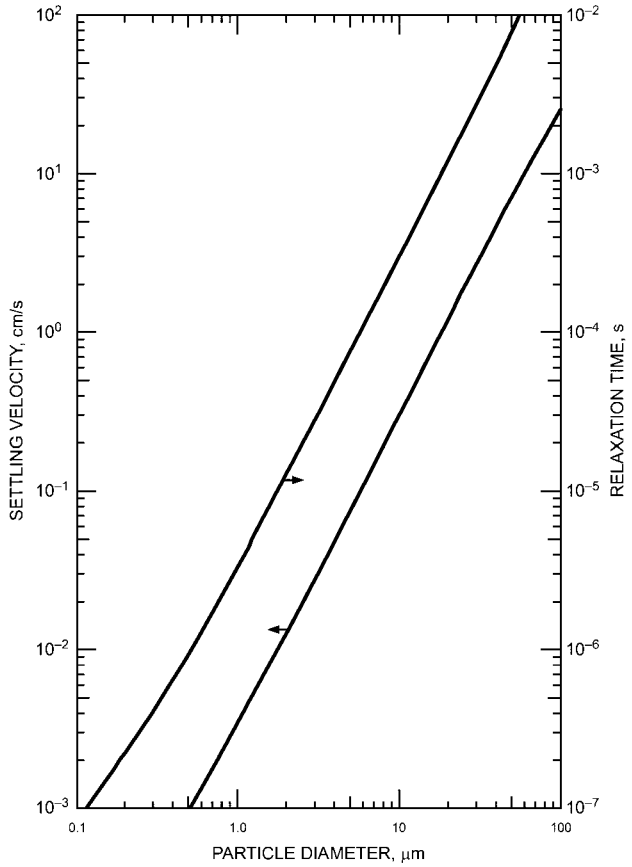


Figure 3.2 Settling Speed and Relaxation Time of Unit Density Spheres in Air at 68°F (20°C) and 1.0 Atmosphere

(Liu and Pui 1988)

where k is Boltzmann's constant and T is the absolute temperature. The theoretical calculation of the particle deposition rate on wafer surfaces is complicated by the airflow pattern and the existence of a boundary layer over the wafer surface.

3.5 SURFACE PARTICLE MEASUREMENT

Because of the low contaminant levels in cleanrooms and clean processing gases (in semiconductor and electronics facilities), only single particle counting instruments (i.e., those capable of counting single individual particles) are suitable for particle measurement in such applications. Instruments such as transmissometers, photometers, electrical aerosol analyzers, etc., which are used for air pollution, industrial hygiene, and related studies involving high particulate concentration levels, are generally unsuited for use in cleanrooms. Figure 3.3 summarizes the measuring ranges of different aerosol measurement devices, for cleanroom and other applications.

3.5.1 TEST METHODS FOR USE IN ASSESSING THE CLEANLINESS OF SURFACES

Surface particle measurement methods are classified according to the type of the particle (i.e., viable or nonviable) and its size. Inspection by ultraviolet light or by high-intensity oblique-angle white light, as well as vacuum sampling, are insufficient in themselves to verify cleanliness. The operations listed in Table 3.3 are performed in a particu-

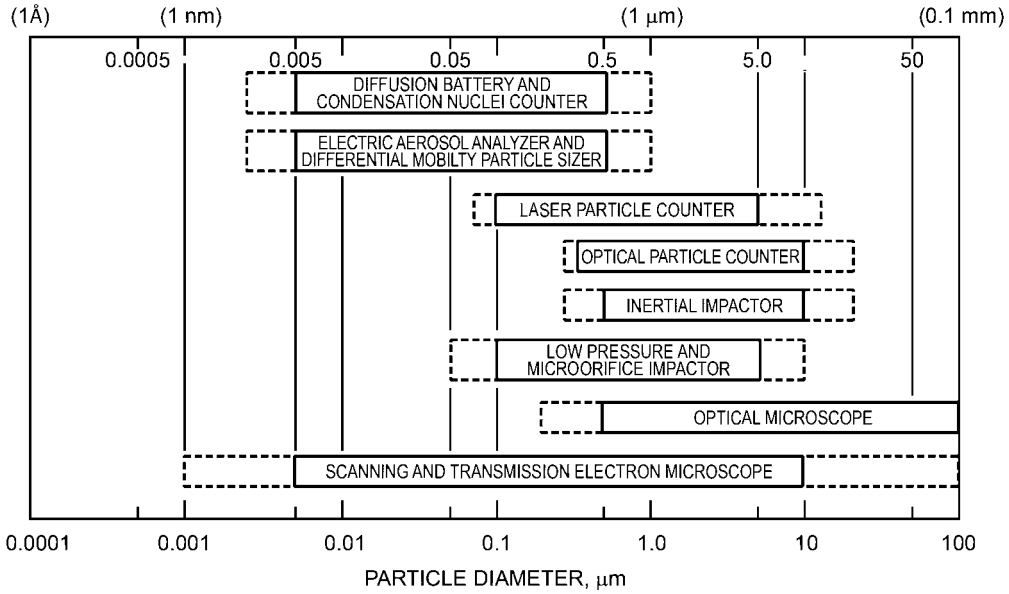


Figure 3.3 Particle Size Ranges of Aerosol Measuring Instruments

(Liu and Pui 1988)

Table 3.3 Sources of Sampling and Measurement Techniques for Surfaces, Liquids, and Gases

(DOD 1994)

	Sampling Techniques	Measurement Techniques
Surfaces	ASTM F51 ASTM F303 ASTM F306 ASTM E1216 ASTM E1234	ASTM F311 ASTM F312 ASTM F331 ASTM E1235
Liquids	ASTM F302 ASTM F303 ASTM F1094	ASTM F311 ASTM F312 ASTM F331 ARP 598
Gases	ASTM F25 ASTMF50 ASTM F307 ASTM F318 ASTM F327	ASTM F25 ASTM F50 ASTM F312 ASTM F331 ARP 743

lar sequence, as required to determine the information desired, in order to constitute a valid certification.

3.5.2 MEASUREMENT OF CLEANLINESS LEVELS

There are many ways to measure cleanliness levels in cleanrooms. A number of ways are discussed in the following subsections in greater detail. Note that the text of these sections is reproduced nearly verbatim from MIL-STD-1246C, *Product Cleanliness Levels and Contamination Control Program* (DOD 1994), except that a footnote has been added and some other minor editorial changes have been made.

3.5.2.1 Direct Measurement

Direct measurement is the analysis of part of the surface, liquid, or gas of interest. Examples are counting particles on the surface by using a microscope or performing NVR analysis on a sample of liquid of interest. Direct measurement of particles or NVR in situ is the most accurate technique, although limited methods exist. A requirement for direct, noncontact microscopic examination of particles on a surface is only feasible if the

Table 3.4 Application of Test Methods According to Type of Contamination

(IEST 2007)

Test Method	Nonviable	Viable
Ultraviolet light inspection	>50 µm	
High-intensity oblique-white light inspection	>20 µm	
Counting and sizing particles with an optical microscope	>5 µm	
Witness plate method	>5 µm (optical microscope) >0.2 µm (laser)	
Surface particle detector method	>0.3 µm	
Contact plate method		x
Swab method		x

surface optical properties allow such examination. Alternative surface or fluid measurement techniques are acceptable, having demonstrated equivalence.

3.5.2.2 Extractive Sampling

Extractive sampling of surfaces, liquids, or gases for off-line measurement is the most widely used approach for particle and NVR cleanliness determination. Sample collection techniques and measurement methods to determine cleanliness should be accomplished using the ASTM procedures shown in Table 3.4 (a partial listing only) or by demonstrated equivalents. Extractive sampling is the analysis of a medium other than that of interest. Examples are counting particles on tape that has been used to remove particles from a surface of interest in accordance with ASTM E1216 (ASTM 2011) or demonstrated equivalent and analyzing a liquid used to flush a surface of interest. Successful extractive sampling requires a technique of known extraction efficiency (preferably close to 100%). Multiple extractions should produce concentrations that approach those of the extraction fluid itself; otherwise, complete removal has not occurred or contaminant generation may be occurring or both. In some cases, the medium of interest is gas or liquid coming from contact with a possibly contaminated surface. This is direct measurement of the gas or liquid and extractive sampling of the surface. Because of uncertainty in sampling efficiency, direct measurement is preferable to extractive sampling.

3.5.2.3 Indirect Sampling

Indirect witness samples are the third and least accurate method for particles and NVR cleanliness determination but may be the only method available when direct scanning or physical sampling of a product is not feasible. One method for NVR witness samples is documented in ASTM E1234 and ASTM E1235 (ASTM 2012a, 2012b). Particle witness samples can take any form that represents the actual condition, and measurement methods should follow the same requirements specified previously.

3.5.2.4 Percent Area Coverage

An alternative method of specifying particulate levels on a surface is expressed as percent area coverage (PAC). Particle area may be directly measured using image analysis or other techniques. Otherwise, particle sizing and counting must be performed and the values converted to a PAC value. Table 3.5 provides the conversion formula and is based on a sample size of 1 ft^2 (0.1 m^2). Other possible methods for PAC determination include obscuration or light scattering, after having demonstrated equivalence with actual measured projected areas.

Table 3.5 Calculating Particle PAC

(DOD 1994)

Particle Size Range	Particles per 1 ft^2 (0.1 m^2)*		Coefficient		
>1 to 10 mm		×	1.737×10^{-8}	=	PAC
>10 to 25 mm		×	1.528×10^{-7}	=	PAC
>25 to 50 mm		×	7.078×10^{-7}	=	PAC
>50 to 100 mm		×	2.435×10^{-6}	=	PAC
>100 to 150 mm		×	5.186×10^{-6}	=	PAC
>150 to 250 mm		×	7.484×10^{-6}	=	PAC
>250 to 500 mm		×	6.522×10^{-6}	=	PAC
>500 to 750 mm		×	1.048×10^{-5}	=	PAC
>750 mm		×	1.922×10^{-5}	=	PAC

Sum all values to obtain total PAC.
** This value may be estimated by multiplying counts within the 10–25 µm range for count in the 1–10 µm range by 3.24.*

3.5.2.5 Alternative Particle Count Specifications

In some cases, it is desirable to specify a particle count limit in a manner different from that shown in Table 3.6.[1] As examples, one might specify total count per unit extent for particles in a specified size range, or the maximum quantity of particles smaller than 1 µm, or the maximum quantity of particles measuring 10 to 50 µm, or the maximum quantity of particles larger than 20 µm, or specification of another size distribution limit. Another approach is to specify certain particle types to be limited. For example, those that contain sodium or are magnetic. Alternative particle count specifications must identify what is to be measured and how it is to be measured and define the limit in terms of count per extent.

3.5.2.6 Volatile Condensable Material

Volatile condensable material (VCM) is determined from a preconditioned sample subjected to a specified temperature with the VCM collected at a lower specified temperature. Cleanliness requirements are specified as collected volatile condensable material (CVCM) when tested in accordance with ASTM E595 and as VCM when tested by methods other than ASTM E595 (ASTM 2015).

3.5.2.7 Turbidity

Turbidity is measured by either the reduction in transmission or the increase in scattering of light by particles in a liquid. The units of measurement are Nephelometric Turbidity Units (NTUs).

3.6 PARTICLE IDENTIFICATION AND ELECTRON MICROSCOPY SCANNING

Many industries face problems from particle contamination, whether the particles are found mixed in solids, liquids, or gases. Eliminating the contamination can more easily be achieved when the source of the contamination is discovered. Finding the source of particle contamination on products or in processes is usually accomplished by isolating the particles then characterizing (by elemental composition and/or size) and understanding the different particle types. Doing so enables comparison of different particles, data col-

1. Table 3.6 shows particle cleanliness levels by particle size, count per 1 ft^2, count per 0.1 m^2, and count per 1 L.

Table 3.6 Particle Cleanliness Levels

(DOD 1994)

Level	Particle Size, μm	Count per 1 ft²	Count per 0.1 m²	Count per 1 L
1	1	1.0	1.08	10
5	1	2.8	3.02	28
5	2	2.3	2.48	23
5	5	1.0	1.08	10
10	1	8.4	9.07	84
10	2	7.0	7.56	70
10	5	3.0	3.24	30
10	10	1.0	1.08	10
25	2	53	57	530
25	5	23	2438	230
25	15	3.4	3.67	34
25	25	1.0	1.08	10
50	5	166	179	530
50	15	25	27.0	230
50	25	7.3	7.88	34
50	50	1.0	1.08	10
100	5	1785	1930	17,850
100	15	265	286	2650
100	25	78	84.2	780
100	50	11	11.9	110
100	100	1.0	1.08	10
200	15	4189	4520	41,890
200	25	1240	1340	12,400
200	50	170	184	1,700
200	100	16	17.3	160
200	200	1.08	10.0	1.0
300	25	7455	8050	74,550
300	50	1021	1100	10,210
300	100	95	103	950
300	250	2.3	2.48	23
300	300	1.0	1.08	10
500	50	11,817	12,800	118,170
500	100	1100	1190	11,000
500	250	26	28.1	260
500	500	1.0	1.08	10
750	50	95,807	105,000	958,070
750	100	8919	9630	89,190
750	250	214	231	2140
750	500	8.1	8.75	81
750	750	1.0	1.08	10
1000	100	42,658	46,100	426,580
1000	250	1022	1100	10,220
1000	500	39	42.1	390
1000	750	4.8	5.18	48
1000	1000	1.0	1.08	10

Note: Limits on particle count at indicated particle size for surface or liquid to meet the level of cleanliness. Sampling areas other than 1 ft² (0.1 m²) are to be calculated to the basis of 1 ft² (0.1 m²). Areas may be estimated if total area is considered by both parties to be too difficult to measure within two significant figures. This condition should be noted, and low/high ranges should be used. Parts with a total significant surface area less than 1 ft² (0.1 m²) and that have had the entire critical surface area sampled will be accepted on the basis of actual count.

lection of the percentages of respirable particles, and evaluation of the particles' impact on products. Particle identification is done by examining information left by the particle after it has passed through a particle detector. Such identification enables improved measurement resolution and is essential for most particle detector analyses. Particle identification analysis can be performed on a wide, wide variety of materials. The primary particle identification tools are optical microscopy and scanning electron microscopy.

A scanning electron microscope (SEM) scans a sample with a high-energy beam of electrons in a raster scan pattern. The electrons interact with the sample's atoms, resulting in signals containing information about properties of the sample, such as its composition, surface topography, and electrical conductivity. A SEM's spatial resolution is dependent on the size of the electron spot, which itself depends on the electrons' wavelength and the electron-optical system producing the scanning beam, and is limited by the size of the volume of interaction (the extent to which the material and the electron beam interact). A SEM's resolution is not high enough to image individual atoms because both spot size and interaction are large compared to the distances between atoms. However, SEMs can image a rather large portion of a specimen as well as bulk materials (not just thin films or foils). SEMs also have a variety of analytical modes for measuring the composition and properties of a specimen. SEM resolution will be between less than 1 and 20 nm, depending on the instrument. By 2011, the highest SEM resolution with high-energy beams was 0.4 nm at 30 kV; with low-energy beams, the best resolution was 0.9 nm at 1 kV.

SEMs can produce extremely high magnification images (up to 200,000 times) at high resolution up to 2 nm. Combining this with the ability to generate localized chemical information (energy dispersive X-ray spectroscopy [EDX]) means that SEM/EDX is a powerful and flexible tool that can solve a wide range of product and process problems for a diverse range of metals and materials. Thus far, SEM/EDX analysis has been used extensively in a wide variety of industrial sectors—from engineering, semiconductor, electronics, aerospace, automotive, and medical devices to pharmaceuticals, petrochemicals, plastics and polymers, chemicals, materials, and metallurgy.

3.7 PRODUCT CLEANLINESS LEVELS

Note that the text of the following subsections is reproduced nearly verbatim from MIL-STD-1246C, *Product Cleanliness Levels and Contamination Control Program* (DOD 1994), except that some minor editorial changes have been made for conformity to the style of this book.

3.7.1 METHODS FOR SPECIFYING PRODUCT CLEANLINESS LEVELS

Only the cleanliness level or levels specified for a particular product are applicable to that product. Product cleanliness must be specified in the following manner:

MIL-STD-1246 LEVEL X Y, Z

where

X = numerical particle cleanliness level from Table 3.6
Y = NVR cleanliness level designation from Table 3.7
Z = alternative or additional cleanliness levels, consisting of one or more abbreviations from the following list and the maximum limit(s) expressed in the units described herein:
  PAC = percent area coverage
  PC = particle count specified independently of Table 3.6

CVCM = collected volatile condensable material in accordance with ASTM E595
VCM = volatile condensable material determined by methods other than ASTM E595
NTU = Nephelometric Turbidity Unit
TML = total mass loss, in accordance with ASTM E595

The log-log[2] distribution of acceptable particle contamination is shown in Figure 3.4.

Table 3.7 NVR Cleanliness Levels

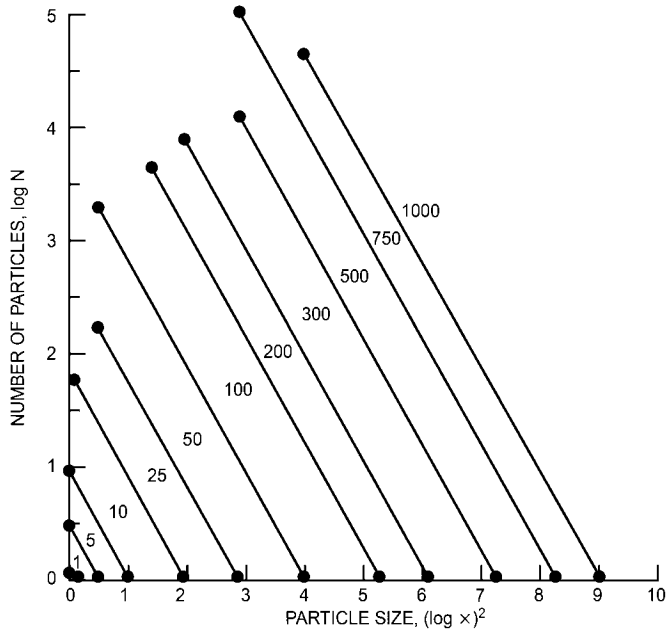
(DOD 1994)

Level	Limit, NVR mg/0.1 m^2 (or µg/cm^2)*	Limit, NVR mg/L
A/100	0.01	0.1
A/50	0.02	0.2
A/20	0.05	0.5
A/10	0.1	1.0
A/5	0.2	2.0
A/2	0.5	5.0
A	1.0	10.0
B	2.0	20.0
C	3.0	30.0
D	4.0	40.0
E	5.0	50.0
F	7.0	70.0
G	10.0	100.0
H	15.0	150.0
J	55.0	250.0

** Limits on NVR (mg) for surface, liquid, or gas to meet the level of cleanliness. 1 ft^2 = 0.0929 m^2.*

Figure 3.4 Product Cleanliness Levels

(DOD 1994)



3.7.2 CLEANLINESS LEVELS

Tables 3.6 and 3.7 prescribe the cleanliness levels established to provide a uniform set of criteria for specifying product cleanliness in terms of particles or NVR or both. Use of these cleanliness levels provides a basis for specifying and determining conformance to cleanliness requirements.

Unless otherwise specified, cleanliness levels must be in terms of maximum amounts per unit extent (area, volume, mass), such as counts per 1 ft^2 (0.1 m^2). Use of a particular unit of extent does not imply that the measurements are to be taken over this extent, but rather that the total amount is to be divided by the total extent. In general, higher accuracy is fostered by the measurement of larger extents. For contaminant levels other than particles or NVR, limits must be designated by the user in the units prescribed in the following paragraph and list.

The cleanliness levels of Tables 3.6 and 3.7 apply to surfaces, assemblies, components, fluids, or materials. Documentation should include sampling details and acceptance criteria. The following units of measure are to be used:

- **Surfaces.** Particles categorized by size and count per 1 ft^2 (0.1 m^2) of significant surface area (areas may be estimated). PAC measured as total particle projected area divided by total significant surface area. NVR in mg/0.1 m^2 of significant surface area (areas may be estimated).
- **Assemblies, Components, or Materials.** Particles categorized by size and count per 1 ft^2 (0.1 m^2) of significant surface area (areas may be estimated). Limits may also be specified on a per-item basis rather than per unit area, volume, or mass. PAC measured as total particle projected area divided by total significant surface area. NVR in mg/cm^2 of significant surface area (areas may be estimated). VCM from bulk material may be reported in mg/0.1 m^2 of significant area or per unit mass of bulk material.
- **Liquids.** Particles categorized by size and count per unit volume in accordance with ARP598C (SAE 2003) or demonstrated equivalent. NVR measured in mass per unit volume. Turbidity is characterized by NTUs.
- **Gases.** Particles categorized by size distribution in units of count per unit volume.

3.8 SURFACE CLEANING

Note that in the following subsections, selected text from the appendix to MIL-STD-1246C, *Product Cleanliness Levels and Contamination Control Program* (DOD 1994), is reproduced nearly verbatim except that some minor editorial changes have been made for conformity to the style of this book.

3.8.1 CLEANING METHODS AND MATERIALS

The selection of cleaning processes and equipment is strongly influenced by the design of items, their constructive material and surface treatments, and the fabrication processes that produce them. Early consideration of the need to clean can result in design, materials, and process changes that do not decrease utility but result in items that can be more effectively cleaned at a lower cost. Included in the considerations should be the health, safety, and environmental impacts of the total manufacturing and cleaning process. Many materials may be subject to local, state, or federal statutory control affecting use and disposal.

3.8.1.1 Gross Cleaning

Gross cleaning is used to achieve visibly clean articles. This method removes contaminants such as weld scale, heat treat scale, corrosion, oxide films, oils, grease, shop soil, fuel, and carbon deposits. The cleanliness level achieved by gross cleaning does not normally require verification beyond visual inspection (wipe test, water break test, ultraviolet inspection, special light and mirrors are considered aids to visual inspection). Gross cleaning is considered a normal shop process and usually does not require especially clean conditions beyond accepted good practice.

The following types of cleaners, or their equivalents, may be used for removing gross forms of contamination. *Note:* Chemical cleaning agents must be compatible to prevent excessive attack or latent degradation.

- **Acid Cleaners.** Acid cleaners are used to remove contamination such as weld scale, corrosion, and oxide films not removable by other solutions. Examples are nitric acid, inhibited hydrochloric acid, inhibited sulfuric acid, inhibited phosphoric acid, mixed acid deoxidizers, and alcoholic-phosphoric acid.
- **Alkaline Cleaners.** Alkaline cleaners are used for the removal of organic and inorganic contamination such as grease, shop soil, scale, and soluble metal oxides. Alkaline cleaners dissolve (etch) certain metals such as aluminum and zinc. Examples are alkaline rust strippers, heavy-duty alkaline cleaners, molten alkali, alkali, and alkali with nitrate or phosphate.
- **Detergents and Mild Cleaners.** Detergents and mild cleaners are used for the removal of organic and inorganic contamination such as oils, fats, shop soil, and grease. Examples are inhibited alkaline cleaners (mild alkaline cleaners), soaps, emulsion cleaners, surfactants, and detergents.
- **Organic Solvent Cleaners.** Organic solvent cleaners are used to remove forms of organic contamination such as oils, grease, and hydrocarbon fuels. Examples are alcohol and acetone. Class I and Class II ozone-depleting chemicals (ODCs) are excluded from use as organic solvent cleaners.
- **Tap Water and Deionized Water.** Tap water and deionized water are used to remove the residue material left by cleaning solutions and as a final flushing or rinsing medium.
- **Neutralizing and Passivating Solutions.** Neutralizing and passivating solutions are used as a supplementary treatment to acid, alkaline, and mechanical cleaning. These solutions prevent corrosion and acid etching. Examples are nitrate, phosphate, alkali with nitrate or phosphate to neutralize, and nitric acid or nitric acid solutions to passivate.
- **Mechanical Cleaning.** The mechanical cleaning process removes contamination by abrasive action and is only used when physical damage to the items being cleaned will not occur. Examples of mechanical cleaning are wire brushing, shot blasting (wet and dry), grinding, sand blasting (wet or dry), and the use of aluminum oxide, abrasive coated papers and cloths, and related methods. *Note:* Mechanical cleaning often leaves foreign deposits that may require additional cleaning for their removal. Compatibility of dissimilar materials, especially metals, is an important consideration when selecting a mechanical cleaning method.

Table 3.8 contains the recommended gross cleaning processes and sequences.

Table 3.8 Gross Cleaning Processes

(DOD 1994)

Material	Surface Condition	Cleaning Processes*†							
		MEC	ORG	ALK	DET	ACD	NEU	DIW	DRY
Aluminum	Bare or machined, free of heat oxidation		X	X				X	X
	Conversion or chemical film coating		X		X			X	X
	Weld scale, corrosion, or heat oxidation	X	X	X				X	X
Copper, brass, bronze	Bare or machined, free of heat oxidation		X	X				X	X
	Conversion or chemical film coating		X		X			X	X
	Weld scale, corrosion, or heat oxidation		X	X		X		X	X
Stainless steel‡	Free of scale		X	X		X	X	X	X
	Weld scale, corrosion, or heat oxidation	X	X	X		X	X	X	X
Carbon steel	Free of scale		X	X		X	X	X	X
	Weld scale, corrosion, or heat oxidation	X	X	X		X	X	X	X
Nonmetallic parts, elastomers	As received				X			X	X
Electroplated parts and dissimilar metals	As received		X	X				X	X

* *"X" denotes a recommended process for the surface condition indicated and will normally be accomplished in consecutive order from left to right.*

† *Cleaning processes defined:*
MEC = mechanical descale/clean
ORG = organic solvent degrease
ALK = alkaline clean and tap-water rinse
DET = detergent clean and tap-water rinse
ACD = acid pickle and tap-water rinse
NEU = neutralize and passivate and tap-water rinse
DIW = deionized water rinse
DRY = drying

‡ *ASTM A380/A380M (ASTM 2013a) describes in detail the recommended methods for descaling and cleaning stainless steel.*

3.8.1.2 Precision Cleaning

Precision cleaning is used to achieve a level of product cleanliness greater than the level normally detected by visual means. Articles should be visibly clean prior to precision cleaning. Precision cleaning is performed in a controlled environment and is intended to remove particles, films, biological forms, fibers, and other forms of contaminants that are usually not visible but that could degrade the product or process. The level of precision cleanliness should be verified, and evidence of inspection and acceptance should be provided. Precision-cleaned articles should be packaged immediately after verification of cleanliness or suitably protected prior to leaving the controlled environment. Some viable precision cleaning methods are as follows:

- **Precision Cleaning Solutions or Fluids.** Precision cleaning solutions or materials should not react with, combine with, etch, or otherwise cause immediate or

latent degradation of the item being cleaned. Precision cleaning fluids should be filtered and controlled. Their cleanliness level should be verified as being sufficient to achieve the specified product cleanliness. Selection of precision cleaning fluid must take into consideration the nature of the contaminant to be removed; the reactivity of the item being cleaned; the health, safety, and environmental hazards of the fluid; and disposal of waste, including spent cleaning fluid. Control technology to either contain the precision cleaning fluid, reuse it, or both must be provided as health, safety, and environmental hazards dictate. Examples of materials commonly used for precision cleaning include abrasive solids, air, carbon dioxide snow or pellets, deionized water, detergent, surfactant, inert gas, and organic solvents.

- **Precision Cleaning Methods or Processes.** Equipment and various methods suitable for precision cleaning are available. The appropriate process and equipment should be selected on the basis of product configuration, compatibility with cleaning fluids, type and quantity of contaminants, desired cleanliness level, economics, safety, and environmental risks. The following equipment and methods are available alone or in combination when selecting the appropriate process for a particular product:
  - **Solution Cleaning.** With solution cleaning, the item is washed in suitable clean detergent/water solution or solvent, followed by a succession of rinses. Normally, mechanical action such as agitation or brushing is necessary to ensure removal of all contaminants.
  - **Spray Cleaning.** Spray cleaning may be divided into three pressure ranges in order of overall effectiveness:
    - **High Pressure—Greater than 1500 pis (10,342 kPa).** High-pressure water cleaning should not include detergents, as foam formation reduces cleaning efficiency. Precision fixtures are also required but can be effective at cleaning complex geometries including threaded, blind, and through holes.
    - **Intermediate Pressure—100 to 1500 psi (690 to 10,342 kPa).** Intermediate-pressure spray cleaning is lower in efficiency than high-pressure spray cleaning. Addition of low-foaming surfactant can improve efficiency in certain cases.
    - **Low Pressure—Less than 100 psi (690 kPa).** Spray cleaning at pressures at this level is relatively ineffective as a primary cleaning process. However, it is very effective at rinsing away contaminants that have been loosened by a previous cleaning process, such as ultrasonic cleaning.
  - **Sonic Cleaning.** Sonic cleaning may be divided into two general ranges based on frequency. Each range exhibits unique cleaning characteristics:
    - **Ultrasonic Cleaning—15 to 100 kHz.** Ultrasonic cleaning provides nondirectional cleaning suitable for complex geometries. Cleaning efficiency is severely limited in holes and in similarly tight geometries. Surface damage may occur as a result of cavitation erosion.
    - **Megasonic Cleaning—Frequencies Greater than 100 kHz.** Megasonic cleaning produces highly directional cleaning suitable for simple geometries. This method tends to produce less surface erosion than ultrasonic cleaning.
  - **Vapor Cleaning.** With vapor cleaning, the item to be cleaned is exposed to heated solvent vapors that condense on the item and wash away contami-

nants. This is effective for soluble contaminants and is used as a drying method. However, this method is relatively ineffective for small particles.

- **Flush Cleaning.** With flush cleaning, the item to be cleaned is flushed with a suitable cleaning solution. The item is agitated thoroughly to wash all surfaces, and the solution is drained away.
- **Spin Rinse and Drying.** The method of spin rinse and drying is used principally after another cleaning method has been used. In this method, the item being cleaned is rinsed while it is turned slowly. The item is then accelerated to a higher speed in revolutions per minute (RPM). The high angular velocity accelerates the liquid, removing particles by shear stress. The rinsing liquid is also removed, thus drying the item.
- **Electropolishing and Chemical Polishing.** With polishing, the material or product to be cleaned is immersed in a solution specifically formulated or energized to remove the base material of the item. Fixturing the item is critical for effective treatment. The dissolution of the base material smooths the surface and releases contaminants embedded on the surface of the item. Treatment baths must be filtered, and processing must be followed by rinsing with deionized water to remove chemical residue.
- **Other Methods.** Consideration should be given to other cleaning methods not described previously, such as argon snow, supercritical fluids, plasma, and ultraviolet-ozone.
- **Ozone-Depleting Chemicals (ODCs).** Substances classified as Class I ODCs by the Clean Air Act Amendment of 1990 and certain Class II ODCs should not be given consideration or recommendation. Class I substances to be avoided are chlorofluorocarbons (CFCs), carbon tetrachloride, methyl chloroform, methyl bromide, and hydrobromofluorocarbons (HBFCs). Class II substances to be avoided are hydrochlorofluorocarbons (HCFCs) 22, 141b, and 142b.

3.8.1.3 Handling During Cleaning

Disassembly, cleaning, reassembly, in-process handling, packaging, and other operations involved in cleaning should be conducted in a manner to preserve critical tolerances, finishes, calibration, and other sensitive attributes of the product. Adequate tooling, fixtures, handling devices, and product protection should be provided. Written instructions for sensitive or critical activities should be provided.

Note that in addition to the methods and procedures outlined by MIL-STD-1246C (DOD 1994), follow-up training and evaluation of personnel responsible for cleaning cleanrooms are critical to ensure the effectiveness of the cleaning method and its application.

3.9 REFERENCES

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4 Airborne Molecular Contaminants

4.1 SUMMARY OF AIRBORNE MOLECULAR CONTAMINATION SOURCES AND TYPES

A large number of chemical contaminants that may be found in cleanrooms are covered by the term *airborne molecular contamination* (AMC). These contaminants can be organic or inorganic, and they can be gases, vapors, or molecular particles. AMC includes organic chemicals, condensables, acids, bases, polymer additives, and organometallic compounds (Muller 2003).

Sources for the AMC found in cleanrooms are numerous and include building and construction material off-gassing, process equipment and chemical supply line emissions, cross-contamination between manufacturing areas, the manufacturing processes themselves, chemical storage areas, spills, the outdoor air, and bioeffluents from cleanroom personnel. AMC can both be detrimental to cleanroom processes and products and present health hazards for personnel (Muller 2003).

AMC can be classified in a variety of ways. Although no one way is definitive, the following classifications are relevant for cleanrooms (Muller 2003):

- **Toxic.** Substances are considered to be toxic if, when ingested, inhaled, or absorbed through the skin, they have the ability to damage living tissue, impair the central nervous system, or cause death.
- **Corrosive.** Corrosive compounds are considered those likely to deteriorate or damage a building's interior or contents; they may also have a detrimental effect on humans.
- **Irritant.** Chemicals that cause discomfort or, in some cases, permanent damage to a person that has been exposed are considered irritating. Such chemicals in gas form cause discomfort or pain to the eyes, skin, mucous membranes, or respiratory system.
- **Odorous.** Odorous materials are those that mostly affect the olfactory senses; these usually carry negative connotations.

AMC is composed of nonparticulate contaminants that can easily penetrate high-efficiency particulate air (HEPA) and ultralow particulate air (ULPA) filters. Like particles, airborne molecular contaminants consist of molecules or clusters of molecules. The major physical distinction between aerosol particles and airborne molecular contaminants is that airborne molecular contaminants are vapor-phase contaminants and are composed of fewer molecules and have less total mass than aerosol particles.

4.1.1 SOURCE CATEGORIES OF AMC

The sources of AMC may be external or internal sources:

- **External Sources.** Contamination from external air exists for any given space. It is primarily brought in through the makeup air in the air-conditioning system. Outdoor air that has not been filtrated enters the cleanroom through building windows, doors, walls, cracks, and penetrations through ducts and pipes. AMC from external sources includes air pollution, local industrial activities and emissions, agricultural sources, and others.
- **Internal Sources.** Primary internal sources include chemicals (e.g., chemical vapors, soldering fumes, and cleaning agents) used in manufacturing processes as well as chemical spills, off-gassing from components and materials, cleaning or construction activities, and even the personnel themselves. Internal AMC often becomes a problem through cross-contamination from other areas via the large quantity of recirculated air that is typical in cleanrooms.

4.2 OFF-GASSED ORGANIC COMPOUNDS FROM CLEANROOM MATERIALS AND COMPONENTS

4.2.1 MATERIAL OFF-GASSING

Off-gassing from materials can occur in the vacuum of space, from the elevated temperatures of a process chamber or the room temperatures of many cleanrooms. Off-gassing occurs due to the partial vapor pressure of molecular compounds that are present in or on various materials. If not specified correctly or cured completely, many cleanroom materials have the potential to off-gas various molecular compounds that may be hazards to products or people. These compounds may be acids, bases, condensables, dopants, metals, biotoxins, oxidants, or organic (SEMI 2016; ISO 2013), with organic compounds being the most common from common cleanroom construction materials, such as the following:

- Coatings
- Paints
- Wall coverings
- Sealants
- Caulking and curing agents
- Adhesives
- Tapes
- Gel seals (potting agents)
- Floor coverings
- Cables
- Pipes, bearings, solder/fluxes
- Tubing (flexible membranes and hoses)
- Plastic labels
- Gaskets
- O-rings
- Plastic curtains
- Packaging
- Lighting fixtures
- Insulation (thermal, electrical, acoustic)

- Wall and ceiling systems
- Wafer carriers
- Filter systems (HEPA and ULPA)
- Assembled products requiring bonding

4.2.2 PARAMETERS AFFECTING MOLECULAR OFF-GASSING

Off-gassing rates are affected by many parameters, such as surface area, vapor pressure, absolute pressure, vapor pressure gradients, and temperature (ITRS 2015). Vapor pressure can influence initial off-gassing as well as later reabsorption. For example, a high-vapor-pressure compound will be off-gassed at a low temperature, but it will not be condensed easily. Conversely, a low-vapor-pressure compound may release slowly, but it may accumulate on surfaces easily. Temperature can cause compounds to desorb from a surface or can increase the diffusion coefficients of compounds through materials (e.g., plasticizers in polymers) (Simonson et al. 1995).

The logarithm of the off-gassing rate to the inverse of the off-gassing temperature ($1/T$) is a linear relationship, expressed as

$$\log V = (T / C_1) + C_2 \tag{4.1}$$

where V is the off-gassing rate, T is the off-gassing temperature (K), and C_1 and C_2 are constants. The off-gassing rate V is shown to be

$$V = \frac{M}{A \cdot t} \tag{4.2}$$

where M is the off-gassing amount, A is the surface area of the test material, and t is the off-gassing time.

For a system consisting of vapor and liquid phases of a pure substance, this equilibrium state is directly related to the vapor pressure of the substance, and vapor pressure changes nonlinearly with respect to temperature given by the Clausius-Clapeyron relation (Smith et al. 2005). The vapor equilibrium is most often expressed by the Clausius-Clapeyron equation in its simplest form with the assumption of ΔH_{vap} as a constant for a limited temperature range:

$$\log P = \left(-\frac{\Delta H_{vap}}{2.303R}\right)\frac{1}{T} + \text{constants} \tag{4.3}$$

where P is the pressure, ΔH_{vap} is vaporization heat, and R is the ideal gas constant. The equation can be further simplified by expressing the constants as C_3 and C_4:

$$\log P = C_3 / (T + C_4) \tag{4.4}$$

where P is the vapor pressure and T is the temperature (K).

Often high-boiling compounds (e.g., antioxidants, organophosphates, silicones, hydrocarbons, plasticizers, etc.) are most problematic because they readily adhere to wafer or disk-drive surfaces. Table 4.1 shows a list of materials that should be evaluated for off-gassing (Muller 1999).

Table 4.1 Components to be Tested for Off-Gassing

Adhesives	Filters	Photoresists
Antistatic coverings	Fire-retardant materials	Pipes
Bags	Floor tiles	Plastic curtains
Cables	FOUPs	Pods
Caulks	Gaskets	Polyimides
Coatings	Gel seals	Reactor components
Disk-drive components	Gloves	Sealants
Ductwork	HEPA filters	Silicones
Elastomers	Insulation	Tapes
Electrical fittings/components	Labels	Tubing
Epoxies	Light fixtures	Wall coverings
Equipment	O-rings	Wet-bench plastics
	Paints	

4.2.3 MATERIAL OFF-GASSING TEST STANDARDS

Several international test standards for off-gassing have been developed with particular emphasis on the environment of the test procedure (e.g., vacuum, elevated temperatures) or the application of the material being tested (e.g., spacecraft material). This section discusses some of these standards.

4.2.3.1 IEST-RP-CC031, *Method for Characterizing Outgassed Organic Compounds from Cleanroom Materials and Components*

IEST-RP-CC031 (IEST 2011) describes a test method for semiqualitative characterization of organic compounds that are off-gassed from materials exposed to the air in cleanrooms and clean spaces. This recommended practice (RP) specifies four off-gassing temperatures—122°F, 167°F, 212°F, and 302°F (50°C, 75°C, 100°C, and 150°C)—to baseline cleanroom materials. The RP may be used as the basis for an agreement between the supplier and the customer regarding the specification, procurement, and certification of materials.

4.2.3.2 ASTM E595, *Standard Test Method for Total Mass Loss and Collected Volatile Condensable Materials from Outgassing in a Vacuum Environment*

ASTM E595 (ASTM 2015) tests two parameters, total mass loss (TML) and collected volatile condensable material (CVCM), to determine the volatile content of materials exposed to a vacuum. A third parameter, amount of water vapor regained (WVR), may be obtained after measurements for TML and CVCM have been completed.

This standard describes the apparatus and operating procedures for evaluating the mass loss of materials subjected to 257°F (125°C) at less than 5×10^{-5} torr (7×10^{-3} Pa) for 24 h. The overall mass loss can be classified as noncondensable or condensable, with the latter characterized as capable of condensing on a collector at 77°F (25°C).

4.2.3.3 ASTM E1559, *Standard Test Method for Contamination Outgassing Characteristics of Spacecraft Materials*

ASTM E1559 (ASTM 2009) describes two test methods for generating data to characterize the kinetics of products off-gassed from spacecraft materials. The methods determine the total mass flux of a material exposed to a vacuum as well as the deposition of this flux on surfaces at specified temperatures. The quartz crystal microbalances (QCMs) used in these methods are sensitive and can measure deposited mass in very small quantities. The test apparatus consists of four subsystems: a data acquisition system, an internal configuration, a temperature control system, and a vacuum chamber. The standard includes procedures for collecting data as well as processing and presenting the data.

4.2.3.4 SEMI E108-0307, *Test Method for the Assessment of Off-Gassing Organic Contamination from Minienvironment Using Gas Chromatography/ Mass Spectroscopy*

The test method provided in SEMI E108 (SEMI 2007a) is for assessing organic contamination off-gassing from minienvironments. This method uses gas chromatography/ mass spectroscopy (GC/MS) to determine organic contamination because GC/MS is commonly used for characterizing and quantifying organic compounds. GC/MS, combined with thermal desorption, provides a method for identifying organic compounds inside the minienvironment as well as from the source materials directly. This method can also be used to evaluate processes and materials used in the semiconductor industry.

4.2.3.5 SEMI E46-0307, *Test Method for the Determination of Organic Contamination from Minienvironments Using Ion Mobility Spectrometry (IMS)*

SEMI E46 (SEMI 2007b), which is based on ion mobility spectroscopy (IMS), is an alternative to the GC/MS and thermal desorption measurement method in SEMI E108 (SEMI 2007a). Additionally, the results of SEMI E46 and SEMI E108 are given in different units. Organic contamination from construction materials may affect silicon wafers stored in or passed through minienvironments; knowledge of such contamination assists when decisions are being made about using minienvironments in semiconductor manufacturing. IMS is used to determine this contamination because it provides an easy, fast, sensitive, and widely applicable way of measuring surface organic contamination. IMS also allows for the possibility of checking the contaminating effects of chemical carryover and processing as well as the characterization of future polymeric materials for use in semiconductor technology.

4.3 CLASSIFICATION OF AIRBORNE MOLECULAR CONTAMINATION

4.3.1 STANDARDS FOR AMC CLASSIFICATION AND RECOMMENDED TEST METHODS

Currently there are two main standards covering AMC classification and recommended test methods: SEMI F21-1016, *Classification of Airborne Molecular Contaminant Levels in Clean Environments* (SEMI 2016), and ISO 14644-8, *Cleanrooms and Associated Controlled Environments—Classification of air cleanliness by chemical concentration (ACC)* (ISO 2013). While they are technically similar, each document has a different focus and classification format.

4.3.2 SEMI F21-1016, *CLASSIFICATION OF AIRBORNE MOLECULAR CONTAMINANT LEVELS IN CLEAN ENVIRONMENTS*

SEMI F21 states its purpose as classifying "microelectronic clean environments with respect to their molecular (nonparticulate) contaminant levels" and states that this classification "provides a consistent means of communicating acceptable contaminant levels of *groups* of specific airborne molecular contaminants" (italics added for emphasis) (SEMI 2016). The focus is on microelectronics and groups of chemicals by one or more categories: molecular acids (MA), molecular bases (MB), molecular condensables (MC), molecular dopants (MD), and molecular metals (MM). SEMI F21 classification is to be used in the specification of semiconductor cleanrooms and clean spaces such as inside a process tool environment. It can also specify contamination control equipment measurement and control performance.

Table 4.2 AMC Classifications from SEMI F21-1016

(SEMI 2016)

Material Category	1	10	100	1000	10,000
Acids	MA- 1	MA-10	MA-100	MA-1000	MA-10,000
Bases	MB- 1	MB-10	MB-100	MB-1000	MB-10,000
Condensables	MC-1	MC-10	MC-100	MC-1000	MC-10,000
Dopants	MD- 1	MD-10	MD-100	MD-1000	MD-10,000
Metals	MM- 1	MM-10	MM-100	MM-1000	MM-10,000

As with particle standards, this classification is defined by the maximum allowable total gas-phase concentration of each category of material, whereas the cumulative total gas-phase concentration of the categories may be different. For example, MA-10 means that the maximum allowable concentration of acidic molecular contaminants is 10 parts per trillion calculated on a molar basis (pptM). Similarly, an MC-100 designation means not more than 100 pptM of condensible molecular contaminants, and so on. Table 4.2 shows how SEMI F21 uses classes that are orders of magnitude of pptM levels.

While SEMI F21-1016 provides a general guideline to follow, it does not distinguish the chemical categories of many compounds, particularly those of organic nature. For instance, an organic molecule can be classified as either MA or MB, even though condensation may be more important in its adverse effect to the fabrication process. Perhaps more significantly, the standard does not correlate AMC cleanliness to device yield or reliability.

4.3.2.1 ISO 14644-8, *Cleanrooms and Associated Controlled Environments—Classification of Air Cleanliness by Chemical Concentration (ACC)*

ISO 14644-8 (ISO 2013) is much more generic than SEMI F21-1016 and is not focused on a specific industry. Its introduction states,

> the presence of chemicals is expressed as air chemical contamination.... This part of ISO 14644 assigns ISO classification levels to be used to specify the level of ACC within a cleanroom and associated controlled environment, where the product or process is deemed to be at risk from air chemical contamination." (ISO 2013, p. V)

For classification classes, ISO 14644-8 is limited to a designated range of air cleanliness by chemical concentration (ACC) and provides standard protocols for specifying such levels with regard to chemical compounds, methods of test and analysis, and time-weighted factors.

ACC is defined as the level of air cleanliness by chemical concentration expressed in terms of an ISO-ACC Class N, which represents the maximum allowable concentration of a given chemical species or a group of chemical species designated N, expressed in grams per cubic meter (g/m^3). While SEMI F21 has five contaminant groups (MA, MB, MC, MD, and MM), ISO 14644-8 suggests eight: acid (ac), base (ba), biotoxic (bt), condensable (cd), corrosive (cr), dopant (dp), total organic (or), and oxidant (ox). The format of the ACC is *ISO-ACC Class N (X)*, where *X* is one of the suggested chemical substances above or a group of substances; an individual substance may also be specified. (See Table 4.3.)

4.3.3 RECOMMENDED AMC CONCENTRATIONS FOR SEMICONDUCTORS

The International Technology Roadmap for Semiconductors (ITRS), published as a joint effort of the various global semiconductor trade associations[1] since 1997, provides AMC guidance and recommendations on process-specific requirements, including pre-gate oxidation, salicidation, contact formation, and deep ultraviolet (DUV) lithography

Table 4.3
ISO-ACC Classes from ISO 14644-8

(ISO 2013)

ISO-ACC Class	Concentration, g/m^3	Concentration, $\mu g/m^3$	Concentration, ng/m^3
0	$10^{'0}$	10^6 (1 000 000)	10^9 (1 000 000 000)
–1	10^{-1}	10^5 (100 000)	10^8 (100 000 000)
–2	10^{-2}	10^4 (10 000)	10^7 (10 000 000)
–3	10^{-3}	10^3 (1 000)	10^6 (1 000 000)
–4	10^{-4}	10^2 (100)	10^5 (100 000)
–5	10^{-5}	10^1 (10)	10^4 (10 000)
–6	10^{-6}	$10^{'0}$ (1)	10^3 (1 000)
–7	10^{-7}	10^{-1} (0,1)	10^2 (100)
–8	10^{-8}	10^{-2} (0,01)	10^1 (10)
–9	10^{-9}	10^{-3} (0,001)	$10^{'0}$ (1)
–10	10^{-10}	10^{-4} (0,000 1)	10^{-1} (0,1)
–11	10^{-11}	10^{-5} (0,000 01)	10^{-2} (0,01)
–12	10^{-12}	10^{-6} (0,000 001)	10^{-3} (0,001)

(ITRS 2015). Since its first publication, additional guidance has been provided covering not only specific process steps but also locations where specific wafers may be exposed to AMC. These include the following:

- Lithography: point of entry (POE) to exposure tool
- Lithography: POE to track and inspection tools; temporary reticle pod storage
- Reticle storage (inside stocker, inside pod, inside exposure tool library, inside inspection tool)
- Gate/furnace area wafer environment (cleanroom front-opening unified pod [FOUP] ambient/tool ambient)
- Gate/furnace area wafer environment (FOUP inside)
- Salicidation wafer environment (cleanroom FOUP ambient)
- Salicidation wafer environment (FOUP inside; wafer environment)
- Exposed copper wafer process environment (cleanroom ambient, tool inside)
- Exposed aluminum wafer process environment (cleanroom ambient, tool inside)
- Exposed copper wafer environment (FOUP inside)
- Exposed aluminum wafer environment (FOUP inside)

At each process step and/or location, a recommended AMC concentration is provided (see Table 4.4). These criteria are based on groups of molecular contaminants as opposed to individual species to account for the possible synergistic effects between the contaminants and surfaces. Note that because of the competitiveness within the semiconductor industry, individual semiconductor manufacturers (including those for both microelectronics and optoelectronics) have tended to set their own criteria for contamination control, which may become proprietary. Therefore, no consensus criteria of AMC control exists; those used depend on the expectations and capabilities of the individual manufacturers. However, the variability in the criteria is expected to decrease significantly as the critical geometries converge to those forecasted by the ITRS (Den et al. 2006).

1. The global trade associations include China Semiconductor Industry Association (CSIA), Taiwan Semiconductor Industry Association (TSIA), European Semiconductor Industry Association (ESIA), Semiconductor Industry Association in Japan (JSIA), Korea Semiconductor Industry Association (KSIA), and Semiconductor Industry Association (SIA).

Table 4.4
ITRS AMC Guidance (ITRS 2015)

Year of production	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Dynamic random access memory (DRAM) 1/2 pitch (nm) (contacted)	**24**	**22**	**20**	**18**	**17**	**15**	**14**	**13**	**12**	**11**	**10**	**9.2**	**8.4**	**7.7**
Critical particle size (nm) based on 50% of DRAM 1/2 pitch (nm) (contacted)	**12**	**11**	**10**	**9**	**8.5**	**7.5**	**7**	**6.5**	**6**	**5.5**	**5**	**4.6**	**4.2**	**3.9**
Airborne Molecular Contaminants in Gas Phase (pptV)														
Lithography: POE to exposure tool														
Total inorganic acids	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Total organic acids	2000	2000	2000	2000	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd
Total bases	20,000	20,000	20,000	20,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000
Propylene glycol monomethyl ether acetate (PGMEA), ethyl lactate	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Volatile organics	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000
Refractory compounds	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Lithography: POE to track and inspection tools; temporary reticle pod storage														
Total inorganic acids	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Total organic acids	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
Total bases	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000	2,000
PGMEA, ethyl lactate	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Condensable organics (see definition in SEMI F21, boiling point 302°F [150°C])	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
Reticle storage (inside stocker, inside pod, inside exposure tool library, inside inspection tool)														
Total inorganic acids	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200
Total organic acids	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200
Total bases	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200	<200
Condensable organics (see definition in SEMI F21, boiling point 302°F [150°C])	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100	< 100
Refractory compounds	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd

Table 4.4
ITRS AMC Guidance (ITRS 2015) *(continued)*

Year of production	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028
Dynamic random access memory (DRAM) 1/2 pitch (nm) (contacted)	**24**	**22**	**20**	**18**	**17**	**15**	**14**	**13**	**12**	**11**	**10**	**9.2**	**8.4**	**7.7**
Critical particle size (nm) based on 50% of DRAM 1/2 pitch (nm) (contacted)	**12**	**11**	**10**	**9**	**8.5**	**7.5**	**7**	**6.5**	**6**	**5.5**	**5**	**4.6**	**4.2**	**3.9**
Gate/furnace area wafer environment (cleanroom FOUP ambient/tool ambient)														
Total metals (E+10 atoms/cm^2/week)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Dopants (E+10 atoms/cm^2/week; front end of line only)	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Volatile organics	20000	20000	20000	20000	20000	20000	20000	20000	20000	20000	20000	20000	20000	20000
Gate/furnace area wafer environment (FOUP inside)														
Total metals (E+10 atoms/cm^2/day)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Dopants (E+10 front end of line only)	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Volatile organics	20000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Total surface metals on wafer, E+10 atoms/cm^2/day	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Salicidation wafer environment (cleanroom FOUP ambient)														
Total inorganic acids	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Total organic acids	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
Salicidation wafer environment (FOUP inside; wafer environment)														
Total inorganic acids	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Total organic acids	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000	5000
Exposed copper wafer process environment (cleanroom ambient, tool inside)														
Total inorganic acids	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Total bases	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Total organic acids	500	500	500	500	500	500	500	500	500	500	500	500	500	500
Total other corrosive species	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
H2S	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Total sulfur compounds	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500	2500

4.3.4 CHARACTERIZING THE DESTRUCTIVE POTENTIAL OF AMC

A unique approach called *reactivity monitoring* has been proposed to characterize the destructive potential of AMC in an environment (Muller 1999). In this approach, using measurement devices such as quartz crystal microbalances (QCMs) or environmental reactivity coupons (ERCs) containing copper or silver test metal films enables quantification of the extent of metal film corrosion, which can be used as the basis for AMC control strategies. Table 4.5 provides cleanroom classification examples based on reactivity monitoring.

4.3.5 CLASSIFICATION OF AIRBORNE MOLECULAR CONTAMINATION AND YIELD EFFECTS

4.3.5.1 Molecular Acids (MAs)

Molecular acids (MAs) comprise nitric acid, sulfuric acid, phosphoric acid, hydrofluoric acid (HF), and hydrochloric acid (HCl), among others.

4.3.5.1.1 Sources

The process chemicals used in manufacturing areas are the main sources for these MAs. Poor airflow design and circulation of acid fumes can spread acid contamination throughout the manufacturing area and into other process areas. Outdoor pollution is another source of MAs. There is benefit to using chemical filters to remove MAs (primarily nitrogen oxides [NO_x] and sulfur oxides [SO_x]) and to limit their associated problems at the air intake or in critical process areas (Anderson 2005).

4.3.5.1.2 Effects

The presence of MAs at concentration levels of parts per billion molar (ppbM) can cause yield problems, including electrical faults, surface hazing (for both products and process tools), and corrosion of copper and aluminum films. Interactions of acids and MBs in the air can produce small particles, which can then settle on product surfaces. HF is an especially critical MA for all silicon-based processing due to its widespread use and its harmful nature. The aggressive nature of HF with silicon dioxide (SiO_2) is critical for the thinner gate oxides now in play with integrated device manufacturing. HF may also attack the borosilicate glass in HEPA or ULPA filters, releasing boron as an airborne contaminant and causing unwanted p-doping of silicon-based processes (Anderson 2005). HF and all MAs need to be closely controlled.

4.3.5.2 Molecular Bases (MBs)

Molecular bases (MBs) include amides (such as N-methyl-2-pyrrolidone [NMP]), amines (such as morpholine from humidifier systems, trimethylamine from exchange resins, and amines present in photoresist strippers), and ammonia.

Table 4.5 Cleanroom Classification based on Material Corrosivity

(Muller 1999)

Copper Corrosion			Silver Corrosion		
Class	**Air Quality Classification**	**Corrosion Amount**	**Class**	**Air Quality Classification**	**Corrosion Amount**
C1	Pure	<90Å/30 days	S1	Pure	<40Å/30 days
C2	Clean	<150Å/30 days	S2	Clean	<100Å/30 days
C3	Moderate	<250Å/30 days	S3	Moderate	<200Å/30 days
C4	Harsh	<350Å/30 days	S4	Harsh	<300Å/30 days
C5	Severe	« 350Å/30 days	S5	Severe	« 300Å/30 days

4.3.5.2.1 Sources

Ammonia is the most common MB due to its inclusion in photoresist chemicals (via hexamethyl disilazane [HMDS]) and process chemicals (via ammonium hydroxide [NH_4OH]) as well as its widespread use as an electronic specialty gas (especially for thin-film transistor liquid crystal display [TFT-LCD] manufacturing). Similar to MAs, MBs must be carefully controlled via proper air handling to limit their presence in process areas (Anderson 2005).

4.3.5.2.2 Effects

The effects of MBs may be similar to those of MAs when MBs and MAs are combined in the air; for example, copper or aluminum corrosion may result or salts may form. MBs may also cause a time-dependent haze on displays, disks, and wafers. Base-specific yield effects include T-topping of chemically amplified DUV photoresists. Lithography processes are susceptible to MB effects due to the large amounts of amines and ammonia byproducts in lithography chemicals and process areas (Anderson 2005). The presence of MBs at ppb levels is an area of concern for causing any of these effects, especially in the latest technology manufacturing processes.

4.3.5.3 Molecular Condensables (Organic Compounds)

Numerous sources in fabrication areas can create molecular condensables (MCs) in the air, which typically have boiling points greater than 302°F (150°C) and can also adsorb and irreversibly bind to surfaces. Table 4.6 provides common examples and sources of MCs.

4.3.5.3.1 Sources

Similar to MAs and MBs, MCs must be controlled through proper air handling. It is also important that the components of the in air-handling systems, materials used in cleanrooms, and materials that come into contact with products be tested for potential MC contamination off-gassing (Anderson 2005).

4.3.5.3.2 Effects

MCs can cause yield problems at many different process steps. Examples of MCs that can cause problems are photoresists in semiconductor and disk-drive manufacturing; plasticizers, silicones, and phthalates that can desorb and cause thin-film delamination; and phthalates that affect gate oxide integrity and can decompose to form silicon carbide. Optic and mask hazing has also become more problematic with the increasing use of lower-wavelength/higher-energy systems (Anderson 2005).

4.3.5.4 Molecular Dopants (MDs)

The most widely used molecular dopants (MDs) are boron and phosphorus compounds.

Table 4.6 Common Examples and Sources of MCs

(SEMI 1995)

Condensable	Example Compound	Source Example
Plasticizers	TXIB, DOP	Vinyl materials, floor tiles, gloves
Antioxidants	BHT	FOUPs, pods, sealants, caulking agents
Phosphates	TEP, TEB	Fire retardant in filter potting compounds
Silicones	Both linear and cyclic	Sealants, O-rings, lubricants

Notes:
BHT = dibutyl hydroxy toluene
DOP = dioctyl phthalate
TEB = triethyl bromide
TEP = triethyl phosphate
TXIB = texanol isobutyrate

4.3.5.4.1 Sources

Sources of both boron and phosphorus include chemical vapor deposition (CVD) compounds, implant molecules, and the materials used within a fabrication cleanroom. Another source for boron compounds is the borosilicate glass in HEPA and ULPA filters. Some shedding of boron occurs naturally over time, but more complete control of boron contamination can be achieved by strict control of HF vapors in the air-handling system and by substitution of polytetrafluoroethylene (PTFE) or boron-free fused silica for filter material. Filtration systems may also be sources of phosphorus compounds, as they are often used as flame retardants in potting compounds. These organophosphates can off-gas and settle on surfaces (Anderson 2005).

4.3.5.4.2 Effects

MD yield issues include unwanted p-doping (boron) and n-doping (phosphorus) of silicon. These effects become problematic at levels around 10 pptM and become more critical as thinner junctions in advanced devices produce higher dopant concentrations (Anderson 2005). The contaminants and their effects in each of the five AMC categories are shown in Figure 4.1 and Table 4.7.

4.3.6 CONTROL OF CONTAMINATION

4.3.6.1 Outdoor Air

Makeup air systems encounter primarily atmospheric contaminants if the outdoor air intake locations are chosen appropriately. This includes standard considerations for locations of plant exhausts and loading docks and environmental effects such as wind direction and microclimates. For makeup air handlers, zero-downtime systems should be considered. Overall, when choosing a control technology or system, a balance should be struck between the desired level of AMC control, the pressure drop, and system service life (Muller and Stanley 2006a).

4.3.6.2 Recirculated Air

Because most of the air handled by the HVAC system in a cleanroom is recirculated from within the facility, the recirculation systems can become major sources of AMC. Airborne molecular contaminants can include chemicals used in other parts of the production processes; cleaning products; and emissions from maintenance, office, or canteen areas, and even the personnel. Controlling these contaminants may involve a combination of source control of emissions, establishing minienvironments with targeted AMC controls, and cleaning within the recirculation system.

4.3.6.3 Construction Materials

The construction materials used to build a cleanroom can be a major source of AMC because of the volatile chemicals that may off-gas from them. For example, the plasticizers added to polyvinyl chloride (PVC) plastic to make pliable products typically come from the chemical group *phthalates* and may be a large percentage of the material's chemical mix. Phthalates do not evaporate easily, they evaporate slowly—this is why soft PVC products harden after a few years. PVC is an option for wall systems and vinyl flooring in cleanrooms. To minimize AMC, this type of walls and flooring should be avoided. Another example of a construction material that might off-gas is silicon mastic, or caulking, which should likewise be avoided for cleanrooms (S2C2 2006).

Figure 4.1
Five AMC Categories

(Adapted from SEMI 1995)

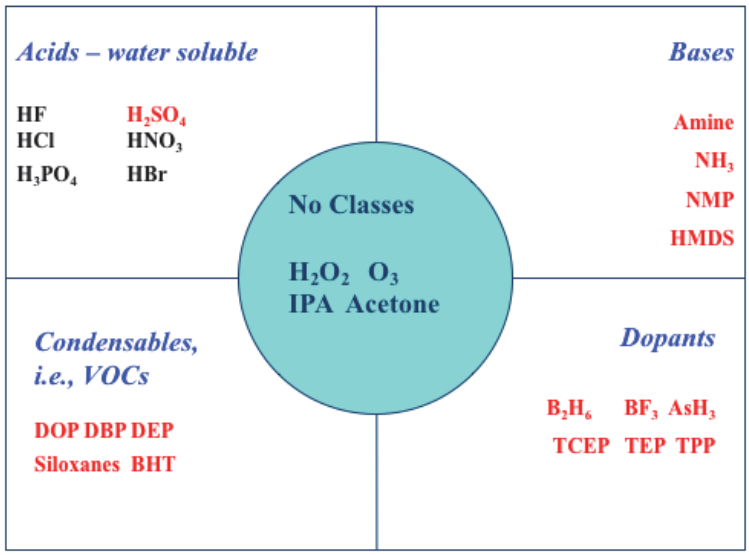

Table 4.7
Airborne Molecular Contaminants in Cleanrooms and Their Effects

(Ayre et al. 2005)

Contaminant	Source	Effect
Acid		
HCl, H_2S, SO_x, NO_x, HF	Outdoor air coming into cleanroom	Acid corrosion of ion chromatography (IC) devices
	Vapor leak from cleaning processes	Formation of surface contaminants reacted with ammonia
Base		
NH_3, amine	Outdoor air coming into cleanroom	Cloudiness on exposure lenses and mirrors
	Vapor leak from cleaning processes	Deterioration of photosensitized resists
	Chemical decomposition of HMDS	
Dopant		
Boron	Deterioration of borosilicate glass of ULPA filters with humidity or hydrogen fluoride	Electrical defects in IC devices
Phosphorus (TEP, etc.)	Flame retarder of cleanroom components	
Condensable		
Polysiloxane	Volatile compounds from sealant	Cloudiness in exposure lenses and mirrors Deterioration of film adhesion to substrates Insulator deterioration of gate oxides
Phthalate	Plasticizer in building materials or resins	
DOP, DBP, etc.	DOP test particles trapped in ULPA filter	
BHT	Antioxidants in resins	
HMDS	Volatile compounds from resist adhesive chemicals	

Notes:
BHT = dibutyl hydroxy toluene
DBP = dibutyl phthalate
DOP = dioctyl phthalate
H_2S = hydrogen sulfide
HCl = hydrochloric acid
HF = hydrofluoric acid
HMDS = hexamethyl disilazane
NH_3 = ammonia
NO_x = nitrogen oxides
SO_x = sulfur oxides
TEP = triethyl phosphate

4.3.7 OPERATION AND MAINTENANCE

4.3.7.1 Operational Considerations

Rotating machines and machines with large amounts of plastic in their construction may present problems in a cleanroom environment. The machines and any process material used by them should be assessed for off-gassing to ascertain if they exceed acceptable AMC concentration levels (S2C2 2006).

During cleanroom and process testing periods such as cleanroom operational qualification (OQ), certification, and commissioning, testing materials should also be assessed even if their presence is only temporary. Some materials may off-gas and then condense contaminants to critical surfaces. Some tests that should be evaluate are: high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filter integrity tests, leak testing of rooms and equipment enclosures, and functional tests of pressurized gas delivery systems.

4.3.7.2 Maintenance Considerations

Equipment needing lubrication is isolated with polycarbonate shields to prevent the spread of grease and to contain its AMC. A gowned maintenance worker must wear three pairs of latex gloves to perform this maintenance. After greasing the equipment, the maintenance worker removes the outer glove and turns it inside out under the shield to contain the grease. Not following this procedure could result in the maintenance worker leaving grease residue on the door or other surfaces, and any operators touching those surfaces at a later date would spread the grease and organic contaminants (Helgeson 2000).

AMC filtration equipment must be routinely maintained or changed out to ensure adequate performance. Several types of off-line or real-time monitoring methods for AMC are useful in determining the frequency of maintenance or change-out.

4.3.7.3 Personnel

People who work in cleanrooms, including factory operators and maintenance personnel, may themselves be a source of AMC. For example, common foods may off-gas through workers' skin or as they breathe. People who smoke in particular emit AMC when they breathe. Many fabrication cleanrooms therefore prohibit smokers from working in the cleanrooms. They also tend to prohibit employees from wearing cosmetics and perfumes (see Section 1.7.1 of Chapter 1). In general, if unusual odors occur in a cleanroom, the quality department will attempt to identify the source and assess the risk to the cleanroom.

Cleanroom garments and how they are cleaned (with water versus by dry cleaning) are also typically assessed, as is the packaging of the cleaned garments. All materials that enter the cleanroom must be assessed for contamination risks to off-gassing.

4.3.8 AIR TREATMENT PROCESSES FOR THE ABATEMENT OF AMC

Several processes are available for controlling or reducing the concentrations of specific AMC categories. These include the following (Muller 2007; Muller and Stanley 2006b):

- **Adsorption/Chemisorption.** Chemical air filtration uses two main processes to remove AMC: the reversible physical process of adsorption and chemisorption, which involves adsorption and chemical reactions.

  Adsorption is a surface phenomenon, which means that an adsorbent's removal capacity is directly related to its total surface area. Having an accessible surface area per unit volume that is as large as possible is therefore important. The most common materials that enable this are granular activated carbon (GAC) and activated alumina.

  Today nearly all of the chemical filtration media commonly available are made from activated carbon, alumina, or both; however, these media do not

remove all contaminant gases equally. Chemicals added during manufacturing give each medium special characteristics and make them more or less specific for removing different chemical species. The technique of chemisorption with impregnated activated carbon is used to significantly increase the performance efficiency and adsorptive capacity for many gases that are difficult to adsorb onto base products. A reaction occurs with contaminants to form stable chemical compounds that either bind to the media or are harmless when released into the air (e.g., water vapor or carbon dioxide).

- **Bonded Media Panels.** Bonded media panels use adsorbents that are granular, such as activated carbon, and are bonded and formed into single-piece panels.
- **Ion Exchange Systems.** Ion exchange systems use synthetic polymers with either positively or negatively charged sites on either spongelike, flat sheets or pleated membranes. These systems are mainly used for liquids, but they are also being used for specific AMC control, such as for ammonia control.
- **Photocatalytic Oxidation.** The photocatalytic oxidation technology involves the application of titanium oxide (TiO_2) photocatalysis for the removal of volatile organic compounds (VOCs) in low-ppb concentrations. In a typical application, energy supplied from an ultraviolet lamp is directed onto the TiO_2 catalyst, creating highly reactive free radicals from the water molecules in the airstream. These free radicals then react with organic contaminants to sequentially break them into smaller by-product compounds. Given enough free radical generation and residence time, some VOCs can ultimately be broken down to simply water and carbon dioxide. However, incorrect design can lead to insufficient removal or the formation of by-products that may be as unwanted as the original contaminants.

4.4 MEASUREMENT, TESTING, AND COMPLIANCE

With increased awareness of AMC sources, cleanroom owners will perform AMC/ACC testing to determine the current operating conditions. Five types of molecular contaminants are typically considered for testing: acids, bases, organic compounds, dopants, and trace metals. These types are discussed in more detail in the following subsections.

4.4.1 ACIDS AND BASES

Acids and bases are typically analyzed by ion chromatography (IC). Table 4.8 shows a list of applicable detection limits.

Table 4.8 Detection Limits for Acids

(SEMI 1995)

Analyte	Method Detection Limit, ng/L in air*
Ammonium (NH_4^+)	0.03
Bromide (Br^-) 0.03	0.03
Chloride (Cl^-) 0.02	0.02
Fluoride (F^-)	0.2
Nitrate (NO_3^-)	0.03
Nitrite (NO_2^-)	0.02
Phosphate (PO_4^{3-})	0.03
Sulfate (SO_4^{2-})	0.03

* $ng/L = \mu g/m^3$

Ion chromatography is an efficient and fast way of separating anions and cations. Two techniques can achieve the separation: ion exchange chromatography and ion exclusion chromatography. Ion exchange chromatography uses a separator column containing resins with a fixed charge and a counterion. After the sample is introduced, a sample ion mixture travels through the column, with the different ions traveling at different speeds because of their different affinities for the charged site when the counterion is exchanged for the sample ion. Ion exclusion chromatography uses a column with a negatively charged membrane that is permeable only for neutral compounds; because of their negative charge, totally dissociated anions cannot penetrate the membrane, and they are excluded from the column. This difference of membrane permeability results in varying travel times through the column and allows for the separation of weak acids from inorganic anions.

4.4.2 MOLECULAR CONDENSABLES (ORGANIC COMPOUNDS)

Organic compounds (see Table 4.9) may adversely affect various processes in a fabrication cleanroom, including high-temperature processes, etching, oxide growth, film deposition, and cleaning. For example, organophosphates in cleanroom air can counter

Table 4.9 Organic Compounds Typically Found in Cleanrooms

(SEMI 1995)

Aldehydes	Benzaldehydes
	Nonyl aldehyde
Amides	1-methyl-2-pyrrolidinone (NMP)
	Dimethylacetamide (DMAC)
Aromatics	Toluene
	Xylene
	Trimethylbenzene
	Alkylbenzenes
	Phenol
	Cresols
Chlorocarbons	Trichloroethane (TCA)
	Tetrachloroethylene (TCE)
	Carbon tetrachloride
Esters	Ethyl lactate
	Ethyl 3-ethoxyproprionate
	Propylene glycol monomethyl ether acetate (PGMEA)
	Ethylene glycol monomethyl ether acetate (EGMEA)
Ketones	Methyl propyl ketone
	Methyl isobutyl ketone
	Methyl ethyl ketone
Organo phosphates	Triethyl phosphate
	Tris(chloropropyl)-phosphate
Plasticizers	Dioctyl phthalate (DOP)
	Texanol isobutyrate (TXIB)
	Dibutyl phthalate
Siloxanes	Hexamethyldisiloxane
	Trimethylsilanol
	Polydimethylsiloxane

dope silicon wafers. For yield enhancement, identifying and monitoring the sources of organic compounds in a cleanroom are becoming more and more critical. The thermal desorption gas chromatography/mass spectrometry (TD-GC/MS) method can identify organic compounds from C_6 to C_{28} and is useful for sampling the air in recirculation, makeup, exhaust, and minienvironments.

4.4.3 DOPANTS

Gate oxidation, diffusion, polysilicon deposition, and epitaxy, as well as other dopant-sensitive processes, should be monitored for dopants that might adhere to wafer surfaces and cause unwanted doping. Some common HEPA and ULPA filters are made with borosilicate glass that will react when exposed to HF at parts per billion (ppb) or higher levels and release boron, which will adhere to silicon wafer surfaces. Heated boron may diffuse into liquid surfaces and affect electrical properties, such as leakage currents, threshold voltages, and resistivity. Analytical methods are available for testing for boron, phosphorus, antimony, and arsenic. Some organophosphate dopants can also be detected in organic compounds. Inductively coupled plasma mass spectrometry (ICP-MS) can detect boron and phosphorus on wafers, and TD-GC/MS can detect organophosphates.

4.4.4 TRACE METALS

There are many sources of trace metals in cleanrooms, such as outdoor air, people, construction materials, equipment, CVD chemicals, reactor by-products, and chemical mechanical planarization (CMP) processes. Trace metals can impact gate oxidation and diffusion and may cause lifetime degradation, leakage currents, threshold voltage shifts, and other problems. Analysis of cleanroom air is useful for identifying these sources as well as for routine monitoring. ICP-MS detection limits for 16 examples are shown in Table 4.10. Witness wafer surface analysis is useful for monitoring for trimethylaluminum, hafnium, and tantalum, which may pass through filtration and onto the wafer.

Table 4.10 Detection Limits for Trace Elements

(SEMI 1995)

Analyte	Method Detection Limit, ng/L in air*
Aluminum (Al)	0.003
Boron (B)	0.008
Calcium (Ca)	0.1
Chromium (Cr)	0.001
Copper (Cu)	0.003
Iron (Fe)	0.02
Lead (Pb)	0.002
Magnesium (Mg)	0.001
Manganese (Mn)	0.001
Molybdenum (Mo)	0.002
Nickel (Ni)	0.002
Potassium (K)	0.1
Sodium (Na)	0.002
Tin (Sn)	0.001
Titanium (Ti)	0.002
Zinc (Zn)	0.002

*$ng/L = \mu g/m^3$

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5

Liquid-Borne Contaminants

Air cleanliness in cleanrooms has been studied extensively, and nowadays it is very well controlled; therefore, airborne particulate contamination from the cleanroom environment itself is no longer a major problem. The major sources of contamination now are processing equipment, process liquids, and personnel. Semiconductor processing usually uses strong acids, bases, solvents, and ultrapure water (UPW), which often contain high concentrations of particles (Wang 2002).

The International Technology Roadmap for Semiconductors (ITRS) has identified particles in UPW and process liquids as a critical parameter associated with the risk of wafer defects in semiconductor manufacturing (Libman et al. 2009; ITRS 2009). Currently, particle concentration measurements are made at sizes slightly larger than the critical particle size (based on 1/2 design pitch or feature size). ITRS estimates that the critical particle sizes (or *killer particles*) for different technology nodes of flash memory devices should be reduced from 10 nm in 2017 to 5 nm in 2023. ITRS was hoping to develop sub-10 nm water and chemical liquid particle counters to help yield enhancement (ITRS 2013). Killer particles are those minimum sizes causing significant effects on the yield of semiconductor manufacturing (ITRS 2009). In this industry, particle concentrations and corresponding size distributions are important process control specifications in process liquids and UPW (Knotter et al. 2007).

For years the concept of critical particle size was used to determine whether particles would impact yield. However, this concept has been rethought because particles do not only impact process yield by their physical size alone—they also impact it by their chemical composition. This means that the allowable particle concentration also depends on parameters such as cell size. Such parameters, therefore, are now aligned with the particle concentration on the surface (derived by the front-end process surface preparation group calculation model) (ITRS 2013).

To correlate process fluid contamination types and levels to yield and to determine the necessary control limits, data, test structures, and methods are required. It is important to define different contaminants' importance to wafer yield, to define a standard test for yield/parametric effect, and to define control limits. Most important is understanding the correlation between impurity concentration in key process steps and device yield, reliability, and performance, because this correlation determines if additional increases in contamination limits are necessary. As the range of process materials increases, so does the complexity of this challenge. For meaningful progress, selection of the most sensitive processes for study is necessary (ITRS 2015).

ITRS (2009) illustrated the set of potential solutions for prevention and elimination of defects, but additional studies on device impact are necessary for validation of the need for increased purities. In seeking higher purities, system concerns such as corrosion potential may lead process concerns (ITRS 2013). The present challenges are development of sub-50 nm particle counters, filtration at sub-0.02 µm with higher flux (1 gpm/0.5 psi/10 in./1 cP), improved metrology for concentration measurements, particle characterization for identifying sources of contamination, yield impacts of various organic species, and particle-counting techniques for direct measurement of smaller particles.

5.1 PARTICLES IN PROCESS LIQUIDS

5.1.1 PARTICLE CONCENTRATION AND SIZE DISTRIBUTION

Process liquids are liquids used in the production or cleaning of semiconductor devices and come in direct contact with the product. Process liquids were largely ignored when particle monitoring and control in air were the object of focus of contamination prevention. However, process liquids are much dirtier than environment air in cleanrooms. For example, the air in a Class 10 (or ISO Class 4) area has fewer than 0.4 particles/L >0.5 µm. However, acids, bases, and solvents have a level of much more than 10,000 particles/L, and UPW has a level of about 100 particles/L.

Researchers have found that the more particles there are in the process liquids, the more there will be on the wafer surface (Mouche et al. 1994; Knotter and Dumesnil 2001). Particles deposited from process liquids onto wafers are related to yield. A simple way to account for particles in yield models is based on the assumption that particles greater than half the size of the critical diameter can result in device failure and are therefore killer particles (Knotter et al. 2007). It is therefore important to know the number distribution of particles in the process liquids being used. Measurement is preferably made on-line. If a sample of the process liquid is taken from a pipe to measure the particle number distribution, it is no longer a process measurement. Process measurements can be made on a bypass line. For example, if there is a 10 in. (0.254 m) diameter main line for the product, a smaller bypass line may be brought off the main line and the measurement can be conducted there. Laboratory measurements are often used to check the performance of sampling instruments. These correlation studies must be carefully evaluated for sample technique, time, color, temperature, and procedural errors (McNab 2004).

5.1.2 TURBIDITY IN PROCESS LIQUIDS

Turbidity is the effect of suspended particles on light passing through a liquid. It is an optical property of the liquid rather than an optical measurement of percent solids. The light absorption or scatter signals often follow the concentration levels of particles in the liquid. This relationship is frequently used to analyze concentrated levels from near zero to 60% concentration (by weight or volume). Process turbidity measurements can be made on-line on a bypass line, and off-line laboratory measurements are often used to check a process turbidimeter's performance. Such correlation studies must be evaluated for sample technique, time, color, temperature and procedural errors (McNab 2004).

Turbidimeters originally did not completely consider light scattering measurement but rather used the absorption method: relative turbidity, percent transmittance, and sometimes the Jackson Candle method with its Jackson Turbidity Units (JTUs). Later research that used scatter design promoted units such as parts per million (ppm), Formazin Turbidity Units (FTUs), and Kieselguhr (silicon dioxide [SiO_2]) units (McNab 2004). The most widely used measurement unit for turbidity now is the FTU. International Organization

for Standardization (ISO) refers to its units as Formazin Nephelometric Units (FNUs). Nephelometric Turbidity Units (NTUs) are a special case of FTUs, where a white light source and certain geometrical properties of the measurement apparatus are specified.

There are several practical ways to check liquid turbidity. The most direct way is measuring the attenuation of light as it passes through a sample column of liquid. Alternatively, the Jackson Candle method (with units of JTU) is the inverse measure of the length of a column of water needed to completely obscure a candle flame. The more liquid needed (the longer the water column), the clearer the water. Water by itself produces some attenuation, as do substances dissolved in the water that produce color. Though modern instruments do not use candles, this approach of measuring the attenuation of a light beam through a column of water should be calibrated and reported in JTUs.

A more meaningful measure of turbidity in process liquids is the scattering of a light beam shining through particles in a medium. If there are lots of small particles scattering the source beam, more light reaches the detector. This way of measuring turbidity is done with a *nephelometer* with the detector set up to the side of the light beam, and the units of turbidity are NTUs.

5.2 LIQUID-BORNE PARTICLE COUNTERS AND TURBIDITY METERS

Real-time particle monitoring of process liquids is commonplace in an integrated circuit manufacturing facility. The ability to isolate the process liquids as the source of particles without the aid of a particle counter requires a considerable expense of time and money. Therefore, liquid particle counters are used for high-volume production. These particle counters are best at quantifying the level of liquid-based contamination as well as monitoring the liquid on a routine basis.

Many commercially available systems are manufactured to measure both particle size and concentration on the wafer surface, in the air, or in UPW and process liquids. The equipment used for particulate contamination control in UPW and process liquids is installed and integrated within the distribution system; monitoring takes place at a central location and any deviation from the control limits signals that maintenance may be required on the lines. Particles that originate in UPW and process liquids are routinely monitored to ensure the liquids perform up to specified purity levels. Particle concentration is monitored at each chemical station. In-line, real-time particle monitoring allows rapid detection of a process that is out of control.

Process monitoring for particles in wet cleaning solutions of UPW or process liquids increases integrated circuit device yield. When concentrations outside of control limits are identified, cleaning or preventive maintenance of the UPW or process liquid delivery systems or the equipment itself can be performed to eliminate the source of the contamination (Terrell and Reinhardt 2008).

5.2.1 DYNAMIC LIGHT SCATTERING (DLS)

The dynamic light scattering (DLS) technique is a unique optical tool used to study particles with diameters much smaller than 0.1 μm. The technology is currently used in commercial light-scattering particle instruments to characterize size distributions of nanoparticles in liquids. The technique can also be used to detect nanoparticles in gaseous streams. The technique measures the degree of spectral broadening of an incident laser beam caused by the Brownian motion of particles. The mean diffusion coefficient of particles can then be derived from the degree of this broadening effect or from the decay of the correlation function. Particle size distributions can be inferred from the mean diffu-

sion coefficient with preassumed unimodal particle size distribution forms. The technique cannot distinguish biomodal size distributions unless the two peaks in the size distributions have a difference in the mean sizes of a factor of 8. Two distinguishable decays on the fluctuation correlation curve allow researchers to decipher the bimodal size distributions. The DLS technique usually requires high concentration of particles in the sensing zone for an ensemble measurement. The technique can be applied to both batch samples (nanoparticles in liquids) and flowing systems (nanoparticles in gases) (Taylor and Sorensen 1986; Willemse et al. 1997). If used for detecting particles in liquid, a stable nanoparticle suspension should be prepared before the measurement. The typical size ranges for these systems are 0.003 to 5 μm. However, very limited particle concentration and shape information can be deduced from the measurement. Recent developments in DLS include application of the technique to low-particle-concentration environments, to reducing errors induced by multiple scattering by using a two-color cross-correlation system, and to the improvement of correlators and optics for better signal processing (Willemse et al. 1997, 1998; Drewel et al. 1990).

5.2.2 OPTICAL PARTICLE COUNTERS (OPCs)

Liquid particle counters or optical particle counters (OPCs) for liquids are the most popular instruments for measuring particles in UPW and process liquids. They provide a reliable, consistent, and efficient method for quantifying particle size and concentration. An OPC measures the equivalent optical size of particles based on the principal of light scattering. In an OPC, a laser beam is focused on a sample cell or capillary through which a liquid is flowing. Individual particles in the liquid scatter light that is detected by a photodetector. The intensity of scattered light is proportional to particle size, with smaller particles scattering less light. Because particle counters are calibrated with polystyrene latex (PSL) standard spheres, particles are assigned a size based on their light-scattering equivalency to PSL spheres.

Liquid particle counters can be classified as either volumetric or nonvolumetric. The term *volumetric* refers to whether a particle counter has a well-defined sample volume (the amount of fluid examined per unit time) and whether it is viewing the entire sample flow (Knollenberg and Veal 1991; Terrell and Reinhardt 2008). In a volumetric particle counter the laser beam has a uniform shape across a capillary. The benefits of volumetric instruments are that their measurement of small-volume samples is accurate, they have good size resolution, and their large sample volumes provide repeatable results. Volumetric particle counters with several channels are referred to as *spectrometers*. The sizing accuracy of these instruments gives them the ability to distinguish different sizes of particles. The main disadvantage of volumetric particle counters is that the capillary is in the viewing region and therefore scatters light, which reduces the size sensitivity. Commercially available devices are limited to 0.1 μm size sensitivity (Terrell and Reinhardt 2008).

Nonvolumetric particle counters provide increased sensitivity because they have tightly focused laser beams. However, often they are referred to as *monitors* because they have poor resolution, a small number of channels, and examine only a small portion of the fluid flow per unit time. For these instruments, the sample volume can be less than 0.25% of the total flow—as small as 0.1 mL/min. With short sample intervals, high variability in the results can occur because very little fluid is being examined, especially when the fluid is UPW or other very clean chemicals. More consistent measurements can be provided by nonvolumetric counters with larger sample volumes, but these instruments lack the sensitivity required for examining the smallest particles. Sensitivity limits for nonvolumetric particle counters are 0.05 and 0.065 μm in UPW and liquid chemicals, respectively. Both volumetric and nonvolumetric particle counters are well suited for on-line process moni-

toring, but because of their large sample volumes, volumetric counters are better for off-line monitoring with syringe or compression samplers (Terrell and Reinhardt 2008).

5.2.3 NEPHELOMETERS

A nephelometer measures the turbidity in a liquid using a light beam and a light detector set to one side (often 90°) of that beam. They can be stationary or portable. Particle concentration can be inferred from turbidity data. Turbidity is then a function of the light scattered into the detector from the suspension. A nephelometer measures the attenuation of light transmitted through a solution containing finely divided suspended particles; there is a direct relationship between the amount of light attenuated and the amount of material in suspension. Nephelometers are typically calibrated in micrograms per cubic metre ($\mu g/m^3$) with a minimum response in the order of 1 $\mu g/m^3$ based on NTUs. Nephelometers have greater sensitivity, accuracy, and provision in measuring small amounts of turbidity than the meters previously discussed.

5.2.4 SPECIAL CONCERNS FOR PARTICLE COUNT MEASUREMENTS

Special concerns that can compromise the accuracy of particle counters include indexes of refraction differences, bubbles, particle counting optical coincidence, and contamination. A particle will scatter light if there is a contrast between the particle's index of refraction and the sample medium. The *index of refraction* is composed of two parts—a real component and an imaginary component—and describes how the phase velocity of light slows down as it passes through a material relative to a vacuum. The light scattering is described by the real component, and the degree of light absorption is described by the imaginary component. For example, when a specific material is used to calibrate the particle count, such as PSL spheres, the actual particle count from the actual material (non-PSL material) may vary. This variation is from the differences between the calibration material/media and the actual particle/specific chemical, and this discrepancy impacts sizing accuracy. However, these effects are not important for very small particles in UPW or many liquid other media (Terrell and Reinhardt 2008). Rayleigh scattering predicts that, for particles less than 0.2 μm, the amount of scattering decreases according to

$$\text{Scattering} = D^{-6} \tag{5.1}$$

where D is the diameter of the particle. The Rayleigh scattering effect is so dominant that the particle shape and index of refraction differences become insignificant for very small particles when compared to similar PSL sphere sizes. When particles closely match the index of refraction of the media in which they are present, however, the particles become difficult to detect, and if they are counted they will be sized much smaller than they really are (Terrell and Reinhardt 2008).

Bubbles have an index of refraction contrast with liquids and are counted as particles. Many process liquids used in semiconductor wafer cleaning easily form bubbles. The effect of bubbles, however, may be reduced by using degasification membrane filters. But when these filters are used, the particles of interest may be filtered out and particle events may be masked. The membrane's wettability characteristics are important to consider, as improper membrane selection can result in the membrane becoming a site for bubble formation. Bubbles may remain in the solution and not be a problem if on-line process particle counting occurs under sufficient pressure, and a compression sampler may be beneficial for off-line samples because it forces bubbles back into the solution before sample measurement. However, if air is entrained when a liquid sample is collected for off-line analysis (often the case for more viscous fluids), these artificial bubbles are hard

to remove with compression sampling. The only solution to this specific problem may be time and proper sample handling practices. Bubbles are easily identified with a volumetric particle counter because they typically occur in larger channels (Terrell and Reinhardt 2008).

When more than one particle is in the viewing region at the same time, particle counting optical coincidence occurs. This is when smaller particles together get sized as one larger particle. Particle counters have specified maximum concentrations that are design dependent; sizing and overall counts are inaccurate above these maximums. In some situations, increasing particle concentrations decrease the total cumulative particle concentrations (Terrell and Reinhardt 2008).

The accuracy of particle counter results can also be impacted by contamination, because contaminants can attach to optical surfaces of the sample lines leading to the counter or of the particle counter itself. Particularly susceptible to contamination are capillaries, which cause more light to be scattered; this, in turn, causes an increase in the direct current (DC) component of the voltage signal and may cause high counts in the most sensitive channel. With high-sensitivity nonvolumetric counters, contamination of the sample cell is not usually an issue because the viewing region excludes optical interfaces. High-sensitivity particle counters are more affected by particles in the sampling lines and valves, though. Thus, it is common after installation of a high-sensitivity particle counter that clean-up times be 24 hours (for very clean UPW systems). Particle shedding can be caused by changes in flow rates that affect the face velocity along the tubing. Because trapping and shedding of particles commonly happens in valves, they should always be fully opened or closed, as partially open valves will continuously shed particles (Terrell and Reinhardt 2008).

5.3 LIQUID FILTRATION

Liquid filtration has been an effective technique for separating suspended particles from a liquid by passing the liquid through a porous membrane or medium (Bowen and Jenner 1995; Grant and Liu 1991; Lee et al. 1993). Ultrafiltration techniques, which are filter membranes with pore sizes below 100 nm (ultramembranes), are widely used in cleanrooms for semiconductor, pharmaceutical, and food and beverage industries (Oganesyan et al. 2001). For example, they play a significant role in mitigation of the risks of nanoparticle contamination in UPW, as well as for the photochemicals used in semiconductor manufacturing processes. With reduced feature sizes of chips (e.g., <65 nm lithography and the extreme ultraviolet lithography [EUVL] process), the required membrane pore sizes reduce to 2–5 nm and quantum dots are increasingly used as the challenging particles (Liu and Zhang 2013; Chen et al. 2016).

Liquid filters are often characterized by means of the geometrical pore size obtained from electron microscopy, the gas permeability, and the bubble point and liquid displacement (ISO 2004; Zhao et al. 2000). However, these representations do not often correlate well with sieving characteristics of liquid filters, and they may not agree accurately with the retention efficiency (Nakao 1994; Singh et al. 2005; Waterhouse and Hall 1995) because the bubble-point test responds to a small fraction of pores that are much larger than those in the remaining fraction. In addition to the desirable sieving mechanism, nanoparticles smaller than 100 nm (especially those below 10 nm) show pronounced diffusion (Chen et al. 2016).

A direct way to evaluate the performance of a small-nanoparticle filter is to experimentally determine its retention efficiency as a function of particle size, yet no standard method is available for reliably evaluating such filters, and suitable model systems with

defined size and surface properties are only just being developed (Wu et al. 2014). This is because below-10-nm liquid-phase particle detection is at the limit of common particle instruments for analyzing particle size distribution and number concentration (Chen et al. 2016).

Current challenges include the need for developing liquid particle counters with not only sub-10 nm sizing limits but also high concentration sensitivity (i.e., counters that are capable of measuring sub-10 nm nanoparticles with low number concentration). Ultraviolet-visible spectroscopy (UV/Vis) absorbance analysis is available (Segets et al. 2009, 2013); however, it requires a large amount of particles (e.g., 10^{16} particles for 1.7 nm zinc sulfide [ZnS] quantum dots) to obtain a sufficient signal in the analysis. In comparison, the inductively coupled plasma mass spectrometry (ICP-MS) method is widely used for the analysis of small nanoparticles. However, time consumption is the main concern with this method. A new method or instrument should be developed for quickly determining sub-10 nm nanoparticles in low concentrations.

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6

Microbial Contaminants

6.1 PRINCIPLE OF BIOCONTAMINATION CONTROL

Biocontamination is the contamination of materials, devices, individuals, surfaces, liquids, gases, or air with viable particles that consist of or support one or more live microorganisms. As shown in Table 6.1, biocontamination can be found in air, in liquids, and on surfaces in cleanrooms serving different purposes. Microbial contamination control has become critical for cleanrooms with various applications such as semiconductor manufacturing, pharmaceutical production, aerospace manufacturing, surgery, medical device manufacturing, food and beverage production, and others. ISO 14698-1 (ISO 2003a) describes the principles and basic methodology for determining a formal system to assess and control biocontamination in clean spaces. This formal system also allows the assessment of factors affecting the microbiological quality of the process and the product.

To assess and control microbiological hazards, the following principles should be addressed (EC 1997):

- Identification of potential hazards to the process or product, assessment of the likelihood of occurrence of these hazards, and identification of measures for their prevention or control
- Designation of risk zones and, in each zone, determination of the points, procedures, operational steps, and environmental conditions that can be controlled to minimize the likelihood of occurrence of a hazard or eliminate the hazard altogether
- Establishment of limits to ensure control
- Establishment of a monitoring and observation schedule
- Establishment of corrective actions to be taken when monitoring results indicate that a particular point, procedure, operational step, or environmental condition is not under control
- Establishment of procedures, which may include supplementary procedures and tests, to verify that the chosen formal system is working effectively
- Establishment of training procedures
- Establishment and maintenance of appropriate documentation as defined by ISO 14698-1

Table 6.1 Most Frequently Found Microbial Contaminants (in Air and Water and on Surfaces) in Cleanrooms Serving Various Purposes

Rank	Most Frequently Found Microbial Contaminants	Sample Locations	Cleanroom Purpose	Reference
1	Coagulase-negative staphylococci (40% to 50%) and micrococcus luteus (25% to 30%)	Surfaces and air	Stem cell lines banking for clinical use	Cobo and Concha (2007)
2	Sphingomonas, staphylococcus	Surfaces	Spacecraft assembly	Cobo and Concha (2007)
3	Firmicutes	Surfaces	Spacecraft assembly	Moissl et al. (2007)
4	Bacillaceae family	Surfaces	Spacecraft assembly, test, and launch preparation	La Duc et al. (2007)
5	Bacillus, actimomycetes, and fungi	Surfaces	Spacecraft associated	La Duc et al. (2004)
6	Bacillus and comamonads	Surfaces	Spacecraft encapsulation	La Duc et al. (2003)
7	Staphylococcus sp. and aspergillus sp.	Surfaces, air, and portable water	International Space Station	Novikova et al. (2006)
8	Staphylococcus, microbacterium, and bacillus	Surface, air, and personnel	Pharmaceutical production	Wu and Liu (2007)
9	Staphylococcus (24.7%)	Air	Pharmaceutical industry	de la Rosa et al. (2000)
10	Bacteria	Air	Hospital	Li and Hou (2002)

In addition, the user of a cleanroom should set microbiological alert and action levels that are appropriate to the field applications and to the classification of the risk zones. During initial start-up and at intervals established according to the formal system defined by the user and as required by the regulatory bodies, data on biocontamination levels should be reviewed to establish or confirm a baseline for the determination of alert and action levels. These levels defined by the user and as required by the regulatory bodies should be reviewed and adjusted as appropriate.

6.2 DETERMINATION OF AIRBORNE BIOCONTAMINATION

Microbiological sampling may be useful for providing baseline data as new installations are constructed and commissioned. Samplings are to be performed routinely in the operational state according to the formal system chosen. The objectives of sampling are to determine the presence of airborne biocontamination, to identify the particular airborne biocontamination, and to quantify the concentration of specific or total airborne biocontamination. Measurement of airborne biocontamination generally requires two steps. First, a representative sample of air in a risk zone is collected, according to a sampling plan, using an appropriate sampling device. Second, the microbial content present in the air sample (e.g., airborne microorganisms) is then analyzed, identified, and quantified using known and industry-proven techniques that have been vetted with regulatory authorities. The final results can help to identify the source of airborne biocontamination and to monitor the environment in the as-built or at-rest state as well as under normal

operation. This section describes a general method for the determination of airborne biocontamination that can be considered by cleanroom owners and operators.

6.2.1 GENERAL SAMPLING METHODS AND PLANS

The U.S. Food and Drug Administration (FDA) published industrial guidance for sterile drug products produced by aseptic processing that provides recommendations for microbial sampling and control in cleanrooms (FDA 2004). According to that guidance, there are three acceptable methods for monitoring microbiological quality: surface monitoring, active air monitoring, and passive air monitoring (settling plates).

There are many sampling devices available for inert (or nonmicrobial) airborne particles that have satisfying performance. However, airborne biocontaminants are different from inert particles due to their biological properties, which impose limitations on collection and handling of the sample (Baron and Willeke 2005). The sampling device should be carefully selected by taking into consideration the following factors: expected type, size, and concentration of the airborne biocontamination; vulnerability of the airborne microorganisms to the sampling process; physical and biological collection efficiency of the sampling device; appropriate culture media; accessibility of the risk zones; ability of the device to detect low/high levels of biocontamination; ambient conditions in the risk zone being sampled; sampling time; sampling flow rate; effect of the sampling device on the process or environment to be monitored; incubation and viable particle detection and evaluation method; efficiency of extraction/rinse fluids, where appropriate; and potential contamination of the sampled environment due to the exhaust air from the sampling device (ISO 2003a).

To assess and interpret biocontamination data accurately, the sampling plan should be well organized and documented. Sampling should be carried out when the area to be tested is in the normal operational condition and during periods of great potential emission, such as before the end of a shift or when the greatest amount of activity is taking place. Sampling in the at-rest condition should also be conducted, as it establishes the baseline contamination level. The cleanliness level of the risk zone and the degree of biocontamination control required should be taken into account in the sampling plan to protect the product, the process, the environment, and personnel. There are quite a few elements that need to be considered—sampling location, number of samples or sampling air volume for representing results, frequency of sampling, methods of sampling, diluents, rinse fluids, neutralizers, etc.—factors pertinent to a particular situation that could affect culturing results and impact of operations, personnel, and equipment in risk zones, contributing to biocontamination (ISO 2003a).

6.2.2 FREQUENCY OF SAMPLING

According to ISO-14698-2 (ISO 2003b), the frequencies of sampling are to be developed and confirmed or modified as necessary. Suggested sampling frequencies based on the criticality of a controlled environment are presented in Table 6.2 (USP 2000).

Table 6.2 Sampling Frequencies Based on the Criticality of a Controlled Environment

Sampling Area	Sampling Frequency
Class 100 or better room designations	Each operation shift
Supporting areas immediately adjacent to Class 100 (e.g., Class 10,000)	Each operation shift
Other support areas (Class 100,000)	Twice/week
Potential product/container contact areas	Twice/week
Other support areas for aseptic processing area but with nonproduct contact (Class 100,000 or lower)	Once/week

6.2.3 SAMPLING SITES

Sampling sites should be determined during the initial start-up or commission of a cleanroom with much consideration given to the sites' proximity to the product, whether air and surfaces might be in contact with products, and sensitive surfaces of container closure systems (USP 2000). Multiple samples may be taken at each site, and different numbers of samples may be taken at different locations, all of which should be defined in a written procedure in the sampling plan (ISO 2003a).

6.2.4 SAMPLING DEVICES

Measurement of airborne biocontamination has been conducted for decades, and various methods exist for sampling airborne microorganisms such as bacteria, fungi, and viruses. Sampling devices can be divided into two categories. One is passive sampling devices such as settling plates, which can provide qualitative environmental monitoring or semi-quantitative measurement of the rate at which airborne microorganisms settle on surfaces. The other is active sampling devices, including impactors, liquid impingers, and filters, which all require the use of a pump connected to the sampler. When used with appropriate collection media, these forced-air samplers provide a way of determining the concentration of microorganisms per unit volume of air. However, no single sampling method can identify, collect, and quantify all biocontamination existing in a particular environment (Baron and Willeke 2005). No samplers are perfect, and they all have different advantages and disadvantages, which results in various collection efficiencies and limitations. Comprehensive reviews of the sampling performance of different methods are given elsewhere (Henningson and Ahlberg 1994; Baron and Willeke 2005; Verreault et al. 2008); some commonly used sampling devices are described in the following subsections. Instruction and additional information, especially on their limitations, are available in the device manuals.

6.2.4.1 Passive Sampling Device

6.2.4.1.1 Settling Plates

Settling plates, one example of a passive sedimentation sampling device, are petri dishes filled with nutrient growth media exposed to the environment that collect viable particles by their settling. The plates are usually positioned in risk zones with high concentrations of airborne biocontamination. Although this method does not provide a representative sampling of airborne microorganisms due to the differential settling of airborne particles (Crook 1995), it is still one of the widely used methods for sampling airborne biocontamination, especially when the sampling time could be long. The settling flux of viable particles can be determined given the information of the number of viable units settled on the plate, the sampling time, and the area of the plate. This data could be useful when presented with data collected by active sampling devices. The performance of this method can be enhanced by using certain media that optimize the airborne microorganism recovery (FDA 2004) and by using a larger-diameter petri dish with an extended sampling time (ISO 2003a). However, excessive desiccation caused by high airflow rate and/or prolonged sampling time should be minimized, as it inhibits the recovery of microorganisms (FDA 2004).

6.2.4.2 Active Sampling Devices

6.2.4.2.1 Impactors

Single-stage, cascade (multiple stages), and slit impactors draw aerosol flow through nozzles or slits, accelerate particles, and impact them onto a collection plate by utilizing

the inertia of the particles. Cascade impactors such as Andersen impactors, with each stage capturing particles of a specific size range, are usually used to determine the size distribution of airborne biocontamination. Slit impactors, with a rotating petri dish placed on the collection plate, are mostly used to determine the concentration of airborne biocontamination as a function of time (Marple 1979).

In some cases (e.g., slit impactors), the collection plate holds a petri dish filled with culture medium, which can be analyzed directly. In other cases, the collection plate can be used as it is, followed by washing the plate using eluents and scrubbers to collect the captured particles. Note that for the former cases the addition of a petri dish may change the cutoff size of each stage due to the change of jet-to-plate distance, which must be taken into account in the representation of the results (Tsai et al. 2012). For the latter cases, attention should be given to the fact that particles can bounce when they impact the solid collection plate and the use of an eluent and a scrubber may not recover all the microorganisms impacted onto the collection plate, which may cause an underestimation of the total concentration or a shifted size distribution of the airborne biocontamination (Chen et al. 2010a, 2010b, 2011, 2013). In addition, the sampling flow rate (thus the impact velocity) and sampling time (thus the sampling volume) should be carefully chosen. For example, the impact velocity should be high enough to collect viable particles down to approximately 1 μm but low enough to ensure the viability of the collected microorganisms (i.e., to reduce sampling stress). The sampling volume should be large enough (e.g., 35 ft^3 [1 m^3]) to enable the detection of low concentration of airborne biocontamination but small enough to avoid overloading of the agar plate and chemical/physical degradation of the collection medium (ISO 2003a). Meanwhile, the sampling time should be short enough to minimize the inactivation of the collected microorganism due to dehydration of the nutrient medium.

6.2.4.2.2 Impingers

Impingers are frequently used to collect airborne biocontamination into a liquid. An impinger accelerates viable particles through one or more orifices placed at a fixed distance above the bottom of a glass bottle containing a collection liquid, such as water, saline buffer solution, or nutrient broth. Liquid containing the captured microorganisms can be poured directly or with dilution onto culture plates for analysis. Most liquid impingers collect viable particles regardless of their sizes, though multistage liquid impingers with different cutoff sizes are also available. Liquid impingers are believed to be less destructive samplers than impactors (Verreault et al. 2008), mainly because the collection liquid minimizes dehydration of microorganisms. However, the high shear stress in the sonic velocity jets and the frequent agitation of the collection liquid may also cause loss of viability. In addition, the evaporation and bubbling of the collection liquid after prolonged sampling time may reduce the physical collection efficiency of the impinger and reaerosolize the collected microorganisms, both of which result in an underestimation of the airborne biocontamination concentration (Lin et al. 1997; Grinshpun et al. 1997; Hogan et al. 2005).

6.2.4.2.3 Filters

An alternative method for sampling airborne biocontamination is to use filters, which collect viable particles using the following five mechanisms: diffusion, interception, impaction, gravitational settling, and electrostatic depositions (Hinds 1999). Unlike impactors and impingers, which can only efficiently collect large particles, some filters can efficiently collect viable particles with a wide range of sizes (Burton et al. 2007). Filters of different compositions, pore sizes, and thicknesses have been used to sample air-

borne microorganisms. Typical examples include track-etched polycarbonate, cellulose, polytetrafluoroethylene (PTFE), and gelatin filters. Ventilation filters have also been used due to their high-volume sampling characteristics (Farnsworth et al. 2006). The collected particles can be examined under an optical microscope, or they can be cultured by placing the filter, particle side up, on a culture medium (Hinds 1999). The captured microorganisms can also be extracted and recovered from the filter samplers, using appropriate eluents and agitation methods (e.g., vortexing), followed by culture analysis. Note that not all collected particles can be removed from the filter media, which may make it difficult to accurately estimate the airborne biocontamination (Zuo et al. 2013).

Filters are not commonly used for sampling viable particles because they are believed to cause significant structural damage to the captured microorganisms (Verreault et al. 2008). The viability of the microorganisms collected may also be significantly affected by desiccation, especially after a long time period of sampling. However, with the aid of modern molecular biology tools such as polymerase chain reaction (PCR), both viable and nonviable microorganisms can be identified and quantified. Gelatin filters are a good choice because they can be aseptically removed after sampling and completely dissolved in a diluent for microbial analysis. Therefore, all collected microorganisms can be recovered and analyzed, though low humidity and long time sampling may make the gelatin dry out and break.

6.2.5 CULTURE MEDIA

A variety of media, either solid or liquid, can be used with the samplers described previously to detect and quantify the airborne microorganisms in controlled environment and risk zones, depending on the type of sampler and the target microorganism(s). The most commonly used all-purpose solid medium is soybean-casein digest agar (FDA 2004). Other solid media include nutrient agar, tryptone glucose extract agar, lecithin agar, and brain heart infusion agar. Commonly used liquid media include tryptone saline, peptone water, buffered saline, buffered gelatin, enriched buffered gelatin, brain heart infusion, and soybean-casein medium (FDA 2004). Note that all solid and liquid media must be sterilized before use. Also note that appropriate neutralizers should be included in the culture media to minimize the effects when antimicrobial activity at the sampling place is expected (ISO 2003a).

6.3 DETERMINATION OF SURFACE BIOCONTAMINATION

6.3.1 PRINCIPLES OF SURFACE MONITORING

Surface biocontamination is one of the five major sources of product contamination that lead to infections in hospitals (Beaney 2006). Generally, surface monitoring is performed on surfaces of contact areas of products, floors, walls, and equipment. Contact plates and swabs can be used for such tests in situations where surface biocontamination control is needed (e.g., to locate areas of contamination, to identify the source(s) of biocontamination, or to determine the effectiveness of remediation and cleanup) (Stetzenbach et al. 2004). This section provides general guidance on the sampling of biocontamination on surfaces; additional instructions from sampling device manufacturers must be followed.

The measurement of surface biocontamination requires the collection of representative samples from surfaces followed by analysis to detect the viable microorganisms that are present in the samples. These sampling methods usually have imperfect recovery effi-

ciencies (Pinto et al. 2009) and might not reflect the total number of viable microorganisms on the surfaces of interest. However, they are applied routinely in the operational condition and, if appropriate, in as-built and at-rest conditions as well because they can give relevant and comparable results under controlled conditions.

An estimation of the total number of viable microorganisms present on a surface is obtained by a contact plate or a swab. For a flat or easily accessible surface, a contact plate of known area filled with a solid nutrient medium can be used. The nutrient medium is then incubated and colonies formed by viable microorganisms are counted. The resultant total number of colonies indicates the relative cleanliness of the surface tested. In addition, the distribution of colonies shown in the contact plate provides a mirror-image map of the original viable units on the surface tested (ISO 2003a). For an irregular surface, a swab soaked with buffer solution can be used to wipe the surface and the number of viable microorganisms can then be determined after incubation.

6.3.2 SAMPLING DEVICES

6.3.2.1 Contact Sampling Devices

Contact plates generally have the shape of a dish and hold a solid culture medium for easy contact with the surface being sampled. The accessible area of the contact surface should be equal to or greater than 3 in.^{2} (20 cm^2). The generally recommended culture media are general-purpose media containing neutralizers that can neutralize the residual disinfectants where the sample is being collected (Brummer 1976). To prevent contamination, the medium should be prepared in a filtered air cabinet and formation of air bubbles during the preparation should be avoided. The plate surface should be applied directly to the surface being tested with moderate vertical pressure for a few seconds, without rubbing the surface. After sampling, the contact plate is incubated for specific period of time as defined by the chosen test method and the sampled surface is cleaned to remove nutrient residues. Note that there are different commercially available contact plates, such as replicate organism detection and counting (RODAC) plates, which may give different recovery efficiencies of viable microorganisms (Pinto et al. 2009)—this casts doubt on their compatible use for the environmental monitoring.

6.3.2.2 Swabs

Surface biocontamination can also be sampled using swabs. Cotton fabric or sponge-like swabs and wipes soaked with liquid are particularly useful for recovering viable microorganisms from defined surfaces that cannot be easily sampled by contact plates. In general, the area to be swabbed is generally in the range of 3.7 to 4.7 in.^{2} (24 to 30 cm^2) (NASA 1967) and is set by the chosen test procedure. The swab should be prewetted thoroughly with a sterile solution that can ease the removal of microorganisms from the surface. According to ISO 14698-2 (2003b), the swab should be stroked in close parallel sweeps over the defined sampling area while being slowly rotated. Sampling of the same area should be repeated, stroking the same swab perpendicular to the initial sweep (ISO 2003a). After collection of the microorganisms, the swab should be rinsed and agitated gently with sterile liquid to help dislodge the microorganisms from the swab; the rinse liquid is then sent for analysis. In addition to the conventional incubation and enumeration of colony-forming units (CFUs), there are also other indirect analysis techniques, such as adenosine triphosphate (ATP) measurement. However, these indirect signals may not be entirely caused by the presence of viable microorganisms in the sample. After sampling, the sample surface should be cleaned to remove any liquid left. The number of via-

ble particles on surfaces should be expressed in viable units or other appropriate units per unit sampled area or per swab.

6.4 DETERMINATION OF LIQUID BIOCONTAMINATION

6.4.1 PRINCIPLES

This section provides general guidance on the determination of biocontamination in liquids. Measurement of surface biocontamination requires the collection of representative samples in risk zones followed by analyses to detect the viable microorganisms that are present in the samples. According to ISO 14698-1 (2003a), appropriate sampling devices and a sampling plan should be used for the collection of samples for the detection and monitoring of biocontamination of liquids in risk zones. Note that the pressure of the liquid should be appropriately reduced for the sampling. In addition, the following four factors should be considered before sampling (ISO 2003a):

- Microbial ecology and related parameters in risk zones
- Estimated concentration of viable particles in the specific liquids
- Condition of the liquids
- Accuracy and efficiency of collection

6.4.2 METHODS

Samples can be analyzed directly or after certain treatments such as dilution, depending on the condition and the estimated concentration of viable particles in the liquid. A variety of methods for total and viable microbial counts are currently used for the determination of biocontamination in liquids. The total counts can be obtained using a staining method, e.g., acridine orange direct counts (AODCs) (Greenberg et al. 1992) and fluorescent stains (Rodriguez et al. 1992), immunofluorescence microscopy (Pederson and Jacobson 1993), a Coulter counter (Kjellenberg et al. 1982), and scanning electron microscopy (Bulla et al. 1973). Pour plates, spread plates, drop plates (Hoben and Somasegaran 1982), and membrane filter examinations (Greenberg et al. 1992) are the common ways for the detection of viable counts. The selection of a particular method depends on the nature of the liquid and the volume of sample required (ISO 2003a). The number of viable particles in liquids should be expressed in viable units or other appropriate units.

6.5 EVALUATION AND EXPRESSION OF SAMPLING DATA

Sufficient information obtained from evaluation and expression of sampling data is critical to maintain biocontamination control in cleanrooms. Generally, for evaluation of sampling data, the enumeration of viable units (VUs) or CFUs in the collected sample should follow standard methods with appropriate level of characterization (e.g., as defined in ISO 7218 [ISO 2007]), since it is well known that the estimation of biocontamination can be influenced by instruments and procedures used to perform these counts and no single method can identify and quantify all the microbial species in a controlled environment. More detailed discussion regarding sampling data is available elsewhere (ISO 2003a). Finally, sampling results are expressed as VUs or CFUs per cubic metre of sampled air or per cubic centimetre of sampled liquid.

6.5.1 RECORD AND EVALUATION OF SAMPLING DATA

The record of the sampling data should include the type of sample, method, collecting device, site, type of activity underway at the time of sampling, number of persons within the sampling area, date and time of sampling, sampling duration, time of examination of samples, conditions and duration of incubation, and variations from the described test method, as well as any factor that may have influenced the results, test results from the examination of the collected samples after initial and final reading, when quantitative tests have been performed, the results expressed using appropriate SI units, description of the isolate if characterized, name of the organization responsible for the test report, date of completion of the test, and name and signature of the individual responsible for performing the test (ISO 2003b). Each occurrence of an out-of-specification test result requires further evaluation to decide whether it was a true result; it is essential that any out-of-specification result that cannot be confirmed as laboratory error needs to be investigated to determine the cause for an appropriate correction. More discussion about the treatment of out-of-specification results is given in ISO 14698-2 (ISO 2003). Statistical analysis can then be applied on sampling data, especially when many observations have been recorded, to obtain a more accurate estimation of biocontamination in the risk zones based on the data, with an acceptable level of risk (McCormick and Roach 1992). For example, an Andersen impactor "positive hole" conversion table can be used to estimate the corresponding true counts based on the sampled counts (Andersen 1958). It is recommended that interpretation and evaluation of results be based on more than one statistical method (ISO 2003b). To determine the time trends, graphical representation of the sampling data over extended time periods should be reviewed. Control charts, including the Shewhart chart (ISO 1991), range-based chart, and cumulative sum chart, are other useful statistically valid methods for quality control of the sampling data and highlighting out-of-specification results.

The evaluation of biocontamination data should be sufficient enough to provide information for effective corrective actions. Further information on the evaluation of biocontamination data is given in ISO 14698-2 (ISO 2003b). Monitoring of microbial contamination may be performed by measuring indirect indicators (e.g., adenosine triphosphate [ATP]). However, note that there may be no direct relation between the presence of such indicators and biocontamination. It is therefore essential that there is a direct estimation of biocontamination when the selected formal system is being verified or the monitoring system is being validated.

6.5.2 REPORTING RESULTS

As noted previously, quantitative results are expressed as VUs or CFUs per unit volume of air. More information on data evaluation is available in ISO 14698-2 (ISO 2003b). Results should be reviewed over extended periods of time to determine trends. Based on such reviews and the test results, decisions should be made on the significance of unusual results as well as the acceptability of the procedures or of the products processed following these procedures (ISO 2003a). The test report should include or make reference to the following: type of sample; method used and, where appropriate, the number and title of the standard that describes the test method; collecting device used; sampling site; type of activity underway at the time of sampling; number of persons within the sampling area; sampling date and time; sampling duration; time of examination of samples; conditions and duration of incubation; variations from the described test method; any factor that may have influenced the results; test results from the examination of the collected samples after initial and final readings; when quantitative tests were performed; the results,

expressed using appropriate SI units; description of the isolate, if characterized; name of the organization responsible for the test report; date of completion of the test; and name and signature of the individual responsible for performing the test (ISO 2003a).

6.6 CLEANING AND DISINFECTION

In food and pharmaceutical cleanrooms, cleaning and disinfection are designed to remove or destroy microorganisms present on the products, appliances, and packaging. Microbial control can be achieved by using defined cleaning techniques with disinfectants and detergents, which must be high quality and effective at killing microorganisms and which represent an important decision for all cleanroom owners and operators. Both the cleaning techniques and correct product selection are important, particularly for some newer cleanroom technologies (i.e., processes, equipment, and materials of construction). Various types of disinfectants exist and have with different modes of action and spectrums of activity (Sandle 2010b).

6.6.1 EQUIPMENT CLEANING AND MAINTENANCE

According to Title 21 of the *Code of Federal Regulations* (CFR), the following procedures must be followed for the cleaning and maintenance of equipment (GPO 2017):

- Clean, maintain, and sanitize equipment and utensils at intervals defined by the owners' standard procedures to prevent contamination or malfunctions that would change the identity, strength, purity, quality, or safety of the food or drug product.
- Establish and follow written procedures for cleaning and maintaining equipment and utensils used in the manufacture, processing, packing, or holding of a food or drug product, including the following:
  - Assigning responsibility for equipment and utensil cleaning and maintenance
  - Setting schedules for cleaning and maintenance, including sanitizing schedules
  - Describing in detail the materials, methods, and equipment that should be used for cleaning and maintenance and the methods that should be used for equipment disassembly and reassembly to ensure proper cleaning and maintenance
  - Removing previous batch identification
  - Protecting clean equipment from contamination before use
  - Inspecting equipment for cleanliness immediately before use

6.6.2 SELECTION OF DISINFECTANTS

Differing disinfectants have different efficacies, so selecting the right cleaning agents and materials is critical. Whyte (2001) summarizes some commonly used disinfectants in cleanrooms. Environmental monitoring can assess the efficacy of cleaning products and procedures by providing the types and numbers of microorganisms detected. Therefore, the development of a cleaning procedure must be carefully planned to fit with a facility's quality systems. Many leading cleaning product manufacturers supply technical advice to assist in accomplishing this (Sandle 2010b).

Some types of disinfectants can change bacterial cells, and removing the disinfectant may enable the surviving bacterial population to grow. Other types of disinfectants destroy bacterial cells, with some being effective against fungi and some being effective against vegetative microorganisms (Sandle 2010b). In general, disinfectants are efficient

against microbial growth but are more expensive than other cleaning methods; therefore, it is suggested that they are used only for the critical area where the product is, with less expensive disinfectants used for general areas that are away from the product, such as floors.

6.6.3 MODES OF ACTION

The chemical diversity of disinfectants causes them to act differently on microbial cells, with some targeting different sites within a microbial cell (such as the cell wall, the cytoplasmic membrane, and the cytoplasm) and some disrupting the membrane or entering through diffusion then acting on intracellular components. Disinfectants can be categorized and subdivided a number of ways, such as by their mode of action, by their effects on microorganisms, or by their by chemical nature (Sandle 2010a).

The different types of disinfectants include nonoxidizing disinfectants, oxidizing disinfectants, and hand sanitizers. Most nonoxidizing and oxidizing disinfectants have specific modes of action against microorganisms, with nonoxidizing types tending to have a narrower spectrum of activity compared with oxidizing types. Nonoxidizing disinfectants include quaternary ammonium compounds (QACs), which cause cytoplasm leakage and coagulation and are some of the most commonly used in the pharmaceutical industry; alcohols, which have a one-minute contact time and disrupt the bacterial cell membrane; phenolics, which can cause bacterial cell damage or leakage of cellular components and can denature proteins; aldehydes, which denature bacterial cell proteins and can coagulate cellular proteins; and amphoterics, which have a relatively large spectrum of activities (Sandle 2010a).

Oxidizing disinfectants have a larger spectrum of activity than nonoxidizing disinfectants but tend to have nonspecific modes of action against microorganisms. They can pose greater risks to human health and therefore require more stringent control. This group of disinfectants includes oxidizing agents, such as peracetic acid (a chemical containing hydrogen peroxide and oxygen deposits) and halogens, such as iodine. Peracetic acid products have excellent material compatibility and in general do not damage most surfaces (Sandle 2010a).

There are many types of hand sanitizers, the most common being commercially available alcoholic hand rubs or alcohol-based gels. With hand sanitizer disinfectants, the hand rubbing technique is the most important factor because the sanitizers are effective due to the rubbing agitation (Sandle 2010a).

Many pharmaceutical manufacturers have two disinfectants in rotation and a third in reserve for times of major contamination incidents, with the reserve disinfectant typically being more powerful. Because of its greater strength, the reserve disinfectant often has more potential to cause damage to the equipment and premises and so is not routinely used, but it can be very effective in times of contamination buildup or when contamination is resistant to or difficult to remove with the other disinfectants (Sandle 2010a).

The rotation of the two primary disinfections is a requirement of regulatory bodies, such as the FDA and the European Medicines Agency (EMA), with the requirement "where disinfectants are used, more than one type should be employed" of Annex 1 in *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use* (EC 2010, p. 10) usually interpreted as a requirement for two types to be used in rotation. On the other hand, USP <1072> (USP 2016) is less specific and questions whether there is scientific need for rotation (Sandle 2010a).

6.6.4 DISINFECTION EFFICACY

FDA's *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (FDA 2004) states that disinfectants chosen for regular use should be effective against the types of microorganisms discovered in the space and that the effectiveness, suitability, and limitations of both disinfecting agents and disinfecting procedures should be assessed. The agents' and procedures' efficacy should be measured by their ability to adequately remove contaminants from surfaces. So that the disinfectants themselves do not contaminate the cleanroom, they should be sterile, handled in sterile containers, and used for the time period prescribed by the written procedures, which should detailed enough to enable reproduction of the procedures. The adequacy of the disinfection procedures should be evaluated using an environmental monitoring program, as mentioned previously. If adverse trends of microorganisms are found by the monitoring program, the microorganisms' sensitivity to the disinfectants can be investigated and remedial actions can be taken if necessary (FDA 2004).

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Part 2

Cleanroom Design and Environmental Control Systems

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7

Planning and Basic Considerations

Cleanroom design and construction planning should incorporate all elements of the project typically developed by a project designer in conjunction with the user and other involved parties. The planning should define the design- and construction-related requirements for the products and the processes specified by the user and facility management. Before defining the design effort, a cleanroom project team consisting of the user and the project designer should jointly establish the goals, objectives, and needs of the project; define the project scope; list the technical performance requirements; outline the schedule and budget; and identify who is responsible for each aspect of the project.

The design should conform to an agreed-upon list of requirements, such as building, environmental, safety, and code regulations; Good Manufacturing Practice (GMP) guidelines; owner's requirements for process equipment, installation flexibility, maintenance, and stand-by capacity; and quality assurance, etc. The design team should also consider design options and associated cost impact, schedule of design progress, or milestones. Risks should be identified and mitigations planned. The design should be reviewed periodically during the various stages of development, including the final construction documents, to ensure compliance with specifications and acceptance criteria (ISO 2001). These final documents, which are used for bidding and construction, commonly include a set of design drawings and a specification book developed by practitioners from multiple disciplines.

7.1 CONTAMINATION CONTROL CONSIDERATIONS

All equipment and processes to be used in the cleanroom should be listed and compiled, and a matrix should be created listing requirements for each piece of equipment and each process. This matrix should define the processes and identify all requirements related to chemicals, gases, liquids, power, temperature, humidity, exhaust, vacuum, vibration, electromagnetic interference (EMI), radio frequency interference, shielding, and waste removal requirements. Additional issues that affect the building design and constructability include the size and weight of the equipment as well as the sizes of the containers to be moved into the building. A defined hierarchy of cleanliness should be specified for a project with a good justification, and a contamination control concept should be developed not only for each critical room but also for each zone within a room. Typical contaminants include particulates, molecular matters, chemical gases/fumes, and biological agents. Contaminant movement in rooms can be analyzed with computational

fluid dynamics (CFD) modeling or smoke visualization. Contaminant migration between rooms under pressure differential and concentration differential, especially with frequent door operations, should be carefully analyzed and addressed during the design stage. Other chapters in Part 2 discuss these analyses in detail.

7.2 SITE SELECTION AND SERVICES REQUIREMENT

Common considerations in site selection of a new cleanroom building may include the following:

- Ground load-bearing capacity
- Ground water and soil toxicity
- Ambient air quality and airborne pollutants such as particulate and microbial pollutants
- Site water supply quality
- Availability of utility and services at site versus the required utility and services to determine if additional services or remote connections from adjacent facilities need to be made; these utilities and services may include water supply, sanitation, storm drainage, gas, electricity, communication, central steam, chilled water, cooling water, and other services as required.
- Environmental issues regarding air emission and waste discharge and treatment
- Site ambient vibration and noise levels and determination of their acceptability for the process with or without special treatments, especially for those sites in proximity to railways, highways, airports, and future construction sites.
- Ambient electromagnetic fields
- Security and access control
- Local zoning ordinances and regulations

For existing facilities prepared for modification, retrofit, or renovation for a need to increase production capacity, to add new functionality, or to upgrade processing technologies, special precautions and measures must be taken during the design and construction phases. A thorough analysis of the project should be undertaken to determine precisely which parts of the cleanroom will be affected by the modification. A plan should be developed to minimize the generation or dispersion of contamination and to subsequently clean up the affected areas. Often temporary treatments, such as the following, may need to be considered:

- Cleanroom air locks for personnel entry and exit and pass-throughs for material and equipment paths
- Differential pressure control to prevent contaminants moving from dirty construction areas to operational cleanroom spaces
- Air-handling and air filtration systems

7.3 CRITICAL FLOW ARRANGEMENTS—PERSONNEL, MATERIALS, PRODUCTS, AND WASTE

A clean zone typically is the area within a cleanroom with critical processes or operations that require the highest air cleanliness class. As illustrated in Figure 7.1, the clean zone is surrounded by a clean area of a lesser cleanliness classification. Both the clean zone and the cleanroom should be as small as practical. The sizes of these areas need to

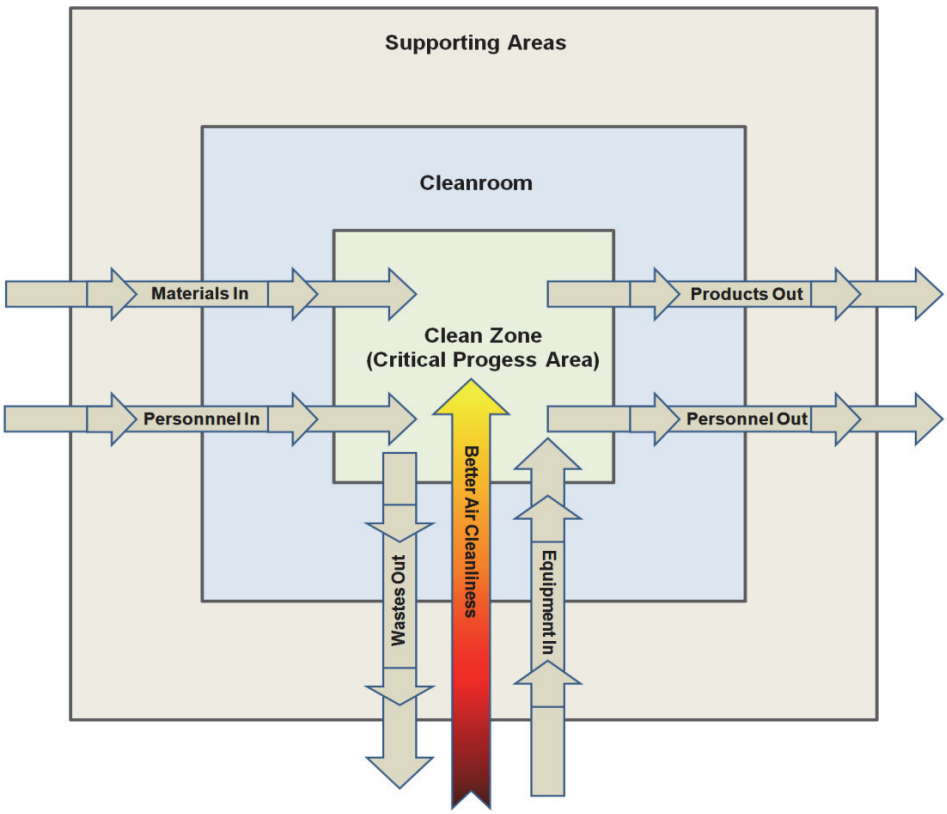


Figure 7.1 Common Cleanroom Layout for Cleanliness Path and Flow Arrangements

be defined by the processes taking place within them. Operations, maintenance, and quality personnel need to be consulted throughout the design, with a focus on minimizing the sizes of the areas. Efficient cleanroom operation demands a systemic design effort to determine functional interdependencies, adjacencies, and efficient flow (movement) of personnel, materials, equipment, products, and waste between adjacent clean zones in order to minimize the migration of contaminants and to optimize process flow; therefore, special attention should be paid to the cleanroom suite layout design.

Figure 7.1 illustrates a common "cascading" contamination control concept, in which the clean zone is regarded as the part of the cleanroom that is most stringently controlled.

Design of personnel flow into and out of the cleanroom needs to consider ancillary areas, including gowning areas, restrooms, and eating and break areas as the project requires. For adjacent spaces with significant cleanliness class differences, typically two classes or more apart, air locks may need to be installed at both the entrance and exit between these two adjacent spaces. Detailed information about air lock applications can be found in Chapter 8.

Equipment and materials entering a cleanroom must be precleaned and moved through either an air lock or a pass-through prior to cleanroom entry, according to the protocols of the cleanroom operation. Exposed room surface finish materials, such as wall panels, flooring, and ceiling, must be compatible with the processes in the cleanroom, including the cleaning methods and cleaning materials used. Gowning and behavior protocols should be strictly enforced.

Design of operational flows for products, equipment, and waste is often manufacturer or industry specific. Part 4 of this book provides more in-depth considerations and analyses for specific industry applications.

7.4 FACILITY DESIGN CONSIDERATIONS

The internationally recognized cleanroom standard, ISO 14644-1 (superseding FS 209E in the United States and BS 5295 in the United Kingdom), defines a cleanroom as "a room within which the number concentration of airborne particles is controlled and classified, and which is designed, constructed and operated in a manner to control the introduction, generation and retention of particles inside the room" (ISO 2015a, p. 8). A cleanroom as defined by this standard must meet the following requirements:

- The class of airborne particle concentration is specified.
- Levels of other cleanliness attributes such as chemical, viable, or nanoscale concentrations in the air, and also surface cleanliness in terms of particle, nanoscale, chemical, and viable concentrations, might also be specified by other documents within the ISO 14644 (ISO 2016) family of standards (e.g., ISO 14644-8 [ISO 2013a] defines chemical concentration classification).
- Other relevant physical parameters need to be controlled as is required for the process, for example, temperature, humidity, pressure, vibration, and electrostatic discharges (see ISO 14644-4 [ISO 2001].

For the purposes of this discussion on cleanroom facilities, we include the entire design-execution team in the definition of the terms *designer* and *design team*, i.e., owner design team, architect/engineer (A/E), construction manager (CM), commissioning and qualification (C&Q), quality assurance (QA), contractors, vendors, owners, and operators—all of the teams involved in bringing a project to fruition.

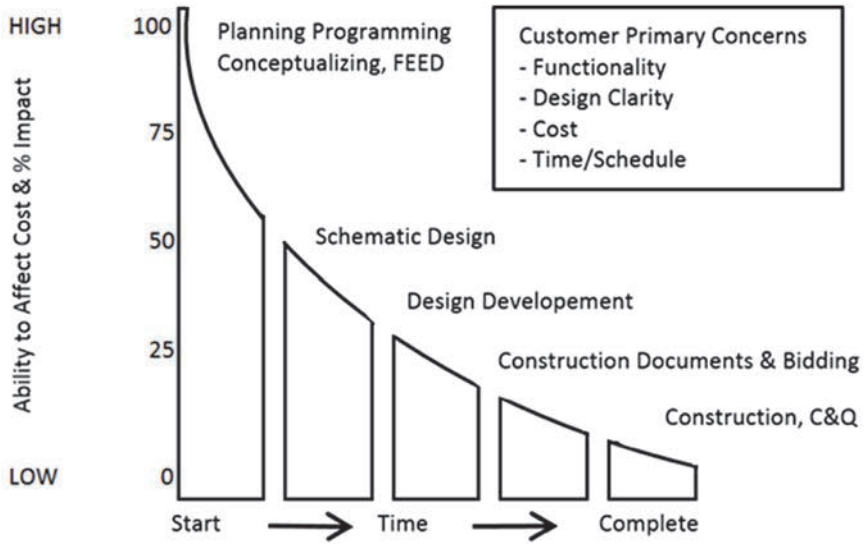
Alexander et al. (1968) cite in the introduction to their seminal book *A Pattern Language Which Generates Multi-Service Centers* that a system of generating principles can be established within facility types and that the system can be changed according to local circumstances but always conveys its essentials, suggesting the system of generating principles to be rather like grammar. Although the book is directed at a different building type, the idea of a system of generating principles is very much pertinent to cleanroom facilities. The value to designers is that principles and patterns are evident within cleanrooms, their design, and their operation. These principles are essential tools to the design team. The book defines a language for the user that suggests that any given design problem needs to be explored from many perspectives and is made up of many parts that can be predefined. Hardly novel 48 years later, but clarifying in that all design problems contain elements that must be explored from a very high level to a somewhat micro view.

In addition, all design situations hold principles that are in our control and those that are less so; and yes, those that are not in our control. With an understanding of those principles, the design is better prepared to support the stated goal: to enable the manufacture of ethical drugs. A few of these principles are discussed in the following subsections.

7.4.1 FACILITY PLANNING AND ARCHITECTURAL PLANNING

Many factors affect the design of a cleanroom project. They can be broadly broken into two general categories: those that are externally driven and those that are internally driven. Subsets include those that are within the owner's (or design team's) control and those that are not. Externally driven factors include the environment and community, the owner, and the market. Internally driven factors are those that design teams are most familiar with and include engineering requirements, user requirements, and quality requirements, among others. What proves to be a constant throughout projects is change. Regardless of the cause of the change, market or otherwise, changes occurring at the beginning of a project can be more effectively integrated into the project, whereas

Figure 7.2
Pareto Effect



changes made during the later phases and into the Detail Design phase (final construction documentation) will result in the most negative impacts on project design cost and schedule with a high probability of design errors. This is often referred to as the Pareto effect: the 80/20 principle as illustrated in Figure 7.2. This is a method of organizing a problem so that the "significant few" items are differentiated from the "trivial many." It is based on the 80/20 rule that states, in general, that 80% of overall project costs are determined by 20% of the project elements.

7.4.1.1 Externally Driven Factors

7.4.1.1.1 The Environment and Community

What is not in the designer's control? The external physical environment, for one. Even when a new site is selected based on a series of favorable attributes, the local climate, the community, the geology, and the topography become elements to which the designer must respond. Additional constraints are distinct in the case of a repurposed or brownfield project. There is no question with regard to climate—summer and winter dry-bulb and wet-bulb temperatures are intrinsic to the locale. The microclimate may be affected by surrounding buildings or the site's location in a valley or near the top of a range. The site geology not only affects the foundation design but also perhaps the depth of a basement or the height of the building if stone, unsuitable soil, groundwater, perched water, or an aquifer is present. The site configuration topography and site access points all affect the master plan and building layout.

Utilities not generated on site, from water to power to sewerage, to name a few, also affect the design of all projects. The same can be said for their location in relation to the facility and the quantity and quality provided.

What about the community within which the project resides? Building code ordinances affect the type of structure and its height. Community ordinances may not only affect the building height but also setbacks, even the color and form of the building. Communities in California have imposed ordinances affecting those as well as exterior materials of construction, the shapes of roofs, and the proximity of offices to the adjacent street. The designer needs to be aware of these issues at the very start of a project. Neighbors could also include those generating particulate, those that are located sufficiently close to the project to affect localized air currents, and those with building or process exhausts.

Where are they in relation to the project? How do they affect the form of the building? Perhaps simply the locations of intakes and exhausts are affected, but perhaps the orientation and configuration of the building are affected.

7.4.1.1.2 Clients

Clients are not generally thought of as an externally driven factor. The immediate client is generally quite identifiable and includes the project management team and procurement, health-safety-environmental, QA, operations, maintenance, and C&Q groups. What about other stakeholders: the board of directors, corporate entities, shareholders? A second perhaps much larger group is the public at large: those that might use the product or are affected by it, or those that reside in the community that the facility is located in.

A continuing design task is the search for the client's needs for the project at hand and how if fits into his or her greater program. To gain an understanding, an area worth investigating is the client's culture. For public companies this can often be discovered in yearly reports to stockholders, which include mission statements, goals, and projections for the short-term and long-term strategic directions. Designers often find clients focus solely on the building for the specific and immediate need. With this client type, internal and external expansion or growth opportunities are sometimes not invested in given the competitive nature of the industry. On the other hand, many clients expend significant efforts in master-planning their strategic growth as well as master-planning the physical site. Many settle for planning for the future more narrowly within the context of that project. At a minimum, designers need to employ best practices and strive to maintain the opportunities for the future considerations so that opportunities are not restricted.

7.4.1.1.3 The Market

It has always been a given that companies are in the business of making money and making a profit for the risks they take. This usually translates to the designer as the need to "bring the product to market," "beat the competition to market," or "gain market share." This is difficult for the designer to control. Every once in a while the market will shift and tell the manufacturer that it does not need that product any more. This can result in the project being put on hold or ramping down. Or, a more positive spin, more product is in demand. At its best, responding to the market means change.

7.4.1.2 Internally Driven Factors

The primary internally driven factor is the criteria the owner provides, presented in several different forms—preferably at the beginning of the project. These criteria include the following elements:

- Engineering requirements
- User requirements (URs) or user requirements specifications (URSs)
- Global quality systems
- Corporate standards (both performance based and prescriptive based)

7.4.1.3 Contracting and Procurement Approaches

Contracting and procurement strategies, although most often in the client's purview, can be influenced by the design team. Such groups as American Institute of Architects (AIA), Construction Industry Institute (CII), and Association of General Contractors (AGC) offer well-studied strategies. The contracting strategies are many, with varying degrees of success, and are highly dependent on the client's culture and experience: design-bid-build; design-build; fast-track; super-fast-track; engineering, procurement, and construction (EPC); engineering, procurement, and construction management (EPCM); and others yielding the client and designer different degrees of control and risk.

Highly promoted in recent years and a yet emerging process is a more holistic approach to project execution: bringing the A/E, CM, C&Q, vendor team, and other contracting entities on board at the project start (again: begin with the end in mind). Termed IPD, *integrated project delivery* is defined by AIA (2007) as

> a project delivery approach that integrates people, systems, business structures and practices into a process that collaboratively harnesses the talents and insights of all participants to optimize project results, increase value to the owner, reduce waste, and maximize efficiency through all phases of design, fabrication, and construction.

Most recently, papers and articles have been written on the subject explaining and exploring the attributes of this approach. But suffice it to say that it requires the development of strong, cooperative, unfettered relationships to bring a project to fruition successfully (i.e., win-win-win). ASHRAE/USGBC/IES Standard 189.1 (ASHRAE 2014) also discusses the value of IPD. By coupling these approaches with the use of building information modeling (BIM) and other documentation and analysis techniques, a successful result can be achieved. The more focused clients, designers, vendors, and constructors with far-reaching and long-term goals will see the inherent wisdom of this approach.

7.4.1.4 Predesign and Design Activities

7.4.1.4.1 Project Profile Development

First and foremost, a business case evaluation, generally driven by clients or one of the large accounting houses, is initiated to help management determine the viability of a project from a fairly high level. One particular client of this author suggested that if the project is to be killed, this is the place to do it, referring to the minimization in lost capital, resources, and schedule. A project profile looks at the business strategy, functional unit strategy, and project criteria and develops a preconceptual layout and order-of-magnitude cost.

Basic consulting includes site searches and evaluation with a focus on the following activities:

- Location analysis, siting, permitting, and licensing
- Energy management, renewables, and carbon and greenhouse gas management
- Integrated water management, air quality, permitting, and compliance assurance
- Ecosystems management, due diligence, waste management, remediation, and sediments
- Lean manufacturing (lean manufacturing is defined by the Lean Enterprise Institute [LEI 2017] as the core idea of maximizing customer value while minimizing waste, eliminating those steps that may be present in a process that add no value to the product [e.g., staging, storage versus just in time]. Simply, lean means creating more value for customers with fewer resources.)

One of the first steps in the development of every project is to determine what its requirements are. What does the owner need? This step in the design process is often called *programming*. Several approaches to programming have been successfully used, the traditional interview-questionnaire being one. A second, more dynamic and yet classic approach is documented in the book *Problem Seeking*, which explains that since designing is problem solving, programming is "the search for sufficient information to clarify, to understand, to state the problem" (Peña and Kelly 1969, p. 15). The core idea is to separate programming (analysis) from design (synthesis). This approach serves to bring significant clarity to the design problem. In essence, it requires focus on goals,

facts, and concepts first and then translation of those into quantifiable needs, independent of the solution; it also encourages innovation and facilitates decision making (Peña and Kelly 1969).

The problem-seeking approach to programming consists of five steps: establish goals, collect and analyze facts, uncover and test concepts, determine needs, and state the problem. Another way to think of it is as follows:

- **Outline the Project Goals.** Identify the primary objectives to be achieved in the process and building design.
- **Collect and Analyze the Facts.** Gather information and data pertaining to the project, including in such areas as the programs being housed in the facility, site conditions, existing infrastructure, etc.
- **Develop Operational and Design Concepts.** Uncover and test ideas on how to design and operate the building to achieve the project goals.
- **Define the Project Needs.** Outline the functional requirements for the project and include such elements as floor area requirements, schedule, budget, etc.
- **State the Problem.** Summarize the main challenges to be addressed and resolved in the architectural and engineering design.

Each of the steps addresses four basic considerations: function (people, activities, and relationships), form (site, environment, and quality), economy (initial budget, operating costs, and life-cycle costs), and time (past, present, and future) (Peña and Kelly 1969).

Programming as described above is often combined with front-end studies. Given many names throughout the industry, front-end planning (FEP) focuses on the creation of a strong and early link between business and mission needs, project strategies, scope, schedule, and cost. A key to all planning efforts is to maintain the foundation throughout the project and to ensure the original goals and needs remain the focus. FEP is often perceived as synonymous with front-end engineering design (FEED), front end loading (FEL), pre-project planning (PPP), feasibility analysis, programming and conceptual planning. The rules and executions of these strategies vary greatly among owners and designers, but the goal is quite the same: define the project and all of its parameters towards minimizing risk. This programming phase is then followed by conceptual, preliminary, and detailed design. The last phase entails the preparation of drawings and specifications for bidding, construction, and C&Q.

Additional techniques used to assist owners in an understanding of the robustness of a process include design charrettes. These are collaborative sessions that often span several days with the intent to bring all stakeholders together to quickly define a problem and draft options responsive to the criteria (technical, quality, cost, and schedule) and the quick but studied selection of one of the options and the path forward. Process modeling using data analysis and simulation software is an excellent tool for engineers to understand the effects of changes in a system. Modeling offers a way to improve process understanding and control and to speed development. In response to this trend, software tools that have improved capabilities and increased user-friendliness are being designed to meet the needs of cleanroom users.

7.4.1.5 Form-Giving Functions and Elements

Along with the fundamental need to identify what the owner wants to build and the above-mentioned approaches to that discovery, the design team needs to focus on the process itself (how the product is to be manufactured). This results in generation of block flow diagrams (BFDs), process flow diagrams (PFDs), and eventually piping and instrumentation diagrams (P&IDs). The BFDs and PFDs are particularly important to the lay-

out of a facility. Many design teams in the industry prescribe that the facility should be designed from the inside out. Additionally, designers must look for those form-giving aspects of the building program. Some are fairly obvious; some are not as clear-cut:

- **Platform of the Processes and Technology.** Liquids, lyophilized products, solid dosages, transdermal patches, ointments, gels, aseptic restricted access barriers (RABs), terminally sterilized barrier isolators (BIs), autoclaves, parts washers, and tunnel sterilizers, as well as their differing HVAC needs.
- **Equipment.** The equipment itself as well as its throughput requirements, size and configuration, workstation requirements, and operator and maintenance access (clean side or gray side).
- **Zoning Requirements (of Functional Elements).** Segregation of products, functions, and HVAC systems and the elimination of cross-contamination.
- **Viewing.** Requirements for viewing unit operations (visitor, auditor, and supervisor) from outside classified areas or from lesser classified areas—Grade D to Grade B or C, for example. Sometimes the need is to minimize or eliminate the need for certain personnel types from gowning and entering an area.
- **Operational Flows.** Flows of materials, products, equipment (used, clean), wastes, and personnel (classified operator and maintenance personnel, auditors, supervisors, and maintenance personnel).
- **Unidirectional Flows.** The requirement for unidirectional flow of personnel and materials into and out of cleanroom suites is borne in 21 CFR 211.42(b) (GPO 2016a) for control of the process to protect the materials, active pharmaceutical ingredients (APIs), product contact parts, and end product from contamination. This is generally manifest in linear operations and layouts creating progressions of functions or work areas. The principle is for the flow of, particularly, materials and people to not cross paths in the progression of the process and as the product becomes more developed. Or more simply stated: entering the production environment from one direction and leaving it in the opposite direction without crossing paths. Examples of unidirectional flows include the following:
  - Material air locks (MALs) and personnel air locks (PALs) “in” (ingress) and MALs and PALs “out” (egress).
  - Unidirectional locker rooms that direct sequential steps in the gowning process with separate returns for degowning.
  - Perimeter supply corridors and separate return corridors
  - Sequential equipment cleaning steps, starting with the moving of equipment or parts to a used equipment staging area and moving to a parts wash area where materials pass through a parts washer. From here the equipment passes to the clean equipment staging step, through an autoclave to sterile equipment staging, where parts await transfer to the filler.
  - Pass-boxes or pass-throughs for the one-way transfer of materials or waste.

  The concept of unidirectional flow often needs to extend beyond the cleanroom, however, into the material delivery supply chain: warehousing, weighing and dispensing, and product QA and environmental management (EM) sample deliveries.
- **Functional Adjacencies.** These are much the same as flows but are generally seen as the need to physically locate programmatic areas next to one another. For example, the cleanroom air-handling equipment room is best located as close as possible to the cleanroom to minimize ductwork and loss of static pressure. Another more obvious example is the location of the capper in relation to the filler. PFDs serve to define physical adjacencies as well.

- **Transition Spaces (i.e., Air Locks).** Spaces such as these require a full understanding of their purpose to function properly. Are they used for materials, products, waste, or people? Are these elements entering or exiting the process space? These transition spaces often serve as gowning areas, particularly transitions from ISO Class 8 to ISO Class 7 (ISO 2015) and higher (cleaner) spaces. PALs demand space for gowning supplies, waste, and benches and people.
- **Equipment and Service Access.** Equipment is typically maintained through preventive maintenance programs. The ability to access the equipment is a significant consideration in the layout of a facility. The industry has made a significant effort to use gray-side maintenance, which is the ability to access and maintain equipment without the need to gown and enter and disrupt classified areas. This approach not only eliminates personnel intrusion into the work environment but also serves to minimize the size of the cleanroom (and therefore the associated operating costs, cleaning costs, and HVAC loads). Equipment may need to be accessed from within the cleanroom, requiring that the designer understand the equipment manufacturer's provision of access panels and door swings as well as the attendant space required for personnel and carts and tools needed in the maintenance operation. For example, certain equipment requires platforms either to elevate that equipment or to allow access above or below that equipment, such as lyophilizers and tanks.
- **Service Areas.** The requirement for walkable interstitial levels and the ability to access equipment outside of the cleanroom to eliminate interference with operations in order to replace lamps and high-efficiency particulate air (HEPA) filters and access valves and control panels, dampers, input/output (I/O) panels, and the like.
- **Plant Areas.** Air-handling units (AHUs), utilities, and electrical gear.
- **Geotechnical Considerations.** Soils, water table, and aquifer.

Collectively, these elements point to that not-overused phrase uttered by Louis Sullivan, an iconic early Twentieth Century American architect, "form ever follows function," more often repeated as "form follows function." As noted at the beginning of this subsection, another expression frequently used is that the facility needs to be designed "from the inside out." That is not to say, however, that the external influences and criteria are completely subjugated. A successful result is a balance, not a compromise. There are several methods to help determine if the layout meets the criteria with a quest for understanding the layout or design concept quantitatively while much of the criteria are qualitative. These include the Kepner-Tregoe and Six Sigma decision analysis techniques (Kepner and Tregoe 2013; Cordy and Coryea 2006), whereas the development and analysis of operational flow diagrams, mock-ups, taping out the layout on the floor, and three-dimensional modeling are all positive result-proving techniques. At minimum, these techniques serve to confirm the "I like it" approach to option selection.

Each step in the process described above must be examined to ensure that the intent is carried out (i.e., that it is confirmed and audited). The quantities of materials and the sizes of equipment required for these operations also influence and determine the sizes and configurations of these areas. Frequency is often an argument for compromising on the concept of unidirectional flow, and not incorrectly. Procedural controls are appropriate as well, but this can obviously enable a higher degree of failure. Although operator training is most often rigorous, "I forgot" is not an answer you wish to hear when the product is compromised. One item to be well understood is that the European Medicines Agency (EMA) requires engineering controls whereas the U.S. Food and Drug Administration

(FDA) allows more procedural controls. Owners and designers understand the risks of procedural controls and strive to implement engineering controls as the rule.

7.4.1.5.1 Expandability

Expandability can be both internal and external to the given project. As part of the master planning aspect of the project, criteria are generated defining the degree and type of expansion required. From either viewpoint, consideration is generally given to operational flows and functional adjacencies. This affects the layout of additional filling lines or packaging lines, for example, that need to be contiguous. Flows include personnel movement as well as materials entering and leaving the facility. Traffic patterns, emergency access, and security are also part of the expandability equation.

7.4.1.5.2 Flexibility

Flexibility is a topic that deserves significant discussion with the client team, as it has many definitions and many more implications. Flexibility can be equated to the design of the staff, facility, equipment, unit operations, and throughput. From a master planning perspective, discussion revolves around the ability to manufacture alternative product types from that initially planned. This certainly affects the type and configuration of the cleanroom areas as well as the facility in total. Facility flexibility suggests that the equipment or layout can be reconfigured with possibly minimal disruption to the structural and utility systems to meet a different need. Sometimes with time as a determinant, modular partitions and ceiling systems enable the degree of flexibility required. At the same time, utility corridors, vertical or horizontal, above the ceiling or below the floor, provide flexibility in the operation and maintenance of the cleanroom.

7.4.1.5.3 Adequacy of Space

As cited in 21 CFR 211.42(b) (GPO 2016a), adequacy of space includes the provision of space for low wall returns. The sizes and locations of low wall returns for ISO Class 5, ISO Class 7, and some ISO Class 8 areas (ISO 2015) is critical to ensure an even flow of air across the room. In the case of MALs and PALs, the air must sweep from the cleaner side to the less clean side. In automatic loading and unloading system (ALUS) aisles, the challenge is the uniform distribution of air and the low wall returns on the lyophilizer wall, which is mostly composed of the chamber and stainless steel fascia. Working with the equipment vendor, clearances between units can be defined and low wall returns can be located between multiple lyophilizers while at the same time addressing the need to minimize the sizes of cleanrooms.

7.4.1.5.4 Minimization of Classified Environments

One of the most significant costs of cleanrooms and clean manufacturing areas is the size of the clean manufacturing space. The primary costs are generally considered to be the initial construction costs for the facility and its support. The smaller the cleanroom and the facility, the lower those initial costs. The challenge is to provide for all the functionality that the cleanroom requires, the equipment, the charging of that equipment (i.e., loading of vials or stoppers), access around the equipment for its operation and maintenance, adequate room for the cleaning of the equipment and cleanroom, and adequate space for the supply and return of air and at the same time minimize or rightsize the space.

Other cost elements include the maintenance and provision for utilities of those areas. These are continuing costs that will be part of the life of the facility. These costs are directly related to the size and complexity of the cleanroom, the ease of cleaning it, the robustness of materials used in its construction, and the cost for providing the air distribu-

tion, HVAC systems, lighting, and everything that makes a cleanroom work. Robust design is often a cited goal.

7.4.1.5.5 Impacts to Site/Environment/Community

As concerned as we are with regard to the quality of materials coming onto the manufacturing site, we also need to show the same degree of concern with regard to things that leave the site. Abatement or scrubbing of exhaust air, bag-in/bag-out filtration for biologicals, pH and biological treatment of liquid waste, and disposal of solid wastes need to be considered.

7.4.1.5.6 Cleaning Methods and Materials

Cleaning, disinfecting, and fumigation agents; strengths of solutions; and methods of application (wet mop, damp mop, etc.) must be considered in the selection of materials of cleanroom construction. (Also see Section 6.6 of Chapter 6.) This easily applies to architectural finishes (floors, walls, ceiling, and the countless accessories found in cleanrooms) but also to piping materials, electrical and communication devices, and the like, and certainly the equipment (passivation is yet another topic that requires discussion). Perhaps the most complete method of ensuring that the materials of construction are compatible with the cleaning materials and methods is to have the client's laboratory test the materials against the cleaning agents they propose to use prior to specification of the materials. Additionally, material suppliers have prepared lists that should be investigated. Suppliers are often most willing to support the evaluation of cleaning agents on their products. Cleaning procedures for the materials of construction need to be understood prior to the specification of those materials. And as the final selection of those materials is often determined by the contractor or subcontractor in a competitive bid environment, the specification needs to include requirements for compatibility testing and cleaning procedures. Alternative materials need to be scrutinized to ensure they fulfill the specified criteria. Certainly materials and methods change, but the best we can do is to evaluate those products and materials that are under our control. Start early.

7.4.1.5.7 Cleanability and Accessibility

Much has been said about the need to provide flush joints at doors, windows, and walls. The same concern needs to be given to other interfaces. It can be said, to a certain degree, that if it looks cleanable, it is cleanable. Where two materials adjoin one another, the resulting joint needs to be treated, very often with a food-safe caulking. Nonetheless, it is good practice for the architect to specify that the interfaces of all materials exposed in the cleanrooms be sealed (wall plates and switches, escutcheon plates, and others.). Piping, if not concealed, needs to stand off from the wall a minimum of 2 in. (50 mm) to allow an operator to clean behind the pipe or conduit. Piping and conduit need to be spaced in a similar fashion or additional work (which equals time and money) will be required to perform the cleaning regimen. Pipe and conduit penetrations through walls or ceilings need to be sealed (depending on the type of wall construction and material passing through, an escutcheon plate may be warranted). The reason for the sealing of these items is both to eliminate cleaning problems and to prevent particulate migration and airflow leakage. If the wall has a fire rating, the sealing material needs to be part of a fire-rated system (see the *International Building Code*® and *International Fire Code*® [ICC 2014a, 2014b] for additional information). Friable materials have no place in a cleanroom. The presence of airborne molecular contamination (AMC) is currently a concern for semiconductor and nano device industries, but it is also a concern for pharmaceutical and biotechnology industries.

The cleanroom and its adjacent support spaces need to be accessible for maintenance. Very often we find that the best location for an autoclave or parts washer is an island within the cleanroom. This requires less than desirable access to a potentially confined space from above or below to allow access to the mechanical side of the equipment. This access may be required at the worst of times, when the facility is in full operation. As noted previously, the need for gray-side access is very much a form giver.

The current approach to above-ceiling maintenance areas is to make them accessible and sometimes walkable. Termed *interstitial spaces*, this approach supports the replacement of lamps and HEPA filters from above, outside of the cleanroom. Equipment serving the process needs are sometimes located in this interstitial space, as are electric and control panels, instruments, reheat coils, dampers, and valves. The value to operations is that this area is accessible by maintenance personnel without the need to gown, avoiding interruption of ongoing operations below.

One avenue that should be touched on in the design of a project is reviewing the layout and details with the operating and maintenance staff to gain their perspective of the project's requirements and also to help educate those teams as to what is going to be handed over to them for cleaning and maintenance. A more aggressive approach is to engage these personnel in the development of the criteria for success and the development of the layout.

Additional design considerations include health, safety, and environmental (HSE) issues, sustainability, and gowning, to name a few.

7.4.1.6 Construction Methods

7.4.1.6.1 Standard Construction

Standard construction techniques remain the primary method used in the construction of cleanrooms, as many projects are quite customized for a myriad of reasons, many of which are dictated by site constraints or unique project requirements. This includes the use of conventional materials such as concrete block, cement board and gypsum drywall with epoxy, fiberglass, and polyvinyl chloride (PVC) or thermoplastic sheeting. If gypsum drywall is contemplated, concern needs to be given to the paper facing and the potential for the growth of mold. Paperless gypsum drywall having a fiberglass face is an option.

7.4.1.6.2 Prefabricated Construction

The prefabricated building approach, utilizing off-site construction, has demonstrated gains in cost and/or schedule and continues to gain favor in the industry. There is no question that as the owner's criteria include cost and schedule implications this type of construction demands evaluation. Given the election to use this type of construction, the design and construction approach needs to be solidified very early in the design process. Select design firms and manufacturers specialize in this construction and offer valuable services that need to be explored and possibly engaged. There certainly are applications for this level of modular construction and significant successes; it remains that prior to electing this direction a full understanding of the owner's needs and long-term goals is required.

When designing a prefabricated module it is critical to consider the equipment that will be used in the operation. Many equipment suppliers offer entire systems in a modular format. Having equipment suppliers work with the module fabricator may allow the equipment to be installed in the module during its fabrication. The entire suite can then be qualified before it is installed in the building.

Modular construction can also mean designing the building in a regular structural or services grid. This is opposed to a custom-designed structural grid for specific unit operations. In either case, design regimen is required. Coordination among design team members is most important. The use of three-dimensional and BIM systems facilitates design work and minimizes system interferences through ongoing coordination by using clash detection techniques.

Each of the above techniques suggests the integration of design teams early in the design process—whether it be the vendor of the cleanroom wall and ceiling systems or the designer-manufacturer of the building modules. The advantages of such integration include a reduction in schedule and the opportunity for a more integrated design.

Attention needs to be paid to the elimination or minimization of horizontal surfaces. Flush-mount doors and windows should be used. Depending on the room classification, sloped window sills are effective. The use of coved corners at walls and ceiling intersections also facilitates cleaning. Care needs to be taken, however, with the use of coved wall-ceiling intersections when used with plenum or 100% HEPA-filtered ceilings, because the desired unidirectional flow is compromised. Flush door and window details are a necessity facilitating cleaning but also for minimizing the adverse effect on airflow.

7.4.1.6.3 Cleanroom Construction Materials

Cleanroom construction materials should be carefully selected to maintain the integrity of the cleanroom. In general, the more monolithic, nonporous, nonshedding, easily cleaned, durable materials of construction will ensure the minimization of particulate generation. Examples of materials that are used in cleanroom construction with some considerations in their use and applicability in cleanrooms are noted in the following list:

- **Aluminum-Framed, Noncombustible Composite Panels with an Unplasticized PVC (uPVC) Finish over Galvanized Steel with a Honeycomb Aluminum Core.** A significant set of attributes of this type of panel is that no gypsum, mineral wool, or foam core insulation can absorb moisture or humidity.
- **Glass-Reinforced Plastic (GRP) Wall Panels.** Care needs to be taken when using these panels because particulate can statically cling to the panels even after cleaning.
- **Sheet Vinyl—Heat and Chemically Welded.** Sheet vinyl is often used on floors and walls in hospital operating rooms for its many attributes, including cleanability, in addition to being used in pharmaceutical cleanrooms.
- **Epoxy-Based Systems, Water and Oil Based, Applied Integral with Wall or Floor.** Consideration should be given to volatile organic compounds (VOCs), odors, cleaning system incompatibilities (discoloration/deterioration), cost for maintenance/replacement, and coved bases.

  Note: All flooring materials need to consider wheel and equipment load impacts. Attention also needs to be given to the type of wheels used on carts, dollies, and forklifts, as many will mar the floor.
- **Friable Materials.** These materials are to be avoided because they can increase the risk of particulate contamination and because they can clog filters.
- **Stainless Steel, Aluminum, Painted Steel, and Fiberglass.** These are standard wall and door material types. Note that with stainless steel or aluminum care needs to be taken if sodium hypochlorite is the cleaning agent of choice, as corrosion can result, and aluminum can oxidize if unprotected. Corrosion problems can also arise with painted steel, particularly due to cleaning solution incompatibility. Fiberglass is often chosen for its durability and cleanability. An article in *CleanRooms Magazine* (Mathis 2009) cites a study showing that standard door

materials visibly deteriorate when exposed to standard chemical solvents used in cleaning agents. Experience has demonstrated that the best material options for doors are fiberglass and stainless steel, although these are not without their own inherent problems.

- **Wall and Ceiling Materials.** Cleanroom modular panels include softwall curtains and numerous hardwall types incorporating monolithic walls or honeycomb cores. Panels are either progressive or nonprogressive; nonprogressive panels yield a greater degree of flexibility when layout changes are required, as each panel can be removed without affecting the adjacent panels. Face materials include coated steel or aluminum, vinyl, and PVC laminates. Ceiling systems are of the same construction. Considerations need to include flexibility, corrosion, and moisture resistance. Some panels that are more adapted to other industries may contain paper, wood, fiber, cardboard, or similar materials in the core. Other systems use battens to join panels. Each of these has potential adverse effects given the need to control humidity and particulates. For example, although the galvanized steel face sheet may have an epoxy or vinyl coating, penetrations in the panel for the installation of (door) hardware or pipe/conduits requires treatment prior to closure, as the metal edge is exposed and subject to rusting. These panel types are to be avoided. A major consideration is the sealing of joints between panels. Caulking is most often used, but as with any caulking, it is difficult to confirm that the seal is complete (unlike with a fish tank, where the joints are under pressure and leaks are easily discovered) and not a source of infiltration and a location for the growth of mold. The benefits of using modular panels have been proven in semiconductor, pharmaceutical, and biotechnology facilities and include clean detailing, ease of integration with equipment, and flexibility with respect to field changes.

As mentioned in Section 4.2.2 of Chapter 4, materials of construction need to be evaluated for off-gassing.

7.4.1.6.4 Pressurization—Door Seals, Direction of Swing

Another detail is the manner in which doors swing in relation to the pressurization of the space. With the exception of exit routes, doors should be “held closed” by the room pressure. A pressure differential of only 0.20 in. w.c. (50 Pa) can cause a door to stand open. Mechanical door closers may be required to overcome the differential pressures between two rooms. These pressures can be enough to keep the doors from closing properly. Easily cleanable door seals often need to be provided for head and jamb conditions in order to maintain the appropriate room pressures and minimize air leakage or to meet fire ratings as proscribed by building code requirements.

7.4.1.6.5 Vibration (Internal/External)

Vibration produced either within the building or external to the building needs to be considered early in the design process. Operating equipment can be the source of the vibration and requires the use of isolation devices to dampen the vibration. Certain equipment needs to be isolated from vibration to function properly. This could simply entail the use of a dampeners or the need for independent support or foundations. Another element that needs to be considered is vibration of adjacent buildings caused during construction, by driving piles, heavy traffic, or moving equipment. The effect to adjacent ongoing operations needs to be considered and alternative construction methods used. Alternatively, construction may need to take place when the adjacent facility is not in operation.

A client recently shared a case that required a change of the foundation design after construction had started. The structural engineer had a geotechnical report prepared to determine soil bearing pressures, the location of water tables, and the soil types, but it was not until the initiation of driving piles for the foundations of the new building that it was discovered that the adjacent facility was subject to vibration. It can be suggested that the designer neglected to inquire as to the nature of the adjacent manufacturing operations and/or the client neglected to provide this information. Nonetheless, the foundations had to be redesigned along with a method of stabilizing the foundation of the adjacent building at considerable design cost and delay.

7.4.1.6.6 Constructability

Constructability is a significant aspect of project design requiring its integration very early in the design phase. It needs to begin on the first day of the project and not stop until the construction is complete. The benefit is significant in terms of cost and schedule. But what is constructability? In general, it is the evaluation of a set of design documents with a focus on determining that the building can, for example, be constructed as it has been designed. Do all the pieces and parts work together? Can they be assembled as detailed? (see Smith [2016]).

A significant aspect of constructability for cleanrooms is the need to address equipment movement that is generally recognized as an operational flow, including the widths of corridors for passage and access to process areas; the logistics of moving equipment into the building initially requires consideration as well. The size of the access door or removable panel and the path to transport equipment to its final location demand attention early in the project. A critical aspect of design, this has been sometimes mistakenly left to the later stages of design or when a CM comes on board. Many larger pieces of equipment rarely require removal from a facility (such as an AHU or lyophilizer, for example), but many items are, in fact, installed when the facility is essentially complete. Sometimes this is a matter of delivery times (fillers can require 8 to 15 months from the release of the purchase order) or the need to complete the finishes prior to installation. Filler-washer-tunnels, autoclaves, and parts washers are examples of equipment having long lead times (as a result of custom designs, complex fabrication, and extended delivery schedules).

Our focus needs to be to plan ahead: how do we (contractor, vendor, and owner) move the equipment into or out of a building with minimal interruption or impact to the facility? How big is it (length, width, and height; number of pieces; crate size; turning radii)? How much does it weigh (compared to the structural live load)? How can it be moved (rollers, mechanical means, or air cushions)?

Temporary or permanent openings in the building are used to move in equipment, including removable walls, panels, louvers, and doors. Louvers, with their ease of removal, are often favored. The path into and through the building needs to be evaluated with respect to curbs, walls, services, and clearances. Cranes, helicopters, hoists, or hoist beams may need to be used to convey the equipment.

Maintaining adjacent operations during construction is a factor that has significant design importance. This is not only from the obvious physical constraints but also includes shared utilities, noise, and particulate generation. The location of air intakes on adjacent operations can be a significant concern not only regarding particulates but also gaseous emissions. Although there is a focus to reduce their usage, VOCs from products that still use them can be emitted by the AHUs of adjacent operations.

7.4.1.6.7 Clean-Build Protocols

The construction process is inherently a dirty task, and achieving the cleanliness level called for by the cleanroom being constructed requires continuous cleaning and housekeeping during all stages of construction. If the cleanroom is not built clean, considerable expense will be encountered to do the level of deep cleaning required to rid the construction of particulate. Even if final ultra-cleaning is performed, there will be particulates hidden inside the cleanroom that can create problems later during production, potentially increasing downtime. Cleaning protocols have to be established up front and followed carefully. After the building shell is closed, the building should be made relatively clean and ready for clean-build protocols. At this stage, it is recommended that supply fans be used to pressurize the building to keep dust from entering the clean zones. After this stage, all tools and materials used in the cleanroom construction should be cleaned prior to entering to the clean zones. Construction workers should also follow cleanroom protocol by using hair nets, gloves, and booties. Piping and ductwork should be cleaned and their ends sealed prior to leaving the fabrication shop and being shipped to the site for installation. Smoking needs to be prohibited on the site (studies show that residual smoke in a person's lungs takes hours to be purged after smoking). The benefit of following clean-build protocol is to certify the area quickly and get ready for production. Clean-build protocols add initial costs to the construction, but the end result saves both time and money.

7.5 ARCHITECTURAL CONSIDERATIONS

Effective cleanroom building design and space layout should consider the multiple aspects of production, process, and operation objectives of the facility. Often, economic benefits could be gained by segregating areas of different functional aspects—for example, grouping offices to allow better communication and reduce floor footprint, reducing the transport distance of utility services, and decreasing unnecessary floor-to-floor heights. The use of a centralized storage area may result in a reduction of stock but increase the travel distance, so the benefits and costs of each option must be weighed in the design phase.

In cleanroom facilities, widths of corridors, doorways, and floor loadings may need to be increased above the norm to accommodate large and heavy equipment and machinery. Additionally, arrangement of the removal and disposal of waste should be incorporated into the design. The classification of hazardous materials dictates the type of facilities and equipment required. For example, highly hazardous biochemical waste has to be made safe by autoclaving within the containment suite before the waste may be transported through the remainder of the building.

7.6 INDOOR ENVIRONMENTAL QUALITY

Factors of indoor thermal comfort and occupant health are typically the air temperature; humidity; supply air distribution speed around occupants; outdoor air intake percentage; ventilation rate; thermal insulation of clothing; levels of noise, vibration, and lighting; and emission rates of chemical fumes, odors, and VOCs from various operations, etc. In 2007 The National Institute for Occupational Safety and Health (NIOSH) defined and published the recommended exposure limits (RELs) for hazardous substances or conditions in the workplace (NIOSH 2007). Design engineers should review these requirements and discuss them with building users to ensure that under normal

operational conditions the indoor environment can meet the requirements for the safety of workers and occupants.

7.7 OUTDOOR EMISSION CONTROL AND OUTDOOR AIR INTAKE

Cleanroom facilities could release relatively high concentrations and high quantities of emissions carrying particulates, chemical fumes, or microbes through their building exhaust systems, even though this air has been pretreated inside the building. This air could have a negative impact on surrounding areas and communities, as nearby buildings often have their own outdoor air intakes to meet ventilation requirements for their occupants in these buildings. In certain cases, cleanroom exhaust air may need to be filtered, wet scrubbed, and/or diluted as pretreatments before discharging it at a higher velocity to atmosphere. In the United States, the U.S. Environmental Protection Agency (EPA) regulates building air emission permits.

In other cases, outdoor air intake quality should be monitored with possible chemical or VOC sensors to ensure the outdoor air intake is of acceptable quality to be used for ventilation, makeup for exhaust air loss, and pressurization purposes. As a general rule, outdoor air intakes for buildings should be placed at least 25 ft (7.6 m) away from exhaust air from a cleanroom, and the intakes should not be placed downstream under prevailing winds of building exhaust airstreams. For solvent exhaust, sometimes carbon bed or cryogenic condensation systems can be used as a pretreatment.

7.8 DESIGN FOR SAFETY CONCERNS

A cleanroom may have exotic chemistries or other processes that could affect human safety. In such cases, the following design features should be considered in the development of a cleanroom's life safety systems:

- Physical barriers and zone separation to reduce the impact of sudden dispersion of hazardous gases and vapors
- Zone- or room-based air purge system to allow contaminated room air to be quickly removed to the outdoors to ensure the quality of breathing air to personnel
- Storage of toxic or flammable materials outside the process floor when possible
- Proper egress path design to reduce the exit distance from the process space to a protected area or outdoors, in case of fire or other emergencies, as required by codes
- Isolation of hazardous materials from personnel

Cleanroom design should follow specific code requirements. The matrix of these requirements should be carefully reviewed to identify the types and quantities of hazardous materials that may be present. The insurance underwriter and internal safety officer should be contacted to evaluate life safety issues that may be specific to the site.

Life safety could be significantly impacted by cleanroom operations, which may have various scenarios. For example, pressurization control is critical to a cleanroom's air cleanliness; without a special design protection, an automatic shutdown or even a flow rate reset of the air-handling systems may destroy or drastically alter the cleanroom intended pressure relationships among rooms.

7.9 SECURITY AND ACCESS CONTROL

Security measures may be required in cleanroom facilities to protect against access by unauthorized personnel. The need for security or access control systems and equipment should be discussed with the client representative and security adviser. The requirement can vary significantly depending on the nature of the work and the location of the facility. Typical devices used for security and access control include closed-circuit television, intrusion alarms (restrictive incoming/outgoing personnel), keypads and biometric readers, status monitoring systems, door sensors, and magnetic contacts, among others.

Protocols to control access to a cleanroom are typically intended to limit the number of people in a cleanroom, often as a part of a cleanliness protocol. Additionally, it is important to ensure that access is limited to personnel trained for the specific operation of each cleanroom.

7.10 BUILDING CODES AND STANDARDS

Worldwide, codes, standards, and regulatory requirements are used in all aspects of design, construction, fabrication, and manufacturing. Codes, standards, and regulations that govern the design and construction of industrial facilities are often adopted and amended by state and local authorities having jurisdiction. In addition, International Organization for Standardization (ISO) cleanroom standards and industry-specific manufacturing and operational guidelines need to be identified and studied. Relevant regulations vary from country to country and from locality to locality. Best practice is to identify local regulations that address the particular needs of cleanroom facilities early in the design process. Thorough understanding of these documents is necessary for the development of a successful operating facility.

In addition, most regulatory environmental control agencies enact facility operating mandates and reporting requirements that must be considered early in the design of a cleanroom project. Most local agencies ratify air, water, and land pollution regulations, as well as specific restraints on the activities that may occur in specified planning and zoning areas.

In the United States, most states have adopted the International Code Council (ICC) family of codes (ICC 2017). These ICC model codes are often viewed as minimum requirements, mainly for safety considerations, with limited requirements for facility operations and performance. Occupational Safety and Health Administration (OSHA) guidelines, of course, also need to be adhered to in the United States.

7.10.1 OVERVIEW

The focus of this section is the use and understanding of the various codes, standards, regulations, and guides used in the design, construction, and operation of facilities and processes with an emphasis on their use for the design of cleanroom facilities. An important element to keep in mind as the design team embarks on a project is that all of these entities, along with the design team, have a common interest: safety—the protection of personnel and the protection of the facility and its ability to manufacturer an effective product. However, this does not mean that collectively the design team will not see conflicts in the requirements, but they will see challenges as to how to integrate into the project these needs that benefit the owner while at the same time adhering to the codes and regulations.

The use of and need for building codes and standards is generally well understood by the design community and facility owners. The *International Building Code*® (IBC; ICC

2014a) is well considered to be the principal code for the design of facilities, particularly in the United States. Many aspects of National Fire Protection Association (NFPA) standards are integrated by reference into the IBC. It is important to note, however, that even if NFPA calls a publication a code, it is still a standard until it is legally adopted by a local or state government as part of their building or fire code. For example, *NFPA 72*® is a standard, even though its title is *National Fire Alarm and Signaling Code* (NFPA 2016b). Similarly, *National Electrical Code*® (NEC) and *Life Safety Code*® (NFPA 2017, 2015a) are not regulatory codes until adopted by the authority having jurisdiction. The same is true of the IBC: it is not law until it is adopted by the governing jurisdiction.

Governing jurisdictions have the authority to adopt sections of NFPA standards not integrated into the IBC (ICC 2014a) as well as other regulations that they deem integral to life safety. Although the majority of governing jurisdictions adopt the IBC, possibly along with self-created modifications, they are not required to adopt the IBC per se, as they are responsible for life safety in their jurisdiction. That is, they may develop or adopt regulations they see as best protecting life safety in their own jurisdiction, and these regulations may be less stringent or more stringent than the IBC. Recently, NFPA has developed a model code of its own, *NFPA 5000: Building Construction and Safety Code*® (NFPA 2015c), which some jurisdictions are evaluating for adoption. Similar in nature and intent to the IBC, this code addresses construction, protection, and occupancy features necessary to minimize danger to life and property.

Building codes, in general, are prepared and enforced by entities, most often countries, for the life-safety protection of its citizenry. Their use and jurisdiction extends to new buildings, greenfields, and brownfields. An element of code compliance very often not well understood in the design and execution of facility projects, however, is the entity sometimes known as the *authority having jurisdiction* (AHJ). AHJs can be local building-code officials, insurance underwriters, and regulatory agencies, such as OSHA, FDA, and EMA. In particular, the building code official is generally responsible for the issuance of building permits, enforcing the building codes, providing periodic inspections, and issuing certificates of occupancy. See Section 7.10.2 for further discussion on AHJs.

What is required of designers is an understanding of the requirements of each of these entities, as well as how the rules they are responsible to enforce apply and impact the design and operation of the facility design and its construction. In many cases, early reviews with the governing agency are either encouraged or required. Industry best practices suggest that early reviews will better ensure that requirements are clearly understood and are effectively integrated into the project design. A lack of understanding or incorrect interpretation can lead to redesign and modifications to construction. Worse is the potential adverse effect on the schedule of bringing the client's product to market. Clearly, cost is another potential adverse affect. At the project onset, a thorough building code analysis must be prepared and reviewed with the AHJ before moving too far ahead in the design process. Most architects engage in the development of a building code analysis at the start of the project. The IBC (ICC 2014a) mandates that the building code analysis be an integral part of the construction drawings.

New and pending regulations also need to be heeded. Confirmation as to the effective date of adoption of the pertinent codes by the AHJ is best understood and documented, as not all jurisdictions adopt codes (or regulations) on the same schedule. A project started using one edition or version of the code might bridge a newer edition. Early confirmation is required as to which version the project will be reviewed against, and only the code authority (the AHJ) can provide that direction based on the laws enforced in that jurisdiction (be it country, state, or local municipality).

Another very important aspect of code and regulatory evaluation is precedence: what comes first, or in other words, what is the top-tier code. Very often designers are attracted to using, for example, NFPA standards as the top-tier codes, as they are excellent regulatory publications and heavily referenced in the IBC (ICC 2014a); but the key word is *standards*. To make standards part of a regulatory code as practiced, AHJs adopt the IBC and sections of NFPA and other standards and guidelines generated by the many professionally led organizations and trade associations due to their expertise in a host of areas. The issue is that the designer must follow the top-tier code as defined by the AHJ. *NFPA 45* (NFPA 2015b), for example, is often looked to as the standard for the design of laboratories, but it is only through the adoption by the AHJ that it is a *required* code to be adhered to in the design of a project. An ancillary code or standard will be cited in the top-tier code if it is a requirement. For emphasis: *if a standard is not cited, it need not be used in the code evaluation or in the design of the facility*. An important factor, however, is that the owner or designer may elect to use a standard or guideline as best practice. In any case, the owner should be informed of the implications of the document's use (i.e., cost, schedule, and operational impacts) before its integration into the design.

Perhaps it is best explained in "A Reporter's Guide to Fire and the NFPA" (NFPA 2016a):

> A code is a model, a set of rules that knowledgeable people recommend for others to follow. It is not a law, but can be adopted into law. A standard tends be a more detailed elaboration, the nuts and bolts of meeting a code. One way of looking at the differences between codes and standards is that a code tells you *what* you need to do, and a standard tells you *how* to do it. A code may say that a building must have a fire-alarm system. The standard will spell out what kind of system and how it must work.

7.10.2 AUTHORITY HAVING JURISDICTION

For building design, the AHJ is the governmental entity responsible for regulating the design and construction process. Typically this is the municipality or local entity (i.e., city, county, or state) in which the project is located. As noted in the *NFPA Standards Directory*:

> Where public safety is primary, the authority having jurisdiction may be a federal, state, local, or other regional department or individual such as a fire chief; fire marshal; chief of a fire prevention bureau, labor department, or health department; building official; electrical inspector; or others having statutory authority. For insurance purposes, an insurance inspection department, rating bureau, or other insurance company representative may be the authority having jurisdiction. In many circumstances, the property owner or his or her designated agent assumes the role of the authority having jurisdiction; at governmental installations, the commanding officer or department official may be the authority having jurisdiction. (NFPA 2016c, p. 20)

Other national AHJs, such as FDA, OSHA, and EPA, are discussed in Section 7.10.4.

During the planning phase of a building, the zoning and planning boards of the AHJ are responsible for reviewing the overall compliance of the proposed building within the jurisdiction's general plan and zoning regulations. Once the building is approved at this level, detailed construction-level civil, structural, architectural, mechanical, electrical and process drawings and specifications are developed and submitted to the municipal build-

ing department (and sometimes the public works fire department) to determine compliance with the building code and sometimes for fit within the existing infrastructure. Another key element particularly pertinent to semiconductor, pharmaceutical, and biotechnology projects is ensuring that the AHJ understands the processes being proposed for use in the project. This needs to include the quantities of hazardous materials and how they are used and stored. In addition, how the fire department is expected to access the building and handle exposure, spills, and fires from hazardous materials (especially exotic materials most often used in semiconductor facilities) is critical to life safety. In the past, many AHJs would not consider the process portion of a facility part of their jurisdictional authority. This certainly has been with exception, particularly in regard to hazardous and toxic materials used in the semiconductor industry. In recent years, however, most AHJs are looking at process equipment and process piping in regards to compliance with building code requirements, including fire hazards, exposure, exhaust, and waste considerations.

Before building foundations can be excavated, contractors are usually required to notify utility companies to ensure that underground utility lines can be marked, lessening the likelihood of damage to existing water, sewage, electrical, phone, and cable utilities, which could cause outages or potentially hazardous situations. During the construction of a building, and dependent on the AHJ, a building inspector or his designee must inspect the building periodically to ensure that the construction adheres to the approved plans and the local building code. In general, once construction is complete and a final inspection has been passed, a certificate of occupancy is issued. In some jurisdictions, the architect or engineer team is responsible by law for ensuring by inspection that the facility (structural or otherwise) is constructed as designed. The IBC now requires third-party inspection of structural elements via a prescriptive Statement of Special Inspections and Schedule of Special Inspection Services (ICC 2014a).

As the design team has designed and constructed the building to be code compliant, it falls to the owner to maintain that compliance. To support life safety, fire marshals conduct periodic visits to confirm that the code integrity of the building is maintained.

Changes made to a building that affect safety, including the building's use, fire protection, expansion, and structural integrity, usually require review and approval by the AHJ concerning building code requirements. The building code official, based on the current legislation, may direct that the latest adopted code be used for proposed changes to a facility. Thresholds for this direction often include the age of the existing facility, the cost of the proposed change, or the size of the proposed changed (as compared to the size of the facility in which the change is being made). At minimum, the AHJ should be consulted for confirmation. Documentation of the findings is always prudent.

7.10.3 INTERNATIONAL CODES

The International Code Council (ICC) develops and maintains numerous international codes dedicated to occupant and building safety. These model codes are focused on the provision of minimum safeguards for people at home, at school, and in the workplace. The codes are a set of comprehensive, coordinated building safety and fire prevention codes. The intrinsic value of these codes is that they benefit public safety and support the industry's need for one set of codes without regional limitations. The international codes address the design and installation of building systems through requirements that emphasize performance and establishes minimum regulations for building systems using prescriptive and performance-related provisions.

In the United States, all 50 states and the District of Columbia have adopted model building codes at the state or jurisdictional level. Federal agencies including the Architect

of the Capitol, U.S. General Services Administration, National Park Service, U.S. Department of State, U.S. Forest Service, and the U.S. Department of Veterans Affairs also enforce the building codes. Continuing their broad reach, the building codes are referenced by the U.S. Department of Defense for constructing military facilities, including those that house U.S. troops, domestically and abroad. Guam, the Northern Mariana Islands, Puerto Rico, and the U.S. Virgin Islands also enforce the codes.

A key word found throughout building codes is *minimum*, as in *minimum requirement*. The question must be raised often: is *minimum* sufficient for the need? The owner and design team are responsible for that decision.

One comprehensive model code, the *International Building Code*® (IBC; ICC 2014a), features safety concepts and structural, fire, and life safety provisions covering means of egress, interior finish requirements, comprehensive roof provisions, seismic engineering provisions, innovative construction technology, occupancy classifications, and the latest industry standards in material design. In addition to the IBC, the ICC has developed and maintains other international codes, some of which are described below. Each of these must be investigated for its applicability to individual project conditions:

- ***International Energy Conservation Code*® (IECC; ICC 2014b).** This code encourages energy conservation through efficiency in envelope design, mechanical systems, and lighting systems as well as through the use of new materials and techniques. The word *encourages* should not be misunderstood; AHJs that have adopted this code require its use in the design and construction of facilities.
- ***International Fire Code*® (IFC; ICC 2014d).** This comprehensive code includes regulations for safeguarding life and property from all fire and explosion hazards. Topics discussed include general fire prevention precautions, planning and preparedness for emergencies, fire department access, fire hydrants, fire alarm systems, sprinkler systems, hazardous materials storage and use, and fire safety requirements for both new and existing buildings and premises.
- ***International Fuel Gas Code*® (IFGC; ICC 2014e).** This code addresses the design and installation of fuel gas systems and gas-fired appliances with requirements that emphasize performance.
- ***International Mechanical Code*® (IMC; ICC 2014g).** This code establishes minimum regulations for mechanical systems using performance-related and prescriptive provisions. The understanding of this code is most important to the success of cleanroom facilities.
- ***International Plumbing Code*® (IPC; ICC 2014h).** This code addresses minimum regulations for plumbing facilities in terms of both prescriptive objectives and performance while providing for the acceptance of new products, materials, and systems. Drain types, particularly in pharmaceutical and biotechnology projects, demand special attention with respect to cleanability and maintainability.

Not used with regularity, but to be kept in mind by the design team, are the following additional ICC codes that may affect the design of cleanroom facilities and most projects:

- ***International Existing Building Code*® (IEBC; ICC 2014c).** This code contains requirements intended to encourage the use and reuse of existing buildings. The scope covers repair, alteration, addition, and change of occupancy for existing buildings and historic buildings while achieving appropriate levels of safety without requiring full compliance with the new construction requirements in the IBC. This code is of value particularly for renovation projects. For projects in existing buildings, the advantages and disadvantages of using this code versus the IBC need to be weighed.

- ***International Property Maintenance Code*® (IPMC; ICC 2014i).** Not generally addressed in the design of facilities but important to owners, this code defines requirements for the continued use and maintenance of mechanical, electrical, plumbing, and fire protection systems in existing structures, both residential and nonresidential. The value of this code to the design team is awareness that the owner will be taking over the operation of the facility and that its design needs to be supportive of this code's requirements.

7.10.4 FEDERAL ACTS, LAWS, REGULATIONS, AND REGULATORY BODIES

7.10.4.1 National and Local Codes and Standards

Although in the past few years there have been extensive efforts to standardize and harmonize codes throughout the United States and the world, local authorities (states, counties, and municipalities) retain the right to adopt, amend, and legislate. In all cases, it is the local jurisdiction that adopts the building code and defines for the public which edition is in force. Many states and local jurisdictions amend the model code prior to adoption to suit their specific needs. Thus, it is important to recall when preparing a code analysis that the AHJ needs to be consulted, and the meetings documented, at minimum, to identify the specific codes to be used for the specific project. Very often a project may be started with one edition of an adopted code and is extended beyond the time that a revision or another edition of that code is adopted. Because of this, it is important that the designer maintain contact with the AHJ and establish the codes to be used by law throughout the life of the project in its design and construction phases. Code officials do understand the difficulties of project schedules but at the same time are mandated to enforce current regulations.

7.10.4.2 Occupational Safety and Health Administration (OSHA)

The broad-ranging mission of the Occupational Safety and Health Administration (OSHA) is to prevent work-related illnesses, injuries, and deaths. Under the Occupational Safety and Health Act of 1970, OSHA's role is to ensure safe and healthy working conditions for working men and women by authorizing the enforcement of the standards developed under the act; by assisting and encouraging states in their efforts to ensure such conditions; and by providing for information, research, education, and training in the field of occupational safety and health (Occupational Safety and Health Act of 1970). The act essentially requires that employees provide a safe work environment. In the construction and design industries, this includes a broad range of issues, from safety devices required by construction workers to the design requirements for toilet facilities. As with all of the codes, standards, and regulations noted herein, OSHA regulations demand a strong understanding by the design team.

It is important to note that The National Institute for Occupational Safety and Health (NIOSH) is a related agency, established by OSHA as a research agency focused on the study of worker safety and health and empowering employers and workers to create safe and healthy workplaces.

7.10.4.3 Americans with Disabilities Act (ADA)

The focus of the Americans with Disabilities Act (ADA) of 1990 is to prohibit discrimination against people with disabilities in employment, transportation, public accommodations, communications, and government activities. Under OSHA regulations, employers are responsible for providing a safe and healthful workplace. It becomes the design team's effort to enable this safe and healthful workplace.

Of particular importance in regard to the ADA is that it is an act, not a prescriptive code or regulation. Fortunately, the IBC translates many of the aspects of this act into the building code. The difference, however, is most important for the designer and particularly the owner to understand.

Title I of the ADA prohibits state and local governments, private employers, employment agencies, and labor unions with 15 or more employees from discriminating against qualified individuals with disabilities during employment application procedures, hiring, firing, compensation, advancement, training, and other terms, conditions, and privileges of employment (Americans with Disabilities Act of 1990). Built responses to the act include such elements as the maximum slope of a walkway, toilet room accessibility, and tactile and Braille signage. It is oftentimes a sticking point with cleanroom project owners, as the act has been interpreted to require access to cleanrooms through the PALs requiring unencumbered access across the bench. This is another issue that needs to be explored early in the design process.

To help the designer understand, as defined in the act (Americans with Disabilities Act of 1990), an individual with a disability is a person who

- has a physical or mental impairment that substantially limits one or more major life activities or
- has a record of such an impairment or is regarded as having such an impairment and
- can, with or without reasonable accommodation, perform the essential functions of the job in question.

Reasonable accommodation may include but is not limited to the following (Americans with Disabilities Act of 1990):

- Making existing facilities used by employees readily accessible to and usable by persons with disabilities
- Restructuring jobs, modifying work schedules, or reassignment to a vacant position
- Acquiring or modifying equipment or devices; adjusting or modifying examinations, training materials, or policies; and providing qualified readers or interpreters

Employers are required to make reasonable accommodations for individuals' known disabilities if the accommodations do not impose "undue hardship" on the employer's business operation. *Undue hardship* is considered to be any action that is significantly difficult or significantly expensive when considered in light of the employer's size, financial resources, and operational nature and structure. Employers are not required to lower production or quality standards to make accommodations, and they are not obligated to provide personal items needed by the individuals, such as glasses or hearing aids (Americans with Disabilities Act of 1990).

These definitions are important, as persons with disabilities are often thought of as solely those with mobility type impairments.

7.10.4.4 U.S. Environmental Protection Agency (EPA)

When Congress writes an environmental law, the government is charged with implementing it by writing regulations. Often, the U.S. Environmental Protection Agency (EPA) sets national standards that states enforce through their own regulations. If jurisdictions fail to meet the national standards, the EPA can support them. Compliance and enforcement are integral parts of environmental protection. While compliance with the

nation's environmental laws is the main objective, enforcement is an important tool for encouraging governments, businesses, and other companies to meet their environmental obligations.

The EPA's Office of Enforcement and Compliance Assurance (OECA) is responsible for enforcement and also provides compliance assistance to areas with the most environmental benefit or reduced risk to human health. Actions of enforcement and compliance are focused on environmental problems and noncompliance patterns instead of provisions of single statutes.

The following laws and executive orders most affecting the design, construction, and operation of companies help to protect both the environment and human health:

- Clean Air Act (CAA)
- Energy Policy Act
- Federal Food, Drug, and Cosmetic Act (FFDCA)
- Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)
- Clean Water Act (CWA) and Federal Water Pollution Control Amendments
- National Environmental Policy Act (NEPA)
- Pollution Prevention Act (PPA)

7.10.4.5 *National Electrical Code* (NEC)

The *National Electrical Code*® (NEC), also known as *NFPA 70* (NFPA 2017), is an international standard developed by NFPA and used in the United States and in other countries throughout the world. For the design and construction industries' interests, this code covers the installation of electrical conductors, equipment, and raceways; signaling and communications conductors, equipment, and raceways; and optical fiber cables and raceways for public and private premises, including buildings, structures, yards, lots, parking lots, and industrial substations. In many respects, the NEC is the Bible of electrical engineers and contractors.

7.10.4.6 Zoning Laws and Ordinances

Zoning laws and ordinances, sometimes referred to as *land use regulations*, are found in virtually every municipality in the United States as well as in most other countries. These laws may be use-based (regulating the uses to which land may be put, i.e., residential, manufacturing, and the like) or they may directly regulate building height, lot coverage, building setback, density of development, greenspace and landscape requirements, parking, impervious area limitations, and other aspects of property use. They are effectively local ordinances enforced by the AHJ. Though the specifics of how individual planning systems incorporate zoning into their regulations vary, the intent is always similar. The review and analysis of these laws is one of the first steps that the designer needs to take to ensure the building type fits into the local economic-geographic structure. The ICC publishes the *International Zoning Code*® (ICC 2014j) for use and adoption by code officials to promote uniformity and consistency in zoning.

7.10.5 GLOBAL AND INDUSTRY REGULATORY BODIES

7.10.5.1 European Union (EU)

The European Union (EU), a political and economic union consisting of 28 European countries, aims to ensure the free movement of people, goods, services, and capital within the internal market; enact legislation in justice and home affairs; and maintain common policies on trade, agriculture, fisheries, and regional development. In regard to cleanroom industries, the EU coordinates regulations among its member countries in regard to the

semiconductor, pharmaceutical, biotechnology, health care, and food processing industries.

The focus through the Public Health sector of the European Commission (EC), which is the executive body of the EU, is to protect human health and support the modernization of Europe's health systems. Before being made available on the EU market, all medicinal products for human use have to be authorized either at the member state or the community level. Special rules exist for the authorization of medicinal products for pediatric use, medicines for treating rare diseases, traditional herbal medicines, vaccines, and clinical trials.

Furthermore, to ensure that medicinal products are consistently produced and controlled against the quality standards appropriate to their intended use, the EU has set quality standards and Good Manufacturing Practice (GMP) guidelines, with compliance to these guidelines being mandatory within the European Economic Area.

The EMA was established to help the EU ensure the highest possible level of public health protection. The primary responsibility of the EMA is coordinating the scientific evaluation of medicinal products for safety, quality, and efficacy. For additional information on EMA, see Section 19.1.3.2 of Chapter 19.

7.10.5.2 The British Standards Institution (BSI)

The standards of The British Standards Institution (BSI) are codes similar in many ways to the ICC codes but at the same time are different. A designer's knowledge of the ICC codes does not necessarily extend to an understanding of the British standards. These standards have been developed as best practices to improve safety, efficiency, and interoperability and, although not pertinent to facility design, to facilitate trade within its jurisdiction.

BSI standards are wide ranging, covering every area of life—from technical guidelines for a variety of industrial production processes to specifications for entities in the service sector and in systems for the management of, for example, closed-circuit television systems, customer loyalty, and even skate parks. More importantly to this discussion, BSI also produces standards for cleanroom industries.

7.10.5.3 Health Products Regulatory Authority (HPRA)

Although it is specific to the pharmaceutical and biotechnology industries, the Health Products Regulatory Authority (HPRA) (formerly Irish Medicines Board [IMB]) has as its fundamental role the protection and enhancement of public and animal health through regulation of human and veterinary medicines, medical devices, and other health products. The HPRA regulates clinical trials and monitors and inspects products to ensure their safety and efficacy.

7.10.5.4 ASTM International

ASTM International (formerly American Society for Testing and Materials) is another one of the largest voluntary standards development organizations in the world and a major source for technical standards for materials, products, systems, and services. ASTM International has developed standards across many industries, from concrete, steel (including stainless steel, used throughout cleanrooms), and floor finishes to essentially any material found in the construction industry. More germane to the subject industries, ASTM International's cleanroom application standards cover design, process control, performance, and quality acceptance/assurance tests as well as, for example, the manufacture of pharmaceutical products and medical devices. A review of any construction specification will reveal the breath and extent of these standards.

7.10.5.5 American National Standards Institute (ANSI)

Although a private-sector voluntary organization, American National Standards Institute (ANSI) helps ensure the safety and health of consumers and the protection of the environment.

As noted in their literature, ANSI

> oversees the creation, promulgation and use of thousands of norms and guidelines that directly impact businesses in nearly every sector: from acoustical devices to construction equipment, from dairy and livestock production to energy distribution, and many more. ANSI is also actively engaged in accreditation—assessing the competence of organizations determining conformance to standards. (ANSI 2017)

ANSI is the official U.S. representative to the International Organization for Standardization (ISO) and, via the U.S. National Committee, the International Electrotechnical Commission (IEC). ANSI is also a member of the International Accreditation Forum (IAF). Regionally, ANSI is the U.S. member of the Pacific Area Standards Congress (PASC) and the Pan American Standards Commission (COPANT). ANSI is also a member of the Pacific Accreditation Cooperation (PAC) and, via the ANSI-ASQ National Accreditation Board (ANAB), a member of the Inter American Accreditation Cooperation (IAAC).

ANSI norms and guidelines are incorporated into ICC model codes as the ICC deems applicable.

7.10.5.6 International Organization for Standardization (ISO)

International Organization for Standardization (ISO) is a network of national standards institutes in over 75% of the world's countries and is the world's largest developer and publisher of international standards, coordinated in Geneva, Switzerland. A nongovernmental organization, ISO is focused on bridging the private and public sectors. Many member institutes are mandated by their countries' governments or are part of the countries' governmental structure. Some members, however, are in the private sector and have been established by national partnerships of industry associations. The intent behind ISO is to enable a consensus on solutions that meet both business requirements and the broader needs of society and ensure product and service quality, safety, reliability, efficiency, environmental friendliness, and interchangeability at an economical cost.

Primary attributes of ISO standards are the enabling of the development, manufacturing, and supply of products and services more efficiently, safely, and cleaner; providing governments with a technical base for legislation covering health, safety, and the environment; and assessing conformity and the safeguarding of consumers of products and services.

7.10.5.7 Industry Organizations

In addition to those entities noted previously, many industry organizations also play a significant role in the design and construction of facilities and the manufacture of products. The caveat remains: their codes and standards are not applicable unless adopted into law by the AHJ. Owners, however, at their discretion, may elect to use them as best practices, and prudently do so. The ICC codes heavily reference the publications of many of these entities in whole or in part, incorporating them into the codes themselves. A partial listing of commonly cited industry organizations follows:

- Associations
  - National Electrical Contractors Association (NECA)
  - National Electrical Manufacturers Association (NEMA)

    - National Fire Protection Association (NFPA)
    - Sheet Metal and Air Conditioning Contractors' National Association (SMACNA)
- Institutes
    - American Concrete Institute (ACI)
    - American Institute of Steel Construction (AISC)
    - American National Standards Institute (ANSI)
    - The Construction Specifications Institute (CSI)
    - Institute of Electrical and Electronic Engineers (IEEE)
    - National Institute of Standards and Technology (NIST)
- Laboratories
    - Intertek
    - Underwriters Laboratories (UL)
- Societies
    - ASHRAE
    - The American Society of Mechanical Engineers (ASME)
    - American Welding Society (AWS)
    - ASTM International
    - Illuminating Engineering Society of North America (IES)
    - International Society for Pharmaceutical Engineering (ISPE)

The key to building codes, standards, and regulations is to understand that these laws and their references are written and enforced to safeguard life or property. Interpretation is often required, with the final interpretation the responsibility of the AHJ, owner, or A/E (depending on the code or standard). Execution is the responsibility of the design team. Because of the complexity of the many codes and regulations, experts in the field should be consulted. Most important is early review and confirmation with the AHJ (local authorities such as those responsible for zoning, building, and fire; insurance underwriters, the FDA, and the like). Follow-through is equally important. There are many lessons learned with respect to not meeting with the AHJ and adhering to the codes prescribed by that entity, and they are not to be ignored. Peer reviews are an excellent method to give the design team and the owner assurance that the product produced is going to be able to perform as anticipated. A good reference guide to building codes is *Building Codes Illustrated: A Guide to Understanding the 2015 International Building Code*® (Ching and Winkel 2016). Another is *2015 International Building Code Illustrated Handbook* (ICC 2015a). And certainly, the *2015 International Code Interpretations* (ICC 2015b).

7.10.6 ADDITIONAL DESIGN CONSIDERATIONS

7.10.6.1 Sustainability

As part of an ever-mounting drive to address sustainability early in the design process, U.S. Green Building Council (USGBC) and Green Business Certification Inc. (GBCI) are two of several entities leading the charge into the investigation and determination of cost-effective sustainable systems that can be integrated into the design at the start of a project and carried out throughout the project life. As defined by many, materials are to be considered "cradle to cradle," that is, designed for continuous recovery and reuse (McDonough and Braungart 2002). Through the use of these groups' programs, various levels of certification can be attained that connote the depth to which sustainability is addressed in a facility. USGBC's Leadership in Energy and Environmental Design® (LEED®) Green Building Rating System (USGBC 2017) provides four categories of cer-

tification: certified, silver, gold, and platinum. The focus, however, is sustainability on both a local and an international scale. ICC has published a code on sustainable construction, *International Green Construction Code*® (IgCC; ICC 2014f), that bears consideration even if not adopted by the AHJ.

7.10.6.2 Risk

Risk is a topic all owners consider in the development of a product and the facility to support the manufacture of that product. It is particularly important in the high-value industries discussed in this book. Some corporations are self-insured and have risk and fire groups to support the understanding and mitigation of risks. There are also independent companies to support owners in this regard:

- One of the leading independent companies providing guidance on mitigating risks is FM Global, which provides engineering-driven underwriting and risk management solutions, commercial and industrial property insurance, property loss prevention research, and claims handling. They offer analysis of specific risks with a focus on loss prevention, generally through data sheets, include general construction (firewalls, roofs, air conditioning, and ventilating systems, etc.), fire protection systems, boilers, mechanical equipment, and more. The data sheets are well studied and definitive in describing the means and methods.
- Similarly, XL Catlin is a risk management company defining a client's property risk potential, creating exposure strategies, and implementing and managing property risk mitigation strategies.
- Industrial Risk Insurers (formerly FIA Factory Insurance Association) is composed of a group of insurance companies and is concerned with all phases of fire protection and other risks insured against by its members. The company provides reinsurance and insurance.

As important as it is to understand the services that these groups or agencies provide, it is just as important to understand what they do not provide. Their focus is property loss prevention—not life safety, not product safety, not product integrity. Second, it is import to understand that clients pay for the protection offered, in the same way they pay for design services. That is to say, if the client does not find the advice of value, they do not need to implement the recommendations. With no disrespect to the importance of the services and expertise, clients may elect to accept a degree of risk, with but a potential increase in their insurance premiums. The need, however, is that these entities be an intrinsic part of the design team. Their function is most important to the success of the client.

Before engaging any of these companies, the first step for the architect or engineer team is to understand with which company the client contracts, if any (many large companies are self-insured with in-house risk management resources). Many owners welcome the expertise that designers bring to the risk management forum, whereas others maintain a very close relationship through their own risk groups and bring the design direction to the A/E. Whatever the strategy, it is most important that these companies have a clear understanding of the project, including such things as the quantity and use of hazardous materials and the designer's proposed engineering solutions for both physical construction and fire detection and suppression.

It is very common that the risk insurer's recommendations exceed the building code requirements. Equally important is understanding that whatever the recommendations the client accepts, they need to be reconciled with the pertinent building code requirements and are best reviewed with the AHJ. Experience tells that full transparency and cooperation are the best practice.

7.10.6.3 Safety and Emergency Response

All companies and facilities are subject to emergency situations requiring the removal or evacuation of personnel. Whether the condition is caused by injury or other physical impairment, a means of exit from the building is required. Building codes define the need for exiting in the case of emergency. These requirements include exit path widths, distances to exits, and areas of refuge. Another element to consider is emergency vehicle access to the building, both for ambulance access and fire department access. Elevators for personnel use are required to be sized for stretchers (as defined in the *Safety Code for Elevators and Escalators* [ASME 2016]).

Although not a code requirement, a provision that should be given consideration is the inclusion of view panels and view windows into every room. This enables personnel outside of any room to be able to see if an operator has fallen or is in need of aid. This is particularly important because many rooms, particularly cleanrooms, are occupied and operated by a single person. An additional benefit is that personnel can observe the operation of an area without gowning and entering the area. As doors are often interlocked, emergency overrides are required. These, in turn, must comply with building code and ADA accessibility requirements. (Note that some jurisdictions do not allow for the use of door interlocks as an overriding life safety consideration.)

7.10.7 ADDITIONAL CODES, STANDARDS, REGULATIONS, AND GUIDES APPLICABLE TO CLEANROOM DESIGN

In addition to the codes, standards, and regulations previously discussed in this section, additional guidelines might be useful for cleanroom design. In general, especially in the United States, the following codes, standards, regulations, and guides may need to be reviewed before cleanroom design efforts are initiated. Familiarization with these documents will lead the design team to successful projects. Additional resources are listed in the Bibliography section.

- International Code Council (ICC), USA
  - *International Building Code*®
  - *International Existing Building Code*®
  - *International Fuel Gas Code*®
  - *International Mechanical Code*®
  - *International Plumbing Code*®
  - *International Property Maintenance Code*®
  - *International Fire Code*®
  - *International Energy Conservation Code*®
- U.S. Food and Drug Administration (FDA), USA
  - *Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*
  - *Current Good Manufacturing Practice for Finished Pharmaceuticals*
- International Organization for Standardization (ISO), Switzerland
  - Standard 14644, *Cleanrooms and Associated Controlled Environments*
    - *Part 1: Classification of Air Cleanliness by Particle Concentration*
    - *Part 2: Monitoring to Provide Evidence of Cleanroom Performance Related to Air Cleanliness by Particle Concentration*
    - *Part 3: Test Methods*
    - *Part 4: Design, Construction and Start-Up*
    - *Part 5: Operations*

        - *Part 7: Separative Devices (Clean Air Hoods, Gloveboxes, Isolators and Mini-Environments)*
        - *Part 8: Classification of Air Cleanliness by Chemical Concentration (ACC)*
        - *Part 9: Classification of Surface Cleanliness by Particle Concentration*
        - *Part 10: Classification of Surface Cleanliness by Chemical Concentration*
        - *Part 12: Specifications for Monitoring Air Cleanliness by Nanoscale Particle Concentration (Draft International Standard, DIS)*
        - *Part 13: Cleaning of Surfaces to Achieve Defined Levels of Cleanliness in Terms of Particle and Chemical Classifications*
        - *Part 14: Assessment of Suitability for Use of Equipment by Airborne Particle Concentration*
    - Standard 14698, *Cleanrooms and Associated Controlled Environments—Biocontamination Control*
        - *Part 1: General Principles and Methods*
        - *Part 2: Evaluation and Interpretation of Biocontamination Data*
- ASHRAE, USA
    - *ASHRAE Handbook—HVAC Applications*, Chapter 18, "Clean Spaces"
    - ASHRAE Standard 52.1-1992, *Gravimetric and Dust-Spot Procedures for Testing Air-Cleaning Devices Used in General Ventilation for Removing Particulate Matter*
    - ANSI/ASHRAE Standard 52.2-2017, *Method of Testing General Ventilation Air-Cleaning Devices for Removal Efficiency by Particle Size*
    - ANSI/ASHRAE/ASHE Standard 170, *Ventilation of Health Care Facilities*
- Institute of Environmental Sciences and Technology (IEST), USA
    - IEST-RP-CC001, *HEPA and ULPA Filters*
    - IEST-RP-CC012, *Considerations in Cleanroom Design*
    - IEST-RP-CC006, *Testing Cleanrooms*
    - IEST-RP-CC034, *HEPA and ULPA Filter Leak Tests*
- International Society for Pharmaceutical Engineering (ISPE), USA
    - *ISPE Good Practice Guide: Quality Laboratory Facilities*
    - *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)*
    - *Sterile Product Manufacturing Facilities* (Volume 3 of *Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities*)
    - *Commissioning and Qualification* (Volume 5 of *Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities*)
- National Environmental Balancing Bureau (NEBB), USA
    - *Procedural Standards for Certified Testing of Cleanrooms*
- National Fire Protection Association (NFPA), USA
    - *NFPA 318: Standard for the Protection of Semiconductor fabrication Facilities*
    - *NFPA 45: Standard on Fire Protection for Laboratories Using Chemicals*
- Semiconductor Equipment and Materials International (SEMI), USA
    - SEMI F21-1102, *Classification of Airborne Molecular Contaminant Levels in Clean Environments*
    - SEMI E51-0200, *Guide for Typical Facilities Services and Termination Matrix*

7.11 CONSTRUCTION PROTOCOL

The cleanroom construction process should include a series of contamination control procedures designed to prevent or minimize the contamination that will be exposed to the cleanroom airflow. Construction is a dirt-generating activity that conflicts with contamination control goals. Conventional construction methods must be modified to accommodate strict cleanroom requirements. General cleaning should be performed on a regular basis. Areas adjacent to the cleanroom should be cleaned daily to prevent the accumulation of debris and contaminants that may migrate into the cleanroom. The cleanroom should be isolated from the normal construction activities by physical barriers and should be kept at positive pressure relative to its surroundings.

Different protocol levels dictate required cleanliness and personnel work habits at each stage, and they may be used simultaneously in different areas throughout the life of the construction, from the original site conditions to the completion of the final desired cleanliness level of the clean space. Protocol levels are often prepared by cleanroom design professionals and executed by the general contractor in the field. Prior to construction, the design professionals and contractors should agree on the allowable materials, methods, gowning, and behavior at each protocol level.

Techniques for this concept are generally noted as *build-clean protocols* and are used in essentially every type of cleanroom facility, all focused on ensuring an environment for the safe and effective manufacturing of products (i.e., semiconductor, life science, and food processing facilities) and for health care facilities (hospitals).

Described in brief below, build-clean protocols are often incorporated into the owner's standard operating procedures (SOPs), the A/E's project manual, and/or the contractor's project manual. Topics include personnel conduct requirements (eating, drinking, tobacco—prohibited activities), personnel entry into the project area (be it site and/or building), contamination control, soils exposure and control, violation processes, safety requirements, gowning and personal protective equipment (PPE) requirements, and pest control. Each project may need unique procedures in each of these areas.

Proper construction techniques for cleanrooms focus on the minimization of dirt and debris at every phase of the work. Initially, or after the demolition phase for a retrofit, the work area is cleaned and kept clean during and in between work periods as much as possible.

After walls are completed, various dusty construction activities are performed using localized HEPA-filtered vacuums (HEPA-vacs) to contain the dust as it is produced. If prefabricated cleanroom modular panels are not used for wall and ceiling construction, the installation of gypsum wallboard uses a wet sanding process for dust-free work. Similar techniques are used for the remaining work to avoid the introduction of debris as the project proceeds. When the room finishes and fixtures are completed with all appropriate construction inspections, a thorough cleaning is performed prior to the HVAC system start-up. At this stage, it is critical to completely seal all potential holes, cracks, or openings of any kind that may be a pathway for contamination to enter the controlled environment.

Lights, electrical switches, outlets, fire sprinklers with gaskets and flush covers, fire alarm devices, access doors, mirrors, and door frames must be caulked and gasketed wherever possible. If these devices penetrate fire-rated assemblies, they must be sealed to maintain the same rating as the wall, floor, or ceiling assembly. Casework, shelves, tables, and other fixed equipment should be fixed in place and sealed at the walls and ceilings. The tops of cabinets and equipment should be significantly sloped or sealed to the ceiling to avoid particulate accumulation. Many times the action of opening or closing doors to

tightly sealed cleanrooms contributes to the sporadic intrusion of contaminants that are difficult to identify. Doors and windows should be set flush to the adjacent wall. Exposed piping must be offset from the wall. All materials must be tested to be compatible with the project cleaning agents, some of which are highly caustic. Smoke studies aid in finding perimeter leaks during cleanroom commissioning activities. In higher-classification cleanrooms, sliding doors are often preferred because they minimize the environmental challenges of room pressurization swings due to the piston action of swinging doors. The use of sliding doors in some cleanroom types, however, brings its own problems, as sliding doors are currently more difficult to clean.

Both ductwork and piping may be prefabricated in shops using build-clean protocols, inclusive of the ductwork and piping ends being sealed in the shop cleanroom and the materials wrapped to protect both the inside and outside prior to delivery to the site. After completion of the HVAC system installation and commissioning but prior to the installation of HEPA filters, the air supply system is operated briefly to remove any remaining dust and debris. HEPA filters are installed after shutting off the HVAC system and cleaning the interior of the HEPA filter housings. After the proper air balancing is done for final airflow quantities and to make the room positively pressurized, the rooms are cleaned again and sterilized with cleaning agents covering the floors, walls, ceilings, and all surfaces of fixed equipment. In a similar manner, piping systems are flushed to eliminate dust and debris.

Once the HEPA-filtered air supply is started, usually with positive room pressurization, it is beneficial to adopt gowning, equipment, and room-cleaning protocols for all personnel (including construction workers, inspectors, and the like). The remaining movable equipment and fixtures are cleaned thoroughly in an air lock before moving them in to place. An additional challenge is to maintain room cleanliness during the installation of movable equipment, as there may be cracks and crevices, including on the equipment underside, that can hide particulates and release them slowly as air flows around them.

7.12 PROJECT SIZE, BUDGET, AND SCHEDULE

During the conceptual design stage, the design process should carefully and clearly identify the basic needs of the project, such as building size, activities and functionalities, available budget, and intended schedule, as well as the engineering requirements, such as cleanliness levels, airflow requirements, system types, and the like. The project design team should prepare professional solutions to satisfy the user's requirements and provide design progress reviews at scheduled intervals with the user groups. Greater design success is attained when those user groups include not only the design team but also the operators and maintenance personnel. Basic design concepts, criteria, requirements, and performances to be achieved should be agreed upon between the cleanroom designer and the user groups and documented as a part of QA.

Cleanroom facility design should align with the owner's available budget. Cleanroom construction projects are typically much more expensive than commercial buildings of the same size; therefore, it is very important to minimize design changes during the construction phase that could be costly. Due to the complexity of cleanroom projects, an initial cost estimate should include contingencies to cover unexpected though necessary requirements and their resulting costs discovered later in the design or construction phases. It is prudent that the designer also provide multiple design alternatives or options with associated cost differences so that the owner and users can make an educated deci-

sion in hopes of reducing chances of mind change later on. The construction schedule should be realistic, especially when customized equipment and parts or new technologies, which typically require long lead times, are incorporated into the design.

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8

Basic Requirements

8.1 AIRFLOW PATTERNS

Airflow patterns or streamlines in cleanrooms are strongly influenced by air supply and return or exhaust configurations, their flow rates, personnel and material traffic paths, and process equipment layout. The first step of good cleanroom design is to select the air pattern configurations. Final air pattern design selection is influenced by the space available for installing air pattern control equipment (i.e., air handlers, clean workstations, minienvironments, process exhaust, etc.), the layout of process equipment, the cleanliness level required by the user, and the project's financial considerations.

Cleanroom airflow patterns can be categorized as either unidirectional or nonunidirectional; *mixed airflow* is the term typically used when a combination of the two patterns is used. Airflow patterns for cleanrooms of ISO Class 5 or cleaner are typically unidirectional, while for cleanrooms of ISO Class 6 (ISO 2015) or less-clean classes, nonunidirectional and mixed flow are more typical.

For all three air patterns, if the application is complex, unique, or critical, during the design phase mock-ups of the cleanroom may help designers avoid turbulent zones and countercurrents. Air streamlines can be made visible in the mock-ups with the use of nitrogen vapor fogs, smoke, or neutral-buoyancy helium-filled soap bubbles.

8.1.1 UNIDIRECTIONAL FLOW (HORIZONTAL OR VERTICAL)

Unidirectional airflow may be in either a horizontal or a vertical flow pattern (see Figure 8.1). The goal is to maintain the airstream as straight and parallel as possible and to minimize air turbulence inside a cleanroom. Unidirectional flow typically uses higher

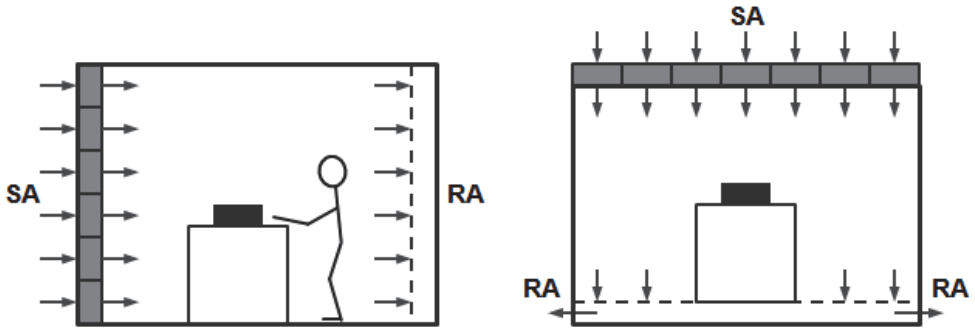

Figure 8.1 Unidirectional Flow (Horizontal and Vertical)

air velocities, air change rates, and high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filter densities (coverage) on ceilings or on walls than nonunidirectional or mixed flows; therefore, unidirectional flow typically produces better air cleanliness. In either a horizontal or a vertical design, the important element is ensuring that the airflow pattern is disrupted as little as possible inside the cleanroom, particularly around the critical process zones.

In a horizontal design, air flows horizontally from a full wall of filters through sidewall returns located in the opposite wall. In a vertical design, clean air is pushed down from HEPA/ULPA filters located in the ceiling; the air then typically carries contaminants generated from people and processes inside the cleanroom, and this contaminated air is further drawn into perforated raised-floor panels. The rule for selecting either a horizontal or a vertical pattern is that vertically distributed processes require horizontal airflow and horizontally distributed processes require vertical airflow. For example, horizontal airflow can be used where operations with strict cleanliness requirements occur close to the wall of filters and operations with lower cleanliness requirements happen farther downstream of the filters. In some industries, such as the pharmaceutical industry, perforated flooring is generally not viable; instead, solid floors and low-level wall returns are most often used.

Major places of particle generation typically are not at HEPA/ULPA filters (unless there is a leak) but at the working and processing height where people, processes, equipment, and furniture emit particles. Therefore, the areas immediately under the HEPA/ULPA filters offer the best air cleanliness and air becomes less clean at lower elevations.

Although personnel, workstations, and equipment are unavoidable obstacles for air streamlines' distortion, flow streamlines for empty cleanrooms should nevertheless be designed and arranged with minimum flow disruptions. Turbulent zones may have countercurrents with no flow at all (stagnancy), reverse flow, or high velocity. When countercurrents produce stagnant zones, small particles may cluster there and settle onto surfaces or product. Countercurrents may also lift particles from contaminated surfaces and deposit these particles on other surfaces or product.

8.1.2 NONUNIDIRECTIONAL FLOW

Nonunidirectional airflow has either nonparallel flow or multiple-pass circulating characteristics, with variations based on the locations of air filters and supply air inlets and outlets (see Figure 8.2). Although airflow parallelism deteriorates much more than in unidirectional flow, if properly designed, nonunidirectional airflow can provide satisfactory contamination control for cleanliness levels of ISO Classes 6 through 8 (ISO 2015).

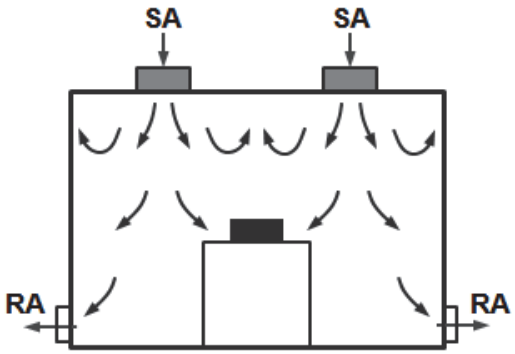

Figure 8.2 Nonunidirectional Flow

In this flow pattern, air can be supplied from HEPA filters located in various positions in the ceiling and returned through low sidewall returns. Ceiling-mounted HEPA filters may be distributed at equal or near-equal intervals throughout the cleanroom and grouped such over critical process areas. The use of HEPA filters at the ceiling without diffusers provides a more directed flow and therefore cleaner air underneath; however, air cleanliness away from the area under the HEPA filters will be worse.

HEPA filters can also be placed at a remote location, such as at the discharge side of an air-handling unit (AHU) or a recirculation fan unit (RFU), which provides HEPA-filtered air directly to the cleanroom, or they can be placed inside an enlarged HEPA filter-bank downstream and separate from the AHU or RFU with lower face velocity through the filters. In both of these cases, air diffusers at the ceiling can be used, and the maintenance and replacement of HEPA filters can be achieved in a mechanical room instead of at the cleanroom ceiling. Supply air ducts typically carry positive pressure, and it is less likely that dirty particles may be drawn into a supply duct. However, special precautions should be taken to avoid contamination introduction between the HEPA filters and the cleanroom.

A ceiling HEPA module with an integral diffuser can also be used to provide well-mixed conditions throughout the cleanroom. Because room air cleanliness (or classification) is determined by the average particle concentration measured throughout the room, typically in equal spacing, it is hard to say that room average concentration will be lower or higher for HEPA filters with or without a diffuser. Care should be taken to distribute the return air grilles to minimize dead zones within the cleanroom.

For nonunidirectional flow, Section 8.4.8 discusses that the benefit of using ULPA filters for ISO Classes 5 through 8 is not significant, because room particle concentration is not reduced much and typically pressure loss across ULPA filters is higher than across HEPA filters.

8.1.3 MIXED FLOW

As shown in Figure 8.3, mixed flow combines unidirectional and nonunidirectional airflow in the same room; separative enclosures such as unidirectional cabinets (clean benches), isolators, or minienvironments can be used to enhance the air cleanliness for more critical zones.

8.2 CONTAMINATION CONTROLS IN ROOM AIRFLOW PATH DESIGN

Cleanroom airflow pattern design is often associated with airflow path design in a larger scope when contamination control and contaminant removal are also requirements. Table 8.1 lists some common concerns and typical treatments.

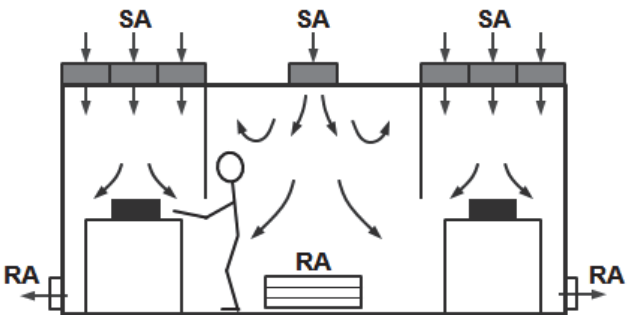

Figure 8.3
Mixed Flow

Table 8.1 Contamination Control Treatment

Common Concern	Typical Treatment	Airflow Path Sequence
Product protection from particle contamination by personnel or process	Keep personnel and process downstream of product and away from up-stream	HEPA-filtered clean air for 1. product, 2. process area, and 3. personnel.
Personnel protection from process associated with harmful contaminants	Position personnel upstream and provide segregation to allow personnel to have indirect contact with process when needed	HEPA-filtered clean air for 4. personnel, 5. process area inside isolator or glove box, and 6. process exhaust.
Remove harmful contaminants from cleanroom to protect room occupants	Provide exhaust air to capture and remove contaminated air by particles, gases, chemical fumes, or microbes, and use filtered clean air supplied to the room as makeup air to offset the exhaust air	HEPA-filtered clean air for 7. personnel, 8. process area, and 9. room exhaust.

8.3 CLEANROOM HVAC SYSTEM CONFIGURATION

The HVAC system configuration for commercial or general-purpose industrial buildings is mainly designed to meet the indoor space's heating and cooling loads, or more specifically to achieve the space's temperature and humidity requirements. For cleanroom facilities, however, the HVAC configuration should be prepared such that it not only meets heating and cooling loads but also satisfies space air cleanliness requirements with the very same HVAC system. Satisfying air cleanliness has been traditionally accomplished by using high airflow rates to dilute a cleanroom's airborne particle concentration, which represents the room's air cleanliness. The challenge is how to configure an HVAC system when the airflow rate required by dilution is significantly higher than that required by heating and cooling loads.

Based on the dilution intensity, typically a cleaner-class cleanroom requires a higher airflow rate (cfm [L/s]), which can also be calculated either in air changes per hour (ACH, ach) or average room velocity (fpm or m/s). For example, commercial buildings may have a "flow rate and cooling ratio" at 250–600 cfm (120–280 L/s) per ton, an ISO Class 7 cleanroom may have a ratio at 2500 cfm (1200 L/s) per ton, and an ISO Class 3 cleanroom may require 25,000 cfm (12000 L/s) per ton. A typical AHU is commonly designed and manufactured at around 400 cfm (200 L/s) per ton, which can be stretched to a possible range of 300–600 cfm (140–280 L/s) per ton. Therefore, it is clear that a single AHU system in the later cases (ISO 7 and 3 cleanrooms) is not capable of achieving both dilution and cooling objectives.

Cleanroom design engineers commonly use multiple AHUs and RFUs to handle this challenge based on cleanliness classes. Figures 8.4 through 8.7 illustrate the typical HVAC configurations of single primary AHU, primary RFU with secondary AHU, primary fan filter units (FFUs) with secondary AHU, and primary RFU with secondary AHU and tertiary makeup AHU.

Table 8.2 provides a general selection guideline for choosing cleanroom HVAC system configurations shown in Figures 8.4 through 8.7. Engineers can first calculate the airflow rate required to meet the heating/cooling load and then calculate the airflow rate required to achieve air cleanliness, then simply use the flow ratio to determine which configuration is the most suitable for the design objectives. The design engineer can select a

Figure 8.4
Single AHU
(Type 1)

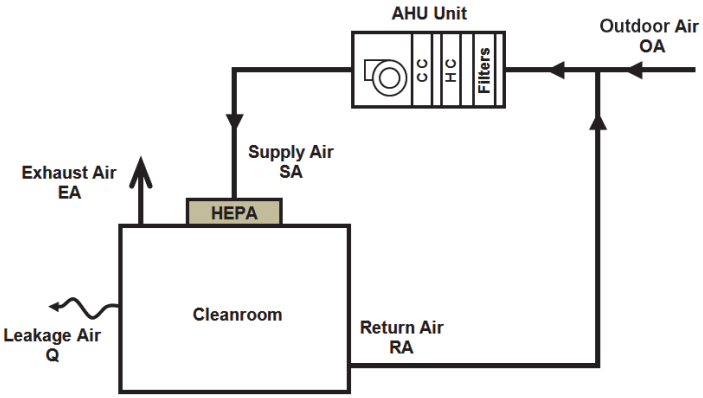

Figure 8.5
Primary RFU
with Secondary
AHU (Type 2A)

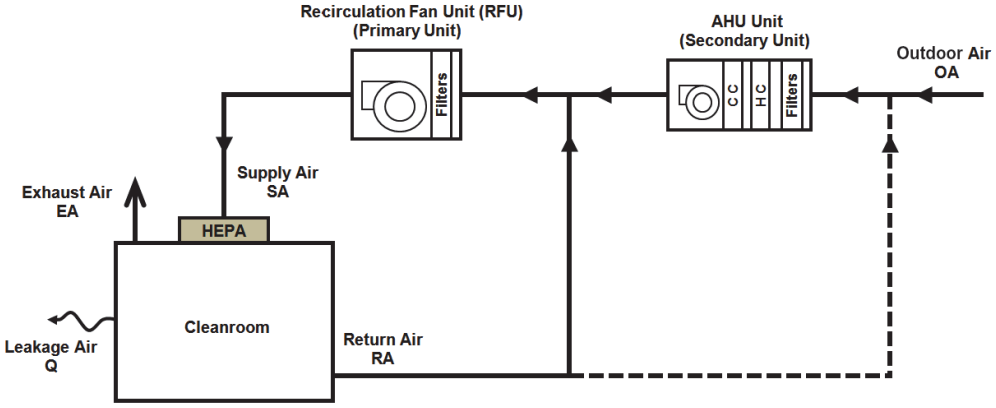

Figure 8.6
Primary
FFUs with
Secondary AHU
(Type 2B)

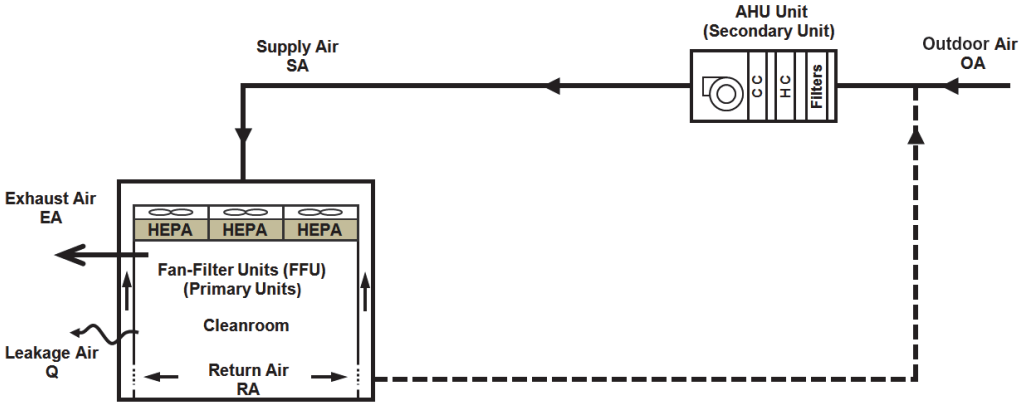

Figure 8.7
Primary RFU
with Secondary
AHU and
Tertiary Makeup
AHU (Type 3)

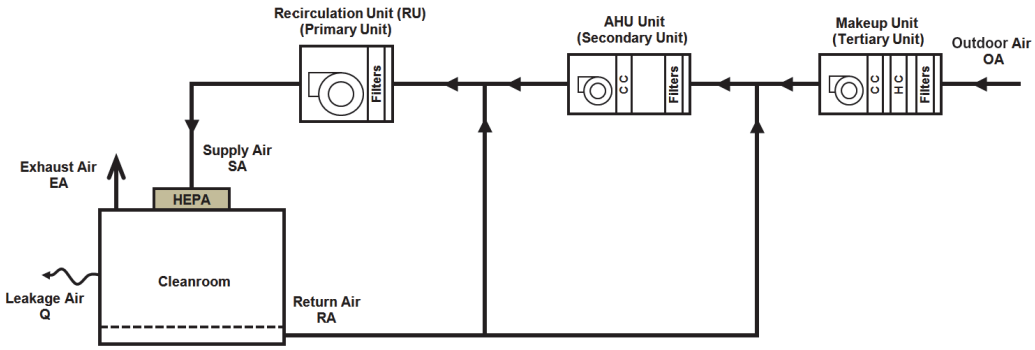

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Table 8.2 Selection of Cleanroom HVAC System Configuration

Type of HVAC Configuration		Typical Application			Referenced Figure
		ISO Class	Airflow Quantity for Room Air Cleanliness and Total Cooling Load	Flow Ratios Between Units	
1	Single AHU	9, 8, 7	AHU to meet both ACH and cooling requirements	n/a	Figure 8.4
2A	Primary RFU and Secondary AHU	7, 6, 5, 4	• AHU mainly to meet cooling requirement • RFU to meet room ACH (or average velocity) requirement	$\frac{\text{Flow rate of RFU}}{\text{Flow rate of AHU}} \geq 4$	Figure 8.5
2B	Primary FFUs and Secondary AHU	7, 6, 5, 4	• AHU mainly to meet cooling requirement • FFUs to meet room ACH (or average velocity) requirement		Figure 8.6
3	Primary RFU, Secondary AHU, and Tertiary Makeup Unit (MU)	4, 3, 2, 1	• Makeup AHU to meet outdoor air, pressurization, and exhaust air compensation requirements • AHU to meet cooling requirement • Makeup AHU to meet room ACH (or average velocity) requirement	$\frac{\text{Flow rate of RFU}}{\text{Flow rate of AHU}} \geq 10$ or $\frac{\text{Flow rate of RFU}}{\text{Flow rate of MU}} \geq 50$	Figure 8.7

configuration with necessary modifications (such as dual return paths) to achieve desired indoor conditions. Airflow streams can be either mixed, diverted, or a sequential combination of both.

Instead of using guesswork for selection of an HVAC configuration, airstream properties (dry- and wet-bulb temperatures, moisture content, flow rate, enthalpy, etc.) need to be calculated and psychometric characteristics can be analyzed to obtain more predictable indoor conditions through computer simulations.

8.3.1 CLEAN DESIGN

Cleanroom interior surfaces and filtered air delivery systems have some impact on final room air cleanliness. The following considerations can contribute to better HVAC system and cleanroom cleanliness:

- Corrosion-resistant interior surfaces inside cleanrooms
- Direct-drive instead of belt-driven fan motors
- Sealed bearings for motors
- Ultraviolet (UV) lights for cooling coils and wetted surfaces
- Antimicrobial coating on cooling coil drain pans

8.3.2 DESIGN FOR REDUNDANCY AND RELIABILITY

Redundancy should be provided at a level that matches the process requirements. Redundancy may be addressed at a component level, such as multiple fans operating in tandem (fan wall), or at the system level with multiple air handlers in parallel operation.

Careful design considerations must be provided all through the design process to minimize or eliminate single points of failure. For example, multiple fans serving one

system may appear to provide redundancy, but if the electrical layout is not designed properly, a single circuit breaker failure may result in an unplanned shutdown.

8.3.3 DESIGN FOR COMMISSIONABLE SYSTEMS

The following items may be considered for system design with future commissioning in mind:

- Critical parameters and operational values monitored and tracked
- Total system power monitored
- Power monitoring of major equipment
- Shutdowns and isolation valves
- Test ports and sensor locations
- Sensor locations selected for stable operation
- Double sensors for stability improvements

8.4 CLEANROOM AIRFLOW RATE DETERMINATION

8.4.1 OVERVIEW

The air supply rate to a cleanroom can be expressed in an absolute volumetric flow rate (cfm [L/s or m^3/min]); however, it is hard to use the absolute rate to compare airflow intensity among cleanrooms when cleanroom size is not included. Therefore, size-neutral relative airflow magnitude is more commonly used.

For unidirectional airflows, air velocity at the filter surface (HEPA filter, ULPA filter, or FFU) is often considered an important criterion. Other times, average air velocity v seems commonly used, which includes the airflow supply rate and room sectional area. The average air velocity for both horizontal and vertical flow patterns is

$$v = \frac{Q}{A} \tag{8.1}$$

where

v = average (either horizontal or vertical) air velocity, fpm (m/min)
Q = supply air, total volumetric airflow rate supplied to room, cfm (m^3/min)
A = wall area (horizontal flow pattern) or floor area (vertical flow pattern), ft^2 (m^2)

For nonunidirectional airflows, it is more common to use air changes rate (ACR), often expressed in air changes per hour (ach):

$$N = \frac{Q}{V} \tag{8.2}$$

where

N = ACR in room, ach
Q = supply air, total volumetric airflow rate supplied to room, ft^3/h (m^3/h)
V = volume of room, ft^3 (m^3)

Note that not all unidirectional-flow cleanrooms are arranged with 100% ceiling coverage of HEPA filters, ULPA filters, or FFUs—some may only have 30% to 90% ceiling filter coverage. In these cases, actual air velocity at a process/operation height could be

much lower than the face velocity at the HEPA/ULPA filters. It has been a long-time misconception that air velocity can be used only for unidirectional flows and ACR can be used only for nonunidirectional flows. In fact, when room dimensions are known and air is supplied from the ceiling, the room average velocity and ACR can be mutually converted as follows, with a similar term for air supplied from the wall where the height of the room is replaced with air traveling the length of the room:

$$N = \frac{60 \cdot Q}{V} = \frac{60 \cdot v \cdot A}{A \cdot H} = \frac{60 \cdot v}{H} \tag{8.3}$$

where

Q = supply airflow rate, fpm (m^3/min)
V = cleanroom volume, ft^3 (m^3)
A = cleanroom floor area, ft^2 (m^2)
v = average vertical velocity, fpm (m/min)
H = cleanroom height, ft (m)
N = ACR in room, ach
60 = number of minutes per hour

8.4.2 CLEANROOM HEIGHT IMPACT ON AIR CHANGES RATE AND AIR VELOCITY DETERMINATIONS

It should be known to cleanroom designers that use of ACH values to compare two cleanrooms with different heights sometimes is meaningless. For example, the aerospace industry uses high-bay cleanrooms for aircraft assembly, which could have 40 to 160 ft (12 to 50 m) room heights. Figure 8.8 shows the relationship between ACH and average vertical air velocity.

8.4.3 CRITICAL CLEAN ZONE IN CLEANROOM

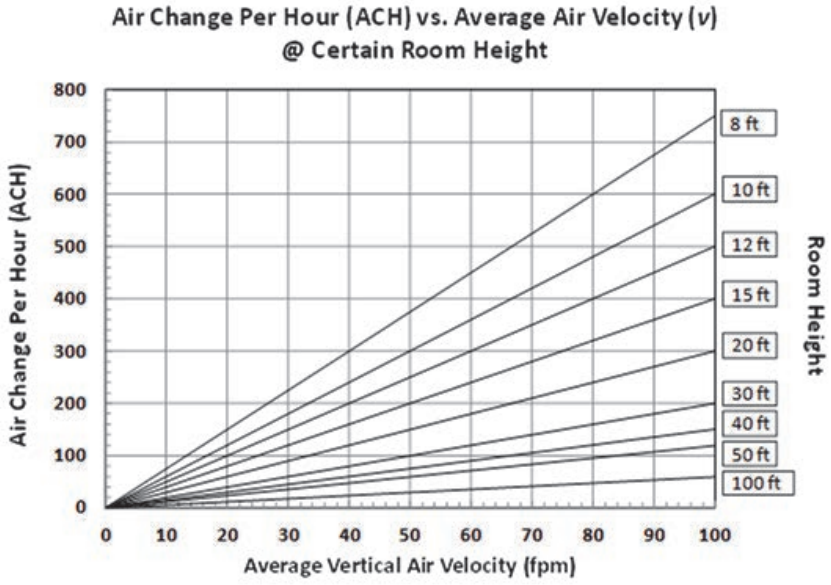
Cleanroom HVAC systems can consume up to 50 times more energy than those used in commercial spaces of the same size. The ACR in cleanrooms is typically higher than that in general-purpose buildings. The airflow rate in cleanrooms needs to meet not only the heating and cooling loads but also the dilution requirement to reduce room particle concentration (Sun 2008a). It is critical to realize that the majority of particles inside a cleanroom are not from HEPA-filtered supply air but are generated inside the cleanroom internally. A super-high air change rate is not typically needed for cooling, heating, or ventilation loads, but mainly for air cleanliness control.

A large cleanroom consumes a lot of energy, and the cleaner the class, the more energy spent. However, quite often not every spot in a cleanroom requires the same cleanliness—only the areas with critical processes or operations need better cleanliness, while the surrounding areas inside the cleanroom can be designed and maintained at a less-clean class in order to save energy. Figure 8.9 shows a critical clean zone within a cleanroom. For this kind of applications, a localized air velocity for the critical operation needs to be maintained to ensure air cleanliness for the critical clean zone. Equation 8.4 and the following discussion explain the method to calculate the overall vertical air velocity of a cleanroom that consists of two areas with different air velocities.

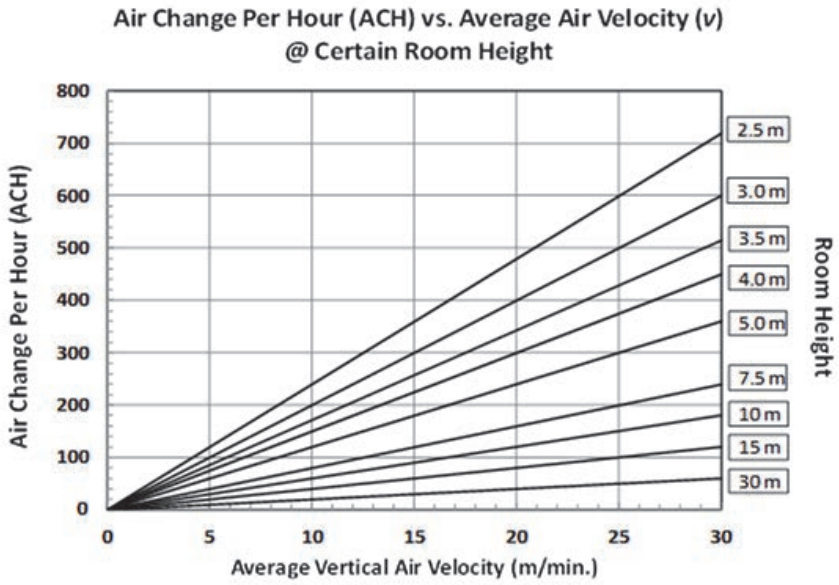
$$v = \frac{Q}{A} = \frac{Q_c + Q_r}{A_c + A_r} = \frac{v_c \cdot A_c + v_r \cdot A_r}{A_c + A_r} = v_c \cdot \frac{A_c}{A_c + A_r} + v_r \cdot \frac{A_r}{A_c + A_r} \tag{8.4}$$

where

Q	=	supply airflow rate to cleanroom (total), ft^3/s (m^3/s)
Q_c	=	supply airflow rate to critical zone, ft^3/s (m^3/s)
Q_r	=	supply airflow rate to the rest of the cleanroom, ft^3/s (m^3/s)
A	=	cleanroom floor area (total), ft^2 (m^2)
A_c	=	critical clean zone floor area, ft^2 (m^2)
A_r	=	rest of the cleanroom floor area, ft^2 (m^2)
v	=	cleanroom average vertical velocity, ft/s (m/s)
v_c	=	air velocity above critical zone, ft/s (m/s)
v_r	=	air velocity above the rest of the cleanroom, ft/s (m/s)



(a)



(b)

Figure 8.8
Relationship between ACH and Average Velocity: (a) I-P and (b) SI

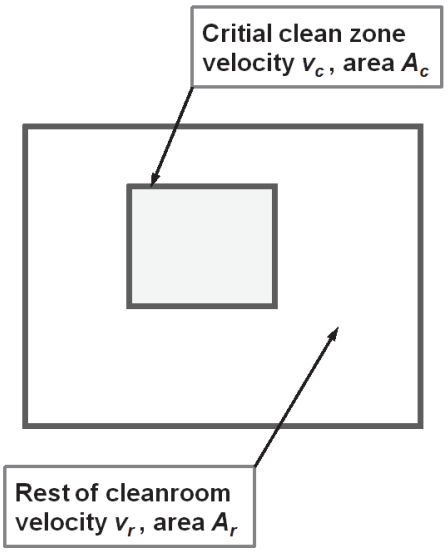


Figure 8.9 Critical Clean Zone in Cleanroom

As an example of applying the equation, if the critical zone's air velocity v_c is 90 fpm (0.45 m/s) and the critical zone occupies 20% of the total floor area, and the rest of the cleanroom has air velocity v_r at 30 fpm (0.15 m/s) and takes up the remaining 80% of the floor area, then the cleanroom average vertical velocity v = (90 fpm × 0.20) + (30 fpm × 0.80) = 42 fpm (v = [0.45 m/s × 0.20] + [0.15 m/s × 0.80] = 0.21 m/s). This value can be used to arrange the required flow rate for the entire cleanroom.

8.4.4 RULES-OF-THUMB TABLE APPROACH

Table 8.3 lists typical airflow ranges for various cleanroom classifications. It should be cautioned, though, that the flow or velocity ranges listed in this table are experience based or opinion based from the experts writing the cited guidelines. Therefore, design engineers should use their own judgment based on the actual site and operational conditions to determine the final airflow rates for their cleanroom designs.

For decades cleanroom engineers traditionally have used these rules-of-thumb values for designs. This table approach, however, uses only the required room cleanliness class to determine an ACR value and ignores many variables that could significantly impact the room particle concentration and the required air change rate, such as particle generations inside the room, efficiencies of HEPA filters and filters installed in AHU and RFUs, outdoor air intake particle concentration, particle surface deposition, particle entry through supply filtered air, particle exit through return air, exhaust air, and leakage air (particle loss or gain) under pressurization or depressurization, among others (Sun 2008a). Intuitively, for example, activities generating higher dust levels require higher ACRs to dilute particle concentrations than those generating dust at lower levels, but the rules-of-thumb table method uses an oversimplified approach that ignores these impacts. Each cleanroom is unique—its room cleanliness requirements, space configurations, production or process activities, HVAC systems, building construction, location, etc., can impact the ACR requirement for each room. Using the table approach without considering all these variables could result in underdesigned HVAC systems or cause energy waste (Sun 2008a), as indicated in many published surveys and articles listed in the References and Bibliography sections of this chapter.

Table 8.3
Historical and Modern Guidance on Air Change Rates
(Naughton 2016)

ISO 14644-1 Class (ISO 2015)	FS 209*	FDA Aseptic Guidance (2004)	*EU Guidelines to GMP* (EC 2010)	WHO (2011)	USP (2004)	ISPE *Good Practice Guide: HVAC* (2009)	PIC/S (2017)	IEST-RP-12.1 (1998)	IEST-RP-12.2 (2007)	IEST-RP-12.3** (2015)
ISO Class 8	Class 100,000	20	—	—	20	—	—	5–48	2–20	2–20
ISO Class 7	Class 10,000	> 20	—	—	50	6–20 for Grade D	—	60–90	20–200	20–200
ISO Class 6	Class 1,000		—	—	—	20–40 for Grade C	—	150–240	>200	>200
ISO Class 5	Class 100	39–98 fpm (0.2–0.5 m/s)	71–106 fpm (0.36–0.54 m/s	71–106 fpm (0.36–0.54 m/s	>100	40–60 for Grade B; Grade A (ISO Class 5) is based on velocity	71–106 fpm (0.36–0.54 m/s	240–480		>200
ISO Class 4	Class 10	—	—	—	—	—	—	300–540	—	—
ISO Class 3	Class 1	—	—	—	—	—	—	360–540	—	—
ISO Class 2		—	—	—	—	—	—	360–600	—	—
ISO Class 1		—	—	—	—	—	—	—	—	—

** All editions of FS 209, A through E (GSA 1966, 1973, 1987, 1988, 1992).*
*** Institute of Environmental Sciences and Technology (IEST) changed guidance in 2015 edition to "rule of thumb."*

8.4.5 CONTAMINANT REMOVAL EFFECTIVENESS

Contaminant removal effectiveness (ε) describes how effective the ventilation system is in removing contaminants:

$$\varepsilon = \frac{C_e - C_s}{C - C_s} \tag{8.5}$$

where

ε – contaminant removal effectiveness
C – average particle concentration in the cleanroom air
C_e – particle concentration in the exit air (either at common return or exhaust air)
C_s – particle concentration in the supply air

The contaminant removal effectiveness is dimensionless as long as the units of all particle concentrations remain the same. It should be cautioned that room average particle concentration is often subject to the referenced measuring height of a cleanroom, typically the higher of the measuring point, the lower of particle concentration. Therefore, the contaminant removal effectiveness is a function of a referenced height of measurement

Table 8.4 Selection of Contaminant Removal Effectiveness ε

Contaminant Removal Effectiveness	Explanation
$\varepsilon \to \infty$	Full exhaust at the sources of contaminants; contaminants do not mix with room air; no impact to room air particle concentration.
$\varepsilon = 1.0$	The most efficient and ideal unidirectional flow design; contaminants do fully mix with room air but are timely and fully removed by return or exhaust air.
$\varepsilon = 0.7$	Effective nonunidirectional flow design and good removal of contaminants but contaminants are in turbulent mixing with room air; good positioning of supply air and return/exhaust air.
$\varepsilon = 0.5$	Average nonunidirectional flow design; some contaminants are removed but the rest reside in the cleanroom.
$\varepsilon = 0.3$	Poor nonunidirectional flow design; a small portion of contaminants are removed but most reside in the cleanroom.
$\varepsilon \to 0$	All clean supply air is fully bypassed to return or exhaust air; supply air does not help to dilute contaminated room air; return/exhaust air does not take out contaminates.

for a specific cleanroom. In addition, after a cleanroom is constructed, typically furniture, equipment, and personnel move in and these additional obstructions may reduce the return air pattern effectiveness, and the contaminant removal effectiveness could become a lower value. In general, the contaminant removal effectiveness is subject to an occupancy state; the value could be gradually reduced from "as built" to "at rest" and "operational" states and is case specific. Table 8.4 supplies explanations of contaminant removal effectiveness.

8.4.6 VENTILATION EFFECTIVENESS AND AIR EXCHANGE EFFICIENCY

Two other commonly used ventilation indexes are ventilation effectiveness and air exchange efficiency. Ventilation effectiveness can be calculated by knowing the percentage of supply air to be bypassed to return air and the percentage of return air to be recirculated back into the room through the AHU. Air exchange efficiency can be estimated by knowing the air change rate in the room and the average of local values of the "age of air." Neither of these indexes count particle concentrations at supply air and exit (return or exhaust) air or the room averaged concentration; therefore, they are less applicable to cleanroom particle concentration analysis. For information on these indexes, readers can review the related ASHRAE publications listed in the References section.

8.4.7 DILUTION EQUATION APPROACH

Selecting a supply airflow rate from a recommended range solely based on cleanliness class has been the main method for cleanroom airflow design. This rules-of-thumb method may be the easiest approach which simply ignores the impacts of room particle generations and many other factors (variables); however, many in the cleanroom industry believe that this method may be oversimplified. The dilution equation (Equation 8.6) can be used as the simplest form of mathematical modeling if the rules-of-thumb method is not desired:

$$C_S = \frac{G \cdot V}{\varepsilon \cdot Q} = \frac{60 \cdot G}{\varepsilon \cdot N} \tag{8.6}$$

where

C_S = airborne particle concentration in cleanroom, counts/ft^3 (counts/m^3)
ε = contaminant removal effectiveness

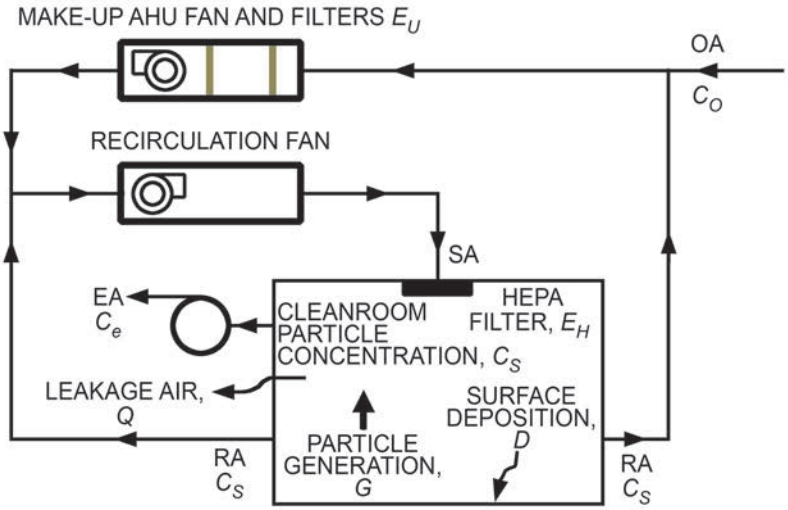


Figure 8.10 Example of an HVAC Configuration and Particle Balance in a Cleanroom

G	=	particles generated (normalized) in cleanroom, counts/ft^3 (counts/m^3) per min
V	=	volume of room, ft^3 (m^3)
Q	=	airflow rate supplied into cleanroom, cfm (m^3/min)
N	=	ACR in room, ach
60	=	number of minutes per hour

This equation suggests that if more particles are generated inside a cleanroom, then a higher airflow rate needs to be supplied to maintain the air cleanliness, in terms of room airborne particle concentration. When other variables are not available to obtain or are unknown, this dilution equation is sometimes used as a quantitative approach to estimate the required airflow rate. However, as many other key variables are not included, applicability is questionable.

8.4.8 MODELING APPROACHES

To save fan energy and design cleanroom HVAC systems precisely, modeling approaches have been developed that provide quantitative tools to estimate or calculate the required airflow (Sun 2008a). A series of publications on modeling technologies that have become available in recent years are listed in the References and Bibliography sections of this chapter. It is anticipated that these modeling technologies will be the trend for cleanroom air change rate calculation in the future.

Mathematical modeling with an intent to include key variables has been conducted by cleanroom researchers for many years. The variables may include makeup AHU's filter efficiencies, outdoor air concentration, percentage of outdoor air in supply air, room HEPA (or ULPA) filter efficiency, surface particle deposition, etc. Some representative models by Morrison (1973), Brown and Lynn (1986), and Wen et al. (2009) are discussed in this section. Figure 8.10 illustrates an example of a cleanroom HVAC configuration that also shows particle concentrations at various locations along airflow paths. For comparison among all discussed models, the same variables, which may be designated by different Latin or Greek characters in their source publications, are designated by consistent mathematical symbols in this discussion.

In the simple dilution equation only two variables, particle generation rate G and air change per hour rate ACH, can be used to determine the room average particle concentration. The dilution model can be expressed as:

$$C_S = \frac{G \cdot V}{\varepsilon \cdot Q} = \frac{60 \cdot G}{\varepsilon \cdot N} = \frac{G}{\varepsilon \cdot \text{ACH}}$$ Dilution model

where

C_S = particle concentration in space, count/ft^3 (count/m^3)
G = particle generation rate (normalized) in room, counts/ft^3 (counts/m^3) per min
V = room volume, ft^3 (m^3)
ε = contaminant removal effectiveness
Q = airflow rate supplied into cleanroom, cfm (m^3/min)
60 = number of minutes per hour
N = ACR in room, ach
ACH = air changes per hour, ach

Morrison's (1973) model may be one of the earliest approaches to a more complex mathematical modeling in which some variables omitted from the dilution equation are included. In this model, outdoor air is considered to be brought into the cleanroom through makeup AHU filters and then through room HEPA filters directly without prior mixing with return air in the RFU. In this case, outdoor particle concentration C_O has a much higher impact on room concentration C_S. Also, an average particle deposition velocity and room height need to be known in order to use this model.

$$C_S = \frac{(1 - E_U) \cdot m \cdot C_O + \dfrac{G}{\text{ACH}}}{m + E_H \cdot (1 - m) + \dfrac{A}{\text{ACH}}}$$ Morrison model (1973)

where

C_S = particle concentration in space, count/ft^3 (count/m^3)
E_U = filter efficiency inside makeup AHU, %
m = ratio of outdoor air in supply air
C_O = outdoor makeup air concentration, count/ft^3 (count/m^3)
G = particle generation rate (normalized) in room, counts/ft^3 (counts/m^3) per min
ACH = air changes per hour, ach
E_H = HEPA or ULPA filter efficiency in room, %
A = average particle deposition velocity divided by room height, 1/h

Brown and Lynn's (1986) model assumes a more common HVAC configuration, in which outdoor air enters first through makeup AHU filters then is drawn into the RFU and then further through HEPA filters to the cleanroom. However, this model does not include particle deposition as a variable.

$$C_S = (1 - E_U) \cdot (1 - E_H) \cdot m \cdot C_O + \frac{G}{\text{ACH}}$$ Brown and Lynn model (1988)

where

C_S = particle concentration in space, count/ft^3 (count/m^3)
E_U = filter efficiency inside makeup AHU, %
E_H = HEPA or ULPA filter efficiency in room, %
m = ratio of outdoor air in supply air
C_O = outdoor makeup air concentration, count/ft^3 (count/m^3)
G = particle generation rate (normalized) in room, counts/ft^3 (counts/m^3) per min
ACH = air changes per hour, ach

Figure 8.11
Effect of Internal Particle Generation Rate

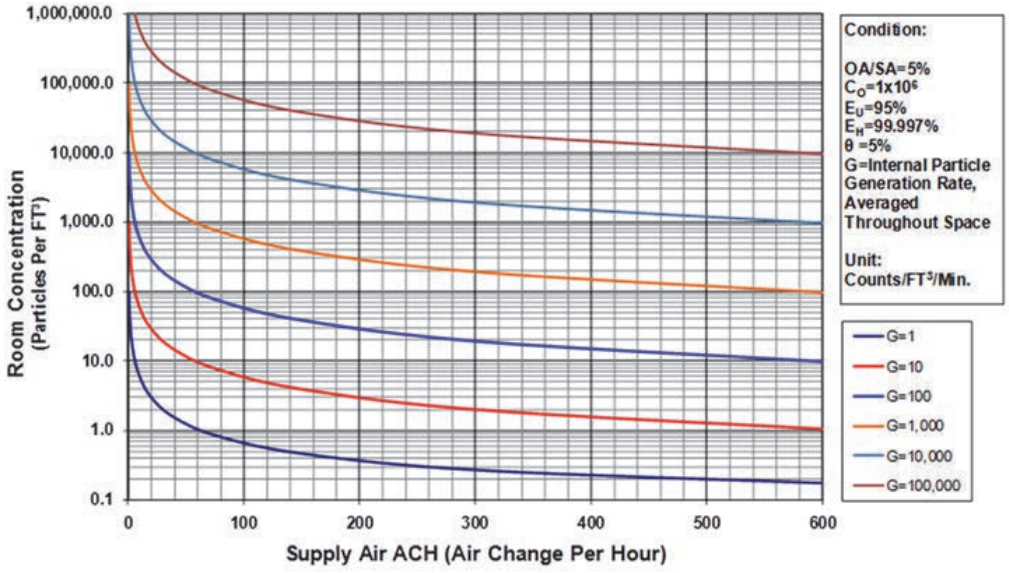
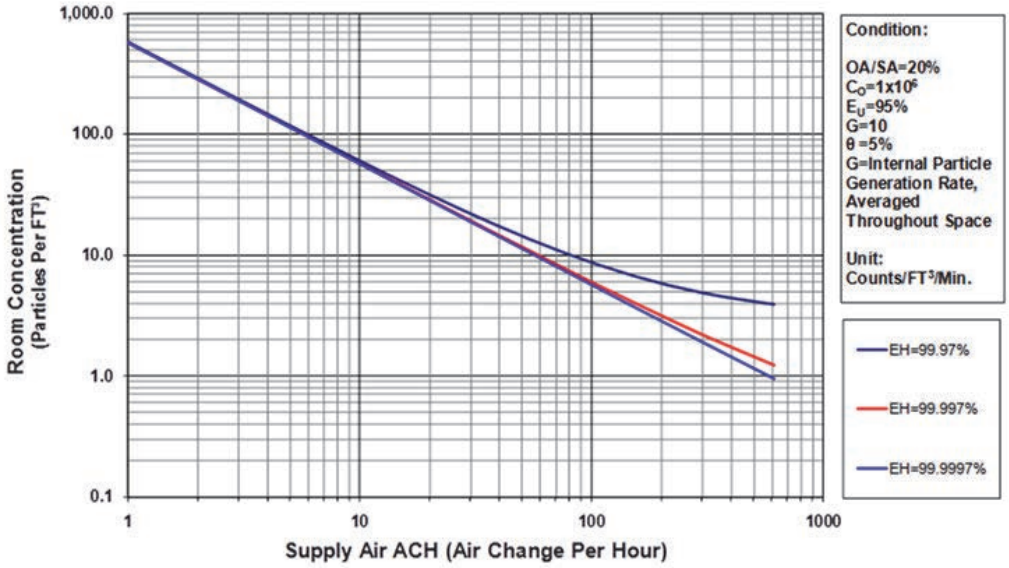


Figure 8.12
Effect of Final HEPA Filter Efficiency



Wen et al.'s (2009) model started with a particle balance differential equation based on multiple cleanroom HVAC configurations as shown in Figures 8.11 through 8.16. The model includes particle deposition, which is expressed in a percentage of particle generation θ. The model considers all filters used not only in the makeup AHU but also in the RFU or recirculation AHU. The combined filters' efficiencies upstream of the HEPA filter is expressed as E_{UC}. The static form of the model (when the time approaches infinity) is

$$C_S = \frac{(1-E_{UC})\cdot(1-E_H)\cdot m\cdot C_O + \dfrac{(1-\theta)\cdot G}{N}}{\varepsilon\cdot[m+(E_{UC}+E_H-E_{UC}\cdot E_H)\cdot(1-m)]}$$

Wen et al. model (2009)

where

Figure 8.13
Effect of AHU Combined Filter Efficiency

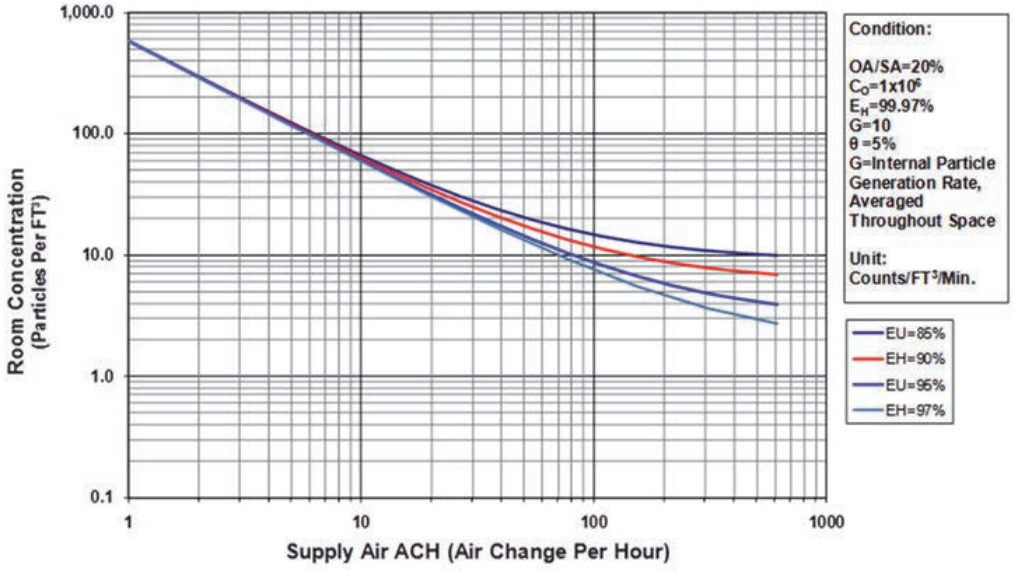
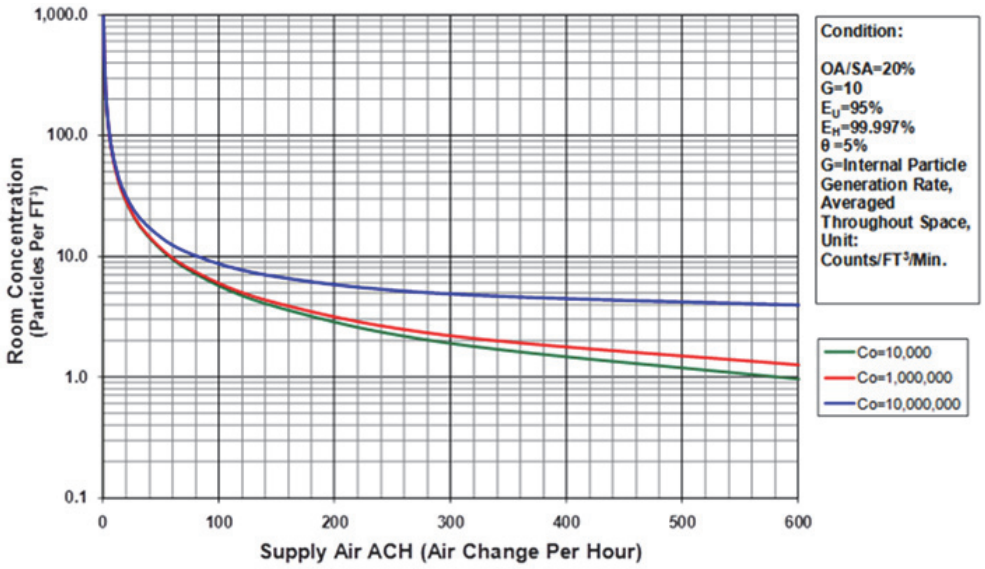


Figure 8.14
Effect of Outdoor Air Intake Particle Concentration



C_S = particle concentration in space, count/ft^3 (count/m^3)
E_{UC} = combined filters' efficiencies (in series) inside makeup AHU and RFUs/AHUs, %
E_H = HEPA or ULPA filter efficiency in room, %
m = ratio of outdoor air in supply air
C_O = outdoor makeup air concentration, count/ft^3 (count/m^3)
θ = percentage of room-generated particles deposited on exposed surfaces, %
G = particle generation rate (normalized) in room, counts/ft^3 (counts/m^3) per min
N = ACR in room, ach
ε = contaminant removal effectiveness

In Morrison's model, if we ignore the particle deposition, consider a 100% efficiency for a HEPA filter, and consider no outdoor air intake or that outdoor air is pure clean air

Figure 8.15
Effect of Outdoor Air Percentage of Supply Air

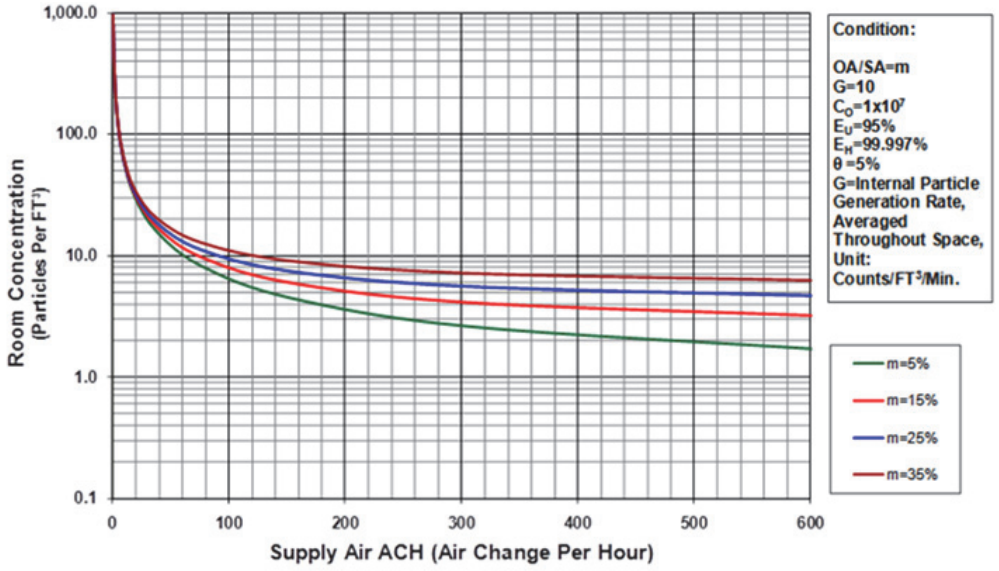
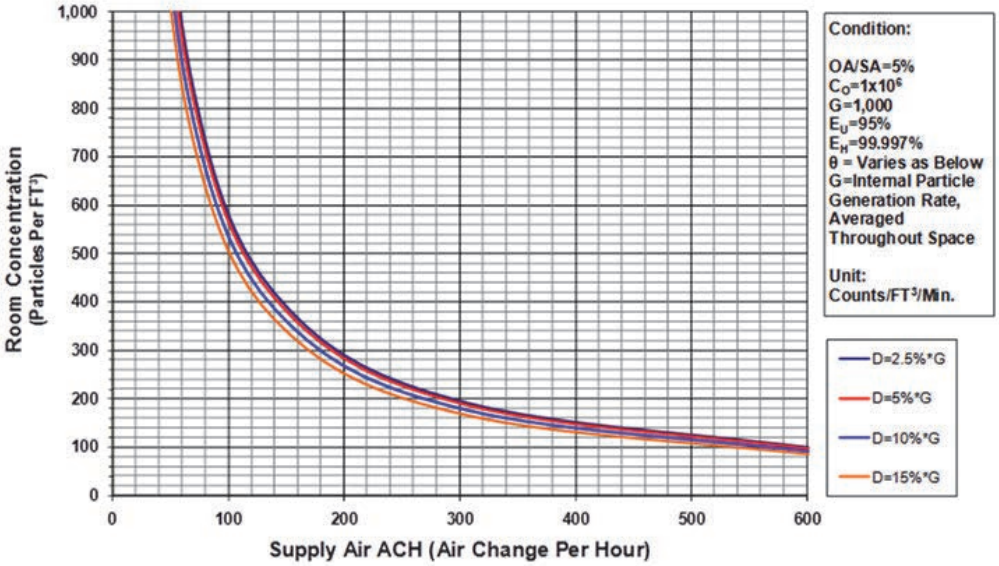


Figure 8.16
Effect of Surface Particle Deposition Rate



carrying no particles, $A = 0$, $E_H = 1$, and either $m = 0$ or $C_O = 0$, then the model becomes the dilution model.

In Brown and Lynn's model, similarly, if we ignore outdoor particle condition or consider no outdoor air in the supply air and consider 100% efficiency for the filter in either the makeup AHU or the RFU, then $C_O = 0$ or $m = 0$ or $E_H = 1$ or $E_U = 1$ and this model also reduces to be the dilution model.

In Wen et al.'s model, if particle deposition is ignored then $\theta = 0$, and if other filters located in the RFUs/AHUs are ignored then $E_{UC} = E_U$, and if we further assume a 100% efficiency for the HEPA filter in the denominator of the equation ($E_H = 1$) but use real efficiency in the numerator of the equation, then the model becomes Brown and Lynn's model.

Therefore, in general, these models consider more variables that have various impacts on overall room particle concentration. When some of these variables are ignored, these

models can be reduced to be the dilution model. Although some variables in the models can be measured, calculated, or estimated in laboratory conditions, it may be hard for engineers to estimate particle generation values during the design stage; therefore, often the traditional rules-of-thumb table method is used instead. See the related articles in the Bibliography section of this chapter for detailed developments and contents of these models.

8.4.9 EXAMPLES OF MODELING TOOLS FOR ANALYZING THE SIGNIFICANCE OF VARIABLES

Modeling methods include many important variables on air change rate determination. Modeling methods can be further used to examine the impacts of these variables. As examples, Figures 8.11 through 8.16 are based on Wen et al.'s (2009) model and show the impacts of some key variables on room average particle concentration under specific conditions as indicated.

8.4.10 COST-EFFECTIVE OPTIONS FOR LOWERING CLEANROOM AIR CHANGE RATES

Based on the discussed models, it is clear that in addition to air change rate, many other variables, such as internal particle generation rate, particle surface deposition, particle entry through supply air, particle exit through return and exhaust air, and leakage air (particle loss or gain) under pressurization or depressurization also impact the room airborne cleanliness. In other words, theoretically, to maintain the same cleanliness, more options are available than using a high air change rate alone; practically altering these (one or more) variables could be more cost-effective. The following measures can be used to lower the air change rate requirement when possible:

- **Select Equipment, Machinery, Furniture, and Room Construction Materials with Lower Particle Generation Levels.** It is intuitive that activities generating higher levels of dust require higher ACH to dilute particle concentration than those generating lower levels of dust. As Figure 8.11 indicates, internal particle/dust generation rate could be the most significant impact on airflow rate requirement. Various ranges of particles can be generated by different items inside a cleanroom, including people, furniture, machinery, process equipment, and room enclosure construction materials, among others (Sun 2008a). One of the major energy and capital wastes is to ignore or allow high-level particle generation from these materials or products to occur in cleanrooms without containment, causing design engineers to use high-level airflow rates to dilute and decrease air particle concentration.

  Design professionals should select cleanroom furniture, machinery, equipment, and room enclosure construction materials at the lowest particle generation levels possible. Manufacturers should list particle generation rates or similar measurements in their product specifications if the products are intended for cleanroom applications.
- **Isolate and Remove High-Concentration Particles Generated in the Cleanroom.** Once the equipment, machinery, furniture, and room enclosure construction materials are selected, local minienvironments and local exhaust could be added to isolate and remove particles from the equipment, machinery, or processes identified as the sources of high-concentration particles.

  For personnel particle generation, one cost-effective way of reducing particle generation is enhanced gowning with better body coverage and gowning protocols. The goal is to minimize the particles from major sources being dispersed into the remaining cleanroom spaces.

- **Enhance Surface Cleaning Protocols to Prevent Surface Particles from Turning into Airborne Particles.** High velocities of supply air and high change rates are intended to dilute and wash down the particles, yet no return and exhaust system can completely remove all particles from a cleanroom. Some particles accumulate on equipment, furniture, and hard-to-reach floor areas underneath the equipment and furniture. Over time these particles build up, until a scheduled cleaning and vacuuming removes most of the residuals (Sun 2008a). Surface particles that are not removed could reenter the air and become airborne particles if there is a disturbance on the exposed surface, which increases the airborne concentration.
- **Control Particle Entry through Supply Air.** Supply air is a mixture of recirculated (return) air and outdoor air. This mixed air should be filtered by ceiling HEPA or ULPA filters before it enters a cleanroom. These filters' efficiencies determine how many particles could be released into cleanroom spaces. Higher filter efficiencies reduce the particle entry through the supply air; however, as shown in Figure 8.12 replacing HEPA filters with ULPA filters at the room level may not be as cost-effective as using higher-efficiency filters inside the AHU in terms of air change rate reduction. Of course design engineers also need to consider the extra operating costs from higher pressure drops across higher-efficiency filter media.
- **Design Return and Exhaust Air Systems Effectively for Particle Exit.** Before its reentry as much of the supply air to a cleanroom, the room return air is drawn through low sidewall grilles or a raised perforated floor and then recirculated and filtered to remove particles generated from processes and process equipment. The particles are removed locally by exhaust air; exhaust devices such as direct connections to process equipment, canopies, and hoods can significantly remove highly concentrated particles. Exhaust air, unlike return air, typically does not allow reentry (Sun 2008a). Proper placement of return or exhaust points close to high-concentration areas can remove particles more efficiently. Effective return and exhaust pattern designs should achieve a higher contaminant removal effectiveness value to ensure fewer particles accumulate on exposed surfaces and become surface particle contamination in cleanrooms.
- **Maintain Proper Pressurization/No Depressurization, which Causes Particle Gain through Leakage.** If a pressure differential exists, then whenever the door to a cleanroom is opened it is inevitable that air leakage will occur between the cleanroom enclosure and its surroundings. Particle migrations following the leakage air paths should be considered, especially under depressurization and when the air in the surrounding area is dirtier than the cleanroom. To prevent or minimize particle migration from surrounding areas, cleanrooms should be kept in relative positive pressure. Usually, the higher the pressure differential, the more effective it is in preventing particle migration.

8.5 CLEANROOM PRESSURE CONTROL

8.5.1 OVERVIEW

Clean spaces use room pressurization, or depressurization, to create the desired flow patterns from less clean rooms to cleaner rooms and to minimize airborne particle, biological, gaseous, and/or chemical contamination. It is achieved by mechanically creating air pressure differences between rooms to cause intentional air movement through room leak-

age openings, which may be intentional (such as doorways) or unintentional (such as air gaps around door frames or cracks of duct/pipe wall penetrations, although best practices require that these air gaps and cracks be sealed). HVAC systems often achieve pressurization through proper arrangement of controlled supply, return, and exhaust airstream flow rates to each room within the space (Sun et al. 2013a).

Traditionally, cleanroom pressurization control technologies have been based on intuitive suggestions rather than well-established guidelines. A pressure differential of 0.05 in. w.c. (12.5 Pa) has been used since it was adopted into U.S. Federal Standard (FS) 209A, *Airborne Particulate Cleanliness Classes in Cleanrooms and Clean Zones* (GSA 1966), and the "Clean Spaces" chapter of *ASHRAE Handbook—HVAC Applications* (ASHRAE 2015).

It was assumed that maintaining a closed-door cleanroom enclosure at 0.05 in. w.c. (12.5 Pa) of pressure differential meant that during door operation the desired flow patterns between the two rooms would be maintained and that contamination caused by air flowing from less-clean areas into the cleanroom would be minimized (even if the pressure differential decreased significantly) (Sun et al. 3013a). However, using 0.05 in. w.c. (12.5 Pa) for each pressure differential step is believed to be oversimplified and may not be precise enough (Sun 2003), especially when a cleanroom is surrounded by a less-clean adjacent area that could be one, two, three, or more cleanliness classes dirtier. Thus, the recommendation is that cleanrooms be surrounded by areas of no more than one class less. (Also see Section 7.3 of Chapter 7.)

The informative section of ISO 14644-4, *Cleanrooms and Associated Controlled Environments—Part 4: Design, Construction and Start-up* (ISO 2001), currently allows a pressure differential range from 0.02 to 0.08 in. w.c. (5 to 20 Pa). However, which value to specify and what could be the resulting effectiveness to resist particle migration or contamination is still left to designers' intuition. Besides, contamination barriers such as minienvironments, clean benches (laminar hoods), and air locks, which practically impose an extra level of resistance to airborne contaminant migration, have not been quantitatively credited (Sun et al. 2013a). Furthermore, the airtightness level of the room enclosure, which is a critical element in design consideration, has for decades often been ignored during pressurization designs.

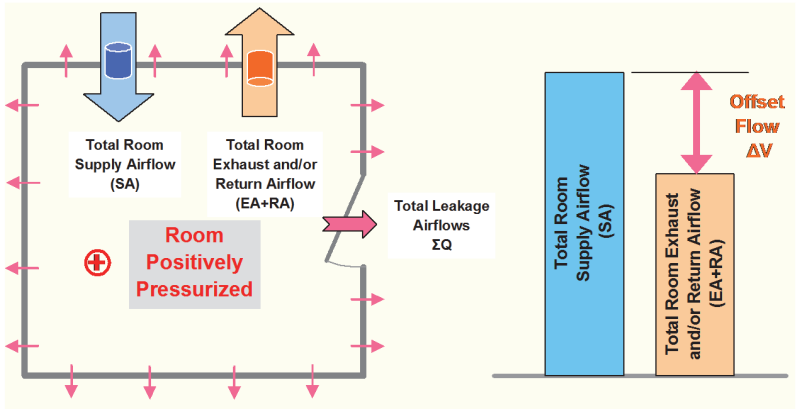
The purpose of cleanroom pressurization is to define a flow pattern and to perform as a particle migration barrier. A specific pressure differential at a closed door between rooms with two different air cleanlinesses can typically prevent airborne cross-contamination from the less clean room into the cleaner room, because even if the door frame has some minor air gaps (cracks), these openings are small and the velocities of air leakage through these cracks are high enough to prevent backflows. When the door is opened, however, the pressure differential changes quickly and the barrier's functionality becomes questionable (Sun et al. 3013a). In addition to the minimum required pressure differential, treatment at door-in-operation condition to prevent backflow needs to be considered.

8.5.2 HOW TO ACHIEVE ROOM PRESSURE DIFFERENTIALS

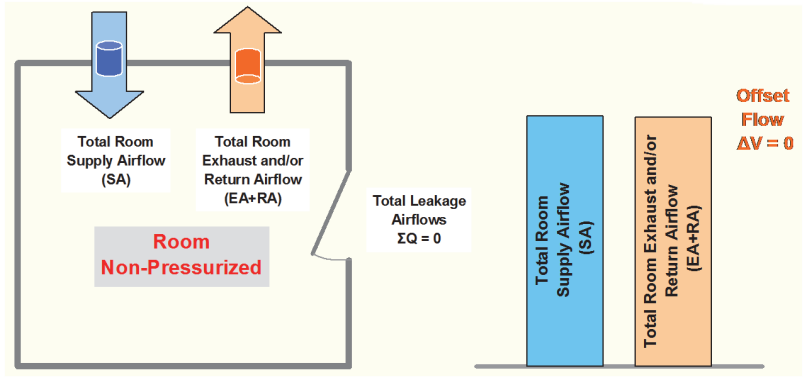
There is an important relationship between room pressure and the flow differential inside the room, which is the flow rate difference between room incoming airflow and departing airflow, typically called *offset* flow. Room pressurization variables and their relationships can be expressed as shown in Figure 8.17. To obtain a pressure differential across a petition wall that separates two rooms, air has to leak between the rooms by an offset flow to allow an air surplus in one room and a deficit in the other (see Figure 8.18).

The next question naturally is how to relate the flow offset value to the room pressure in respect to adjacent spaces; before moving forward, we have to introduce the common

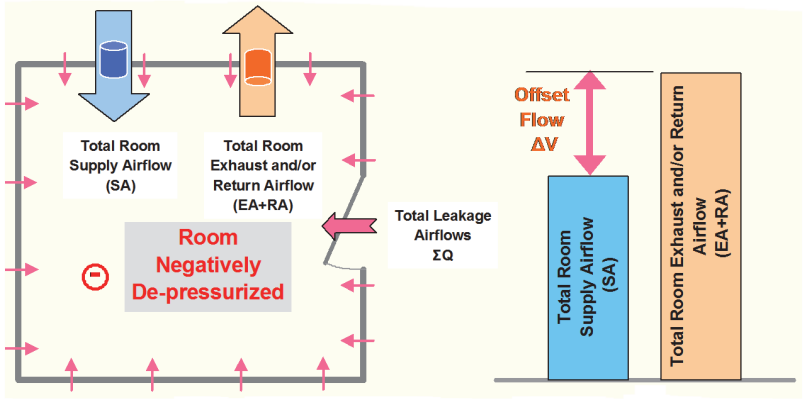
Figure 8.17
Room Pressurization Scenarios



Scenario 1: Room Pressurized
SA - (EA+RA) = ΔV = ΣQ > 0



Scenario 2: Room Unpressurized
SA - (EA+RA) = ΔV = ΣQ = 0



Scenario 3: Room Depressurized
SA - (EA+RA) = ΔV = ΣQ < 0

Notes:
SA = supply air, RA = return air, EA = exhaust air, ΔV = room offset flow,
ΣQ = total leakage flow, which is a mathematic sum with possible leak-in air and leak-out airs.
SA is the total entering air, (EA + RA) is the total leaving air.

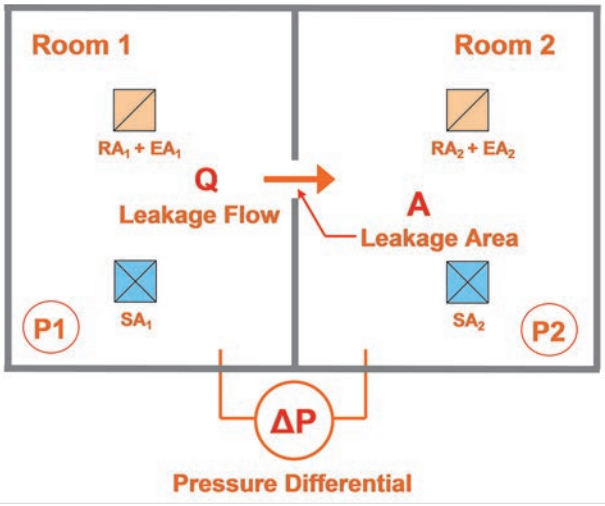


Figure 8.18 To Obtain a Pressure Differential, Air Has to Leak Between Rooms by an Offset Flow to Allow Air Surplus in One Room and Deficit in Another

equations that describe the relationships among leakage opening size, leakage flow rate, and pressure differential across the opening.

8.5.3 EQUATIONS TO CALCULATE LEAKAGE AIRFLOW THROUGH AIR LOCK DOORS

To study air lock performance quantitatively, one has to analyze the airflow leakage through doors in both closed and open conditions. Commonly the "power equation" is used:

$$Q = C \cdot (\Delta P)^n \tag{8.7}$$

where

Q = volumetric flow rate, cfm (L/s)
C = flow coefficient, cfm/(in. of water)^n (L/s per Pa^n)
ΔP = pressure drop across opening, in. of water (Pa)
n = flow exponent, dimensionless

This equation is used to describe air leakage through irregular cracks, such as an air gap between a door and its frame or through joints between floor and walls, walls and ceiling, ceiling tiles and ceiling grids, and wall penetrations for ductwork, conduits and piping, etc.

Another single parameter to quantify the leakage opening is the effective leakage area (ELA). The definition of ELA and its data tables for building components can be found in *ASHRAE Handbook—Fundamentals* (ASHRAE 2017). Once a Q-ΔP data set is obtained, C and n can be calculated as follows (Sun 2005):

$$n = \frac{\left(\sum_{k=1}^{m} \ln Q_k \cdot \sum_{k=1}^{m} \ln \Delta P_k\right) - m \cdot \sum_{k=1}^{m} (\ln Q_k \cdot \ln \Delta P_k)}{\left(\sum_{k=1}^{m} \ln \Delta P_k\right)^2 - m \cdot \sum_{k=1}^{m} (\ln \Delta P_k)^2} \tag{8.8}$$

$$C = EXP\left(\frac{\sum_{k=1}^{m} \ln Q_k - n \cdot \sum_{k=1}^{m} \ln \Delta P_k}{m}\right) \tag{8.9}$$

The characteristics of airflows through large designated openings, such as doorways, are somewhat different than those for small crack openings. The sharp-edge orifice flow equation is more suitable for describing larger openings (ASHRAE 2017):

$$Q = 2610 \cdot A \cdot \sqrt{\Delta P} \qquad \text{(I-P)} \tag{8.10}$$

$$Q = 840 \cdot A \cdot \sqrt{\Delta P} \qquad \text{(SI)} \tag{8.10}$$

where

A = large designated opening area(s), ft^2 (m^2)
2610 = unit conversion factor, dimensionless
840 = unit conversion factor, dimensionless

8.5.4 AIR LEAKAGE RATE VS. PRESSURE DIFFERENCE UNDER VARIOUS LEAKAGE AREAS

Both the power equation and the orifice equation can be presented in a group of curves which can be easily used by design engineers. Figure 8.19 illustrates the orifice equation in a group of curves. Among three variables of leakage air rate, pressure differential across the leakage path, and leakage area, once two of them are known the third variable can be identified. Readers can find power-equation-based curves in the work by Sun (2003).

8.5.5 BALANCE EQUATIONS AND PRESSURIZATION RATIO

The key relationships in airflow rates between the central AHU and room pressurization variables can be found in Figure 8.20, where SA is supply air, RA is return air, EA is exhaust air, FA is relief air, and Q is leakage air.

Two mass balance equations can be simplified as volumetric balance equations when air density is ignored:

$$\text{SA} = \text{RA} + \text{EA} + Q \qquad \text{(Volume balance for a space)}$$

$$\text{SA} = \text{OA} + (\text{RA} - \text{FA}) \qquad \text{(Volume balance for a typical AHU)}$$

The space's pressurization ratio R, to be used as an indicator of pressurization scale, can be defined as

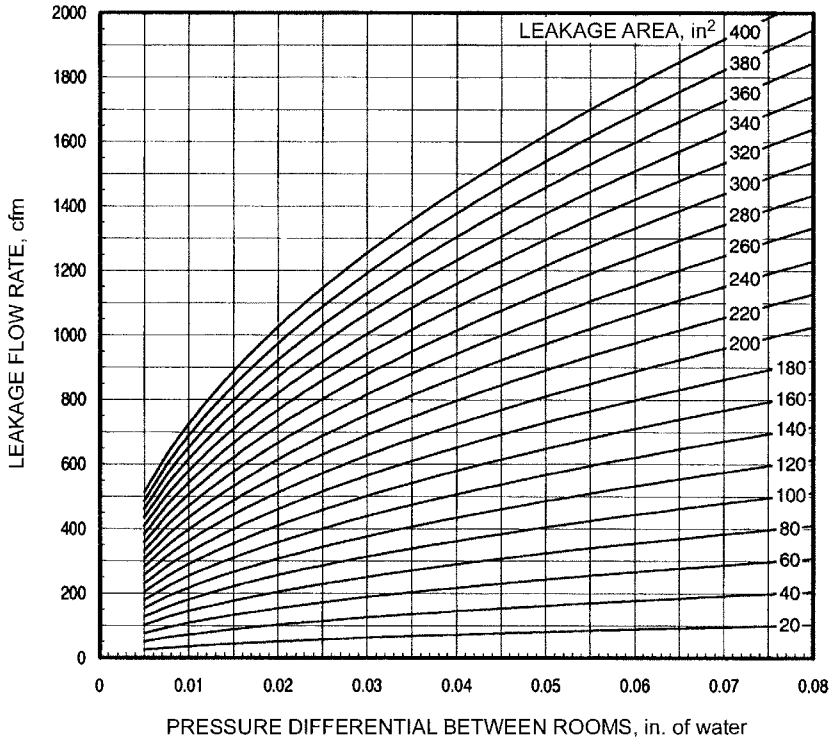
$$R = \frac{\text{SA}}{\text{RA} + \text{EA}} = \frac{\text{SA}}{\text{SA} - Q} \tag{8.11}$$

The R-value is convenient for design engineers to determine the SA and (RA + EA) ratio during air distribution arrangement (see Figure 8.21).

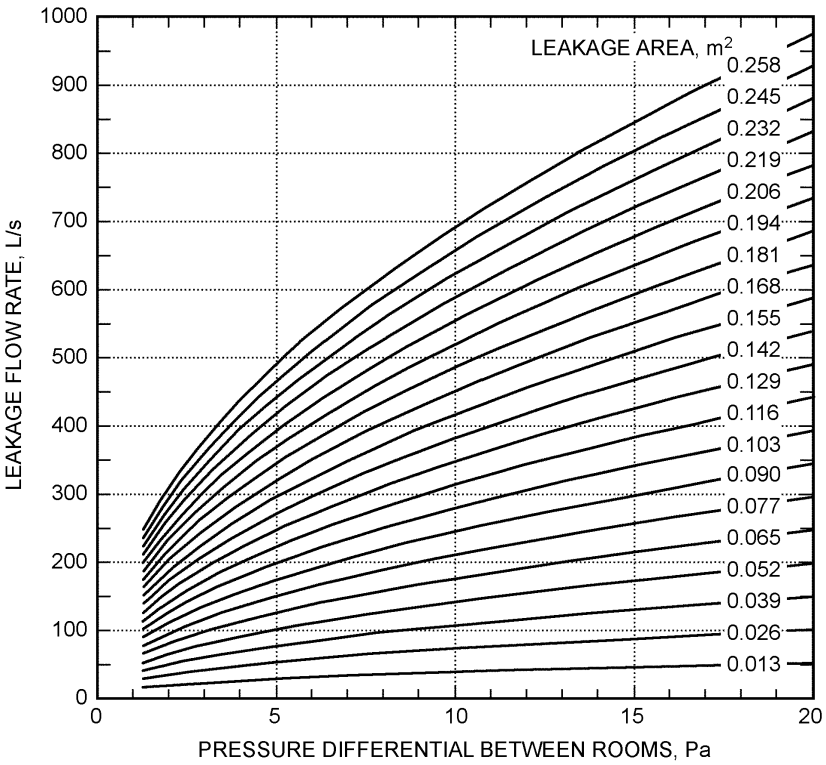
The relationship between the space's pressurization ratio and its individual rooms' pressurization ratios is shown in Equation 8.12:

Figure 8.19
Air Leakage Rate versus Pressure Difference for Various Leakage Areas: (a) I-P and (b) SI

(ASHRAE 2015)



(a)



(b)

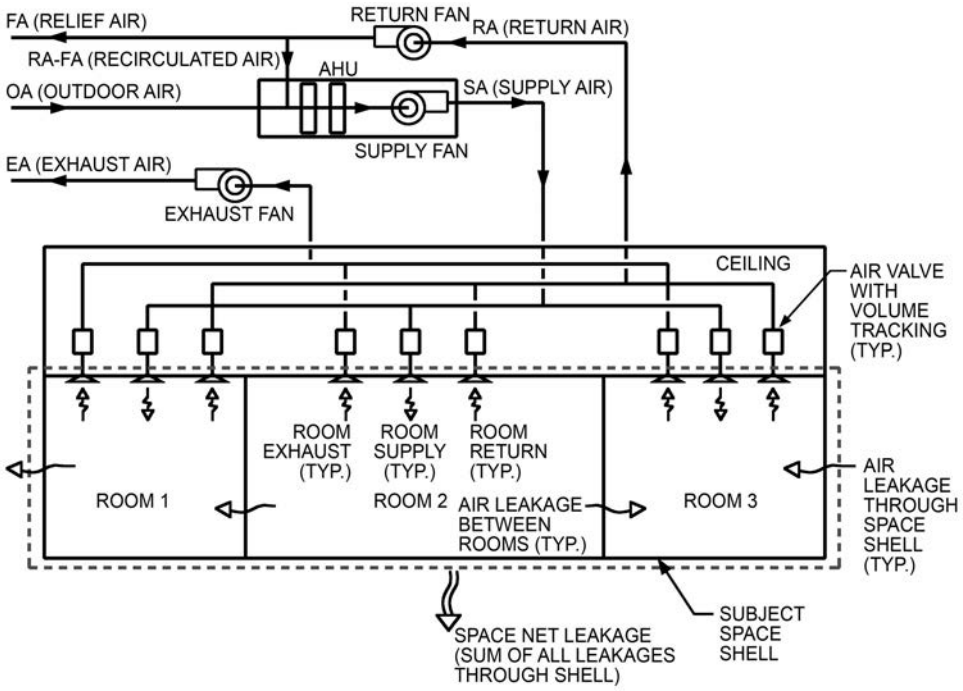


Figure 8.20 Air Balance Equations for AHU and Served Rooms

$$R = \frac{1}{\sum_{i=1}^{n}\left[\frac{(\mathrm{SA}_i/\mathrm{SA})}{R_i}\right]} \tag{8.12}$$

The space pressurization ratio, an indicator of relative pressurization level, can be used to adjust air gains or losses among zones in order to arrange desired airflows within a building.

If a room has several leakage openings with adjacent rooms, the room's pressurization ratio is

$$R_R = \frac{\mathrm{SA}_R}{\mathrm{SA}_R - \sum_{i=1}^{n} Q_i} \tag{8.13}$$

8.5.6 TRADITIONAL RULES-OF-THUMB METHODS IN DETERMINATION OF FLOW OFFSET VALUES

Many rules-of-thumb, opinion-based approaches have been used to determine the absolute or relative offset values during room pressure design. The following are some typical examples.

- **Flow Percentage Offset Method.** An example of this approach is the method recommended by the HVAC design manual of the U.S. Department of Veterans Affairs (VA 2008):

  Neutral: SA – (RA + EA) = 0
  Positive (+): SA – (RA + EA) = 15% of SA

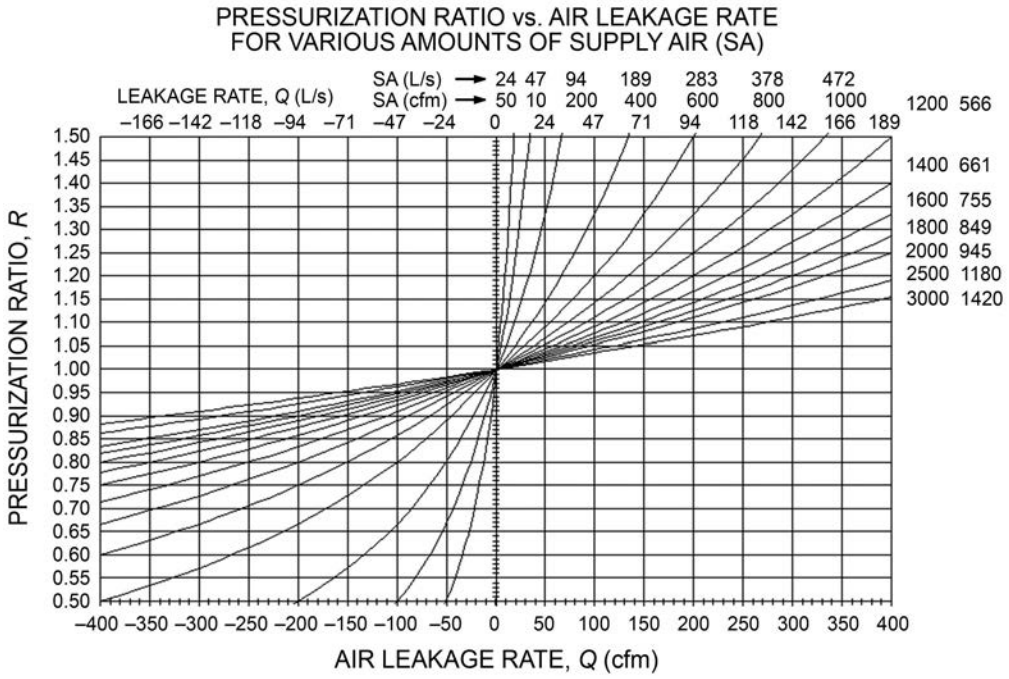


Figure 8.21 Pressurization Ratio vs. Air Leakage Rate Under Supply Air Rates

Positive (++):	SA – (RA + EA) = 30% of SA
Negative (–):	(RA + EA) – SA = 15% of SA
Negative (– –):	(RA + EA) – SA = 30% of SA

- **Flow Differential Offset Method.** An example of this approach is the method recommended by Centers for Disease Control and Prevention (CDC) (CDC 2003):

Neutral:	SA – (RA + EA) = 0
Positive:	SA – (RA + EA) = min. 125 cfm (60 L/s)
Negative:	(RA + EA) – SA = min. 125 cfm (60 L/s)
Room envelope sealed at:	max. 0.5 ft^2 (465 cm^2) leakage area; min. pressure differential (ΔP) is 0.01 in. (2.5 Pa)

The CDC approach advanced from the flow percentage offset method, and it indicates the requirement of airtightness of the room envelope; however, the method to estimate the leakage area is not addressed or provided in the guideline. Also, a pressure differential at 0.01 in. (2.5 Pa) seems well below that recommended by other guidelines and standards for cleanrooms and laboratories, which often demand pressure differentials of 0.04 to 0.05 in. (10 to 12.5 Pa).

This discussion is not intended to alter the existing health care design practices; rather, the preceding guidelines are quoted as examples of traditional rules-of-thumb approaches used in room pressure control today.

8.5.6.1 Pressure Differential and Crack Air Velocity

To quantify or measure the level of pressurization, there are two commonly used criteria. One is the pressure differential and the other is the average crack velocity, which is the leakage flow rate divided by the leakage area.

Table 8.5
Corresponding Pressure Differential Across Opening Based on Orifice Equation versus Opening (Crack) Average Leakage Velocity

Pressure Differential ΔP across Leakage Opening	0.002 in. (0.5 Pa)	0.004 in. (1 Pa)	0.02 in. (5 Pa)	0.04 in. (10 Pa)	0.06 in. (15 Pa)	0.08 in. (20 Pa)
Average Velocity *V* through Opening	117 fpm (36 m/min)	166 fpm (51 m/min)	370 fpm (113 m/min)	524 fpm (160 m/min)	641 fpm (195 m/min)	741 fpm (226 m/min)

- Criterion 1 (pressure differential ΔP)
  For a single room:
  ΔP: 0.05 in. of water (12.5 Pa)
  For a multiple-room space with staged pressurizations:
  ΔP: 0.02 to 0.03 in. (5 to 7.5 Pa) for each pressure step
- Criterion 2 (average crack velocity V)
  100 fpm (30 m/min)

From Table 8.5, the pressure criterion of ΔP = 0.05 in. (12.5 Pa) is much more conservative than the velocity criterion of V = 100 fpm (30 m/min).

8.5.7 PRESSURE DIFFERENTIAL CONTROL STRATEGIES

Room airtightness is the key element in the relationship between the room's flow offset value and the resulting pressure differential, and each room airtightness is unique and unknown unless tested. Treatment of a room's offset value defines a pressurization control strategy. Basic pressurization control techniques include the following:

- **Direct Pressure-Differential Control (DP).** This method uses a pressure differential sensor to measure the pressure difference between a controlled room and an adjacent space (e.g., a corridor). DP is suitable for a tightly constructed room with limited traffic. It basically ignores the specific offset value as required; instead, it directly controls the airflow control devices to achieve the required pressure differential between the controlled room and an adjacent space. A door switch is recommended to trigger a reduced pressure differential set point or allow a limited time period for normal traffic when the door opens. Figure 8.22 is an example diagram of direct pressure-differential control.
- **Differential Flow Tracking Control (DF).** This method assumes an offset value based on intuitive guesswork; the value is then used as a volumetric or mass flow difference between the supply and return/exhaust airflows through their airflow control devices. This method is suitable for open-style rooms or rooms with frequent traffic. DF normally maintains the same airflow offset value throughout operation to keep constant pressurization. A constant-percentage airflow offset value is sometimes used, but this creates a weaker pressurization at lower flow conditions. Figure 8.23 is an example diagram of differential flow tracking control.
- **Hybrid Control (DF + DP) (or Cascaded Control)**. This approach combines the pressure accuracy of DP and the stability of DF. The offset value is resettable based on the pressure differential reading. The offset value reset schedule is predetermined, and the controller's parameters are fixed manually in the field. Figure 8.24 is an example diagram of hybrid control.
- **Adaptive Control (Self Tuning).** The three previously listed traditional control pressure methods (DP, DF, and DF + DP) either ignore, assume, or manually fix

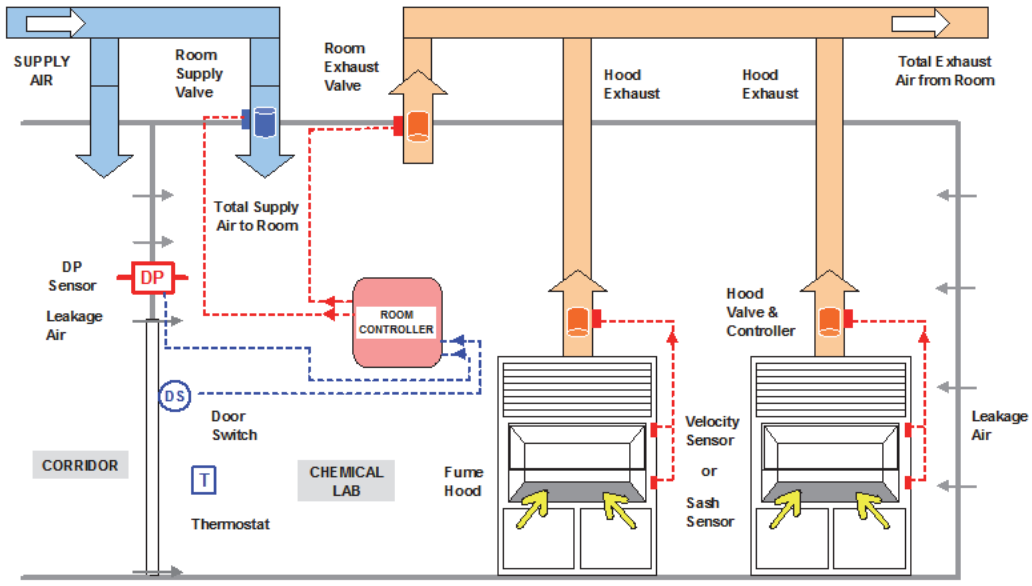


Figure 8.22 Example of a DP Control Technique

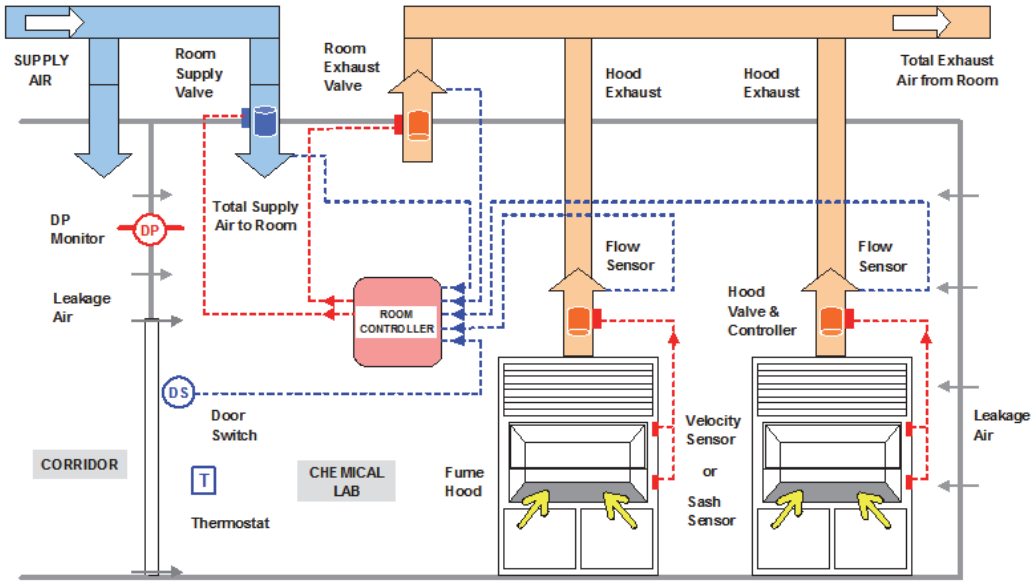


Figure 8.23 Example of a DF Control Technique

in field the offset value. A better strategy is to control the pressures of all the rooms together as an optimized system instead of independently. Adaptive control directly accounts for leakage flows between spaces in a suite and actively adjusts each room's flow offset according to an online pressurization model. It uses airflow and pressure differential measurements to estimate characteristics of leakage between spaces and adjust flow offsets automatically. This adaptive approach may be more suitable for suite pressurization, as discussed in the following section. For design procedures and control strategies, see the works by Wen et al. (2009) and ASHRAE (2015).

8.5.8 MULTIPLE-ROOM (SUITE) PRESSURIZATION

Pressurization for a suite of clean manufacturing spaces is more complex than pressurization for a single cleanroom. In practice, air leakage interactions between spaces

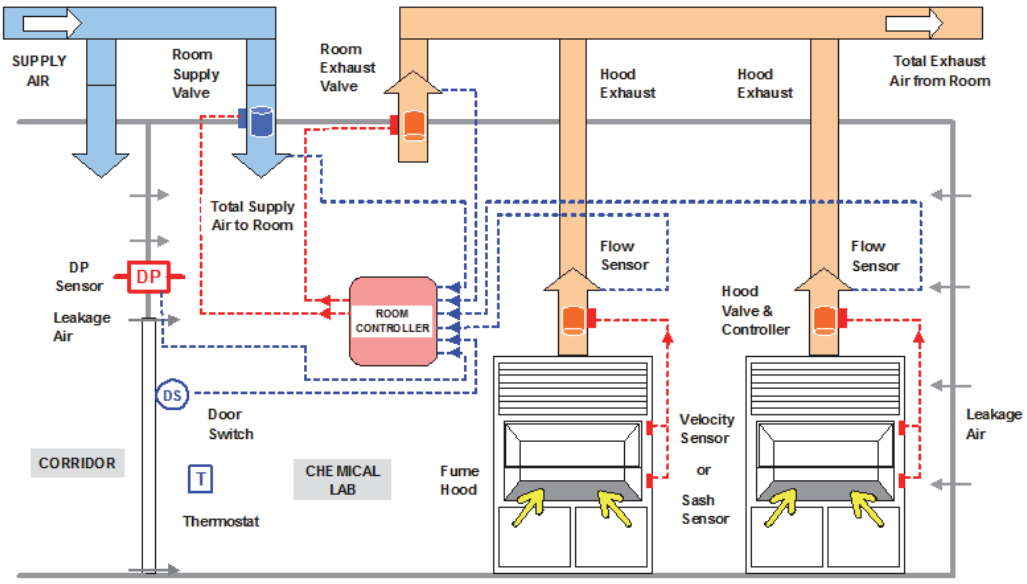


Figure 8.24 Example of a Hybrid Control Technique

have sometimes been neglected. However, because when air leaks out from one space it enters into another room or rooms, adjusting one room's offset value often affects adjacent rooms' previously balanced air pressures. Overlooking this fact can cause difficulties in commissioning and operation. Poorly designed pressurization could become unpredictable, unstable, or even fail to perform. For more information and procedures, consult the work by Wen et al. (2009).

A room pressure and flow (P&F) diagram for the controlled area (suite, zone, or floor) is often provided in design documents and can be used as the basis of continuous verification of cleanroom pressure control. As a best practice, the P&F diagram should typically indicate the following:

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

Figure 8.25 shows an example of a suite of four cleanrooms. Each room is equipped with a pressure differential sensor, supply air valve(s), and return or exhaust air valve(s). The suite controller can automatically adjust each room's offset value in order to achieve each room's desired pressure setting.

8.6 QUANTITATIVE ANALYSIS OF PARTICLE MIGRATION UNDER PRESSURE DIFFERENTIALS

How to quantify the level of particle migration into a cleanroom has been a topic of interest for many years. ASHRAE Research Project 1431 (Sun et al. 2011) revealed a new method to assess and quantify this level. An aerosol particle sensing method is typically used to measure the containment level. The risk level of cleanroom particle contamination

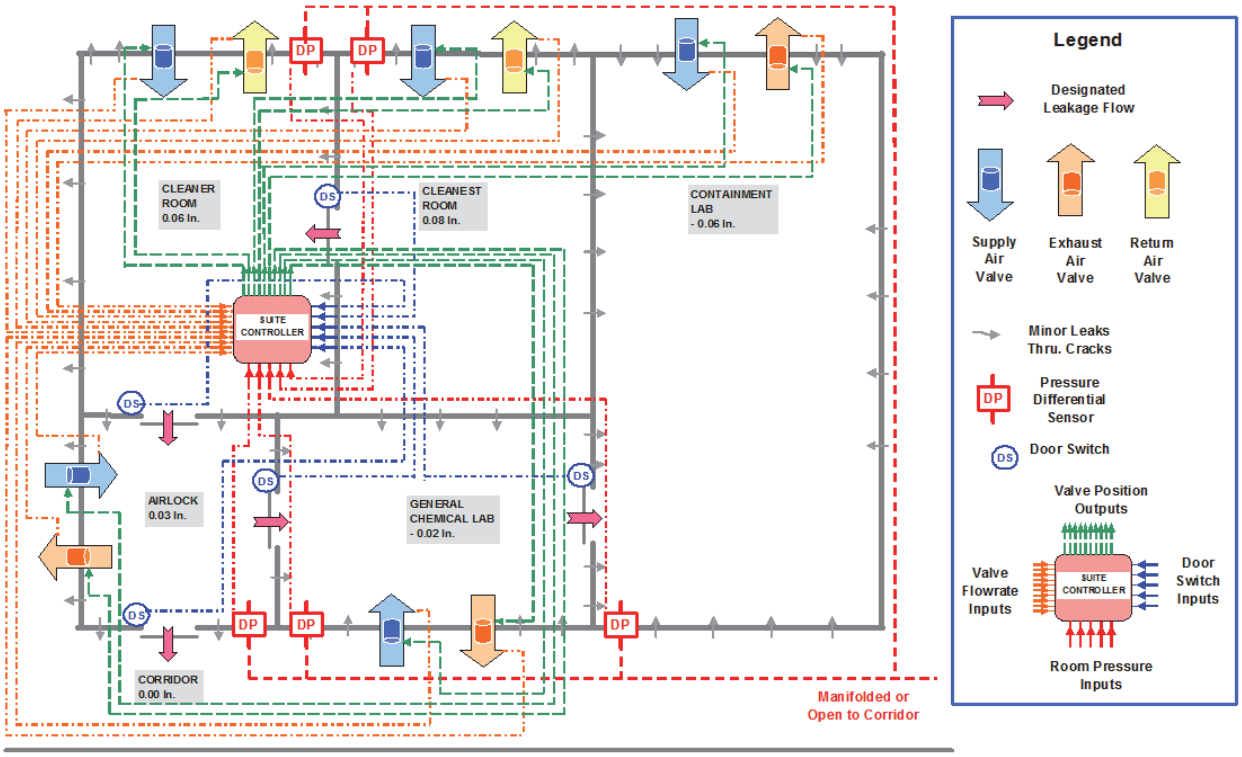


Figure 8.25
Example of an Adaptive Control Technique for a Suite of Multiple Rooms

can be expressed as a new terminology called *contamination rate* (CR) as follows (Sun et al. 2011, 2013a, 2013b):

$$\text{CR} = (P_C - P_B)/P_O \quad \text{or} \quad \text{CR} = P_C/P_O \ \text{(when } P_C \gg P_B\text{)}$$

where

CR	=	particle contamination rate, %
P_C	=	particle concentration inside cleanroom behind door under challenge
P_B	=	initial background particle concentration inside cleanroom behind door without challenge
$P_C - P_B$	=	particle concentration gain inside cleanroom behind door due to challenge
P_O	=	particle concentration in corridor or in front of cleanroom entrance door as contamination challenge

CR is defined as the airborne particle concentration gain above the initial background concentration in a protected cleanroom over the particle concentration in the corridor that is the source of the particle challenge. CR is a criterion to quantity the effectiveness of a cleanroom barrier in preventing particle migration into the cleanroom. Obviously the lower the CR level, the better the performance of the barrier's effectiveness. A single door can act as a simple form of a barrier, and a two-door in-series air lock is a more complex barrier, as are a minienvironment, a glove box, or an entire sealed enclosure. Their common goal is to minimize particle migration into a protective or clean space.

In order to compare the relative contamination levels in terms of CRs for future tests by others, the locations of the particle sensors inside a protected cleanroom and in the

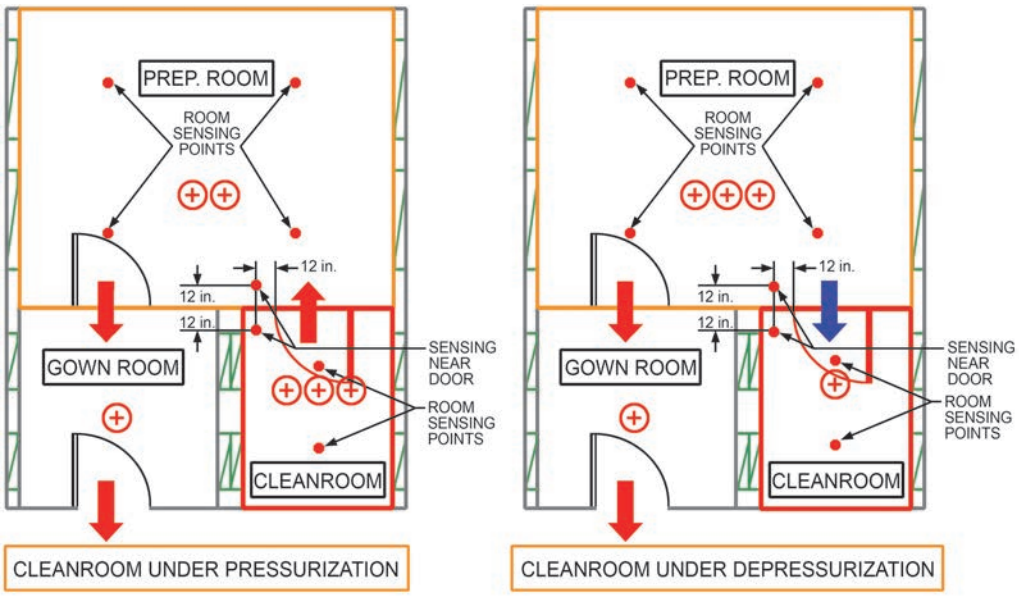


Figure 8.26 Protocol of Particle Sensor Locations in an Example Study of a Suite of Three Cleanrooms

corridor across the barrier door must be in a defined protocol or standardized; if the locations are not clearly defined, the CR values could vary. To satisfy the majority of real-world applications, ASHRAE RP-1431 (Sun et al. 2011) set up a test protocol of standardized sensor locations as follows:

- Sensor height: half of door height (if a door is 84 in. [2.2 m] tall, the height for sensors is 42 in. [1.1 m])
- Sensor distance from wall: two sensors, one on each side of the door, 12 in. (300 mm) away from the wall that holds the door
- Sensor distance from door edge (next to traffic path): 12 in. (300 mm)

Figure 8.26 shows the sensing locations for the CR definition in relationship with average room concentration sensing. The reasons to define the sensors' positions as indicated in Figure 8.26 are follows: First, the vicinity around the door opening is the most sensitive area to study particle migration, as the dirty particles have to pass through this area to impact the rest of the cleanroom space. Second, for convenience and undisrupted traffic, in real-world applications it is rare to place process or production equipment so close to a door, so the door vicinity (not on the traffic path) is a commonly feasible area for sensor placement. Last, the mid-height can be easily identified for a door of any height or size.

8.6.1 PARTICLE MIGRATION ACROSS A CLOSED DOOR WITH A PRESSURE DIFFERENTIAL

Figure 8.27 shows the test result of a door-closed condition where the CR value increased significantly for both 0.5μm and 1.0 μm particle sizes when the cleanroom pressure differential ΔP changed from negative to positive and further increased; however, when ΔP is further increased above 0.04 in. w.c. (10 Pa), the CR may not decrease much further. A minimum of 0.04 in. w.c. (10 Pa) for room pressure differential is adequate; anything below that level could be risky, and the benefits of setting the pressure differential higher above that level are not very significant.

8.6.2 PARTICLE MIGRATION DURING DOOR-IN-OPERATION UNDER AN INITIAL PRESSURE DIFFERENTIAL

The CR value is much higher during the door-in-operation condition than at the door-closed condition, as indicated in Figure 8.28. This figure also illustrates the impact of human walk-through influence during door operation. It was found that human traffic can decrease the CR value slightly when the cleanroom is under negative pressure and increase the CR value slightly when the cleanroom is under positive pressure.

8.6.3 ILLUSTRATION OF CONTAMINATION RATE FOR DOOR-IN-OPERATION CONDITION

The definition of CR during door operation is shown in Figure 8.29. Of course, a similar figure can be generated for a door-closed condition, but the time duration would be much longer to show the effect from next-door particle challenge.

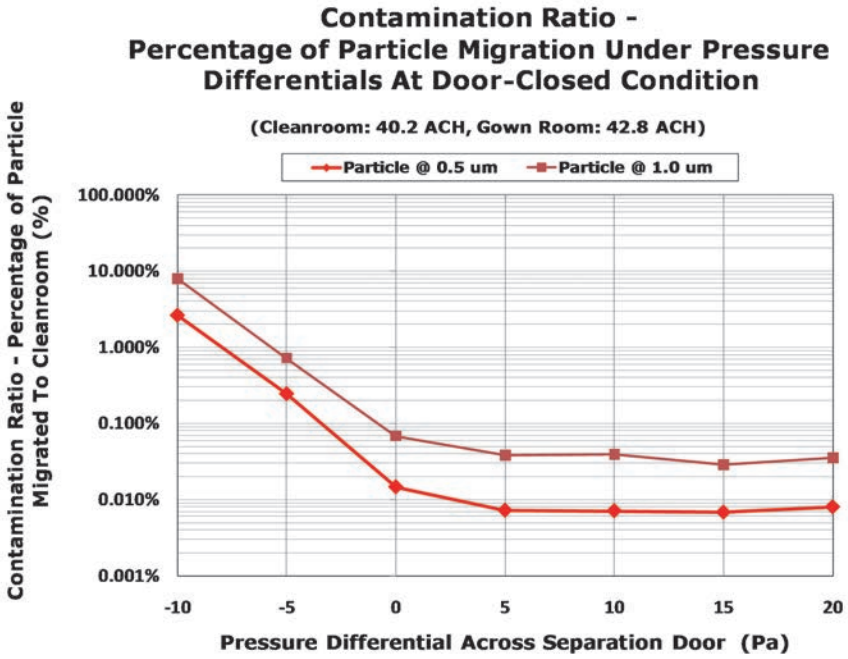


Figure 8.27 CR Values Across a Closed Door Under Pressure Differentials

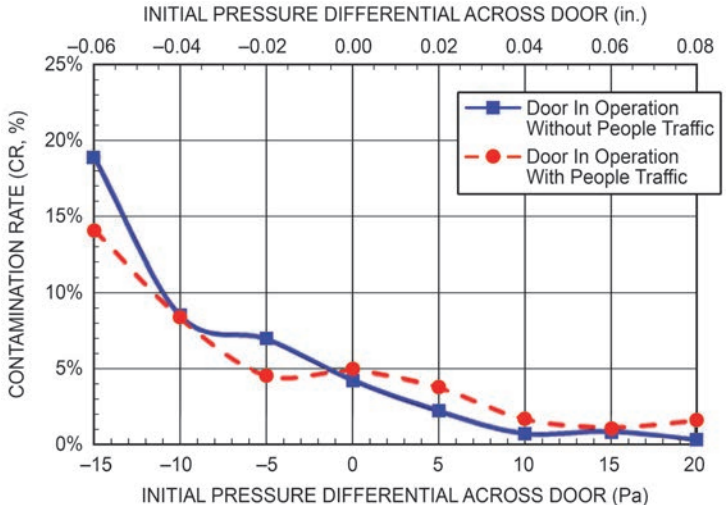


Figure 8.28 CR Values During Cleanroom Door-In-Operation Under Initial Pressure Differentials

8.6.4 WHY BOTH STATIC AND DYNAMIC CONTAMINATION CONTROLS NEED TO BE CONSIDERED IN DESIGN

A typical cleanroom door could be operated many times a day. Test data show that the CR at the door-open condition is much higher than at the door-closed condition, although its duration is much shorter. Many factors, such as pressure differential, cleanliness class difference, leakage condition, etc., can greatly impact the daily accumulated contamination results. Figure 8.30 illustrates that the impacts from both static (door-closed) and dynamic (door-in-operation) conditions could be equally important for practical applications. The daily frequency of door operation is also a key element in overall daily contamination. It is recommended that a daily door operation over 30 times be considered "frequent operation" and that dynamic contamination control should be considered.

8.7 PARTICLE MIGRATION ACROSS A CLOSED DOOR UNDER SIGNIFICANT CONCENTRATION DIFFERENCE

It is very important to understand that in addition to the pressure differential, which can force a desired airflow path carrying particles, the particle concentration differential can also create an air exchange due to mass diffusion between two areas with a significant particle concentration difference to allow the concentrations in both rooms to reach an equilibrium. If the time is adequately long enough, the path of the particle exchange is through the connecting cracks or openings. In a typical pressurized cleanroom case, these

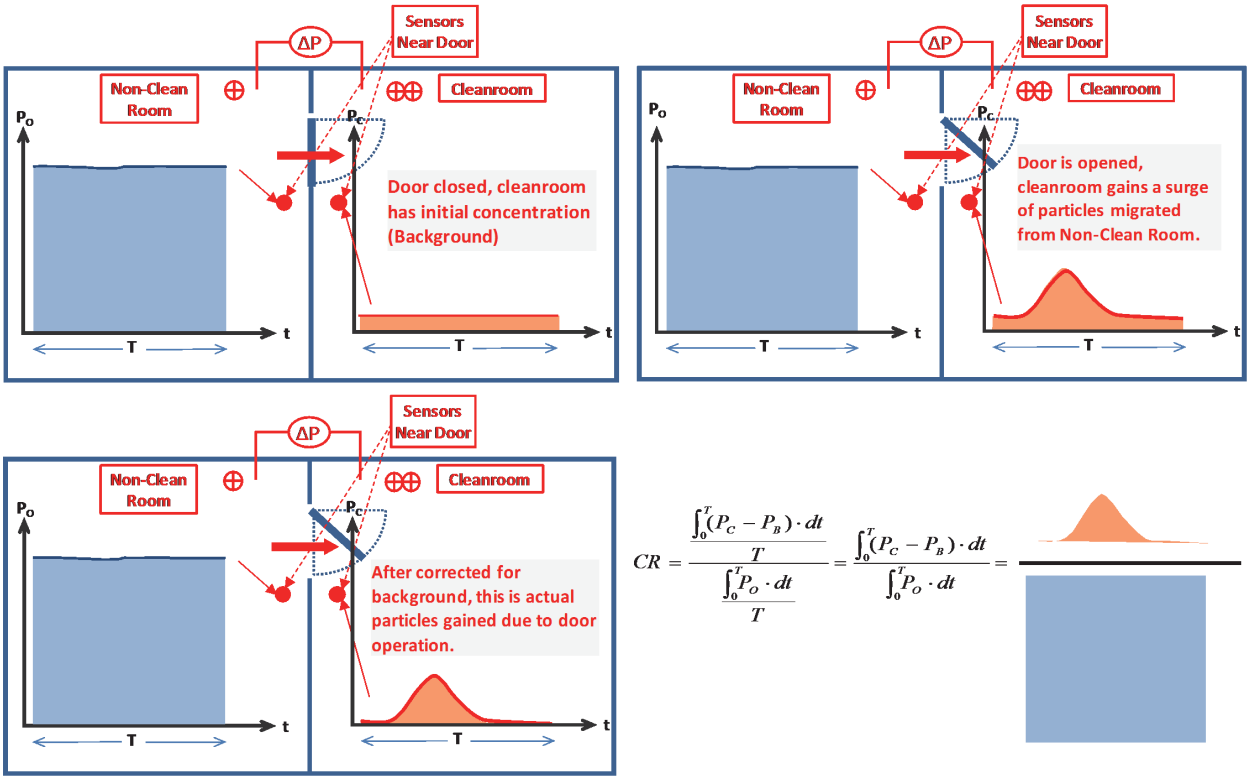


Figure 8.29
Illustration of Contamination Rate for Door-in-Operation Condition

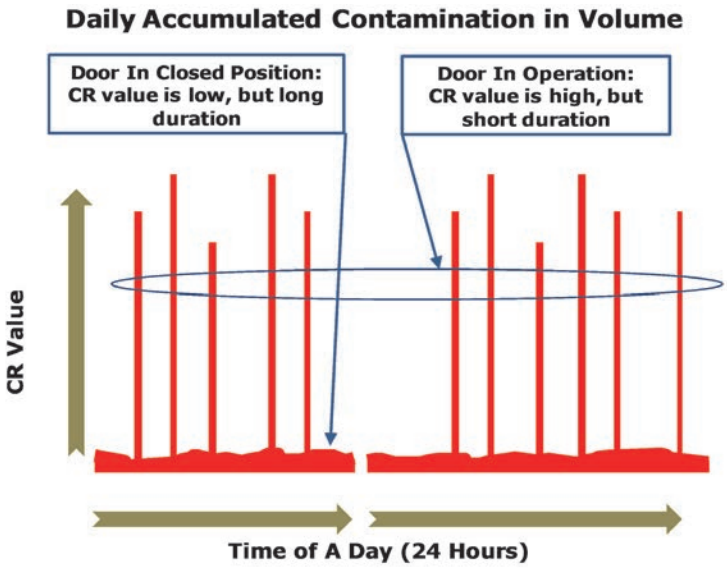


Figure 8.30 Daily Accumulated Contamination During Door-Closed and Door-in-Operation Conditions

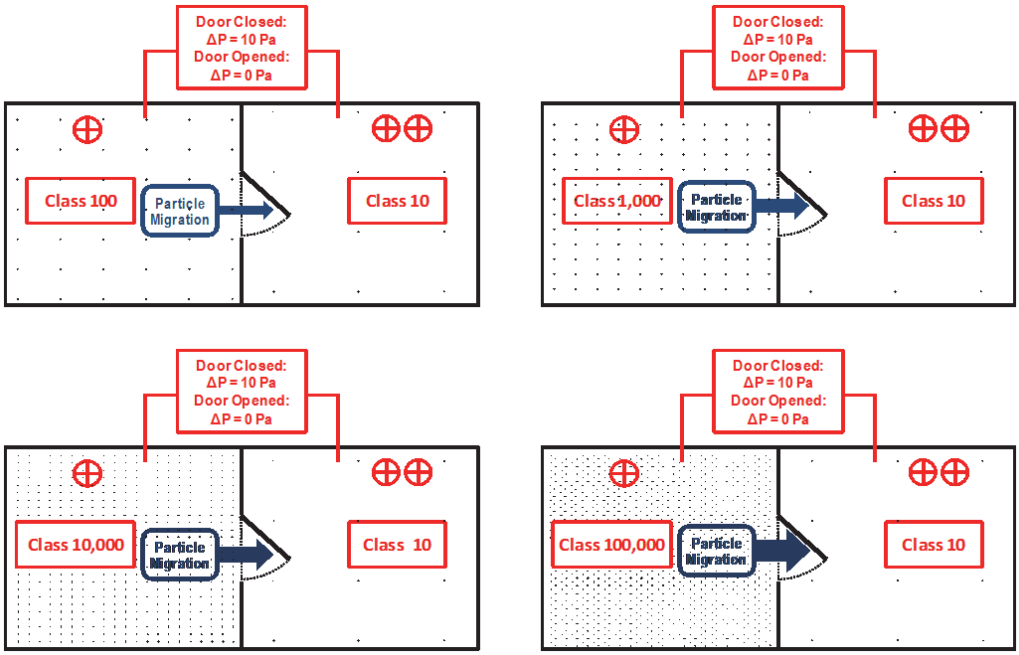


Figure 8.31 Increased Transport of Particles (Mass Diffusion) into Cleanroom when Adjacent Area is Much Dirtier

two particle flow paths (by pressure differential and particle concentration differential) are in the opposite directions, the sum of two opposite flows is the net leakage flow, and the net particle exchange is typically that a cleaner room gains more particles from the dirtier side though the cleaner room's pressure is higher, because the ΔP brings fewer particles to the dirtier room and the dirtier room releases many more particles to the cleaner room due to mass diffusion, as illustrated in Figure 8.31.

8.8 REQUIRED PRESSURE DIFFERENTIAL ACROSS CLEANROOM ENVELOPE

A cleanroom envelope (including doors) is a natural barrier to contain particle migration. However, when a door is opened for traffic, the initial pressure differential across the

Table 8.6 Recommended Minimum Pressure Differential (ΔP) Across Cleanroom Envelope to Control Nonviable Particle Migration from Adjacent Less-Clean Area

Cleanliness Class Difference Between Cleanroom and Adjacent Less-Clean Area	Door Closed (Static) Minimum ΔP Between Rooms	Door In Operation (Dynamic) Installation of Air Lock
One-class difference (e.g., ISO Classes 7 and 8 adjacent rooms across door)	0.04 in. w.c. (10 Pa)	Not Required
Two-class difference (e.g. ISO Classes 6 and 8 adjacent rooms across door)	0.04 in. w.c. (10 Pa)	Required if door operation is frequent (more than 30 times daily) • Install a two-door air lock to replace a single door that separates two areas • Minimum 0.02 in. w.c. (5 Pa) across each door of the air lock • Time delay between two doors in air lock Not Required if door operation is not frequent (30 times or less daily)
Three-class or more difference (e.g., ISO Classes 5 and 8 adjacent rooms across door)	0.04 in. w.c. (10 Pa)	Required • Install a two-door air lock to replace a single door that separates two areas • Minimum 0.02 in. w.c. (5 Pa) across each door of the air lock • Time delay between two doors in air lock
Cleanroom surrounded by non-cleanroom areas		

door/envelope disappears much more quickly (typically in less than 0.25 s) before a door operation cycle (typical 6–10 s) to close the door, also much more quickly than any airflow control devices (such as air valves) modulate from prior flow positions to the new positions (1–2 s).

The magnitude of particle migration is much higher at the door-in-operation (dynamic) condition than at the door-closed (static) condition. Additional treatment is required and associated design criteria need to be considered for door-in-operation conditions.

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

Table 8.6 shows the recommended minimum pressure differential (ΔP) across the cleanroom envelope. This table is intended to be used by cleanroom design professionals without the need to utilize calculation tools. It shows that a minimum ΔP of 0.04 in. w.c. (10 Pa) is required to minimize particle migration under door-in-operation conditions and that under door-closed conditions, a ΔP over 0.02 in. w.c. (5 Pa) does not result in extra reduction of particle migration. In other words, if a door is never opened, then a ΔP of 0.02 in. w.c. (5 Pa) is adequate. But doors are purposely used for traffic of people, materials, or products. Therefore, considering particle migration under the door-in-operation condition becomes the dominant factor, and 0.04 in. w.c. (10 Pa) is therefore selected as the minimum requirement.

8.9 CLEANROOM AIR LOCKS

8.9.1 OVERVIEW

A unique feature in cleanroom facilities is the installation of an air lock at each entrance and exit for equipment, materials, personnel, and/or product traffic. Air locks are critical components of cleanrooms to ensure both the safety of workers and product qual-

ity. An air lock acts as a barrier of particle and/or biological contaminant by minimizing the flow of contaminated air from less-clean or unclassified corridors into clean spaces (Sun et al. 2011).

A cleanroom air lock is a transitional space with two doors in series that separates two rooms with different air cleanlinesses that are often also maintained at different pressures. The two doors should be interlocked to avoid them being opened at the same time. An air lock space is often equipped with HEPA-filtered supply air and return/exhaust air at a low sidewall or raised floor. However, the relative air volumes for supply, return, or exhaust could vary significantly based on the type and functionality of the air lock. Air locks can be classified as cascading, bubble, sink, or dual-compartment types (see Figure 8.32). Each of these types exhibits different airflow directions and pressure differences between the cleanroom, air lock, and corridor.

The most stringent air locks are installed in cleanrooms and laboratories classified with biosafety levels (BSLs) 3 and 4, as described in *Biosafety in Microbiological and Biomedical Laboratories* (CDC 2009). Mechanisms similar to air locks but less stringent (with pressure but without cleanliness requirements) are often found as anterooms in isolation suites in health care facilities and as vestibules in commercial buildings; these typically have no pressure control requirements.

Poor air lock design could result in severe failures, such as leakage of microbiological agents (toxic, harmful, and/or infectious) or chemical fumes into the corridor and other general or office areas or contamination of clean products with excessive particles or microbes. Where product quality or personal safety is critical, unreliable, poor-performing, or malfunctioning air locks are unacceptable (Sun et al. 2011).

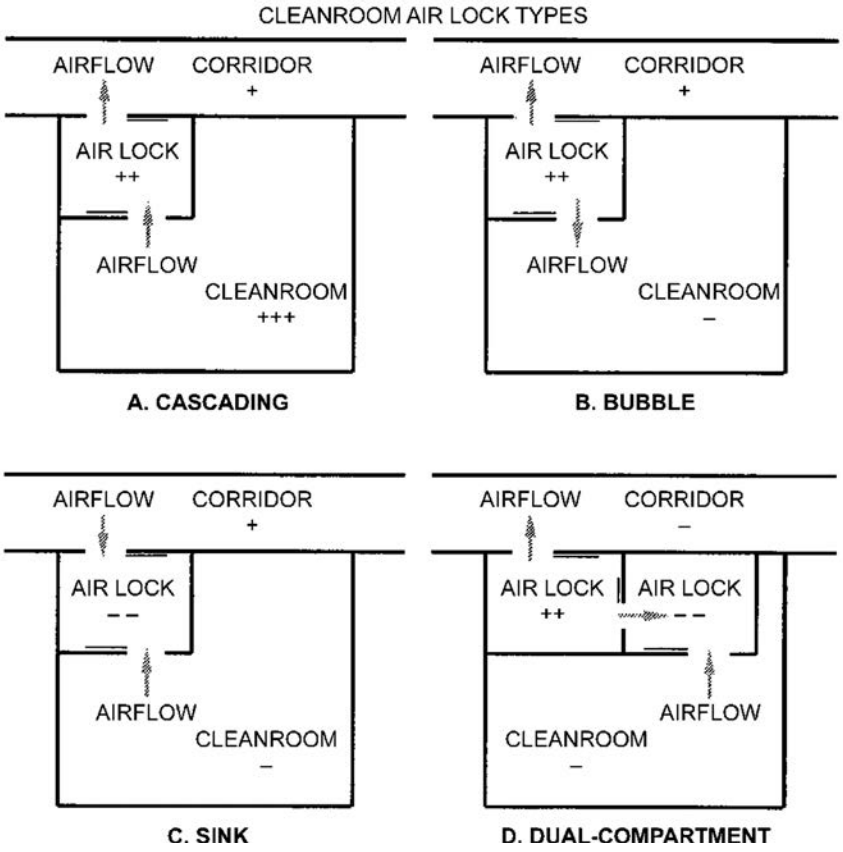


Figure 8.32 Types of Cleanroom Air Locks

8.9.2 BARRIER EFFECTIVENESS AGAINST PARTICLE MIGRATION

Related to CR, barrier effectiveness (BE) is defined as the percentage of airborne particles (expressed in concentration) blocked from entering the protected cleanroom from the outside corridor:

$$BE = 1 - CR \tag{8.14}$$

where

BE = barrier effectiveness against particle migration under challenge, %
CR = contamination rate

BE is a criterion to quantify the effectiveness of cleanroom particle containment in preventing particle migration into the cleanroom through a barrier device, such as a single door or a double-door air lock, etc.

8.9.3 ANALOGY OF TERMINOLOGIES BETWEEN FILTRATION AND AIR LOCK

Air filters are known as effective devices to resist particle transmissions and trap particles in AHU systems. In open air, similarly, air locks can impose barriers to minimize particle migration from corridors into cleanrooms, and an analogy can be made between air filter and air lock performances in Table 8.7. Figure 8.33 illustrates this performance analogy. Like filters, which are good barriers to capture particles and to reduce particle transport inside air ducts, air locks are good barriers to reduce particle migration from less-clean areas into cleanrooms.

8.9.4 TIME-AVERAGED CONTAMINATION RATE AND DAILY ACCUMULATED CONTAMINATION RATE

As CR values vary between door-closed and door-in-operation conditions, to analyze the overall contamination over a period of time that also counts the frequency of door operations, a new terminology called *time-averaged contamination rate* (Sun et al. 2011) is necessary:

$$CR_T = \frac{\int_0^T CR_{(t)} \cdot dt}{T} = \frac{\int_0^T \left(\frac{P(t)_c - P_b}{P(t)_o} \right) \cdot dt}{T} = \frac{\int_0^T \left(\frac{P(t)_c}{P(t)_o} \right) \cdot dt - \int_0^T \left(\frac{P_b}{P(t)_o} \right) \cdot dt}{T} \tag{8.15}$$

where

CR_T = time-averaged contamination rate over a time period, dimensionless
$CR_{(t)}$ = contamination rate at any time, dimensionless
T = time period under consideration, s
$P(t)_c$ = particle concentration in cleanroom near door at any time, counts per ft^3 (m^3)
$P(t)_o$ = particle concentration in corridor near door at any time, counts per ft^3 (m^3)
P_b = cleanroom initial background particle concentration, counts per ft^3 (m^3)

Typically, an initial background concentration reading P_b is taken without corridor particle challenge, so $P_b < P_c \ll P_o$; if P_c is less than 0.1% of P_o, then $\frac{P_b}{P(t)_o}$ can be ignored, so Equation 8.15 becomes Equation 8.16:

Table 8.7
Analogy of Terminologies Between Filtration and Air Lock Performances

Terminology		Mathematical Definition
Air Filter	**Air Barrier Device (Single Door, Air Lock, etc.)**	
Penetration rate	Contamination rate (CR)	Percentage of particles that penetrate through a filter media or a barrier device
Efficiency	Barrier effectiveness (BE)	Percentage of particles blocked by a filter media or a barrier device
Penetration rate + Efficiency = 100%	CR + BE = 100%	

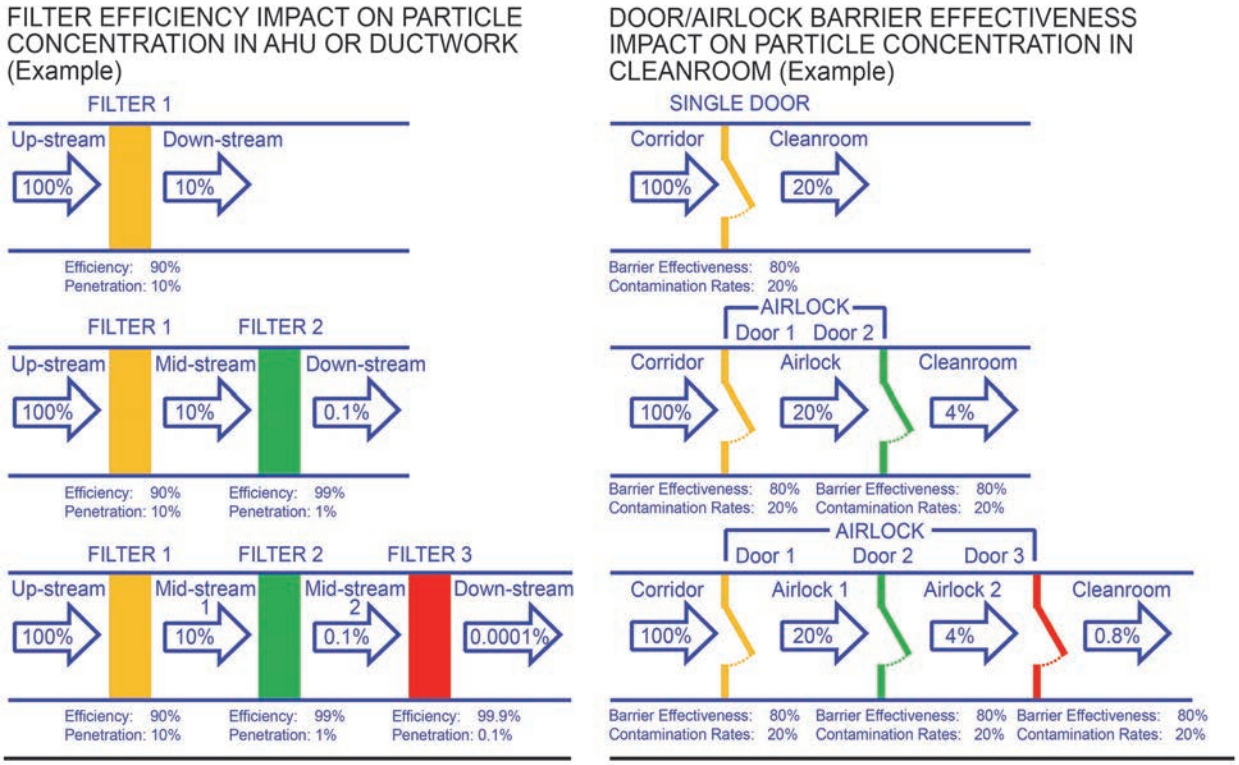


Figure 8.33
Analogy between Filter and Air Lock Door Performance

$$CR_T = \frac{\int_0^T CR \cdot dt}{T} \approx \frac{\int_0^T \left(\frac{P(t)_c}{P(t)_o}\right) \cdot dt}{T} \tag{8.16}$$

where $\int_0^T CR \cdot dt$ can be called the accumulated contamination rate during a time period; if a 24-hour day is used, then we can call it the daily accumulated contamination rate. The daily accumulated contamination rate can be taken during a typical operational day, which is a good representation for analyzing the overall contamination for an extended time period. This value includes the scenarios not only at door-closed and door-open conditions but also the frequency of door operations. Table 8.8 well illustrates how these three factors influence the overall particle contamination.

Table 8.8 Daily Accumulated Contamination for Door-Closed and Door-in-Operation Conditions (Example)

	Door in Operation	Door in Closed Position
Times of door operation per day	54	
Total seconds per day (24 h)	86400 (= 24 × 60 × 60)	
Total duration per door operation	8 s	
Resulting contamination duration each time	16 s	
Resulting contamination duration total seconds per day	864 (= 16 × 54)	
Door status, percentage of time per day	1% (= 864/86400)	99%
CR value (cleanroom @ 0.04 in. [10 Pa])	0.8	0.008
Accumulated contamination (cleanroom @ 0.04 in. [10 Pa])	0.8% (=1% × 0.8)	0.8% (+ 99% × 0.008)
CR value (cleanroom @ –0.04 in. [–10 Pa])	8	0.08
Accumulated contamination (cleanroom @ –0.04 in. [–10 Pa])	8% (= 1% × 8)	8% (= 99% × 0.08)

Assumptions are CR values and that an air lock, as a main entrance to a cleanroom, is operated (opened) 54 times a day.

8.10 AIR LOCK GENERAL APPLICATION

A cleanroom air lock is constructed as a transitional space with two or three doors in series to separate two rooms of different air cleanliness and often maintained at different pressures. In a single air lock design, the two doors are interlocked to avoid opening of both doors at the same time.

Air locks not only demand energy and floor space but also constitute a critical component of cleanrooms to ensure product quality and the safety of workers. An air lock performs as a particle and/or biological contaminant barrier by minimizing the flow of contaminated air between clean spaces and less-clean or unclassified corridors.

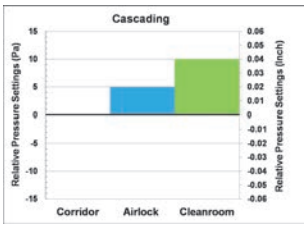
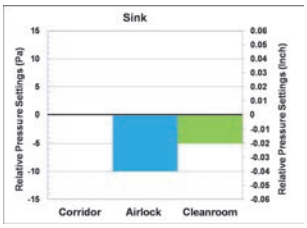
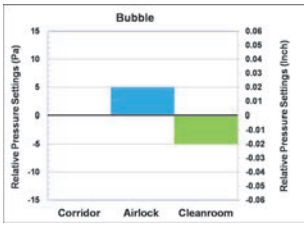
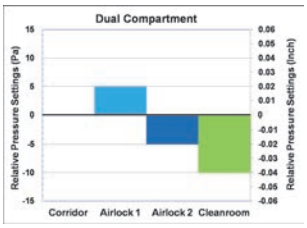
Air lock spaces are often equipped with high-volume ceiling HEPA-filtered supply air and low sidewall returns or raised floors for air return or exhaust. The room pressure is stringently controlled, and depending on the pressure difference between the cleanroom and the corridor, air locks can be classified as cascading, bubble, sink, or dual-compartment types. Each of these types exhibits different airflow directions and patterns based on the pressure difference between the cleanroom, the air lock, and the corridor. General cleanroom air lock applications are summarized and tabulated in Table 8.9.

8.11 PERFORMANCE COMPARISON AMONG AIR LOCKS

Figure 8.34 illustrates an average testing result from multiple cleanroom suites equipped with various types of air locks: the x-axis lists four types of air locks; the y-axis indicates the tested CR values after the first, second, or third door of each air lock type; and the three colors show the CR test values at three pressure differentials across each door of an air lock.

Among the types of air locks, barrier effectiveness against airborne particle migration through the first door, in the order of increasing effectiveness, is sink, dual-compartment, cascading, and bubble. The first door of a sink air lock does not perform as well as the others; because it has the lowest pressure in the air lock, it actively draws dirty particles from the corridor. It is a similar case for the dual-compartment air lock since its second air lock acts as a sink.

Table 8.9 Air Lock Types, Purposes, and Pressure Arrangements

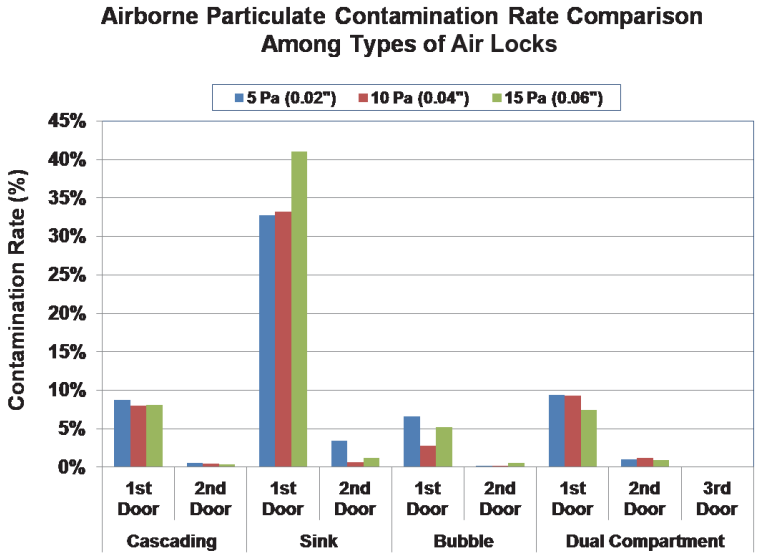
Cleanroom Characteristics	Air Lock Type	Air Lock Purposes	Recommended Relative Pressure Relationship
• Positive pressure • No fume or biological agent • No containment needed	Cascading	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom being contaminated from surrounding spaces through cracks	
• Negative pressure • Has fume or biological agent contamination • Containment needed	Bubble	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom fume or biological agent releasing to corridor	
• Negative pressure • Has fume or biological agent contamination • Containment needed • No personal protective equipment (PPE) needed	Sink	• Prevent cleanroom being contaminated by dirty corridor air • Allow cleanroom fume or biological agent releasing to air lock (no PPE needed)	
• Negative pressure • Has toxic fume or hazardous biological agent contamination or has potent compound substances • Containment needed • PPE (such as pressurized suit and respirator) required	Dual-compartment	• Prevent cleanroom being contaminated by dirty corridor air • Prevent cleanroom fume or biological agent releasing to corridor	

Notes:
A pressure differential value (pressure gap) across each air lock door is recommended. Typically each gap can be set at a minimum of 0.02 in. w.c. (5 Pa).
Excessive negative pressure in cleanrooms is not recommended. If a clean space is not surrounded by other clean spaces, untreated dirty air can infiltrate through cracks in cleanroom enclosure.
A cleanroom service corridor often is designed with slightly positive or neutral pressure. Do not design it with negative pressure unless a dual-compartment air lock is used.

Barrier effectiveness against airborne particle migration through the second door, in the order of increasing effectiveness, is sink, dual-compartment, cascading, and bubble. Because the dual-compartment air lock has two air locks together, commonly bubble first then sink, the entire air lock set has three doors between the corridor and the cleanroom.

It is very obvious that dual-compartment air locks have the most effective overall performance. Therefore, for selection of a good barrier effectiveness among air locks, the order is dual-compartment, bubble, cascading, and sink. Trade-offs in cost and an increase in floor area must be considered in the selection of the most appropriate air lock type based on project requirements.

Figure 8.34 Performance Comparison among Air Locks



8.12 ENERGY-EFFICIENT AND COST-EFFECTIVE CLEANROOM DESIGN

Proper HVAC and filtration system sizing is essential for energy-efficient design and operation. Designs should also consider flexibility for future expansion. Careful planning and design execution strategies using an integrated design approach can produce more value on limited capital budgets, which is key to the definition of good engineering. Incorporating the following considerations can significantly improve the value of cleanroom facilities:

- Rightsizing Equipment
  - Slightly oversizing system design capacities can be critical to a well-functioning facility, but avoid compounding or multiplying safety factors applied at different stages of planning and design. Also, oversizing utility distribution systems to accommodate future expansions can yield energy-efficiency benefits.
  - Safety factors are often used to accommodate control process unknowns, temperature or operational extremes, future flexibility or known expansions, outdoor air unknowns, capacity and efficiency on air side
  - Diversity factor
  - Expandable design strategies, such as including utility connections for future equipment to defer capital expenditures
  - Flexibility and efficiency of distribution layouts
  - Ceiling heights and overall room volume reductions where air change rates impact system capacity
  - Energy-efficient components
  - Efficiency at the system level
  - Efficiency at the facility level
  - Efficiency at the site level
- Low Pressure Drop
  - Slower air velocities
  - More straight duct runs

- Improved turning vane and duct-fitting designs
- Oversized main trunks
- Prefilters and final filters with more surface areas and more media fill
- No bypass filter frames to improve filtration effectiveness
- Recirculation fans or FFUs to reduce the amount of ductwork for the highest airflow requirements
- Minienvironments or localized containment to reduce the size of the most critical cleanliness zones
- Multiple fans or pumps operated simultaneously for systems with redundant components

8.13 DEMAND-BASED CONTROL FOR CLEANROOMS

Demand control is an approach that is in use in many applications, such as with variable-air-volume systems to control room temperature, variable water flow to control a coil's capacity, and demand-controlled ventilation to decrease airflow to spaces when there is no demand, such as during low occupancy. Additionally, demand-based control has been widely applied to research laboratory spaces to vary laboratory room air change rates based on both particulate and chemical containment levels in a very similar control approach to what is proposed here (but in a laboratory environment, not a cleanroom). An *ASHRAE Journal* article, "Demand-Based Control of Lab Air Change Rates" (Sharp 2010), presents the results of a large study evaluating the results of applying this approach to laboratories and vivariums.

Although less commonly used in the past, this same technology and approach can also be applied to control cleanroom airflows. An in-progress ASHRAE Research Project, RP-1604, *Demand-Based Control for Cleanrooms* (Sun et al. forthcoming), is examining this concept and collecting qualitative data on the effectiveness of this approach.

The benefit of applying this demand-control concept in a cleanroom is a significant reduction in the average airflow rate and thus a large reduction in energy use. This is because the amount of time that the room is challenged with particle emissions is typically very small. Consequently, the best approach regarding setting cleanroom air change rates is to determine or vary the rate as needed based on the real-time quality of the air in the cleanroom. Implementing a dynamic approach to controlling minimum air change rates requires the ability to continuously measure particles in the cleanroom, but other parameters of interest may be desirable as well, such as total volatile organic compounds (TVOCs), carbon dioxide, and humidity. This information may then be integrated with the building management system for this or other control purposes.

Such an approach has not always been cost-effective, primarily because of the quantity and quality of sensors necessary for safely implementing this approach. The associated calibration and maintenance costs have also rendered this approach impractical for populating a large number of particulate sensors and potentially other sensors throughout a facility.

One approach for reliably and economically sensing cleanroom environmental conditions is to use multiplexed sensing (Sharp 2010), which uses a central set of multiplexed sensors to sense many different rooms or areas (not just one). This networked system routes samples of air sequentially and in a multiplexed fashion to a set of sensors instead of requiring multiple sensors to be placed in each room. Every 40 to 50 seconds, a sample of air from a different area is routed through a hollow structured cable to the centralized

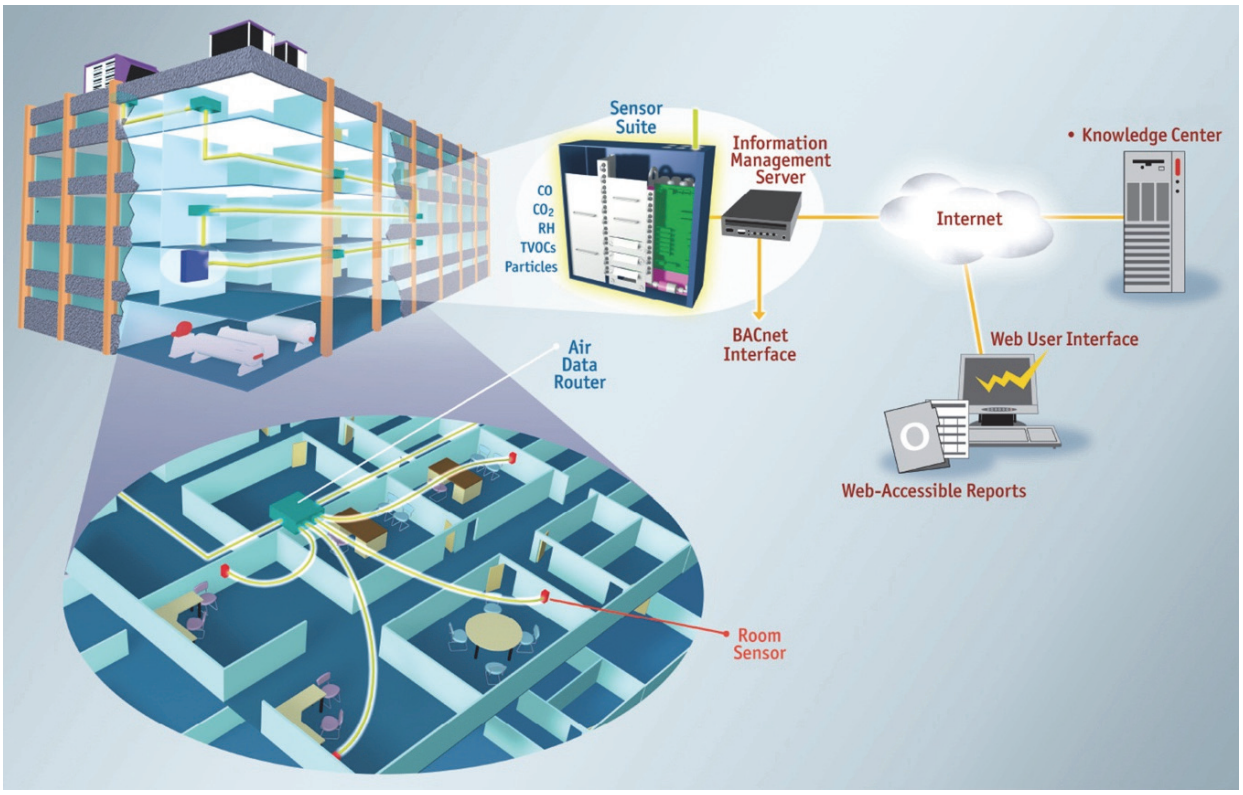


Figure 8.35
Facility-Wide Multiplexed Sensing Architecture
(Sharp 2010)

sensor set for measurement. These sequential measurements are then de-multiplexed for each sampled area, creating distinct sensor signals that can be used for monitoring and control (Sharp 2010). One set of sensors can sample 15 to 20 areas approximately every 15 minutes. Transport and tubing technologies now exist that can transport particles at least in the under 1 μm size range reliably with only small losses over distances up to about 500 ft (150 m).

This multiplexed sensing approach (Figure 8.35) can measure many different air parameters. In addition to a laser-based particle counter, a photo-ionization detector (PID) type of TVOC sensor may be beneficial for accurately detecting hundreds of commonly used chemicals that can volatize and become a safety concern. Carbon dioxide sensors and accurate dew-point or humidity sensors also can be very cost-effectively employed for other control and monitoring purposes.

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9 General Indoor Design Conditions and Considerations

9.1 TEMPERATURE

Cleanroom temperature is specified by indicating a desired value, either in degrees Celsius or degrees Fahrenheit, and a tolerance within which the actual temperature may be permitted to vary (e.g., 72°F±5°F [22°C±3°C]). Temperature fluctuations over time should be specified to define control parameters (e.g., ±0.1°F [±0.1°C] over 20 minutes).

9.1.1 PERSONNEL CONSIDERATIONS

In general, the need to maintain an environment within which personnel can function effectively is the prime reason for specifying temperature. Temperatures in the range of 70°F to 76°F (21°C to 24°C) are common for personnel engaged in light labor who are wearing garments such as smocks or lab coats. Where a full cleanroom garment is required, including headgear and foot coverings, the specified temperature is frequently lowered to within the range of 65°F to 72°F (18°C to 22°C). If personnel are engaged in vigorous activity, lower temperatures may be specified. To maintain comfort, the range over which temperature may be permitted to fluctuate is commonly specified as ±2°F or ±3°F (±1°C or ±1.5°C). If the range exceeds these values, personnel are likely to complain of feeling too hot or too cold, which in turn adversely affects their ability to work efficiently.

9.1.2 PROCESS-RELATED CONSIDERATIONS

Other common reasons for temperature control are process related. For example, temperature stability may be required for obtaining precise measurements. Certain chemicals are affected if temperatures are too high or too low, and precise temperature limits may be needed to achieve certain chemical reactions. The user should identify such process-related requirements and the acceptable range for temperature fluctuation. Requirements should be specified as early as possible in the cleanroom design process to allow for appropriate budget and design determinations.

When process considerations take precedence over human comfort needs, changes in required garments or work schedules should be considered to provide a suitable work environment.

Heat-generating equipment in a cleanroom may cause localized temperature fluctuations as a result of the effects of radiant heat. Special consideration should be given to this phenomenon if such equipment will operate only intermittently.

9.1.3 CONSTRUCTION MATERIALS AND TEMPERATURE SPECIFICATIONS

Standard cleanroom construction materials will easily perform within the range of 60°F to 80°F (15°C to 27°C). If a cleanroom with an unusually low or high operating temperature is required, care should be taken to select materials that can withstand the rigors of temperature cycling as well as provide a nonshedding, low-off-gassing surface consistent with cleanroom requirements.

9.1.4 MONITORING AND CONTROL

Temperature should be monitored on a continuing basis to observe trends in the performance of the facility. Temperature trend changes may point to a need to perform maintenance on the mechanical equipment or may indicate a change in a cleanroom procedure that is affecting temperature levels. Chart recorders or computerized data acquisition trend analysis are commonly used for this purpose.

9.2 HUMIDITY

Cleanroom humidity is specified as a desired value of percent relative humidity and a tolerance range for variation (e.g., 45±5% rh). An alternative to the use of relative humidity is the specification of a dew-point temperature (e.g., 50±2°F [10±1°C]).

Dehumidification to dew points approaching freezing or below freezing may be achieved via refrigeration or subcooling, but allowance for ice accumulation must be considered. Dehumidification via chemical desiccants may also be used, but unforeseen contamination from the desiccant may occur. A complete cost of ownership analysis should be performed when designing low-dew-point cleanroom environments. Specifying cleanroom humidity levels that are higher or lower than necessary may result in high initial and operating costs.

Cleanroom designers should be aware of process equipment that adds to moisture levels. Open baths frequently are part of a cleanroom environment. Specification of unrealistically low humidity in a space housing such equipment may be costly, and the desired levels of humidity may never be achieved. This type of process equipment should be segregated from processes that require low humidity levels and should be served by dedicated air-conditioning equipment.

A tolerance of ±5% rh can usually be achieved with standard air-conditioning controls. A tolerance of ±2% rh may be achievable with direct digital control (DDC) systems coupled with humidifiers and reheat coils for precise control. A tolerance of less than ±2% rh may be achievable with high-quality industrial electronic controls where outdoor air is preconditioned before entering the cleanroom conditioning system. Stringent tolerance requirements tend to be expensive and difficult to achieve and maintain over an extended period. Therefore, cleanroom designers should work carefully with cleanroom owners when very precise humidity control is needed to support process requirements.

9.2.1 CONSTRUCTION MATERIALS

Standard cleanroom construction materials easily perform within the range of 30% to 70% rh. If a cleanroom requires an unusually low or high operating humidity, care should be taken to select materials that can withstand the rigors of humidity cycling and provide a nonshedding surface consistent with cleanroom requirements. In applications requiring very low humidity levels, the materials should be impervious to water vapor, and all joints in walls, floors, and ceilings should be of vaportight construction.

9.3 EXHAUST

The exhaust of large quantities of air from the cleanroom requires a large volume of makeup air to be introduced into the cleanroom to replace the exhaust air. This replacement air should be conditioned before entering the cleanroom. The greater the amount of outdoor air introduced, the higher the cost of conditioning. Exhaust air therefore should be kept to a minimum, consistent with code, personnel, and process requirements.

9.4 COST CONSIDERATIONS

As previously discussed, controlling the environment is the purpose of a cleanroom. Meeting the environmental requirements requires large amounts of HVAC equipment and their corresponding costs. In general, the more stringent the environmental requirements, the more sophisticated and larger the HVAC systems and thus the more costly they are. Cleanroom designers may discuss the cleanroom owner's specifications and highlight specific needs for temperature, humidity, pressure that are driving large capital equipment costs. For example, a low dew-point requirement requires special refrigeration equipment for desiccant dehumidification. The cleanroom designer can highlight this and confirm whether the low humidity specification is truly warranted. Each element of the cleanroom design (cleanliness classification, temperature and humidity specifications, exhaust requirements, etc.) can be assessed for its cost impact and discussed with the owner. The proposed operating hours can also have significant cost impacts. Does the owner need 24/7, 365 days per year operation requiring extensive equipment redundancies, or will the cleanroom only operate five days per week with little or no equipment redundancies? For many 24/7 cleanrooms redundant equipment costs are one of the most significant cost elements.

9.5 AIRBORNE MOLECULAR CONTAMINATION

Contaminants may be smaller than or have different characteristics from those specified in the standards used for classifying cleanrooms. Possible contamination by particulate contaminants that are smaller than 0.1 μm (the smallest size discussed in the normative section of ISO 14644-1 to classify air cleanliness [ISO 2015]) or that have characteristics other than physical size that may make them detrimental to the desired cleanroom environment should be considered in the development of the cleanroom design.

The particle generation mechanism is chemical rather than mechanical; therefore, the effects may be independent of the physical size of the process product. Because the force of adhesion of particles to a surface is inversely proportional to particle size, it is difficult to remove smaller particles from surfaces. Care should be taken to prevent the introduction of such particles into the cleanroom environment.

Contamination of this kind may also result from organic vapors due to solvent evaporation, plasticizers from off-gassing of polymers, acidic and basic compounds that react to form salts, dopants, and, less commonly, metallic or other elemental compounds.

See Chapter 4 for a detailed discussion of airborne molecular contamination (AMC).

9.6 MAKEUP AIR

Makeup air-handling units (AHUs) require a series of filters to remove particulates from the ambient air. These filters protect the coils and extend the life of the cleanroom's final high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filters.

Coarse prefilters or roughing filters of 25% to 30% dust spot efficiency (DSE) or minimum efficiency reporting value (MERV) 7 per ASHRAE Standard 52.2 (ASHRAE 2017) (extended media) are followed by bag or box extended-surface filters with a rating of 85% DSE, MERV 13, or greater. In some situations, rigid-frame 95% DSE, MERV 14, or 99.97% HEPA filters are installed as a third filtration stage of makeup AHUs.

Carbon or other adsorbents may be a consideration in facilities where AMC is a concern to the process or product. Multiple adsorbent types may be used together to most effectively remove the contaminants of most concern to the particular product or process, such as to remove acids, bases, organics, ozone, sulfur dioxide, or other compounds of concern.

9.7 PROCESS EXHAUST

Process exhaust is very process specific. See specific application chapters of this guide for discussions of process exhaust for particular activities.

9.8 FILTRATION SYSTEMS

For most cleanrooms, particle control is the first priority to achieve a desired cleanliness class. Preventing particles from entering the cleanroom is achieved with one or more stages of filtration. These stages may be remote from the cleanroom or contained within the cleanroom recirculation air handlers (RAHs).

HEPA filters are located downstream of the RAH fan. The filters should have a minimum efficiency of 99.97% for 0.3 µm particles. Higher-efficiency filters (99.99% or greater) should be considered if the filter installation is required to meet a minimum total penetration (integrity) test.

The quality of the filters is determined by the room cleanliness and filter integrity testing requirements. Integrity of terminal filters is determined using a scan test method described in IEST-RP-CC034 (IEST 2016). Appropriate aerosol injection ports as well as ports to measure challenge aerosol concentrations upstream and downstream of the filter bank are required. Aerosol mixing and uniformity should be considered when selecting port locations. Installations having multiple filters should also be accessible from upstream and downstream of the filter bank for visual inspection, troubleshooting, and repair.

Critical nonunidirectional-flow cleanrooms and all unidirectional flow cleanrooms typically have the final HEPA/ULPA filters mounted in the cleanroom ceiling. The cleanroom HVAC systems use a pressurized plenum, ducted filters, or fan filter units (FFUs).

The normal expected media penetration of the most penetrating particle size (MPPS) and the methods and materials needed to perform in-place testing of the filters should be considered when specifying the filter type and efficiency requirements. The penetrating aerosol may appear as "background" when performing the scan test. The selection of alternative types or higher-efficiency filters may reduce or eliminate the background from most on-site integrity tests. A thorough understanding of filter manufacturer test methods versus how the filter will be tested in-place is also advantageous.

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AIR CONDITIONING COMPANY

10 Cleanroom Electrical Systems

Cleanrooms can have an energy use index (EUI) of 27,373 to 41,107 kWh/ft^2 (2543 to 3819 kWh/m^2) for pharmaceutical factories (Boyd 2011) and greater than 100,000 kWh/ft^2 (10,000 kWh/m^2) for semiconductor factories (ITRS 2013). Each has been classified as an "energy intensive industry" in Europe (EC 2014). The high EUIs require significant power distribution within the overall facility. Additionally, cleanrooms require a high degree of power system reliability in the incoming power and the internal distribution system. For many 24/7 factories, power interruptions are not acceptable.

Detail and focused attention need to be provided to various aspects of the power distribution system and its components. A thorough understanding of the relevant codes, standards, and insurance carrier's requirements is the key to successful power distribution and operation of these facilities.

With a primary focus on microelectronics facilities, this chapter describes normal, emergency, and uninterruptible power supply (UPS) distribution concepts, including grounding, lighting, lightning protection, electromagnetic interference (EMI), and equipment types.

10.1 INTRODUCTION

A typical modern high-volume semiconductor manufacturing facility, called a *fab*, is composed of multiple floors, with a cleanroom on level 3. The level directly below the cleanroom is the "clean subfab," where the tool support equipment is located. This level is also clean, because it is part of the airflow path, meaning the same clean air travels from the level 3 through it. The level directly below the clean subfab is considered a "utility subfab" and is not considered clean. Most of the facility support equipment is located on this floor. This level is normally at the ground level in a single fab configuration. The level directly above the cleanroom is called *interstitial* and acts as the plenum for the pressured air compartment. See Figure 10.1 for a section of a flow-through fab with broken lines representing the airflow path.

The manufacturing tools are located within the designated cleanroom boundaries, isolated by a physical barrier from the rest of the facility. The facility equipment is mostly located in the non-cleanroom areas, such as support areas of the fab.

10.2 SITE MASTER PLANNING

Historical and benchmark data are used for load projections associated with a fab cleanroom. A growth factor is used for future unknown loads. Once the load projections

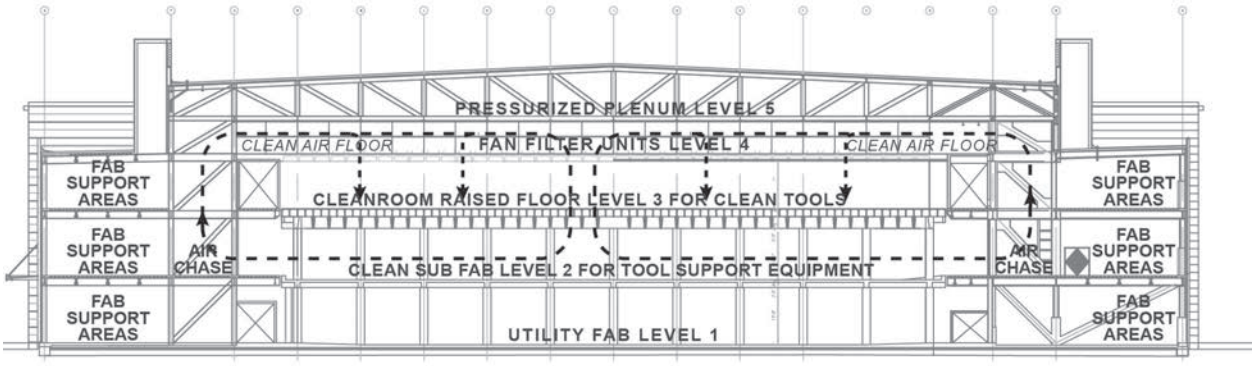


Figure 10.1
Cross Section of a Fab

are done, close coordination is essential for the timely availability of the power to the site. Capacity, right-of-way issues, and aggressive project schedules are some of the constraints that can stand in the way of the power company to commit to delivery of power.

Initial contact with the power company is recommended at the earliest stage of the project. In addition to needed capacity and the project schedule, the power company should be made aware of the need for two independent sources of power from separate substations of the power grid. The routing should be separate to avoid common mode fault conditions and total loss of power to the cleanroom. As a minimum, the two sources can be from the different buses of the same power company substation. The whole idea is to maintain continuity of power and avoid shutdown of the cleanroom.

10.3 RELIABILITY AND REDUNDANCY

10.3.1 RELIABILITY

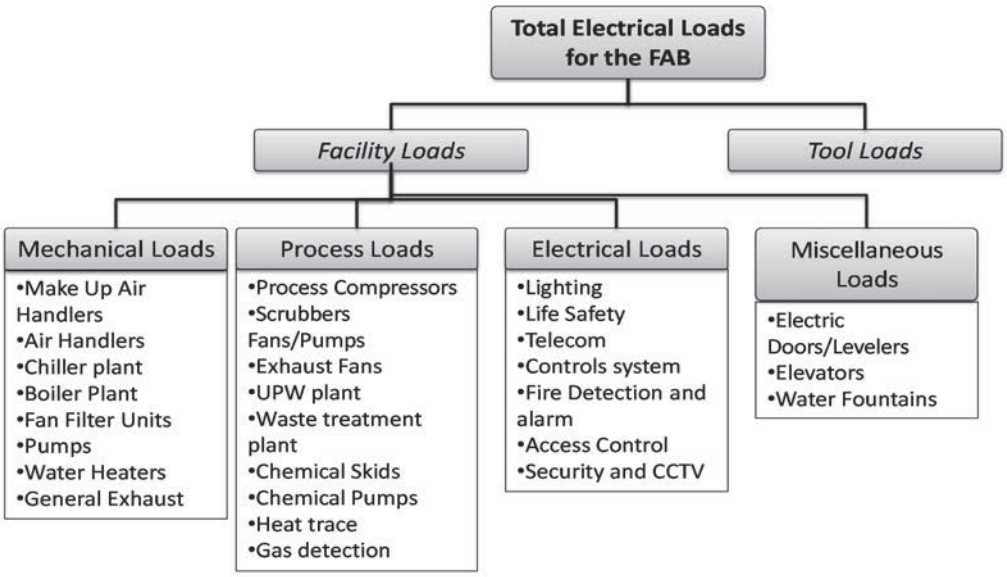
Power distribution to a fab starts with the local utility then goes through the various distribution transformations (e.g., 12.5 kV to 480 V) and to the individual power users. Within the fab power is also subdivided into normal power (power with little to no backup), emergency power (where codes may require backup power via a generator), standby power (where the owner may wish for backup via a generator), and critical power (as decided by the owner via a UPS). At each step the reliability must be assessed. Detailed investigation of the site location relative to the power company infrastructure needs to be part of the site assessment criteria. Remote location from the grid will impact the reliability of the incoming power supply due to exposure to environmental elements and other factors.

Selection of the electrical equipment requires a thorough investigation and is usually limited to well-known manufacturers in the industry. The equipment should have a low mean time between failures (MTBF) and offer the highest degree of reliability and perform its functions.

10.3.2 REDUNDANCY

Redundancy is provided in the electrical distribution network. Two sources of dedicated power are routed to a site substation, where multiple paths and redundant equipment make it possible to maintain continuity of power to the fab in the event of loss of line or the equipment within the substation.

Figure 10.2
Electrical
Load Blocks



Lighting systems within the cleanroom boundary and in the clean and/or utility subfab are provided from different, multiple sources to avoid single-mode failure.

Fan filter unit (FFU) power distribution is from different sources within the electrical network. Engine generators and UPS systems provide backup power to emergency, standby, and critical loads as defined by code or the owner.

Equipment requiring high reliability is provided power from different sources to avoid total loss of the power to that equipment. Diverse routes are used for power distribution to the redundant equipment.

10.4 ELECTRICAL LOADS

The electrical loads for a fab are broadly classified into tools and facility loads. Tool loads are for the manufacturing processes equipment and facility loads are for the support equipment, such as makeup fans, air handlers, chillers, ultrapure water (UPW) plant, and gas plants. See Figure 10.2 for an overall block diagram for the load classifications.

10.5 VOLTAGE AND FREQUENCY CONSIDERATIONS

A good understanding of the different types of electrical voltages and frequency requirements in the fab is fundamental to the design of the electrical distribution system. An approximate rule of thumb for many semiconductor fabs located in the United States is that around 80% of the tools need 208/120 V, three-phase, four-wire, 60 Hz power while 20% of the tools require 480 V, three-phase, three-wire, 60 Hz power. Table 10.1 lists systems and their corresponding voltages in different countries.

In some countries, depending on the tools' countries of origin, other voltages and frequencies may be required for tool operations and need to be provided as part of the electrical infrastructure. The solution to such isolated cases is to use local point-of-use (POU) transformers for voltage compatibility or a frequency converter to meet the frequency requirements.

Table 10.1 Typical Distribution Voltage and Frequency by Country

Country	Frequency, Hz	Tool Voltages	Facility System Voltages
United States	60	208Y/120 V, 3ph,4w 480 V, 3ph, 3w	480 V, 3ph, 3w Lighting: 277 V, 1ph FFU: 277 V, 1ph Receptacles: 120 V, 1ph Chillers: 4160 V, 3ph, 3w
Singapore	50	208Y/120 V, 3ph,4w 400 V, 3ph, 3w	400 V, 3ph, 3w Lighting: 230 V, 1ph FFU: 230 V, 1ph Receptacles: 230 V, 1ph Chillers: 3300 or 6600 V, 3ph, 3w
Taiwan	60	208Y/120 V, 3ph,4w 480 V, 3ph, 3w	480 V, 3ph, 3w Lighting: 277 V, 1ph FFU: 277 V, 1ph Receptacles: 120 V, 1ph Chillers: 4160 V, 3ph, 3w
China	50	208Y/120 V, 3ph,4w 400 V, 3ph, 3w	380 V, 3ph, 3w Lighting: 230 V, 1ph FFUs: 230 V, 1ph Receptacles: 230 V, 1ph Chillers: 6600 or 10000 V, 3ph, 3w

Notes:
Y = Wye
ph = phase
w = wire
FFU = fan filter unit

10.6 POWER (VOLTAGE) QUALITY

To compensate for steady-state voltage depressions, usually the main incoming site substation transformers are specified with automatic tap changers to compensate for the excursions in the incoming power supply. No-load tap changers are also provided on the unit substation transformers at the fab level.

Tools are sensitive to voltage transients, generated within the electrical system due to load switching, large motor starting, and lightning strikes. Transients may also be generated in the external power company network and transmitted to the fab through the incoming power lines. Various strategies such as surge-protective devices and UPSs are used to mitigate the effect of the transients. Information Technology Industry Council (ITI) characteristics curves depicting voltage dips versus the time duration of the dips (ITI 2000) are important guidelines for investigating the quality of the incoming power supply. The tools are also specified to meet SEMI F47-0706 (SEMI 2012).

For fabs with incoming power issues, high-quality power systems are installed on site.

10.7 HARMONICS MITIGATION AND POWER FACTOR CORRECTION

10.7.1 HARMONICS

A relatively large number of harmonic generators are present in a typical modern-day fab. Most of the fans, air handlers, pumps, cooling towers, and others use adjustable-frequency drive controllers for energy efficiency reasons. These controllers produce pre-

dominantly fifth- and seventh-order harmonics. In addition, single-phase power supplies are extensively used by the tools, thereby adding further to the harmonics.

Solid-state electronic ballasts, controllers, rectifiers, and controllers for the FFUs are also contributors of the harmonics. The cumulative impact of these harmonic generators results in sine wave distortion and equipment misoperation. IEEE Std 519 is applied as a guideline in the understanding and analysis of the electrical system. Strategies from input and output filters on the adjustable-frequency drives, harmonics-mitigating transformers, using 12-pulse inverters as opposed to 6-pulse inverters, and limiting the total distortion at the point of common coupling, as defined by IEEE Std 519 (IEEE 1992), are used. If left unattended, harmonics may cause shutdowns of critical systems.

10.7.2 POWER FACTOR CORRECTION

Facility loads have a good power factor and are controllable by specifying premium efficiency and high-power-factor equipment. The tools, on the other hand, have a relatively low power factor, in the 80% to 85% range. Most power companies have a minimum power factor clause in the rate structure, typically above 90%. Failure to comply with the minimum power factor results in low-power-factor penalty charges, which could be a significant cost. To avoid low-power-factor charges, power-factor capacitors are used in the electrical network, typically at the unit substation level. For cost savings, capacitors and harmonic filters are often integrated into the unit substation rather than installed separately.

10.8 TYPES OF POWER

Three types of power are required by the electrical loads in the fab. Most of the loads require normal power, whose failure will not cause severe detrimental effect on the fab operation. Emergency power can equal 15% to 25% of the total electrical loads. Life safety loads such as makeup air handlers and exhaust fans are on emergency power. These loads have to be operational upon the loss of normal power. Standby power is similar to emergency loads except that the life safety requirements are less demanding (e.g., standby generators must start in 10 s for emergency loads and 30 s for standby loads). Many fabs combine emergency loads and standby loads to avoid the cost of two systems, but some fabs divide their distribution. Critical loads that are not part of the life safety system but require emergency power are also connected to the emergency power. The *National Electrical Code*® (NEC; NFPA 2017a) requires that life safety loads and the critical load power distribution system are to be kept segregated and that life safety loads are to have first priority of power from the emergency power source over the other emergency power loads. Figure 10.3 shows emergency power loads that are typically connected to the emergency power source.

A certain percentage of tools are supported by the UPS system. The number of tools on UPS is dependent on the quality of the incoming power, process needs, and the fab owners. The range of loads on the UPS can be in the range of 10% to 15% of the total emergency loads. UPSs are backed typically by emergency generators.

Knowledge of the total electrical load projections is an important factor in the design of a fab. Most owners keep track of electrical loads, both for facilities and tools, as part of the benchmark data. Tools loads are normally captured in the "utility matrix," which is a listing of the proposed tools to be used in the cleanroom with nameplate and sometimes electrical demand data and is generated by the owner's industrial engineer.

However, for those owners without the historical database, load projections need to be made as the basis of the electrical infrastructure design. The electrical load projections

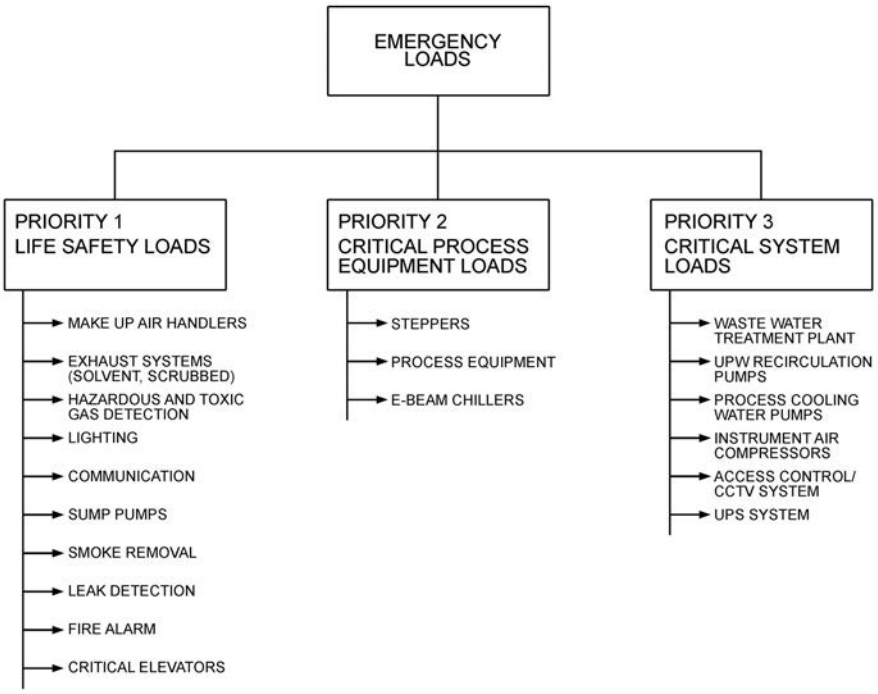


Figure 10.3 Typical Emergency Power Loads

are typically related to the size of the cleanroom as watts per square feet (kilowatts per square metre) of the cleanroom if a detailed analysis is not available. There is a correlation between the tool loads and the facility electrical loads, generally ranging from 1.3 to 1.5 times the tool loads.

10.9 CODES AND STANDARDS

The local jurisdiction where the fab will be located has codes that govern the design of the electrical systems. *National Electrical Code*, or *NFPA 70* (NFPA 2017a), is the code most commonly used and adopted by local jurisdictions. Other codes such as *Life Safety Code*, or *NFPA 101* (NFPA 2015); *Standard for the Installation of Lightning Protection Systems*, or *NFPA 780* (NFPA 2017c); *Standard for the Fire Protection of Information Technology Equipment*, or *NFPA 75* (NFPA 2017b); and *International Building Code*® (IBC; ICC 2014) also have electrical requirements that need to be incorporated into the design of a fab.

In addition to codes, there are national electrical standards that have electrical requirements and govern the design and manufacture of equipment. Laws such as the Americans With Disabilities Act (1990) and organizations such as Certified Ballast Manufacturers Association (CBM), Illuminating Engineering Society (IES), Institute of Electrical and Electronics Engineers (IEEE), National Electrical Manufacturers Association (NEMA), Occupational Safety and Health Administration (OSHA), and Underwriters Laboratories (UL) provide some of the standards that should be followed.

10.10 POWER DISTRIBUTION CONFIGURATIONS

There are various power system configurations for cleanroom power distribution. The type of configuration used is dependent on the project criteria, the project location, and

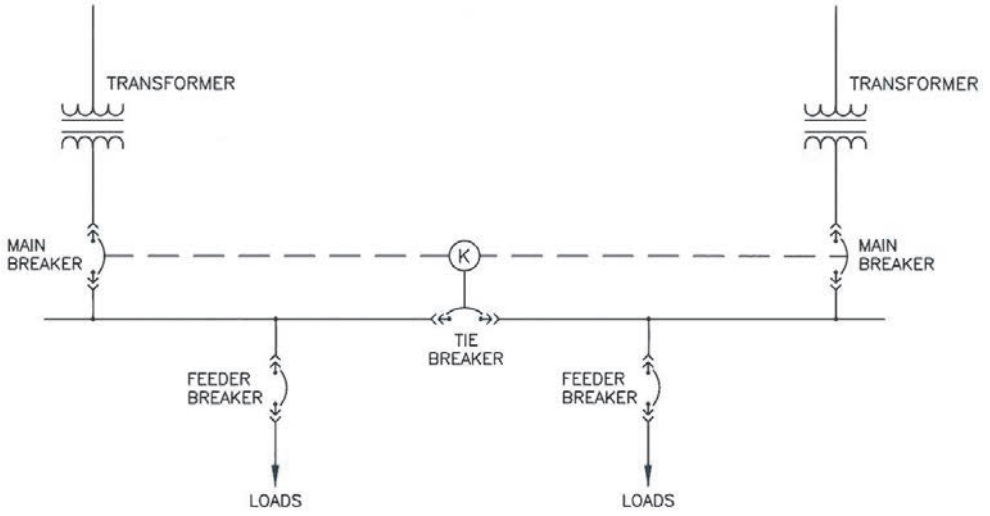


Figure 10.4 Double-Ended Redundant System

the desire to keep the system downtime to a minimum. Common configurations are discussed in the following sections.

10.10.1 DOUBLE-ENDED CONFIGURATION

In the double-ended configuration, two distribution unit substation transformers supply power to a double-ended switchgear with mains and tie protective devices. Unit substation transformers back up each other for any failure mode. Loss of one unit substation transformer results in load transfer to the healthy unit substation transformer.

In this configuration, the unit substation transformers are loaded to 50% of their nameplate rating in order to maintain 100% redundancy and support the entire load upon failure of one unit substation transformer or the source.

Because each unit substation transformer is loaded to half its rating during normal operation, the overall system efficiency is low. This configuration results in more electrical equipment and therefore requires large premium space in the fab building. Figure 10.4 illustrates this configuration.

10.10.2 TRIPLE-ENDED CONFIGURATION

In the triple-ended configuration, the unit substation transformers are connected in such a way that one unit substation transformer ends up as a standby unit to the two other active unit substation transformers. The standby unit is sometimes referred to as a *swing* unit substation transformer. In this concept, two of the active unit substation transformers are loaded to their full nameplate rating. Transfer of loads to the backup transformer is more complex than with the double-ended configuration. Even though the number of unit substation transformers is fewer than with the double-ended configuration option, the space required with this electrical configuration is more than that required for the double-ended configuration. Only one transformer acts as a backup to the other two transformers at a time. In general, transfer of power is manual. Figure 10.5 shows this configuration.

10.10.3 SINGLE-ENDED CONFIGURATION

In the single-ended configuration, each unit substation transformer is loaded to its nameplate rating. Redundancy is provided by an active spare unit substation transformer serving as an N+1 unit, where N is the number of active unit substation transformers. Only one unit substation transformer at a time will be backed up in this concept. In this

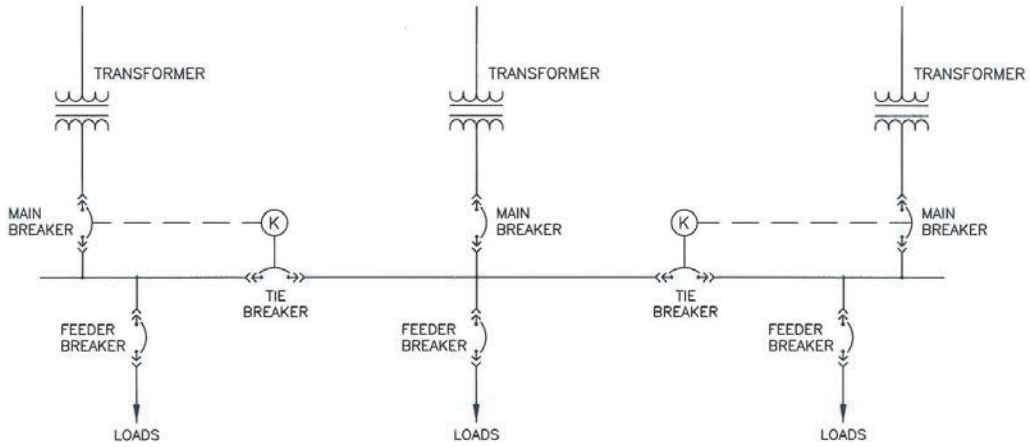


Figure 10.5 Triple-Ended Redundant System

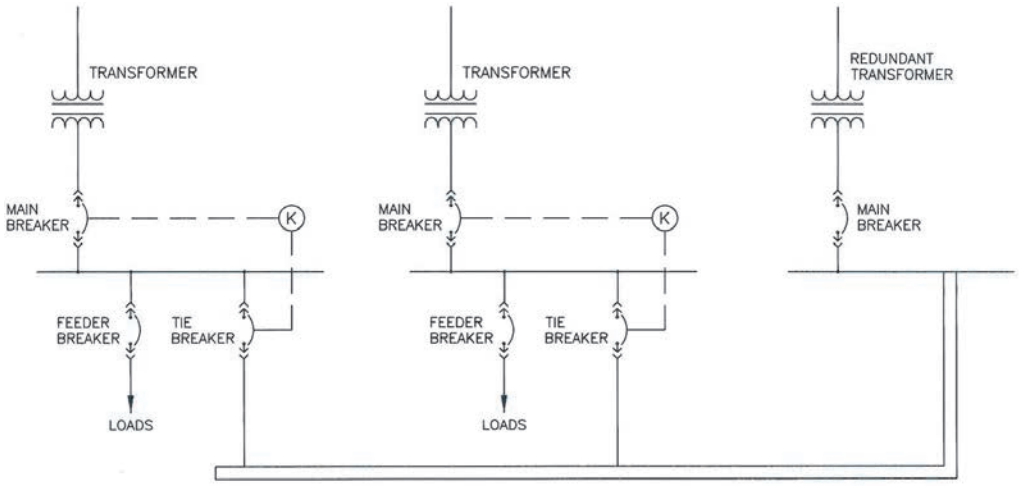


Figure 10.6 N+1 Redundant System

configuration, fewer unit substation transformers are required to support the electrical load. Though it offers the lowest redundancy this is configuration also offers the lowest first cost and lowest heat dissipation into the space. Reduced structural loads and less heat gain by the mechanical system are other advantages. Figure 10.6 shows this configuration.

10.11 ELECTRICAL EQUIPMENT LOCATION

The main electrical switchgear and the unit substations are typically located in the fab support areas on the fab utility level (see Figure 10.1). Distribution panels serving the FFUs and the lighting in the cleanroom are located in fab support areas of level 3 or the FFU area of level 4 (see Figure 10.1). Because the interstitial level is a pressurized plenum space, electrical equipment and the associated wiring system are rated for plenum applications as required by *National Electrical Code* (NFPA 2017a). Electrical equipment serving the tools on levels 2 and 3 is located on the subfab level 2 and placed against columns.

The tool loads are located in the fab, spread out between the cleanroom on level 3 and the clean subfab on level 2 in Figure 10.1. For a typical fab, the facility equipment loads are located on levels 2 and 4. Access to the FFUs is from the interstitial plenum space.

Makeup air handlers, scrubbers, and exhaust systems are located on level 4, either on the support building portion of the fab or directly over the roof of the pressurized plenum.

10.12 POWER MONITORING SYSTEM

The scope of a power monitoring system varies from a minimum of digital power meters in the main incoming switchgear, unit substations, UPS, and other critical switchboards to a full-blown interconnected power monitoring system with monitoring system computers, printers, and storage capability. In a stand-alone system, information can be downloaded at the meter location. Important system parameters can be analyzed both for normal operations and for system-upset conditions. A full-featured power monitoring system includes power meters and integral power quality meters allowing for complex wave capture and signal analysis. The system would also include peripheral equipment such as interconnecting cables, a central data server, and printers as needed. All critical system parameters are monitored and recorded continuously.

10.13 UPS POWER

Whether driven by code requirements or the criticality of the electric load, an uninterruptible power supply (UPS) is an integral part of a fab power distribution network. A UPS is composed of power conditioners (for voltage and waveform stabilization) and an energy storage device. All UPSs rely on stored energy to provide power to a load during loss of normal power. There are three primary energy storage devices used: batteries, flywheels, and generators. For each storage method, the time between the loss of normal power and the switching in of the stored energy varies, as does the quantity of stored energy. The three general categories of modern UPSs are on-line, off-line/standby, and line-interactive, meaning that the backup stored energy is always on, off-line, or in-line. An on-line UPS uses stored energy from the battery and a double-conversion method of AC input, rectifying to DC for the rechargeable battery, then inverting back to the required output voltage (e.g., 208, 400, or 480 V) for powering the protected load. On-line systems do not have a gap between normal power and backup power, because the backup power is always on-line. In a standby/off-line system, the load is powered directly by the input power and the backup power (e.g., batteries) is only switched on when the utility power fails. An off-line UPS has a gap between normal power and backup power that may be unacceptable for some sensitive equipment loads. A line-interactive UPS maintains the inverter in line and redirects the battery's DC current from the normal charging mode to supplying current to the load when power is lost, thus minimizing or eliminating any transfer gap between normal and backup power. The common element of these three categories is the stored energy in batteries. Batteries may off-gas contaminants, and as such their proximity to a cleanroom may be problematic. Batteries also require maintenance and special rooms. Therefore, the decision to use a UPS device containing batteries must be weighed against alternative UPS methods.

Energy storage using flywheels or other mechanically stored energy offsets the risks from batteries, but because these devices rely on inertia effects, their storage capacity is much less than that of batteries and they can provide no more than about 25 s of storage. This is enough for many short-duration power losses or voltage sags, but is not sufficient for longer outages. To compensate for the short duration of a flywheel, some manufacturers offer a combination flywheel and generator such that the flywheel provides backup power for the first 10 s while the generator starts and comes on line. Once the generator is on line it can provide backup power for as long as the generator runs. The decision to

choose a battery, flywheel, or flywheel/generator system is based on cost, system size, proximity to the cleanroom, footprint, vibration, and off-gassing.

A UPS power system may be protecting large numbers of equipment loads or it may be very equipment specific, with dedicated POU UPSs designed for very precise power conditioning and backup power durations. Each factor—centralized or local POU and UPS type—must be weighed by the fab design team and the owner. In practice, most fabs use several combinations of UPS strategies.

10.14 CENTRAL VERSUS POINT-OF-USE UNIT SUBSTATION TRANSFORMERS FOR TOOL POWER DISTRIBUTION

10.14.1 CENTRAL UNIT SUBSTATION TRANSFORMERS

In the central unit substation transformer concept, the incoming power is stepped down to the 208 V, three-phase, four-wire voltage and distributed to the tools. Another set of unit substation transformers step down incoming power to 480 V, three-phase, three-wire voltage for distribution to facility equipment. The size of the unit substation transformers for the facility power is generally limited to 2500 kVA, three-phase, three-wire. The impedance is generally limited to 5.75%.

Separate unit substation transformers with capacity and voltage ratings are needed for tool power and the facility equipment, resulting in more unit substation transformers. In this concept, the size of the tool unit substation transformer is not larger than 1250 kVA, three-phase, four-wire to limit the downstream short-circuit currents. The unit substation transformer impedance is normally kept to around 5.75%. If large transformers are used, high impedance will have to be specified to limit the short-circuit fault current at the tool level. This approach, however, will result in higher copper losses and operating expenses. Also, there is no segregation between harmonics generated by one set of tools on the other and the resultant tool misoperation. Neutral-to-ground voltages is another issue that needs to be reviewed. Voltage drop is a concern in view of the long runs of circuits and the distance from the unit substation transformer locations. See Figure 10.7 for this configuration.

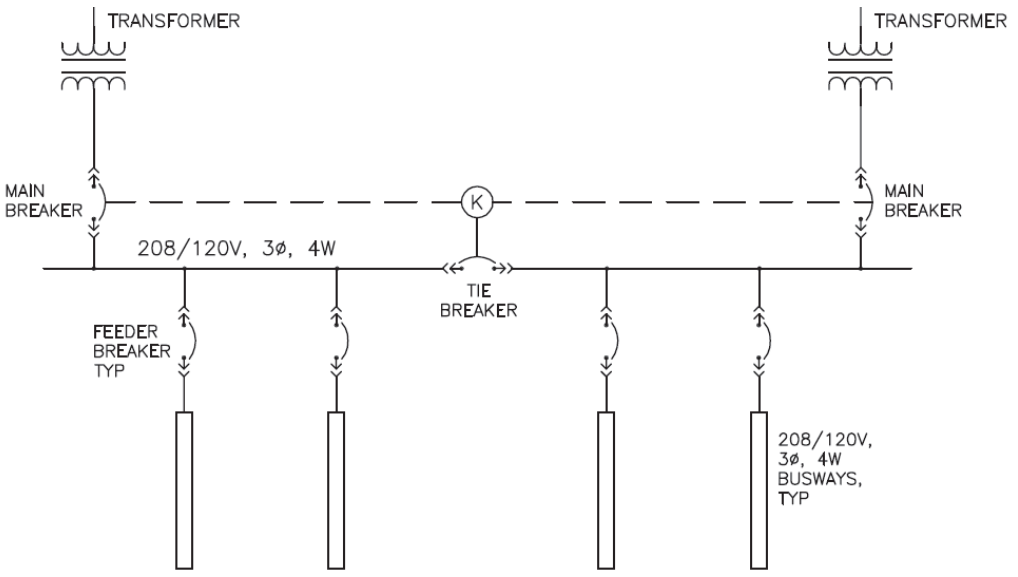


Figure 10.7 Tool Power—Central Transformers

10.14.2 POINT-OF-USE UNIT SUBSTATION TRANSFORMERS

In the POU unit substation transformer concept, the incoming power is stepped down by using 2500 kVA, 480 V, three-phase, three-wire power and distributed to facility electrical equipment located in utility level 1 (see Figure 10.1) and in the interstitial pressurized plenum. The 480 V, three-phase, three-wire power network is further routed to distributed unit substation transformers, where the voltage is stepped down to 208 V, three-phase, four-wire for distribution to the panels. These unit substation transformers are normally 300 kVA and are solidly grounded. The unit substation transformers and panel combinations are strategically located on the subfab floor adjacent to columns and away from the tools' support equipment location. Power is routed from the panels to the tools either in the cleanroom on level 3 or in the tool support equipment on the subfab floor level 2. Due to the size of the unit substation transformer, the fault currents at the tools are low and within the ratings of most of the equipment. The POU unit substation transformers provide a degree of segregation between harmonics generated by the tools. Also, the voltage drop is kept within limits by using the taps on the POU unit substation transformers. A final advantage of the POU design is that each POU substation transformer can be identical in capacity, voltage rating, physical size, and configuration, allowing for flexibility in installation and in purchasing multiple units. See Figure 10.8 for this configuration.

10.15 GROUNDING

Grounding is a critical aspect of a fab's infrastructure. Both safety and power system grounding are provided. Overall ground resistance of the system is maintained in the range of 1 to 5 ohms. Two types of power system grounding are used in fabs: solidly grounded and impedance grounded. In addition to power system grounding, additional grounding is provided for various purposes, such as grounding the cleanroom or grounding electromagnetic interference (EMI).

10.15.1 SOLIDLY GROUNDED SYSTEM

In this system, separately derived sources such as unit substation transformers are solidly grounded at the source. However, under the ground fault conditions, and depending

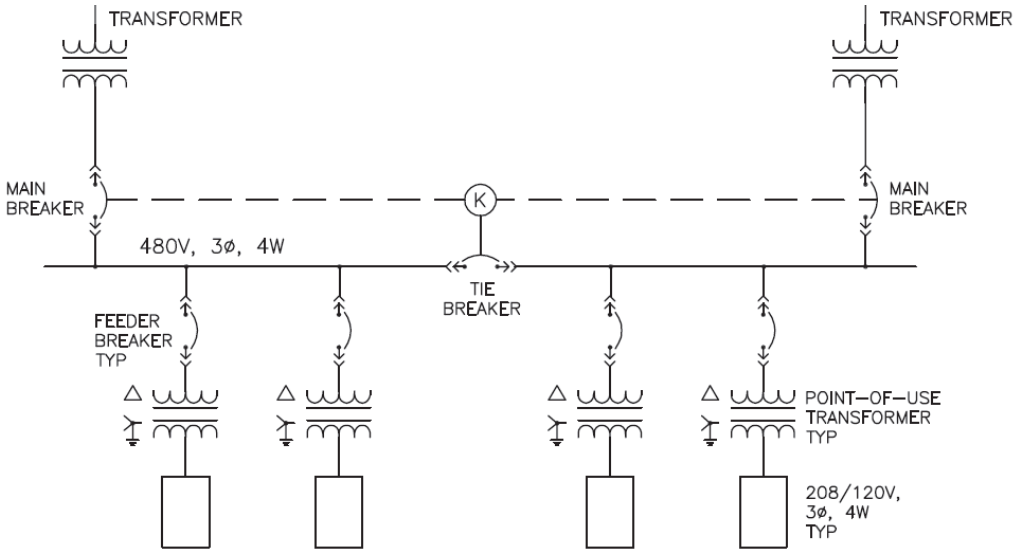


Figure 10.8 Tool Power—POU Transformers

on the location of the ground fault, the entire system may be shut down due to the protective device operation. This is not an acceptable mode of operation for many fabs. However, it is still used in small fabs.

10.15.2 IMPEDANCE-GROUNDED SYSTEM

In this system, separately derived sources such as unit substation transformers are grounded through a resistance, intentionally inserted at the star point of a three-phase unit substation transformer. Impedance grounding is commonly used in fabs to maintain continuity of power for a single line to ground fault conditions. Article 250.36 of *National Electrical Code* (NFPA 2017a) recognizes the importance of maintaining continuity of power in process-related and other businesses but requires the installation of a ground fault detection system to warn operators of a ground fault condition and the need to initiate an orderly shutdown of the system.

10.15.3 CLEANROOM GROUNDING SYSTEM

For cleanroom grounding, a signal reference grid is established below the raised floor in the cleanroom. The signal reference grid is made up of copper conductors laid in a grid pattern and connected to the raised-floor pedestals and framing. Tools are in turn connected to the signal reference grid. A raised-floor stringer system is also used as a signal reference grid, which in turn is connected at multiple points to the power system ground grid. Ground buses are embedded strategically in the slab under the raised floor. These ground buses are in turn connected to the buried ground ring. Ground buses are also provided in the columns at the subfab levels for providing a reference ground for equipment connection.

10.15.4 GROUNDING FOR EMI

There are two primary reasons for grounding devices, cables, equipment, and systems. The first reason is to prevent shock and fire hazards in the event that an equipment frame or housing develops a high voltage due to lightning or an accidental breakdown of wiring or components. The second reason is to reduce EMI effects resulting from electromagnetic fields or other forms of interference coupling. Tools such as scanning electron microscopes (SEMs) are particularly sensitive to EMI and interference coupling from any surrounding metal studs, pipes, or conduits entering the EMI-sensitive space. Fab designers must coordinate their EMI grounding design with the specific properties of the process equipment as specified in the equipment installation guide.

10.16 LIGHTNING PROTECTION SYSTEM

The need for a lightning protection system in a fab is dependent on the severity of the lightning and the number of thunderstorm days in the area where the fab will be located, a risk analysis study, and the requirements of the insurance carriers. Once the site for the fab has been selected, isokeraunic maps that show the number of thunderstorm days per year can be used as guides to decide on the need for a lightning protection system. Lightning strikes to a fab can be very disruptive; therefore, fab owners or their insurance carriers may provide their own requirements that are more stringent than for the frequency the isokeraunic maps indicate. Because the cost of lightning protection is very small compared to overall factory cost, these more stringent requirements may be justified.

A direct lightning strike and associated transients and overvoltages traveling on overhead lines, cables, and the unit substation transformers will have a devastating effect on the electrical system of a fab if the components are not adequately rated and lightning

protection strategies are not in place. In general, lightning arrestors are located at the point of entrance of the service conductors. In addition, electrical system equipment and components are specified with adequate impulse levels to withstand the overvoltages.

The lightning protection system should be designed in accordance with the requirements of *NFPA 780* (NFPA 2017c) and *National Electrical Code* Article 250.106 (NFPA 2017a). The system components include lightning arrestors on the roof, down conductors, and test links at the base of the building. Connections between the conductors and the building steel are exothermic weld type. The down conductors are connected to a ground loop around the building. In some parts of the world, a totally separate loop from the power system grounding is required; however, for most fabs in the United States, local codes allow the same ground loop to be used for the power system and the lightning protection system. Also, some parts of the world require that the main substation grounding loop be kept separate from the fab ground loop; in the United States, codes require interconnection of the two systems.

10.17 POWER DISTRIBUTION EQUIPMENT

10.17.1 HIGH-VOLTAGE SWITCHGEAR

The main incoming high-voltage switchgear is located on level 1 of a fab. The most common circuit breakers are either vacuum or sulfur hexafluoride (SF_6) types, in which the breaker contacts are operating within a vacuum or the gas medium. These types of switchgear have decades of track history and a proven record. They have a small footprint, are easily expandable, and are cost-effective. Many configurations along with relaying and metering functions are available.

Gas-insulated switchgears are also gaining popularity in the fab world. In this type, the entire switchgear is enclosed in a gas environment. These are higher in first cost compared to vacuum or SF_6 switchgear but have the advantage of a small footprint.

10.17.2 UNIT SUBSTATIONS

Unit substations with primary, transformer, and secondary switchgear in one free-standing structure are used for voltage transformation. Units can be specified to be complete and ready for installation when shipped to the site.

Both dry and liquid-filled transformer substations are available. In the liquid-filled type, both mineral-oil-filled or silicone type transformers are common. *National Electrical Code* (NFPA 2017a) recognizes these and lays out guidelines for their installation. Concern for oil leaks or silicone spills in the fab environment is an important factor in the selection of these types of transformers. In general, containments are provided to contain oil or silicone leaks. Fire-rated construction may be required for these transformer types. For outdoor units, oil/water separators are used to contain oil or silicone and allow rain water to flow through. The specific gravity of both mineral oil and silicone is less than one and therefore they will float. Caution needs to be exercised in the placement of the units. Unit substation transformers with oil or silicone should not be placed in the air return paths of the cleanroom.

Cast coil encapsulated, both primary and secondary, windings are also very commonly used in fabs. These transformers are lightweight and higher in first cost, but they do have not have issues like the liquid-filled types. These transformers are specified with voltage settings and fan ratings.

The primary incoming section can be a fused switch, circuit breaker, load break switch, or just termination lugs for the primary cable. The main and feeder breakers are

located on the secondary switchgear section. The main and feeder breakers are available in both 80% and 100% of the rating, programmable and with multifunction protective relays.

10.17.3 POWER CONVEYANCE MEDIUM

Busways and cable/rigid conduits and cable trays are used for power distribution. Bus ducts are located in the subfabs and require close coordination with process and mechanical piping and duct systems. Busways require a minimum of 42 in. (1 m) on both the front and back side in accordance with *National Electrical Code* (NFPA 2017a). It is, however, not possible to provide clearance on the back sides due to other utilities such as gas lines and mechanical ducts, so the back sides of the busways cannot be used.

Rigid conduit and cabling systems require considerably more space and extensive coordination with other utilities. For fabs in the United States, rigid conduit and cabling are very common, while the fabs located in overseas countries typically use busway systems.

10.18 EMERGENCY POWER

Emergency backup power is provided to life safety and critical systems in accordance with the requirements of *National Electrical Code* (NFPA 2017a) and, if required by the authority having jurisdiction (AHJ) or owner, *NFPA 101: Life Safety Code* (2015).

Life safety systems include cleanroom lighting, fire alarm and smoke detection, communication systems, toxic and flammable gas monitoring, elevators, critical air handlers, makeup air handlers, exhaust fans, scrubber systems, and associated pumps. Approximately 20% of cleanroom lighting is provided with emergency power to facilitate in the evacuation process.

The most common and reliable form of emergency power generation is diesel generators. The emergency power is around 15% to 25% of the total projected load. About 40% of this load is associated with the fab. The emergency generator is sized for the total load to be supported, including emergency and other standby loads. The emergency generators are always located away from the fab due to concerns over the hazardous fuel and vibration and sound issues. Depending on the magnitude of the emergency power, multiple generators running in parallel may be required. Emergency generators may be specified for 480 V stepped up to high voltage by unit substation transformers, or generators can be rated for high voltage and therefore no step-up unit substation transformers are needed.

For small cleanroom electrical loads, generation voltage is typically 460 V and supplies power through multiple segregated automatic transfer switches as required by *National Electrical Code* (NFPA 2017a). Grounding must match the ground system used for the unit substations.

Generators serving large emergency loads operate at higher voltages (i.e., 5 kV compared to a normal distribution voltage of 480 V), and the output is connected to the electrical network at that voltage. The high voltage is stepped down to utilization voltage at the POU by the equipment used for normal power. Generators operating at high voltage are to be impedance grounded.

Differential, reverse power, instantaneous and time overcurrent, ground fault, over/under voltage, over/under frequency, and automatic synchronization are common protective functions provided. These functions are usually part of multifunction digital relays.

An automatic start-up and sequencing control logic will start and load the generator system. In the cleanroom, all noncontrolled elements such as lighting, fire alarm, etc. will be provided power. Other systems such as exhaust start first, followed by the air-handling

equipment, to avoid negative pressure buildup inside the cleanroom envelope and contaminating the cleanroom.

National Electrical Code requires emergency power for egress lighting to be on line within 10 s for a minimum of one and a half hours (NFPA 2017a). Sometimes the insurance carrier's and the owner's requirements are longer, and this needs to be coordinated.

10.19 LIGHTING SYSTEM

Fab cleanroom lighting levels range from a low of 65 fc (700 lux) to a high of 100 fc (1076 lux). The lighting is generally fluorescent, high output, and white in color in the cleanroom and the subfab. In the photolithography area, yellow lighting with a cutoff wavelength of 470 nm is provided both at the cleanroom level and in the subfab. The lamps are provided with solid-state electronic ballasts, flush mounted in the cleanroom ceiling grid. The fixtures are installed between the air filters and the wiring is routed inside the ceiling channel and accessible from the pressurized plenum above the cleanroom.

Normal, emergency-backed, and UPS-based lighting are provided. The lighting system is controlled at the panels in the subfab.

10.20 FFU POWER DISTRIBUTION

Integrated fan and high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filter units, or fan filter units (FFUs), are located in the ceiling of the cleanroom. These fans draw clean air from the pressurized plenum and distribute it in the cleanroom. The power to the fans is provided from the electrical distribution panels in the plenum space. To maintain redundancy, the fans' power distribution is spread over many power panels. The fans are modulated from the a centralized control system that communicates with the plant-wide facility monitoring system.

10.21 SUBFAB POWER DISTRIBUTION

Vertical and horizontal space in the subfab and the below raised floor of the cleanroom is organized by various trades, with preference to the tool hookup routing. Approximately 1 ft (300 mm) space below the floor of the cleanroom is reserved for routing of the various utilities between the equipment on the cleanroom and the subfab floor. This space cannot be used for facility services. The same principle applies for utility routing under the raised floor. All connections are at the bottom of the tools.

10.22 EMI ISSUES

Radiated EMI is a serious concern in the operation of certain fab tools. It is important to find out the sensitivity levels of the tools and their distances from EMI sources such as cables, panels, transformers, and large-capacity feeders. Tool manufacturers should be consulted on the acceptable EMI levels. In general, experience suggests that large power sources such as transformers should be kept at a distance or should shielded from the sensitive equipment if a sufficient distance from EMI-sensitive tools is not practical.

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11

Cleanroom Control Systems

HVAC control systems provide environmental conditions required for human comfort. In cleanroom facilities, HVAC control systems also maintain environmental conditions required for process operations. A cleanroom control system may also be necessary to provide documented monitoring in a regulated environment. Coordinated control of several key cleanroom unit processes is critical: makeup air, recirculation air, and exhaust. There are benefits when controls for these and other unit processes (e.g., chillers, waste treatment, etc.) function together. A single integrated system may be used to control all this equipment. Various types of control systems can accomplish this, ranging from commercial building automation systems (BASs) based on direct digital control (DDC) controllers to programmable logic controller/human-machine interface (PLC/HMI) systems to high-performance distributed control systems (DCSs). The type chosen should depend on the owner's performance, cost, and reliability criteria.

11.1 INTRODUCTION

Compared to the environments in many factories, the physical environment in a cleanroom is benign. Nonetheless, cleanrooms have unique and demanding control requirements. There are several key cleanroom unit processes where controls play an important part in achieving and maintaining the rated classification. Makeup air, recirculation air, and exhaust are the most important cleanroom unit processes.

11.1.1 MAKEUP AIR

Makeup air-handling units (AHUs) provide pressurization and humidity control in cleanrooms. A sophisticated control system can tightly control both these parameters and do so in the most economical manner possible.

11.1.1.1 Pressurization

The makeup air system keeps the cleanroom pressurized to the positive set point chosen to prevent infiltration—one of the most important functions of the control system. The makeup air must be supplied to keep up with leakage and dynamically respond to changes in exhaust. This is usually done by a control loop that sets the makeup air fan speeds, modulating them to keep cleanroom pressure at set point. A strategy that modulates makeup air fans together so they do not "fight" each other and prevents oscillations is important.

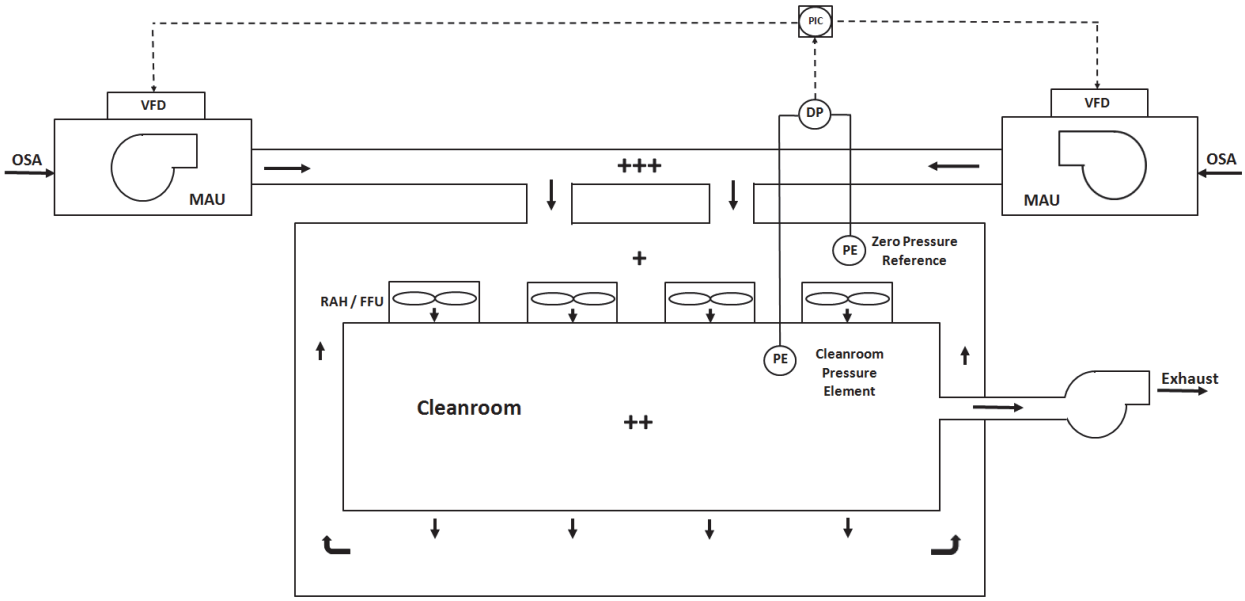


Figure 11.1
Cleanroom Pressurization Control

Differential pressure sensors measure the difference between the cleanroom and the outdoor air or an adjacent space. Where a pressure hierarchy exists and one clean zone must be kept pressurized to a different value than another zone, a good strategy is to provide a single common "zero" point that all zones use as a reference. This may require a pressure element installed in a stable location at the lowest referenced pressure and a network of leaktight piping to the other areas using the reference. (See Figure 11.1.)

11.1.1.2 Humidity Control

Humidity control in makeup AHUs may include several steps, such as preheat, humidification, dehumidification, and reheat. Some cleanrooms require only that humidity is maintained below a certain level. In this case, there will be dehumidification but no humidification capability. Other cleanrooms require that the humidity be kept within a tight band of high and low limits, requiring the ability to either dry or humidify the incoming air.

In this second case, a careful preheating strategy can provide significant energy savings. This is particularly important when an evaporative humidifier is used. The key in this case is to choose the proper preheat set point so that overall energy use is minimized. Consider the case where cold, dry air is brought into a makeup AHU and requires both heating and humidifying to meet the cleanroom set point. If the outdoor air is brought to the enthalpy line that intersects the cleanroom condition, even though it is a higher temperature than required for discharge, this will use much less energy than heating to the discharge set point, humidifying to saturation, dehumidifying, and reheating. Note that good control of the humidifier is required to arrive at set point and actually achieve these savings. (See Figure 11.2.)

Another challenge is to maintain the humidity set point throughout the cleanroom and coordinate the operation of multiple makeup AHUs. A proven scheme is to use local control of discharge-air dew point at each makeup AHU with the discharge set point reset by a slow-acting loop based on dew-point measurement from the cleanroom itself. This

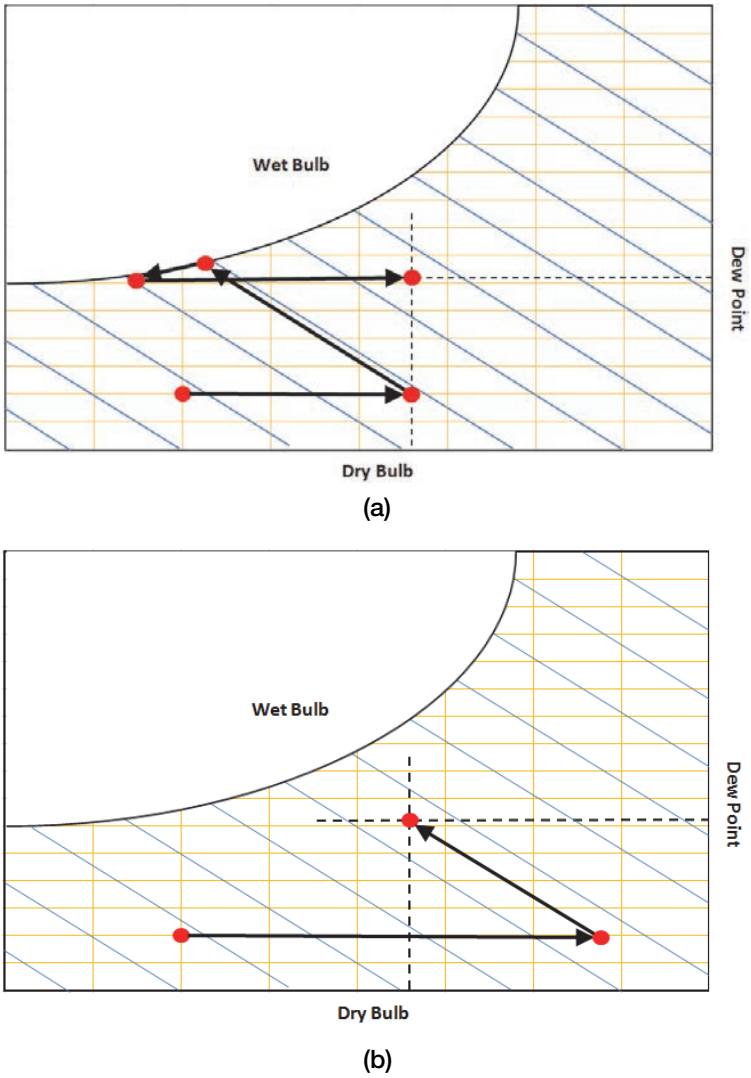


Figure 11.2 Makeup AHU Humidity Control with (a) Standard Preheat Set Point and (b) Optimal Preheat Set Point

allows the makeup AHUs to respond to individual variations and provides responsive yet accurate control. Note that dew-point measurement (either calculated or measured directly) is the process variable for both the local and remote loops.

Intelligent reheating offers another opportunity for economical operation. A typical cleanroom specification may require a dry-bulb temperature of 70°F (21°C). That does not mean that the makeup air needs to be provided at that temperature. Continuing with the previous example, the leaving temperature from the dehumidifying coil may be as low as 50°F (10°C) and still meet the dew-point discharge condition. Rather than reheat the makeup air to the cleanroom set point, providing the cool makeup air to the cleanroom lowers the energy spent in reheating and offsets some of the cooling load normally provided by the recirculation air system. (See Figure 11.3.)

11.1.2 RECIRCULATION AIR

Recirculation air handlers (RAHs) and/or fan filter units (FFUs) with cooling coils keep a cleanroom at the proper airflow velocity and dry-bulb temperature. Airflow through a cleanroom is crucial to maintain particle counts below required levels. Airflow is set during the commissioning process typically by setting damper positions and/or fan speeds.

Note that many FFUs have variable-speed motors but do not use variable-frequency drives (VFDs). Furthermore, RAHs and FFUs are sometimes configured so that if one or more unit in an area is out of service, the remaining units automatically speed up or increase flow to maintain airflow at the required set point.

RAHs and FFUs also work with cooling coils for temperature control. Feedback from sensors in the cleanroom may control a single unit or a group of coils. A successful strategy is to control the local discharge temperature of a single RAH or cooling coil and have the discharge set point reset by the actual cleanroom dry-bulb temperature. This provides responsive yet stable temperature control. (See Figure 11.4.)

Also, as described Section 11.1.1, coordinating the dry-bulb temperature of makeup AHU discharge with the cooling capabilities of the recirculation system can result in considerable savings. A control strategy that allows the makeup AHU discharge temperature set point to rise until the RAH or FFU cooling coils are doing some work but as little as necessary is called *herding* control. With herding control, the makeup AHU discharge set point is slowly adjusted to bring the most-open cooling coil valve position below a nominal value of 90%—"herding" the valves. This typically requires that the positions of the cooling coil valves be made available to the makeup AHU controllers.

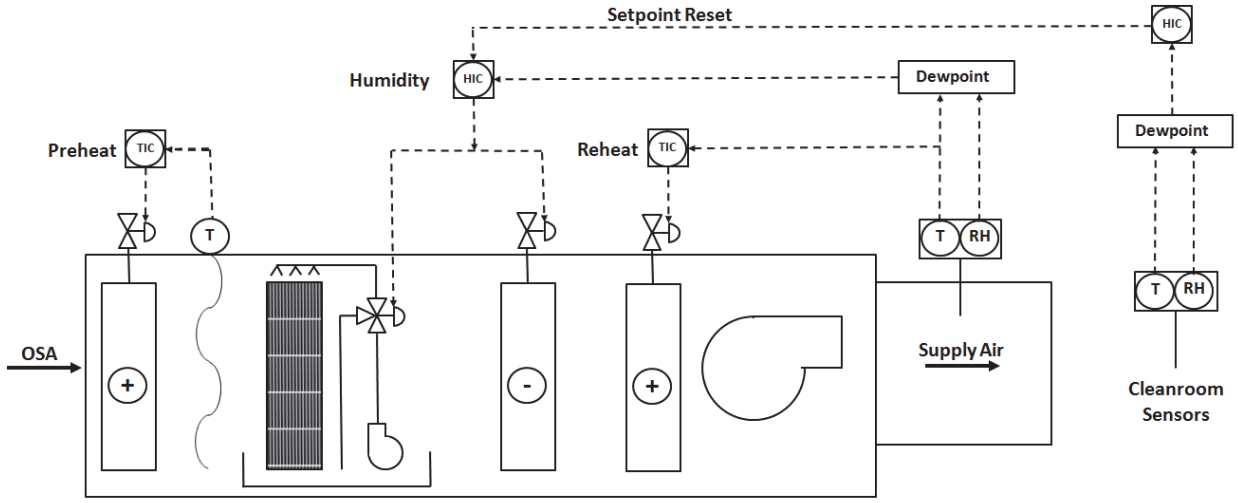


Figure 11.3
Makeup AHU with Discharge Dew-Point Set Point Reset from Cleanroom Sensors

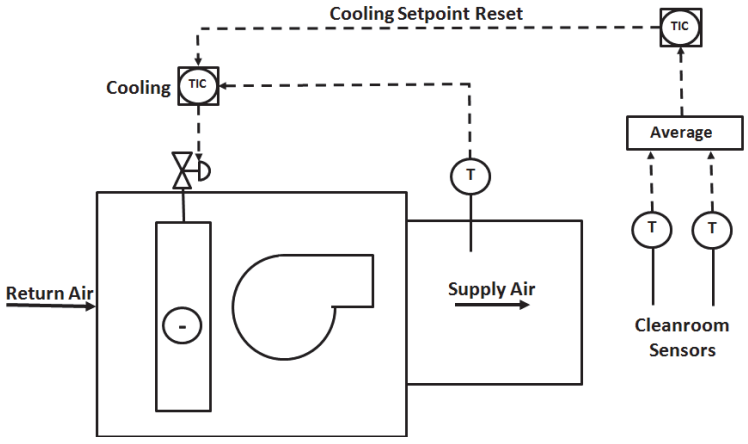


Figure 11.4
RAH with Discharge Temperature Set Point Reset from Cleanroom Sensors

FFUs are a special type of RAH. Often installed in numbers up to several thousand units, FFUs can be specified with their own dedicated control system. This is necessary in large systems because wiring individual controls to thousands of FFUs would be prohibitively costly. Manufacturers therefore offer FFU control systems with built-in, multidrop network controls that connect to a purpose-built computer. The computer provides monitoring (fault, status) and control (speed, on/off command) of individual units or groups of units. The FFU controls may still need to interface with the overall cleanroom system for coordinated response to smoke exhaust conditions or simply to allow remote monitoring from the plant-wide system. Interface can be done at the individual controller or supervisory computer level, but consideration of the update speed and critical nature of the points communicated will affect the choice of the best solution.

11.1.3 EXHAUST

There are often several types of exhaust streams from a cleanroom. Maintaining a balance between the air removed by exhaust and the air supplied from makeup is critical for pressure control. Generally, the most effective and economical method of controlling the exhaust flow is with fan motors operated by VFDs. Systems are typically sized so that multiple fans are connected to common exhaust ducts. A differential pressure sensor (or sensors) measures the difference in pressure between the inside of the duct and the ambient condition outside of the duct. Fans are modulated and sequenced to maintain that difference at a constant value.

The location of sensors and tuning of the control loop modulating the exhaust fan VFDs are important. If isolation or bypass dampers are part of the system, their operation must be carefully programmed and tested so they do not upset the system. A well-designed and programmed exhaust system can respond to variations in system demand without significant variations in the distribution duct exhaust pressure.

Exhaust system flows vary as cleanroom tools or system demands change. The makeup AHU pressure control loop responds by modulating the makeup AHU supply fans, replacing the air removed from the cleanroom by the exhaust fans. Note that the exhaust systems do not need to reference the zero reference since the makeup air system will provide the necessary airflow to keep the cleanroom at the chosen set point. (See Figure 11.5.)

11.2 CONTROL SYSTEM ARCHITECTURE

Most control systems consist of these essential elements: sensors, output devices, controllers, a way to see and interact with the control system—i.e., a human-machine interface (HMI)—and a control network to tie these things together. The elements can further be selected and arranged to meet a range of system performance and system reliability criteria. Different types of control systems are available that satisfy these criteria. Any one of them may be the appropriate choice for a particular cleanroom. Cleanroom control system architecture should also consider requirements for interfacing with other control systems, including life safety systems (i.e., gas detection) and fire alarm systems.

11.2.1 SENSORS

Control begins with system parameter measurement. Many parameters can be important, but most cleanrooms require the measurement and control of three parameters: temperature, humidity, and pressure. The measurement process is a chain of sensors, transducers, analog to digital conversion, and software processing. Errors and uncertainties at any point in the chain affect measurement accuracy and therefore control system

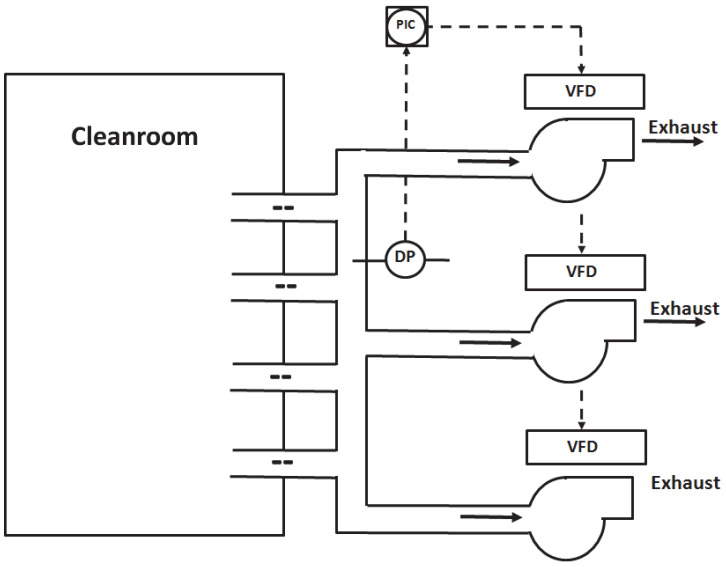


Figure 11.5
Exhaust Control System Ducted from Cleanroom

capability. For most control systems, the sensor itself is typically the largest source of inaccuracy (Blaine 2007).

11.2.1.1 Temperature Sensors

The most common sensors in a cleanroom measure temperature. Commercial systems use resistance temperature devices (RTDs) or thermistors, often with the sensing element directly wired to a controller. Both RTSs and thermistors rely on change in resistance to indicate change in temperature. Because the sensor may be wired directly to the controller without a transmitter, installations of this type can be less expensive. However, eliminating the transmitter removes some noise immunity, and the lead length between the sensor and the controller can impact the accuracy of the measurements (Blaine 2007).

Industrial HVAC systems typically use RTD sensors with matched or integral transmitters. RTDs can be specified with 100 or 1000 Ω resistance. The higher resistance values provide better resolution. Overall accuracy can be similar for both RTDs and thermistors (typically ±0.5°F [±0.3°C]), but combining an RTD and a transmitter provides a standard 4-20 mA signal whose accuracy is not affected by differences in lead length. RTDs have excellent sensitivity, stability, and repeatability, and they can be produced with rugged construction and with compartments for terminals and electronics (Blaine 2007).

Temperature sensors are installed in ducts, air handlers, and the cleanroom itself. Choice of sensor location can be difficult when equipment within a cleanroom operates at high or low temperature. The return air path is often the most representative location for temperature measurement, even under a raised floor.

Typical specifications for these sensors are as follows:

- Accuracy should be ±0.5°F (±0.3°C)
- Sensor and transmitter should be provided as a matched pair
- Duct and air handler sensors should be rigid or averaging as specified

11.2.1.2 Humidity Sensors

Control sensors for humidification equipment must be fast, stable, and accurate. Otherwise, humidifying and dehumidifying may be started too late or may be performed simultaneously, leading to no control at all (Blaine 2007).

Lower-grade relative humidity sensors are typically resistive sensors with a typical accuracy rating of 5%. Better sensors may have 3% accuracy, but even so these sensors also have considerable drift and slow response time. These sensors are housed in plastic cases with little environmental protection. Industrial humidity sensors are typically capacitive and rated at 2% accuracy or better. They tend to be housed in more rugged enclosures that can withstand full liquid immersion. The best industrial capacitive sensors experience very little drift and have a quick response time (Blaine 2007).

Like temperature sensors, humidity sensors are installed in ducts, air handlers, and the cleanroom itself. Unlike temperature sensors, these devices must be kept away from fumes that can affect their reading. Humidity generally equalizes rapidly in open spaces, so local variations are not as troublesome. However, most cleanrooms have relative humidity criteria that are directly affected by local temperature. Therefore, measuring both relative humidity and temperature at the same location and converting to dew point or other absolute humidity measurement is a good strategy for control points. Many combination sensors offer multiple signal outputs. This is possible since the device measures temperature and humidity and can calculate other psychrometric parameters.

Typical specifications for these sensors are as follows:

- Accuracy should be ±2% rh between 10% and 80%
- Mounting should be specified for duct, wall, or pendant
- The sensing element should be capacitive and solid state
- The measurement range is 0% to 100% rh
- Combination sensors should provide calculated dew point and one other variable (i.e., temperature, enthalpy, or relative humidity)

11.2.1.3 Pressure Sensors

Pressure sensors for cleanroom service are used to measure and control the balance between makeup and exhaust flows. Pressure sensors come in a wide variety of packages and accuracies. For building pressure control, the scale is very low (±0.10 in. w.c. [25 Pa] or smaller), so carefully placed, high-accuracy, low-drift sensors are a necessity.

Often, a well-chosen pressure reference that is responsive to outdoor air conditions—but not too responsive—must be located and connected to one leg of the differential sensors throughout the facility. A static air probe or "pressure element" at both the reference and measured points is required to shield the sensor point from high airflow but allow the system to respond to static air pressure changes. Note that sensors intended for exhaust duct static measurement must also be specified with static pressure probes.

A typical specification for these sensors is as follows:

- The pressure transmitter should be electronic-variable capacitance type
- Accuracy should be ±1% of full scale
- The transmitter should be able to withstand an overpressure of 5 times the full scale or 1.0 in. w.c. (250 Pa), whichever is greater

11.2.1.4 General Sensor Considerations

There are several general options for all sensors that should be considered during cleanroom design. Local indicators for sensor readings provide convenience but are not generally included—particularly in low-cost sensors. If there are no control system workstations in the area, local indicators may be the only way to observe system operation. The ability to field-set the measurement range of devices is also convenient but is typically not available without investing more money. Without this capability, some sensors simply need to be replaced if process conditions change. Finally, there are fieldbus networks available for devices that should be considered for large cleanroom projects. Most

commonly, highway addressable remote transducer (HART) devices provide significant diagnostic and configuration capability generally without adding cost.

11.2.2 OUTPUT DEVICES

Output devices are the elements of the control system that actually perform work. Output devices include control valves and dampers; there are both commercial and industrial versions for most of these devices. Output devices also include the elements that energize and modulate motors, typically for pumps and fans.

11.2.2.1 Control Valves

The HVAC function in a cleanroom that is the most important is cooling. Flow through air handler cooling coils is typically controlled by a modulating globe valve. Commercial valves of this type typically have a bronze body and an electric actuator. Industrial globe valves are made of carbon steel and use pneumatic actuators with positioners, which sense the location of the valve plug and use a feedback loop to adjust the output until set point is reached. The valves are essentially operating in open-loop mode when they are without positioners. Open-loop mode can be much less accurate, especially as the valve wears over time. More recent "smart" positioners have built-in diagnostic capabilities that enable maintenance staff to monitor for problems or adjust valves without putting the system out of service; this capability greatly reduces and sometimes even eliminates downtime (Blaine 2007).

11.2.2.2 Dampers

Valves and dampers can be electric or pneumatic; each type has its own disadvantages and advantages. Electric actuators can be very slow, sometimes taking several minutes to fully open or close. Pneumatic actuators typically move much faster—usually just seconds depending on how they are adjusted. Damper speed can be important when exhaust fans or air handlers connect to a common plenum. On the other hand, pneumatic devices can be more expensive to install since they require an instrument air connection and all its accessories (gages, filters, regulators, etc.). But electric actuators themselves require wiring and may even need a separate source of voltage.

Electric actuators are most commonly used in commercial systems and pneumatics are more common in industrial systems. Electric actuators can fail to the last state if spring returns are specified (meaning that if it loses power or the control signal, the device stops moving). Pneumatic actuators require careful consideration of the failure response, for loss of control signal as well as loss of air pressure (Blaine 2007).

11.2.2.3 Motor Controls

Motor starters and VFDs are also important components in cleanroom control systems. At a minimum, three signals are necessary to control a single-speed motor: start/stop, running, and auto. For a VFD, the minimum signals required are start/stop, running, auto, fault, and speed command.

The simplest method used to connect motors to control systems is to hardwire the signals described above. Today most drives and many motor starters have "smart" devices that can be networked to a control system. Generally there are many more parameters available than the signals listed above. This presents a dilemma for the control system designer, since the extra data are valuable but communicating over a network link adds complexity and at least the question of reliability. Even further complicating this decision is the quantity of motors involved in large cleanrooms. There is considerable cost impact no matter which choice is made. Some projects respond to this dilemma by choosing both options: hardwiring the control signals but reading the additional data over a network.

11.2.3 CONTROLLERS

Eventually, all input and output signals connect to a controller of some type—the central element of any control system. In commercial systems, a mix of unitary controllers is used to control a single piece of equipment and larger building controllers are used to control facility-wide programming or monitoring of general input/output (I/O) points; in industrial systems, programmable logic controllers (PLCs) are used. PLCs are available in a range of sizes and for various types of application. These controllers can be differentiated by I/O type and capacity, form factor and physical robustness, and processor programming capability and flexibility (Blaine 2007).

11.2.3.1 DDC Controllers

Direct digital control (DDC) unitary controllers are the basic component of most BASs. Unitary DDC controllers typically come with built-in I/O capability and network connections, and some have small interface displays. They are made for operating a specific piece of HVAC equipment and may be preprogrammed for specific applications (e.g., a fan-coil unit with a reheat coil, a cooling-only air handler with an economizer, etc.). They often are packaged for HVAC installations with field-wiring termination directly on the controller, and they typically accept 24 V alternating current power. Unitary controllers have network capability so they can receive plant-wide data (e.g., outdoor air temperature), connect to the supervisory system, and respond to data polling requests from a higher-level controller (Blaine 2007).

Larger primary or building DDC controllers perform both control and supervisory functions. These controllers, like unitary controllers, may come with I/O capability or network connections and can accomplish local DDC via preprogrammed HVAC applications. Primary controllers can perform more complex controls and have more memory, and they may enable alarming and trending. They also are able to carry out site-wide scheduling and reset functions and connect unitary DDC controllers to the operator interface computers by acting as routers. Almost all DDC systems have at least one building controller as the centerpiece (Blaine 2007).

DDC controllers provide standard built-in functions called *control algorithms* for specific applications that were developed based on many years of HVAC control experiences throughout the industry. Standardization of these control systems has reduced the costs of BASs and introduced other functionalities into the systems. These are typically the most cost-effective controllers for standard applications.

11.2.3.2 Programmable Logic Controllers

Programmable logic controllers (PLCs) are built for industrial facilities and therefore have several differences from DDC controllers. First, PLCs typically come with a variety of form factors and more rugged packaging. Comparable in function to unitary DDC controllers, small PLCs have a fixed number of built-in inputs and outputs and limited program memory, though expansion is typically possible if the base model does not have enough I/O points. Larger PLCs come with expandable I/O connections and more memory, and they can handle a greater amount of I/O points. These controllers typically are modular, meaning they come with a chassis or rack with space for different communication modules and I/O connections. A single large PLC may be used to control an entire facility. A single processor can control several remote racks with capacity for thousands of inputs and outputs. So that racks can be close to field devices but away from the processor, which reduces wiring costs, the system uses a special high-speed communication link. This allows for system architecture options that DDC systems are not usually to offer (Blaine 2007).

PLCs are available with a large assortment of I/O card types and densities. The cards can come with individual channel fusing and prewired, separate blocks, and often cards can be inserted and removed without having to cut power. Analog PLC cards typically have greater resolution than DDC versions—14 or 16 bit for PLC versus 10 or 12 bit for DDC (Blaine 2007).

Languages available for writing control programs differ for PLCs and DDC controllers. PLCs are mostly programmed in the manufacturer's version of "ladder logic," while DDC controllers have a variety of vendor-specific formats. PLCs have generally higher capability due to sophisticated instruction sets and program controls, but there are pluses and minuses for each. Programs for both types of controllers are written separately from the graphics programs that allow operators to interact with the system—the human-machine interface (HMI). When an entire PLC-controlled system is being described it may be referred to as a *programmable logic controller/human-machine interface* (PLC/HMI) system. The term *DDC* may refer to both the controller and the HMI.

11.2.3.3 Distributed Control Systems

Distributed control systems (DCSs) are high-performance systems found at the top end of the automation system spectrum. The description of capabilities for PLCs applies to DCS controllers as well. DCSs differ from PLC systems because of their integrated control logic and HMI programming environment—a very powerful feature. A DCS typically combines fewer but more powerful and even redundant processors with numerous, strategically located remote I/O drops to control an entire facility. Libraries of preprogrammed functions, including sophisticated diagnostics and program documentation, are available from DCS vendors. Even if the individual components are more expensive than other control systems, a DCS may provide a lower total cost of ownership if these features are required. However, the capabilities and costs of DCSs and PLC/HMI systems have gradually merged to the point where there is a significant area of overlap. Higher-end PLC/HMI systems are now often referred to as programmable automation controllers (PACs). The distinguishing feature of a PAC is the provision of integrated logic and HMI functions—making it, arguably, just like a DCS.

11.2.4 HUMAN-MACHINE INTERFACES

To actually run any type of control system, some kind of operator interface is required. This "window" into the system may be called an *operator workstation* or a *HMI terminal*. The operator interface provides these functions: representation of system status, ability to change set points or commands, presentation of alarms, and historical and immediate data trending. For the various kinds of control systems, the graphical interfaces and other capabilities can be quite similar. However, differences in performance are still possible, with update rates for reading and writing varying from less than one second to several minutes. These differences are mostly due to the underlying network communication speed and program execution rates.

The quantity and location of operator interface workstations is an important consideration for the system. There is often a cost associated with each workstation, with the software license sometimes the most costly piece. Mobile devices including laptops, tablets, and smart phones can serve as workstations too, although there are programming considerations to make the interface compatible with the chosen devices. The decision to use such devices for operator interfaces should therefore be made before programming development gets under way.

Data collected from a cleanroom control system can be used for preventive maintenance, early warning of control parameter deviations, and optimization of utility costs by

both data logging and making intelligent decisions to use best efficiency points for different equipment that can reduce the overall energy use of the facility. For example, the chiller plant energy consumption can be reduced by evaluating the equipment efficiencies as a whole to find the best matching combination of chillers to cooling towers and associated pumps. By operating single or multiple chillers at their best efficiency points, determining how to operate the cooling towers and associated pumps with the operating chillers can reduce the overall plant electric and water consumption.

11.2.5 CONTROL NETWORKS

All control systems generally use a layered network hierarchy. Two, three, or even more layers are possible. A variety of protocols and media are available for each layer. Network protocol selection is influenced by data capacity, the needs for speed, and the number of connections required. Whether the network media is coaxial cable, optical fiber, shielded twisted pair, or some other type is decided by requirements for redundancy, system topology, noise immunity, and distance between nodes. The network type chosen usually determines the required media (Blaine 2007). DDC systems use commercial control networks, and PLC systems and DCSs both use industrial control networks.

11.2.5.1 Commercial Control Networks

In a commercial controls system, the primary building controllers and some unitary controllers are connected to the operator interface computers by a high-level network. This network connection is necessary so that operators can view data, make changes remotely, and receive alarming and trending data. Typically Ethernet is chosen for this function (Blaine 2007).

The unitary and building controllers are connected by lower-level networks to enable control functions decoupled from system monitoring requirements. If a sensor is in one place but the control requirement happens in another place, equipment on different subnets is likely going to have to use the monitoring network to share control data. If these data are delayed, control operation will suffer (Blaine 2007).

While it used to be common that commercial control system vendors developed network protocols particular to their equipment, these days the HVAC industry uses the BACnet® building automation and control networking protocol (ASHRAE 2016), which enables interoperability of devices and equipment from different manufacturers. Field sensors and devices may also communicate using BACnet, but this is uncommon (Blaine 2007).

Many types of networks (including Ethernet, ARCnet, LonTalk, and MS/TP) can transmit the BACnet protocol. MS/TP, or master slave/token passing, is a four-wire RS-485 system operating at 76.8 kb/s and the most common network for unitary controllers. Although its deterministic nature is has been a slow implementation, it is a positive feature of MS/TP because it guarantees each network node time to receive a token and transmit a message. The fact that there is a known maximum amount of time for all nodes to receive the token means that regardless of network traffic, communication is deterministic (Blaine 2007).

11.2.5.2 Industrial Control Networks

PLCs and DCSs have faster and more secure network communications than DDC controllers. Most industrial systems have controllers designed with their own deterministic, high-speed, error-checking protocols. Typical industrial communication standards are Modicon ModbusPlus (2 Mb/s), Allen Bradley ControlNet (5 Mb/s), and Siemens Profibus (12 Mb/s). Almost all of these are being superseded by some form of industrial Ether-

net. While not necessarily deterministic, these networks can operate at speeds up to 100 Mb/s. This network speed is a major reason why industrial system performance is faster than that of commercial systems (Blaine 2007). Note that it is still a challenge for industrial controllers to share data between different vendors. There is no common protocol equivalent to BACnet for industrial controllers.

A well-accepted method for connecting equipment from multiple vendors at the supervisory level that has become the standard for industrial controllers to interface with supervisory systems is the client/server protocol OPC, or object linking and embedding for process control. OPC works by having a data server program expose available data from a subsystem or separate controller (e.g., points in a PLC) and having the client application (e.g., the HMI software) read these data points and other information (such as data quality) to determine whether the system is communicating properly and if the data are valid. This simple, interoperable method enables supervisory computers to "talk" simultaneously with equipment from a variety of vendors (Blaine 2007).

11.2.6 SYSTEM PERFORMANCE

Conceptually, the various types of systems are similar; the difference is their performance. All control programs look at input from sensors, perform logic or calculations, and write outputs. However, both processing speed and communication speed are faster in industrial systems than in commercial systems. This enables *real-time* input reading from anywhere in the system, solving logic, and output writing anywhere else in the system. The time it takes for a controller to read inputs, solve logic, write outputs, and carry out overhead functions is called the *scan rate* (see Figure 11.6). PLC scan rates are generally measured in milliseconds, even for large PLC programs with distributed I/O points. DDC controllers have program execution frequencies measured in seconds (Blaine 2007).

Though not all control loops need such fast update times (such as temperature control loops), other loops do (such as exhaust fan or chilled-water distribution pressure control loops). Because of the faster scan rate with an industrial controller, system response to a set point change or process upset can be dramatically better than in a DDC controller (Blaine 2007).

An operator's window into the system is the operator workstation or HMI terminal. For all systems, the supervisory platform enables representation of system status, ability to change set points or commands, presentation of alarms, and historical and immediate data trending. DDC and DCS vendors typically offer proprietary supervisory software packages, and several leading PLC vendors offer HMI software packages such as RSView, Wonderware, Intellution, and others. Most of these packages have similar features and powerful user-interface and graphical capabilities. However, the systems can have significant differences, particularly in update rates.

A well-designed industrial system can refresh data and display a new screen in less than one second. Though there are some DDC systems that can approach this update rate,

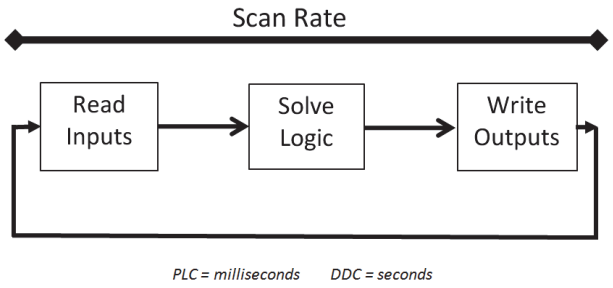


Figure 11.6
Scan Rate

typically DDC update rates are 30 s or longer. Operator commands should trigger an immediate response in the system. Industrial systems typically respond immediately, but DDC systems may take up to 1 min, depending on system architecture. Alarming will be seen within 1 s in an industrial system, whereas it may take up to 1 min for an alarm to show in a DDC system. These differences are due mostly to the slower program execution rate and the underlying network communication speed in DDC systems (Blaine 2007).

11.2.7 SYSTEM RELIABILITY

Reliability should be thought of in terms of not only the dependability of individual elements of a system but also the dependability of the system as a whole, in which a failure in one part will not affect other parts. Careful engineering can design control systems for fault tolerance so that the control system will not be prevented from working by any single failure in a part of the system (Blaine 2007).

11.2.7.1 Distributed Control

Controller fault tolerance is commonly achieved by providing distributed control. In both commercial and industrial systems, each individual machine or process can have its own small, inexpensive controller. This way, the facility as a while will not come to a stop because a single controller is lost. This design is called *passive automation*, which implies that even if the automation system is not functioning correctly, the system will continue to operate properly. While this is acceptable for most cleanroom systems, there are situations where this may not be acceptable, particularly if control functions need to span multiple controllers. In these cases, a single controller must perform logic that requires inputs from or outputs to various systems. Some such cases follow (Blaine 2007):

- **Temperature Control.** The output from several sensors may need to be averaged and used to reset control loops within several air handlers. At no time must these air handlers be allowed to fight each other (i.e., attempt to provide heating and cooling simultaneously).
- **Power Restart.** The restart of electrical equipment must be coordinated after a power failure. If the system is on generator power, the status of the generator(s) may need to be considered when allowing equipment to restart. A site-wide control system that receives and propagates this information in real time provides a more secure restart.
- **Load Shedding.** Similar to power restart, the ability to shed electrical load is best handled by a control system with fast site-wide capability. As the cost of electricity rises, the necessity of advanced energy-saving schemes increases.
- **Humidity Control.** Sensors for room humidity may need to be averaged and used to control humidifying coils or makeup air handlers for dehumidifying. This control typically involves sensors and equipment in various parts of the facility.
- **Pressurization.** Coordination of exhaust and makeup air to maintain static pressure may require inputs from and outputs to different controllers. These items are usually in several different locations with controllers spread out accordingly.

11.2.7.2 Redundancy

Building a fault-tolerant, redundant control system is another way to achieve high reliability. In this approach, no single failure can prevent continuous operation, and a few controllers or a single controller pair can run the whole facility. This type of design requires careful consideration of each component of the system, such as the following (Blaine 2007):

- **Redundant Controllers.** For PLC applications that require fault tolerance and high availability, hot standby processors are often used. A hot standby system provides "bumpless" standby control in case of a component failure or power source interruption. The scans of the primary and standby controllers are synchronized. If a failure occurs in the primary controller, the I/O modules hold their last state for one scan while the backup controller takes over. This is a very effective means of control that is not available with DDC.
- **Redundant Network Media.** The control network in PLC systems is normally installed in the rugged environment of a factory floor. To prevent loss of control in the event of a damaged cable or failed component, PLC vendors offer dual media capability for their systems. This is not available with DDC systems.
- **Redundant Power Supplies.** Separate power supplies can be provided for PLCs. (Note that externally powered devices may also need a separate pair of power supplies.) Two 24 V direct current (DC) power supplies are connected through a diode redundancy module. PLC manufacturers offer these supplies with factory-supplied connectors and built-in monitoring capability. This is a commonly used feature in PLCs that is not typically available with DDC.
- **Dual Power Feeds.** Where fault tolerance is essential, the redundant power supplies described above can be fed from two separate power feeds. This is quite simple in PLC control panels but not generally feasible with DDC controllers. This concept is quite analogous to supplying dual power feeds to data center loads.
- **Redundant HMI Servers.** While not as critical as the controllers themselves, provision of separate HMI servers can guarantee access to the control system even if one of the servers fails. This is a feature offered in most HMI systems and is possible with some DDC systems. Note that the HMI system itself may be inoperable without disrupting the facility itself.
- **Separate Supervisory Networks.** HMI systems may separate networks for data collection (servers – PLCs) from networks for viewing data (clients – servers). Segmenting allows uninterrupted data collection no matter how many clients are online or what they are doing. This also means that the HMI servers are not necessarily functioning as operator workstations. DDC systems generally have one computer that functions both as a data collecting server and the operator workstation.

11.2.8 MONITORING AND ALARMS

Environmental parameters critical for manufacturing products are sometimes required to be monitored and recorded to demonstrate compliance with the registered process. For example, in pharmaceutical manufacturing, the registered drug as tested and approved by the U.S. Food and Drug Administration (FDA) for use in humans has to be produced for commercial sales in the same environment as that provided prior to registration.

HVAC systems and environmental parameters need to be defined and evaluated early in the design process to determine whether they have direct impact, indirect impact, or no impact to the products being produced. Depending on the extent of the HVAC systems, HVAC controls might employ a simple local controller or a wide area network with multiple controllers and a central station for monitoring, deploying control sequences, changing control set points, alarm management, and data storage.

11.2.8.1 Validated versus Nonvalidated Systems

In regulated environments, early decisions need to be made regarding whether the BAS will also be used for building automation, including HVAC system controls and data acquisition along with alarm functionality, operator response management, and electronic data recording to prove that the environment is maintained within the parameters defined to manufacture products or other Good Manufacturing Practice (GMP) processes.

The extent of validation required is determined by the manner in which the BAS impacts the production of health care products. Validation is a documented program that provides a high degree of assurance that a specific process, method, or system will produce a consistent result meeting predetermined acceptance criteria: simply, that it will do what you say it will do.

HVAC systems, including utility generation and distribution and process systems, can be identified as direct impact, indirect impact, or non-impact systems. Generally only direct impact HVAC systems require validation. The test is: if the plant environmental control system fails and the product is adulterated, the system is considered a direct impact system. Utility generation and distribution systems can be considered indirect impact systems since they do not come in direct contact with the products. Office-space and support-space HVAC systems are considered nonimpact systems. If the BAS is performing controls along with data acquisition, setting off alarms, and keeping records, the system requires validation.

Depending on the extent of the HVAC system, the validation and upkeep of the whole system as well as the documentation required for validated systems as required by 21 CFR 11 (GPO 2016) could be very time consuming and expensive. The other option is to keep a parallel dedicated control system that is used for alarming and managing critical data. In this case, the BAS needs only to be commissioned; the critical system-monitoring and record-keeping system needs to be validated. The BAS controls the critical environmental conditions such as temperature, humidity, space pressure, and particulate levels; the parallel system monitors these parameters. The sensors used to control and monitor can be separate sensors to keep the two systems totally isolated. However, the calibration, accuracy, and repeatability of the instruments can be different. This creates a question as to which input is accurate, because the inputs can be different due to the nature of the sensors. Determining the correct inputs requires that they be investigated; this demands operator diligence.

The maintenance of separate parallel systems without validation of the control loop can be challenging if not carefully undertaken. Using a common device to control and monitor the parameters can be achieved by using the same sensor and sending the output signal to both validated and nonvalidated control systems with isolation (see Figure 11.7).

Using one system to control and monitor increases the validation cost but reduces the first cost. Using two separate systems increases the first cost and maintenance cost but reduces the risk and reduces the validation cost.

11.2.8.2 Critical Parameter Control and Monitoring

Critical parameters are those that directly impact the product quality and repeatability of the process. As these parameters have direct impact on the product, they must be monitored continuously. Sensors and transmitters are preferred methods of monitoring due to their high quality with tight accuracy and high repeatability. Devices used for noncritical applications can be commercial-grade sensors. The design of the BAS needs to balance the use of the different grades of devices to reduce the costs of the overall system while still delivering least-risk-based control and monitoring systems.

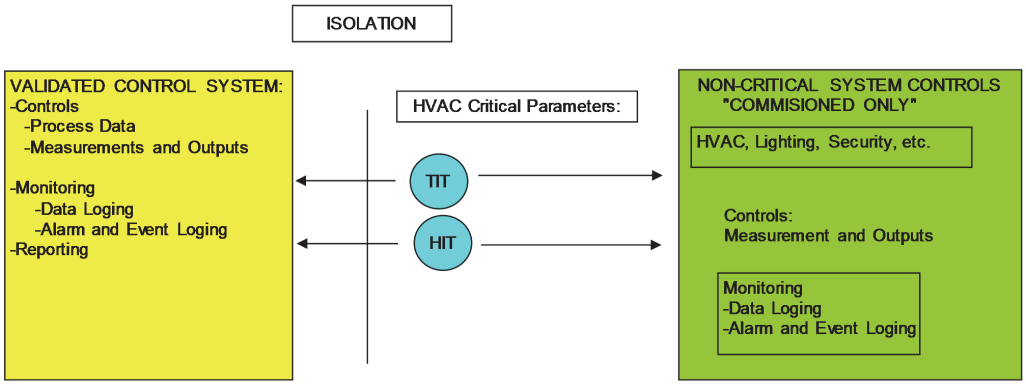


Figure 11.7 Validated and Nonvalidated Control Systems and Interface

In short, evaluating risk is part of a greater evaluation. Generally risk assessment, as it is commonly termed, is a methodology, conducted throughout the design of the facility, to determine, analyze, and manage potential risks to product quality (and to the project as a whole) and to define measures to prevent or mitigate the hazard or unwanted condition from taking place. From an HVAC perspective, depending on the risk for contamination and product safety, during design the parameters that need to be trended include temperature, humidity, pressure, etc. With these, the locations of the sensors to measure and monitor can be determined.

The use of a high-quality temperature and humidity sensor will result in a tighter space condition control. Using a less accurate pressure sensor that modulates the fan speed, however, might be acceptable. Airflow fluctuation is not critical because changing the airflow rate in a higher range still provides the airflow to the space and does not directly impact the process or eventually the product (see Figure 11.7).

The critical parameters such as temperature and humidity can be logged via a validated control system. This system can generate alarms and keep records if the critical parameters sway outside of the acceptable limits (see Figure 11.8).

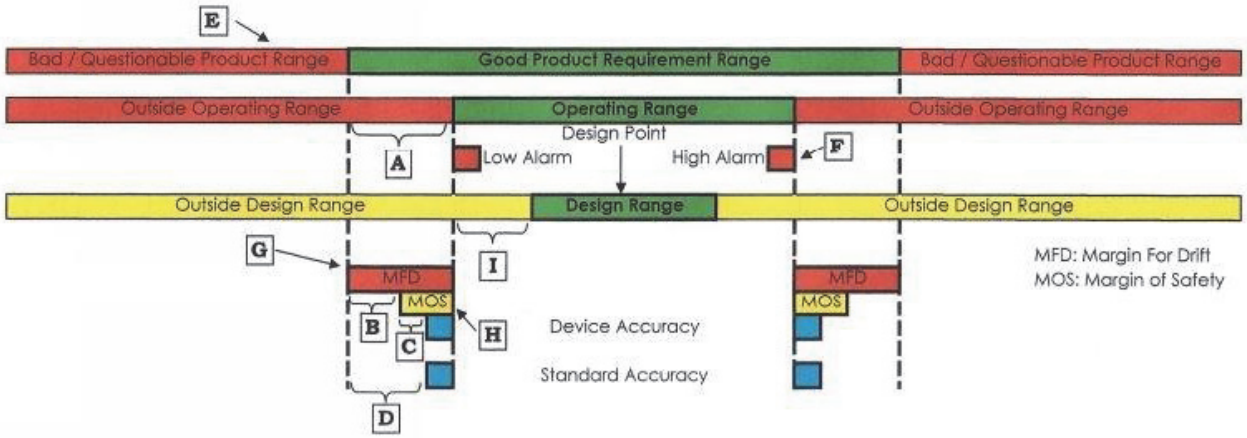
11.2.8.3 Defining BAS Alarm Strategies

Alarms are used to inform users that the operating parameters are exceeding the limits set for GMPs. The design conditions are determined from good product requirement ranges by defining the control ranges and alert and alarm limits. The user requirements specification (URS) should define the appropriate product requirement range.

The operating range should be set within this range with a safety factor that defines low and high alarms limits. The engineer should determine the design range by considering the control tolerances and alert limits including the device accuracy and calibration standards. Carefully selected design and alert/alarm levels should provide adequate time for the maintenance staff to take action and correct the problem before the critical parameter drifts outside of the operating range. If it drifts outside of the good manufacturing requirement range, the product batch needs to be quarantined until cleared by documented investigation.

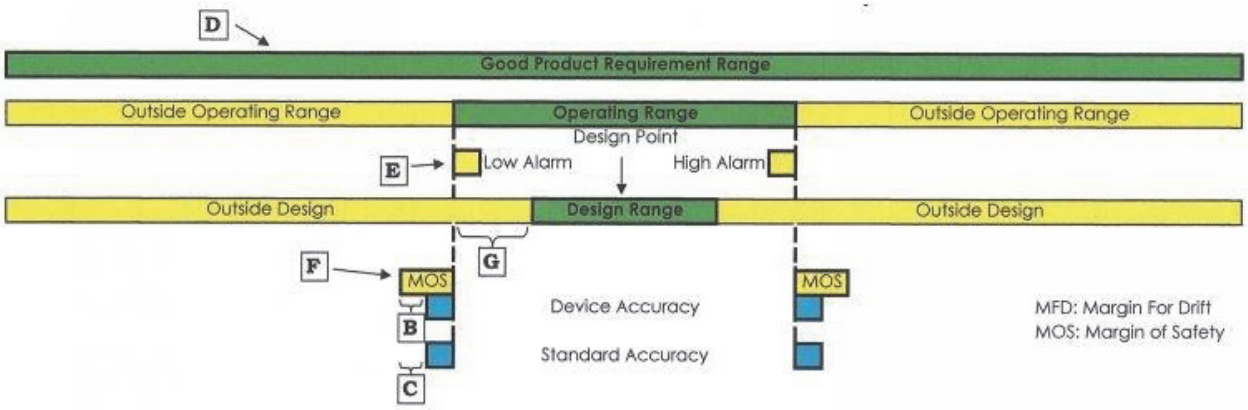
Setting the alarm limits for noncritical devices is less complicated than for critical devices since there is no impact to the product. The alarm and alert limits can be used for preventive maintenance purposes to detect system failures before they happen and lose productivity and comfort of the users (see Figure 11.9).

The actual environmental conditions such as temperature and humidity that are influenced by the HVAC systems change slowly. The nature of the rate of change determines



A The MFD is derived from the difference between the Requirement Range and the Operating Range.
B The MFD should at a minimum be no less than 2X the MOS.
C The MOS should at a minimum be no less than 2X the manufacturer's specified device accuracy.
D The MFD should at a minimum be no less than 4X the accuracy of the calibration standard to be used.
E Suspected operation outside the Requirement Range requires lots to be on hold until cleared by documented investigation.
F Operating outside the Operation Range is generally protected by alarm or SOP. Should such operation occur, then operation outside the Requirement Range is possible, depending on device accuracy at that time. See E.
G Calibration check outside the MFD is protected by calibration SOP. Should such operation occur, then operation outside the Requirement Range is possible, depending on position within the Operating Range at the that time. See E.
H Calibration check outside the MOS is not a quality issue, but it can be an indicator that the device is degrading or drifting. Instrumentation cannot be retumed to service if it cannot be adjusted to within the MOS.
I Design Range is set to be within Operating Range by enough to prevent hitting alarms during normal operation.

Figure 11.8
Critical Device Limit Relationship



A There is no MFD for non-critical devices.
B The MOS should at a minimum be no less than 2X the manufacturer's specified device accuracy.
C The MOS should at a minimum be no less than 2X the accuracy of the calibration standard to be used.
D Since the device is not critical, the Requirements Range for good product is infinite. No value will call product into question.
E Alarms can be set at the high and/or low operating limits for control purposes, but setting them off will not adversly affect quality.
F Calibration check outside the MOS is not a quality issue, but it can be an indicator that the device is degrading or drifting. Instrumentation cannot be returned to service if it cannot be adjusted to within the MOS.
G Design Range is set to be within Operating Range by enough to prevent hitting alarms during normal operation.

Figure 11.9
Noncritical Device Limit Relationship

the frequency of data logging. Space pressures, however, change rapidly with doors opening and closing. Space differential pressures should be monitored continuously but recorded at predetermined intervals to determine if the space pressure changes outside of the limits set. A door position switch is best used to determine if the door is open or closed. If an air lock door is simply open, an alarm should not be set off. However, if both doors to an air lock are opened at the same time, the space pressure will be lost and an alarm should be set off. If the space pressure is within the alert rage, the space pressure should be recorded until the space pressure is recovered. If the space pressure is recovered before it reaches the alarm level, this should be acceptable to operations and quality groups. If there are numerous fluctuations of the actual data as seen in space pressure measurements, a time averaging of the measured data can be used. If the averaged data is outside of the limits, then action should be taken to correct the problem.

Regulatory agencies such as the FDA require quality control for product manufacturing, directing that a local alarm to be set off to notify the operator when the conditions are outside of the acceptance criteria limits defined by the GMPs. There should be, however, a written course of action defined for each action alarm: who sees it, who is responsible for responding to it, where it is recorded, what action will be taken, and where the information on that action will be stored. The frequency of data recording needs to be determined as to how that data changes (rapidly or slowly) and how it may affect product quality. The recorded data need to be stored in a secure data logging system that is password protected.

11.2.9 OTHER CONTROL SYSTEM INTERFACES

Besides the cleanroom control system, there are additional controls that may require interface to the cleanroom, such as life safety systems and fire alarm systems.

11.2.9.1 Life Safety Systems

Cleanrooms in the electronics industry often contain toxic gases or chemicals that require a dedicated detection and alarm system. Typically, leak detection or manual operation of an evacuation pull station will trigger operation of evacuation horn/strobe indicators. The alarm system may also interact with the cleanroom controls. For instance, detection of a gas leak may need to trigger increased exhaust.

There may be additional regulatory or testing requirements for the life safety system that do not apply to the cleanroom control system. Careful delineation of boundaries between them is therefore important.

11.2.9.2 Fire Alarm Systems

Fire alarm systems are yet another type of control system that is found in a cleanroom. By code, fire alarm systems have specific requirements for installation, wiring, and testing that are not discussed here. There is a typical interaction between the fire alarm system and the cleanroom controls that should be described in the design documents.

Smoke detectors throughout the cleanroom are wired to the fire alarm system. These can be ionization detectors in ductwork or early warning detectors mounted in return air paths, such as a VESDA, or very early smoke detection apparatus. Responding to a smoke alarm, the fire alarm system will shut down an air handler or a group of air handlers by energizing an addressable relay. The controls for air handlers must be designed to accept this relay input and respond appropriately.

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AIR CONDITIONING COMPANY

12 Cleanroom Lighting System Design

Cleanrooms must operate continuously with no unscheduled shutdowns. All elements of the cleanroom, including lighting, must support this mode of operation; the equipment must be reliable, durable, and low maintenance. With a primary focus on microelectronics facilities, this chapter describes general cleanroom lighting principles. Lighting for support areas such as subfabs, utilities, and hazardous areas is also covered.

12.1 INTRODUCTION

As discussed in Chapter 10, a semiconductor manufacturing plant, referred to as a *fab*, is a multistoried factory with the cleanroom located primarily on one level, a clean subfab on the level below the cleanroom, and a utility subfab below the clean subfab. Manufacturing tools are located in the cleanroom. Support tools such as pumps and radio frequency (RF) receiver transmitters are located on the clean subfab level. The level directly above the cleanroom is the pressurized plenum, also called the *interstitial level*, where air-handling equipment is located. Both ballroom and bay and chase types of cleanrooms are used for semiconductor manufacturing. Spaces for support functions such as gowning, meetings, and wafer test laboratories are located on the outer wings of the main cleanroom.

Fluorescent lighting is currently the primary light source used in fab cleanroom design. Future fabs may use alternative technologies such as light-emitting diode (LED) lighting, which continue to improve in lighting color and efficiency. LED technology may not currently be cost-effective for every project, but the trend is improving year after year. An analysis of the local power cost, utility rebates, and expected return on investment (ROI) may demonstrate the cost-effectiveness of LEDs for a given project.

12.2 CODES AND STANDARDS

In the design of cleanroom lighting it is important to understand that building codes, as defined by the authority having jurisdiction (AHJ), are the starting point for life safety aspects of design. In the case of the United States, these are the international building codes published by International Code Council (ICC). They are a family of codes including those that affect lighting and electrical design:

- *International Building Code*® (IBC; ICC 2014a)
- *International Energy Conservation Code*® (IECC; ICC 2014c)
- *International Fire Code*® (IFC; ICC 2014d)

- *International Green Construction Code*® (IGCC; ICC 2014e)
- *ICC Performance Code*® *for Buildings and Facilities* (ICCPC; ICC 2014b)

The international codes also adopt *NFPA 70: National Electrical Code*® (NFPA 2014) and reference other codes from organizations that have pertinence and expertise in the lighting field, such as Illuminating Engineering Society of North America (IES) and Certified Ballast Manufacturer Association (CBMA).

12.3 REDUNDANCY AND RELIABILITY

Redundancy in a fab lighting system is provided by multiple lighting panels and circuits serving the cleanroom, subfab, utility subfab, interstitial level space, and other support areas. Reliability of the equipment and lighting system is critical to the operation of the fab.

12.4 LIGHTING SOURCES AND SYSTEM INSTALLATION

12.4.1 CLEANROOM

Fab cleanrooms are made up of ceiling systems that are premanufactured and installed within the cleanroom envelope. The ceiling is made up of standardized modules assembled on site. The ceiling grid is typically a 2 × 4 ft (600 × 1200 mm) or 4 × 4 ft (1600 × 1600 mm) grid. Within the grid are mounted high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filters or HEPA/ULPA fan filter units (FFUs). For many cleanrooms with a cleanliness class of ISO Class 5 or cleaner (ISO 2015), the ceiling grid may contain 75% to 100% filters with no room for conventional lighting fixtures. The ceiling grid is a nominal 2 in. (50 mm) wide steel U or C channel. Lighting fixtures are designed to fit into the grid channel. For cleanrooms with ISO Class 6 or less clean (ISO 2015), the filter coverage will be less than 50%, allowing for the installation of a more conventional 2 × 4 ft (600 × 1200 mm) lighting fixture with multiple lamps. Ballasts are located in the same channel. In this mounting concept, the fixtures are accessible from the cleanroom side only for replacement purposes. The channels are provided with a prismatic lens. Wiring is brought out at the end of the run into the interstitial space above with the channel sealed to avoid penetration of dust and other contaminants.

In older fabs, surface-mounted single-tube fluorescent "tear drop" fixtures were mounted below the ceiling. Most new fabs use flush-mounted light fixtures in the steel channel.

The light fixtures are fluorescent types using T8 and T5 normal and high-output lamps, generally ranging in color temperature from 3500 K to 4000 K. Yellow lighting that blocks light wavelengths below 520 nm is provided in photolithography areas. The yellow lighting zone at the cleanroom level extends beyond the zone of the photolithography areas by a bay width in all directions. Yellow lighting is obtained either by the use of special yellow-coated fluorescent tubes or by using yellow sleeves over regular fluorescent tubes, the latter being the preferred approach in newer fabs.

One of the challenges in a modern-day fab is the coordination of the locations of lighting fixtures and the placement of the automated material handling systems (AMHSs). AMHSs are installed for efficient operation due to the complexity of the production process and the ergonomic challenges of handling large wafers. The ceiling-

mounted AHMS configuration allows maximum use of the cleanroom floor for production tools; however, it presents a unique situation for locating light fixtures.

In the cleanroom, both normal and emergency power lighting systems are provided as required by the *National Electrical Code*. The maximum allowable duration between the loss of normal power and the availability of emergency power is 10 seconds (NFPA 2014). In newer fabs, the 10-second gap is supported by light fixtures powered from the uninterruptible power supply (UPS) system. In the cleanroom ceiling channel, multiple rows of channels are normal light fixtures, followed by a row of emergency lights. In between the normal and emergency lights, some of the rows are provided with light fixtures connected to the UPS source. Close coordination is required amongst the various designers of the cleanroom (architectural, mechanical, HVAC, and lighting).

In a fab cleanroom, walls, floors, and ceiling are built of highly reflective materials. Lighting calculations are based on high-reflectance values. Due to the clean nature of the envelope, room surface dirt depreciation and luminaire dirt depreciation factors are negligible, though lamp lumen depreciation and lamp burnout factor must still be considered in the determination of the number of fixtures to be provided.

12.4.2 SUBFAB

The subfab space is the most utility-intensive area of a high-volume manufacturing facility. Support piping, gas lines, air ducts, exhaust, and electrical raceways are all competing for the space, leaving little room for light fixtures.

Light fixtures are normally chain hung below the utilities. In some fabs, light fixtures are also vertically mounted on columns. Successful lighting installation requires coordination with other utilities that have position priority over the lighting location.

The light fixtures are fluorescent types, generally 1 × 4 ft (300 × 1200 mm) with an enclosed wrap-around acrylic lens. As noted previously, yellow lighting is provided under photolithography areas and extends beyond the zone by a bay in all directions. Approximately 10% of the lighting is connected to the emergency power source to provide illumination along the egress paths out of the building. Dirt depreciation factors are negligible in this space.

12.4.3 UTILITY SUBFAB

Utility systems and conveyances such as unit substation transformers, high-voltage switchgears, chilled-water supply and return piping, and exhaust and supply air ducts are some of the large space users on this level. Lighting fixtures installed in available spaces are normally chain hung from the ceiling, allowing the fixtures to be easily relocated, if necessary.

The light fixtures are fluorescent types, generally 1 × 4 ft (300 × 1200 mm) with a wire cage for mechanical protection. UPS lighting is not always provided on the utility subfab floor, and approximately 10% of the lights are on emergency power. Emergency egress paths are illuminated during a loss of normal power to enable safe evacuation from the building. Dirt depreciation is much higher in the utility subfab, resulting in a calculated light loss factor (LLF) of about 70%.

12.4.4 INTERSTITIAL LEVEL

Some of the supply and exhaust air ducts are located in the interstitial level, but space is available for mounting of lighting systems. Light fixtures are normally chain hung from the building steel structure and coordination is easily achieved with other systems.

Fluorescent lighting is used in the plenum spaces. Fixtures are enclosed with a wrap-around acrylic lens. Approximately 10% of the lighting is on emergency power to enable

evacuation of the space during a loss of power. UPS-backed lights are not provided. A dirt depreciation factor of around 70% is used in the lighting calculations for this level.

12.5 LIGHTING CONTROLS AND LIGHTING LEVELS

Lighting control concepts are dependent on the functional areas in semiconductor manufacturing plants. Lighting control may be line voltage switching using local switches or via low-voltage relays. Lighting voltage in the United States is typically 277 V, single phase; outside the United States lighting voltage is typically 220 V. For power systems where impedance grounding is used for the main service transformers to maintain process continuity, 277 V single-phase voltage is created by the use of dedicated one-to-one ratio transformers with the secondary solidly grounded. The following subsections discuss the current trends in lighting controls in each level of a fab.

12.5.1 CLEANROOM AND SUBFAB

There are no local lighting switches in the cleanroom and the subfab. Lights are directly powered from circuit breakers in panels located in the interstitial plenum for lighting in the cleanroom and in subfab areas for lighting in the subfab.

Lighting levels generally range from a low of 65 fc (650 lux) to a high of 75 fc (750 lux). In some fabs, lighting levels are higher, in the 100 fc (1000 lux) range. Support functions such as gowning are designed for low light levels in the range of 50 to 60 fc (500 to 600 lux).

Subfab lighting is most often provided by T5 or T8 fluorescent fixtures with solid-state electronic ballasts.

12.5.2 UTILITY SUBFAB

Local switches are provided for lighting controls. Both motion-actuated and proximity switches are used for some applications.

Lighting levels range from 65 fc (700 lux) to a high of 75 fc (800 lux). The light levels on this level match those on cleanroom levels. Two-lamp fluorescent fixtures using T5 or T8 lamps with solid-state electronic ballasts are used.

12.5.3 INTERSTITIAL LEVEL

Access to FFUs and other components such as light fixtures is provided from the interstitial plenum space and therefore requires life safety and maintenance lighting. This lighting is controlled by local lighting switches at the access to the plenum space. All wiring used within the pressurized plenum is rated for air plenum applications as required by *National Electrical Code* (NFPA 2014).

Lighting levels are designed for life safety and maintenance purposes only and are about 30 fc (320 lux). T5 or T8 fluorescent fixtures with electronic solid-state ballasts are most often used.

12.5.4 FAB SUPPORT AREAS

Local switches and or occupancy sensors are provided for lighting controls in fab support areas. This provides the ability to turn off the lights when support areas are not occupied. In less-used areas, motion sensors can be used for lighting controls.

Lighting levels are in the range of 50 to 65 fc (540 to 700 lux). Most often, T5 or T8 fluorescent fixtures with electronic solid-state ballasts are used.

12.6 LIGHTING FIXTURE ACCESS AND MAINTAINABILITY

Access to lighting fixtures is required for replacement and maintenance purposes. In the utility subfab and the interstitial plenum space, lighting fixtures are usually readily accessible.

Cleanroom and subfab clean spaces require cleanroom gowning protocols and special precautions to avoid impacting production.

The cleanroom ceiling height in a modern fab is usually around 16 ft (4.9 m) in height and in the future is expected to go higher, driven by the height of the process tools. Access to the fixtures requires temporary scaffolding for lamp and ballast replacement, resulting in costly disruptions. Other options are available where the light fixtures and associated ballasts are designed to be accessed from the interstitial plenum above the cleanrooms, eliminating costly disruptions within the cleanroom.

12.6.1 CLASSIFIED AREAS OF THE FAB

The main cleanroom and the subfab space below are not classified as hazardous spaces per *National Electrical Code* Article 500. However, on the utility subfab level, there are rooms where hazardous chemicals and gases are stored, processed, and dispensed. These rooms are classified as Class I Division 2 per *National Electrical Code* Article 500 (NFPA 2014). Fluorescent lighting fixtures and all associated electrical work in these rooms is specified for Class I Division 2 requirements. Coordination with the building code is required to ensure a safe environment.

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AIR CONDITIONING COMPANY

13 Computational Fluid Dynamics for Cleanroom Design

Air is the primary carrier of moisture, heat, particles, and contaminants in cleanroom facilities. The distribution of the supply air is what determines the air velocities, temperatures, and concentrations of particles at various locations in a cleanroom. This distribution also determines thermal comfort and air quality. Satisfactory thermal comfort of the occupants, higher energy efficiency of cleanroom HVAC systems, and maintaining the desired cleanliness are mutually competing goals. Attaining these goals through optimization of various design and operating parameters of cleanroom air distribution systems is a daunting task.

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

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

CFD involves solving and analyzing transport equations of fluid flow, mass transfer, heat transfer, and turbulence. The transport of mass, momentum, energy, and chemical species are governed by a generalized conservation principle that can be described in the form of a general differential equation. During this CFD procedure, first the calculation domain (extent of space) is divided into non-overlapping control volumes, such that there is one control volume surrounding each grid point. Then, each governing differential

equation is iteratively balanced over each control volume to conserve the mass, momentum, energy, and other similar physical entities. During the iterative process, the residual error for each governing equation is monitored and reduced. This process continues until the overall balance in the conservation of all the governing entities is achieved up to an acceptable desired level. Finally, such converged numerical solutions reveal a detailed distribution of pressure, velocities, turbulence parameters, temperature, concentration of chemical species, etc., in the calculation domain.

After successful completion of the above procedure, the CFD results can be presented in color contour plots showing three-dimensional distributions of temperatures and particle concentrations in cleanrooms. Flow pathlines and vector plots are used to reveal airflow patterns in a room. Flow animations also help in visualizing air and particle movement in a room.

Figure 13.1 shows CFD analysis of airflow patterns in a minienvironment and in a cleanroom. This analysis was performed to analyze the impacts of reduced supply airflow rates and supply diffuser location on the airflow patterns and resulting distribution of particle concentration (Khankari and Sun 2014). The airflow patterns are colored by the concentrations of the particles in the room. The figure shows almost unidirectional flow patterns in the minienvironment and nonunidirectional flow patterns in the cleanroom. The supply air entering in the room from the ceiling diffuser flows straight downward behind the operator and exits from the two returns located on the opposite sides of the room. This air jet remains almost unidirectional in the upper section and starts spreading around the operator and the minienvironment in the lower section of the room. The return air exiting from the minienvironment does not flow directly toward the room returns—it gets entrained into the room supply air jet and creates recirculation patterns around the operator. The airflow patterns in the minienvironment show strong unidirectional patterns without any recirculation. Because the supply air enters the minienvironment through the high-efficiency particulate air (HEPA) filters covering the entire ceiling of the minienvironment, maintaining such unidirectional flow becomes much easier for a smaller section.

Figure 13.2a shows the distribution of particle concentration (number of particles/ft^3) in the cleanroom. It shows the particles generated from the sample in the minienvironment are carried by the air and enter the room from the bottom return outlets. As a result, the particle concentrations in the lower section of the room are higher than in the upper section. The particle concentration in the minienvironment increases from the top to the bottom. As expected, the highest concentration remains near the sample, where particles are generated.

The other source of particle generation is from the operator's gown near the chest of the operator. Figure 13.2b shows a "cloud" of particles with a concentration of 1000+ particles/ft^3. The particle concentration beneath this cloud can be more than 1000 particles/ft^3. As shown in this figure, the zones of highest particle concentration are in the vicinity of the sources and in the return airstreams. Depending on the nature and composition of the particles, a high particle concentration around the operator may not be desirable. As mentioned previously, the high velocity air jet emerging from supply diffusers in the room causes strong entrainment of the return dirty air into the clean supply air, which results in high particle concentrations surrounding the operator. The particles exiting the minienvironment outlet travel upward in front of the operator and then downward behind the operator.

This study (Khankari and Sun 2014) provide valuable insights into the operation of minienvironments. It indicates that minienvironments can be operated at lower air change

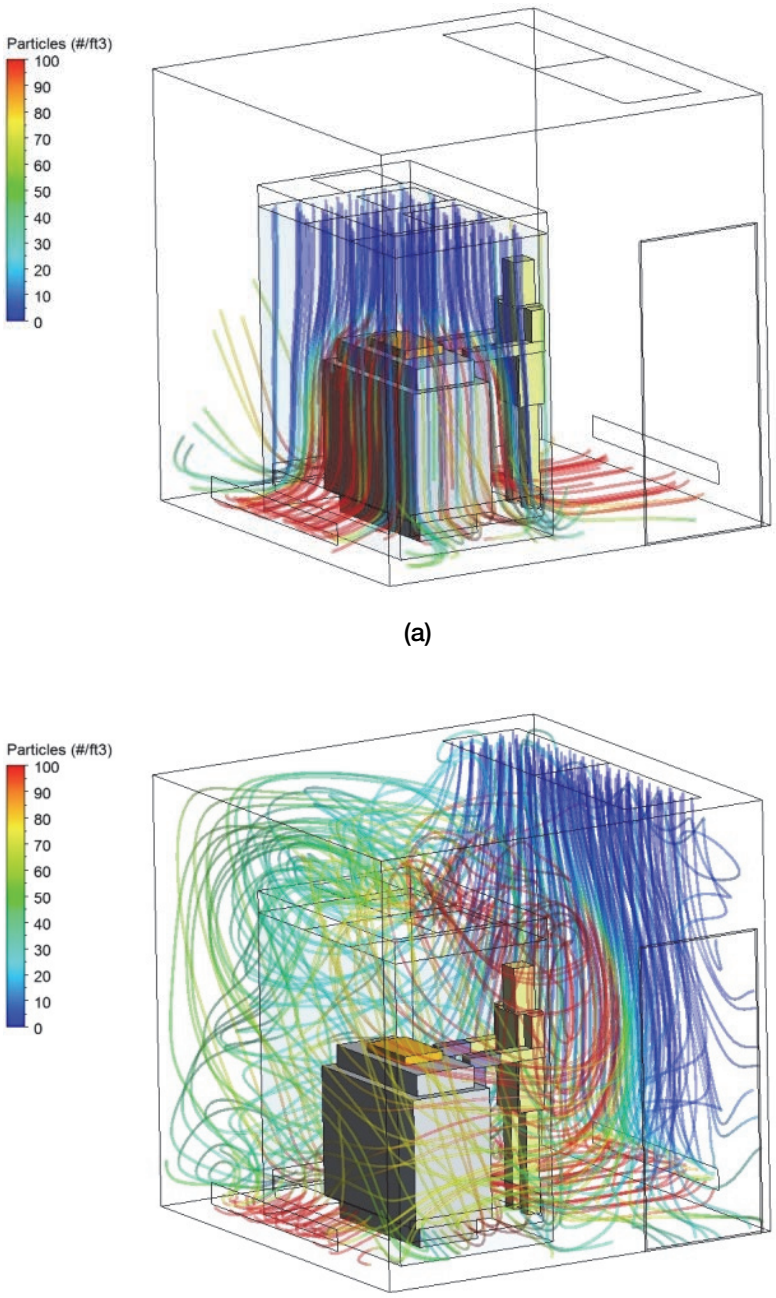

Figure 13.1 Airflow Patterns Colored by Particle Concentration (a) in Minienvironment Showing Unidirectional Flow and (b) in Cleanroom Showing Mixed-Flow Conditions

(CFD analysis provided by Dr. Kishor Khankari, PhD, AnSight LLC, Ann Arbor, MI)

rates without significantly affecting the cleanliness level of the minienvironment provided the lower cleanliness levels in the surrounding room are acceptable. It further indicates that the rate of supply air has little impact on airflow patterns. However, reducing supply airflow rates further contaminates a room by spreading the zone of high particle concentration to a larger area occupying the operator and the minienvironment. Strong entrainment flows can distribute the particles exiting the minienvironment to the rest of the room and can result in high concentration levels surrounding the operator. The location of supply diffusers has greater impact on the airflow patterns and on the resulting distribution of particles in the room. Moving the air supply directly over the operator helps in lowering

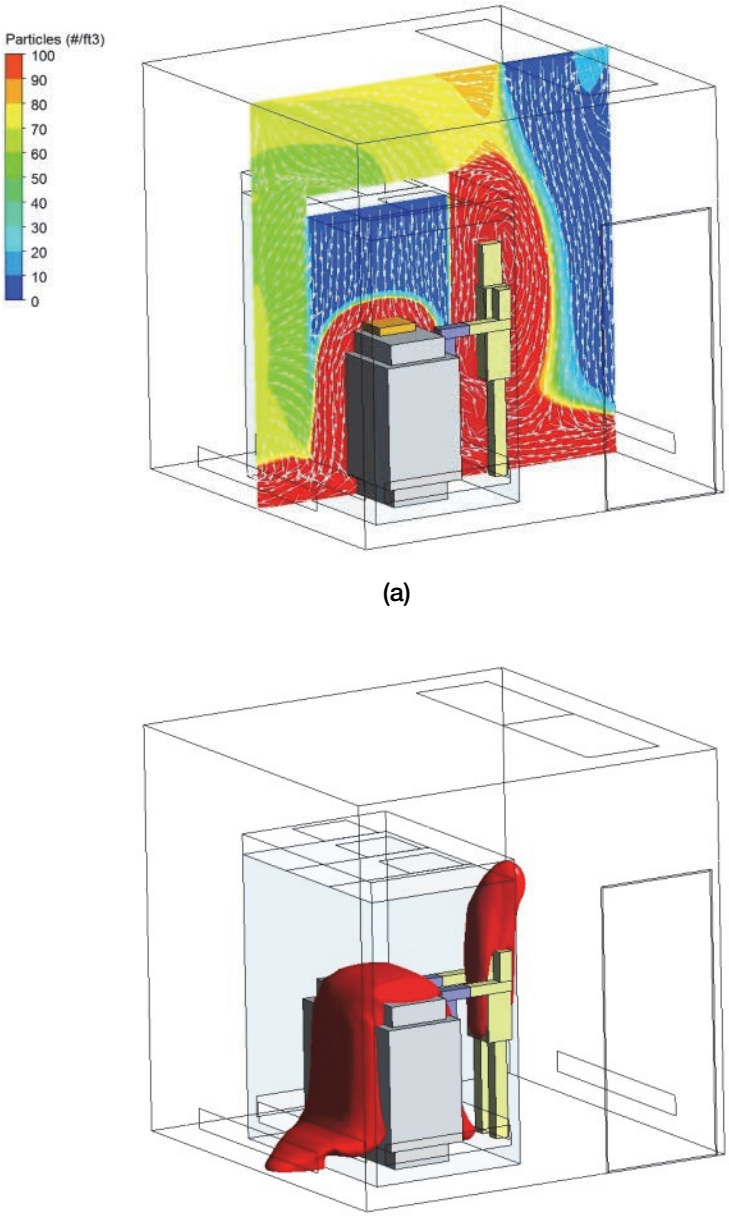

Figure 13.2 (a) Lower Particle Concentration within the Minienvironment and Higher Concentration near the Operator due to Recirculation of Air around the Operator and (b) Particle Cloud of 1000 particles/ft^3 Indicating Higher Particle Concentration near the Face of the Operator

(CFD analysis provided by Dr. Kishor Khankari, PhD, AnSight LLC, Ann Arbor, MI)

the zone of high particle concentration from higher to lower elevations in the room, which may help to reduce the risk of exposure to the particles exiting the minienvironment. These analyses further indicate that particle concentration in the cleanroom is not uniform and well mixed, as is often assumed during the design process.

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14

Utility Services for Cleanrooms

Cleanrooms provide stringent environmental space conditions to prevent contamination and/or increase product yield. Cleanrooms typically have many complex process tools and equipment that require extensive utility services. These utility services are necessary for the process tools and equipment to function properly but are also a primary contributing source of contamination. Due to the substantial utility service requirement differences between various industries, this section separates cleanroom utility requirements into the different industry categories of health care, pharmaceutical, electronic and general, and semiconductor manufacturing and nanotechnology.

Cleanroom utility services may include compressed air, gases, vacuum, cooling water, heating water, chilled water, steam, high purity water, and exhaust systems. It is important to know whether the utility service is closed to the cleanroom and its associated process (e.g., cooling water to piece of process of equipment) or open to the cleanroom and/or process (e.g., silane gas). Open utility services tend to have higher purity and cleanliness requirements than closed utility services. Typical utility service selection parameters include following:

- Required purity
- Safety requirements to eliminate/reduce danger to people, process, and facility
- Required generator and distribution system material and method of construction to prevent contamination
- Required flow rate, pressure, and temperature
- Required particulate/contamination filtering
- Required generator type
- Required distribution system layout and material of construction
- Required reliability and backup
- Required sequences and modes of operation
- Required cleaning and/or passivation
- Required commissioning
- Required controls, monitoring, and alarming

Depending on the specific requirements of the industry, facility, and process, there may be additional selection parameters that need to be considered for a particular utility service.

14.1 HEALTH CARE

Though the primary health care cleanrooms are major surgery operating rooms, other spaces such as general operating rooms, cathlabs, burn units, and immunocompromised patient rooms may be designed to meet cleanroom requirements. Health care utility services may include oxygen (O_2), nitrogen (N_2), nitrous oxide (N_2O), carbon dioxide (CO_2), vacuum, medical air, and waste anesthetic gas disposal exhaust. The primary health care medical gas standard is *NFPA 99* (NFPA 2015), which provides the different utility service technical requirements. The following are a number of health care utility service systems:

- Gas utility services (oxygen, nitrogen, nitrous oxide, carbon dioxide) are provided by bulk liquid storage tanks (oxygen) or bottles (nitrogen, nitrous oxide, carbon dioxide). On-site gas generators are not common in health care facilities.
- Vacuum systems and waste anesthetic gas disposal systems are provided with vacuum pumps and discharged to the outside. The waste anesthetic gas disposal system should be a separate dedicated system. The vacuum pumps should be oil-less or have lubricating oil that will not combust when exposed to pure oxygen or waste anesthetic gas.
- Medical gas systems should have duplex oil-less compressors and receiver and a duplex air dryer.

Health care utility service distribution systems should be made of clean type L copper piping that is joined together by brazing. Health care utility services have either a single distribution main or a ring main where two distribution mains are installed. The ring main provides convenience to shut down one main for repair, maintenance, or modification but does not significantly increase the utility service system reliability.

Health care utility service distribution systems have zone valving with each operating room or critical space having dedicated zone valving with pressure monitoring and alarming.

Per *NFPA 99*, some of the standard utility services performance requirements are as shown in Table 14.1.

14.2 PHARMACEUTICAL

Cleanrooms are used for many pharmaceutical processes and finishing spaces including sterile fill, capping, compounding, granulating, and tableting. Pharmaceutical utility services may include pure water (PW), water for injection (WFI), nitrogen, vacuum, breathing air, compressed air, instrument air, pure steam, cooling water, natural gas, and

Table 14.1 Selected Standard Health Care Utility Service Requirements

Utility Service	Nominal Supply Main Pressure	Utility Service Purity
Oxygen	55 psig (379 kPa)	≥99%
Nitrogen	180 psig (1241 kPa)	≥99% N_2, ≤1.0% O_2
Nitrous oxide	55 psig (379 kPa)	≥99%
Carbon dioxide	55 psig (379 kPa)	Not defined
Medical air	55 psig (379 kPa)	19.5% to 23.5% O_2
Vacuum	–19 in. Hg (–64 kPa)	N/A
Waste anesthetic gas disposal	–19 in. Hg (–64 kPa)	N/A

process exhaust. The primary pharmaceutical utility standards are published by U.S. Pharmacopeial Convention (USP) and U.S. Food and Drug Administration (FDA). Pharmaceutical utilities typically are divided into two categories, process systems and process support systems. Process systems come in direct contact or become part of a pharmaceutical product and have a direct impact on the product quality. Example process systems include WFI, which becomes part of the product, and nitrogen, which might be used as a blanket within a reactor vessel. Process support systems do not come in direct contact or become part of a pharmaceutical product but can indirectly impact product quality. Example process support systems include instrument air and cooling water.

Additional utility service parameters that need to be considered for pharmaceutical utility services include the following:

- All materials within a sterile environment must be compatible with cleaning agents and sterilants used.
- All process systems and process support systems must be validated via installation qualification (verifying the installation meets the design intent), operational qualification (verifying the operational performance of the individual equipment and systems), and functional performance qualification (verifying the functional performance of all equipment and systems together).
- All process systems must have a batch numbering system. Process support systems typically do not require a batch numbering system.

The following are a number of pharmaceutical process utility service systems:

- Water is an important component in many pharmaceuticals, including as a solvent and ingredient. The water used in pharmaceuticals must meet stringent requirements and be pretreated by a multistep process. The raw water must meet National Primary Drinking Water Regulations (40 CFR 141) (GPO 2015). Most municipal water supplies should meet this regulation, and well water systems need to be tested to ensure they conform to the regulation. It is important to know what the water quality requirements are for the equipment and systems using the pretreated water. Raw water treatment may include prefiltering, softening, dechlorination, indemnification, organic scavenging, deionization, reverse osmosis, distillation, ultrafiltration, and ultraviolet (UV) light.
- PW is used for sterile wash and preparation of nonparenteral compendial dosage forms (pills, inhalers). The PW must meet the requirements for ionic and organic chemical purity and protect from microbial contamination. PW may be produced through deionization, distillation, ion exchange, reverse osmosis, or filtration.
- WFI is used for parenteral dosage forms (injectable) and other forms that require endotoxin content be controlled and is used for cleaning of equipment involved in parenteral dosage form production. WFI is typically produced through distillation by multieffect still. WFI water systems are either hot systems (167°F to 176°F [75°C to 80°C]) or cold systems (149°F to 158°F [65°C to 70°C]).
- Pure steam is used for steam sterilization of process equipment product contact surfaces and may be used for air humidification. Pure steam must meet the same requirements as WFI and is typically produced through distillation by multieffect still.
- PW, WFI, and pure steam distribution systems are typically made of 316 L stainless steel pipe with internal pipe Ra average ≤15.0 for WFI and pure steam with Ra average ≤25.0 for PW. The distribution piping needs to be orbital welded, sloped, and completely drainable; have no dead leg length greater than

six times the branch piping; and have polytetrafluoroethylene (PTFE) gaskets and diaphragm valves.

- Nitrogen is supplied by bottles or bulk tank depending on anticipated nitrogen usage requirements. The nitrogen distribution piping can be made of clean copper piping up to the space being served. On-site nitrogen generators are typically not used in the pharmaceutical industry. At the space, the nitrogen should have a 5.0 μm filter for non-aseptic spaces/processes and a 0.2 μm filter for aseptic spaces/processes. The nitrogen piping downstream of the filter should be made of 316 L stainless steel.
- Compressed air is supplied by bottles or oil-less air compressor. Compressed air should have no oil contamination and have a dew point of –40°F (–40°C). Compressed air has the same distribution requirements as nitrogen.
- Per *USP 29* (USP 2006), some of the process system utility services performance requirements are as indicated in Table 14.2.

The following are a number of pharmaceutical process support utility service systems:

- Breathing air may need to be used to protect the operators where cytotoxic or high-potency manufacturing is being performed. Breathing air must meet Compressed Gas Association (CGA) *Commodity Specification for Air* (CGA 2011) Grade D (OSHA breathing air), which has requirements shown in Table 14.3.
- Compressed air must follow process system compressed air requirements. For compressed air used for pneumatic operation of process equipment, verify how the compressed air is exhausted. The exhausted compressed air may need high-efficiency particulate air (HEPA) filtration or to be piped outside the cleanroom to prevent contamination.
- The process equipment cooling water system supply water temperature needs to be 3°F to 5°F (2 to 3 K) above the cleanroom air dew point. If the process equipment requires a specific cooling water temperature that is below the cleanroom air dew point, it might be necessary to dehumidify the cleanroom air. ***Caution:*** low-humidity air (≤30% rh) can cause the entrainment and release of contaminants within the cleanroom.

Table 14.2 Selected Pharmaceutical Process Utility Service Requirements

Characteristics	Pure Water	Water for Injection	Nitrogen
Purity	N/A	N/A	≥99.0% N_2, ≤1.0% O_2, ≤0.001% CO
Electrical conductivity	1.3 μS/cm	1.3 μS/cm	N/A
Total organic carbon (TOC)	500 ppb	500 ppb	N/A
Bacteria alert	100 cfu/mL	10 cfu/mL	N/A
Endotoxins	N/A	0.25 EU/mL	N/A

Table 14.3 Pharmaceutical Manufacturing Breathing Air Requirements

(CGA 2011)

Characteristics	Breathing Air
Oxygen content	19.5% to 23.5%
Oil (condensed)	≤5 mg/m^3
Carbon monoxide	≤10 ppm
Carbon dioxide	≤1000 ppm
Water content	≤65°F (≤18.3°C)
Odor	No odor

There a number of active pharmaceutical ingredient (API) processes that require process exhaust with HEPA filtration, carbon filters, scrubbers, and/or incineration. It is important to work with the manufacturing engineers, site air permit officials, and state and federal regulation officials to determine the specific exhaust treatment requirements. There are a number of pharmaceutical finishing processes that require process exhaust that typically include weighing, screening, grinding, fluidized bed drying, milling, tableting, and packaging. The finishing process exhaust may need bag filtration. Some questions to consider in designing a pharmaceutical process exhaust include the following:

- What are the characteristics of the material being exhausted?
- What is the required exhaust airflow rate and variability?
- How is the exhaust system isolated during space sterilization?
- Does the exhaust system require sterilization?
- Does the exhaust system require a clean-in-place (CIP) system?
- Is a dedicated exhaust system required to prevent cross-contamination?
- What are the required sequences and modes of operation?
- Does the exhaust system require grounding and/or blowout panels?

14.3 ELECTRONIC AND GENERAL

Cleanrooms are used for a number of electronic processes, including screening, conformal coating, and circuit board manufacturing. Cleanrooms are also used for food packaging, plastic sheet manufacturing, glass laminating, and other contamination-sensitive processes. Utility services may include nitrogen (N_2), vacuum, compressed air, instrument air, cooling water, natural gas, and process exhaust. It is important to research the specific industry utility standards when designing and building these cleanrooms.

The following are utility service systems for electronic and general cleanrooms:

- Nitrogen is provided by bulk liquid storage tanks or bottles based on nitrogen load requirements. On-site nitrogen generators may be economically attractive. Evaluate whether terminal filtration is needed for each specific process.
- Vacuum systems are provided with vacuum pumps and discharge to the outdoors. Evaluate whether there are any vapors or other materials in the vacuum airstream that are combustible or explosive or could interact with the vacuum pump lubricating oil. If so, the vacuum pumps should be oil-less or have lubricating oil that will not combust when exposed to the vacuum airstream. A typical vacuum system has a 19 to 25 in. Hg (65 to 85 kPa) vacuum. The process vacuum requirements and distribution losses need to be taken into account when determining vacuum pump selection.
- Compressed air/instrument air generation is by bottles or oil-less air compressor. Compressed air/instrument air should have no oil contamination and have a dew point of –40°F (–40°C). Compressed air has the same distribution requirements as nitrogen.

Utility service distribution systems are made of clean type L copper piping that is joined together by brazing. It is important to verify that the copper piping will not cause contamination of the process being serviced. Utility services have either a single distribution main or a loop main. The loop main provides convenience to shut down one main for repair, maintenance, or modification but does not significantly increase the utility service system reliability.

The process equipment cooling water system supply water temperature needs to be 3°F to 5°F (2 to 3 K) above the cleanroom air dew point. If the process equipment

requires a specific cooling water temperature that is below the cleanroom air dew point, it might be necessary to dehumidify the cleanroom air. ***Caution:*** low-humidity air (≤30% rh) can cause the entrainment and release of contaminants within the cleanroom.

Process equipment exhaust must be evaluated for contaminants and chemicals being exhausted. Filtering, scrubbers, or incinerators on the exhaust airstream may be needed. Process exhaust should be designed not to adversely affect process equipment operation.

14.4 WAFER FABRICATION AND NANOTECHNOLOGY

Semiconductor manufacturing and nanotechnology facilities have the highest cleanliness and contamination control requirements of any industry. Due to the extremely small product tolerances (nanometer ranges), any contamination within the utility service gases will be detrimental to the product and product yield. Semiconductor and nanotechnology processes basically consist of adding material (vapor deposition) to a substrate, photolithography, removing material from a substrate (etching), or cleaning the substrate. Semiconductor and nanotechnology utility services include gases, water systems, and process exhaust.

14.4.1 GASES

There are many utility service gases used in performing semiconductor, nanotechnology, and other manufacturing processes. The utility service gases used in semiconductor manufacturing are divided into five categories: corrosives, toxics, pyrophorics, flammables, and bulk gases. Some gases are listed in more than one category. Table 14.4 provides the typical gases used in wafer fabrication for the different categories of gases.

Semiconductor Equipment and Materials International (SEMI) is an international semiconductor manufacturing organization that has developed semiconductor utility services gas system standards and guidelines. The following are a number of semiconductor gas system requirements:

- Gas generation can be via on-site gas production plant, bulk tanks, high-pressure trailers, bottles, or gas cabinets.
- Gas distribution piping is typically “double melt” 316 L stainless steel. There are different double melt stainless steel manufacturing processes, with the argon oxygen decarburization (AOD) and vacuum oxygen decarburization (VOD) processes being fairly common. Gas distribution piping is typically electropolished and passivated with in interior surface finish of Ra ≤10 µm max. The gas distribution piping is joined by orbital welding.
- Dead ends in the gas distribution piping should be avoided, and end-of-branch purging may be necessary where long dead ends cannot be avoided.
- Each gas system should have a continuous monitoring system to enable faster identification of and response to contamination within the system. It is recommended that moisture monitoring be performed for gases that are corrosive to stainless steel at higher moisture content.
- Gas generators located in gas cabinets need ventilation and fire protection.
- The gas distribution system may need to be purged after usage.
- Gases used in the semiconductor industry require higher purity to prevent product contamination and lower yields. Table 14.5 provides the standard gas purities used in semiconductor industry.

Table 14.4 Typical Gases Used in Wafer Fabrication

(Collins 1998)

Category	Gases
Corrosives	Ammonia, boron trichloride, boron trifluoride, chlorine, dichlorosiline, hydrogen chloride, hydrogen fluoride, phosphorous pentachloride, phosphorous oxychloride, silicon tetrachloride, silicon tetrafluoride, trichlorosilane, tungsten hexafluoride, hydrogen bromide
Toxics	Arsine, chlorine, diborane, germane, phosphine, silane, stibine, corrosives
Pyrophorics	Diborane, dichlorosilane, phosphine, silane
Flammables	Arsine, diborane, dichlorosilane, germane, hydrogen, phosphine, silane, trichlorosilane, stibine
Bulk gases	Argon, clean dry air, hydrogen, helium, nitrogen, oxygen

Table 14.5 Standard Gas Purities Used in the Semiconductor Industry

Gas	Purity	Gas	Purity
Ammonia	99.998%	Hexafluorethane	99.97%
Arsine	99.94%	Hydrogen bromide	99.98%
Boron trichloride	99.98%	Hydrogen chloride	99.997%
Boron trifluoride	99.0%	Nitrogen	99.9995%
Carbon dioxide	99.99%	Nitrogen trifluoride	99.98%
Carbon tetrafluoride	99.997%	Phosphine	99.98%
Chlorine	99.996%	Silane	99.994%
Disilane	97%	Sulphur hexafluoride	99.97%
Helium	99.9995%	Tungsten hexafluoride	99.8%

14.4.2 WATER SYSTEMS

The process equipment cooling water system supply water temperature needs to be 3°F to 5°F (2 to 3 K) above the cleanroom air dew point. If the process equipment requires a specific cooling water temperature that is below the cleanroom air dew point, it might be necessary to dehumidify the cleanroom air. ***Caution:*** low-humidity air (≤30% rh) can cause the entrainment and release of contaminants within the cleanroom.

14.4.3 PROCESS EXHAUST

Process equipment exhaust needs to be evaluated for contaminants and chemicals being exhausted. Depending on what is being exhausted, it might be necessary to have filtering, scrubbers, or incinerators on the exhaust airstream. Process exhaust should be designed not to adversely affect process equipment operation.

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Part 3

Cleanroom Testing, Certification, Commissioning, and Qualification

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15 Cleanroom Testing and Certification

Cleanroom testing and certification is conducted using specific tests in accordance with a predeveloped master plan (MP), a predeveloped Functional Requirement Specification (FRS), the latest industry standards, recommended practices, and other documents so that the requirements and specifications for the cleanroom can be achieved. Testing and certification is normally conducted by specialized individuals knowledgeable in cleanroom design, high-efficiency particulate air (HEPA) filter theory, airflow testing, and particulate cleanliness classification. Formalized training programs, quality systems, and maintaining calibrated test equipment traceable to a National Metrology Institute (NMI) are key components of organizations conducting testing and certification.

15.1 TERMINOLOGY

The following are definitions related to testing and certification.

airborne molecular contamination (AMC): A vapor or aerosol chemical contamination that has a negative effect on a cleanroom product or process.

coincidence: The presence of two or more particles in the sensing volume of the instrument at the same time, which causes the instrument to interpret the combined signal erroneously as resulting from one larger particle.

colony-forming unit (CFU): Either one or an aggregate of microbial cells that, when cultivated on solid media, will develop into a single visual colony; a microbiological term that describes the formation of a single macroscopic colony after the introduction of one or more microorganisms to microbiological growth media.

condensation nucleus counter (CNC): An instrument for counting airborne particles, in the nanometer size range and larger, by optically detecting droplets formed by condensation of a vapor upon the particles.

diluter: A device that reduces the particle concentration by dilution. Such a device typically mixes a known volume of sample air with a known volume of particle-free or filtered air to achieve the dilution. The ratio of the sample volume to filtered air volume (reversal) is the dilution ratio.

Functional Requirement Specification (FRS): Describes specific details and limits of acceptable ranges of a facility's or system's operation; identifies a system's capacity required for meeting performance objectives as outlined in a master plan.

macroparticle: A particle with an equivalent diameter greater than 5.0 µm.

master plan: An overview of a project process approved by senior management. It summarizes the project, identifies the criteria for success, and defines the criteria for project acceptance.

National Metrology Institute (NMI): An organization providing national and international primary test standards used in the unbroken chain of traceability of test equipment. Traceability to NMI standards does not always require the use of the NMI of the country in which a calibration laboratory is located.

particle size cutoff (or inlet) device: A device that, when attached to the inlet of a discrete particle counter or condensation nucleus counter, will remove particles smaller than the desired ultrafine particle size for airborne particle count testing.

polydisperse aerosol: An oil-based aerosol having a mass mean diameter of approximately 0.45 µm, a light-scattering geometric diameter of approximately 0.72 µm, and a light-scattering mean droplet-size distribution defined by Echols and Young (1963).

ultrafine particle: A particle with an equivalent diameter less than 0.1 µm.

viable particle: A living organism capable of performing biochemical processes and reproducing.

15.2 TEST SELECTION

The choice of certification tests is dependent on several factors, including but not limited to the following:

- As-built, at-rest, or operational phases
- Cleanroom design type (e.g., unidirectional or nonunidirectional airflow patterns)
- Industrial application for which the cleanroom is designed
- Industry regulatory guidelines or requirements
- Individual customer-specific needs for cleanliness

15.3 ORDER OF TESTS

While the order of performing testing and certification tests is often optional, certain tests should be performed before others, as they have direct impacts on later tests. Table 15.1 is a guide for selecting tests in regards to cleanroom airflow design and modes of operation. When testing cleanrooms with unidirectional airflow, the following test order should be followed:

- Airflow velocity or volume and uniformity
- Airflow direction and visualization
- Air pressure difference

15.4 INDUSTRIAL APPLICATION REQUIREMENTS

The cleanroom tests required are determined by the different applications per industry. The industry served by the cleanroom may influence which tests are required based on the specifications, needs of the product or process, and regulations. For example, microelectronics cleanrooms have requirements for particulate, electrostatic, conductiv-

Table 15.1 Tests by Airflow Design Type

Cleanroom Test	Unidirectional	Nonunidirectional
Airborne particle counts for classification	A, B, C	A, B, C
Ultrafine particles	A, B, C	A, B, C
Macroparticles	A, B, C	A, B, C
Airflow velocity, volume, and uniformity		
Airflow velocity	A, B	A, B (Note 1)
Airflow rate	A, B (Note 1)	A, B
Air pressure difference	A, B	A, B
Installed filter system leakage	A, B	A, B
Airflow direction and visualization	A, B, C	N/A
Air temperature, humidity, and uniformity	A, B, C	A, B, C
Electrostatic and ion generator	A, B, C	A, B, C
Particle surface deposition	A, B, C	A, B, C
Recovery	N/A	A, B
Containment leak	N/A	A, B
Airborne microbial counts	A, B, C	A, B, C
Surface microbial counts	A, B, C	A, B, C
Lighting level and uniformity	A, B, C	A, B, C
Noise levels	A, B, C	A, B, C
Vibration	A, B, C	A, B, C
Filter differential pressure	A, B	A, B
Compressed air line sampling	A, B, C	A, B, C

A: Test for the as-built phase
B: Test for the at-rest phase
C: Test for the operational phase
N/A: Not applicable

Note 1: *Typically, airflow velocity measurement is predominantly used for unidirectional applications where the sweeping action of air is the primary method of maintaining the level of airborne particulate cleanliness. Airflow rate measurement normally occurs within nonunidirectional flow applications using the airflow dilution method for particulate control.*
Caution: *This chapter cannot possibly attempt to address all safety and health concerns resulting from the testing and certification of cleanrooms. An industrial hygienist or occupational safety and health professional should be consulted for guidance.*

ity, and airborne molecular contamination (AMC), while the goals of pharmaceutical manufacturers are to control microbial and nonviable particulate contamination.

The following is a partial listing of cleanroom testing standards or recommended practices and is broken out by the category of interest related to cleanroom testing:

- **Airborne Nonviable Particle Count Testing**
  - ISO 14644-1, *Cleanrooms and Associated Controlled Environments—Part 1: Classification of Air Cleanliness by Particle Concentration*
  - IEST-G-CC1001, *Counting Airborne Particles for Classification and Monitoring of Cleanrooms and Clean Zones*
  - IEST-G-CC1002, *Determination of the Concentration of Airborne Ultrafine Particles*
  - IEST-G-CC1003, *Measurement of Airborne Macroparticles*
  - IEST-G-CC1004, *Sequential-Sampling Plan for Use in Classification of the Particulate Cleanliness of Air in Cleanrooms and Clean Zones*

    - ASTM F312, *Standard Test Methods for Microscopical Sizing and Counting Particles from Aerospace Fluids on Membrane Filters*
- **General Cleanroom Testing Requirements**
    - ISO 14644-2, *Cleanrooms and associated controlled environments—Part 2: Monitoring to provide evidence of cleanroom performance related to air cleanliness by particle concentration*
    - ISO 14644-3, *Cleanrooms and Associated Controlled Environments—Part 3: Test Methods*
    - ISO 14644-7, *Cleanrooms and Associated Controlled Environments—Part 7: Separative Devices (Clean Air Hoods, Gloveboxes, Isolators and Mini-Environments)*
    - ISO 29463, Parts 1–5, *High-Efficiency Filters and Filter Media for Removing Particles in Air*
    - IEST-RP-CC001, *HEPA and ULPA Filters*
    - IEST-RP-CC002, *Unidirectional-Flow Clean-Air Devices*
    - IEST-RP-CC006, *Testing Cleanrooms*
    - IEST-RP-CC007, *Testing ULPA Filters*
    - IEST-RP-CC028, *Minienvironments*
    - IEST-RP-CC034, *HEPA and ULPA Filter Leak Tests*
- **Cleanroom Criteria Reference Documents**
    - ISO 14644-4, *Cleanrooms and associated controlled environments—Part 4: Design, construction and start-up*
    - IEST-RP-CC012, *Considerations in Cleanroom Design*
- **Testing Organization Qualifications**
    - IEST-RP-CC019, *Qualifications for Organizations Engaged in the Testing and Certification of Cleanrooms and Clean-Air Devices*
- **Viable Monitoring**
    - ISO 14698-1, *Cleanrooms and Associated Controlled Environments—Biocontamination Control, Part 1: General Principles and Methods*
    - USP <1116>, *Microbiological Evaluation of Clean Rooms and other Controlled Environments*
    - IEST-RP-CC023, *Microorganisms in Cleanrooms*
- **Particle Surface Deposition**
    - ISO 14644-9, *Cleanrooms and Associated Controlled Environments—Part 9: Classification of Surface Cleanliness by Particle Concentration*
    - IEST-RP-CC016, *The Rate of Deposition of Nonvolatile Residue in Cleanrooms*
- **Electrostatic and Ion Generator**
    - IEST-RP-CC022, *Electrostatic Charge in Cleanrooms and Other Controlled Environments*
- **Vibration**
    - IEST-RP-CC024, *Measuring and Reporting Vibration in Microelectronics Facilities*
- **Cleanroom Test Equipment Calibration—General**
    - IEST-RP-CC013, *Calibration Procedures and Guidelines for Selecting Equipment Used in Testing Cleanrooms and Other Controlled Environments*

- ISO 21501-4, *Determination of Particle Size Distribution—Single Particle Light-Interaction Methods—Part 4: Light-Scattering Airborne Particle Counter for Clean Spaces*
- IEST-RP-CC014, *Calibration and Characterization of Optical Airborne Particle Counters*

- **Compressed Gas Systems**
  - ISO 8573, Parts 1–9, Compressed Air
- **Industry-Specific Reference Documents**
  - *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* (U.S. Department of Health and Human Services, U.S. Food and Drug Administration)
  - Annex 1, Manufacture of Sterile Medicinal Products, in *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use*, Volume 4 of *EudraLex—The Rules Governing Medicinal Products in the European Union* (European Commission, Directorate-General for Health and Food Safety)
  - USP <797>, *Pharmaceutical Compounding—Sterile Preparations* (United States Pharmacopeial Convention)
  - TO 00-25-203, *Technical Manual: Contamination Control of Aerospace Facilities, U.S. Air Force* (U.S. Air Force)
  - *NASA Standard Procedures for the Microbiological Examination of Space Hardware* (National Aeronautics and Space Administration)

15.5 TYPICAL CLEANROOM TESTING EQUIPMENT

A wide variety of test equipment is available for use in cleanroom testing and certification. The following list provides general guidance to aid in the proper selection, calibration, and support documentation of test equipment:

- Each piece of test equipment used for cleanroom certification and testing should be calibrated using procedures that are nationally or internationally recognized. Standards and materials used for calibration should be traceable to a National Metrology Institute (NMI), primary standards, or a recognized equivalent.
- A certificate of calibration and supporting data should be available for all test equipment used in testing and certification. This record should be available for inspection or a requested copy and should accompany the cleanroom test report results as supporting data.
- Test equipment should be selected to meet the required readability, use range, and tolerance specified in industry standards or recommended practices or agreed upon between the cleanroom customer and the testing provider.

15.6 CLEANROOM ACCEPTANCE CRITERIA

The Functional Requirement Specification (FRS) predetermines the goals for a cleanroom. Using the FRS as a directive, the selection of appropriate tests and review of acceptance criteria begins the certification and testing process. Ideally, cleanroom acceptance criteria are selected during the design development phase at a level appropriate for the application, usually based on regulatory guidance or user specifications. The engineering design criteria, or basis of design (BOD), is often more stringent than the acceptance crite-

ria to ensure compliance. Once a cleanroom is ready for testing and certification, a verification of construction completion as well as a review of the specific acceptance criteria details helps to ensure project success. Reviewing commissioning or qualification documentation, engineering design drawings, design criteria, engineering as-built documentation, and/or equipment specifications are common for delivering a properly operating cleanroom.

When an FRS or acceptance criteria information is unavailable, industry design criteria may be used after the following are reviewed: the cleanroom processes, nonviable/viable particulate counts, equipment heat loads, capabilities of the environmental system (HVAC, filtration), overall construction and design, and historical data of previous certifications. In addition, airflow visualization (unidirectional), particulate measurements, and room recovery testing (nonunidirectional) may be used in establishing the optimum ranges of airflow velocity, airflow rate, or uniformity.

Cleanroom certification testing can have a major impact on the cleanroom design phase and the selection of critical components. The group responsible for the design/component selection phase should take the unique needs of testing and certification into account, such as the selection of high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filter types. Room configuration and how a filter is field certification tested may determine what type of filter can be installed into a typical cleanroom. The HEPA/ULPA efficiency and factory test methods must be compatible with the method of installed filter system leakage once the filter is in place in the cleanroom system. Filters selected for installation must have factory efficiency and scan testing more stringent than the certification testing methods conducted at installation. Unidirectional-flow cleanroom applications may require filters with media specified to provide uniform airflow across the whole filter face. In a way this is reverse engineering, but if these types of considerations are not recognized in the design phase, failed certification testing, delays in cleanroom start-up, replacement of HEPA/ULPA filters, or system redesign may result.

Designers may need to provide aerosol challenge locations to introduce the aerosol concentration to the filters and test ports to quantify the amount of challenge for the installed filter system leakage test. Filter housings and configurations must be compatible with the testing methods used during operation; for example, proper test ports must be provided if room-side testing will be used, or a duct test port may be needed for testing a filer bank as an assembly. Duct test port mounting is best if located on a negative portion of the ductwork, although this may not always be an available option. Fire monitoring/suppression systems may require a way to disable or bypass alarms for the duration of the certification test to avoid alarms and fan system shutdowns.

15.7 REQUIRED TESTS FOR CERTIFICATION

15.7.1 AIRBORNE PARTICLE COUNTS FOR CLASSIFICATION

Acceptance testing criteria values for different operational states of the cleanroom or clean zone, commonly referenced as *as built*, *at rest*, and *operational*, must be established. Much of the information needed for these tests may be found in ISO 14644-1 and 14644-2 (ISO 2015a, 2015b). Document the cleanroom or clean zone cleanliness classification and desired particle size(s) to be sampled using the master plan, FRS, customer design criteria, and appropriate particle count testing standard(s) or recommended practices/guidance documents.

Based on the particle size(s) of interest and cleanliness class, use Equation 15.1 to calculate the level of particle concentration:

$$\text{Particle concentration} = 10^{N} \times (0.1/d)^{2.08}, \text{ in particles/m}^3 \quad (15.1)$$

where

N = numerical designation of an ISO cleanliness class (e.g., ISO Class 7)
d = alternative particle size (0.3 µm)

Establish the sampling height or distance to sample the air as it reaches the clean zone, typically no more than 12 in. (30.5 cm) upstream of the critical zone, work area, or process equipment. The isokinetic probe should be oriented to point into the airstream for unidirectional-flow applications and to point vertically towards the ceiling for nonunidirectional-flow applications.

The sample locations should be uniformly spaced throughout the clean zone except as limited by equipment within the clean zone or where the cleanliness level is particularly critical, as determined by the customer. In nonunidirectional-flow rooms, particle count sampling should not be positioned directly under ceiling filters or diffusers, as such locations are not representative of the air quality of the room as a whole.

The minimum sample volume (expressed in liters per minute, lpm) should be established based on the class limit of the largest particle size of interest to achieve a statistically valid sample.

Complete the particle count sampling plan at the reported locations using the appropriate sample time. Document any required statistical analysis reports based on the sampled particle count data.

15.7.1.1 Ultrafine Particles

Optional (additional) particle count tests when sample particle sizes are smaller than 0.1 µm (ultrafine particles) may be found in ISO 14644-1 (ISO 2015a) and IEST-G-CC1002, *Determination of the Concentration of Airborne Ultrafine Particles* (IEST 1999a).

Sampling of ultrafine particles may be conducted using either a discrete particle counter (DPC) or a condensation nucleus counter (CNC), along with a particle size cutoff (or inlet) device, if required. These devices must meet stringent criteria described in greater detail in ISO 14644-1 and ISO 14644-3 (ISO 2015a, 2005) and IEST-G-CC1002 (IEST 199a). Particle count sampling uses the same methods as described in the previous Airborne Particle Counts for Classification section.

The U descriptor format may be expressed as a supplement to the ISO 14644-1 cleanliness classes or independently. The U descriptor is expressed in the following format:

$$\text{U } (x; y)$$

where

x = maximum permitted concentration of particle reported in particles/m^3
y = size expressed in micrometers where the counter detects such particle with a 50% counting efficiency

A 100,000 particles/m^3 concentration limit in a particle size range of >0.05 µm would be expressed as

$$\text{U } (100000; 0.05 \text{ µm})$$

15.7.1.2 Macroparticles

Airborne particle counts for sample particle sizes larger than 5.0 µm (macroparticles) may be found in ISO 14644-1 (ISO 2015a) and IEST-G-CC1003, *Measurement of Airborne Macroparticles* (IEST 1999b).

Two generalized categories of testing are available for macroparticle measurement: macroparticle measurement by collection and macroparticle size and concentration measurement without particle collection. Note that the use of different test methods and equipment may result in values that are not consistent with each other and may not be directly comparable.

Macroparticle measurement by collection uses filtration or inertial effects, followed by microscopic measurement of either the number and size or the mass of collected particles. Measurement by collection is further broken down into three subcategories:

- **Filter Collection and Microscopic Measurement.** A labeled filter holder and membrane filter with a set micrometer pore size and a vacuum source to draw air through the filter holder should be used. The filter membrane faces vertically at all times until analyzed. The air sample volume may be dependent on the room classification, with higher sample volumes for cleaner rooms. Particle counting may be accomplished using methods described in ASTM F312 (ASTM 2008).
- **Cascade Impactor Collection and Microscopic Measurement.** Air passes through a series of jets having smaller orifice sizes at each collection (stage). Each collection stage is individually removed and examined under a microscope for evaluation.
- **Cascade Impactor Collection and Weight Measurement.** Air passes through a series of jets having smaller orifice sizes or microbalance sensors at each collection (stage). The impactor is operated for periods from a few minutes up to several hours, depending on the cleanliness classification. The results from the impactor collection are based on the sample total airflow versus the total weight of the samples.

Macroparticle size and concentration measurement without particle collection measures the macroparticles within the airstream using one of two following equipment types:

- **DPC Method.** This method is the same as the airborne particle counts for classification test, except there is not a sensitivity requirement for detecting particles smaller than 1 µm. Sample tubing should be kept as short as possible, because longer tubing will increase the chance of particle fallout within the tubing. At least one DPC channel should monitor sizes smaller than 5 µm to verify that the coincidence level for the counter is not being exceeded.
- **Time-of-Flight Particle Size Measurement.** This measurement method accelerates the sample air by expansion through a nozzle, and the sample is drawn into a partial vacuum measurement region. Any particle within the airstream will accelerate to match the air velocity in the measurement region. The particle's mass to its acceleration rate is inversely proportional. The calculated air velocity versus particle velocity relationship can be used to determine the particle diameter. The particle velocity is determined the time of flight between two laser beams. The sample acquisition procedures are the same as those for the DPC method for sampling macroparticles.

The macroparticle count sample air volume must be sufficient to achieve a statistically valid sample. The M descriptor format may be expressed as a supplement to the

ISO 14644-1 cleanliness classes (ISO 2015a) or independently. The M descriptor is expressed in the following format:

$$M\ (a;\ b);\ c$$

where

a = maximum permitted concentration of particles reported in particles/m^3
b = equivalent diameter (or diameters) expressed in micrometers associated with the specified method of detection
c = specific measurement method

A 1000 ppcm concentration limit in a particle size range of >15 µm using the time-of-flight counter method would be expressed as

M (1000; >15 µm); time-of-flight particle counter method

15.7.2 RECOMMENDED TESTS FOR CERTIFICATION

15.7.2.1 Airflow Velocity, Volume, and Uniformity

The choice of airflow velocity, volume, and uniformity testing method depends on the design criteria requirements:

- Velocity as design criteria
  - Measurement of the airflow velocity and uniformity within the cleanroom, clean zone, or unidirectional-flow work zone
- Total volume (airflow rate or air changes per hour) as design criteria
  - Measurement of total airflow rate entering the cleanroom or clean zone

15.7.2.1.1 Airflow Velocity Method

Typically, airflow velocity measurement is used where the sweeping action of air and directional flow control within a range of air velocity and/or velocity uniformity are the primary methods for maintaining the level of airborne particulate cleanliness (i.e., unidirectional-flow clean-zone applications). Airflow volume measurement is normally used for nonunidirectional flow applications using the airflow dilution method for particulate control (see Section 15.7.3.1.2). The resulting total airflow rate will determine the room air volume changes per hour for the cleanroom.

Airflow velocity should be measured at the cleanroom entrance plane (approximately 6 to 12 in. (150 to 300 mm) from the last point of resistance from the filtration source (i.e., diffuser screen, protective grille, or filter face). The number of velocity readings should be sufficient to determine the average velocity rate and uniformity at the filter face. This grid size should be a matter of agreement between the cleanroom customer and the testing provider.

Grid size guidance includes the following:

- From ISO 14644-3: “The number of measuring points should be sufficient to determine the supply airflow rate in cleanrooms and clean zones, and should be the square root of 10 times the area in square meters, but no less than 4. At least one point should be measured for each filter outlet or fan-filter unit” (ISO 2005, p. 23).
- From IEST-RP-CC006: “Divide the plane into a grid of equal areas. Individual areas should not exceed 4 ft^2 (0.4 m^2)” (IEST 2004a, p. 11).

While the above documents provide minimum grid sizes, the final determining factor for setting grid size should be the answer to the question *Am I taking enough velocity*

points to get an accurate and realistic cross section of the critical filter face velocity area to determine overall average velocity and uniformity?

This can be best answered by looking at the surface sample area of the velocity-measuring device. A thermal anemometer velocity sensor has an extremely small cross-sectional sampling footprint. Sampling only one or two velocity points on a filter may result in values that do not truly represent the filter velocity because of the local velocity variations in HEPA filter media construction. Therefore, requiring more velocity points on the filter face might be prudent practice. A reading within every 1 ft^2 (0.1 m^2) of the filter face may give a better picture of filter face velocity and uniformity. On the other hand, a multipoint, averaging velocity array may require fewer velocity readings since it samples a larger cross-sectional area. The multipoint array samples an averaged velocity pressure (V^p) converted to velocity by the use of an electronic micromanometer. While the multipoint array samples a greater area of the filter face, it also averages out locally high or low velocity points found on the filter face. Therefore, the multipoint array normally displays better airflow uniformity across the filter face than velocity sensors having a small cross-sectional sampling area.

The sample area should be unobstructed during the airflow measurement. When filter frames, teardrop lighting, fluorescent bulbs, or filter-clamping cross bars interfere with the sampling grid location, adequate downstream distances should be used to obtain repeatable velocity measurements once the airstream returns to unidirectional flow patterns.

Once the sampling of the velocity profile is completed, the airflow uniformity determination should be calculated. This may be as simple as verifying that individual filter average velocities fall within a set percentage or calculating relative standard deviations for all of the velocity points.

15.7.2.1.2 Airflow Rate Method

The direct airflow rate method is preferred to the sampling of airflow velocity measurement and is a more representative test when determining the final filter air supply flow rate. This test is broken into two sections based on test equipment use: the primary method of using the flow hood and the secondary method of using a thermoanemometer when physical restrictions prevent the use of the flow hood.

Primary Method: Flow Hood Measurement Method

Select the appropriate size flow hood shroud for the filter or diffuser being tested. The shroud should be of the smallest size possible to surround the entire filter. Seal the flow-measuring hood at the ceiling around the room supply filter, diffuser, or grille to capture and direct the airflow through the flow-measuring hood base. Airflow through the unit should not be blocked or influenced by any object downstream of the flow-measuring hood base. Record the airflow rate at each room air supply location.

Note: In the event a flow-measuring hood is impractical due to obstructions, the (secondary) thermoanemometer velocity method can be used.

Secondary Method: Thermoanemometer Velocity Measurement Method

This method compares a flow hood average volume versus an airflow rate achieved by an anemometer and a correction factor determined by a ratio of the difference of the readings. The detailed procedure may be found in IEST-RP-CC006 (IEST 2004a).

Once the filter, diffuser, or grille airflow rates have been recorded, calculate the sum of all supply airflow rates within the room to determine the total supply volume. The room air changes per hour (ACH) may be calculated by the using the following formula:

$$ACH = 60 \times (Q_1 + Q_2 + \ldots + Q_L) / ((l \times w \times h) / 1728) \quad \text{(I-P)} \quad (15.2)$$

$$ACH = 3600 \times (Q_1 + Q_2 + \ldots + Q_L) / (l \times w \times h) \quad \text{(SI)} \quad (15.2)$$

where

Q = airflow rate measured at each discharge of room air supply, cfm (m^3/s)
L = number of filters
l = length of room wall, in. (cm)
w = width of room wall, in. (cm)
h = height of room wall, in. (cm)

Establishing Acceptance Criteria

Establishing the airflow velocity and flow rate acceptance criteria should be a cautious undertaking if this was not completed in the cleanroom design phase. Many reference and source documents apply generic airflow criteria that have historically worked. Competent design practices often include providing sufficient capacity to achieve facility goals and operating the cleanroom at lower airflow values based on start-up and commissioning testing. This lower airflow approach promotes energy efficiency and infrastructure reliability simultaneously and requires careful design considerations to minimize increased first costs. Cleanroom air change rates are not the main criteria for controlling room contamination because internal particle generation rate, personnel activities, air supply and return register locations, and air-balancing adjustments have significantly more impact.

Typical ACH per cleanliness classification guidance values may be found in ISO 14644-4 (ISO 2001), IEST-RP-CC012 (IEST 2015), and U.S. Food and Drug Administration (FDA) guidelines (FDA 2004).

Note: Room air change acceptance criteria are more critical for nonunidirectional applications (ISO Class 6 and less-clean areas). Unidirectional cleanroom acceptance criteria are typically based on filter average velocity, not air changes per hour.

Meeting the guidance ACH values does not necessarily mean that the air changes will work in an application. Items to consider for airflow velocity, volume, and uniformity include (but are not limited to) the following:

- Regulatory and/or customer expectations of the cleanroom application (cleanliness classification)
- The adjustment capability (range) and control of the air-handling system
- The sensitivity of automated/manual controls of the air-handling system
- Uniformity of the individual filter velocity (filter quality/factory uniformity criteria) in its final installed location
- Locations/types of internal particulate- or contaminant-generation sources (process or personnel)
- Energy conservation and cooling/heating loads

Establishing airflow velocity criteria may best be approached by setting the airflow near an industry recommended value then increasing and decreasing the airflow to establish acceptable operating ranges. The airflow is validated by the use of video-recorded airflow smoke studies to verify favorable airflow patterns at the low, middle, and high set points. Airborne particle counts, the work surface velocity profile, and air pressure difference monitoring should accompany these tests for verification of acceptable operation.

15.7.2.2 Air Pressure Difference

Th air pressure difference test verifies the capability of the cleanroom suite to maintain specified pressure differences between the controlled areas, adjacent spaces within the controlled areas, and surrounding uncontrolled environments. Before this test is started, all airflow should be confirmed and balanced as specified on design documents.

With all doors closed, measure the pressure difference with an electronic or mechanical manometer between the cleanest section of the facility and the next adjacent room until all applicable room pressures have been recorded. The last reading should be to the surrounding uncontrolled environment. It is advisable to verify that there are no localized pressure reversals at the perimeters of doors with a visible smoke test; even if the overall room differential pressure is correct, local air currents at doorways may be influenced by nearby air supply outlets, vents, and/or room air returns to produce unacceptable airflow reversal, enabling undesirable particle intrusion.

Report all measured differential pressures to at least the nearest 0.01 in. w.c. (2.5 Pa) along with their corresponding locations. Also note the accuracy of the pressure measurement instrumentation and the stability and range of room differential pressure trends so that final system adjustments ensure proper pressurizations will be achieved consistently during normal operations.

Airflow movement is normally set up to cascade from cleanest areas to less-clean areas for sterile applications. When containment and sterility are both concerns, airflow should flow from rooms of lowest hazard to rooms of highest hazard. The level of pressure differential across doorways or room penetrations should be sufficient to prevent particle ingress while under all cleanroom operating phases or conditions. Actual pressurization recommendations can be found in Part 2 of this book and industry standards/recommended practice documents, including the following:

- ISO 14644-4, *Cleanrooms and Associated Controlled Environments—Part 4: Design, Construction and Start-Up*
- IEST-RP-CC012, *Considerations in Cleanroom Design*
- FDA's *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*
- European Commission's Annex 1, Manufacture of Sterile Medicinal Products, in *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use*, Volume 4 of *EudraLex—The Rules Governing Medicinal Products in the European Union*
- USP <797>, *Pharmaceutical Compounding—Sterile Preparations*
- USP <800>, *Hazardous Drugs—Handling in Healthcare Settings*

15.7.2.3 Installed Filter System Leakage

The installed filter system leakage test is performed to confirm that the filter system is free of leaks or defects. This system leakage test refers to testing of the HEPA or ULPA filter media, frame, gasket, and mounting frame or housing. The test is performed by introducing an aerosol challenge upstream of the filter and scanning or probe-testing downstream to detect leaks. The test methodology is broken into two groups based on the detection instrumentation, the aerosol photometer and the DPC. The aerosol photometer test is further subdivided into the scan test method and the overall filter leak test method.

While the aerosol photometer and DPC methods both detect leaks, the test results are not directly comparable. This can be partially attributed to the principle of how each device detects the leak and the method of determining the leak quantity.

An aerosol photometer is a forward-light-scattering, mass-measuring device that compares the upstream aerosol concentration (sampled or calculated) to the detected downstream concentration and directly converts this value into a percentage of penetration. The DPC sizes and counts individual particles referenced to a specified volume of air. It determines the leak percentage using a calculation taking into account the upstream and downstream particles counted, sample times, and upstream challenge dilution ratios. Each equipment method has its own advantages and disadvantages that cannot be completely addressed in this chapter.

A reference document that provides great detail of HEPA and ULPA filter leak test methods is IEST-RP-CC034 (IEST 2016a).

One determining factor for selecting which test method to use is the contamination concern of the aerosol to equipment or materials within the cleanroom environment. This decision is predominantly industry driven.

Pharmaceutical, biotechnology, and medical device manufacturers historically use aerosol photometers and oil-based aerosol generators because this test equipment can function in both sterility and containment applications without the introduction of solid particulate contamination. A Laskin-nozzle-generator (Echols and Young 1963) produces a polydisperse aerosol with a mass mean diameter of approximately 0.5 μm with a geometric standard deviation of up to 1.7 (ATI 2016). An alternative polydisperse aerosol generator that produces higher aerosol concentrations is commonly used. It should be noted that the particle size distribution is measurably smaller than that of the Laskin nozzle generator.

The microprocessor and semiconductor industries almost exclusively use the DPC, diluter, and polystyrene latex (PSL) generated aerosol for leak testing due to the problem of off-gassing from oil-based aerosols through the filter, thereby potentially affecting their AMC-sensitive product. The cleanliness levels for ISO Classes 1 through 4 use ULPA and super ultralow particulate air (SULPA) filters best tested using the DPC. The final decision will ultimately fall upon the cleanroom owner, who must answer to regulatory authorities, their key stakeholders, product buyers, and outside auditing agencies.

Detailed instruction on this test is found in ISO 14644-3 (ISO 2005) and IEST-RP-CC034 (IEST 2016a).

15.7.2.3.1 Aerosol Photometer Test Methods

Aerosol Photometer 100% Scan Test Method

In this test, the challenge aerosol is introduced to the filter(s) in a manner that will produce a uniform challenge concentration over each filter's surface and at each of the filters being exposed at the same time.

With the aerosol photometer, measure the upstream aerosol concentration immediately upstream of the filter(s) in question. The upstream concentration should be adjusted to a specified level.

The nozzle of the photometer scanning probe should be held approximately 1 in. (25 mm) downstream from the HEPA filter media or frame being tested.

Scan the perimeter of each filter pack and the downstream side of the HEPA filter(s) by passing the photometer probe in slightly overlapping strokes at a specified scan rate. Separate passes should made around the seal between the filter and the device, along the bond between the filter pack and frame, and around the periphery of the filter. The filter frame mounting rack construction should be tested to ensure there is no bypass of air through unsealed construction joints.

Aerosol photometer aerosol leaks should not have a penetration greater than 0.010% of the upstream concentration. Alternative acceptance criteria may be established as a matter of agreement between the cleanroom customer and the testing provider.

Whenever a leak is detected during the scan test, the probe should be repositioned to be stationary over the maximum detected signal. Note the maximum sustained leakage value.

Make any necessary repairs as deemed appropriate as a matter of agreement between the cleanroom customer and the testing provider. Retest affected filter(s) upon completion of the repair, allowing for curing/setup times of sealant compounds. Measure and calculate any filter media repairs, if required by the customer, to calculate patch size and percentage of patch area.

Aerosol Photometer Total Leakage Test Method

When it is not possible to scan filter(s) due to remote locations or inaccessibility, a complete leakage test should be performed. The downstream sample location should be located at a point to allow for adequate mixing. Samples taken downstream should be the representative aerosol penetrating through the filter(s) including locations along the duct walls.

Aerosol photometer aerosol leaks should not have a penetration greater than 0.010% of the upstream concentration. Alternative acceptance criteria may be established as a matter of agreement between the cleanroom customer and the testing provider.

Complete any necessary repairs as deemed appropriate as a matter of agreement between the cleanroom customer and the testing provider. Retest the affected filter(s) upon completion of the repair, allowing for curing times of sealant compounds. Measure and calculate any filter media repairs, if required by the customer, to calculate patch size and percentage of patch area. Seal any upstream concentration sampling ports using preexisting plugs or expandable plugs to prevent bypass leakage.

15.7.2.3.2 Discrete Particle Counter (DPC) Test Methods

Much of the general scan testing and probe testing methodologies are somewhat the same for DPCs as they are for aerosol photometers.

One significant difference between the methods is the value considered a scanned leak and the calculation of the actual leak. ISO 14644-3 (ISO 2005) describes in great detail the rather complex preparatory calculations required before scanning. The calculations are used to determine what detected particle count value would be indicative of a leak requiring further action. Once this value is exceeded, the particle counter must remeasure the highest detected value while being held stationary. If the observed particle count continues to exceed the desired level during the extended sustained residence time, it should be considered a leak requiring attention.

Due to the complexity and length of descriptions needed to explain these calculations, a thorough review of ISO 14644-3 Section B.6.3 (on the particle count installed filter system leakage test) should be undertaken to get a full and complete understanding of these testing expectations.

Repairs to the filter and grid structure should be agreed upon by the cleanroom customer and the testing provider. After repairs are completed, a suitable curing time should be allowed, followed by retesting of the affected filter location. Material selection for repair should take into account off-gassing and molecular deposition on products and processes. The cleanroom owner may have a “no patch” policy or procedures based on governing organizations or industry guidelines. Specific filter media patch recommendations

maybe found in IEST-RP-CC034 (IEST 2016a), IEST-RP-CC001 (IEST 2016b), and ISO 29463-4 (ISO 2011a).

15.7.2.4 Airflow Direction and Visualization

The airflow direction and visualization test helps to confirm that unidirectional flow from the source to the product/process location provides effective sweeping action away from the critical area without reentrainment. Four methods are available to accomplish this test, as discussed in the subsections that follow. Not all methods may be acceptable for a particular application, as certain industries or regulatory bodies may have preferences as to the method of how airflow direction and visualization should be demonstrated.

15.7.2.4.1 Tracer Thread Method

The tracer thread test uses single fibers, silk threads, or film tape strips that are affixed within the critical airstream and move with the airflow currents. They provide a visual representation of the airflow direction, any turbulence, and undesirable airflow patterns as demonstrated by the movement of the thread material.

15.7.2.4.2 Tracer Injection Method

The tracer injection method uses a visible smoke source such as chemically generated glycol/alcohol, deionized water, etc. The aerosol contamination of surfaces and neutral-buoyancy characteristics (particle size) should be key concerns in selecting the aerosol for the specific cleanroom application. The aerosol is introduced at the entrance plane of the unidirectional air source and is monitored for sweeping actions to the critical surfaces and eventually to the room returns. The test may verify the airflow parallelism or angle of offset from the airflow entrance plane before it reaches the critical surface.

15.7.2.4.3 Airflow Visualization Method by Image Processing Techniques

This method uses the tracer injection method with additional video or film processing and computer software to enhance the airflow direction presentation. Additional lighting may be needed to make the airflow smoke pattern more visible to the video recording device. Video or film processing should capture the airflow patterns from the airflow critical zone entrance plan, across critical surfaces or equipment, and through the critical zone exit plane or to the room wall or floor returns. The operational cleanroom phase airflow visualization study should include a standard compliment of assigned personnel performing all normal processes within the zone as well as any personnel interventions to clear faults. Note that regulatory inspection agencies may request to view the “raw” video evidence versus a “cleaned-up” computer-generated or edited final product.

15.7.2.4.4 Airflow Visualization Method by the Measurement of Velocity Distributions

This method uses close-interval airflow velocity measurement from ultrasonic or thermal anemometers to develop a three-dimensional picture of the airflow pattern using computational fluid dynamics (CFD).

15.7.2.5 Air Temperature, Humidity, and Uniformity

Th air temperature, humidity, and uniformity test is designed to test the capabilities of the air-handling system to control and maintain the room air temperature and humidity within specified ranges. ISO 14644-3 (ISO 2005) references IEST-RP-CC006 (IEST 2004) for this test. The test is broken into two methods: general and comprehensive.

15.7.2.5.1 General Air Temperature, Humidity, and Uniformity

The general test method uses any number of temperature-measuring devices, such as thermometers, resistance temperature devices (RTDs), thermocouples, thermistors, or other calibrated temperature sensors capable of indicating air temperature changes as small as 0.2°F (0.1°C). Air humidity can be measured by a sling psychrometer, capacitive humidity monitor, or dew-point sensors. The tests take a snapshot of the spatial uniformity of the cleanroom temperature and humidity environmental controls. Both air temperature and humidity are measured at work-level height after the sensors have stabilized.

15.7.2.5.2 Comprehensive Air Temperature, Humidity, and Uniformity

The comprehensive method monitors the temperature and humidity over time to observe the cyclic or temporal changes from the air-handling system. The test equipment used may be of the same types and have the same locations as with the general test or may use more sophisticated chart recorders, data loggers, or other automated sampling sensors to improve the ease in data collection. Temperature and humidity readings should be sampled at least every few minutes over a period of several hours. It may be preferred to continue the comprehensive test across operational shift changes or process cycles, as well as seasonal cycles. Local outdoor weather conditions should be tracked, as they may impact how the air-handling system controls the treatment of outdoor air.

Statistics may be useful in determining the uniformity across either spatial or temporal readings. The criticality of the area under test should be considered when determining which technique to use.

15.7.2.6 Electrostatic and Ion Generator

The electrostatic test evaluates the level of electrostatic charge voltage on critical work and product surfaces and the dissipation rate of floor, workbench top, or other installation component electrostatic voltage. The ion generator portion tracks the discharge time of initially charged monitors to determine how well static charges are neutralized or eliminated.

15.7.2.6.1 Surface Voltage Level Measurement

An electrostatic voltmeter or fieldmeter is zeroed to a grounded metal plate and then compared to critical object surfaces whose charge is to be measured.

15.7.2.6.2 Static-Dissipation Property Measurement

Using high-resistance meter electrodes, measurements are taken to establish the surface resistance and leakage resistance.

15.7.2.6.3 Ion Generator Discharge Time Test

Monitoring plates are charged to a known positive or negative voltage from a power source. The plate charge voltage is monitored by an electrostatic voltmeter and timed while exposed to airflow ionized by the bipolar ion generator undergoing evaluation. The timed discharge voltage monitoring should continue until the voltage achieves a specific level of the original voltage. Both positive- and negative-charged plate discharge times should be measured.

15.7.2.6.4 Ion Generator Offset Voltage Test

A charged plate monitor mounted on an isolator measures the offset voltage with an electrostatic voltmeter. The zero-potential plate is then exposed to the ionized air and the voltage is monitored until stability is achievable. The electrostatic charge sensitivity of

objects within the work area should be considered when determining the acceptable offset voltage.

15.7.2.7 Particle Surface Deposition

This test defines procedures for the counting and sizing of particles that fall from the airstream onto work surfaces or products. Witness plates are used to collect the deposited particles on the same plane as the critical surfaces. Counting and sizing of the particles is accomplished by electron microscope, optical microscope, or surface scanning equipment. The following is a partial listing of available witness plate examples:

- Microporous membrane filters
- Semiconductor wafer blanks
- Microscope slides
- Glass or metal mirror plates
- Petri dishes

Determine the background particle level for each clean witness plate. A fixed percentage of the witness plates will act as controls that will be handled in the same manner as the other plates but without exposure to the environment.

Witness plates are exposed to the cleanroom air for extended time periods, depending on the cleanliness classification, mode of operation, and particle-counting apparatus. The exposure time must be long enough to obtain statistically valid data.

Count and size the particles on all witness plates, including the controls. Determine the surface concentration of deposited particles for each witness plate.

The particle deposition rate data are reported in terms of number or mass of particles per unit surface area per unit of time.

15.7.2.8 Recovery

The recovery test as described in ISO 14644-3 (ISO 2005) determines whether the cleanroom can return to a specified cleanliness level within a specified time period after exposure to an airborne particulate challenge. This test is extremely valuable in verifying the cleanup capabilities of a cleanroom with differing operational and at-rest particulate cleanliness requirements. This test is recommended for either as-built or at-rest nonunidirectional installations only. It is not recommended that the DPC test be used for areas that have class limits of ISO Class 8 or 9. The coincidence limit for the DPC should not be exceeded, as this may affect the overall accuracy of the particle count results. An airflow diluter may be used to reduce the aerosol concentration to the DPC to quantify the actual concentration. Sampling at multiple locations and room returns within the cleanroom may identify inadequate or stagnant airflow zones requiring better mixing, redistribution of air, or a need for greater quantities of HEPA-filtered air.

The test requires a DPC, an aerosol source to generate submicron-sized particles, and a method of mixing or distributing the particles evenly throughout the room, as well as an optional dilution system to keep particulate levels below the coincidence limit for the DPC.

It is recommended to sample in the center of the room and at the wall returns, in addition to specific areas where work may be performed.

Sample multiple particle counts at each location to determine baseline data. This is used to determine the minimum two-log particulate increase. The two-log increase value should be established so that when the particulate levels have recovered by two logs it is still well above established baseline values.

Introduce the challenge aerosol and mix it throughout the room.

Begin particle count measurements. Continue sampling for a minimum time agreed between the cleanroom customer and the testing provider, or less if all sample locations in the area being tested have recovered completely to the original particulate concentration.

Recovery time data interpretation may be used in either of two methods:

- 100:1 recovery time
- Recovery rate

The recovery time or recovery rate is a matter of agreement between the cleanroom customer and the testing provider. A typical guidance value recovery time of 15–20 min from operational particulate levels to at-rest particulate levels is referenced in Annex 1, Manufacture of Sterile Medicinal Products, in *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use*, Volume 4 of *EudraLex—The Rules Governing Medicinal Products in the European Union* (EC 2010).

15.7.2.9 Containment Leak

The containment leak test verifies if there is an intrusion of contaminated air into the cleanroom from outside uncontrolled environments. It also checks common-plenum, positive-pressure ceiling systems for leaks. This test has two methods: the DPC method and the aerosol photometer method.

15.7.2.9.1 Discrete Particle Counter (DPC) Method

Outside a cleanroom, generate aerosol that is significantly greater than the room particle count levels. For the testing of construction seams or service conduits, scan inside the cleanroom in close proximity of surfaces.

Any reading detected greater than a set log value below the outside aerosol concentration is indicative of a leak requiring attention/repair.

Note: Airflow visualization methods are recommended for testing intrusions at open doorways.

15.7.2.9.2 Aerosol Photometer Method

Produce an aerosol using generators from the installed filter system leakage test to achieve a set concentration. Construction seams, service conduits, and doorway openings are scanned inside the cleanroom. Any value in excess of a set log value below the set percentage indicates a leak requiring attention/repair.

15.7.3 ADDITIONAL TESTS NOT LISTED IN ISO 14644-3

Additional tests are available and are often requested by customers as part of the cleanroom certification process. With each additional test discussed in the following subsections, source references are provided for additional guidance.

15.7.3.1 Viable Monitoring

Daily monitoring of airborne particle counts, including air and surface viable monitoring, is a regular occurrence of environmental tests performed in some cleanrooms, particularly in pharmaceutical manufacturing operations. Viable monitoring is critical in applications where the presence of viable materials could prove hazardous or deadly if allowed to enter or contaminate a sterile product. Viable monitoring for cleanroom facilities is made up of two main groups: airborne and surface microbial count sampling.

15.7.3.1.1 Airborne Microbial Counts

Most airborne viable sampling devices use one of two processes to collect viable materials within the airstream: impactors and impingers. Please note there are other

mechanisms such as collection on filter and sedimentation, but these are not discussed here because they are used under much larger size applications.

Impactors blow or draw air at high velocity towards media material. Due to its mass, a particle leaves the airstream and impacts the media, where it is held for incubation, growth, and detection. Impactors are the most common of airborne microbial sampling devices. Impingers work along the same principle, except they use liquids as their collection and holding medium.

Many of the current airborne microbial sampling systems are designed to sample a known volume of air. This way the number of colony-forming units (CFUs) may be quantified into a known volume of air. The volume of air may be dependent on the airborne particulate cleanliness classification or regulatory guidance.

15.7.3.1.2 Surface Microbial Counts

Surface microbial sampling uses two types of collection devices: contact plates and swabs. The selection of collection device is based on the type of surface to be sampled. Contact plates are typically used on smooth, flat surfaces where the tester can roll the plate over the test area, giving maximum contact of growth media to the surface. Swabs are ideal for testing irregular surfaces where a contact plate is impractical.

One key component of successful viable monitoring is the proper use, handling, storage, and transportation of the viable samples. Aseptic technique is critical to prevent contamination of the sample, sampling equipment, sampler's gloves, and sterile surfaces before, during, and after the test.

Once all sampling is complete and samples are collected, microbiological incubation, testing, and analysis will determine the quantity of CFUs. In addition to quantifying, the microbiology laboratory may be asked to enumerate and characterize the type of viable contamination into a number of categories.

How-to reference documents for viable monitoring include the following:

- ISO 14698-1, *Cleanrooms and Associated Controlled Environments—Biocontamination Control, Part 1: General Principles and Methods*
- USP <797>, *Pharmaceutical Compounding—Sterile Preparations*
- USP <1116>, *Microbiological Evaluation of Clean Rooms and other Controlled Environments*
- IEST-RP-CC023, *Microorganisms in Cleanrooms*

15.7.3.2 Lighting Level and Uniformity

Although a test method for lighting level and uniformity is not published in ISO 14644-3 (ISO 2005), other reference documents are available for lighting level testing guidance. Advanced lighting level testing may be found in *The Lighting Handbook* by Illuminating Engineering Society of North America (IES) (IES 2011), commonly referred to in the cleanroom industry as "the Lighting Bible." A more generalized test may be used from IEST-RP-CC006 in applications where lighting does not have a critical impact to the cleanroom operation processes or products.

All new fluorescent lighting systems should be operational to allow for temperature stabilization. A test grid of equal dimensions should be established. Lighting level readings are to be taken in the center of each grid. One reading per room (or zone) is required, at a minimum.

Lighting level measurements should be taken at work surface elevation. When a work surface height is not available, default to a height agreed upon between the cleanroom customer and the testing provider. Report the lighting levels in the units of measure preferred by the customer (e.g., footcandles or lux).

15.7.3.3 Noise Levels

The noise levels test measures sound pressure levels produced by cleanroom components within the room and in adjacent occupied spaces. Two testing options are available from IEST-RP-CC006: a general test and an octave band test. Both tests are performed at the same location, but differing instrumentation and documentation are used.

The testing location may be a grid of equal areas. (An easy rule of thumb is to use the same grid and sampling location as in the lighting level and uniformity test.)

The sound level meter should be supported at the height of the average human ear.

15.7.3.3.1 General Test

At the center of each grid location, measure and record the sound level pressure in decibels A-weighted scale (dBA). Report the location and value of the maximum dBA scale reading.

15.7.3.3.2 Octave Band Test

At the center of each grid location, measure and record the sound pressure level for each octave band. From each of the octave bands, find the maximum value per location.

15.7.3.4 Vibration

Many applications or products within a cleanroom may be sensitive to vibration. Testing for vibration has become a specialty in the cleanroom industry that goes well beyond simple pressure transducer mounting onto work surfaces. Detailed procedures for vibration analysis may be found in IEST-RP-CC024.1, *Measuring and Reporting Vibration in Microelectronics Facilities* (IES 2002a).

15.7.3.5 Filter Differential Pressure

While the filter differential pressure test is not mentioned in most industry standards and recommended practices, it has become a valuable tool for both the cleanroom customer and the testing provider. The filter differential pressure used in conjunction with the filter airflow rate may be useful in determining filter loading to predict or trend future filter replacement or to diagnose airflow problems. It is crucial to keep the complete history of the filter airflow rate and pressure from initial installation to the present.

Filter differential pressure is simply the static pressure measured across the filter at a given airflow. Pressure monitoring may be accomplished by a device as simple as a single mechanical differential pressure gauge or a calibrated micromanometer or complex and validated computer systems that monitor entire facility filtration systems.

15.7.3.6 Compressed Air Line Sampling

Many facilities use compressed air or gases for their processes and equipment. These gases may be required to be of the same purity (e.g., free from oil) and microbiological and particle quality as the cleanroom air cleanliness classification. Although this testing may be considered specialized, it is a common area of cleanroom facilities requiring recurring testing. The following are areas of interest in relation to compressed air:

- Nonviable particulates
- Viable particulates
- Water content
- Hydrocarbons or oil

Breathable-air compressed systems may have more robust testing and criteria that may affect the lives and health of system users. They may include the percentages of oxygen, carbon dioxide, carbon monoxide, and detectable odors.

Compressed air testing procedures are explained in greater detail in ISO 8573, *Compressed Air* (ISO 1999, 2001b, 2001c. 2003b, 2003c, 2004b, 2004c, 2007b, 2010), as well as numerous industry-specific documents from regulatory agencies or professional organizations such as the Parenteral Drug Association (PDA).

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16

Cleanroom Commissioning

Commissioning (Cx) is a formal process to verify that a facility's design, purchased equipment, construction, start-up, and operation meet the design intent and the owner's operational requirements. Because cleanrooms have many more operational requirements than a typical office or manufacturing space, cleanroom Cx processes are substantially more extensive and complex. To provide the best project outcome for the owner, it is critical that a qualified cleanroom commissioning authority (CxA) is identified and retained from the beginning of the project design phase. The cleanroom Cx process consists of the following phases: design phase, installation verification, operational verification, and post occupancy.

16.1 DESIGN-PHASE COMMISSIONING

During the design phase, the CxA must understand the owner's established vision for the facility or master plan and the Owner's Project Requirements (OPR). The OPR provides high-level, general project requirements for the purposes of the facility and technical requirements for the different spaces and processes. The master plan and OPR should include the following:

- Specific project goals (e.g., dedicated manufacturing facility that produces a certain number of products per day)
- Design goals (e.g., design manufacturing facility that meets industry standard of care, regulatory requirements, flexibility, energy efficiency, and owner's needs)
- Measurable performance (e.g., percentage of product defects, space particulate levels)
- Budget
- Schedule

Other considerations include product flow, flow of personnel, waste flow, airflow, room pressurization plan, etc., as developed in the master plan and OPR.

To fulfill the project requirements, the engineer of record issues the basis of design (BOD) to define the system details that will fulfill the OPR. The CxA's design-phase role begins with a review of the BOD for overall effectiveness, robustness, and risk. The BOD should include applicable weather data, codes, standards, regulations, guidelines, space performance requirements (e.g., air temperature and humidity), and system performance requirements (e.g., system process flow diagram, system process instrumentation diagram, equipment schedules, and system sizing). The BOD should also include space pres-

surization diagrams; space cleanliness classification diagrams; personnel and material flow diagrams; and air handler zoning airflow diagrams showing supply, return, exhaust, and infiltration/exfiltration airflows for each room. The CxA should review the BOD to verify that

- the established room pressurization layouts and control strategies are coordinated to prevent air flowing from less-clean spaces to spaces with higher cleanliness classifications;
- material and personnel flow will not bring contamination into a cleanroom or cause cross-contamination between cleanrooms;
- cleanroom air change rates meet accepted industry standards efficiently;
- cleanroom supply, return, exhaust, and infiltration/exfiltration airflows are balanced; and
- air-handling unit (AHU) and exhaust system design and zoning meet all cleanroom space environmental requirements and do not create potential cross-contamination between cleanrooms or other spaces.

Using the BOD as a basis, the CxA should develop a Cx plan and develop a Cx budget. In developing the Cx plan, the CxA coordinates with all other project team members to prevent complications and duplication of efforts for seamless integration with validation activities. Most cleanroom project Cx plans require several design progress review submissions, and the CxA needs adequate time to review each design progress submission. It is important to understand that the Cx plan is a living document and must be updated to incorporate approved changes to meet the project's scope of work and design.

A Cx design review determines whether the OPR and BOD requirements are being met and whether the facility design is constructible, maintainable, and commissionable. In addition, the CxA needs to verify space pressurization and airflow stability during each mode of operation (e.g., on/off and variable exhaust airflows, variable airflow controlled by space particle counter, occupied/unoccupied, process operation, shutdown). For pharmaceutical and other cleanrooms that require cleaning and/or sterilization, the CxA must verify the HVAC systems design philosophy will properly allow for the introduction of cleaning agents/sterilants and the removal/evacuation of the cleaning agents/sterilants. The CxA needs to verify the cleanroom control system design includes adequate environmental monitoring and alarming and provides sufficient stability, preventing operation outside of the ranges documented during validation.

The Cx plan scope of work should include reviewing submittals to verify the specific material and/or equipment approved by the architect/engineer of record and the request for information documentation to understand all design/construction changes that were made since the construction documentation was issued.

16.2 INSTALLATION VERIFICATION COMMISSIONING

During installation verification, the CxA must verify that the purchased equipment and materials match the submittals approved by the engineer of record. Equipment verification should include verification of nameplate numbers, physical dimensions, components, electrical service, and control components. All equipment and component factory calibration, balancing, and testing certifications must be included in the equipment verification scope of work. The equipment verification must occur before equipment installation. Where factory acceptance testing is required, the equipment verification must occur before factory acceptance testing is performed. Factory acceptance testing is performed

for critical/specialized equipment that would be difficult to repair or test outside the manufacturing facility and to verify the critical/specialized equipment meets intended operational requirements. The engineer of record needs to develop the equipment factory acceptance testing protocol, while the CxA needs to review the protocol and witness the factory acceptance testing.

It is very important that cleanroom construction is performed with a clean construction protocol to prevent building contamination into the cleanroom facility. Once contamination is built into a cleanroom, it is inaccessible and can only be removed by demolishing the cleanroom. The Cx plan scope of work must include reviewing the clean construction protocol and its adherence verification. The clean construction protocol adherence verification scope of work should include verification of construction worker clean construction protocol training; verification of proper cleanroom construction area isolation, cleaning, and pressurization; verification of equipment and material proper cleaning and installation; and verification that construction work performed in the cleanroom was performed during the proper clean construction protocol phase.

The installation verification scope of work should include architectural envelope (floor, walls, ceiling, doors, windows, pass-through), electrical systems (lighting, power, IT data), process equipment, and mechanical systems (HVAC, exhaust, gases, cooling systems, heating systems, fire protection). Simply, any system inside, penetrating, or servicing a cleanroom envelope must be commissioned. The installation verification should verify that furnished materials meet approved submittals; are installed per drawings, manufacturer's installation instructions, and clean construction protocol; and have properly sealed openings/interfaces (closed cell gaskets, caulking, etc.).

During initial installation verification, initial airflow balancing for the HVAC and exhaust systems must be verified. The airflow verification must include supply and return airflow adjustment to achieve required space pressurization ranges.

The installation verification must verify and document that all equipment was installed per the manufacturer's and engineer of record's installation and pre-start-up activity requirements. Equipment installation verification could include levelness, orientation, maintenance of shipping seals, removal of shipping blocks, bolting/anchoring, loose-shipped component installation, labeling, and connection of utilities (electrical, gases, HVAC, exhaust, cooling water, drains, etc.). Equipment pre-start-up verification could include instrumentation field calibration, valve and damper range of operation verification, component alignment, lubrication, working fluid installation, proper motor rotation, safety feature functional verifications, alarm adjustments, and utility service pressure and flow rate adjustments to meet the manufacturer's requirements.

Depending on the different modes of operation, sequence of operation, and variability of process operation, the HVAC and exhaust systems will require air balancing during each mode of operation, sequence of operation, and process operating point. This testing is to be performed during operational verification.

The assembly of the operation and maintenance (O&M) manuals should be completed during installation verification so the manuals are available to the maintenance staff during the operational testing.

16.3 OPERATIONAL VERIFICATION COMMISSIONING

Operational verification Cx is performed in three different phases: as built, at-rest, and operational. The purposes for three different operational phases are to make it easier

to diagnose a specific operational deficiency and to reduce the extent of modifications needed to address a specific deficiency. The testing performed for each operational verification phase is as follows:

- **As Built.** As-built testing is performed when the cleanroom enclosure and electrical and mechanical systems are completed while there is no process equipment or workbench installed in the cleanroom. The as-built operational verification must be performed during every mode of operation and sequence of operation. As-built operational verification includes HVAC and exhaust system operation to verify space pressurization stability, supply/return/exhaust airflows, space temperature and humidity, space particulate levels, space particulate recovery time, and airflow parallelism; high-efficiency particulate air (HEPA) filter testing to include leak testing, airflow, and filter face velocity profile; space lighting levels and operation; cleanroom enclosure leak testing; space noise levels; and space vibration. It might be necessary to install blind flanges or plates in walls or ceilings where process equipment penetrates the cleanroom enclosure. Any deficiencies discovered during as-built operational testing need to be corrected before installing process equipment and workbenches.
- **At Rest.** At-rest testing is performed when all the process equipment and workbenches are installed in the cleanroom and operational but the cleanrooms are not occupied by operators. The at-rest verification must be performed during every mode of operation, sequence of operation, and process operational range. At-rest verification includes HVAC and exhaust system operation to verify space pressurization stability, supply/return/exhaust airflows, space temperature and humidity, space particulate levels, space particulate recovery time, and airflow parallelism; process equipment operation; space lighting levels and operation; cleanroom enclosure leak testing; space noise levels; and space vibration. Any deficiencies discovered during at-rest testing need to be corrected before operational testing.
- **Operational.** Operational testing is performed when all the process equipment and workbenches are installed and operational and operators, if any, are simulating actual work practice. It needs to be verified with the owner who will provide the product materials that will be used during operational testing. Operational verification must be performed during every mode of operation, sequence of operation, and process operational range. It is important that the sequence of operation failure cascade be tested. Operational verification includes HVAC and exhaust system operation to verify space temperature and humidity, space particulate levels, space particulate recovery time, pressurization, and airflow parallelism; process equipment operation; space noise levels; and space vibration.

16.4 POSTOCCUPANCY COMMISSIONING

The postoccupancy Cx scope of work includes alternate season testing (testing in a season of the year opposite that in which the cleanroom was commissioned), development of a recommissioning plan, and cleanroom recertification. Depending on the specific industry standard, cleanrooms may require recertification every 6 to 12 months. The recertification can range from basic to extensive. Basic recertification includes HEPA filter leak testing, supply/return/exhaust airflow balancing, space air temperature and humidity, space air pressurization, and particulate concentration. Typically, the cleanroom envelope becomes less structurally sealed as time passes and it is necessary to adjust air-

flows to maintain space pressurizations. Cleanroom recertification should include all the operational verification requirements of the original construction.

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17

Qualification of Clean Spaces

This chapter describes why clean spaces need to be qualified and briefly outlines some of the different principles involved. It is not the intention of this chapter to describe in detail the process of qualification; resources for further reading are supplied in the References and Bibliography sections of this chapter.

17.1 QUALIFICATION TERMINOLOGY

Note: If a source is indicated after a definition, that definition has been reproduced nearly verbatim from the source, except that some minor editorial changes may have been made.

acceptance criteria: Measures used to determine if a test has passed, for example, a predetermined temperature range or particle count.

change control: A formal system by which qualified representatives of appropriate disciplines review proposed or actual changes that might affect the validated status of facilities, systems, equipment or processes. The intent is to determine the need for action to ensure and document that the system is maintained in a validated state (EC 2015).

commissioning (Cx): A formal process to verify that a facility's design, purchased equipment, construction, start-up, and operation meet the design intent and the owner's operational requirements.

corrective action: An action to eliminate a nonconformity.

critical aspects: Critical aspects of manufacturing systems are typically functions, features, abilities, and performance or characteristics of a product that are critical for consistent quality.

critical control point (CCP): A function or an area in a manufacturing process or procedure, the failure of which, or loss of control over, may have an adverse affect on the quality of the finished product and may result in an unacceptable health risk (FDA 2016).

critical process parameter (CPP): An attribute of a product that may have an inverse impact on the product's quality.

direct impact system: A system or component of the system that will have a direct impact on a product's quality.

design qualification (DQ): A formal, documented test on the design of a system, facility, or piece of equipment to verify its suitability to manufacture products of a consistent quality.

design review: A formal meeting of project stakeholders, whereby the suitability of the design of a system, facility, or piece of equipment is reviewed or approved.

deviation: Variation to an intended result or instruction.

engineering change management (ECM): Prior to system or facility acceptance, changes managed by and approved through subject matter experts (SMEs). Changes affecting critical aspects should be communicated to the quality unit (ASTM 2013).

factory acceptance test (FAT): Formal testing of a system or piece of equipment at a vendor's manufacturing facility prior to delivery to site; may be supplemented by a formal site acceptance test once installed.

good engineering practice (GEP): Proven and accepted engineering methods, procedures, and practices that provide appropriate, cost-effective, and well-documented solutions to meet user requirements and compliance with applicable regulations (ISPE 2008a).

Good Manufacturing Practice (GMP): Good Manufacturing Practice is a manufacturing and testing process that controls medicinal product quality. It may also be referred to as *CGMP*, where the C stands for *current*, ensuring the latest standards are used. GMPs are a legal requirement in many countries.

impact assessment: A formal assessment conducted to determine the impact of a system or component within a system on a product's quality.

incident: Unplanned event to a normal, planned operation.

indirect impact system: A system or component of the system that is not expected to have a direct impact on a product's quality but may influence it indirectly.

installation qualification (IQ): A formal, documented test that a system, facility, or piece of equipment has been installed or modified in accordance with an approved design.

medicinal product: Any substance or combination of substances that may be used in, or administered to, human beings, either with a view to restoring, correcting, or modifying physiological functions by exerting a pharmacological, immunological, or metabolic action or to making a medical diagnosis (MHRA 2016).

no impact system: A system or component of the system that will not influence a product's quality, either directly or indirectly.

operational qualification (OQ): A formal, documented test that a system, facility, or piece of equipment operates in accordance with predetermined results.

performance qualification (PQ): Documented verification that the actual facility, utilities, equipment (each now qualified), and trained personnel with the commercial manufacturing process, control procedures, and components produce consistently acceptable commercial batches. A successful PQ will confirm the validity of the process design and demonstrate that the commercial manufacturing process performs as expected (ICH 2000).

qualification: Action of proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results (ICH 2000).

quality: The suitability of either a drug substance or a drug product for its intended use. This term includes such attributes as the identity, strength, and purity (ICH 1999).

quality control unit: The group who is responsible for and has the authority to approve or reject materials used, packaging, labeling, records, procedures, and specifications relating to the manufacture of drug products (GPO 2017).

risk: Combination of the probability of occurrence of product and/or process harm and the severity of that harm (ICH 2005).

risk analysis: A systematic process of organizing information to support a risk decision to be made within a risk management process. It consists of the identification of hazards and the analysis and evaluation of risks associated with exposure to those hazards (ICH 2005).

risk management: Systematic application of quality management policies, procedures, and practices to the tasks of assessing, controlling, communicating, and reviewing risk (ICH 2005).

site acceptance test (SAT): Formal testing of a system or piece of equipment once installed in the planned location.

subject matter expert (SME): Individuals with specific expertise in a particular area or field. SME responsibilities include technical design review, planning, and defining verification strategies defining acceptance criteria, selection of appropriate test methods, execution of verification tests, and reviewing/approving technical testing results (ASTM 2013).

validation: The action of proving and documenting that any process, procedure, or method actually and consistently leads to the expected results (WHO 2006).

Validation Master Plan (VMP): A high-level document that establishes an umbrella validation plan for the entire project and is used as guidance to the project team for resource and technical planning (FDA 2011).

verification: A systematic approach to verify that manufacturing systems, acting singly or in combination, are fit for intended use, have been properly installed, and are operating correctly. This is an umbrella term that encompasses all types of approaches to ensuring systems are fit for use such as qualification, commissioning, and other related activities (ASTM 2013).

17.2 INTRODUCTION

Clean spaces are used extensively in the pharmaceutical, biotechnology, and medical devices industries for the manufacture of medicinal products for human and animal use. Unlike other manufacturing industries, finished product testing is not sufficient to guarantee the product reaching the consumer is safe to use and that it can deliver what it is designed to deliver. Instead, these products are subjected to regulations throughout the entire product life cycle. These regulations are globally known as *Good Manufacturing Practice* (*GMP*) or, to ensure they are up to date, *Current Good Manufacturing Practice* (*CGMP*). These regulations vary from country to country and are designed to ensure products are manufactured consistently to quality standards. The CGMP regulations are produced, regulated, and enforced by governmental agencies such as the U.S. Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) in Europe. Products that fail to conform to CGMP regulations at any stage can be discontinued or recalled, and heavy fines or criminal proceedings can be placed on the manufacturer of such products.

The CGMP regulations define the cleanliness classification that is required at each stage of the process (as well as other regulatory requirements). To ensure medicinal products consistently deliver the correct quality, purity, and efficacy, a system of qualification is required for any part of the process that may impact product quality. *Qualification* is defined as the action of "proving and documenting that equipment or ancillary systems are properly installed, work correctly, and actually lead to the expected results" (ICH 2000, p. 41).

A clean space is one of the key systems used in the manufacture of high-purity or sterile medicinal products and is required by law to meet certain obligations such as a specified cleanliness level, temperature and humidity levels, microbial surface limits, and recovery periods. Thus, to ensure a clean space is suitable to meet the classification requirements set in the CGMP regulations, it needs to be qualified. It is worth noting that CGMP clean space requirements may differ from the ISO 14644 standards (ISO 2016) and can differ from country to country. It is the country that the product is being sold into that determines the regulation and not where it is manufactured; so, for example, a drug product manufactured in Europe but being sold in the United States will be regulated by the FDA and not the European regulator.

17.3 WHY DO WE NEED TO QUALIFY?

To conform to CGMP regulations, medicinal products must show that they are completely safe for the patient. This, however, was not always the case. As with many other industries, the pharmaceutical industry has had its fair share of controversy. For example, in 1937, the Elixir of Sulfanilamide disaster caused the death of more than 100 people, mostly children (Ballentine 1981). In response, the U.S. government passed a revised Federal Food, Drug and Cosmetic (FD&C) Act into law in 1938 requiring all drug products to be tested before sale. Then in 1962, further tragedy struck in Europe, this time by a drug called thalidomide causing the deformed births of approximately 10,000 babies (Kim and Scialli 2011). Again, regulators in the United States reacted, passing an amendment to the FD&C Act called the Kefauver-Harris Amendment (U.S. Congress 1962). This was followed the year after by the first issue of the GMP regulations requiring proof of safety and effectiveness prior to approval for sale. The new GMP regulations allowed the FDA to withhold the license for sale from a manufacturer if "facilities and controls used for the manufacture, processing and packing of such drug are inadequate to preserve its identity, strength, quality and purity" (FDA 2015). The FDA pursued a two-year inspection mandate, performing audits and quality checks on various companies. These quality checks were mainly done by finished product sampling only, and this mode of sampling does not necessarily represent the complete batch.

Two ground-breaking papers were published, "Design for Quality" by Ted Byers in 1974 and "Validation and Stability" by Bernard Loftus in 1978, assessing the legal basis to validate the whole process. A complete revision to regulations 21 CFR 211 and 210 for drugs and 21 CFR 820 for medical devices was issued in 1978, requiring for the first time drug manufacturing systems to be validated systems and documented accordingly:

> a drug is deemed to be adulterated unless the methods used in its manufacture, processing, packing and holding, and the facilities and controls used there for, conform to current good manufacturing practice so that the drug meets the safety requirements of the act and has the identity and strength and meets the quality and purity characteristics that it is represented to have. (FDA 1978)

To assist compliance within the industry, the FDA issued various guideline documents, including *Guide to Inspection of Computerized Systems in Drug Processing* in 1983 and *Guideline on General Principles of Process Validation* in 1987.

In August 2002, following pressure from manufacturers and suppliers to get their products to patients faster and maximize commercial sales during patent lifespan, the FDA reviewed the GMP regulations "to integrate quality systems and risk management approaches into its existing programs with the goal of encouraging industry to adopt modern and innovative manufacturing technologies" (FDA 2006). This new approach set out to modernize the prerequisites expected by regulators to guarantee product quality (FDA 2004). With the advent of globalization, the risk-based scientific approach has been adopted by other global regulatory bodies such as World Health Organization (WHO), EMA in Europe, and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), which includes harmonized regulatory bodies of the United States, Europe, and Japan.

In 2011, the FDA revised *Guideline on General Principles of Process Validation* (FDA 2011) to align process validation with product life-cycle concepts and existing guidance, including ICH guidelines Guide Q8, *Pharmaceutical Development*; Guide Q9, *Quality Risk Management*; and Guide Q10, *Pharmaceutical Quality System*.

The GMP regulations exist to ensure the medicinal products we consume meet expected outcomes. Qualification of the systems used in their development, manufacture, storage, and transportation is one of the ways in which patients can be assured that the drugs they are consuming will make them better and not the opposite.

The following sections highlight the various stages of a qualification process and briefly describe the requirements of each.

17.4 DOCUMENTATION REQUIREMENTS

Documentation is a key component of any qualified system and should be prepared, maintained, and modified using a predefined system to ensure full traceability throughout the life cycle of the manufacturing process. Any document that impacts the quality of the product must be controlled. Documentation requirements are defined under the umbrella of good engineering practice (GEP), which is defined as "proven and accepted engineering methods, procedures, and practices that provide appropriate, cost-effective, and well-documented solutions to meet user-requirements and compliance with applicable regulations" (ISPE 2008a). GEP, although not mandatory, is accepted as preferred by both industry and regulators. Actual documentation requirements differ from manufacturer to manufacturer but typically include the following:

- All documents should follow version control.
- All stakeholders, including any external suppliers and contractors, should conform to the documentation procedures and may require training.
- Written records must be completed using indelible ink in a specific color.
- All records should be fully recorded and need to be legible and accurate.
- Written records that require corrections should undergo a specific set of rules, for example, the use of correction fluid not being allowed and instead crossing out the incorrect entry with a single line and placing the correct entry above it, complete with the signature of the person responsible and a date.
- Date entries should follow a specific format, such as day, month, and year, with the date denoted by the first three letters of the month (for example, 27-Jun-2016).

- Documents should be fit for purpose and should be signed, checked, and approved by the relevant subject matter expert (SME) and quality control unit representative.
- All deviations from expected results must be recorded, investigated, and resolved. Where the expected results cannot be resolved, an alternative approved solution should be applied.

Any document identified as having an impact on product quality must be approved by the quality control unit and maintained through a system of approved change control throughout its life cycle. All other documents should adhere to engineering change management.

17.5 QUALIFICATION PROCESS FOR CLEAN SPACES

There are four key stages in a qualified system (ASTM 2013):

- Requirements definition
- Specification and design
- Commissioning and qualification (C&Q)
- Acceptance and release

The key quality aspects required for the product are defined during pilot studies and/or clinical trials, where the manufacturer should gain a very high level of assurance that the production processes used consistently deliver the expected strength, quality, purity, and potency of the product, allowing for the product's commercial manufacture and distribution (FDA 2011). Knowledge of the product and the processes required for its manufacture to maintain product quality will lead to the understanding of the potential risks to the quality of the commercialized product. To ensure the product is manufactured consistently to the same quality, manufacturers should (FDA 2011):

- understand the sources of variation,
- detect the presence and degree of variation,
- understand the impact of variation on the process and ultimately on product attributes, and
- control the variation in a manner commensurate with the risk it represents to the process and product.

Regulators promote a team-based approach made up of the key stakeholders, including the SMEs for each part of the process, project management personnel, and system end users, but the product quality is the regulatory responsibility of the quality control unit.

17.6 REQUIREMENTS DEFINITION

Early in a GMP project, a number of essential documents should be created to ensure all requirements are clearly defined. Like all other projects, the better the definition early in the project, the lower the risk of change later. Some of the key documents include the user requirements, systems list and boundaries, risk assessments, and the Validation Master Plan (VMP). These documents are discussed in more detail in the following subsections.

17.6.1 USER REQUIREMENTS

One of the most important documents for any GMP project is known as the *user requirements* (URs) or *user requirements specification* (URS). The URS, simply put, defines the attributes and requirements to manufacture a quality product consistently. All the key quality and regulatory requirements should be clearly defined in this document, including the product's critical process parameters (CPPs) and the environmental conditions required within the clean spaces. The URS may also contain other general requirements, for example, business requirements and health and safety requirements. For a GMP project to be approved by the quality control unit and have its product released to the marketplace, it must meet the quality and regulatory requirements defined in the URS. All quality-related aspects of the URS should be approved by the quality control unit and, once approved, should be controlled for the life cycle of the product using a change control system.

17.6.2 SYSTEMS LIST AND BOUNDARIES

A systems list is simply a list of the systems used to develop, manufacture, and store the product within a manufacturing facility. It is defined as "a limit drawn around a system to logically define what is, and is not included in the system" (ISPE 2007). Providing a detailed list of the systems allows the facility to be broken down into manageable pieces for the risk assessment, commissioning (Cx), and qualification stages. An example of a system may be the HVAC system feeding the manufacturing clean spaces, including all controls, fans, and components of that system, while the steam and chilled water conditioning the air could be defined as separate systems. For a clean space, the system boundary for the HVAC system could be defined at the high-efficiency particulate air/ultralow particulate air (HEPA/ULPA) filters at the clean space envelope, as the filters are what ensure the risk to product quality from particulate and bioburden in the airstream is removed. Thus, other components of the system outside the boundary, for example, the ductwork and air-handling unit (AHU) feeding the space prior to the HEPA/ULPA filter, may not require qualification. The same methodology can be applied to the automation system controlling the HVAC system. Many pharmaceutical facilities have installed separate environmental monitoring systems (EMSs) specific to the clean spaces as well as larger building automation systems (BASs). The smaller EMS is used to monitor the environmental parameters critical to product quality (temperature, relative humidity, and differential pressure between clean spaces) and is the system that is qualified instead of the larger BAS. As the control system is deemed a single system, qualifying the smaller EMS will save effort and avoid qualifying control loops in the BAS that will not impact the product quality.

17.6.3 RISK ASSESSMENTS

Generally there are three types of risk assessment: quality risk assessment, system impact assessment, and technical evaluation. These are discussed in the following subsections.

17.6.3.1 Quality Risk Assessment

Quality risk assessment is a relatively new approach to validating process systems and is intended to ensure the level of effort required in qualifying a system is reflected by the risk to the product's quality (i.e., there is no requirement to qualify something if there is no risk to the quality of the product). The risk-based approach is a life-cycle approach and can facilitate continuous improvements through continuous monitoring of product attributes and is the method of risk assessment preferred by regulators.

There are many proven methods for quality risk assessment, for example, Hazard Analysis Critical Control Point (HACCP) (FDA 2017) and failure modes and effect analysis (FMEA). However, as defined by Guide Q9, *Quality Risk Management* (ICH 2005), the assessment method selected must identify three key elements to any risk identified:

- What can go wrong
- What is the severity of effect if it goes wrong
- What is the likelihood of it going wrong

Where risks are identified, the best solution is to remove the risks through redesign or other means. The output of the quality risk assessment is to identify all the critical aspects relating to the product quality and meet the requirements defined in the URS. Any item deemed to be a critical aspect needs to be qualified. If the environmental aspect of a space poses a risk to product quality, it must be qualified. However, if during the pilot testing of the product (known as *product stability tests*), temperature and humidity had no impact on product quality, then they may not be deemed critical aspects and may not need to be qualified (or more relaxed tolerances can be acceptable). This reduced risk can be applied for energy-saving measures, such as reduced air change rates at night (nighttime setback). If the reduced air change rate has no risk to product quality, then it could be acceptable.

17.6.3.2 System Impact Assessment

A system impact assessment is one of the traditional methods used to determine what systems (or parts of a system) need to be qualified. This method is a simpler risk assessment method and its main outputs are whether a system has a direct impact, an indirect impact, or no impact on a product's quality. Any system that is deemed to have either a direct or an indirect impact must be qualified; a no-impact system does not require qualification and will come under GEP, and its documents do not need to follow change control. A system impact assessment relies on brainstorming about each system with the SMEs, end users, and other stakeholders to determine its impact level. Although this method was the chosen method prior to the introduction of the quality risk assessment method, it does have drawbacks when compared to the quality risk assessment method. For example, critical aspects are not defined in a system impact assessment, which means qualification of certain aspects of a system that may not need to be qualified happens and thus requires resources, time, and money.

17.6.3.3 Technical Evaluation

Another method used before the introduction of the quality risk assessment method was the technical evaluation method, which is the most unstructured and informal method. In this approach, SMEs prepare the technical evaluation based on their technical expertise; it is then approved by the quality control unit. Similar to the system impact assessment method, critical aspects are not defined and there is a strong reliance on the SMEs' process knowledge and experiences.

17.6.4 VALIDATION MASTER PLAN

The Validation Master Plan (VMP), also known as the Commissioning and Qualification Plan (C&Q Plan) or Verification Plan (ASTM 2013), sets out the what, how, and when of systems to be commissioned and qualified. It can contain the following information:

- Project scope and system boundaries
- Schedule
- Systems list
- Documentation requirements, including change control requirements

- System impact assessments or quality risk assessments
- Roles and responsibilities
- Acceptance criteria
- Test methods to be used
- Leveraging of tests from Cx to qualification (for example, allowing data collected during factory acceptance tests to be used for qualification)
- Training requirements

Like other quality documents, the VMP should be controlled once approved throughout the product's life cycle to ensure the same approaches are used for all future process changes.

17.7 SPECIFICATION AND DESIGN

To ensure a well-defined design basis, details of various systems should be defined using drawings and specifications and, where applicable, approved by the quality control unit. For clean spaces, these documents may consist of the following:

- Area classification layouts (cleanliness levels)
- Airflow schematics (which may be called airflow and instrumentation diagrams [A&IDs] or piping and instrumentation diagrams [P&IDs], depending on the nomenclature used by the manufacturer)
- Room pressure cascade layouts
- Equipment specifications and data sheets
- AHU zone layouts
- Temperature and humidity maps

To achieve a solid basis of design, with clear product risk assessments and approved quality-related documentation and URs, changes should be minimized during the detailed design phase to ensure confidence to stakeholders. All design documents having an impact on quality must be maintained through a system of approved change control. All other documents should adhere to engineering change management.

17.7.1 DESIGN REVIEW OR QUALIFICATION

A design review or qualification is a formal, documented process where all stakeholders, including the quality control unit, analyze the design deliverables against the URS to identify potential risks to product quality and propose corrective actions. Although not mandatory, the design review is beneficial, as it can identify issues before construction, reducing the need to make changes in the field. It is recommended to perform a design quality risk assessment at the end of the detailed design phase prior to going to construction, with the amount of effort applied to the review being linked to the level of risk to product quality.

For clean spaces, the design qualification should assess whether all critical aspects meet the desired requirements set out in the approved quality-related documentation and URs—for example, do the AHUs have sufficient airflow and pressure drop capacity to maintain the room classification in operation? Put simply, is the design of the system associated with the critical aspects identified in the clean space fit for purpose? Where a system design does not meet the stated requirements, a corrective action is raised and must be remedied and approved prior to the system being issued for construction.

17.8 COMMISSIONING AND QUALIFICATION

17.8.1 COMMISSIONING

Commissioning (Cx) is defined as a formal process to verify that a facility's design, purchased equipment, construction, start-up, and operation meet the design intent and the owner's operational requirements. Commissioning is discussed in greater detail in Chapter 16. For medicinal products, acceptance criteria should be determined by the critical aspects for quality-related systems and by the limitations set out in the design documents for systems with no product quality impacts. Once a system has been commissioned and approved, it can proceed to qualification. Only systems that have a direct or indirect impact on the critical aspects require qualification.

Some tests, such as factory acceptance tests (FATs), may be carried out at the vendor's facility (for example, the AHU components check), and these tests may not need to be redone once the unit is in place. However, the supplier should be trained in the documentation practices agreed upon, especially where Cx is used as part of the qualification process.

17.8.2 INSTALLATION QUALIFICATION

Installation qualification (IQ) is the part of the qualification process that checks all critical aspects are installed correctly. The document used to verify the installation is called a *protocol* and must be approved by the SME and the quality control unit prior to testing. As this is a quality-related document, it must be controlled and follow the change control procedure. If a test indicates a system does not meet its assigned acceptance criteria, a corrective action is opened and must be resolved and approved before moving to the next stage in the qualification process. Where the corrective action requires a design change, the change needs to be preapproved by the quality control unit and any impacts to other systems must be assessed. Where a nonconformance can be repaired without a design change, the details of how the repair is made should be documented. Once all tests are completed and the protocols are approved by the SME and the quality control unit, formal, written authorization should be made so that operational qualification (OQ) can commence.

A clear demarcation between the end of IQ and the beginning of OQ can be challenging with HVAC systems because there may be impacts from many interrelated facility features. In many existing facility modification projects, construction complications make final verifications of proper system design and installation difficult—for example, when existing facility challenges result in more duct pressure drop than estimated in the design phase. Special arrangements with the quality control unit can minimize complicated change control and project schedule issues by enabling preliminary operation of the HVAC system for capacity testing purposes prior to the final IQ approval signatures. When this is necessary and implemented properly, the beginning of OQ and formal change control can proceed with greater confidence that future system alterations and project schedule impacts will not be needed. This strategy can assist energy efficiency and reduce project cost concerns by avoiding the need to design with excessive system capacity.

17.8.3 OPERATIONAL QUALIFICATION

The purpose of operational qualification (OQ) is to prove the system operates correctly within the predetermined acceptance criteria. Again, any deviation from the acceptance criteria and requires corrective action before moving on to the next step. Once all

tests and corrective actions are completed and approved by the SME and the quality control unit, performance qualification can commence. Clean space qualification requires the cleanroom to be qualified in its operational state, as it would be when the product is being manufactured within the space. Although ISO 14644-2 (ISO 2015) details the monitoring requirements required for clean spaces, regulations in some cases may require more stringent monitoring needs. For example, in Europe, continuous air monitoring is mandatory in ISO Class 5 (Grade A in Europe) clean spaces and recommended in ISO Class 6 (Grade B) clean spaces (EC 2010).

17.8.4 VERIFICATION

Verification is defined in ASTM E2500 (ASTM 2013) and does not distinguish between Cx and qualification as two separate processes but instead allows the use of Cx tests as the necessary evidence for qualification, or allowing the leveraging of Cx into qualification. This reduces the need to do the same test twice, once in Cx and again in qualification. However, if verification is used, the Cx process must follow good documentation practices and change control procedures and requires approval from the quality control unit.

17.8.5 PROCESS PERFORMANCE QUALIFICATION

Process performance qualification (PPQ), or simply *performance qualification* (PQ), is the final stage of the qualification process and is described by the FDA as combining

> the actual facility, utilities, equipment (each now qualified), and the trained personnel with the commercial manufacturing process, control procedures, and components to produce commercial batches. A successful PPQ will confirm the process design and demonstrate that the commercial manufacturing process performs as expected. (FDA 2011)

Typically, the manufacturer must successfully produce three consecutive batches of product of a quality consistent with the predetermined limits for passing the PPQ stage.

17.9 ACCEPTANCE AND RELEASE

Once the qualifications are successfully completed, corrective actions are closed and approved, and all documentation is completed, the system can be licensed by the relevant regulatory body and begin manufacture for the market. Before acceptance and release, all training should be completed and logged, all standard operating procedures should be available and approved, a change control system and a logging system should be activated, and maintenance/calibration plans should be established.

17.10 OPERATION AND CONTINUOUS IMPROVEMENT

As part of the life-cycle approach, qualified cleanrooms should be maintained during the product's life in the same condition as they were at the original qualified state. Any variance outside of the acceptance criteria must be documented and the risks must be measured to determine whether to recall the product produced in that space from the market. Clean spaces should be monitored and periodically checked to ensure compliance with the predetermined environmental criteria established before qualification as set out by ISO 14644-2 (ISO 2015) or more frequently where required by risk assessments and regulations or by the quality control unit. All critical aspects should be continuously mon-

itored and data-logged for inspection by the quality control unit or auditors. The FDA's *Guidance for Industry: Process Validation: General Principles and Practices* states "equipment and facility qualification data should be assessed periodically to determine whether re-qualification should be performed and the extent of that re-qualification. Maintenance and calibration frequency should be adjusted based on feedback from these activities" (FDA 2011).

17.11 CONCLUSION

The qualification of pharmaceutical, biotechnology, and medical device clean spaces may seem energy intensive and time consuming when compared to other industries. However, unlike with other industries, using medicinal products of an inferior quality can cause serious health problems and even death to the consumer. Qualifying clean spaces used for the manufacture of medicinal products and continuously monitoring the spaces thereafter provides assurance to regulators that products released to the market are safe and to consumers that the product they are using will treat them.

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AIR CONDITIONING COMPANY

Part 4

Cleanroom Design in Select Industries

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18 Cleanrooms in Semiconductor and Electronics Facilities

18.1 A BRIEF HISTORY OF SEMICONDUCTORS AND INTEGRATED CIRCUITS

Driven by the need to miniaturize the electrical devices integrated into airplanes (1944 B-29 bombers had as many as 1000 vacuum tubes aboard their aircraft) and the ever-increasing complexity of computers[1] (Kilby 1976), researchers in the 1940s invented the transistor. This was followed by Jack Kilby's invention of the integrated circuit in 1958 at Texas Instruments. The integrated circuit, as the name implies, integrates into a single device multiple electrical components such as transistors, diodes, resistors, and capacitors. While Kilby's invention led to the first commercially available integrated circuit (or *chip*) in 1960, there were still many problems with integrating the various devices. Individual wires were used by Kilby's devices, but this method was expensive and not easily mass produced. Researchers looked for other forms of interconnecting the devices, and ultimately Jean Hoerni and Robert Noyce developed the planar integrated circuit concept in 1959 and later the concept of metalization, which opened the door for mass production of integrated circuits.

It was the need to electrically isolate the interconnecting materials that led to the use of masking one device from another with nonconducting materials during the metalization process. The masking of one area of a device to protect it during other processing steps, also known as *photoengraving*, were first adapted to produce metal strips 200 μm wide in 1957 and then later adopted by Kilby, Noyce, and others. In 1961 the David W. Mann division of GCA Corporation was the first firm to make commercial step and repeat masking tools, which later became known as *photolithography* or *litho* to semiconductor process engineers. Photolithography remains an essential step in semiconductor manufacturing today, with feature sizes (the smallest dimension used in the masking process) now below 0.001 μm (see Tables 18.1 and 18.2).[2]

While feature size in and of itself is not the primary technological driver to fit more transistors into a given space, it is the result of the desire to do so. To increase the performance of an integrated circuit, circuit designers needed to fit more and more transistors

1. ENIAC computers contained 17,468 vacuum tubes, 7200 crystal diodes, 1500 relays, 70,000 resistors, 10,000 capacitors, and approximately 5,000,000 hand-soldered joints.
2. In Tables 18.1 and 18.2 and throughout the rest of this chapter, *wafer* refers to the monocrystalline silicon disks on which semiconductor devices are fabricated.

Table 18.1 Minimum Feature Size History

Year	Feature Size	Year	Feature Size
1971	10 µm	2001	130 nm
1974	6 µm	2004	90 nm
1977	3 µm	2006	65 nm
1982	1.5 µm	2008	45 nm
1985	1 µm	2010	32 nm
1989	800 nm	2012	22 nm
1994	600 nm	2014	14 nm
1995	350 nm	2016–2017	10 nm
1997	250 nm	2017–2018	7 nm
1999	180 nm	2020–2021	5 nm

As the feature sizes went from 200 to 0.007 µm, the wafer sizes inversely increased.

Table 18.2 Historical Wafer Sizes

Year*	Diameter
1960	0.9 in. (23 mm)
1960	1 in. (25 mm)
1963	1.1 in. (28 mm)
1969	2 in. (50 mm)
1972	3 in. (75 mm)
1976	4 in. (100 mm)
1981	5 in. (125 mm)†
1983	6 in. (150 mm)
1992	8 in. (200 mm)
2002	12 in. (300 mm)
????	18 in. (450 mm)

** Year of high-volume adoption.*
† 120 and 130 mm variations were also used.

into a limited space. This increase in more dense circuits was accomplished with smaller conduction paths or, in other words, smaller feature sizes. Due to the scaling of chip designs and the lithographic manufacturing processes, chip designers tended to decrease feature size and increase transistor density in multiples of 2 (see Figure 18.1). For example, a halving of the scale produced a quadruple increase in the number of chips for a given area. This explains why many memory chips increase as the square of the previous generation: 1 GB, 2 GB, 4 GB, 16 GB, 64 GB, and so on. Chip or die size also plays a role and accounts for intermediate differences, such as 8 GB or 32 GB, and changes in the frequency of doubling.

The relationship between denser integrated circuits (i.e., with more transistors) to how frequently circuit designers change the scale is uniquely captured by Moore's law, which is the observation that the number of transistors in an integrated circuit doubles approximately every two years (see Figure 18.2). This observation is named after Gordon E. Moore, who co-founded Intel and Fairchild Semiconductor. In 1965 Moore described a doubling of the number of components per integrated circuit every year, and at the time of his writing he projected this rate of growth would continue for at least another decade (Moore 1965). In 1975 Moore revised the forecast to doubling every two years in the next decade (Braun and MacDonald 1982).

Figure 18.1
Microporocessor Transistor Counts 1971–2011 and Moore's Law

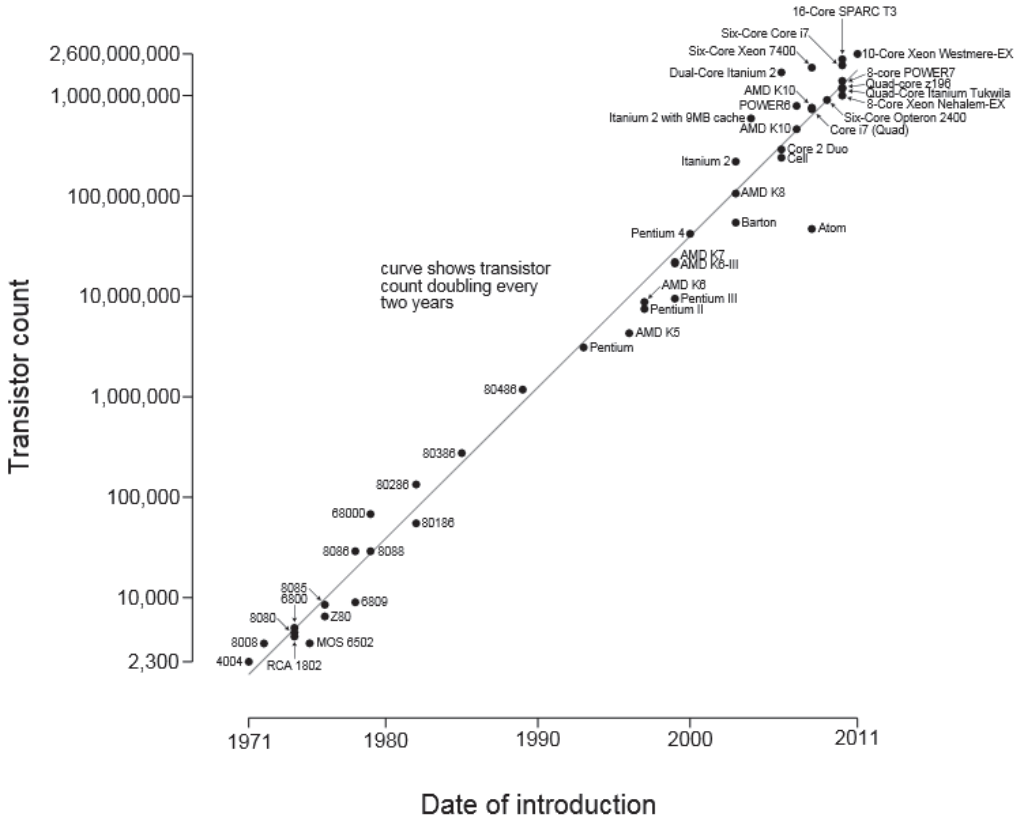
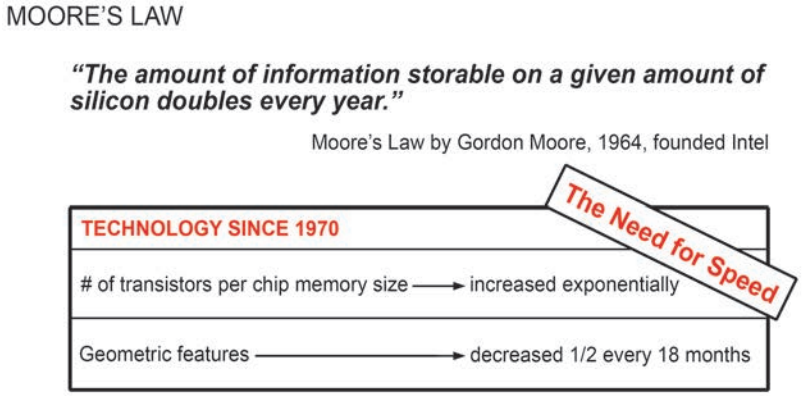


Figure 18.2
Moore's Law



18.2 SEMICONDUCTOR MANUFACTURING—AN EVER-CHANGING INDUSTRY

High costs and pressure to reduce products' selling prices have resulted in a need for competitors to somewhat work together. The semiconductor industry demands facilities that are flexible, environmentally benign, extendable, reliable, and cost-effective and have services that come online quickly. However, production equipment requirements, factory operational flexibility, and environmental, safety, and health (ESH) compliance demand increased facility capital and operating costs. Production and support equipment are becoming larger, heavier, and more complex, thus driving the need for continuous increases in factory size and tool packing density (ITRS 2015a).

Since the first National Technology Roadmap in 1997 and later the International Technology Roadmap for Semiconductors (ITRS) in 2003 (SEMATECH 2003), there have been updates to the ITRS every other year. These roadmap documents have enabled various companies in the supply chain to understand and discuss the long-term needs of wafer fabrication. Table 18.3 provides insight into the type of technology documents issued with a 15-year look ahead.

Wafer and *chip* are ubiquitous terms used to describe the base manufacturing units. Throughout this chapter *wafer* refers to the mono-crystalline silicon disks used to produce integrated circuit devices, or *chips*. The wafers and chips are produced in a fabrication facility or wafer fab, shortened to *fab*. Facility engineers and designers of fabs are given guidance on the needs of the manufacturing equipment suppliers, who in turn work with the chip designers. Figure 18.3 outlines a typical semiconductor process flow.

18.3 FAB DESIGN PROCESS

Semiconductor wafer fabrication cleanrooms (also called *wafer fabs*, *fabs*, or *chip cleanrooms*) have historically been some of the largest cleanrooms. Recently, mega and giga cleanrooms (the names coined for the megabyte and gigabyte memory chips made in these facilities) that exceed 400,000 ft^2 (40,000 m^2) of filtered-air clean area and produce more than 200,000 wafers per month have been constructed. While it is not a rule like Moore's law, the cost of semiconductor factories has increased inversely proportional to the manufacturing technology. A new fab today may cost upwards of 10 to 15 billion U.S. dollars, is expected to be built in less than 10 to 12 months, and is expected to recover its investment in less than 3 years. These financial requirements mandate continuous improvement in productivity, in excess of 20% per year. Preserving the decades-long trend of 30% per year reduction in cost per function also requires capturing all possible cost-reduction opportunities, including opportunities in front-end and back-end production, yield management and improvement, facilities, and improving environmental health and safety (ITRS 2015a). In addition, a fab must be upgradeable to produce next-generation technology with both minimum amounts of new equipment and minimum impact on the logistics for layout and materials (SEMATECH 2000).

For a semiconductor manufacturer to remain competitive, the manufacturing cost per unit area of semiconductor devices (cost/cm^2) must decrease continuously. Semiconductor manufacturers have seen that wafer size increases result in reductions in cost per unit area (cost/cm^2) of silicon. To achieve this, equipment and factory costs should not increase as much as the wafer area increases, and the equipment output (wafers per hour) should be equal to or greater than the previous wafer size generation (ISMT and J300E 2000). See additional discussion in Section 18.27.

A new semiconductor fab represents an enormous investment of time, money, and corporate resources. Business conditions can change rapidly; competitors can introduce new products before a company has time to manufacture their own products. Some fab construction costs can exceed the annual revenue of the entire company, especially with mega and giga fabs. The success or failure of an entire company can depend on that fab's return on investment (ROI). Advanced planning, well-defined design principles, and exacting execution will help maximize the ROI of these investments.

All of this complexity and pressure to execute in a very short time frame requires advanced planning and, for most companies, an advanced design guide for their particular manufacturing needs. This section presents a typical design and construction process that has been used successfully to build many wafer fabs.

Table 18.3
Facility Technology Requirements
(Adapted from ITRS tables)

Year of Production	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Dynamic random access memory (DRAM) 1/2 pitch, nm (uncontacted poly)	**23.8**	**21.9**	**20**	**18.4**	**16.9**	**15.5**	**14.2**	**13**	**11.9**	**10.9**	**10**	**9.2**	**8.4**	**7.7**	**??**	**??**
Wafer diameter, mm	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Wafer diameter, mm						**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**
Manufacturing (cleanroom) area, m^2/wafer starts per month/number of mask layers (300 mm)	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058	0.0058
Manufacturing (cleanroom) area m^2/wafer starts per month/number of mask layers (450 mm)				0.013	0.011	0.009	0.0075	0.0075	0.0075	0.0075	0.0075	0.007	0.0065	0.0065	??	??
Subfab to fab ratio	0.6	0.6	0.6	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	??	??
Facility cleanliness level (ISO 2015)	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest	Class 6 at rest
Wafer environment control such as cleanroom, standard mechanical interface (SMIF) pod, front-opening unified pod (FOUP)																
Number of particles (/m^3)	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1
Airborne molecular contaminants in gas phase, parts per trillion volume (pptV)																
Lithography: point of entry to exposure tool																
Total inorganic acids	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Total organic acids	2000	2000	2000	2000	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd	tbd
Total bases	20,000	20,000	20,000	20,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000	50,000
Propylene glycol monomethyl ether acetate (PGMEA), ethyl lactate	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000	5,000
Volatile organics (with gas chromatography/mass spectrometry [GC/MS] retention times ≥ benzene, calibrated to hexadecane)	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000	26,000

Table 18.3
Facility Technology Requirements *(Continued)*
(Adapted from ITRS tables)

Year of Production	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Dynamic random access memory (DRAM) 1/2 pitch, nm (uncontacted poly)	**23.8**	**21.9**	**20**	**18.4**	**16.9**	**15.5**	**14.2**	**13**	**11.9**	**10.9**	**10**	**9.2**	**8.4**	**7.7**	**??**	**??**
Wafer diameter, mm	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Wafer diameter, mm						**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**
Refractory compounds (organics containing, for example, sulfur, phosphorus, silicon)	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000	2000
Design criteria for facility critical vibration areas (lithography, metrology, other), μm/s	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)	6.25 (VC D)
Design criteria for facility non-critical vibration areas, μm/s	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)	50 (VC A)
Maximum allowable electrostatic field on facility surfaces, V/m (for electrostatic discharge prevention)	2700	2400	2200	2050	1850	1700	1550	1450	1350	1200	1100	1000	900	850	??	??
Continuous radiated emission limit for facility allowable low-frequency (0–30 kHz) magnetic field for electromagnetic interference (EMI)-sensitive area, nT	80	70	60	50	40	30	20	10	10	9	8	7	6	5	??	??
Continuous radiated emission limit for facility allowable low-frequency (0–30 kHz) magnetic field for very-EMI-sensitive area, nT	8	7	6	5	4	3	2	1	1	1	1	1	1	1	??	??
Continuous radiated emission limit for facility allowable high-frequency (30 MHz to 3 GHz) electric(/magnetic) field for EMI-sensitive area (far field), V/m	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.2	0.2	0.2	0.2	0.2	0.2	??	??

Table 18.3
Facility Technology Requirements *(Continued)*
(Adapted from ITRS tables)

Year of Production	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030
Dynamic random access memory (DRAM) 1/2 pitch, nm (uncontacted poly)	**23.8**	**21.9**	**20**	**18.4**	**16.9**	**15.5**	**14.2**	**13**	**11.9**	**10.9**	**10**	**9.2**	**8.4**	**7.7**	**??**	**??**
Wafer diameter, mm	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**	**300**
Wafer diameter, mm						**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**	**450**
Continuous radiated emission limit for facility allowable high-frequency (30 MHz to 3 GHz) electric(/magnetic) field for EMI-sensitive area (near field), V/m	1.0	1.0	0.8	0.8	0.7	0.7	0.7	0.7	0.5	0.5	0.5	0.5	0.5	0.5	??	??
Ratio of tool idle versus processing energy consumption, kW/kW	0.60	0.60	0.60	0.50	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	??	??
Total fab water consumption, L/cm^2																
300 mm/450 mm fabs	7.8	7.8	7.3	7.0	6.4	6.4	5.8	5.5	5.5	5.3	5.0	5.0	5.0	4.6	4.6	4.6
200 mm fabs	7.6	7.6	7.0	6.4	5.8	5.8	5.0	4.8	4.8	4.3	4.1	4.1	3.9	3.5	3.5	3.5
Total ultrapure water (UPW) consumption, L/cm^2	6.5	6.5	6.5	6.0	6.0	6.0	5.0	5.0	5.0	4.5	4.5	4.5	4.5	4.5	4.5	4.5
Site water recycled/reclaimed, % of use	50%	50%	60%	60%	70%	70%	70%	75%	75%	75%	80%	80%	80%	90%	90%	90%
Total fab energy usage, kWh/cm^2																
Not extreme ultraviolet (EUV)	1.0	1.0	1.0	0.9	0.9	0.9	0.8	0.8	0.8	0.7	0.7	0.7	0.6	0.6	0.6	0.6
EUV			1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2	1.2

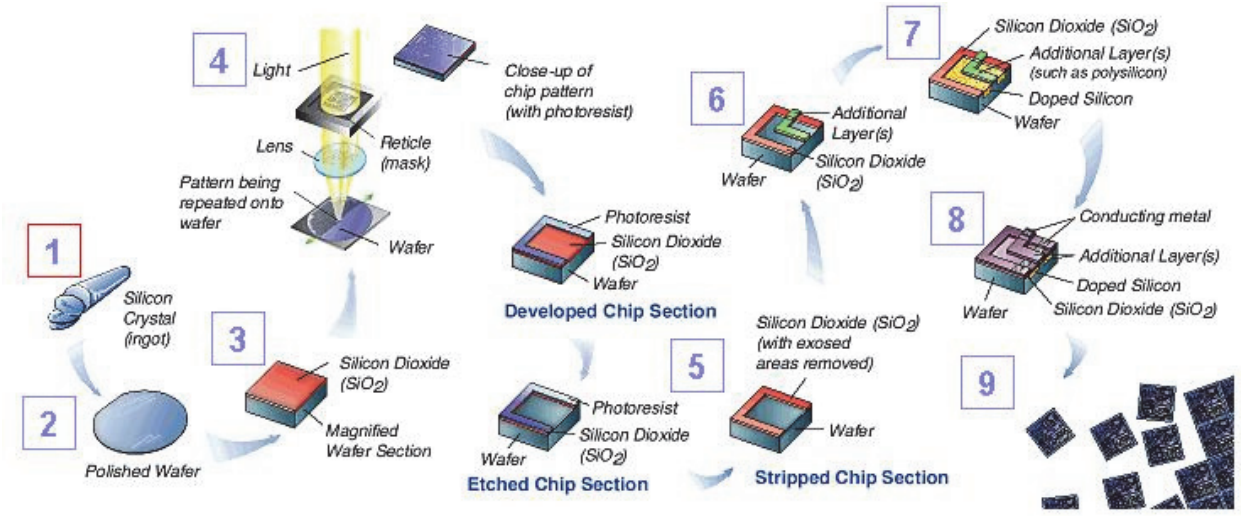


Figure 18.3
Semiconductor Process Flow
(Reproduced from SemiWiki [2016] with permission of SemiWiki)

Figure 18.4
Complex Utility Distributation in Wafer Subfab Area

Semiconductor wafer fabs are extremely complex with dozens of complex utility systems. Their complexity is best demonstrated by a visual of a subfab (Figure 18.4), which is a subset of the total fabrication space. The design process for these factories has historically followed proven architectural and engineering practices. To reduce the time from groundbreaking to the first wafer out, a paradigm shift in the way facilities are designed and constructed has been evolving. Demands from various stakeholders (e.g., factory owners, insurance companies, and government officials) that must be integrated into the facility include the following (ITRS 2015a):

- The fabrication process and the production equipment will increase in complexity.
- Factory operations will seek more flexibility.
- Global codes, standards, and regulations will increase in variability.

The project team of process engineers, manufacturing engineers, facility architects and engineers, design consultants, construction contractors, ESH personnel, and manufacturers of process equipment and facility components must be assembled at an early stage and have the following goals (ITRS 2015a):

- Development of building information models, standardized design concepts, generic fab models, and off-site fabrication to meet cost-reduction goals for delivering a facility capable of meeting current and future process technology requirements. Process equipment suppliers must be part of the solution with more emphasis on standard utility specifications, which will help control capital costs and reduce time to market.
- Development of factory construction and operation sustainability concepts to improve resource use as well as to reduce the environmental impact during both construction and operation.
- Earlier awareness of novel production equipment designs, standardization of production equipment connections and construction materials, and the availability of measured utility consumption data in a standardized database system to allow for appropriate construction of the base build.
- Substantial reduction of construction costs by lowering exhaust/makeup air requirements, raising the cooling water inlet temperatures of noncritical process equipment such that no central chiller plant is required for this equipment, and using higher voltage power for production equipment as much as feasible.

Although facility infrastructure reliability is currently sufficient for supporting manufacturing, it has mostly been achieved through costly redundancy. Improvements are needed in the design and operation of individual components and systems (such as electrical, mechanical, chemical delivery, and telecommunications and facility control) to reduce manufacturing interruptions. Collaboration among manufacturers of facility components and the suppliers of the equipment may change the N+1 redundancy philosophy and positively affect costs but not sacrifice reliability (ITRS 2015a).

Executing a complex project such as the design and construction of a modern wafer fab relies on a proven design process that is composed of a basis of design phase (sometimes called a *preschematic phase*) covering the overall goals of the project stakeholders. This is followed by the traditional schematic design, design development, and construction document phases. While there may be a few unique attributes based on specific building code requirements or the needs of the factory owner, the design phases presented here are typical regardless of the building type:

- Basis of Design Phase
  - Definition of scope and manufacturing expectations
  - Description of facilities and systems
  - Definition and documentation of design criteria for each area of the facility
  - Determination of acceptance criteria for performance testing
  - Determination of utility systems design criteria
  - Analysis of codes and standards
  - Basis of design report with project team sign-offs
- Schematic Design Phase
  - Further development of design criteria
  - Development of process flow diagrams (PFDs) for each utility, including cleanroom systems
  - Creation of building volumetrics and schematic design
  - Calculation of preliminary area tabulations

- Analysis of schematic design codes
- Schematic design of project systems (e.g., electric block diagram and power one-line)
- Development of schematic-level project construction budget
- Report with stakeholder sign-offs

- Design Development Phase
  - Final development of project design criteria
  - Development of piping and instrumentation diagrams (P&IDs) from PFDs
  - Development of system specifications
  - Finalization of systems design
  - Review of design with local code officials and the owner's insurance carrier
  - Final input into project budget
  - Preliminary preparation of bid packages
  - Design development documents issued for review
- Construction Documents Phase
  - Final preparation and release of construction documents

This design process flow may seem to be very linear, but in fact there are many overlapping steps. To achieve construction schedules of < 10 months, a fast-track design and construction process is often used (see Figure 18.5). The fast-track process can be described as an accelerated integrated project delivery (IPD). (IPD is "a project delivery approach that integrates people, systems business structures and practices into a process that collaboratively harnesses the talents and insights of all participants to optimize project results, increase value to the owner, reduce waste, and maximize efficiency" [AIA 2007].) Having all of the stakeholders engaged early enables factories to be built faster, though not necessarily cheaper. Working 24/7 on a project has its costs, but the rewards to the company can mean beating the next technology change and getting maximum prices for their products. Having local code officials be part of the design process and present on the construction site may help meet the fast-track goals of the project.

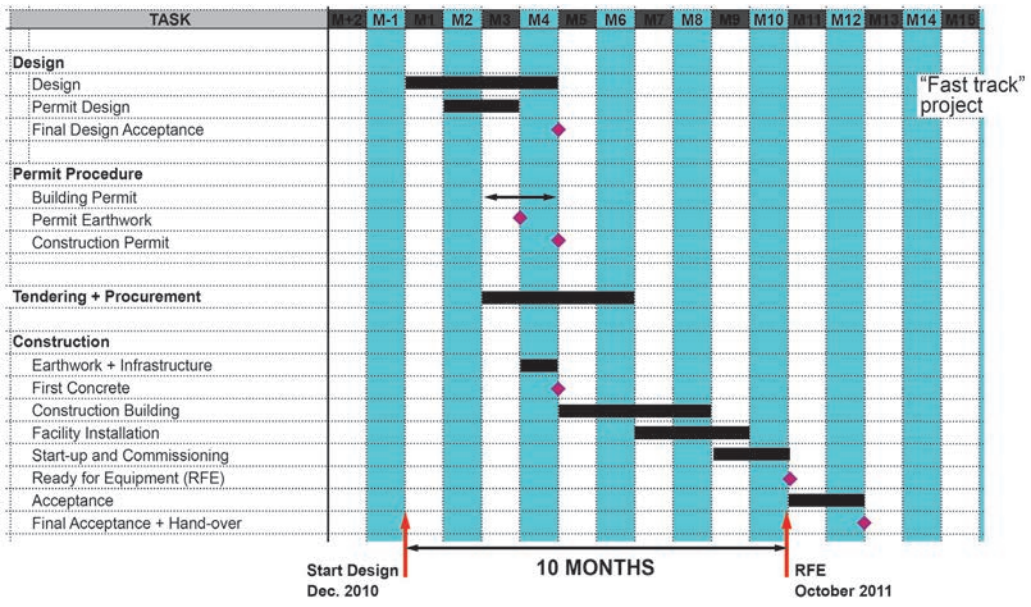


Figure 18.5 Wafer Fab Typical Fast-Track Construction Duration

18.4 BUILDING CODES

In the absence of the regulatory oversight of the manufacturing processes in pharmaceutical and other biotechnology facilities, building codes have been the most consistent regulator of semiconductor fab construction. The collaborative development of specific codes addressing semiconductors between code officials, owners, designers, and insurance industry representatives has provided an evolved set of codes that have attempted to meet the changing needs of the factories.

The products produced by semiconductor factories go into consumer electronics, industrial electronics, automobiles, and wearable electronics, among other things. There is some regulatory oversight for these products, especially those used where life safety may be a factor. The products themselves are tested in accordance with appropriate standards, but the manufacturing processes do not have the oversight that occurs for pharmaceutical and medical device products. Semiconductor fabs can be extremely hazardous, as they contain many dangerous chemicals and gases. Government authorities want to protect the public and the workers in these factories, so the factories are regulated according to the hazardous materials used in the manufacturing processes using building, fire, and other life safety codes. In the United States, the International Conference of Building Officials (ICBO) and National Fire Protection Association (NFPA) have been the primary drivers of building codes for facilities containing hazardous materials. Semiconductor facilities in general contain numerous hazardous materials, both in process and in storage. Before 1985, wafer fabs were generally classified as a business occupancy (e.g., B-2) with either manufacturing or assembly operations in the space; the unique hazards of such spaces were not considered. In 1985, however, the ICBO's then *Uniform Building Code* and *Uniform Fire Code* published Section 911 and Article 51, respectively, that specifically covered the design of semiconductor facilities. These building codes had a tremendous impact on the design and construction of wafer fabs initially in the United States, and recently jurisdictions outside the United States have begun to rely on the more recent editions of these codes, as well. In addition to the design requirements from building codes, the property insurance industry, notably the underwriters consortium FM Global, has also had a significant impact on the design of these very expensive buildings, because the insurance underwriters want the best design to insure for their clients.

The unique multilevel building design and operation of wafer fabs led the ICBO to specifically identify semiconductor fabrication and the special needs when constructing these facilities in the codes (Acorn 1993). The various code areas (building, fire, and mechanical) have addressed the handling and storage of hazardous materials, the fire resistance of the materials of construction, the conveyance of hazardous materials, egress paths, safe zones, fire protection, occupancy separations, etc. To maintain their cost reduction goals, semiconductor fabs are being built larger and larger (i.e., mega fabs become giga fabs) so as to produce more products on larger wafers with lower product costs. Code officials and insurance underwriters seek to reduce the risks to the public and the loss of property. To balance the factory owner's desire for bigger fabs against the building code officials' and insurance underwriters' desire to "keep it small," there are severe restrictions on the construction of the manufacturing cleanroom area, the maximum quantity of hazardous materials, the maximum building height, and materials of construction. Most of the limitations seek to enhance the emergency egress paths, increase protection of the public, and maintain needed access for fire departments.

Within a factory there will be multiple occupancy areas, including office spaces, cafeterias, assembly areas, chemical and gas storage areas, and the process area. In general, wafer fab process areas are classified by the Group H, High Hazard, section of the Inter-

national Code Council's *International Building Code*® (IBC; ICC 2011), which replaced the ICBO's *Uniform Building Code* in 2000. The typical fab includes H-2, H-3, H-4 and H-5 areas. These occupancy designations are discussed in the following subsections in greater detail. Note that the text of these sections is reproduced nearly verbatim from the *2012 International Building Code*® (ICC 2011) except that footnotes have been removed and some other minor editorial changes have been made.

18.4.1 HIGH-HAZARD GROUP H-2

Buildings and structures containing materials that pose a deflagration hazard or a hazard from accelerated burning shall be classified as Group H-2. Such materials shall include, but not be limited to, the following:

1. Class I, II or IIIA flammable or combustible liquids which are used or stored in normally open containers or systems, or in closed containers or systems pressurized at more than 15 psig (103.4 kPa [gage])
2. Combustible dusts
3. Cryogenic fluids, flammable
4. Flammable gases
5. Organic peroxides, Class I
6. Oxidizers, Class 3, that are used or stored in normally open containers or systems, or in closed containers or systems pressurized at more than 15 psig (103 kPa [gage])
7. Pyrophoric liquids, solids and gases, nondetonable
8. Unstable (reactive) materials, Class 3, nondetonable
9. Water-reactive materials, Class 3

18.4.2 HIGH-HAZARD GROUP H-3

Buildings and structures containing materials that readily support combustion or that pose a physical hazard shall be classified as Group H-3. Such materials shall include, but not be limited to, the following:

1. Class I, II or IIIA flammable or combustible liquids that are used or stored in normally closed containers or systems pressurized at 15 psig (103.4 kPa [gage]) or less
2. Combustible fibers, other than densely packed baled cotton
3. Consumer fireworks, 1.4G (Class C, Common)
4. Cryogenic fluids, oxidizing
5. Flammable solids
6. Organic peroxides, Class II and III
7. Oxidizers, Class 2
8. Oxidizers, Class 3, that are used or stored in normally closed containers or systems pressurized at 15 psig (103 kPa [gage]) or less
9. Oxidizing gases
10. Unstable (reactive) materials, Class 2
11. Water-reactive materials, Class 2

18.4.3 HIGH-HAZARD GROUP H-4

Buildings and structures which contain materials that are health hazards shall be classified as Group H-4. Such materials shall include, but not be limited to, the following:

1. Corrosives
2. Highly toxic materials
3. Toxic materials

18.4.4 HIGH-HAZARD GROUP H-5

Semiconductor fabrication facilities and comparable research and development areas in which hazardous production materials (HPM) are used and the aggregate quantity of materials is in excess of those listed in Tables 307.1(1) and 307.1(2) shall be classified as Group H-5. Such facilities and areas shall be designed and constructed in accordance with Section 415.8.

18.4.5 GROUP H OCCUPANCY MINIMUM FIRE SEPARATION DISTANCE

Regardless of any other provisions, buildings containing Group H occupancies shall be set back to the minimum fire separation distance as set forth in Sections 415.5.1.1 through 415.5.1.4. Distances shall be measured from the walls enclosing the occupancy to lot lines, including those on a public way. Distances to assumed lot lines established for the purpose of determining exterior wall and opening protection are not to be used to establish the minimum fire separation distance for buildings on sites where explosives are manufactured or used when separation is provided in accordance with the quantity distance tables specified for explosive materials in the *International Fire Code*.

18.4.6 GENERAL

In addition to the requirements set forth elsewhere in this code, Group H-5 shall comply with the provisions of Sections 415.11.1 through 415.11.11 and the *International Fire Code*. The following are areas and systems within an H-5 occupancy.

1. Fabrication areas.
2. Corridors.
3. Service corridors.
4. Storage of hazardous production materials.
5. Piping and tubing.
6. Continuous gas detection systems.
7. Manual fire alarm system.
8. Emergency control station.
9. Emergency power system.
10. Automatic sprinkler system protection in exhaust ducts for HPM.

18.5 SEMICONDUCTOR FAB ARCHITECTURAL LAYOUT

Semiconductor fabs traditionally have been designed around common manufacturing processes such as photolithography, metal deposition, etching, thin film deposition, implanting, diffusion, planarization, etc. These process area layouts were coupled to the subfab utility distribution with some decoupling to allow for flexibility in equipment tool sets. Photolithography areas with their tight vibration control, tight temperature and humidity control, and susceptibility to molecular contamination were always isolated from other process areas. This allowed for the building structure to be tailored to the specific needs of the photo areas and save costs for other process areas. Today, with ever-changing product mixes and high-speed wafer delivery direct to the tools, the process area layouts are designed around common process parameters such as vacuum-based processes, plasma processes, wet processes, and photolithography processes.

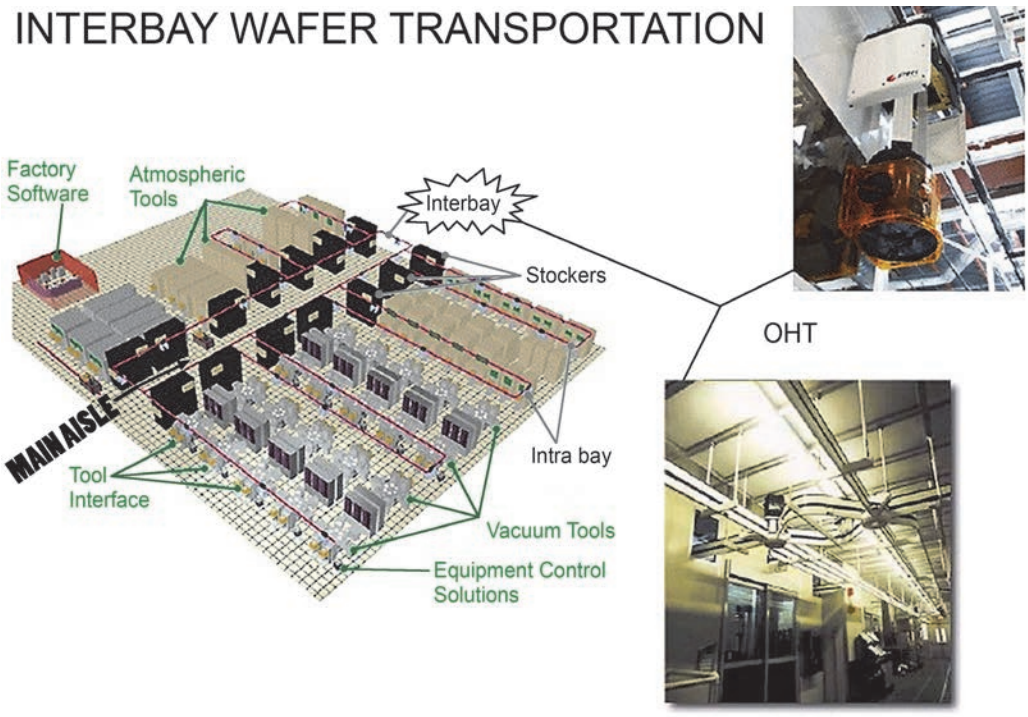


Figure 18.6 Automated Material-Handling System

18.6 MATERIAL-HANDLING SYSTEMS

Material-handling systems (MHSs) cover transport, storage, identification, tracking, and control of direct and indirect materials used throughout the manufacturing process as well as the requirements for the automated MHS hardware and control systems (ITRS 2015a). An MHS is an integral part of the cleanroom.

The need for efficient and rapid material transport as well as ergonomic and safety issues are the major concerns defining MHSs for 300 mm wafer fabrication cleanrooms. Automated material handling systems (AMHSs) must deliver the materials timely in order to support critical equipment and minimize wait time and must directly interface with all in-line production and metrology equipment (see Figure 18.6). Additionally, MHSs must be designed to accommodate a factory's extendibility, flexibility, and scalability demands with minimum downtime (ITRS 2015a).

The larger capacity of high-volume manufacturing fabs and the need for direct delivery to all process equipment means that AMHSs have become larger and their impact on cleanroom volume is significant.

18.7 CONTAMINATION CONTROL

18.7.1 YIELD

Wafer fabs seek to produce complicated products with extremely small feature sizes. Contamination at the wafer level can result in unsustainable yield losses. *Yield* can be defined in its most basic understanding as the proportion of successfully fabricated products (i.e., chips) compared to the total number of products that started the manufacturing process. Wafers that are scrapped for a variety of reasons contribute to wafer yield loss. Identifying problem wafers early in the manufacturing process reduces the added investment of labor and materials if the problem wafer were to continue. Difficulties in early

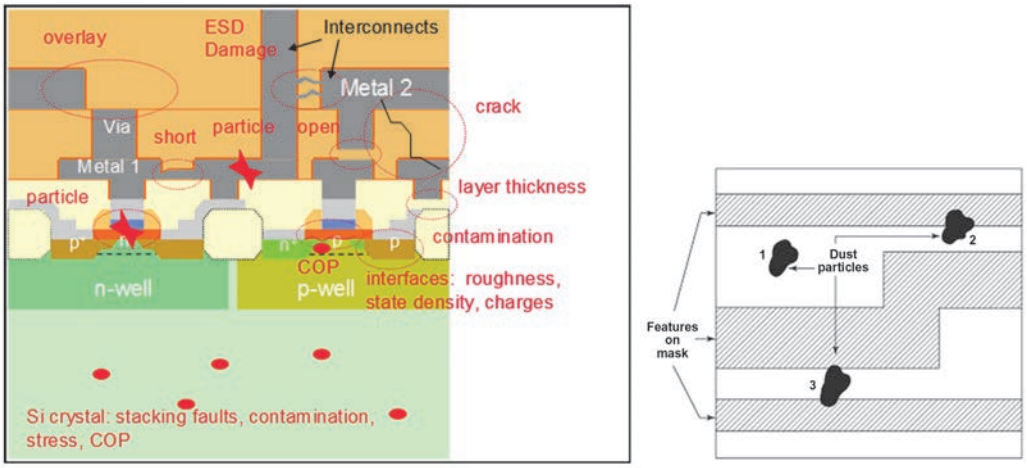


Figure 18.7 Ways Foreign Particles Can Interfere within Interconnect Patterns

identification are a continual problem, as many times problem wafers are not known until near the end of the manufacturing process. For this reason, yield is often considered the most important financial factor in the manufacturing of semiconductor devices. Yield is inversely proportional to manufacturing cost—the higher the yield, the lower the cost (May and Spanos 2006). Figure 18.7 shows a typical chip cross section with various forms of contamination that may occur.

There is a yield associated with each of the multiple process steps required to produce a wafer containing dozens, hundreds, or thousands of individual chips. This is known as *process yield*, and maximizing process yield is part of an overall yield plan. Extensive research and statistical analysis is performed using various yield models. For semiconductor wafer fab owners, achieving and maintaining yield throughout the manufacturing process is vital to the financial success of the factory (ITRS 2015c).

Risks to wafer yield are influenced by the wafer environment during the manufacturing process. Wafers are transported in pods or front-opening unified pods (FOUPs) during manufacturing. Protecting the wafers within the pod/FOUP from an ever-growing list of contaminants is driving the need for an inert gas environment within the pod/FOUP rather than in the cleanroom air. Using inert environments for transporting and storing wafers is expected to increase with process sensitivities—pre-gate and pre-contact clean and salicidation processes require this capability currently, and wafer storage containers themselves may damage wafers due to their internal environments (ITRS 2015d). The most common contaminants impacting yield are airborne molecular contaminants.

18.7.2 AIRBORNE MOLECULAR CONTAMINANTS

Chapter 4 discusses airborne molecular contamination (AMC) in cleanrooms in general; this section provides detail related to AMC in semiconductor wafer fabs specifically. Wafer fab owners and equipment suppliers have realized the need for continuous wafer-level AMC protection as process complexity has increased and more exotic chemicals have come to be used. Wafers must be protected in the front end and the back end of the factory, whenever they may be exposed to the room environment. Most fabs deploy a fab-wide protection scheme that includes contaminant monitoring and mitigation of high contaminant levels. For more sensitive processes, a process-specific protection plan is used to further decrease contaminants.

An increasing source of AMC in fabs is being detected from fugitive emissions associated with the maintenance of local process exhaust scrubbers (e.g., for dopants). The

fugitive emissions are exhausted to the building exterior and subsequently reentrained into the makeup air and eventually back into the cleanroom. Including the monitoring and mitigation of these fugitive emission sources is no longer optional for a good AMC protection plan, it is essential.

Wafer exposure to the chemicals within the cleanroom environment presents another challenge. The typical wafer carrier (i.e., pod or FOUP) is exposed to cleanroom chemical species at many points in wafer handling. The wafers themselves also off-gas chemicals that can "infect" the interiors of the wafer carriers. To mitigate this problem, designers use a two-prong attack: 1) wafer carriers are being designed with inert gas purges and carriers are being replaced or changed during those steps between potentially contaminating processes, and 2) carriers are designed for specific processes only and wafers are moved from one carrier to another. For cleanroom environments, the deployment of fab-wide AMC filtration systems is becoming the rule rather than the exception for most process areas. Combining the fab-wide system with AMC filters at high-risk process tools, fab operators are hoping to minimize exposure to killer molecules.

Reductions of this cross-contamination can be achieved by applying best practices to abatement maintenance as well as improving the overall removal efficiency for the abatement and central facility scrubbers.

18.7.3 STATIC CHARGE AND ELECTROMAGNETIC INTERFERENCE

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

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

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

18.7.4 ELECTROMAGNETIC INTERFERENCE CONTROL

Electromagnetic interference (EMI) is defined in SEMI E33 as "the degradation of the performance of an equipment, transmission channel, or system caused by an electromagnetic disturbance" (SEMI 2012, p. 2). EMI causes a number of problems for semiconductor manufacturing, such as equipment lockup and malfunction, sensor misreading, metrology errors, and sensitive component damage. Sources of EMI in semiconductor environments include electromagnetic emission from ESD; operation of equipment, especially high-energy tools; motors and actuators; wireless communication; and the like. Colocation of sensitive equipment with high-energy tools, cabling, ground problems, improper maintenance of equipment, and other issues further aggravate EMI problems (ITRS 2015a).

Current practices for mitigating EMI impact are either passive-shielding the sensitive equipment or shielding the sources. Electrical transformers are a major source, and shielding of these in metrology areas is common practice.

18.8 AIR PATTERN EFFECTIVENESS AND COMPUTER-AIDED FLOW MODELING

Similar to other cleanroom applications, computational fluid dynamics (CFD) modeling has proven to be a useful tool in enhancing cleanroom designs and evaluating the effectiveness of the expected air patterns. More advanced computers have allowed even large fab cleanrooms to be modeled using a relatively small mesh size.

Some of the more common applications of CFD modeling for semiconductor wafer fabs include the following:

- Particle deposition risks to open wafers in some metrology tools
- Temperature hot spots
- Projected particulate loading in the air spaces
- Calculation of flow fields and their effect on particulate control
- Chemical dispersion to aid AMC mitigation strategies
- Identification of recirculation zones and design features that may lead to detrimental airflow
- Raised-floor damper balancing
- Preliminary damper position settings

18.9 INDOOR DESIGN CONDITIONS

Typical indoor design conditions are shown in Table 18.4. In the past, process requirements dictated the primary design criteria for temperature and humidity set points. Temperature stability is needed in many atmospheric pressure processes that are exposed to the cleanroom ambient temperature to minimize changes in dimensions from expansion or contraction. Good control of dry-bulb temperature is needed to provide stability in relative humidity. Relative humidity changes can affect the performance of many hygroscopic materials used in semiconductor manufacturing. Controlling dry-bulb temperature and dew point can provide uniform relative humidity. Processes that are sensitive to relative humidity or dew point have been developed to operate in typical ranges common to many cleanrooms (see Table 18.4). Spaces where dew points are below freezing may require the selection of desiccant-based dehumidifiers or refrigeration using complex defrost cycling. For the more common application where space dew points are above freezing, refrigeration is used for dehumidification, though desiccants may also be used.

The process requirements may dictate the criteria on temperature and humidity control tolerances, but providing a comfortable work environment is also needed. For fabs where workers will be performing significant manual tasks such that they may perspire, a cooler work environment may be warranted, whereas the environment in fabs whose workers are somewhat sedentary may be warmer. Changing the room environment to suit worker activity levels is balanced against the process. In general, making cleanrooms cooler and dryer enhances worker comfort unless it gets too cold or too dry. Table 18.4 requirements, when overlaid on the human comfort boundary (see ANSI/ASHRAE Standard 55 [ASHRAE 2013]), show many cleanrooms tend towards the cold end (see Figure 18.8). Cleanroom workers are generally clothed in special clothing sometimes called *bunny suits* or *cleanroom suits*. Depending on the cleanliness classification of the

Table 18.4
Process Area Environmental Conditions

	Temperature Set Point Range	Tolerance	Relative Humidity Set Point Range	Tolerance	Dew-Point Set Point Range	Tolerance
Critical process areas	65°F to 74°F (18°C to 23°C)	±1°F to ±2°F (±0.5°C to ±1°C)	35% to 50%	±2% rh to ±3% rh	36°F to 53.6°F (2.3°C to 12°C)	±2°F to ±3.5°F (±1°C to ±2°C)
Noncritical process areas	65°F to 78°F (18°C to 26°C)	±2°C (±3.5°F)	35% to 60%	±2% rh to ±5% rh	36°F to ±62.6°F (2.3°C to 17°C)	

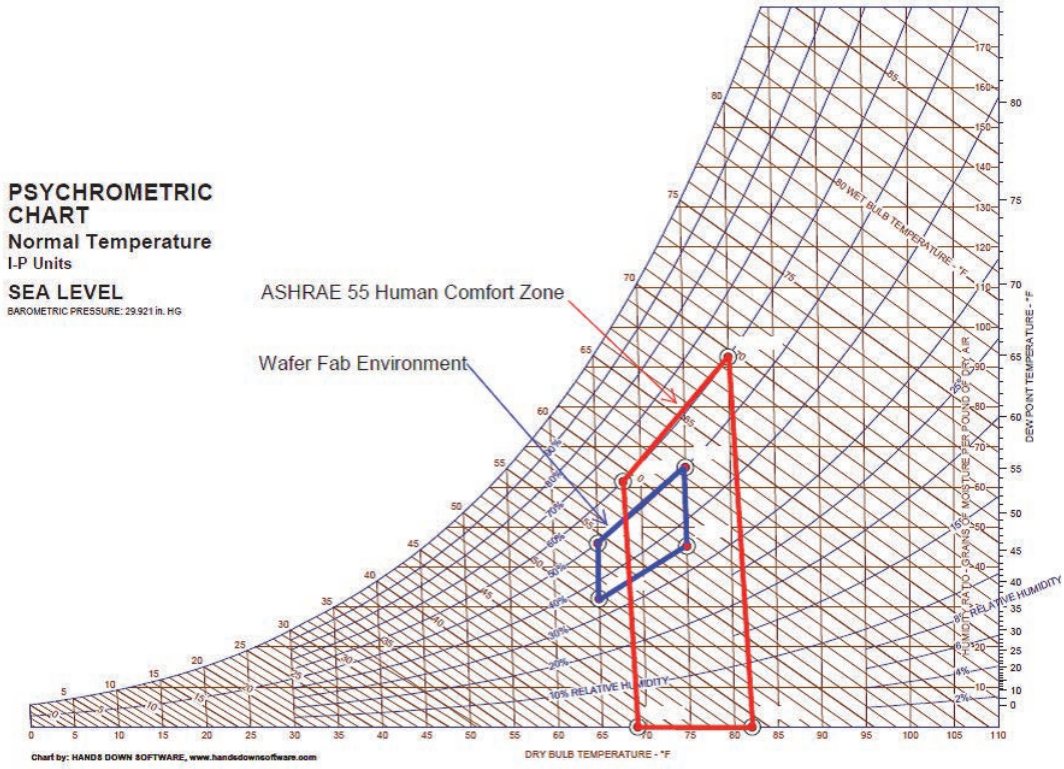


Figure 18.8
Fab Environment

space, cleanroom suits may be full coverage or partial coverage. Cleanroom suits are generally manufactured from a polyester material such that moisture generated by the worker is generally contained within the suit and any excessive perspiration may make the worker uncomfortable. To make workers feel more comfortable, cleanroom dry-bulb temperature may be reduced. As dry-bulb temperature is reduced but dew point remains constant, relative humidity increases. If the processes limits are reached, the dew point must be decreased to maintain the same relative humidity at the same dry-bulb temperature.

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

18.10 MAKEUP AIR

Makeup air plays a crucial role in the environmental conditions of a wafer fab by providing replacement air for the air exhausted for process requirements, providing excess air to provide positive pressure in cleanrooms, and providing a source of wetter or dryer air to help control moisture levels inside the fab. Wafer fabs require a relatively large amount of makeup air due to the physical size of their factories, and depending on the local climate, makeup air may be 20% to 30% of the total fab chiller load. For new cleanrooms where the final process exhaust requirements are not known, cleanroom designers rely on rules of thumb for the initial impact to the chiller plant. While commercial facilities may consider ventilation rates per person, wafer fabs tend to use a design criteria based on the area of the cleanroom. Common rates for consumer semiconductor products (memory and CPU devices) are 3–6 cfm/ft^2 (50–100 m^3/h·m^2), while code requirements are 1 cfm/ft^2 (18.3 m^3/h·m^2). There has been a trend toward lower ventilation rates due to changes in tool configurations where there are fewer liquid chemical ventilation hoods (e.g., wet chemical etchants) and more dry plasma-based processes.

The control of dew point or relative humidity in a semiconductor wafer fab is also needed in many contamination control schemes. Humidity levels can affect ESD rates, particle adhesion, and corrosion of metal surfaces deposited on a wafer. Typically, the most critical need for control of humidity in a particular band is sensitivity of photoresists used in the photolithography process. Relative humidity and temperature are both critical for precise dimensional control and resist stability. With increasing relative humidity, photoresist viscosity decreases rapidly, even at constant temperature. Changing the viscosity changes the thickness of a resist film spun-on by a fixed coating recipe (Donovan 2003).

Makeup air provides a source of dehumidifying or humidifying air. The makeup air introduced into the fab environment is either below the space dew point, at the space dew point, or above the dew point. When it is below the space dew point, moisture must be added (humidification). When the makeup air dew point is above the space-required dew point, moisture must be removed (dehumidification). Makeup air treatment schemes must be designed for the expected climate. Fabs located in tropical climates where outdoor dew points rarely go below 68°F (20°C) may not need any humidification equipment, while fab locations in diverse climates may need both humidification and dehumidification capabilities.

18.10.1 MAKEUP AIR TREATMENT OPTIONS

The treatment of makeup air prior to its addition to the cleanroom space includes moisture control and filtration of external contaminants, particles, and airborne molecular contaminants.

18.10.1.1 Moisture Control

Moisture control may refer to one or more psychometric processes (see Figure 18.9). It may be achieved by the removal of moisture (dehumidification) or the addition of moisture (humidification). For the final cleanroom air, moisture control may occur with the mixing of treated makeup air and recirculated cleanroom air.

18.10.1.1.1 Dehumidification

When dehumidification moisture control is needed, the methods are as follows:

- Cooling the air using water condensation (subcooling method)
- Absorption of the water by absorption material (absorption method)
- Mixing in dry air

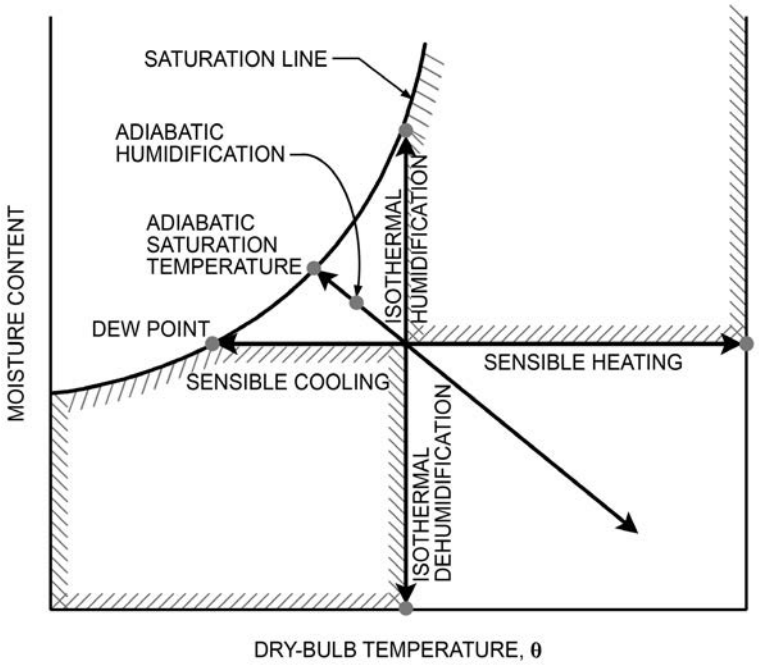


Figure 18.9 Makeup Air Psychrometric Processes

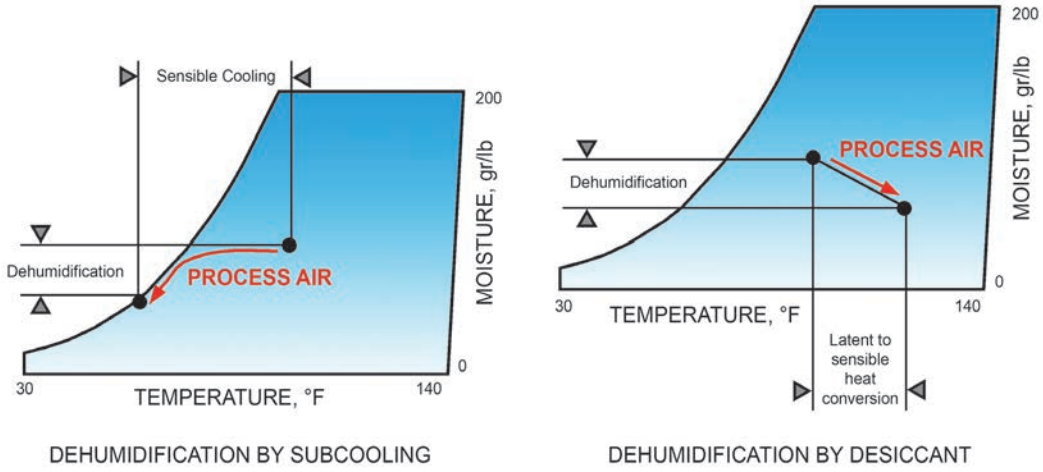
Dehumidification can be achieved by subcooling via refrigeration or desiccants. There are pros and cons to each method when considering capital costs, operating costs, equipment configurations, controllability, etc. A complete discussion of each method is beyond the scope of this book, but this subsection briefly discusses how each method can be used, the typical configurations, and some typical operating parameters.

Subcooling by refrigeration involves the cooling of the airstream to below the dew point of the air, thereby condensing the moisture—the air has been dehumidified by the process of cooling and condensation. For a makeup air handler, this usually involves passing the air through a cooling coil that may be a direct expansion coil or a chilled-water coil. The amount of moisture that is removed depends on how cold the dew point of the coil apparatus is—the lower the temperature, the drier the air.

Desiccants can be solids or liquids, because either can collect moisture. For example, sodium chloride, lithium bromide, silica gel, and molecular sieves are solid desiccants, while liquids include triethylene glycol. Lithium chloride can be both, absorbing water vapor as a solid, hydrated salt, or as an aqueous solution. Liquid and solid desiccants behave similarly—their surface vapor pressure is a function of their temperature and moisture content (Lowenstein 2008; Munters 2002).

The typical semiconductor wafer fab space dew point is between 44.6°F and 53.6°F (7°C and 12°C), though it may be as low as 28.4°F (–2°C) or as high as 57.2°F (14°C). For the 44.6°F to 53.6°F (7°C to 12°C) range, cooling via chilled water is the most common method. When using chilled water to achieve 44.6°F (7°C), the chilled-water supply temperature will typically be 5.4°F to 10.8°F (3°C to 6°C) colder than the desired leaving air dew-point temperature. This will provide good control of the leaving air dew-point temperature, usually ±1.8°F (±1°C). Providing consistent dew-point control of the makeup air enables consistent moisture content of the makeup air when it is mixed with cleanroom recirculation air and can result in good relative humidity control (±5%) when combined with good dry-bulb temperature control. Some semiconductor wafer fabs may have process areas requiring better than ±2.5% rh. To achieve control of ±2.5% rh, the makeup air dew point must be controlled ±0.9°F (±0.5°C).

Figure 18.10
Dehumidification Process



The acceptable tolerance in makeup air dew-point control may limit which dehumidification process is suitable, as not all processes can control makeup air dew point precisely. Direct expansion and desiccant-based dehumidification may be limited in their control capability, whereas chilled water can normally achieve this type of control. Some metal salt desiccants have also been avoided due to concern over the salts as potential sources of contamination.[3] Referring to Figure 18.10, we can see the two main psychrometric processes: subcooling and adiabatic dehumidification (using a desiccant). In general we can see that both processes remove moisture from the makeup air.

Dehumidification by subcooling results in leaving-air temperatures from the coil at or below the space dew-point requirements and provides a source of sensible cooling to the cleanroom. If the adiabatic mixing of the makeup air and cleanroom recirculation air is uniform with little to no stratification, then the sensible cooling effect of the makeup air is a significant energy efficiency measure recovering upwards of 25% of the makeup air chiller plant load (Naughton 1990). This energy conservation measure is dependent on the degree of adiabatic mixing. Some semiconductor wafer fab designers prefer to reheat the makeup air to avoid the potential of overcooling the space (see Figure 18.11).

18.10.1.1.2 Humidification

Humidification, or adding moisture to the makeup airstream, is part of the process to add moisture to the semiconductor wafer fab space. Moisture is lost to adjacent spaces operating at lower relative humidity. Moisture can be added by direct injection of water in the form of steam, hot water, or cold water. The temperature of the air at the point of the water injection may determine which fluid is most effective. The effectiveness is a function of the mean surface temperature of the water and the dry-bulb temperature of the air. Nonadiabatic humidifying air undergoes a change in enthalpy and is accomplished by heating and humidifying using steam or hot water or isothermal humidifying using water with a mean surface temperature close to the dry-bulb temperature of the air. Adiabatic humidification or evaporative cooling results in the air dry-bulb temperature decreasing along the wet-bulb line until adiabatic saturation is achieved.

3. Highly reactive metals such as sodium and lithium can be disastrous to many semiconductor processes. While there is no evidence that metallic salt desiccants can add sodium or lithium to the airstream, some cleanroom designers prefer not to take the risk. See Section 18.7.2 for a discussion of airborne molecular contamination.

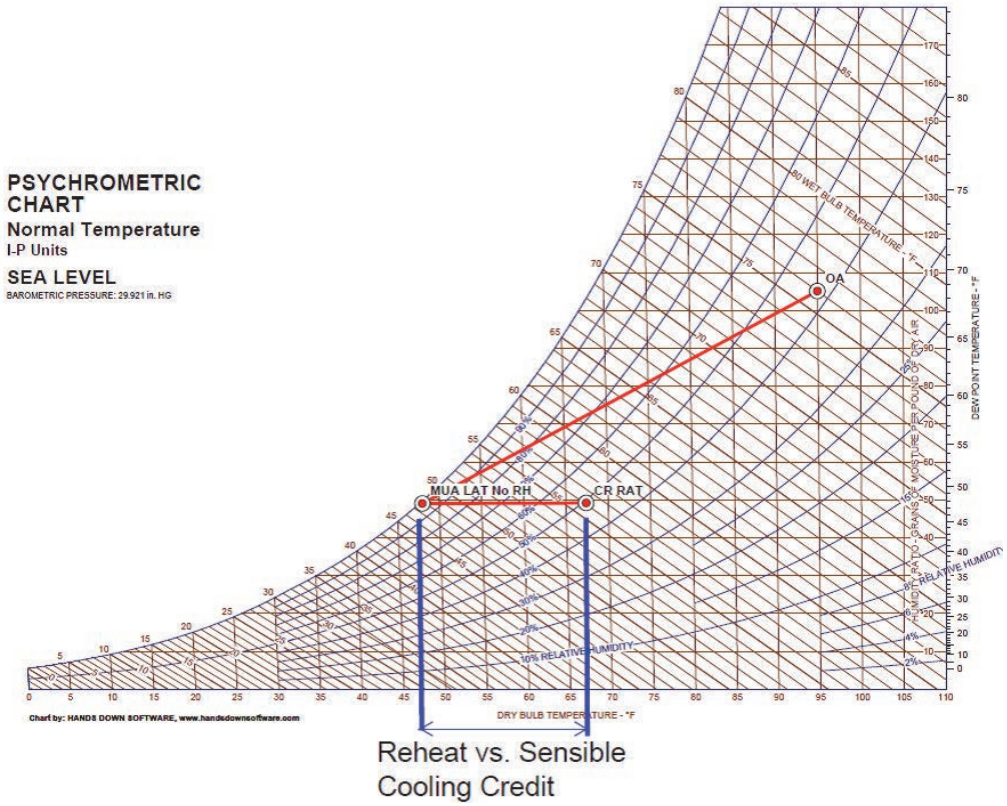


Figure 18.11 Makeup Air Treatment—Reheat or Sensible Cooling

There are pros and cons of adiabatic and nonadiabatic humidification (i.e., isothermal humidification) where equipment capital and operating costs, local climate, and other factors may influence the final design decision. The degree of required control will influence the selection regardless of the capital and operating costs. Some makeup air configurations (see Figure 18.12) may actually overhumidify and then use dehumidifying coils to achieve tighter control tolerance on the final moisture content of the air entering the cleanroom. Other designs rely on two stages of humidification, stage one occurring in the makeup air unit and stage two in the cleanroom recirculation. As with dehumidification, the intent of the makeup air system is to provide consistent moisture control so that the adiabatic mixing between makeup air and cleanroom recirculation air results in a dew point at the design dew point of the space.

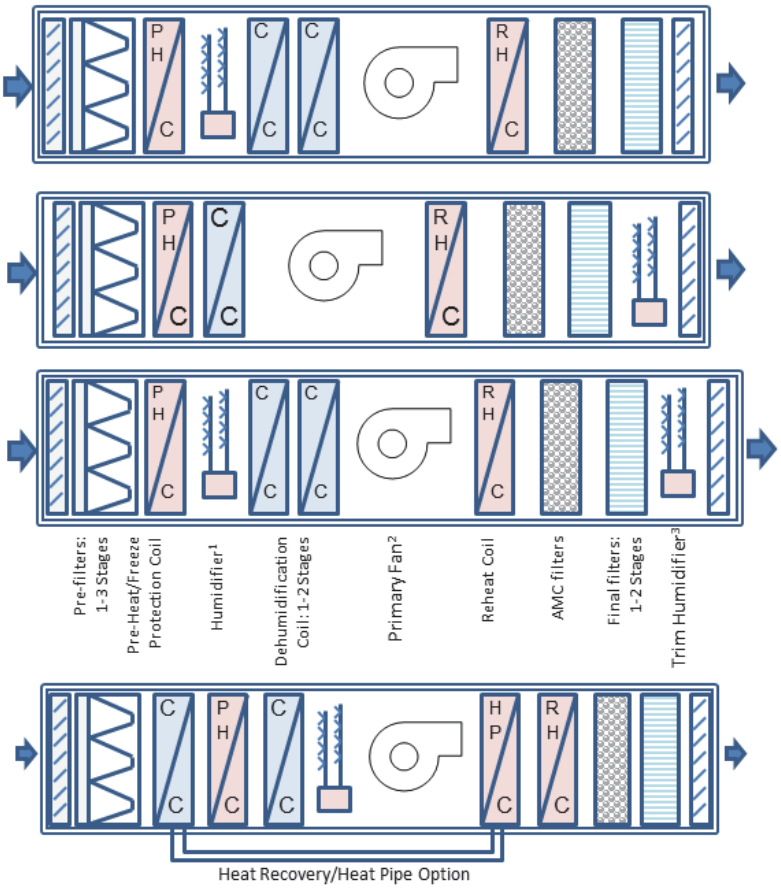
When steam or adiabatic humidification is used for moisture addition, the source of the water is crucial. Water sources that contain chemicals such as water treatment chemicals or naturally occurring impurities must be purified to avoid the potential of impurity carryover into the cleanroom air and becoming a source of contamination. Water sources may be cleaned via reverse osmosis, distillation, or deionization. For steam humidification the use of purified water is commonly referred to as *clean steam*.

18.10.1.2 Filtration

Since most semiconductor wafer fab makeup air is introduced into the cleanroom recirculation air path there is a fundamental need to minimize external sources of contamination from the makeup air. Makeup air is air from the outdoors; this air contains all of the environmental characteristics of the outdoors, including the following:

- **Outdoor Pollution.** Outdoor pollution includes ozone, soot, smog, nearby exhausts (reentrained), organic materials, inorganic particles, hydrocarbons,

Figure 18.12
Makeup Air Configuration Schemes



1. Adiabatic or Isothermal humidifiers may be deployed
2. Fans may be in blow through position though draw through is more common as fan heat is after primary cooling coils
3. Trim humidifiers may be located in cleanroom recirculation air path for fine humidity control in sensitive areas like photolithography

amines, salts, and many other industrial contaminants that may be in areas surrounding the fab. Depending on the fab location, designers may need to provide complex particle and chemical filtration in the makeup air equipment.

- **Particles.** Outdoor air may contain tens of millions of particles per cubic area in some locations and billions of particles in heavily polluted metropolitan areas. As part of the overall cleanroom air management plan, the control of particles within the makeup airstream is typically handled by particle filters, air washers, and occasionally electrostatic-enhanced particle filters. Typical configurations involve multistage filtration, and a balance of total air pressure drop and filter costs are considered in the equipment design. Prefiltration prior to any heating or cooling coils may include filters with minimum efficiency reporting values (MERVs) of MERV 6 to MERV 10 depending on local pollution, while final discharge filters are typically MERV 16 and/or U-15 or U-16 high-efficiency particulate air (HEPA) or ultralow particulate air (ULPA) filters.

As discussed previously, control of AMC is critical to maximizing yield by minimizing contamination of the photoresist and mitigating progressive defects forming on masks during exposure (Mueller 2013). For makeup air equipment, the inclusion of AMC filters is commonplace for most semiconductor wafer fab locations due to local pollution and reentrainment of process exhaust. AMC filters typically involve a chemical adsorption

process using activated carbon sometimes doped with other activated chemicals (e.g., permanganate-embedded alumina) or ion-exchange resins.

Most makeup air units integrate their AMC filters as part of a multistep particle and AMC filtration scheme. Some AMC filters are available with particle removal efficiencies of MERV 8 to as high as MERV 15, which can help reduce the overall air pressure drop through the makeup air equipment.

18.10.2 MAKEUP AIR EQUIPMENT CONFIGURATIONS

Cleanroom designers configure makeup air handlers based on local climate, pollution, control tolerances, and expected equipment costs. Within the typical configuration of an air handler are many common elements, including inlet and outlet dampers, heating and cooling heat exchangers, fans, particle filters, and perhaps chemical filters. Cleanroom designers may change the order of the elements or the specific types of the elements. Some examples of changeable elements include the following:

- **Heat Exchangers.** Typically a counter-current serpentine-coil type is used for heating or cooling. Indirect heat recovery heat exchangers may be used in conjunction with exhaust stream heat recovery. Cooling coils may also function as dehumidifiers. With regard to preheat coils, some designers prefer to preheat then humidify, while others eliminate the preheat coil entirely if the local climate is above freezing conditions in the winter.
- **Humidifiers.** Types of humidifiers include isothermal types, such as steam humidifiers, adiabatic atomizing humidification using compressed air, ultrasonic, or centrifugal, and adiabatic wetted media types. Humidification may also be achieved in multiple stages, with the second stage sometimes located in the cleanroom recirculation airstream.
- **Dehumidification.** Dehumidification types include cooling based or chemical based types. Chemical-based dehumidifiers must be evaluated for possible contamination of air from the chemicals.
- **Filtration.** Filtration stages may be both before and after the fan.

The final order of the elements is selected by the cleanroom designer. Typical orders using various element choices are shown in Figure 18.12, though the actual choices could be much greater.

18.10.3 MAKEUP AIR EQUIPMENT LOCATION AND REDUNDANCY

Makeup air equipment must be located in areas where

- entrainment of process exhaust is minimized,
- locations near heavy sources of pollutions such as boiler stacks, parking garages, highways, chemical processing, kitchen exhaust fans, or truck exhaust at loading docks or waste treatment areas are avoided, and
- locations near open cooling towers that may add unnecessary latent loads are avoided.

Building and fire codes require emergency power to exhaust systems for Group H occupancies (ICC 2011). While makeup air is not required to be redundant or on emergency power, practical considerations may warrant this. The importance of makeup air to maintaining a semiconductor wafer fab environment is that any loss of makeup air would result in a compromising situation to the fab environment and may necessitate a shutdown of the fab. Today's billion-dollar fabs cannot tolerate these losses.

For H occupancies (see Section 18.4), many code authorities prohibit the recirculation of cleanroom air within a makeup air handler as the risk of reentrainment of hazardous materials is too high. Cleanroom contamination control managers may also prohibit recirculation to avoid reentrainment of airborne molecular contaminants. Therefore, most fabs use dedicated makeup air units with no cleanroom recirculation.

18.10.4 MAKEUP AIR CONTROLS

18.10.4.1 Volume Control

Makeup air equipment using variable-speed drives (VSDs) is very common. Due to the relationship between space dew-point control and pressure control, the control of the makeup air fans may have a complex control algorithm to avoid undershooting the volume needed for pressure control and the condition of the air for dew-point control. In general, the makeup air discharge dew point becomes fixed with some reset capability based on room relative humidity sensors. The volume of the makeup air tends to be based upon a fixed distribution system pressure with resets based on room pressure sensors.

18.10.4.2 Temperature and Dew Point

Each stage of cooling and humidifying are precisely controlled using industrial-quality control valves and high-precision sensors.

18.10.4.3 Smoke Controls

Makeup air is part of a comprehensive smoke control strategy. During a smoke event, any variable-speed makeup air handlers are ramped to 100% to mitigate the damage that may occur in the fab from a smoke event. Insurance underwriters tend to have very specific smoke control requirements.

18.11 CLEANROOM CLEANLINESS AND AIRFLOW CONCEPTS

The primary goal of a cleanroom is to provide a controlled environment that meets contamination control goals such as maximum particle concentrations (i.e., the particle cleanliness class per ISO 14644-1 [ISO 2015]). In semiconductor cleanrooms, in additional to particle concentration control, more and more cleanrooms seek a controlled level of AMC concentration (i.e., chemical cleanliness class per ISO 14644-8 [ISO 2013]) (see Section 18.7). While not an explicit requirement, the airflow concepts used in a cleanroom have a direct impact on particle concentration and may also impact chemical cleanliness. Cleanroom designers have had to change the airflow design concepts to meet the changing semiconductor process technology.

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

Referring to Table 18.3, we can see that the suggested cleanroom cleanliness classifications have changed to lower classifications while the environment that wafers is exposed to has reached the current limits of ISO 14644-1 (ISO 2015). In other words, semiconductor cleanrooms are getting “dirtier” (they have lower cleanroom requirements) yet the semiconductor industry seeks wafer environments that are cleaner than ISO Class 1 spaces. The gap between the suggested cleanroom environment and the

wafer-level environment is a risk management issue that each fab owner must address. Questions to consider include the following:

- How reliable is the containment of the wafer-level environment?
- What happens if the wafer-level environment is exposed to a less clean environment?
- What happens to the process tool environments during maintenance, and is there a risk to the wafer once maintenance is complete?

Semiconductor wafer fab owners must answer these questions based on their tolerance for risk and a thorough cost/benefit analysis.

Wafer fabs are multilevel manufacturing spaces (see Figures 18.13 and 18.14). Fab spaces are composed of process areas, subfabs (more than one), chases, return air plenums, and supply air plenums. Above the ceiling of the process area are the cleanroom supply air plenums, ductwork, fan filter units (FFUs) and, in some fabs, process utilities. Many times these spaces, though not normally occupied, will be designed for access by maintenance personnel. The ceiling structure is designed to support cleanroom filters or FFUs, the MHS, lighting, ionization, maintenance personnel, and optional monitoring devices for temperature, humidity, and particles. The area where most wafer processing occurs is typically referred to as the *process area*, though some companies have their

Figure 18.13 Multilevel Fab Options

(Courtesy M+W Group [2015])

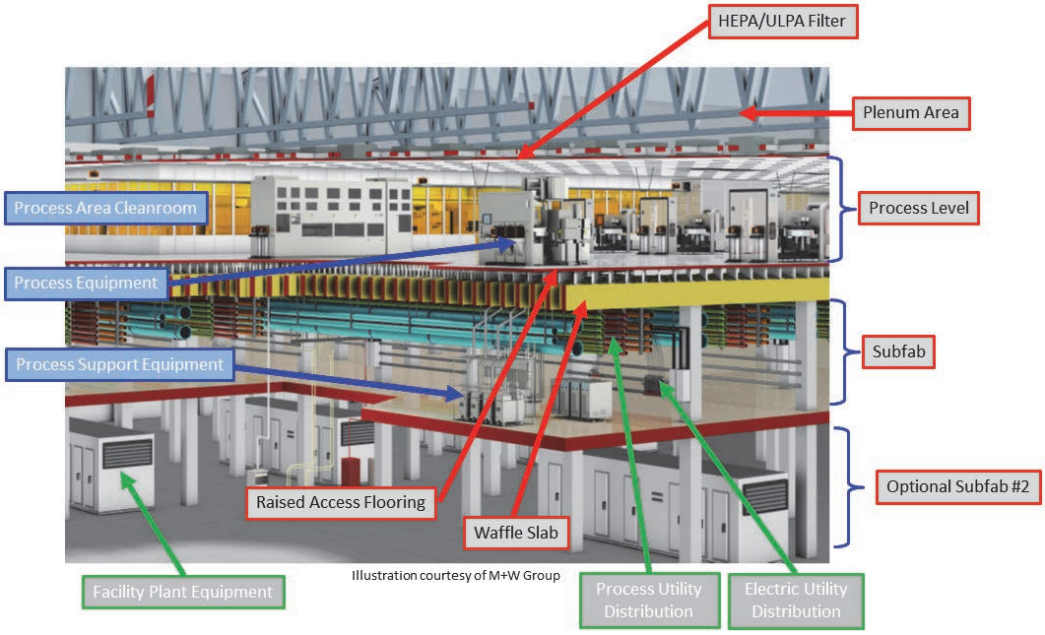


Figure 18.14 Multilevel Fab with Complex Utility Distribution

(Courtesy M+W Group [2015])

own vernacular for describing the different areas of the fab. The process area is where most cleanroom operators work and contains the process equipment main frames, wafer delivery equipment, metrology equipment, and other wafer-handling equipment (see Section 18.6). Below the process area is the subfab or subfabs, which, like an iceberg, is where a hidden mass of equipment is located. Visitors to fabs are shown the gleaming super cleanroom spaces of the process level, but the subfab is where cleanroom designers earn their keep. Subfabs may be divided into clean subfabs and dirty subfabs, isolating potential contamination sources from the clean subfab, which in turn protects the process area.

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

As mentioned in Section 18.4, semiconductor fabrication facilities codes understand the multilevel design of fabs and do not require the same occupancy separation between floors that may occur in other building types. Wafer fabs constructed according to the *International Building Code*® (IBC; ICC 2014) are normally limited to three levels, though some authorities having jurisdiction may calculate the definition of a level differently, such that some fabs may actually contain three or more recirculation air paths. There are fabs constructed that may be multiple fabs stacked on top of each other when land is scarce. Whether a fab is one level or nine levels, the cleanroom air management must consider all of the air paths, how to distribute makeup air to each area, control of temperature and humidity in each area, and pressurization between the areas.

Part of the justification of multiple levels is the need for extensive utility distribution. Table 18.5 shows that a typical semiconductor wafer fab can have in excess of 50 unique utilities. Some of the major challenges facing designers when the number of utilities is high are as follows:

- Identifying all required utilities for the expected process area.
- Determining whether the utilities will be transported into the space or generated in the space (e.g., ultrapure water [UPW] is generated outside of the space but the final polishing is normally inside the space; process cooling water (PCW) may have its heat exchangers outside the space and piped into the space, or the heat exchangers may be located inside the space).
- Determining which air path the generating sources or conveyance equipment (i.e., pumps) should be located in and whether this equipment should be isolated due to potential contamination.
- Deciding how to distribute the mass of utilities in a manner that allows for maintenance, future expansion, movement of subfab process equipment, and other design criteria, all the while maintaining proper safety clearances.

During the basis of design phase, considerable time is spent finalizing a hierarchy of utilities. For example, gravity drains are typically the highest since liquids cannot flow uphill, process exhaust is a priority due to its large volumetric requirements, and power tends to be near the bottom due to the flexibility of routing cables. Refer to Table 18.5 for specifics from some wafer fab projects, though note that each project generates its own utility matrix.

Table 18.5
Typical Fab Utility Matrix

Service Type	Service	Label	SEMI E6-0303 Category	Supply Temperature, °F (°C)	Supply Pressure, psi (kPa)	Return Pressure, psi (kPa)	Filtration (micron)	Point of Connection (POC) Material
Water service	Fire protection	FP	500	N/A	125 (861.875)	N/A	N/A	Carbon steel
Water service	Safety shower water	SSW	500	>50 (>10)	80 (551.6)	N/A	N/A	Copper, ASTM B88, Type L
Water service	Chilled water	CHW	500	42 (5.5)	50 (344.75)	N/A	N/A	Copper, ASTM B88, Type L
Water service	Glycol chilled water	GCHW	500	32 (0)	50 (344.75)	N/A	N/A	Copper, ASTM B88, Type L
Water service	Hot water	HW	500	180 (82.2)	50 (344.75)	N/A	N/A	ASTM A53 Grade B (A53B), seamless or ERW, Schedule 80
Water service	Process cooling water	PCW	500	65±1 (18.3)	90 (620.55)	5 (34.475)	As needed	Copper, ASTM B88, Type L
Water service	Industrial city water	ICW	500	>50 (>10)	60 (413.7)	N/A	As needed	Copper, ASTM B88, Type L
Water service	High-quality water	HQW	500	>68 (>20)	60 (413.7)	20 (137.9)	Yes	Schedule 80 PVC, ASTM D1785, Type I, Grade I, normal impact
Water service	Deionized water	DIW	500	>68 (>20)	60 (413.7)	20 (137.9)	Yes	Schedule 80 PVC, ASTM D1785, Type I, Grade I, normal impact
Water service	Hot deionized water	HDIW	500	>160 (>71)	50 (344.75)	20 (137.9)	Yes	Schedule 80 PVC, ASTM D1785, Type I, Grade I, normal impact
Water service	Ultrapure water	UPW	500	>68 (>20)	60 (413.7)	20 (137.9)	Yes	ASME B31.3, PPI, high-purity PVDF
Water service	Hot ultrapure water	HUPW	500	>160 (>71)	50 (344.75)	20 (137.9)	Yes	ASME B31.3, PPI, high-purity PVDF
Gas service	Compressed air	CAIR	800	N/A	60 (413.7)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Compressed dry air	DAIR	800	N/A	90 (620.55)	N/A	Yes	316L, ASTM A269, seamless, bright anneal
Gas service	High-pressure air	HPAIR	800	N/A	125 (861.875)	N/A	Yes	316L, ASTM A269, seamless, bright anneal
Gas service	Dry purified nitrogen	1N2	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Wet purified nitrogen	2N2	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Clean utility nitrogen	3N2	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, bright anneal

Table 18.5
Typical Fab Utility Matrix *(Continued)*

Service Type	Service	Label	SEMI E6-0303 Category	Supply Temperature, °F (°C)	Supply Pressure, psi (kPa)	Return Pressure, psi (kPa)	Filtration (micron)	Point of Connection (POC) Material
Gas service	Process nitrogen	4N2	800	N/A	90 (620.55)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Facility nitrogen	5N2	800	N/A	90 (620.55)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Oxygen	O2	800	N/A	90 (620.55)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Ultrapure oxygen	UPO2	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Argon	AR	800	N/A	90 (620.55)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Ultrapure argon	UPAR	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Welding argon	WAR	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Hydrogen	H2	800	N/A	90 (620.55)	N/A	Yes	316L, ASTM A269, seamless, bright anneal
Gas service	Ultrapure hydrogen	UPH2	800	N/A	90 (620.55)	N/A	0.003	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Helium, bulk	HE	800	N/A	90 (620.55)	N/A	Yes	Copper, ASTM B88, Type L
Gas service	Ultrapure helium, bulk	UPHE	800	N/A	90 (620.55)	N/A	Yes	316L, ASTM A269, seamless, electropolished, 10 Ra avg.
Gas service	Process vacuum	PVAC	900	N/A	–27 in. Hg (–91.4 kPa)	N/A	No	Copper, ASTM B88, Type L
Gas service	Natural gas	NG	800	N/A	90 (620.55)	N/A	Yes	ASTM A53B, seamless or ERW, Schedule 80
Gas service	Specialty gas	—	800	N/A	Site specific	N/A	Yes	Site Specific
Miscellaneous	High-pressure steam	HPS	500	>300 (>149)	100 (689.5)	N/A	N/A	ASTM A53B, seamless or ERW, Schedule 80
Miscellaneous	Low-pressure steam	LPS	500	<230 (<110)	15 (103.425)	N/A	N/A	ASTM A53B, seamless or ERW, Schedule 80
Bulk chemicals	ACT 935	ACT 935	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Ammonium hydroxide	NH4OH	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Buffered oxide etch	BOE	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Photo developer	CD-26	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450

Table 18.5
Typical Fab Utility Matrix *(Continued)*

Service Type	Service	Label	SEMI E6-0303 Category	Supply Temperature, °F (°C)	Supply Pressure, psi (kPa)	Return Pressure, psi (kPa)	Filtration (micron)	Point of Connection (POC) Material
Bulk chemicals	Edge bead remover	EBR	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Ethylene glycol	EG	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Hydrochloric acid	HCL	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Hydrofluoric acid	49% HF	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Hydrogen peroxide	H2O2	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Isopropyl alcohol	IPA	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Nitric acid	HNO3	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Neutral oxide etch	NOE	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Phosphoric acid	85% H3PO4	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Sulfuric acid	H2SO4	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Oxide slurry	OX SL	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Tungsten slurry	W SL	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Bulk chemicals	Copper slurry	CU SL	600	N/A	60 (413.7)	20 (137.9)	N/A	PFA resin Grade 440 or 450
Drains	Condensate drain	CD	700	<122 (<50)	N/A	Gravity	N/A	Copper, ASTM B88, Type L
Drains	Low-pressure condensate	LPC	700	<200 (<93)	N/A	<10 (<68.9)	N/A	ASTM A53B, seamless or ERW, Schedule 80
Drains	Industrial waste	IW	700	<122 (<50)	N/A	Gravity	N/A	Type II copolymer pigmented PP pipe
Drains	Fluoride waste	ACDF	700	<122 (<50)	N/A	Gravity	N/A	Type II copolymer pigmented PP pipe
Drains	Sulfuric drain	ACDS	700	<122 (<50)	N/A	Gravity	N/A	Virgin, unpigmented PVDF pipe
Drains	Mixed acid	ACDM	700	<122 (<50)	N/A	Gravity	N/A	Type II copolymer pigmented PP pipe
Drains	Mixed solvent	SOLM	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40

Table 18.5
Typical Fab Utility Matrix *(Continued)*

Service Type	Service	Label	SEMI E6-0303 Category	Supply Temperature, °F (°C)	Supply Pressure, psi (kPa)	Return Pressure, psi (kPa)	Filtration (micron)	Point of Connection (POC) Material
Drains	Glycol-based solvent	SOLG	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Drains	Solvent NMP	SOLN	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Drains	IPA drain	SOLA	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Drains	Rinse reclaim	RR	700	<122 (<50)	N/A	Gravity	N/A	Type II copolymer pigmented PP pipe
Drains	Slurry waste, oxide	SW1	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Drains	Slurry waste, tungsten	SW2	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Drains	Slurry waste, copper	SW3	700	<122 (<50)	N/A	Gravity	N/A	ASTM A106B, seamless or ERW, Schedule 40
Exhaust	Scrubbed exhaust	PES	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	FM Global-approved FRP ductwork, PFA lined SS, Schedule 40 PVC, or PP ductwork
Exhaust	Heat exhaust	PEH	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	GS-90 galvanized steel, minimum 20 gauge
Exhaust	VOC exhaust	PEV	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	Welded GS-90 galvanized steel, minimum 20 gauge
Exhaust	Ammonia exhaust	PEA	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	FM Global-approved FRP ductwork, PFA lined SS, Schedule 40 PVC, or PP ductwork
Exhaust	Particle exhaust	PE	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	GS-90 galvanized steel, minimum 20 gauge
Exhaust	Pyrophoric exhaust	PEP	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	Welded GS-90 galvanized steel or 304 SS, minimum 16 gauge
Exhaust	PFC exhaust	PPE	1000	<122 (<50)	–2.5 in. w.c. (–622 Pa)	N/A	N/A	GS-90 galvanized steel, minimum 20 gauge

Notes:
ERW = electric resistance welding
FRP = fiber-reinforced plastic
IPA = isopropyl alcohol
NMP = N-methyl-2-pyrrolidone
PFA = perfluoroalkoxy alkane
PFC = perfluorochemical
ph = phase
PP = polypropylene
PPI = Plastics Pipe Institute
PVC = polyvinyl chloride
PVDF = polyvinylidene fluoride
SS = stainless steel
UPS = uninterruptible power supply
VOC = volatile organic compound
w = wire

Considering the most common three-level fab or 3+1 fab (three levels and a raised-floor plenum), there are two air management concepts: fabs with common process-level and subfab air paths and fabs with separated process-level and subfab air paths. There may be several variations, but in general these are the two fundamental concepts.

Wafer fab cleanliness requirements have changed as the technology has changed (see Table 18.3). The International Technology Roadmap for Semiconductors (ITRS) (ITRS 2015b) currently recommends ISO Class 6 where operators are present and possibly ISO Class 7 in the future, though this practice is not uniformly adopted by all fab owners. ISO Class 6 does not necessarily warrant unidirectional airflow to support the cleanliness requirement. The fact is, wafer fabs continue to support unidirectional airflow because it makes sense in light of the multilevel layout of their facilities. Having air move in the same direction allows the spaces themselves to become transport conveyances. Therefore, cleanliness class does not always dictate classical unidirectional/nonunidirectional air management paths.

Options for process area air management with separate subfab airflow are as follows (see Figure 18.15):

- 100% unidirectional downflow
- Unidirectional downflow for operator and wafer exposed areas, through the raised floor and return air upflow in service chases

18.12 PROCESS AREA AIR MANAGEMENT

18.12.1 PERFORMANCE CHARACTERISTICS

18.12.1.1 Air Velocity Uniformity

A uniform discharge velocity from ceiling FFUs or HEPA or ULPA filters is desired to enhance the ability for good parallel airflow and to ensure similar air distribution around the process tools. Most semiconductor wafer fabs measure the air velocity at several elevations within the cleanroom: 6 in. (15 cm) below the face of the filter as a check of the uniformity of the filter construction and in conjunction with the filter leak scanning, below any AMHS equipment tracks, and at nominal work surface heights of 30 to 36 in. (76 to 90 cm) above the raised floor. The acceptance criteria for air velocity uniformity vary by company and the assessment of the risk of contamination to the wafers. Areas where wafers are to be exposed to the cleanroom airflow will normally have higher acceptance criteria (e.g., ±5 ft/min [±0.025 m/s]) at the filter face).

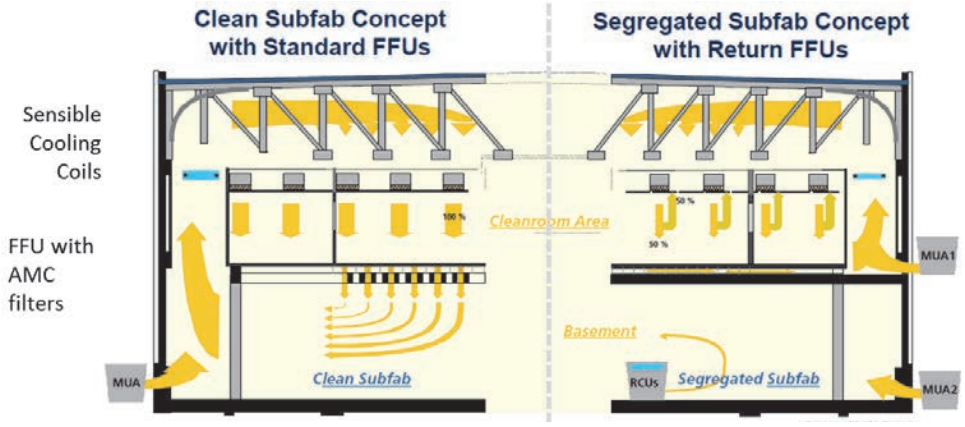


Figure 18.15 Subfab Airflow Options

(Courtesy M+W Group [2015])

18.12.1.2 Airstream Parallelism

As discussed in Part 1 of this Guide, unidirectional air management results in nominally parallel airstreams. Parallelism and velocity uniformity tend to go hand in hand. Fabs try to maintain parallel airstreams, but with the process area floor being covered with process equipment, sometimes 50% of the floor area is blocked to airflow and the ability to maintain good parallel airflow from ceiling to floor is diminished. Areas where wafer exposure is high, such as metrology areas, may seek to have very tight acceptance criteria (e.g., <14° to 18° deviation from vertical).

18.12.2 PROCESS EQUIPMENT IMPACT TO CLEANROOM AIRFLOW

Cleanroom designers have little if any input into the type of process equipment selected for the semiconductor wafer fab. During the basis of design phase, designers and fab owners attempt to identify critical tool criteria to ensure the fab can accommodate the requirements.

Fab process equipment suppliers are not cleanroom designers *per se*, but they are aware of how cleanrooms are designed and the potential risks to the products they are processing. Two challenges to the cleanroom as a result of the processing equipment are hot surfaces and local environmental enclosures.

Many of the process tools have exposed hot surfaces with surface temperatures greater than 120°F (50°C) and some hotter than 210°F (100°C) (see Figure 18.16). When contacting the relatively cool (70°F [<20°C]) supply airflow, these hot surfaces may result in a negative buoyancy effect and actually produce a reverse airflow condition.

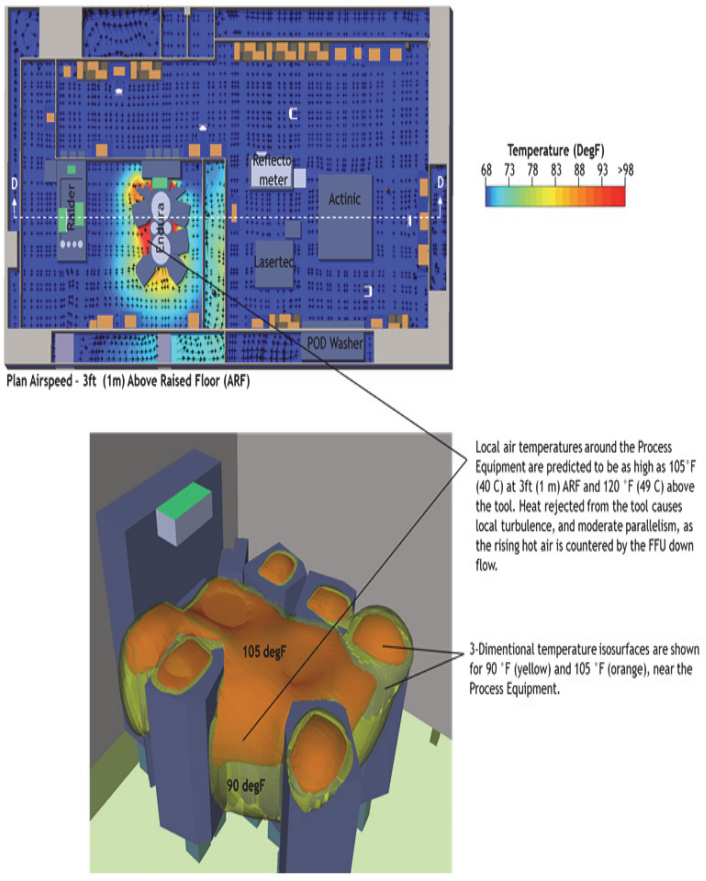
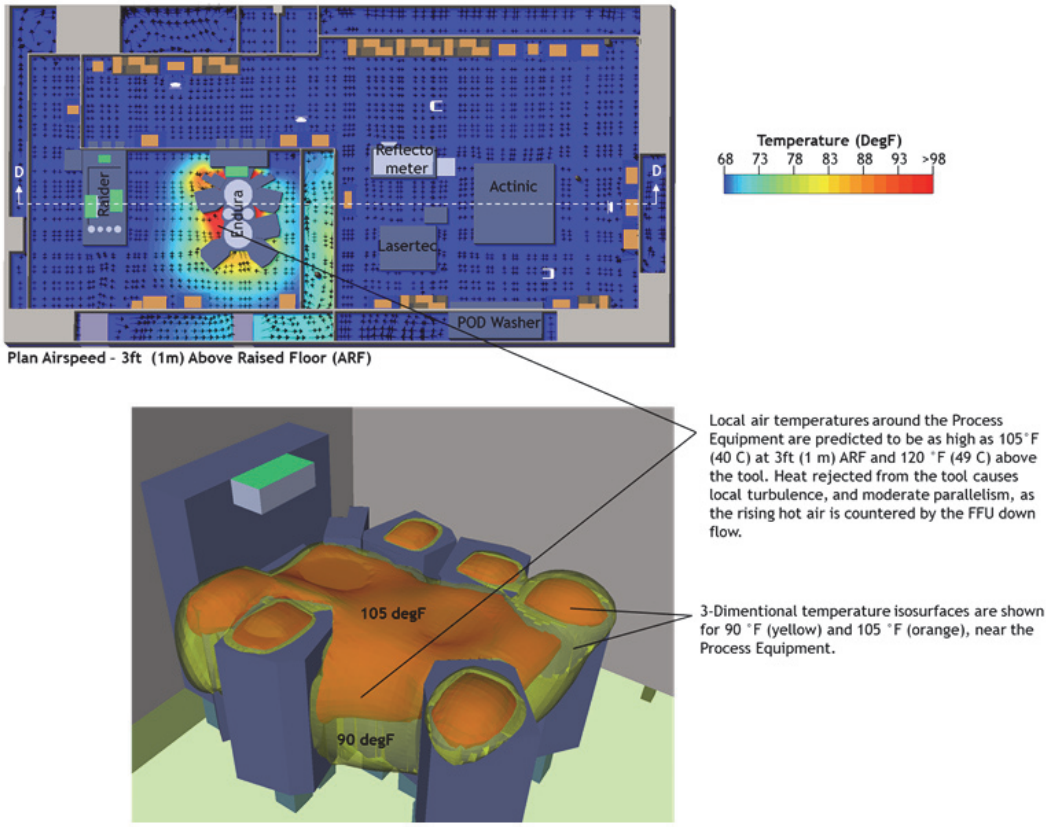


Figure 18.16 Infrared Image of Hot Tool Surfaces

Figure 18.17 CFD Analysis of Hot Tool Surfaces



Many of the tools within the process area contain their own wafer-level containment and environmental enclosures. With the AMHS delivering wafers in enclosed pods (e.g., FOUPs) to the tool factory interface (FI) module, the wafers are rarely exposed to the actual cleanroom environment. These environmental enclosures many times have their own FFUs and/or HEPA or ULPA filters where cleanroom air may be taken into the tool and then discharged below the raised floor or exhausted back into the cleanroom.

Hot surfaces and local enclosures are disruptions to the airstream parallelism in the cleanroom. The impact or risk to the product from these disruptions must be taken into account by semiconductor wafer fab designers or owners. The advent of CFD modeling including the ability to take into account surface temperatures and local environmental enclosures can help identify hot spots or areas where significant deviation to expected performance is identified and can be mitigated (see Figure 18.17).

18.13 RAISED-FLOOR AIR PLENUM AIR MANAGEMENT

As the air leaves the process area it enters the raised-floor return air plenum space or flows directly into the subfab space (i.e., open waffle floor). For wafer fabs using raised floors, the cleanroom air may be directed horizontally to a return air chase, enter an adjacent process equipment chase, or enter the subfab (i.e., open waffle). Cleanroom air that is recirculated through an equipment chase or a support chase will be mixed with the makeup air in the return loop. Adiabatic mixing is desired, and the mixing point needs to be evaluated as part of the air management plan.

The pros and cons of open versus closed waffle floors include the following:

- Pros
  - Utility distribution from the subfab to the process level does not need as much coordination of penetrations through a closed waffle (i.e., pop-out management).
  - The subfab may use cleanroom air to achieve some cleanliness level.
  - The subfab heat load is handled by the same cleanroom air.
  - Allocation of makeup air is not as complicated when process exhaust may be spread between the subfab and the process level.
  - Below-raised-floor smoke detection may not be needed, subject to the authority having jurisdiction (AHJ) and insurance underwriter approval.
  - Below-raised-floor fire protection may not be needed, subject to the AHJ and insurance underwriter approval.
- Cons
  - Open waffles may require more costly concrete casting to overcome vibration and seismic requirements.
  - Process-level equipment tool supports must span openings in the waffle.
  - Raised-floor understructures must span openings in the waffle.
  - Hazardous materials may spill into subfab from the process level.
  - Contamination sources in the subfab have direct access to the process level.
  - The closed waffle is a form of secondary containment to the process level equipment containing hazardous materials.

18.14 SUBFAB AIR MANAGEMENT

All wafer fabs include extensive subfab spaces where a significant amount of support equipment is maintained. Figure 8.4 shows a person in a cleanroom suit working in a subfab. Closed and open waffle subfabs are normally designated as clean or dirty depending on the types of tools they contain. The use of both a clean subfab and a dirty subfab is now quite common. There are added complexities for the utility distributed between the various subfabs and the process level.

In general, subfabs that are dirty use large central station air handlers and/or fan coils. Clean subfabs are generally ISO Classes 7–9 (ISO 2015) but are not certified nor are any normal cleanroom performance factors on air movement included. The cleanliness level dictates the clean protocol practices. There are not criteria for air change rates other than the necessary air change needed to remove the subfab heat.

Clean subfabs allow the clean air from the process area to flow directly into the subfab when using an open waffle floor system, or they install HEPA filters into air handlers serving the clean subfab. The air management concept of a clean subfab is rarely used unless there is good justification for maintaining a cleanliness class in the subfab space, such as in photolithography subfab areas where subfab equipment must also be protected from contamination.

Risks from contamination of subfab equipment to the process area cleanroom air or risks of hazardous materials falling from the process area into the subfab have limited the open waffle design.

Subfabs may contain the majority of the heat load depending on the location of process vacuum pumps; therefore, a large amount of cooling air is needed in the subfab.

Subfabs are typically considered part of the multilevel H occupancy (see Section 18.4) and are required to provide the minimum ventilation of 1 cfm/ft^2 (18.3 m^3/h·m^2). Provid-

ing a separate source of ventilation air (versus using the air from the process area) may also be factored into the air management decision.

When subfab air is separated from process-level air, the process of identifying process exhaust sources becomes more of a challenge. If the main frame of a tool is on the process level but its vacuum pumps are in an isolated subfab, where is the exhaust from the process main frame or the vacuum pump taken? The source of the gas to be evacuated may go through the main frame into the subfab and therefore the makeup air is needed in the process level, but if there is a gas cabinet in the subfab connecting gas lines to the main frame, the process exhaust to the cabinet does not pass through the process level and all of the makeup air requirements are in the subfab.

18.15 PRIMARY PROCESS AREA AIRFLOW

18.15.1 FILTER CONFIGURATIONS

Particle control in semiconductor wafer fabs is managed by minimizing the introduction of particles from outside of the cleanroom and transporting particles generated within the cleanroom away from the wafer or manufacturing materials (i.e., minimizing both external and internal sources of particles). Continuous particle monitoring is recommended for those process areas where wafers may be exposed to external or internal particle sources.

Figure 18.18 shows the typical filtration sequence of (1) makeup, (2) process area cleanroom ceiling filters, and (3) specific manufacturing process equipment filtration. Makeup filtration is discussed in Section 18.10.1.2. Process area cleanroom filtration is integrated into the cleanroom ceiling FFUs. Ceiling-integrated FFUs may contain prefilters prior to the HEPA or ULPA filtration media. They may also include AMC filters, though the high cost of AMC filters may warrant careful examination of the cost benefit of these filters. Process area cleanroom filtration involves the use of HEPA or ULPA filters with ratings of ISO 50U–60U (ISO 2011) or MERV 18–20 (ASHRAE 2017)—basically 99.999% to 99.9999% removal efficiency at 0.12 μm particle sizes. Polytetrafluoroethylene (PTFE) media HEPA and ULPA filters have gained some acceptance, though their higher costs warrant their application only where necessary to avoid the more traditional boron silicate glass media filters.

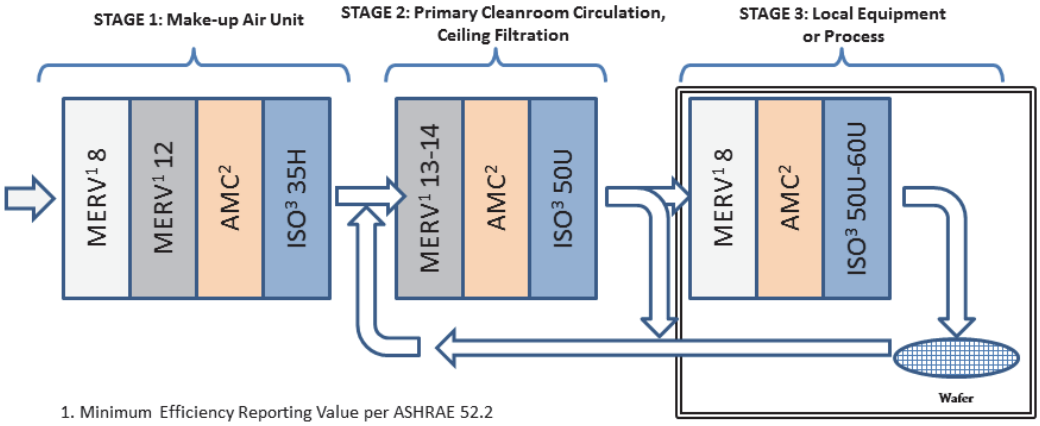


Figure 18.18 Typical Filtration Train—Outdoor Air to Wafer

1. Minimum Efficiency Reporting Value per ASHRAE 52.2
2. Airborne Molecular Contamination chemical filter.
3. Classification per ISO 29463, *High-efficiency filters and filter media for removing particles in air*

The final stage of filtration occurs at the manufacturing process equipment, as this is last barrier to protect the wafer. The type of filtration is very specific to the process within the equipment, with those sensitive to AMC deploying process-specific AMC filters (see Section 18.7.2). Deploying AMC filtration only where needed can help reduce the overall filtration costs.

18.16 PRESSURE CONTROL

Pressure control for wafer fab cleanrooms in general deploys a cascading pressure control scheme where the highest positive pressure starts at the primary process area where wafers are at the highest risk for exposure and pressure reduces to adjacent spaces. Pressure balance diagrams such as that in Figure 18.19 are common during the schematic design phase. The flow percentage offset method (see Section 8.5.6 of Chapter 8) is a quite common methodology for wafer fabs. The difference between pressure zones is normally 0.02 in. w.c. (5 Pa), though flow offset rules of thumb may result in higher differential pressure. See Section 18.10 for a discussion of the makeup air volumetric control.

Pressure control for open waffles tends to be based on process area differential pressure sensors monitoring the different pressures between process area and adjacent nonclean spaces or corridors. Because the same cleanroom air enters the subfab and the subfab is on the return side of the recirculation loop, the subfab will normally be less positive compared to the process level. The location of the makeup air injection points may disrupt this approach, but makeup air is normally injected just before the recirculation fans or FFUs and it is unlikely that a subfab will be positive compared to the process area.

For closed waffle designs, the ability to control the pressure relationship between the subfab and process level involves monitoring the differential pressure between the two spaces and making sure the makeup air injected into the subfab is controlled to maintain the negative relationship.

The more complex pressure relationships are between process areas on the process level. Some process areas such as doping areas can become a significant source of contamination to other process areas. Protecting recirculation air from these spaces from entering adjacent process areas is critical. A further cascade may be necessary. The pho-

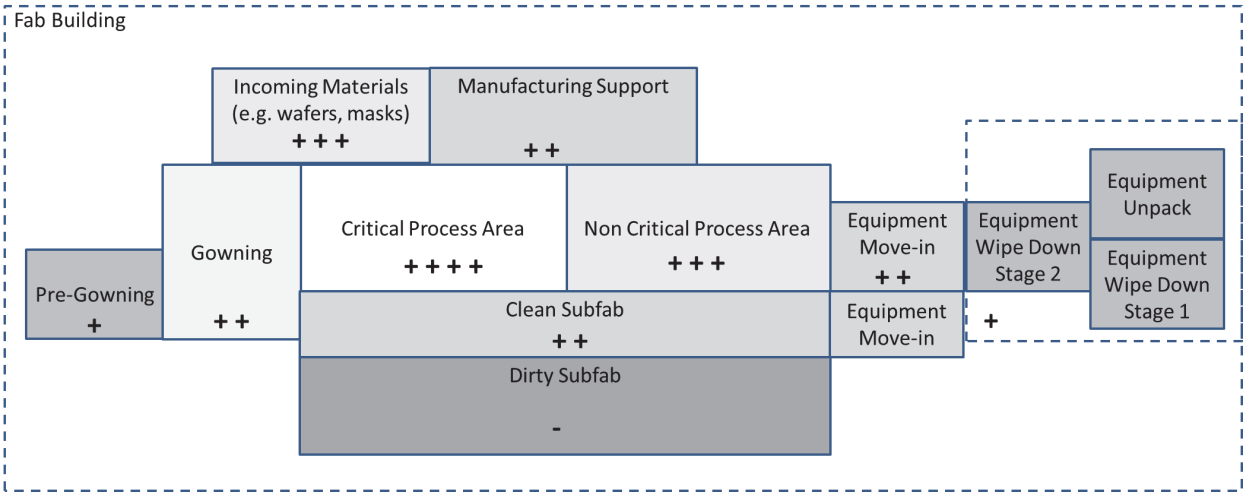


Figure 18.19
Pressure Hierarchy

tolithography area has always been considered the most critical process area, yet it is also one of the areas with a small amount of process exhaust such that there is insufficient makeup air. False exhaust (recirculated cleanroom air that is exhausted from a given pressure control zone to help maintain pressurization set points and not exhaust associated with a process or code-related exhaust requirements) is used, or a small amount of recirculated air is exhausted from the space.

18.17 TEMPERATURE AND HUMIDITY CONTROL

Table 18.4 presents the typical environmental conditions within the process area. Semiconductor wafer fabs seek precise control more than accurate control. They want repeatability of results. For dry-bulb temperature it is not the absolute value of the temperature but how precise the temperature dead band is. Therefore it is quite common to locate control loop sensors in the plenum area or just below the ceiling to measure the temperature of the supply. In the past, tools were very sensitive to temperature deviation and sensors may have been located next to the process equipment. As wafer-level environmental control becomes more important, it is more common to have tools contain their own minienvironment control. The air entering the minienvironment must be within a given tolerance and the air inside the minienvironment may be an order of magnitude more precise.

Relative humidity is controlled by maintaining precise dew-point control of the makeup air and identifying moisture leakage routes that may contaminate the space with air that is too dry or too wet.

Process areas typically have very high sensible heat ratios where very little latent cooling is needed. Cleanroom designs have typically selected sensible-only cooling coils located in the clean air recirculation paths with latent cooling taking place at the makeup air handlers. The mixing of the sensible cooling airstream and latent cooling sources can be configured three ways:

- Cleanroom recirculation through sensible coils and adiabatic mixing of makeup air. Makeup air is normally introduced before the coils to enhance the mixing, but space limits and the location of the makeup air may have makeup air introduced directly into the plenum after the coils.
- Separate sensible cooling air handlers with adiabatic mixing of makeup air followed by adiabatic mixing with cleanroom recirculation.
- Configurations where makeup air will be mixed before or after the coil.

18.18 ROOM AIR CHANGE RATE AND AIR VELOCITY

Semiconductor wafer fab owners may relax some room cleanliness requirements depending on their risk model assumption. They may still be using ISO Class 3 to 5 cleanliness classes (ISO 2015), but they have aggressively reduced the typical air change rates and average room velocity. Table 18.6 shows current practices for air changes per hour (ACH) and velocity compared to previous practices.

Wafer fab process area room heights have increased over the years to accommodate taller process equipment and, more importantly, MHSs. The typical ceiling heights are 12–16 ft (3.7–4.9 m),[4] and when combined with the lowering of average room velocity the result is a significant decrease in ACH. With no regulatory requirement for minimum

Table 18.6 Cleanliness Class (ISO 2015) Filter Coverage and ACH Evolution

	1995	2000	2005	2010	2015	2020
Primary Process Areas	ISO Class 3	ISO Class 5	ISO Class 5	ISO Class 6	ISO Class 6	ISO Class 6
Wafer Level Environment	N/A	ISO Class 3	ISO Class 1	ISO Class 1	ISO Class 1	ISO Class 1
Typical Filter Coverage (% of Ceiling)	100%	80% to 100%	60% to 100%	50% to 80%	40% to 75%	40% to 75%
Nominal Average Room Air Velocity, fpm (m/s)	90 (0.45)	70 (0.35)	60 (0.3)	60 (0.3)	50 (0.25)	50 (0.25)
Typical ACH, 10 ft (3 m) Ceiling Height	540	420	360	360	300	300
Typical ACH, 12 ft (3.7 m) Ceiling Height	450	350	300	300	250	250
Typical ACH, 16 ft (5 m) Ceiling Height	338	263	225	225	188	188

ACH, the decreases in ACH for fabs is being driven by comprehensive review of contamination risk versus cost reduction. Reducing room filter coverage and average room velocity impacts cleanroom construction costs and operating costs. Operating cost savings can be 10–20 W/ft^2 (100–200 W/m^2) (range based on 1.3–2.0 in. w.c. [325–500 Pa] total pressure). There are limits to decreases in ACH, filter coverage, and average room velocity based on risk evaluation to exposed wafers, recovery time, and ability to maintain temperature control. With high internal heat loads from the process equipment, the equipment must be cooled with sufficient cleanroom ACH or by other sources, such as water-cooled process equipment.

18.18.1 CLEANROOM FAN SELECTION

The selection of process area cleanroom fans is contingent upon the process area layout and its relationship to the overall building configuration. Many fab cleanrooms were built using a large cleanroom recirculation air handler (RAH) located adjacent to the cleanroom space. This design approach tended to result in longer cleanroom recirculation air paths. The proliferation of small, compact FFUs that contain a fan and appropriate cleanroom filters has become ubiquitous for wafer fab cleanrooms. Fab operators desire high reliability, low first costs, negative pressure plenums, and low operating costs. FFU technology has developed to provide all three. With networked FFUs, cleanroom operators can monitor the performance of each FFU and remotely control them if they desire. While central station fans may have lower cost per unit of capacity, when one adds in the installation and ductwork costs, the cost advantage is minimized. Having thousands or tens of thousands of FFUs in a fab provides thousands of failure points. However, when one unit fails, only a small portion of the overall air volume is lost, and with remote monitoring the failing units can be identified and replaced. New electronically commutated (EC) motors

4. Some fab ceilings may be as high as 24 ft (7.3 m) when overhead cranes or transport systems are within the cleanroom.

provide superior efficiency over the older fractional horsepower split capacitor or shaded pole type motors. EC motors are the current motor choice of fabs deploying FFUs. EC motors are typically at a premium cost, but the energy savings both in terms of the motor power and the reduced heat load provide a very significant cost-saving opportunity.

Fab facility teams need to perform maintenance and repair on FFUs without significant interruptions to the process area. As mentioned, an FFU contains a small motor; the ability to replace a failed motor is important. Accessibility to the FFU can be from the cleanroom side or from above the cleanroom. The maintainability of the equipment versus the cost to create a work space above the cleanroom must be evaluated.

18.18.2 PROCESS AREA CEILING PLENUMS

The ceiling plenum area is designed to contain and convey the cleanroom air into the process space. Plenums may be negative pressure or positive pressure with respect to the process area. Their materials of construction may be sheet metal (normally aluminum or steel), galvanized or epoxy coated, from double-wall metal honeycomb panels, or sheet rock (sealed and treated to avoid particle shedding). The selection of the materials of construction should take into account the contamination control scheme, fire ratings, constructability, flexibility to changes, and cost.

Some designers have begun using the building structural walls and roof to provide the containment area. When using FFUs, the plenum will be negative pressure compared to the process area and the outdoors, while for pressurized plenums the space is positive to the process area and the outdoors. The decision to have a fabricated plenum or use the building structure and negative pressure or positive pressure must be part of the overall contamination control scheme.

Negative plenums ensure all of the air will go through the FFUs and their filtration system. Positive-pressure plenums must perform a more thorough leak check between the FFU and its ceiling support system. Positive-pressure systems tend to use a gelatin seal between the edge of the filter and the ceiling track.

For negative-pressure plenums, FFUs are typically sealed with a gasket material, though gelatin seals are sometimes used. Since the air going through the plenum is intended to have 100% go through the filters, any exfiltration in a positive plenum is the same as exhaust from the process space, and this leakage must be accounted for by the makeup air and can be viewed as an energy loss.

Positive-pressure plenums use the differential static pressure of the plenum to the process area to force air through the ceiling filters. If the ceiling filters are not sealed correctly to the ceiling system, some air may bypass the filter and become a source of contamination to the process area.

The advent of FFUs and negative-pressure plenums has helped designers and engineers overcome the faults of the positive-pressure design, but they do introduce their own risks of contamination when using the building structure as the walls of the plenum. The joints of the roof and walls must be sealed to avoid leakage of unconditioned outdoor air. A metal plenum enclosure separated from the outside wall surfaces will minimize such infiltration.

In lieu of a pressurized plenum (negative or positive), ducted HEPA or ULPA filters may be used on smaller fabs, but the large fabs (with process areas larger than 100,000 ft^2 [10,000 m^2]) that are being constructed rarely use ducted filters due to their higher capital and operating costs. Ducted HEPA or ULPA filters do allow for some additional segregation of air zones, which may be beneficial in avoiding contamination from one process area to another, but as more and more wafer-level containment is used there is less depen-

dency on cleanroom-level containment. If ducted HEPA or ULPA filters are used, designers must factor in the higher pressure losses in the fan selection.

The ceiling system in a wafer fab is not just for supporting the FFUs or HEPA or ULPA filters. AMHSs are now fully integrated into cleanroom systems. Ceiling systems must support wafer transport systems as well as lighting and filtration (see Section 18.6).

18.19 COOLING AND HEATING LOADS

Heat loads in wafer fabs can be quite high, especially for open waffle designs where the cleanroom air is used to cool both process-level equipment and subfab equipment. For example, new extreme ultraviolet (EUV) photolithography tools may require 1 MW per tool when considering all of the needed support equipment. The densification of tools means there will be higher power densities in the fabs.

Fab tool suppliers are aware of the impact of higher tool heat loads and have been redesigning their tools to provide more cooling via process cooling water (PCW) and less via the cleanroom environment. Tool sets today are cooled 50% via PCW.

If a cleanroom designer has a list of proposed manufacturing equipment, data sheets from SEMI E6 and SEMI E51 (SEMI 2003, 2000) provide process equipment manufacturers' data of the power consumption of their equipment, including the quantity of power expected to be transferred to the clean HVAC. If the manufacturing equipment list is unknown, designers can use historical data for similar wafer fabs.

18.20 UTILITIES

Utilities serving a wafer fab are normally divided by those that touch the wafer, those that are supplied to the process equipment, and those that serve facilities systems (see Figure 18.20). Utility management is also divided into gravity based utilities (e.g., drains)—pressurized between 0 and 15 psig (0 and 100 kPa [gage]), above 15 psig (100 kPa [gage]), and above 150 psig (1000 kPa [gage])—and vacuum based utilities—pressurized between 0 to –200 in. w.c (0 to –50 kPa), –200 to –400 in. w.c. (–50 to –100 kPa), and greater than –400 in w.c. (–100 kPa).[5]

18.21 PROCESS EXHAUST

Exhaust systems in wafer fabs are used to remove hazardous effluents from the manufacturing and support spaces for protection of the workers and the environment. Exhaust system design criteria follow building codes, governmental pollution regulations, insurance underwriter requirements, industrial hygiene requirements, and owner safety and environmental practices that are not included in other requirements. Due to the role that exhaust can have on makeup air requirements, exhaust systems are also part of an overall capital and operating cost control strategy. The need to mitigate or eliminate fugitive emissions from exhaust systems is also part of a comprehensive contamination control strategy.

There are typically three to five central exhaust systems and numerous local exhaust systems all based on the fundamental chemical composition of the exhaust and best practices for abating the effluent.

5. The division points are somewhat arbitrary and subject to local codes and pressure vessel ratings.

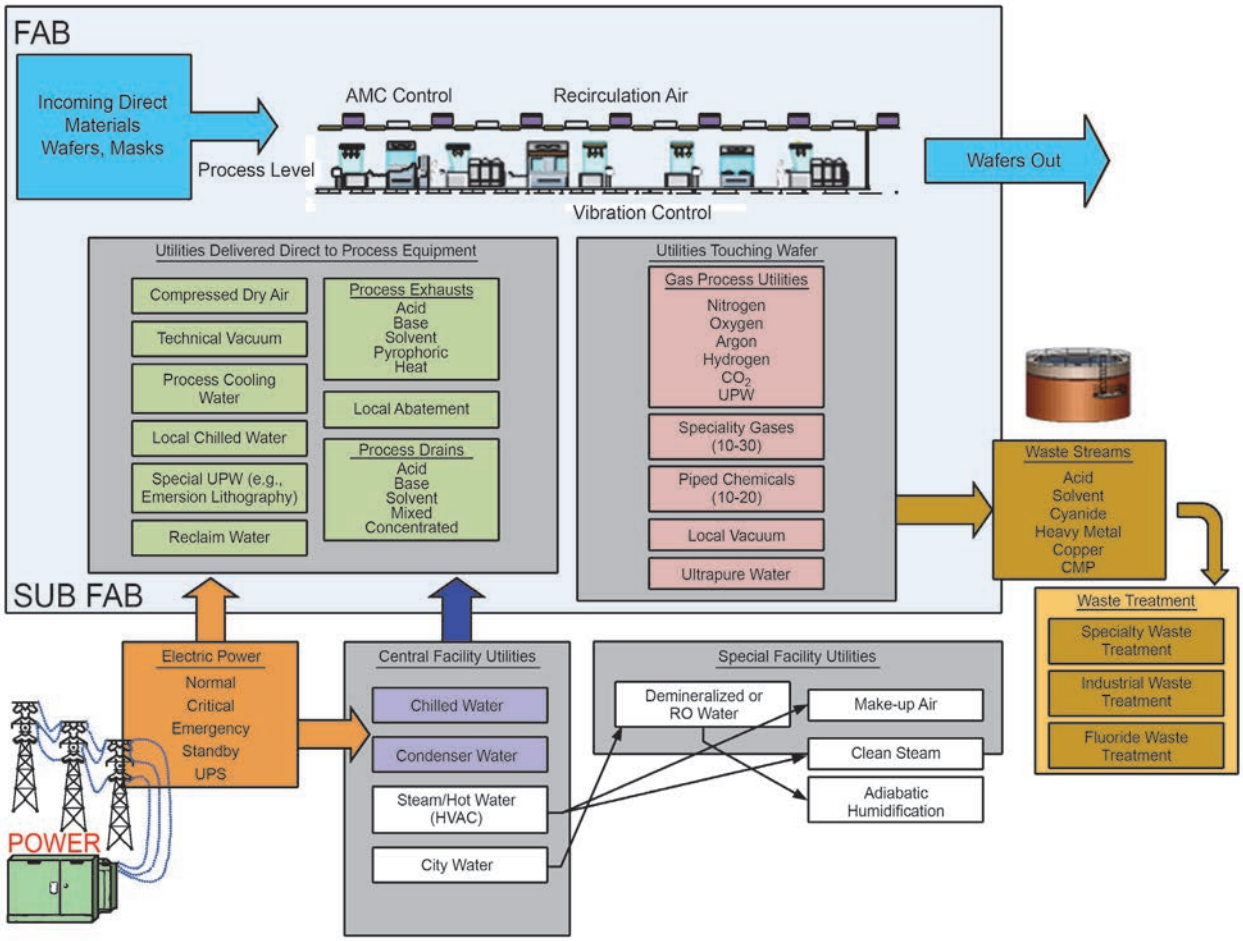


Figure 18.20
Fab Utility and Material Schematic

18.21.1 NONABATED EXHAUST

Nonabated exhaust systems include smoke exhaust and any exhaust required by building, fire, and mechanical codes. Generally the large amount of process exhaust meets all of the minimum requirements of the code. Smoke exhaust is not always mandated by codes but rather by the insurance underwriters due to the large maximum foreseeable loss that can occur in many fabs.

The major nonabated exhaust streams are process equipment heat exhaust, recirculated exhaust, and "false exhaust," which is described in Section 18.16. False exhaust and recirculated exhaust are basically the same exhaust, though the former is discharged from the process equipment while the latter is part of the facility systems. Many heat exhaust streams are also recirculated depending upon their heat content and the possibility that the exhaust may contain hazardous substances. Implant exhaust from the magnet and pump area is normally just heat from the electronics and the vacuum pumps. Many fab operators recirculate this exhaust back into the cleanroom airstream or into the subfab. Some fab operators, though, feel there is a risk of fugitive emissions from the vacuum pumps or source gas cabinets within the tool and route the exhaust either into a scrubbed exhaust system or through a chemical adsorption system and then into the subfab or cleanroom air path.

18.21.2 ABATED EXHAUST

Process exhaust that must be abated can have its abated device at the source of the process effluent (i.e., a local abatement device) or the exhaust may be ducted to a central abatement exhaust system that serves the entire process area or fab. These exhaust streams are physically separated by their abatement process and/or by their chemical species within the exhaust.

More and more process equipment is configured with its own process-specific (local) exhaust system connected to the discharge of equipment vacuum pumps, tool exhaust fans, or gas cabinets. Local abatement technologies include wet scrubbing, incineration, and dry chemical adsorption. A combination of the three may also be used (e.g., wet/burn). The discharge of these systems are in turn connected to one of the fab's central exhaust systems.

There are some abated systems that are routed directly to the outdoors due to their high risk for fire; these include hydrogen and pyrophoric gases (pyrophoric gases, such as silanes, which are a nonmetallic hydride, can ignite immediately upon exposure to air). The fire hazard of these gases may warrant a dedicated exhaust conveyance.

Other effluents, which tend to fall into the categories of acids, bases, and solvents, are conveyed to abatement equipment designed to handle their chemical content. Where local laws do not require abatement, the exhaust is separated by the chemical content, where the mixing of different species may produce an unsafe effluent, such as a water-reactive chemical mixing with exhaust from wet hoods or mixing of acids and bases such that a precipitate may be formed.

18.21.3 EXHAUST SYSTEM CONSTRUCTION MATERIALS

Construction materials for exhaust are also prescribed by building, fire, and mechanical codes where ductwork must be installed within internal fire protection if constructed of materials that do not meet flammability and smoke generation of UL 723 (UL 2008) (e.g., FM Global-approved phenolic resin fiber-reinforced plastic [FRP]). Fiberglass, unless fabricated with approved fire-retardant material, must contain fire sprinklers inside the duct. Exposing fire sprinklers to some of effluents may not be practical unless they are wax coated to protect them from the corrosive effluents. To avoid the need for internal fire protection, the use of metallic ducts with an internal chemical resistance lining such as PTFE or ethylene chlorotrifluoroethylene (ECTFE) have become commonplace.

18.21.4 EXHAUST DESIGN CRITERIA

Design criteria include estimates for exhaust loading for each process area and process exhaust type. For many years, process exhaust in wafer fabs was 50% to 75% acidic, 10% to 15% heat, 10% to 15% base, and 5% to 10% solvent. With fewer and fewer wet processes and more local abatement, some factories have used only stainless steel lined exhaust ductwork. Total exhaust requirements have also decreased from 6 to 3 cfm/ft^2 (109 to 54.8 m^3/h·m^2).

18.22 OTHER PROCESS UTILITIES

Process exhaust was described in sufficient detail in the previous section due to its role in environmental control and the dependency of makeup air on process exhaust. Semiconductor wafer fabs also include dozens of other process utilities that are somewhat specific to the type of products being made and often very company specific. However, a typical list of common utilities found in almost all wafer fabs includes deionized/ultra-

pure water (UPW), clean dry compressed air, process vacuum, cleaning vacuum, PCW, process drains and exhaust systems including distribution mains, but not including the distribution to or within specific occupancy rooms, and bulk gas piping.

Bulk gases are typically gases used by both the process tools and other support systems where their consumption is quite large and whose generation is via on-site generators or very large cryogenic storage vessels. Bulk gases typically are nitrogen, oxygen, and hydrogen and occasionally may include helium, argon, and carbon dioxide. See Table 18.5 for a bulk gas list.

Many process utility systems come in various quality levels such that a typical wafer fab may have in excess of 40–50 unique process systems. Process system distribution includes mains in the subfab or interstitial space but not the lateral distribution. Due to the complex nature of the process system distribution, a significant amount of analysis is warranted during the planning phases of the project.

Process utility systems that are large and bulky, such as exhaust, and those requiring gravity flow, such as drains, take priority over pressurized systems and electrical power. Most wafer fabs divide utility distribution into three-dimensional utility zones and require very careful coordination where utilities cross each other (refer to Figure 18.4). Process utility systems are also segregated by those that touch the product or wafer (e.g., UPW, process gases and chemicals), those that connect to a process tool but do not touch the wafer (e.g., PCW), and those that are needed to support equipment other than process equipment (e.g., cooling water to cleanroom HVAC).

Ultrapure or deionized water is used for wafer cleaning and dilution in certain wet processes. UPW is normally room temperature (68°F to 77°F [20°C to 25°C]) or hot (185°F to 200°F [85°C to 95°C]). Reclaim and/or recycle of waste UPW (little to no chemical contaminants) is commonplace.

Electrical distribution is from a high-voltage source to all equipment included in the base building and to distribution panels in the subfab. Electrical systems are designed by primary voltage: utility voltage, >15 kV; primary site distribution voltage, <15 kV and > 5 kV; high-voltage motors, 5 kV; and medium-voltage distribution, < 600 V and > 100 V. Power is also divided by its criticality, into normal power, power for life safety systems, and power for critical processes. There may be multiple distribution levels of each variety covering uninterruptible power, emergency generator backed power, standby generator backed power, and other forms of power, allowing for the mitigation of detrimental power quality events.

Maintaining power for life safety systems is specified by code authorities, while selection of other power distribution levels is decided by local power quality conditions. The loss of power to key manufacturing equipment can be very disruptive; therefore, wafer fab designers examine the various power distribution schemes to identify areas where voltage sags and spikes might need some mitigation. Process tool designers are also expected to provide tools that are capable of handling some voltage sags and spikes (see SEMI F47-0706 [SEMI 2006] for power for process tools).

Industrial waste, waste collection, and sanitary waste treatment systems are heavily segregated to avoid adverse chemical reactions and to enhance opportunities for reclaim and recycle of the numerous waste streams. Typical segregation is acids, bases, solvents, heavy metals, and chemical mechanical polishing, among others.

There are also very specialized process utility systems that may change as the fab's product changes or as the technology used in the process changes (such as specialty gases and chemicals, point-of-use (POU) waste collection, deep ultraviolet (DUV) lithography, UPW, etc.).

Specialty gases are gases normally associated with direct process gases, meaning the gases are used in the manufacturing process and are very process specific. Specialty gases are normally distributed in cylinders whose volumes vary from <0.018 to greater than 7 ft^3 (<0.5 to greater than 200 L) depending upon the process requirements. Life safety codes determine whether the location is outside the fab space (e.g., a gas bunker) or within the subfab area. These gas systems may require life safety gas detection, which is another type of utility.

Liquid chemicals are more likely to be transported by pressurized piping rather than delivered in gallon- or liter-sized containers. Both the chemical dispense system and its distribution piping are treated as a utility to the process equipment.

Whatever the need of a manufacturing process, fab designers will create specific utility designs and specifications to meet the manufacturing process needs. See Table 18.5 for the large number of utilities that may exist in a wafer fab.

18.23 ARCHITECTURAL COMPONENTS

Architectural finishes within a semiconductor wafer fab are part of the contamination control strategy, including cleanroom walls, floors, ceiling, lighting, coatings, glazing, etc. This section describes physical and performance aspects of the architectural systems.

18.23.1 CEILING SYSTEM

As previously discussed, a cleanroom ceiling system contains the primary process area filtration. As such, its design must be capable of handling the integrated filters plus other support systems such as the AMHS. Two types of ceiling systems are as follows:

- **Heavy-Duty Cleanroom Ceiling Grid with Support for AMHS**
  - Ceilings should consist of a nominal 2 × 4, 3 × 3, or 4 × 4 ft (600 × 1200, 1000 × 1000, or 1200 × 1200 mm) extruded aluminum ceiling grid. The ceiling grid may be channel cross section for gelatin-sealed systems or a T shape for gasket-sealed filters. The ceiling grid should have surface-mounted lights with teardrop lenses or recessed lighting, have sprinkler piping with flush heads, and be prewired for an ionization system.
  - The ceiling grid will accept HEPA or ULPA filters and blank panels. The grid system should also accept FFUs that match the grid spacing.
  - All metallic members must be specified with a corrosion-resistant material or have a corrosion-resistant finish.
  - The grid is to be capable of supporting overhead wafer-handling systems and tool enclosures or air curtains with a maximum distributed loading of 100 lb/ft (1460 N/m) of grid and a maximum point load of 750 ob (300 kg). Any slots in the grid for this purpose should be sealed for contamination control.
  - Filter-to-grid sealing (a positive plenum) should be accomplished with silicon gel or an approved alternative gel.
- **Standard-Duty Cleanroom Ceiling Grid**
  - Same requirements as heavy duty but without mounting points for AMHS.

18.23.2 LIGHT FIXTURES

Lighting systems in fabs are generally energy-efficient florescent lamps, though light-emitting diode (LED) lighting is beginning to be used. Lighting in photolithography areas should have sleeves that filter unwanted frequencies as defined by the process engi-

neers. Florescent ballasts may be remote mounted or accessible from the walkable areas of the plenum space.

18.23.3 WALL AND DOOR SAMPLE SPECIFICATIONS

It is important to note that the wall and door sample specifications supplied in this section are just that—samples. Other systems have proven equally viable and are accepted by owners, code officials, and insurance underwriters.

Interior fire-rated partitions and permanent perimeter fire-rated walls should be 5/8 in. (15 mm) type X gypsum board with epoxy coating. All gypsum wall surfaces within the cleanroom environment are to be clad with 1/4 in. (6 mm) aluminum cleanroom panels on studs or clips. No direct adhesion to a substrate is allowed.

Fire-rated wire glass with hollow metal frame assemblies are to be used at viewing windows in perimeter corridors. Viewing windows should be maximized within code requirements to allow for visitor viewing into the cleanroom and to allow operators to enjoy some visibility beyond the perimeter of the cleanroom.

Equipment access doors through rated corridor walls to the cleanroom should be a pair of 4 × 12 ft (1200 × 3600 mm) fire-rated hollow metal doors (providing an 8 × 12 ft [2400 × 3600 mm] clear opening). Factories using freight elevators must ensure elevator sizes and corresponding tool move-in paths have been sized for the largest expected tool sizes.

All holes cut through perimeter walls should be carefully sealed to control particle migration and air leakage. Fire stopping should be used as required to meet code at all penetrations through fire-rated walls.

Interior cleanroom walls are to be non-fire rated, modular, nonprogressive, and easily demountable. Interior cleanroom walls usually will be 1/4 and 1 7/8 in. (6 and 46 mm) aluminum honeycomb panels with static dissipative powder-coated epoxy finish. Structural members or trim pieces must be anodized aluminum or epoxy powder coated. The 1 7/8 in. (46 mm) panels should be specified to have a U-channel closure piece at all four sides of the panel.

The wall system panels should be capable of field cutting for process support piping, duct penetrations, and process tool penetration, with a minimum of dust particles. The wall system must include a means of thoroughly sealing cut edges against further particle emission. The wall system should be noncombustible, with a conductive powder-coated epoxy finish with a flame spread classification of at least Class II or better, as defined in ASTM E-84 (ASTM 2016). The cleanroom wall members should be held to within ±1/8 in. (3 mm) of true vertical. The work zone side of the wall, including glazing at framed openings, should be flush with the edge of the ceiling grid and filter.

Automatic doors should be provided for access to the work zone from the clean aisle and at other locations where appropriate. Doors should be cleanroom rated, automatic, biparting sliders with anodized aluminum frames and tempered safety glass. Hinged doors should be provided integral with the wall system. Door modules should have integral door jambs.

Glazing for cleanroom walls and doors should be 1/4 in. (6 mm) clear tempered glass (building code dependent), with the addition of tinted plastic film at glazing in the walls and doors at the perimeter of the Photolithography area.

18.23.4 RAISED-ACCESS FLOORING

Raised-access flooring in a semiconductor wafer fab cleanroom should be 2 × 2 ft (600 × 600 mm) cast aluminum alloy grate panels with a static dissipative powder-coated epoxy finish or cast aluminum perforated and solid panels with conductive vinyl cover-

ing. Panels should be supported on pedestals to maintain a uniform space between the top of the access floor and the top of the waffle slab. Pedestals should be adhered to the coated concrete waffle slab by use of an epoxy-based adhesive in seismic zones 1–2. For seismic zones 3–4, pedestals should be bolted into the waffle slab.

Slide dampers should be used to adjust cleanroom airflow, and dampers should be used to establish parallelism in unidirectional cleanrooms.

Angle bracing is required at the floor perimeter, columns, voids in the floor system, and high-traffic areas.

The floor system should be grounded for electrostatic dissipation. The surface resistivity of the floor finish should be $1 \times 10^6\ \Omega$

Welded steel panels are to be temporarily substituted for grates in designated paths for equipment move-in. As an alternative, stainless steel flat plates may be used over the aluminum floor panels during tool move-in to distribute the load properly.

Where separate air/smoke zones are required, plenum dividers of sheet aluminum should be provided from the bottom of the raised-access floor panels to the top of the waffle slab. The plenum divider system should also provide formed sheet aluminum panels in the waffle slab opening when the demising wall intersects the openings.

18.24 AIR SHOWERS

Air showers are not used in many semiconductor manufacturing facilities, though some fab owners still feel they have value. Air tunnels or pressure locks have been found to be a suitable alternative to air showers.

18.25 CONSTRUCTION PROTOCOL

Construction protocol will establish levels of protocol pertinent to the nature and schedule of construction activity. Provisions need to be made for controlled personnel access as well as a controlled delivery point for cleanroom materials and equipment to support the protocol requirements for the clean areas under construction. A detailed construction protocol procedure must be included in the master specification for any cleanroom project. Table 18.7 provides a simplified description of a common six-level construction protocol program for a semiconductor cleanroom.

18.26 CLEANROOM CERTIFICATION

A more detailed discussion of cleanroom certification is presented in Chapter 15, but in general an independent contractor will conduct the certification process for a semiconductor cleanroom. Exact testing requirements are to be based upon room requirements per fab owner specifications. Certification may include the following tests:

- Filter leak test
- Air velocity test
- Room pressurization test
- Airflow parallelism test
- Airborne particle counts
- Temperature and humidity tests
- Noise level tests
- Lighting level tests

Table 18.7 Simplified Construction Protocol

Level	Beginning Activity	Ending Activity	Other Key Construction Activities
1	Groundbreaking	Building shell is weathertight	Site work, utilities, and structural frame are complete; exterior skin and roof are in place
2	Building shell is weathertight	Clean zone boundary is complete	Fire separation walls are complete, floors are coated, structure is painted, and makeup air system is installed
3	Clean zone boundary is pressurized	Clean zone walls, floors, and ceiling grid is complete	Cleanroom is pressurized; installation of clean zone finish products and process utilities is begun
4	Clean zone walls, floors, and ceiling grid is complete	Clean zone is ready for certification	Clean zone filters or FFUs are installed, zones are tested and balanced, control system is tested, and a final super cleaning is conducted prior to certification
5	Clean zone is ready for certification	Certification is complete, clean zone is ready for tool installation	None
6	Certification is complete, clean zone is ready for tool installation	Process tools are installed	Install and qualify process tools

Table 18.8 Expected Changes in Process Equipment Footprint and Utility Consumption due to 300 to 450 mm Wafer Size Changes

(M+W Group 2015)

Tool Type	Average Change,%				
	Footprint	Utility Consumption			
		Power	UPW	PCW	Exhaust
Vertical Furnace Metrology Tools Small Vacuum Cluster Tools	+40%	+50%	N/A	+100%	+20%
Large Vacuum Cluster Tools Chemical Mechanical Planarization (CMP) Tools Implant Tools	+20%	+30%	+50%	+50%	+20%
Wet Bench Tools Litho Tracks Litho Scanners	+15%	+20%	+80%	—	+20%

18.27 NEXT-GENERATION WAFER FABS

The International Technology Roadmap for Semiconductors (ITRS) (ITRS 2015b) charts long-term technology trends, including wafer sizes. The next watershed event for semiconductor cleanrooms is the change to 450 mm wafers. There are many ramifications and precautions that fab owners must understand before they can make a decision on this new trend (see Table 18.8). Conversion to manufacturing 450 mm diameter wafers will only occur if economic advantages for the entire supply chain can be demonstrated. For previous diameter conversions, chip makers were not often concerned about the conversion's effects on wafer manufacturers or process equipment manufacturers. However, the change to 450 mm wafers might differ significantly from previous conversions because of the financial burden for wafer producers and the development costs for process equipment suppliers (ITRS 2005).

Historically, semiconductor manufacturers have migrated to larger wafer sizes to gain productivity improvements (SEMATECH 2000). Moving to a larger wafer size encompasses significant capital investment in new equipment and facilities. Several key considerations are included in this decision process:

- Merely scaling up the new facility is not a practical option.
- Considerations of moving up to 450 mm wafers must be evaluated for planned conversions of existing wafer manufacturing facilities.
- Meeting the requirements for production equipment (such requirements as vibration and air, gas, and liquid purity levels) at the POU may be more cost-effective for meeting future requirements without sacrificing flexibility or increasing facility costs.
- Evaluation of POU utility control versus subfab process controls or point-of-generation (POG) may help reduce overall instrumentation and control system costs.
- Reduction of fluid purity specifications on central supply systems with more localized purification systems help improve flexibility, enhance operating reliability, and control costs (ITRS 2015a).

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AIR CONDITIONING COMPANY

19 Cleanrooms in Pharmaceutical Facilities

19.1 GENERAL CONSIDERATIONS

19.1.1 OVERVIEW

On its campus in Indianapolis, the pharmaceutical manufacturer Eli Lilly has a poster quoting one of its earliest presidents: "the drug you take is the one not tested." What does that mean? Clearly, it means no matter how much testing is performed on a product, 100% testing is not available—the product must perform.

From the perspective of pharmaceutical cleanrooms, the objective of design teams is to design a process and facility that enable the product to perform. That is, the design team needs to design the facility, the equipment, and the operation to enable the manufacture of ethical, clean, unadulterated products. Towards that, like people in all walks of life, design teams have adopted the dictum "begin with the end in mind" from *The 7 Habits of Highly Effective People* (Covey 1989).

19.1.2 CURRENT GOOD MANUFACTURING PRACTICES (CGMPs)

Current Good Manufacturing Practice (CGMP) is part of a universal quality system covering the manufacture and testing of active pharmaceutical ingredients (APIs), diagnostics, foods, pharmaceutical products, and medical devices. CGMPs are regulations, guidelines, or advice published by a recognized body (governmental or nongovernmental) outlining minimum manufacturing, quality control, and quality assurance requirements for the preparation of drugs or medical devices. The U.S. Food and Drug Administration (FDA) defines CGMPs as providing for systems that ensure proper design, monitoring, and control of manufacturing processes and facilities. The FDA (2015) further notes:

> Adherence to the CGMP regulations assures the identity, strength, quality, and purity of drug products by requiring that manufacturers of medications adequately control manufacturing operations. This includes establishing strong quality management systems, obtaining appropriate quality raw materials, establishing robust operating procedures, detecting and investigating product quality deviations, and maintaining reliable testing laboratories. This formal system of controls at a pharmaceutical company, if adequately put into practice, helps to prevent instances of contamination, mix-ups, deviations, failures, and errors. This assures that drug products meet their quality standards.

Importantly, as universally understood, the C in CGMP stands for *current*, meaning that companies are required, by legislation, to use up-to-date technologies and systems in order to comply with these CGMP regulations.

The definition of CGMP varies slightly across the worldwide spectrum of regulatory agencies. Of significant note is the use of the term *robust* throughout these regulations. The dictionary defines *robust* as "capable of performing without failure under a wide range of conditions" and "strongly formed or constructed" (Merriam-Webster). Pharmaceutical facilities demand this robustness. Beyond this, the regulatory bodies generally have no intention toward providing instruction on facility design and operation addressing the regulations, codes, and statutes that are germane to the project. They recognize they are not the experts and expect the experts to execute the design. These regulatory bodies would, however, like to be consulted. Bringing the design to the regulatory agencies early and often generally results in a facility design that is likely to prove acceptable.

It is important to note that there is a slight but significant difference in the use of Good Manufacturing Practice (GMP) and Current Good Manufacturing Practice (CGMP). GMPs have been accepted and followed by most countries throughout the world for the past 50 years. GMPs have, in fact, become a precondition to export products in most countries worldwide. The addition and use of the *C* as a prefix to GMP is an essay, or attempt, by regulatory authorities to ensure that countries—especially manufacturers—follow the directions set by the authorities using current techniques and methodologies, not simply those used in the past.

GMP and *CGMP* are both used in this chapter, although they are not fully interchangeable, as some regulatory agencies use the term *GMP* where as others use *CGMP*. Fundamentally they mean the same thing: GMPs entailing current approaches to producing quality products. *GMP* is therefore used in this document to describe the regulatory requirements in general, and *CGMP* is used to specify *current* GMPs.

The primary elements of GMPs are to ensure the drug is safe (will not cause unwanted effects), has the identity and strength defined by the manufacturer (meets the stated efficacy of the product), and meets quality and purity characteristics (as specified by the manufacturer). Typically regulations cover manufacturing, processing, packaging, and holding of the drug and define the methods used to produce the product, the design and operation of the facility where the product is made, and the controls that are used to ensure product quality.

Failure to comply with regulations will render the drug adulterated.

Although numerous, the CGMP guidelines follow a few basic principles, with traceability and accountability often cited as the aspects of GMPs that are of most importance (GPO 2016a):

- Processes used in the manufacture of products are clearly defined and controlled, with critical processes undergoing validation to ensure consistency and specification compliance.
- Good documentation practices are used for instructions and procedures and are written clearly and unambiguously.
- Operators responsible for the manufacture of products are trained to perform and document procedures.
- Records are prepared during product manufacture that document that all the required procedural steps and instructions were taken and that the quality and quantity of the drug is as expected. These can be prepared manually or with instruments. Deviations from the records are examined and documented.

- Manufacturing records, including records of distribution, are traced and retained in a comprehensible and accessible form, enabling recall of the complete history of a batch if necessary.
- Distribution of the manufactured product minimizes risks to the quality of the products.
- There is a system available to recall a batch of drugs from sale or supply if necessary.
- Complaints regarding products are examined, and the causes of any quality defects are investigated. When necessary, measures with respect to the defective products are taken to prevent recurrence of the defects.

Of significant importance is the fact that GMP guidelines for the most part are not prescriptive instructions on how to manufacture products or how to design and construct a facility for the production of products—they are general principles that must be observed during manufacturing. When a company has elected to build or renovate a new manufacturing facility, or when it is setting up its manufacturing process and quality program, there are most often many ways in which it can fulfill GMP requirements, but it is the responsibility of the company to determine the most effective and efficient manner of doing so. With the owner it is the design team's responsibility to understand these guidelines, understand how they affect the design and operation of a process or facility, and reinforce and support these guidelines to assist the manufacturer in effectively providing the product.

Very much like the trend of building codes in their search for uniformity in codes and regulations throughout the world, the World Health Organization's (WHO) GMPs are used by the pharmaceutical industry and pharmaceutical regulators in more than 100 countries, primarily developing countries. WHO enforces similar requirements to the European Union's GMP (EU-GMP), as does the FDA's version in the United States. In the United Kingdom, the Medicines Act (1968) covers most aspects of GMP in its *Rules and Guidance for Pharmaceutical Manufacturers and Distributors* (MHRA 2017). Canada, Japan, Australia, Singapore, and others have equally highly developed and sophisticated GMP requirements.

Since the publication of *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH 2000) by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), GMPs have applied to the countries and trade groups that are signatories to ICH (the European Union, Japan, and the United States) as well as to other countries, such as Australia, Canada, and Singapore.

Within the European Union (EU), national regulatory agencies perform GMP inspections. That is, GMP inspections are performed by each country's agency. Several are noted below:

- Australia: The Therapeutic Goods Administration (TGA)
- Brazil: The Agência Nacional de Vigilância Sanitária (National Health Surveillance Agency Brazil) (ANVISA)
- China: China Food and Drug Administration (CFDA)
- Iran, India, and Pakistan: Each country's Ministry of Health
- Republic of Korea (South Korea): The Korea Food and Drug Administration (KFDA)
- South Africa: The Medicines Control Council (MCC)
- United Kingdom: Medicines and Healthcare Products Regulatory Agency (MHRA)

Other countries are governed by similar national organizations worldwide. Each inspectorate performs routine GMP inspections to make sure the country's drug products are produced safely and correctly. In addition, many countries carry out GMP compliance preapproval inspections (PAIs) before a new drug can be approved for marketing.

GMPs are part of the greater library of GxPs—a general term for "good practice" quality guidelines and regulations used in many fields, particularly the pharmaceutical, biotechnology, food, and cosmetics industries. Although quite extensive in reach, they are commonly referenced and used as guidelines in the design, construction, and operation of these facilities. Some of the GxPs include the following:

- Good Clinical Practice (GCP)
- Good Distribution Practice (GDP)
- Good Documentation Practice (GDocP)
- Good Engineering Practice (GEP)
- Good Laboratory Practice (GLP)
- Good Manufacturing Practice (GMP)

The purpose of these guidelines is to help ensure a product is safe and meets its intended use. The importance of the guidelines to the architects and engineers responsible for the design of the facilities and processes is that they clearly understand the regulations, as the facilities and processes must stand the test of time and be robust. Owners are clearly responsible for maintenance of the facilities, equipment, and processes. Both entities are bound by the regulations to help ensure the quality of the products being manufactured.

19.1.3 BRIEF COMPARISON OF FDA AND EMA

There are many country-specific GMP guidelines globally, but most, if not all, are based on either the U.S. or the European guidelines listed below.

- U.S. guidelines, enforced by the U.S. Food and Drug Administration (FDA):
  - United States *Code of Federal Regulations*, Chapter 1, Title 21, Parts 11, 210, 211, 600–680, and 820 (GPO 2016c)
  - ISO 14644, *Cleanrooms and Associated Controlled Environments* (ISO 2016)
- European guidelines, enforced by the European Medicines Agency (EMA):
  - *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use*, Volume 4 of *EudraLex—The Rules Governing Medicinal Products in the European Union* (EudraLex) (EC 2010)
    - Annex 1: Manufacture of Sterile Medicinal Products
    - Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use

The major differences between the two agencies' regulations are summarized in the following subsections. As an illustration of the differences, see Table 19.1 in Section 19.3.2 for a comparison of air cleanliness classes between the FDA and the EMA. Not only are the air cleanliness classifications different, but differences are found in, for example, the classifications of vial capping areas and gowning rooms. Their approaches to environmental monitoring differ as well.

There has been strong emphasis on and coordination of harmonizing global GMP standards among the regulatory agencies of various countries, but there are still areas that are under discussion. For example, the FDA has accepted the ISO 14644 series (ISO 2016) as the replacement for FS 209E, and the EMA has indicted that it will also be using

the ISO 14644 series, but up to this point the EU requirements are still slightly different than those in ISO 14644-1 and 14644-2. Important to the pharmaceutical community for consistency's sake, both entities agree that the definitions of room air quality in manufacturing facilities focus on the key parameters: particulate and microbial contamination.

19.1.3.1 U.S. Food and Drug Administration (FDA)

The U.S. Food and Drug Administration (FDA) is an agency within the U.S. Department of Health and Human Services that is responsible for the following (FDA 2017):

- Protecting the public health by ensuring the safety, effectiveness, and security of human and veterinary drugs, vaccines and other biological products, medical devices, our nation's food supply, cosmetics, dietary supplements, and products that give off radiation.
- Regulating tobacco products.
- Advancing the public health by helping to speed product innovations.
- Helping the public get the accurate, science-based information they need to use medicines and foods to improve their health.

FDA's responsibilities extend to the 50 United States, the District of Columbia, Puerto Rico, Guam, the Virgin Islands, American Samoa, and other U.S. territories and possessions.

FDA regulations are found within Title 21 of the *Code of Federal Regulations* (CFR) (GPO 2016c), which is itself the codification of the general and permanent rules published in the *Code of Federal Registrations* by the executive departments and agencies of the U.S. federal government. The CFR is divided into 50 titles that represent broad areas subject to federal regulation. Pertinent to pharmaceutical and biotechnology industry regulations are 21 CFR 210, Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General, and 21 CFR 211, Current Good Manufacturing Practice for Finished Pharmaceuticals (GPO 2016a).

Without going into extensive detail, these regulations are prescriptive but without definition as to how the regulations are to be carried out. For example, Section 211.42, Design and Construction Features, identifies in paragraph (a) that "Any building or buildings used in the manufacture, processing, packing, or holding of a drug product shall be of suitable size, construction and location to facilitate cleaning, maintenance, and proper operations," and in paragraph (b) it notes that

> Any such building shall have adequate space for the orderly placement of equipment and materials to prevent mixups between different components, drug product containers, closures, labeling, in-process materials, or drug products, and to prevent contamination. The flow of components, drug product containers, closures, labeling, in-process materials, and drug products through the building or buildings shall be designed to prevent contamination.

As another example, with respect to equipment construction, paragraph 211.65(a) states, "Equipment shall be constructed so that surfaces that contact components, in-process materials, or drug products shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements" (GPO 2016c).

Adequate and *suitable* are not definitive, but they set more than the tone for the direction that needs to be taken. The meaning of *adequate* and *suitable* must therefore be critically examined and determined by the owner and design team. The 21 CFR 211

regulations govern the above-cited elements plus responsibilities of the quality control unit; personnel qualifications and responsibilities; consultants; lighting; ventilation; air filtration; air heating and cooling; plumbing; sewage and refuse; washing and toilet facilities; sanitation; maintenance; equipment design, size, and location; automatic, mechanical, and electronic equipment; and filters.

The fundamental concept behind 21 CFR 210 and Subpart C, Building and Facilities, of 21 CFR 211 is to reduce or eliminate the chance of cross-contamination. Product can be contaminated with foreign substances, active ingredients from other products, or microorganisms.

19.1.3.2 European Medicines Agency (EMA)

The European Medicines Agency (EMA), formerly known as the European Agency for the Evaluation of Medicinal Products (EMEA), is a decentralized body of the European Union (EU) headquartered in London. The main responsibility of the EMA is protecting and promoting public and animal health through supervision and evaluation of medicines for human and veterinary use (EC 2017).

The EMA scientifically evaluates applications for medicinal products for European marketing authorization. It is a centralized procedure under which companies submit a single marketing authorization application (EC 2017); once granted, a centralized (or community) marketing authorization is valid in all EU member states and European Economic Area/European Free Trade Association (EEA/EFTA) states (Iceland, Liechtenstein, and Norway).

This centralized procedure must be used for approval of all medicinal products derived from biotechnology and other high-technology processes, including human medicines intended for the treatment of viral diseases, diabetes, cancer, HIV/AIDS, autoimmune and other immune dysfunctions, and neurodegenerative diseases, as well as to medicines designed for treating rare diseases and all veterinary medicines intended to be used as performance enhancers to promote the growth of or to increase the yields from treated animals (EC 2017).

Medicinal products not falling under the above-mentioned categories can also be submitted to EMA for a centralized marketing authorization, provided the product constitutes a significant therapeutic, scientific, or technical innovation or is otherwise in the interest of human or animal health (EC 2017).

Medicinal safety is constantly monitored by the EMA through a pharmacovigilance network. If adverse drug reactions suggest that there should be changes to the benefit-risk balance of a medicinal product, the EMA takes appropriate actions. The EMA also establishes safe limits for medicinal residues in food of animal origin for veterinary medicinal products (EC 2017).

Additionally, the EMA stimulates pharmaceutical research and innovation and provides scientific advice as well as protocol assistance to companies for the development of new medicinal products. The EMA has published guidelines on safety, quality, and efficacy testing requirements (EC 2017).

Six scientific committees, composed of members of all EU and EEA/EFTA states, some including patients' and doctors' representatives, conduct the main scientific work of the EMA: the Committee for Medicinal Products for Human Use (CHMP), the Committee for Medicinal Products for Veterinary Use (CVMP), the Committee for Orphan Medicinal Products (COMP), the Committee on Herbal Medicinal Products (HMPC), the Paediatric Committee (PDCO), and the Committee for Advanced Therapies (CAT).

The EMA brings together scientific resources from more than 40 national authorities in 30 EU and EEA/EFTA countries—more than 4500 European experts. It also contrib-

utes to international activities by working with the European Pharmacopoeia, WHO, and the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and the trilateral (EU, Japan, and United States) International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products (VICH) conferences on harmonisation, among other international organizations and initiatives (EC 2017).

19.1.4 WORLDWIDE REGULATORY AGENCIES

The following is a listing of worldwide regulatory agencies. It is not intended to be an all-inclusive list but rather to indicate the number of agencies that may have to be considered when designing, building, and validating a pharmaceutical facility. It is important to know which countries/agencies you are dealing with, as not all regulatory requirements are the same and no single agency is considered the single authoritative source, although as previously stated most worldwide agencies base their requirements on those of the United States (FDA) and Europe (EMA).

- ICH—International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
- MHLW—Ministry of Health, Labour, and Welfare (Japan)
- MHRA—Medicines and Healthcare Products Regulatory Agency (United Kingdom)
- NIH—National Institutes of Health (USA)
- CFDA—China Food and Drug Administration (China)
- TGA—The Therapeutic Goods Administration (Australia)
- TPD—Therapeutic Products Directorate (Canada)
- PIC/S—Pharmaceutical Inspection Co-operation Scheme
- WHO—World Health Organization

Along with global agencies that regulate the pharmaceutical industry with regard to manufacturing of products there are many other agencies that may either support or come into conflict with these agencies. For example, along with the FDA, the following agencies apply further regulations to pharmaceutical operations in the United States:

- ATF—Bureau of Alcohol, Tobacco, Firearms and Explosives (U.S. Department of Justice)
- CPSC—U.S. Consumer Product Safety Commission
- DEA—U.S. Drug Enforcement Administration (U.S. Department of Justice)
- EEOC—U.S. Equal Employment Opportunity Commission
- EPA—U.S. Environmental Protection Agency
- DOE—U.S. Department of Energy
- DOT—U.S. Department of Transportation
- FTC—Federal Trade Commission
- USITC—U.S. International Trade Commission
- NIOSH—The National Institute for Occupational Safety and Health (U.S. Department of Health and Human Services)
- NLRB—National Labor Relations Board
- NRC—U.S. Nuclear Regulatory Commission
- OSHA—Occupational Safety and Health Administration (U.S. Department of Labor)
- SEC—U.S. Securities and Exchange Commission

A key to understanding which regulations are to be followed is knowing where the product will be manufactured and where it will be marketed. We also need to understand that there are differences in the requirements of each authority having jurisdiction that must be addressed if the project is to be successful.

19.1.5 CODE BRIEF AS RELATED TO PHARMACEUTICAL FACILITIES

The majority of pharmaceutical and biotechnology manufacturing facilities are regulated by the *International Building Code*® (IBC; ICC 2014a), as adopted by the authority having jurisdiction (AHJ), under the classification of Factory and Industrial, either Group F-1 or F-2 (moderate or low hazard; generally moderate based on the code definitions). This classification is based on the fire safety and relative hazard of such facilities. With the type of construction and the degree of fire protection provided, the classification defines the maximum size, height, and number of stories that can be built. Care should be taken with respect to incidental use areas, those spaces that are not the main occupancy. A degree of fire separation is often required between the main occupancy and the incidental use area. For example, a storage room of over 100 ft^2 (9.29 m^2) must have a one-hour separation or include automatic fire protection. Incidental use differs from accessory areas and mixed occupancies.

Chemical and solvent use and storage are elements that must be addressed in the design of pharmaceutical and biotechnology facilities, and they can affect the building layout significantly. (Note: the IBC also defines other hazardous materials that may direct the need for special attention, but chemicals and solvents are most frequently used in pharmaceutical facilities.) The type, quantity, and method of use of these materials must be defined, as fire and explosion hazards are intrinsic to the use of these materials. Material types include aerosols, gases, dusts, liquids, and solids and include corrosives, explosives, flammables, unstable reactives, water reactives, and others. The degree of protection required is based on the quantities of the specific materials and their use in open or closed systems.

Depending on the quantities and use, either the building is classified, as noted above, as Group F-1 or F-2 (moderate or low hazard) or, potentially, a portion of the building may need to be classified as Group H (high hazard). (Refer to Section 18.4 of Chapter 18 for additional discussion of Group H classifications.) This classification affects the design of the building, as special protective measures may be required—rated construction, explosion relief, and location within the building being three potential requirements.

Group H occupancies include the use of a building or structure, or a portion of a building, that involves the manufacturing, processing, generation, or storage of materials that constitute a physical or health hazard in quantities in excess of those allowed in control areas constructed and located as required in the IBC. Based on the conditions, control areas can be designated within a building where quantities of hazardous materials not exceeding the maximum allowable quantities per control area are stored, dispensed, used, and/or handled. The use of control areas generally provides a degree of flexibility that needs to be explored by the design team.

Seemingly innocuous, even such things that are not under the control of the architect or engineer, like hand sanitants containing isopropyl alcohol, can trigger a hazardous material warning if the quantities stored are in excess of that allowable by code. Special concern needs to be given in the location of hazardous products, as they can sometimes end up in stairwells or interstitial spaces, as the owner may consider these areas "convenient" or "out of the way" storage.

Adjunct codes and regulations that are referenced and require scrutiny and analysis in regard to hazardous materials are the *International Fire Code*® (ICC 2014b) and various

National Fire Protection Association (NFPA) guides. FM Global Data Sheets (FM Global n.d.) are of significant help and are often required as part of the owner's insurance underwriter's suggested requirements.

19.2 HVAC DESIGN FOR VARIOUS TYPES OF PHARMACEUTICAL FACILITIES

With regard to pharmaceutical facilities, the HVAC system may have a significant impact on the product being produced. Whenever the product is exposed to the room environment, the HVAC system becomes the primary means of protection from cross-contamination. The product can become contaminated when it is exposed to the room environment or when surfaces that come in contact with it are exposed. It is in these areas where the HVAC system plays a key role. Examples include the following:

- A mixing tank is opened in the processing suite, exposing the product to airborne contaminants.
- Bottles are being filled with tablets. The tablets are exposed when they are placed in the bottles.
- The bottles themselves are being handled in an environment with a lower air classification. They are blown out with ionized air just before entering a higher-classification area.
- Vials and syringes are being filled with sterile products for injection. They must be cleaned and sterilized prior to being filled with the sterile solutions. The containers are washed and sterilized in machinery that is directly connected to the filling suite.
- The bottles, vials, and syringes are not yet closed. When the product is being filled, it must be protected from contamination until the container is capped or a plunger is inserted. Therefore, the filling suites must be maintained as an aseptic environment with operators gowned to protect the product from contamination.

19.3 FACILITY DESIGN CONSIDERATIONS

Basically pharmaceutical products can be categorized in two categories: those that do not directly enter the bloodstream (nonsterile products) and those that do (sterile products). This seems simple enough at first. Tablets taken orally are in one group, and drugs that are injected into the body with a syringe are in the other. But, in the case of an inhaler for asthma, the drug could be considered to be in the first group since it is taken through the mouth, but it is actually in the second group since the active ingredient can pass through the walls of the lungs and directly into the bloodstream.

All pharmaceuticals are composed of two basic ingredients: inactive ingredients and active ingredients. Active pharmaceutical ingredients (APIs) are those that have an actual pharmacological effect.

19.3.1 FACILITIES FOR NONSTERILE PRODUCTS

Nonsterile products include tablets, capsules, liquids, creams and ointments (topicals), and medical devices that are noninvasive. As previously stated, the main objective of the pharmaceutical cleanroom design team is to reduce or eliminate the possibility of cross-contamination.

On the simplest level of design, the HVAC requirement for a nonsterile area is to reduce airborne particulate by exchanging the air inside the room with air that has passed through a filter. Pressure differentials between the process area and the adjacent space

protect the room or the environment (see Section 19.3.4). For this section, the focus is on protecting the product.

In a typical nonsterile facility there are six basic areas:

- Administrative
- Laboratory
- Warehousing
- Manufacturing
- Primary packaging
- Secondary packaging

19.3.1.1 Administrative

Administrative areas include offices, conference rooms, locker rooms, cafeterias, and general support functions. HVAC for these areas is designed to meet the basic requirements of comfort of the employees.

19.3.1.2 Laboratory

Laboratory areas may require more stringent controls than unclassified spaces, including adjacent corridors and administrative spaces, depending on their function (for additional discussion see Section 19.3.5).

19.3.1.3 Warehousing

HVAC is designed to meet the minimum requirements for the materials being stored. Warehouses typically have basic heating requirements with no cooling other than air circulation. But when materials that require special conditions are stored, such as empty capsule shells and hygroscopic powders, the area must be designed to maintain temperature and relative humidity requirements governed by the materials in question.

The first area where the raw and packaging materials are exposed to the room environment is in the incoming sampling room. Here containers must be opened to take samples of the raw and packaging materials. The requirements for this area must be the same as in the manufacturing areas where the materials are processed, typically ISO Class 8 (Grade C) Equivalent (ISO 2015). "ISO Class 8 Equivalent" refers to designing an area to meet the requirements but not validating it. This classification is often referred to as *controlled not classified* (CNC).

In a properly designed facility, the transition point between a warehouse and the manufacturing area is the dispensary or weigh room. In this area the containers of raw materials are opened and weighed in preparation for making the products. This weighing space is a "controlled" space in which an environment is provided to reduce the opportunity for product contamination.

Typically a weighing area will have at least one down flow booth (DFB) designed to create a minienvironment within the room. All dispensing activities occur inside the booth, inside which a constant flow of air is maintained to move airborne particulate into the filter chambers where it is collected, mitigating contamination.

The room HVAC system acts as a secondary system and is generally protected by positive pressure to the surrounding areas.

19.3.1.4 Manufacturing

Once inside the manufacturing area, the materials are transferred through corridors to the designated process suite. If the operation in the process suite is not "closed," where one side of the room is open to the environment, the airflow will be into the room to protect the adjacent room or corridor from contamination. Ideally a combination of air locks and room pressurization create a better defense (see Figure 19.1).

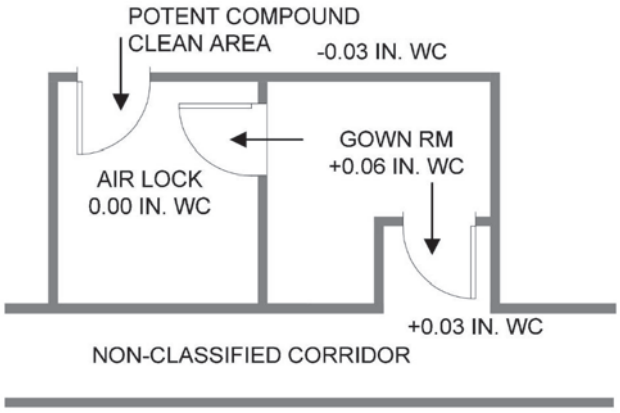

Figure 19.1
Containment Airlock

In the design of new facilities, the process equipment can be designed as the first-level protection for the product by using closed systems for transferring materials from one container to another or from containers into the equipment. This is considered the most direct and reliable method of protection, but at cost.

19.3.1.5 Primary Packaging

Once the materials are processed into bulk product they must be packaged. Again the focus must be on protecting the product and the product contact surfaces (in this case, the inside of the packaging materials), as the package now becomes an additional contact surface. In the case of solid dosage forms, current designs for packaging lines including capping in a filling suite that meets the same ISO Class 8 (Grade C) Equivalent (ISO 2015) environmental requirements as the process suite where the product was made. The classification requirement can vary widely depending on the jurisdiction. For example, the China Food and Drug Administration (CFDA) directs the use of Grade C and in these areas and requires the use of complete operator coverage as required for Grade B in other countries.

As an example of primary packaging, filling tablets into a bottle requires that the bottle be blown out with ionized air, filled, capped, and sealed within the controlled space. Once the bottle is closed it passes out of the fill suite to the secondary packaging area.

19.3.1.6 Secondary Packaging

Because the product is now protected, the secondary packaging area can be maintained at a particulate level no higher than the warehouse. This is the case even though a high degree of particulate is generated by the labels, cartons, and corrugated shippers being bent and folded as the product progresses through the packaging line. Consideration, however, must be given to the appearance of the final package, as imperfections in the presentation of the final product are reason for rejection in some countries. The HVAC system is the primary system for reducing airborne particulates that may adhere to the bottles. The focus of the HVAC system is primarily on employee comfort, but the area is still pressurized positively to the finished goods warehouse.

19.3.2 FACILITIES FOR STERILE PRODUCTS

Products that directly enter the bloodstream need to be prepared in an aseptic environment where the facility and equipment are design to keep microbiological contaminants at a minimum. Sterile products include those that are injected using a syringe or intravenous catheter, medical devices that are inserted into the body such as pacemakers, and inhaled products such as those used for asthma.

Studies continue to confirm that human beings present the highest degree of particulate shedding in an aseptic suite, requiring that the operator needs to gown appropriately or the product needs to be isolated from the operator. At each cleanliness level, a change in operator gowning is required. The basic process is as follows. Entering a controlled not classified (CNC) space requires a change from street clothes into a plant uniform. Entering an ISO Class 8 space requires hair and shoe covers or dedicated plant shoes. The next level, ISO Class 7, requires sterile gowning, which is donned in an ISO Class 7 gowning room before entering the ISO Class 7 aseptic core. Skin cannot be exposed; therefore, along with a sterile coverall, the operator must don a hood, face mask, and wraparound goggles. A laminar-airflow ISO Class 5 environment created by supplying air filtered through high-efficiency particulate air (HEPA) filters from directly above the machine is provided within the ISO Class 7 process suite where product or product containers are exposed. See Table 19.1 for recommended gowning requirements for each cleanliness class.

19.3.2.1 Support Functions

GMP warehouse sampling and weighing operations have the same environmental conditions as those for GMP products, but once raw materials enter the processing areas, a higher level of environmental control is required. The rooms and corridors are designed to be of higher classification until the aseptic core is reached. Each level is designed to protect the next level (see Table 19.2). Gowning requirements for each cleanroom cleanliness class get stricter to reduce the contaminants introduced by operators (see Table 19.1).

Even though there are industry good practice guidelines for air changes and velocities, which have been developed over time from the experiences of many people and the studies they have performed, only the FDA aseptic guidelines (FDA 2004) define suggested minimum airflow rates for cleanrooms. There continues to be a great deal of discussion regarding sustainability and methods for calculating the actual air changes by using activities and particulate generation. The key values are recovery time and level of filtration required to maintain cleanliness levels. The suggested value for recovery time from in-operation to at-rest conditions is 15 to 20 min according to EudraLex Annex 1 (EC 2010). The International Society for Pharmaceutical Engineering (ISPE) aseptic

Table 19.1 Recommended Gowning Requirements for Each Cleanliness Class

Cleanliness Level	Gowning Level
ISO Class 8	Head cover, frock, and boots
ISO Class 7	Head cover, frock, and boots
ISO Class 6	Hood, beard cover, boots, and gloves
ISO Class 5	Hood, mask, coverall, boots, and gloves
ISO Class 4	Hood, facial enclosure, coverall, boots, and gloves

Table 19.2 Progressive Cleanliness Levels for Each Process Step

Working Zone	FDA Requirements (FDA 2004)	EMA Requirements (EC 2010)
Aseptic core	ISO Class 5	Grade A
Aseptic processing area	ISO Class 7	Grade B
Controlled processing area	ISO Class 7	Grade C
Controlled support area	ISO Class 8 or Class 9	Grade D

guidelines (ISPE 2011a) define the calculation methods and provide graphs for recovery time depending on particulate generation and cleanliness levels.

19.3.2.2 Manufacturing Support Zones

The support zones for a facility designed to make sterile products are usually ISO Class 8 or Class 9 (in operation) and include the following:

- Formulation, where a bulk material received from an API facility is added to a liquid that is to be transferred into a container. This takes place prior to sterile filling.
- Component preparation, where packaging materials that will come into direct contact with the product (vials, syringes, and ampoules) are washed as the first step in the cleaning process. The next step is sterilizing these components.
- Equipment preparation, where equipment parts that come into direct contact with the product (tubing, pumps, manifolds, and fill nozzles) or components that are in direct contact (stopper feed bowls, which transfer stoppers and plungers to the filler for insertion) are prepared for sterilizing.

19.3.2.3 Filling Suite

The filling suite is composed of multiple rooms that include rooms for gowning, air locks to separate each operation and to maintain room pressurization, and the filling room.

Gowning rooms are for donning sterile garments to cover every portion of the body so that the operator's skin is not exposed. Gowning rooms constitute a transition zone from ISO Class 8 to ISO Class 7 and are usually designed to create an ISO Class 7 environment. Because operators enter in nonsterile gowns, however, the space is considered ISO Class 8.

Once operators have donned their sterile suits, they are able enter an ISO Class 7 air lock. The air lock doors are interlocked so that only one door can be opened at a time. (*Note:* certain local codes do not allow interlocks for life safety reasons. If this is the case, go/no-go lights are used with a higher degree of reliance on procedures.) Air pressure is to be maintained so that the air flows into the gowning room when the door is opened. When the operator opens the second door, the direction of the airflow should be from the filling suite into the air lock.

The filling suite can be set up in a number of ways. One option is for operators to directly access the filler. A second is the use of a restricted access barrier system (RABS). A RABS is a glove box that separates the operator and the room environment from the open product. In either case, the operator gowning and room requirements are the same, although the gowning requirement is currently being challenged by the industry when a RABS is used. The filling suite is ISO Class 7, and within the suite the filling equipment is protected by unidirectional airflow from above. The method of providing unidirectional airflow may be part of the filler and will recirculate room air through HEPA filters, or the air can be supplied from the room through HEPA filters from the air handlers supplying the room.

The aseptic core needs to be designed and maintained to be the cleanest room in the operation. This room also has the highest differential pressure. Therefore, when doors are opened to the surrounding air locks, the direction of the airflow should be out of the filling room and into the air lock. See Figure 19.2 for a typical suggested airflow diagram for an aseptic filling suite.

The critical parameters such as temperature, humidity, space pressure, and space cleanliness level need to be defined by the requirements of the products. The relative

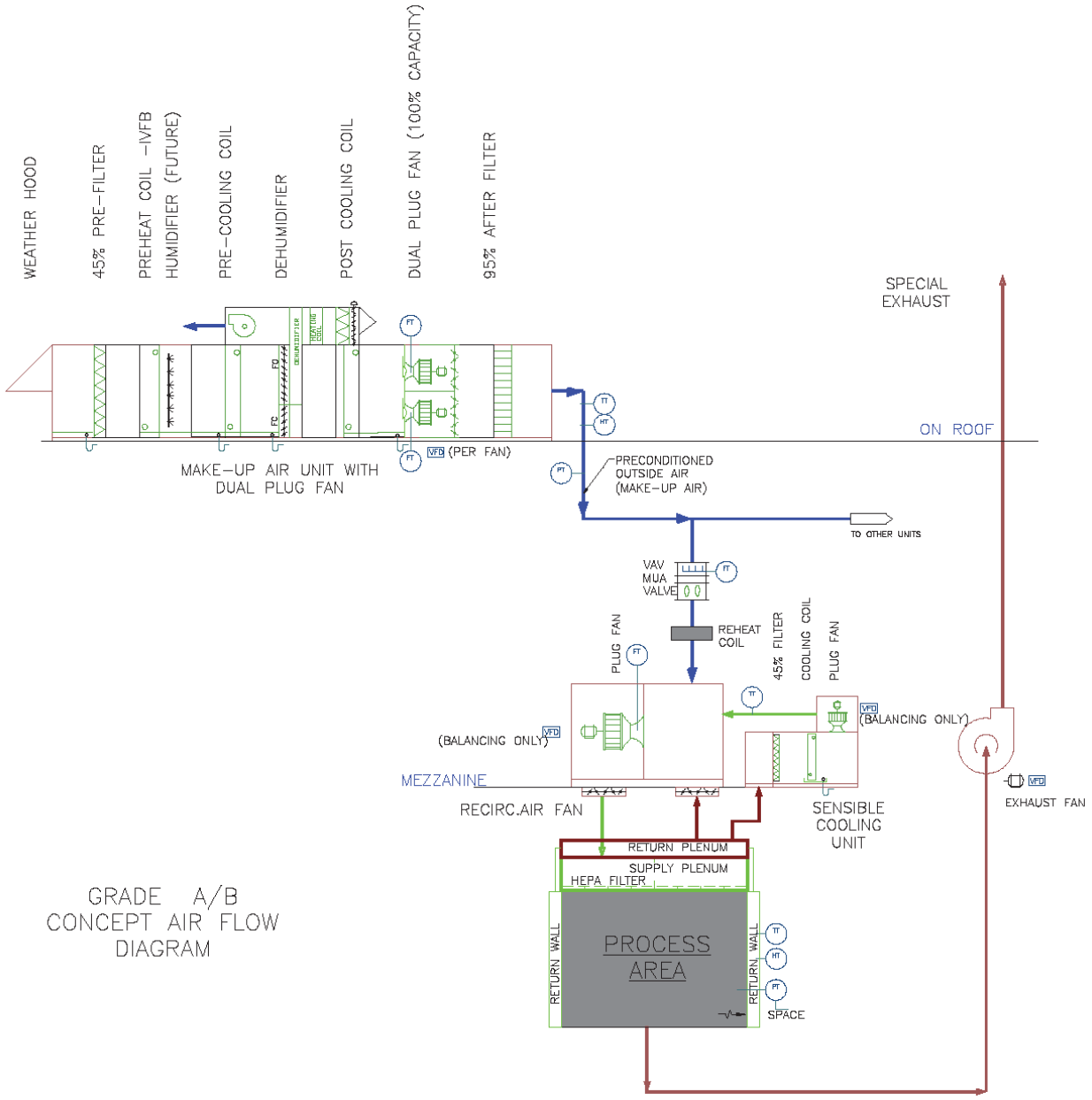

Figure 19.2
Typical Aseptic Processing HVAC System Schematic

humidity level, however, should not be more than 60% and should be controlled at 50% ±5% unless determined differently by specific product requirements. Lower humidity levels during summer months simply increase the HVAC operational cost. Space temperature is usually maintained between 62°F and 66°F (16°C and 19°C) primarily due to the heavy gowning requirements. While determining the space temperature and humidity levels, operator comfort should be considered along with the product requirements.

In aseptic core areas, the airflow rate is considerably higher than it is in the adjacent support areas. Using recirculated air reduces the HVAC energy consumption. The outdoor airflow is derived from the exhaust and pressurization requirements. The quantity of out-

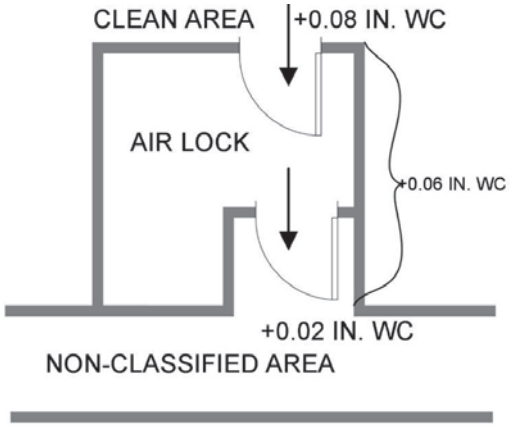

Figure 19.3
Cascading Pressure Air Lock

door air might direct the use of a dedicated outdoor air-handling unit (AHU). The outdoor air can be preconditioned via a 100% outdoor AHU to maintain a space dew point that is driven by the space temperature and humidity set points. Preconditioned outdoor air is distributed to cleanroom recirculation units to maintain space dew point and pressure. The cleanroom recirculation units can have a recirculation fan, which should be a direct-drive, plenum type fan to increase reliability (protecting against belt failure) and eliminate the particulate generation from the fan belt drives. Recirculation units are also provided with a sensible cooling coil to maintain space temperature. If the mechanical space is limited, the recirculation air and cooling air can be separated as shown in Figure 19.3. In this air management concept, smaller sensible cooling units can be used to maintain space temperature and larger fan-only units still provide the HEPA-filtered air recirculation to maintain space cleanliness level.

Air to aseptic areas is to be filtered via ceiling-mounted terminal HEPA filters at minimum 99.99% most penetrating particle size (MPPS) efficiency. The terminal HEPA filters define the boundaries of the aseptic processing area and protect the space from cross-contamination of the particulates coming from outside of the aseptic space. Return air should be taken at the floor level and located strategically to avoid any recirculation zones and provide a good sweep of the airflow within the room. The locations of the returns are very critical in order to achieve good air recirculation in the space. Computer modeling using a computational fluid dynamics (CFD) method provides a good visual representation of the airflow within the space. Using the model, the return air locations can be determined, which is of significant benefit in the qualification process during validation.

Aseptic spaces should be kept in positive pressure in respect to adjacent spaces, and egress of the material and people needs to take place through air locks.

19.3.2.4 Air Locks

A key to the protection of products and personnel are air locks. As the name implies, they represent the retention of a specific environmental condition. The cascading air lock is generally considered for use in aseptic operation (see Figure 19.3).

When operating an aseptic facility for the production of parenteral products, the primary objective of an air lock is to segregate the clean space from surrounding areas. This is accomplished by maintaining a pressure differential of 0.08 in. w.c. (20 Pa) where the aseptic suite has the higher pressure. This will cause the direction of the airflow to be into the air lock when the air lock door is opened. The air lock will have a 0.02 in. w.c. (5 Pa) overpressure when compared to the corridor. It is recommended to have a 0.04–0.06 in. w.c. (10–15 Pa) pressure differential between spaces with different classifications (FDA 2004).

FDA's (2004) *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice* recommends that a minimum of 20 air changes per hour (ACH, ach) be maintained in ISO Class 8 spaces. The same guideline also recommends using 90 fpm (0.45 m/s) with uniformity within ±20%, measured just below the filter face (6 in. [150 mm]) over aseptic processing areas (ISO Class 5).

The values provided are suggestions, a starting point that needs to be evaluated for each operation by considering the process, activity levels, number of people that might be present in the space, and filtration levels. Air recirculation should be maintained 24/7 in aseptic areas. The airflow can be reduced over the adjacent ISO Class 7 areas to the ISO Class 5 area during idle periods. However, continuous particulate counting is a must, and the particulate level needs to be maintained at the level required at all times. In EudraLex (EC 2010), the space cleanliness level is identified as a grade level and is defined as at-rest and in-operation particulate levels. The regulation does not dictate any air change rate; however, it is required that the space recover within 15 to 20 min from the in-operation condition to the at-rest condition particulate levels.

19.3.3 API FACILITIES

In the making of pharmaceuticals there are two basic ingredients: inactive ingredients and active ingredients. Inactive ingredients are materials used to form a tablet that can be handled easily; for example, a typical tablet is composed of inactive ingredients that can include lactose, corn starch, and colorants, among others. Active pharmaceutical ingredients (APIs) are those that have an actual pharmacological effect.

API facilities, buildings designed for the manufacturing and processing of APIs, are divided in two zones, for upstream and downstream processes. Upstream processes are those that use liquid processes that take place during the initial preparation of the products. This stage is not required to follow CGMP requirements. The processes are regulated, however, by ICH Guide Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients* (ICH 2000). Also, *Active Pharmaceutical Ingredients* (ISPE 2007) and *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)* (ISPE 2009) provide extensive information on the subject that needs to be heeded.

Drying, granulating, and packaging processes are considered downstream processes and need to meet CGMP requirements. These stages are called the *dry end* of API processing.

Successful facilities demonstrate a focus on personnel and material flow (see Figure 19.4). Ideally, these operational flows should be unidirectional so that contaminated personnel or containers cannot move into clean areas. Any area where an operator can be exposed to airborne contaminants should be provided with both gowning and degowning suites. The gowning room can be an air lock with positive pressure relative to the manufacturing area and the corridor. The operator enters the air lock from a corridor; puts on a full coverall, gloves, and a positive air-purifying respirator (PAPR); then enters the manufacturing space through a second door. Both doors of the air lock should be interlocked so that only one can be opened at a time. (As noted previously, certain local codes do not allow interlocks for life safety reasons. If this is the case, go/no-go lights are used with a higher degree of reliance on procedures.) Materials brought into the room should enter through a separate air lock that is dedicated for this purpose.

Ideally, when an operation is complete and materials are ready to leave the manufacturing space, personnel should pass through an additional material air lock. If space in the area is limited, it is permissible to use one air lock for both inbound and outbound items. If this approach is selected, the flows must be segregated even if by a rail or at minimum

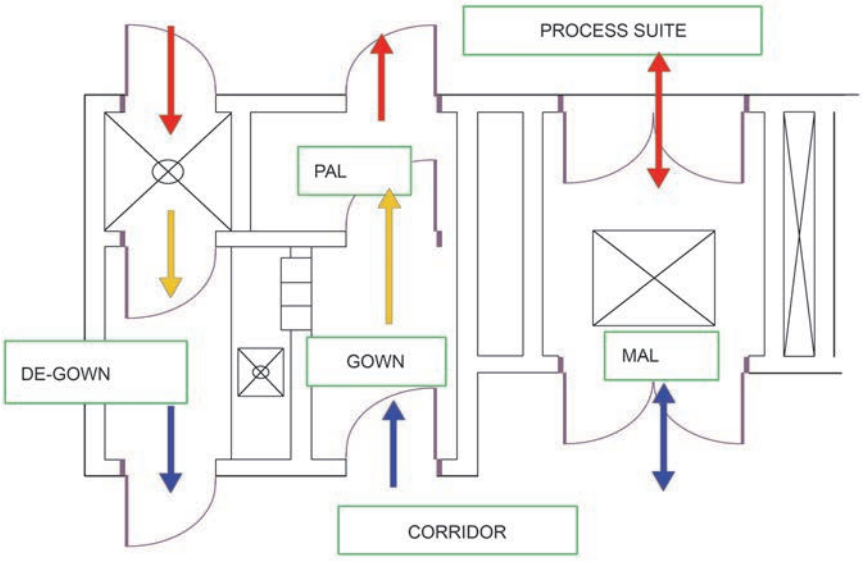

Figure 19.4
API Facility
Personnel Flow

a taped line on the floor, both for safety and segregation of people and materials. Materials cannot be positioned so as to block an egress path. The operator places the items into the air lock and inspects and cleans the outside surface to prevent cross-contamination.

When potent compounds are being handled, once the operator has entered the manufacturing space, their outer garment is considered contaminated and must be removed after leaving the classified area and prior to entering the general corridors. To do this he/she must enter a degowning area. Because the operator must remove the outer garment, he/she will be exposed to any contaminants on its surface. This requires that the surface of the garment be treated in some way prior to its removal to reduce the risk of exposure to contaminants. There are three basic conditioning techniques that effectively address this; each requires that the personnel enter a room prior to the degowning suite. The first technique is to use a shower to wash the powders off the surface. This requires either waterproof garments, which are hot and uncomfortable, or a complete disrobing of the operator since inner garments may also be wet. The second is a misting booth; the intention is to adhere the material to the surface of the gown so that when the operator enters the degowning room the particulates will not become airborne. The third is an air shower, which has been shown to be the least effective, as particles are dispersed into the air. Air showers can be used in very specific situations if the material to be removed is not sticky or prone to static.

After conditioning, the operator enters the degowning area. This room is equipped with sinks and, if necessary, personnel showers. Operators remove their respirators and clean them in the sinks, then place the cleaned units in pass-through lockers to be picked up from the general corridor. Outer garments are carefully removed and placed in a bin for washing or disposal. If necessary the operator will shower. At this point he/she may exit the degowning room into the general corridor.

All the standard concerns of production facilities must also be accommodated, such as safety showers and eye wash stations, sprinklers and fire extinguishers, fire-rated construction and pressure relief panels, egress stairs and doors, and emergency lighting.

19.3.3.1 HVAC for Open-Process Operations

In an open process, ingredients are added to open vessels. This requires the room to be the primary means of avoiding cross-contamination. In an API facility, which is typi-

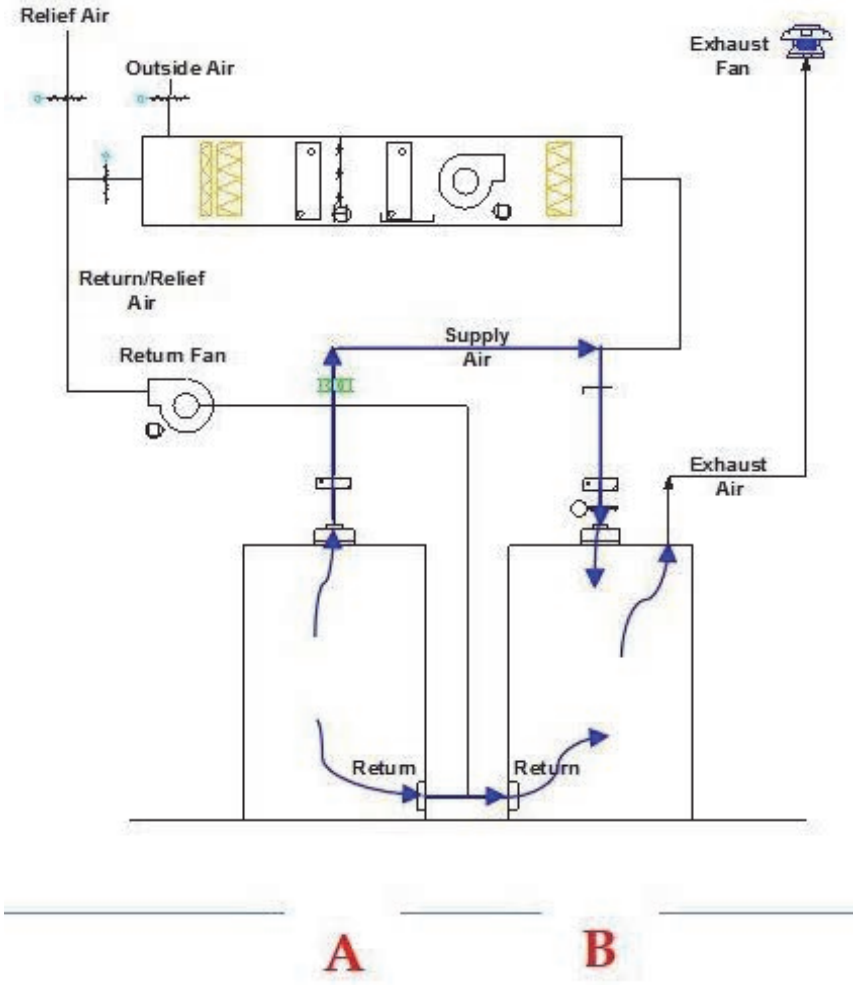

Figure 19.5
HVAC Schematic for Open Process

cally open process, HVAC systems can be significantly different from what is normally seen in a GMP facility. AHUs may require an increase in the number of air changes in the operating area. If solvents are present, a once-through system must be used with no recirculation (i.e., 100% outdoor air). (See Figure 19.5 for an HVAC schematic for an open process.). Modifications to a normal GMP system can include the following:

- Increasing the supply ACH to a minimum of 20 ach in the process and support areas.
- Providing filters for AHUs with a minimum of 30% for primary and 95% for secondary filtration efficiency.
- Providing terminal supply-side HEPA filtration.
- Providing HEPA filtration on return air ducts to reduce the chance for contamination of ductwork.
- Upgrading the supply fan motor and motor control unit (MCU) to a variable-frequency drive (VFD) and a larger size. This change is required not only due to the additional amount of air but also due to the additional resistance from the new HEPA filters.
- Providing process suites, where powders are being handled, with low wall returns with HEPA filters of minimum 99.97% filtration efficiency at MPPS. Access to these filters should be from mechanical/gray-side space using the bag-in/bag-out technique.

- Installing HEPA filters on dedicated exhausts from shower and supporting rooms. This will keep the exhaust ductwork clean, reduce or eliminate the cost of contracting for cleaning, and eliminate the possibility of cross-contamination.
- Upgrading the exhaust fan motors, along with the VFD, to a larger size due to the additional resistance from the exhaust bag-in/bag-out HEPA filters.
- Providing stainless steel ductwork for supply and exhaust distribution system to reduce the possibility of leakage and to aid in cleaning.
- Supplying air from ceiling or wall-mounted air devices and returning it through a low wall return duct on the opposite side of the room to provide proper airflow through the room. The process equipment needs be located so that it is between the inlet and outlet ducts. The operator and the operator control panels should be on the opposite side of the machine from the low wall return.
- Providing a control and monitoring direct digital control (DDC) system dedicated exclusively to the contained operations areas. The system should have pressure differential, temperature, and humidity sensors and controllers for each room, maintaining airflow according to the required direction and pressure. The system should have a dedicated panel connected to the central monitoring and control system. It also must include necessary alarms within the operating areas. Status panels are to be mounted in each operating area and the mechanical areas. The operating status of AHUs needs to be displayed and can be viewed on these monitoring panels.

Under certain conditions particulate can migrate from one room to another through the ductwork. For example, consider two adjacent rooms on the same air handler with common return ducts. Both rooms are designed for handling powders. Room A is handling potent compounds and room B excipients. The AHU shuts down, an alarm is sounded, and the operator in room A closes the slide gate to the dust collector and leaves. No one is working in room B and the room air exhaust continues to run. The resulting condition is that room B has a lower room air pressure than room A. If the registers and returns are open, there is an opportunity for airborne contaminants to migrate through the ductwork from room A to room B. A number of system design changes can obviate this concern:

- Install terminal HEPA filters on return air and supply air into and out of the room.
- Set up the control system to ensure dust collectors are not operating if the AHUs are out of operation.
- Automatically close dampers if the air handler goes down.
- Do not use the same ducts for adjacent rooms; consider running the ducts to a plenum if necessary.
- Separate air-handling systems for each room in lieu of providing a once-through system.

19.3.3.2 HVAC for Closed-Process Operations

The use of containment at the source, which includes closed systems and glove box isolators, makes the design requirements for HVAC systems much simpler. In a closed process, the room and air-handling systems are not the primary form of containment. Operators are not required to wear protective garments, and the requirement for multiple levels of air locks and unidirectional flow is eliminated (see Figure 19.6).

For liquid systems, the primary means of containment is the vessel and piping; secondary containment is added in areas where leakage can occur.

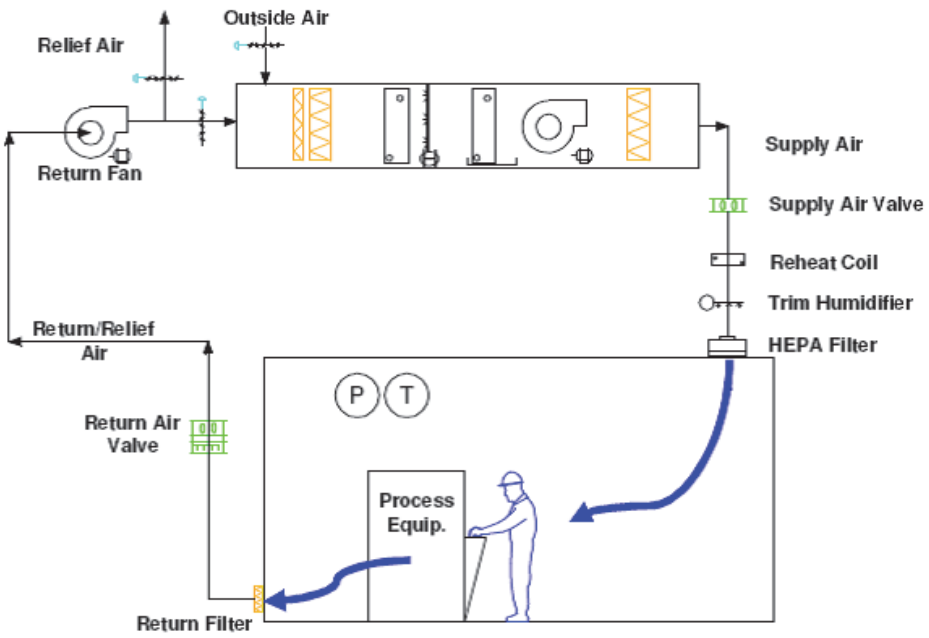

Figure 19.6 HVAC Schematic for Closed Process

For powders, a properly designed glove box isolator serves as both primary and secondary containment. As with the liquid vessels, the glove box is a sealed unit that affords the primary means of containment. The unit is kept under constant negative pressure so that if there is a leak in the system (usually from the gloves) nothing escapes into the room.

Every operating company has a different view of the level of risk they are willing to take. This drives the room requirements criteria to require a range of solutions, from basic environmental controls to terminal HEPA filtration to single-pass air.

19.3.3.3 Mechanical Support

All fumes and vapors from charging process equipment such as reactors and dryers on each level need to be contained by laminar-flow units or glove boxes. This eliminates the need to use flexible trunks when the manways are open. All process area fumes collected by the exhausts on the glove boxes are to be sent to a scrubber or thermal oxidizer. Flexible trunks may be used when handling drums of solvents (containing no actives) for additions and transfers.

19.3.4 CONTAINMENT/ISOLATION

19.3.4.1 Overview

The trend in today's pharmaceutical industry is toward the production of higher-potency compounds. These compounds provide more saleable material from each production batch by requiring a lower quantity of active ingredient in each dose, thereby providing a more efficacious product. Although these highly potent compounds have great benefits to the end users and manufacturers, they increase the risk of exposure for manufacturing personnel.

As the chemical industry has always been involved in the handling of toxic materials, the increased knowledge of the long-term effects of some of the chemicals used in these high-potency compounds has led to a better understanding of the controls required in han-

dling; dyes and pigments; and various fine chemicals, intermediates, and agricultural chemicals (especially herbicides and pesticides). In very small quantities, these materials may be toxic, carcinogenic, teratogenic, or mutagenic. In addition, the levels of acceptable risk to personnel and the definition of acceptable working conditions have been continually evolving to higher standards, challenging our technology to meet the new criteria for operator safety.

Designers are exploring innovations in equipment design and developing new procedures and techniques for detection to better contain these more hazardous compounds. These are being applied to production facilities, to pilot plants, and to research and development (R&D) facilities to improve the protection of the plant and laboratory personnel. The development of these procedures and equipment is a two-step process: the level of controls required and the methods for achieving them must be determined and implemented.

The need for containment when handling hazardous materials applies to various operations within manufacturing. When a material may have an adverse effect on personnel during handling, a number of steps are taken. The first is to determine the occupational exposure limit (OEL) and to determine what category the material falls into, and the second is to determine, based on a particular containment category, the best method for protecting the operator. The best method may be a simple change in the procedure the operator is following, or it may require the use of personal protective equipment (PPE), down flow systems, or closed processes.

19.3.4.2 Determination of the Required Control Levels

Any evaluation of the handling of hazardous materials requires close attention to occupational exposure limits (OELs). Establishing permissible OELs is critical to selecting the appropriate technology to achieve the desired containment level. Industrial and governmental hygienists and toxicologists establish criteria based on laboratory tests, analyses of similar compounds, biological testing, and epidemiological data. Although the Occupational Safety and Health Administration (OSHA) has published *recommended* exposure levels based on OELs set by The National Institute for Occupational Safety and Health (NIOSH), the American Conference of Governmental Industrial Hygienists (ACGIH) and each company's safety and health departments usually set the OELs by analyzing the following parameters from outside sources and the company's own tests and experience:

- Maximum daily dose
- Lethal dose
- Lethal concentration
- Short-term exposure levels
- Performance-based exposure limits
- Nature of exposure problem (i.e., conditions where the contaminant may be dermatologically absorbed or inhaled and its effect on exposed skin surfaces, eyes, mucus linings, etc.)
- Reversible effects (effects that can be recovered from; for example, administering an anti-toxin)
- Nonreversible effects (effects from which there will be no recovery; for example, genetic mutations)

A major source of information for companies are the OELs stated on the Safety Data Sheets (SDSs) for raw materials. Along with the criteria mentioned above, companies may use additional criteria per ingredient. OSHA uses permissible exposure limits (PELs), NIOSH supplies recommended exposure limits (RELs), and ACGIH has thresh-

old limit values (TLVs®). See OSHA Annotated Table Z-1 (OSHA n.d.) for a summary of some of these values.

OELs, PELs, RELs, and TLVs are usually stated in parts per million (ppm) for gases and vapors and in milligrams per cubic metre (mg/m^3) for solids (although other units are sometimes used, such as fibers/m^3 for asbestos). Pharmaceutical companies usually describe their chemicals in micrograms per cubic metre ($\mu g/m^3$) because of their high potency.

A team made up of a company's safety and industrial hygiene group along with engineering, research, and operating personnel usually establishes a set of containment categories for measuring and assessing the risks of handling chemicals. The containment categories, or exposure bands, are based on the agreed-upon OELs and define the types of protection required to maintain operator safety. Each band has a predetermined method. Lower levels may only require a dust mask, while higher levels require containment at the source. See the following subsections for further descriptions of the procedures and equipment required.

Typically the bands are categorized by the contaminants' potential hazards in airborne concentrations, which is the concern for most nonacute (not immediately reactive) agents. An example of typical containment categories as defined by one pharmaceutical firm is as follows:

- Cat-1 >5000 $\mu g/m^3$—Materials in this category are relatively nontoxic or nonpotent.
- Cat-2 <1000 to >100 $\mu g/m^3$—Materials in this category have low to moderate toxicity or pharmacological potency; however, they may exhibit some systemic toxicity or sensitization potential with occupational use.
- Cat-3 <100 to >10 $\mu g/m^3$—Materials in this category have moderate toxicity or pharmacological potency and require significant engineering containment and strictly enforced work practices.
- Cat-4 <10 to >1 $\mu g/m^3$—Materials in this category have high toxicity or pharmacological potency and require total engineering containment and strictly enforced work practices.
- Cat-5 <1 $\mu g/m^3$—Materials in this category have high toxicity or pharmacological potency and require specialized total engineering containment and strictly enforced work practices.

While the company processing the compounds determines the containment categories internally, the ranges chosen are usually based on the types of technology that must be implemented to achieve the containment levels and the degree of employee testing that is to be implemented for monitoring exposure levels.

Once the chemical exposure data for a specific chemical are evaluated by the company and its control category is identified, the process is reviewed to identify points of potential exposure and the quantities involved. Having established the control limit, it is possible to select an appropriate technology to achieve the desired containment level. These are usually set as time-weighted average (TWA) exposures over an eight-hour shift, with a maximum instantaneous exposure level.

19.3.4.3 Determination of the Control Methods to be Implemented

The start of controlling exposure risk is at the laboratory and development stages. The first analysis is if the hazardous chemicals are raw materials or intermediates and whether an alternative chemical and/or a different chemical reaction sequence can be used. The next step is to evaluate the process steps and minimize the potential for exposure, mini-

mizing transfers and modifying the process if possible. If the product itself is the concern, or if the above evaluation cannot remove the risk, then containment steps must be implemented in the design.

The operations that need to be examined include any areas in which hazardous or potent compounds are handled. These typically include, but are not exclusive to, the following operations:

- Warehouse/material handling
- Sampling
- Pharmacy/weighing/dispensing
- Processing/formulation
- Intermediate/in-process testing
- Packaging
- Mechanical space
- Maintenance
- Laboratory/R&D/quality control (QC)

Containment of the hazardous chemical involves the establishment of a protective barrier between the chemical and the employees. This barrier may be a barrier around the employee, which keeps the chemical out, or a barrier enclosing the chemical, which keeps the chemical in. Depending on the hazard level and the risk of failure of the primary containment barrier, secondary barriers are installed to lower the risk.

Care in the design of the operating facilities is also required to ensure that hazardous materials do not travel from the work area to nonoperations personnel.

19.3.4.3.1 Containing at the Employee Level—Personal Protective Equipment

The common belief is that personal protective equipment (PPE) is the lowest-cost method of employee protection, since capital expenditure is not involved in equipment purchase or modifications. This does not take into account, however, the capital investment in building modifications and the operating expenses for additional airflow requirements for air locks and gowning and degowning facilities. In addition, protective clothing must be either cleaned or, if disposables are used, discarded under special conditions, usually incineration, and new garments must be purchased.

The choice of PPE is based on the mechanism of the exposure—whether the chemical is ingested, inhaled, or absorbed through the skin. This determines the type of equipment to be used. At minimum, dust masks approved for the handling of the specific compound should be used or, if materials such as organic vapors are handled, a negative-pressure cartridge respirator should be used. If the hazardous chemical can be absorbed through the skin, full-body high-density polyethylene (HDPE) coveralls and a PAPR must be used. A PAPR draws air from the surrounding areas through a HEPA filter into the operator's mask and then exhausts it through the mask perimeter.

An alternative to a PAPR is a dry-type breathing-air compressor and distribution system. In this system, the operating personnel connects air to the mask or suit through a hose, which is attached to a quick-connect coupling at air stations situated at various locations in the process area. These systems require that the operator drag this hose connection around, creating a tripping hazard and an additional surface for contamination.

At the extreme, a full rubber suit with integral hood, boots, and gloves is used. The air supply to these is usually provided by a hose and a quick-connect coupling to a breathing air system. The suit is heavy and the air hose is cumbersome. These suits are expensive and have to be decontaminated before exiting and reuse.

19.3.4.3.2 Containing at the Source—Placing a Barrier around the Chemicals

While PPE is currently in use globally, containment at the source is preferred when possible. In many countries, including the United States, it is mandatory. For example, in the United Kingdom, the Control of Substances Hazardous to Health Regulations, enacted in 1988, require that "so far as is reasonably practicable, the prevention or adequate control of exposure of employees to a substance hazardous to health shall be secured by measures other than the provision of personal protective equipment" (Section 7, Part 2). With the development of alternative containment strategies, PPE is increasingly being used only as a secondary containment approach for temporary upset conditions and for maintenance, when required.

19.3.4.3.3 Solids (Powders) Containment

There are several approaches to providing a barrier around a solid chemical in a process:

- Hard-fixed materials may be placed around the process equipment.
- A discontinuous barrier may be inserted between the process and the worker.
- A barrier of directional airflow may be created between the operation and the employee.

Solids containment takes place wherever there is an opportunity for airborne particulate to occur, which is usually when a transfer of material is taking place. This includes the following operations:

- Weighing and sampling
- Charging and discharging of reactors and other closed equipment
- Filtering and drying of powdered materials
- Centrifuging
- Milling and sieving
- Blending
- Coating and granulating

Directional Airflow Control

For relatively low-toxicity materials handling, control of airflow is typically used for containment. Since powders need to be sampled and are usually received in bulk quantities that must be weighed out for specific operations, the dispensing rooms can create one of the highest levels of probable exposure. In these areas, the first level of containment to be considered is airflow control.

As discussed in Section 19.3.4.2, categories are assigned internally by companies. Using the example categories outlined in that section, the following represents some recommendations based on the levels. In Category 1 applications, local air pickup connected to a dust collector alone can often be used. For more toxic Category 2 products (or for larger quantities of low-toxicity materials) and for relatively low Category 3 products, down flow booths (DFBs) are implemented. These can effectively maintain a safe environment for employees down to OEL levels of 20 $\mu g/m^3$ or lower if the system is modified with additional curtains and panels.

Closed Equipment Systems for Solids

Closed systems contain all the chemicals in some form of sealed containment. Reactors and many other types of process equipment are closed inherently by design and require a failure before containment is considered lost. However, not all equipment is presently available in a closed form. Charging, sampling, discharging, and maintenance

of the closed units must be done safely. Cleaning and decontamination of these units using clean-in-place (CIP) systems, seals, and other leakage sources must be carefully evaluated for longevity, and programmed maintenance must be executed.

While liquids and gases are usually contained in piping, powder handling provides a greater challenge. Moving powdered materials into and out of closed units such as reactors usually requires transport though containment devices at all points where connections are made between various pieces of equipment ("makes and breaks"). Split butterfly valves (SBVs) are used for dispensing powders into closed reactors and are good to 5 $\mu g/m^3$ when used alone or 1 $\mu g/m^3$ when used with special local exhausts. Continuous plastic tubes, or "sausage bags," are sometimes used down to 10 $\mu g/m^3$ for discharging or sampling powders.

Glove box isolators are totally enclosed devices with transparent windows and glove ports through which an operator performs the work. These devices were initially developed as a rectangular box design but have been adapted to different geometries. These units have the highest degree of barrier for containment, handling materials to below 1 $\mu g/m^3$ levels. As a less expensive alternative to glove box isolators, glove bags may be used. These bags have gloves like isolators and can be disposed of after use; typically they cannot be reused.

Rapid transfer ports (RTPs) are used to transfer materials from one container or piece of equipment to the other and consist of two halves that fit together and are sealed with O-rings. One half of the RTP is placed on the container and the mating half is placed on the equipment. RTPs provide a higher degree of containment than SBVs, allowing operations in the very low nanogram range.

When extremely high levels of containment are required, as in the handling of radioisotopes, automation (mechanical grippers), in combination with the approaches previously discussed, are used, automation most often used in a restricted sense to reduce the level of exposure using the above approaches. For example, the docking and undocking of SBV halves can be automated to reduce the peak exposure that occurs with these devices during makes and breaks.

19.3.4.3.4 Liquids and Gases Containment

The containment of liquids and gases poses some issues different from those of handling powders. Major sources of exposure risks from active liquids or liquids containing actives are the following:

- Aerosol or splashing from open containers
- Heated/vaporizing liquids forming an aerosol and carrying over material
- Leakage/sprays from leaking seals/gaskets
- Active solid residue from evaporated liquid

Failure of metallic equipment and piping walls is unusual for batch operations if pressure/vacuum checks are made between runs, safety venting is properly considered, and testing for corrosion/erosion is executed as part of the maintenance regimen.

Mechanical seals are commonly used on agitators, pumps, and other rotating equipment. A single mechanical seal presents a high risk factor; therefore, double mechanical seals are used to prevent leakage. Diaphragm and magnetically driven pumps are frequently used in applications where mechanical seal leakage is a problem, since these eliminate all seals.

Another approach is to totally enclose the gasketed/packed area in a sealed enclosure, which is typically capable of withstanding some pressure or vacuum, thereby ensuring

control of leakage. Many of these closed systems contain sensors at the source to report on leakage.

Atmospheric closed containment devices, splash guards, and drip pans are sealed fabric or sheeting "aprons" that can be installed around flanges and valves, attached with tie cords or metal clamps. These units vary from simple shields, which break up sprays but do not contain them, to units that have moderate containment and units that are available with flush and drainage connections.

When lines are connected to valves, flanges, and similar devices, there is a potential that they will leak when placed in operation. The best method of making and breaking these types of connections is a double-valved system that stops flow at both ends. These valves should also be contained, since there is a potential for leakage and spray during operation. A simple box with access ports that is negatively purged and connected to a drainage system can be used to accomplish this valve containment.

19.3.5 LABORATORY DESIGN CONSIDERATIONS

According to the National Fire Protection Association (NFPA), a laboratory can be defined as an environment where research, tests, and experiments are conducted using potentially hazardous materials. ANSI/AIHA/ASSE Z9.5, *Laboratory Ventilation* (AIHA 2012), requires that laboratory processes be limited to using benchtop apparatus and should not be a part of the process for producing finished goods.

The following subsections cover laboratory types, general HVAC considerations for laboratory spaces, specific laboratory types and their HVAC considerations, and laboratory ventilation systems and control applications.

19.3.5.1 Types of Laboratories

The type of laboratory varies depending on its purpose and the industry group in which it is being used, such as college laboratories, pharmaceutical QA/QC laboratories, biological laboratories, R&D laboratories, and the like. The various laboratory types are as follows:

- **General Laboratories.** General chemical and analytical laboratories are the most common types of laboratories. In these laboratories, fume hoods are widely used to contain hazardous fumes released during experiments. Safety and environmental goals in a chemistry laboratory are achieved by providing minimum overall ventilation (supply and exhaust) and adequate fume hood face velocity control. The airflows are balanced to ensure that laboratory airflow does not migrate to adjacent areas.
- **Animal Laboratories (Vivariums).** Animal laboratories house various quantities and types of animals for research work, demanding the highest level of equipment reliability and robust system controls.
- **Quality Assurance/Microbiology Laboratories.** Biological laboratories, the second most common type of laboratory, involve biological research and activities. Classified by the Centers for Disease Control and Prevention (CDC), biological laboratories are divided into four levels ranging from biosafety level 1 (BSL-1) (minimum hazard) to biosafety level 4 (BSL-4) (involving the most dangerous substances).
- **Aseptic Laboratories.** In support of pharmaceutical manufacturing, aseptic laboratories are used to test the process and final product along with the quality of incoming materials used for production.

- **Potent Compound Laboratories.** Potent compound laboratories are high-toxicity laboratories that have high hazard levels posed by the substances and chemicals being used depending on their OELs.

The primary objective of a laboratory HVAC system design is to achieve the following:

- **Occupational Safety.** The capture and containment of fumes by maintaining constant airflow across the fume hood face area.
- **Room Pressurization.** The provision of space pressurization control with respect to adjacent areas ensuring that the correct airflow direction is maintained by creating a differential between supply and exhaust airflows (offset control).
- **Ventilation.** The provision of adequate air changes to avoid accumulation of hazardous fumes in the laboratory (between 6 and 15 ach, usually 12 ach, is the industry common practice used for periods of occupancy).
- **Internal Cooling Loads.** The heat rejection from people, lights, and equipment. The user requirements (URs) define the acceptable range of space temperature control. Laboratories house devices used for measurement and research along with incubators and biosafety cabinets that reject heat into the space that might require more air than the minimum air change set for safety. Rightsizing internal loads is very critical so that the equipment is not oversized and that airflow rates are not higher than required (adversely affecting energy utilization). Studies have shown that the design criteria used for internal loads varies between 4 and 25 W/ft^2 (43 and 269 W/m^2). Benchmarking studies performed by Labs21 (Mathew et al. 2010) suggest that using 8 W/ft^2 (86 W/m^2) for internal load calculations is more realistic.
- **Comfort Control.** The provision of proper temperature and humidity control.

The scope of this section is limited to microbiological, quality control, aseptic, and potent compound laboratories as they are commonly used in pharmaceutical facilities.

19.3.5.2 General HVAC Considerations

Ventilation systems used for laboratories consume the majority of the energy required to operate laboratories. Ventilation air is not recirculated to prevent the accumulation of the dangerous chemicals in the laboratory air. This requirement is stipulated in OSHA's (2011) *Laboratory Safety Guidance*, *NFPA 45* (NFPA 2015), and AIHA/ASSE Z9.5 (AIHA 2012). However, each regulation can be interpreted slightly differently. (Refer to Section 7.10 of Chapter 7 for code precedence considerations.) While 29 CFR 1910 states that the ventilation system is to ensure that laboratory air is "continuously replaced so that concentrations of odoriferous or toxic substances do not increase during the workday" (GPO 2017), *NFPA 45* states that "air exhausted from laboratory hoods and other special local exhaust systems shall not be recirculated" (NFPA 2015, §8.4.1). AIHA/ASSE Z9.5 sets requirements for recirculation of the general exhaust; that is, exhaust other than exhaust air from the fume hoods. Acceptance of recirculation systems depends on the degree of the health hazard associated with the particular contaminant being exhausted as well as other technical, safety, and economic factors. The criteria allow that the general exhaust can be recirculated as long as the requirements are met. In summary, if any recirculation is considered, the air must not be recirculated from one laboratory to another laboratory or from high-hazard areas to low-hazard areas. The risks should be carefully evaluated and approval from the environmental, health, and safety officer should be obtained.

19.3.5.2.1 HVAC Design Parameters

The critical parameters for cleanroom HVAC systems are generally defined as space temperature, humidity, cleanliness classification (and microbial concentration within the space), filtration, pressurization, fresh makeup supply and return air, exhaust, and air change rates. Redundancy and reliability needs should be considered for the research functions performed in the laboratories. Redundant supply and exhaust air systems are required for the safety of the occupants.

Space Temperature

Outdoor design conditions need to be carefully evaluated and the proper design conditions selected. For 100% outdoor air units, which are used for laboratories, amongst other conditions, a 0.4% wet-bulb temperature should be used with coinciding dry-bulb temperatures as defined in Chapter 14, "Climatic Design Information," of *ASHRAE Handbook—Fundamentals* (ASHRAE 2013). The higher wet-bulb temperature means that higher outdoor air enthalpy will result in a higher cooling load, because the total cooling load is driven by the difference between outdoor air enthalpy and supply air enthalpy as defined in the following formula, where LMTD is logarithmic mean temperature differential:

$$Q_{total} = U \times A \times \text{LMTD}$$

where

$$\text{LMTD} = \frac{\Delta T_2 - \Delta T_1}{\ln(\Delta T_2 - \Delta T_1)}$$

Using a higher dry-bulb temperature along with a higher wet-bulb temperature is not the appropriate approach. This is because a lower dry-bulb temperature will result in a larger coil, as the coinciding dry-bulb temperature is always lower than the maximum dry-bulb temperature seen during high-humidity conditions. This is shown in Figure 19.7.

Low dry-bulb temperatures will reduce the LMTD used to calculate the coil face area. This will result in a larger coil to deliver the same cooling capacity. Note, however, that unlike laboratories, for design conditions for office-type spaces designers should use the ASHRAE 0.4% dry-bulb and coinciding wet-bulb temperatures (ASHRAE 2013) since these types of spaces are more building-envelope-load driven. Using a higher dry-bulb temperature will result in higher envelope loads, which is a better design approach for office-type buildings.

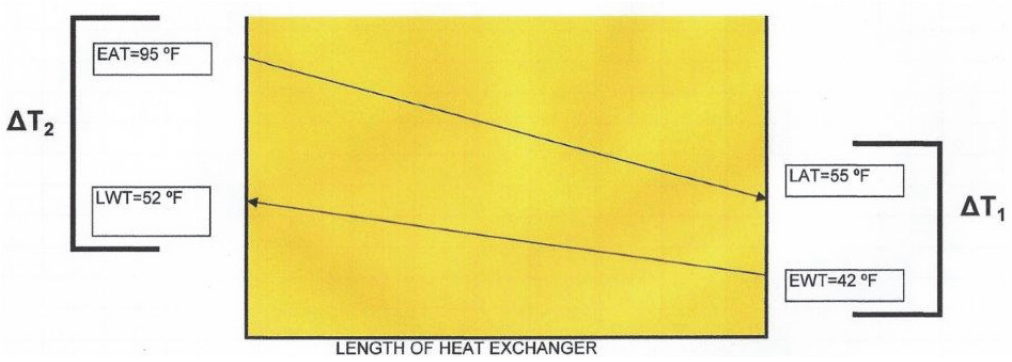

Figure 19.7 LMTD for Heat Exchangers

Indoor space temperatures can range from 65°F to 75°F (18°C to 24°C) based on the laboratory type. National Institutes of Health (NIH) guidelines direct that the space temperature be maintained between 70°F – 2°F (21°C – 1°C) for winter and 73°F + 3°F (22.8°C + 1.7°C) for summer. ASHRAE Standard 55 (ASHRAE 2016) should be taken in consideration for human comfort. However, each laboratory space should be evaluated individually for its function and processes performed. The product quality and accuracy of the test performed might require a different, tighter temperature control.

Humidity

The industry-accepted criteria for laboratory humidity is 30% – 10% for winter and 50% + 10% for summer. The summer conditions are for comfort and to limit microbial growth, and the winter conditions are for human comfort and to prevent the buildup of static electricity.

Cleanliness Classification

Space cleanliness levels might be required for some laboratories in pharmaceutical facilities. The cleanliness level can be classified as defined by ISO 14644-1 (ISO 2015). The laboratory space cleanliness is generally classified between ISO Class 5 and ISO Class 8. It should be noted that EU requirements, not fully equivalent, are Grades B to D (EC 2010).

Cleanliness levels also define microbial concentrations, in colony-forming units (CFUs). This is more detailed in EudraLex (EC 2010) and defined for each cleanliness classification.

Filtration

Filtration levels vary depending on the laboratory use group. General analytical laboratories that do not require any cleanliness level can be provided with air-handling level filtration minimum efficiency reporting values (MERVs) at MERV 8 (30%) prefiltration and MERV 14 (85%) after-filtration. It is recommended to use higher filtration at the final stage downstream of the coils and the fan. This can range from MERV 16 filters (95% at 0.3 μm) to HEPA filters at 99.97% at the MPPS to control the particulates at the source. Clean spaces can be provided with terminal HEPA filters installed in the ceiling or HEPA filters installed inside the AHUs serving the cleanrooms.

Pressurization

Space pressure control is limited to directional airflow into or out of the laboratory space. Active pressure control is very difficult to achieve because personnel traffic into and out of the laboratories is usually quite high and air locks are not commonly used. Space pressure control is further discussed in Section 19.3.5.4.

Fresh Makeup Supply and Return Air

General analytical laboratories, biological laboratories (BSL-2 and above), and quality assurance laboratories using hazardous chemicals are required to have once-through supply air (100% outdoor air). Microbiology and quality assurance laboratories that are classified as cleanrooms can be designed with a recirculation system as long as the supply air is not recirculated to the other spaces. Avoiding recirculation between spaces reduces the energy use and prevents cross-contamination.

Exhaust

Exhaust air from fume hoods and other equipment that use hazardous chemicals must discharge to atmosphere. General exhaust from laboratories is not allowed to be recircu-

lated through other spaces and should be exhausted to atmosphere as well. The general laboratory exhaust and equipment exhaust can be combined as long they are chemically compatible. The exhaust airstreams coming from different laboratory units defined by *NFPA 45* (NFPA 2015) and the NIH *Design Requirements Manual for Biomedical Laboratories and Animal Research Facilities* (known as DRM; NIH 2008) cannot be combined inside the building unless they penetrate the last fire wall, such as duct shafts connecting floors to each other. In accordance with the *International Mechanical Code*® (ICC 2014c) and *NFPA 45*, fire dampers are not allowed in laboratory exhaust systems. Special attention is required when designing the exhaust systems. The exhaust discharge points and intakes should be evaluated and adequate separation should be provided to prevent reentrainment of the exhaust air into the fresh-air intakes. A minimum 3000 fpm (15.25 m/s) is an acceptable criterion for discharge velocity. Concentration of the chemicals used in fume hoods needs to be reduced to their 1/2 immediately dangerous to life and health (IDLH) level at the discharge point to the atmosphere, as defined in Section 3704 of the *International Fire Code*® (ICC 2014b).

Treatment of the exhaust air might be required to reduce the contamination concentration level to a safe level. This can be achieved by filtering, scrubbing, abetting, or simply diluting the exhaust air. The need for treatment is governed by the *International Fire Code*® (ICC 2014b). Dilution can be achieved by using venturi type exhaust fans. Dilution rates and separation between the intake and exhaust locations should be evaluated by using computational fluid dynamics (CFD) modeling. After modeling, the exhaust locations and discharge velocities can be confirmed for safe operation.

Air Change Rates

29 CFR 1910 states that "4 to 12 room air changes per hour is normally adequate general ventilation if the local exhaust system, such as fume hoods, is used as the primary method of control" (GPO 2017). The NIH DRM states that the "Ventilation rate for research laboratories is typically driven by three factors: fume hood demand, cooling loads, and removal of fume and odors from the work area" (NIH 2008, pp. 6–14). The minimum ventilation rate for a laboratory space is 6 ach, regardless of the space cooling requirement. Normally the cooling load, due to the equipment, drives the air change rate in biological research laboratories. The air change rate can be as high as 25 ach in a research laboratory. If the laboratory space is classified as cleanroom, it can be as high as 40 ach (ISO Class 7).

19.3.5.3 Specific Laboratory Types and Their HVAC Considerations

19.3.5.3.1 Quality Assurance/Microbiology Laboratories

Quality assurance/microbiology control types of laboratories are usually seen in biotechnology and pharmaceutical facilities and are used for microbiology testing and quality assurance (QA) and control areas. As defined previously, these laboratories are not chemical or analytical laboratories. In a solid dosage or API facility, however, chemical analysis is the primary testing being done. It is industry practice not to classify microbiology laboratories. These laboratories, however, are often designed as ISO Class 8 cleanrooms that require air recirculation rates between 15 and 30 ach. This, however, is not a regulatory requirement. If once-through airflow is required, a considerable amount of operational energy could be expended. Recirculation of the supply air can be considered as long as it is filtered with HEPA filters before being introduced back into the same space. To achieve the desired cleanliness level, as long as adequate outdoor air is used to replenish the space air, recirculation can be considered.

19.3.5.3.2 Biological Laboratories

The NIH guidelines for laboratory facilities having a BSL-2 containment level require once-through air systems (100% outdoor air) (NIH 2008). However, Appendix K-IV of *NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules* (NIH 2016) does not require 100% outdoor air for HVAC systems. Similarly, no specific reference to once-through building air systems is found in Directive 98/91/EC for BL-2 Large-Scale facilities (containment level 2 for the European Commission), which was established by the European Commission's expert working group on containment for genetically modified organisms for containment level 2 facilities for Europe. The NIH (2016) guideline requires segregation of the areas for biocontainment by providing adequate gowning/degowning procedures, air-handling system zoning, and pressurization control between spaces. Also, International Society for Pharmaceutical Engineering (ISPE) guidelines (ISPE 2009) cautiously recommend using a recirculation system within the same area if no hazardous materials exist in the airstream. From a GMP regulatory and operations perspective, the key requirement of the HVAC system is to prevent contamination of the product from environmental sources and to prevent cross-contamination of the product from batch to batch or strain to strain. In addition, the HVAC system should provide secondary containment to ensure operator safety and to protect the environment. For additional discussion, see the article by Babur (2008).

19.3.5.3.3 Aseptic Laboratories

In aseptic laboratories, differing from other laboratory types, the space pressure is maintained positive in relation to the adjacent spaces and corridors. Aseptic laboratories need to be isolated from the corridors via air locks as shown in Figure 19.8. The doors opening to the air locks are interlocked to prevent simultaneous opening and closing. (*Note:* it must be remembered that certain local codes do not allow interlocks for life safety reasons. If this is the case, go/no-go lights are used with a higher degree of reliance on procedures.)

It is recommended that a 0.04–0.06 in. w.c. (10–15 Pa) pressure differential be maintained between adjacent spaces and aseptic laboratories. Laboratory samples are manipulated in laminar-flow cabinets that use HEPA-filtered recirculation air. If samples are hazardous, isolators, biosafety cabinets, or glove boxes are used to protect the users and the environment.

The space temperature should be maintained between 65°F and 70°F (18°C and 21°C) due to the special gowning requirements needed to maintain space aseptic conditions. Relative humidity is designed to be a maximum of 50% to minimize microbial

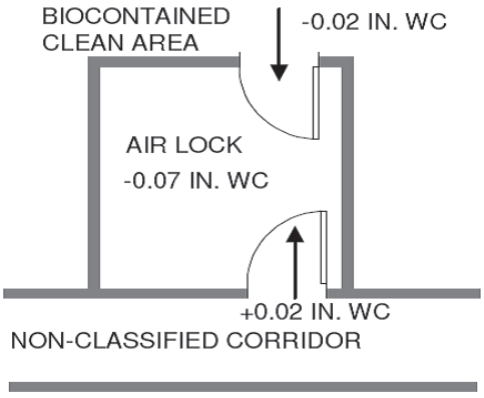

Figure 19.8 Aseptic Laboratory Air Lock

growth within the laboratory. Some aseptic laboratories are designed as cleanrooms if required by the owner, but this is not a GMP requirement. Air change rates of 30 to 60 ach can be seen in these kinds of laboratories. Supply and exhaust/return locations should be carefully evaluated for proper air recirculation within the space. Terminal HEPA-filtered supply air in the ceiling and low-level returns provide good air movement and serve to remove contaminants from the space quickly.

19.3.5.3.4 Potent Compound (Kilo) Laboratories

The primary requirement in the design of potent compound laboratories is containment. In these laboratories, potent compounds are manipulated within isolators or glove boxes. No recirculation of the supply air is allowed for this type of laboratory. Exhaust air is extracted from the space and, depending on the hazard level, it is treated before being discharged into the atmosphere. Pressure hierarchy is strictly maintained for containment. Air locks are used to isolate the space from the adjacent spaces. Usually double air locks are used to ensure absolute protection of the adjacent spaces. The first air lock is designed as a sink (negative pressure) type air lock and the second air lock is designed as a bubble (positive) type air lock that makes the potent compound room negative in respect to the air lock (see Figure 19.9). Space temperature and humidity conditions are similar to those for aseptic laboratories, as operations personnel may require special gowning for protection from the potent compound.

19.3.5.4 Ventilation Systems and Control Applications

Deciding how to best control the HVAC needs of a laboratory depends on many factors: safety, energy use, installation cost, size, flexibility, and maintenance. The most common ventilation systems applied to laboratories are the following:

- Constant-air-volume (CAV) system—Monitoring only
- CAV system—Monitoring and control
- CAV system—Two State, Occupied and Unoccupied”
- Variable-air-volume (VAV) system

19.3.5.4.1 CAV System—Monitoring Only

Constant-air-volume (CAV) systems are the simplest systems from design, installation, and maintenance viewpoints. In a CAV monitoring-only system, in the room a constant air supply and exhaust are provided, controlled by manual valves. A manual balancing damper is set to maintain a constant face velocity across the face of the fume hoods. Fume hoods used in this design concept must be the bypass type that maintain constant exhaust airflow regardless of the fume hood sash opening. The laboratory

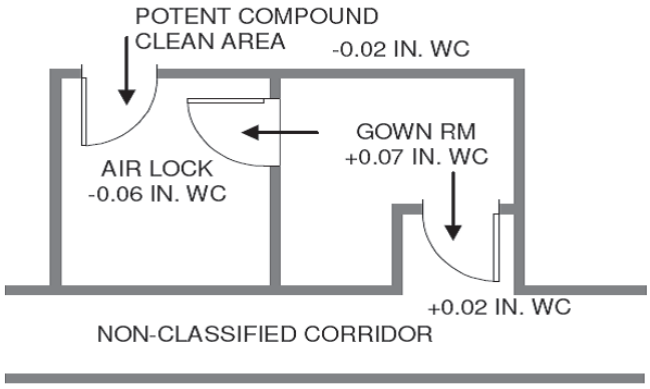

Figure 19.9 Potent Compound Laboratory Airlock

makeup air is balanced to a slightly lower rate to maintain space pressure. However, if the space internal loads are the driving force of the space makeup airflow, general space exhaust needs to be provided to maintain space pressure. Laboratories with high internal loads could result in more than a 12 ach ventilation rate. The space temperature control is provided by reheating the makeup air. This design does not take the fume hood or internal load diversification into consideration. The system runs at full flow and capacity during occupied and unoccupied periods, 24 hours a day, 7 days a week. For a CAV monitoring-only system, airflow control devices are not installed in the ductwork serving the space. All branch ductwork is manually balanced and locked in place, having pressure-dependent control. See Figure 19.10 for a CAV monitoring-only system.

19.3.5.4.2 CAV System—Monitoring and Control

The CAV monitoring and control system (Figure 19.11, similar to a CAV system using venturi type air valves) is similar to the CAV monitoring-only system except that this type of system makes use of fixed flow valves that constantly adjust the flow by using either a flowmeter that provides feedback to control damper position or spring tension that changes the orifice size to maintain constant flow. Because this system employs some level of controls, it has a higher initial cost than the monitoring-only system. This system is a self-balancing system and does not use any control wiring or pneumatics.

19.3.5.4.3 CAV System—Two State, Occupied and Unoccupied

In the two-state CAV system approach (Figure 19.12), the laboratory HVAC system uses valves with two fixed positions, full flow and low flow. The operating position is at full flow during occupied periods. Low flow, which maintains a safe environment, is used when the laboratory is not occupied. This is also called *night setback mode*.

There are two control modes that can be executed by the building automation system (BAS). An occupancy schedule is the most commonly used control strategy and can be overridden by a phone call or occupancy sensor. Light switches or sash opening position

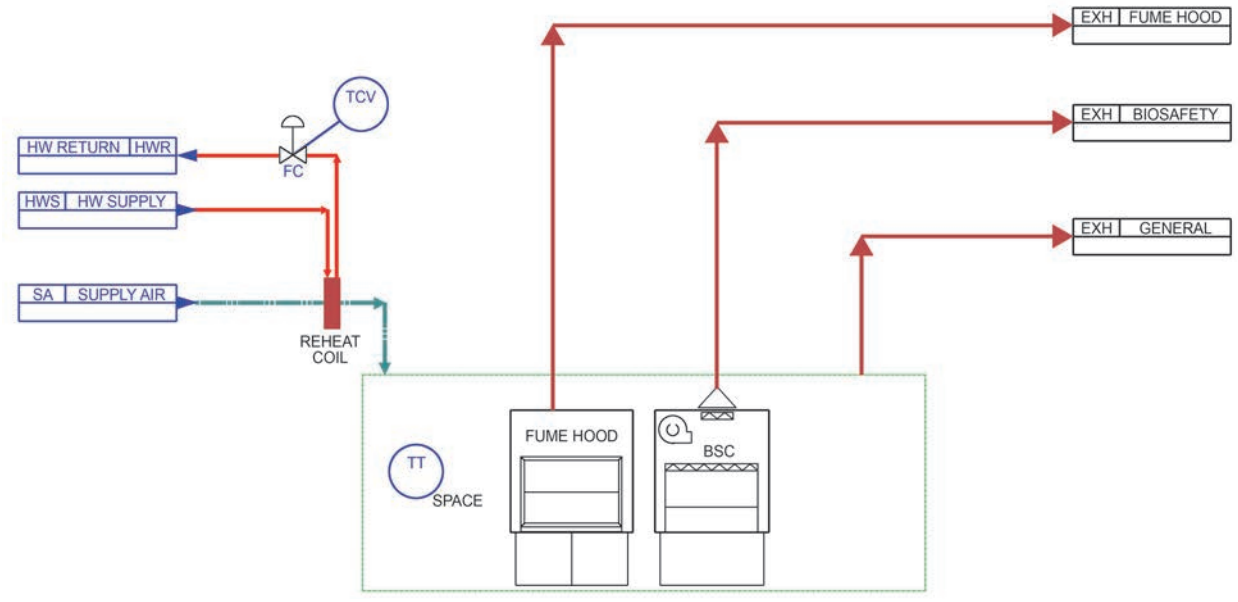

Figure 19.10
CAV System—Monitoring Only

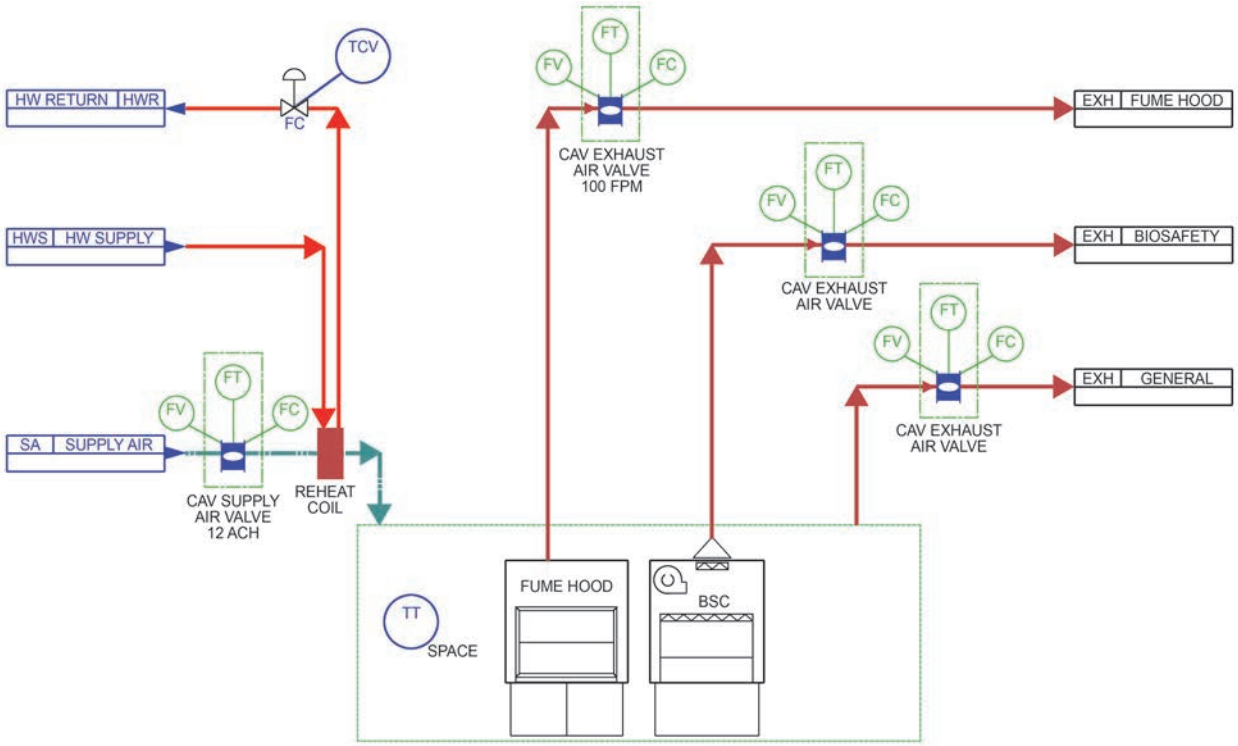

Figure 19.11
CAV System—Monitoring and Control

switches are also used; however, their use might not result in a significant energy savings since the lights and sashes could be left in the on or open position, respectively. The best solution is to use motion sensors along with a time schedule.

19.3.5.4.4 VAV System

A variable-air-volume (VAV) system modulates the exhaust and makeup airflow rates to ensure safety in the laboratory. The exhaust airflow varies depending on the fume hood sash opening and maintains a safe face velocity. The makeup airflow rate tracks the exhaust airflow rate within the calculated airflow offset value and maintains accurate directional airflow across the doors to contain laboratory air within the space.

This system is beneficial if the fume hood exhaust or the internal loads are driving the makeup airflow. Each space is provided with general space exhaust along with fume hood exhaust. If the fume hood exhaust drops below the minimum ventilation airflow, depending on day or night operation mode, the general exhaust makes up the difference. For a laboratory that is fume hood or internal load intensive, the operating cost savings can be substantial.

A VAV laboratory system (Figure 19.13) is installed and operated in conjunction with a BAS. The controls are very complicated, and this is the most costly system among all laboratory systems. However, first-time savings of reduced-size HVAC equipment can be realized by using a diversity factor, which is calculated based on the reasonable and agreed-upon assumption that at any given time some of the hoods will be in the closed position. In addition, a diversity factor can be taken on all the equipment in the room to reduce airflow. This calculation reduces the sizes of the fans as well as the heating and cooling coils, ductwork, and associated components of the system for the diversified

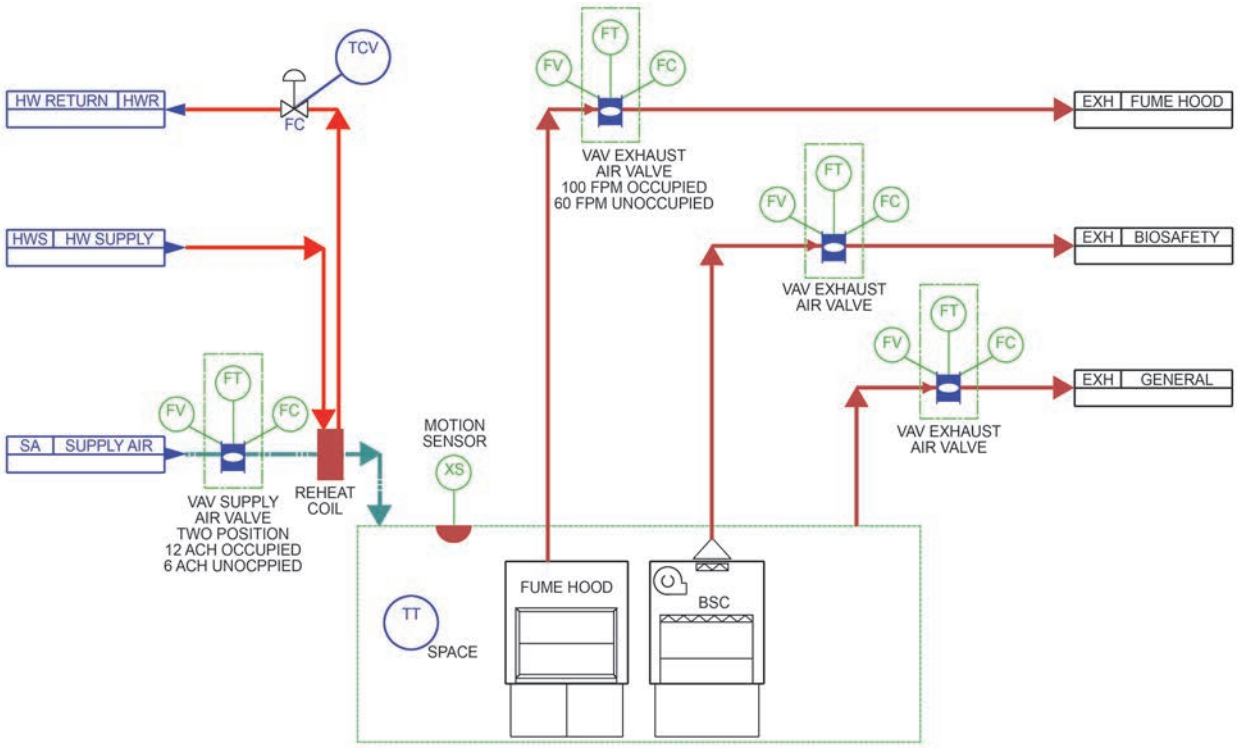

Figure 19.12
CAV System—Two State, Occupied and Unoccupied

reduced loads and airflows. It is most important, though, that the owner and the laboratory operators understand that the use of such factors may limit the laboratory's operational capabilities and flexibilities, because diversity factors are determined from experiences and cannot be realized if the system operation differs from the design conditions.

19.4 RESOURCES

The resources listed in the following subsections are those that the authors find of particular value throughout the design of pharmaceutical and other life-science cleanrooms.

19.4.1 ORGANIZATIONS

- Agency for Healthcare Research and Quality (AHRQ), www.ahrq.gov
- Bureau of Alcohol, Tobacco, Firearms and Explosives (ATF) (U.S. Department of Justice), www.atf.gov
- Centers for Disease Control and Prevention (CDC), www.cdc.gov
- Centers for Medicare and Medicaid Services (CMS), www.cms.gov
- China Food and Drug Administration (CFDA), http://eng.sfda.gov.cn
- European Medicines Agency (EMA), www.ema.europa.eu
- Health Products Regulatory Authority (HPRA), www.hpra.ie/default.aspx
- International Society for Pharmaceutical Engineering (ISPE), www.ispe.org
- Medicines and Healthcare Products Regulatory Agency (MHRA) (United Kingdom), www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency

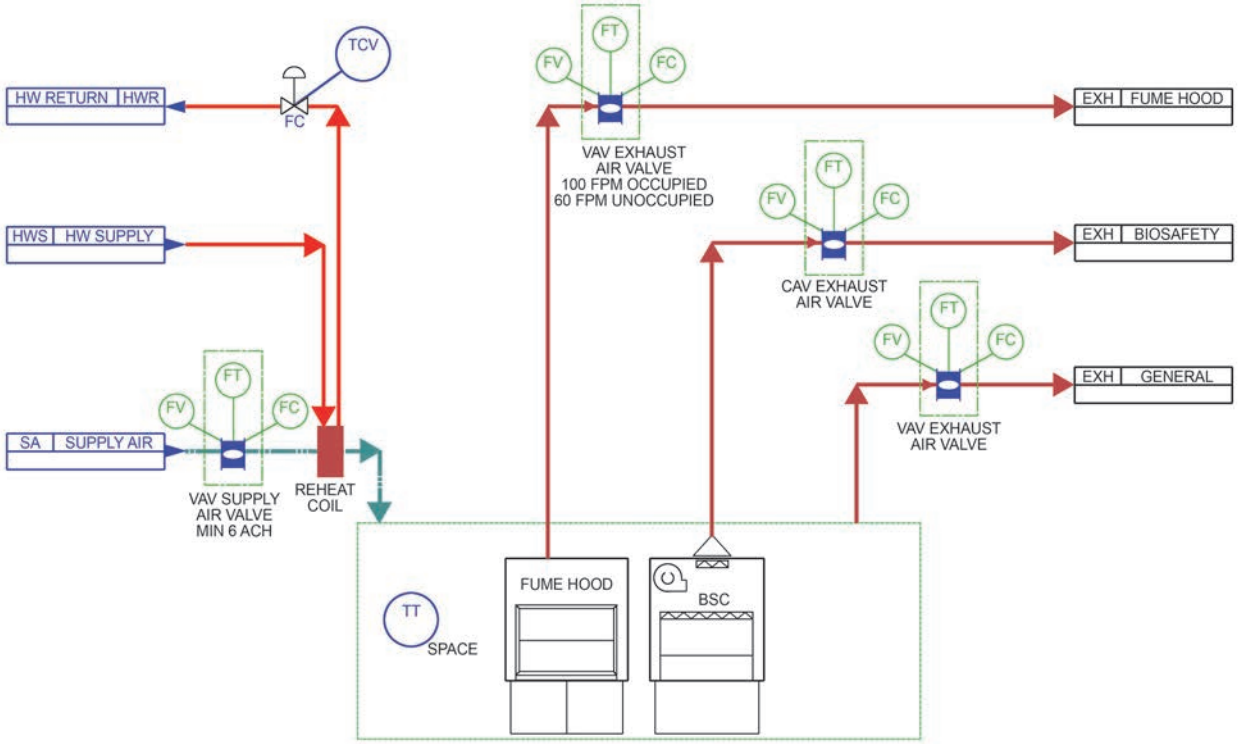

Figure 19.13
VAV System

- Ministry of Health, Labour and Welfare (MHLW) (Japan), www.mhlw.go.jp/english
- National Institutes of Health (NIH), www.nih.gov
- Pharmaceutical Inspection Co-Operation Scheme (PIC/S), www.picscheme.org
- The National Institute for Occupational Safety and Health (NIOSH) (U.S. Department of Health and Human Services), www.cdc.gov/niosh
- Therapeutic Products Directorate (TPD) (Canada), www.hc-sc.gc.ca/ahc-asc/branch-dirgen/hpfb-dgpsa/tpd-dpt/index-eng.php
- The Therapeutic Goods Administration (TGA) (Australia), www.tga.gov.au
- U.S. Drug Enforcement Administration (DEA) (U.S. Department of Justice), www.dea.gov
- U.S. Food and Drug Administration (FDA), www.fda.gov
- World Health Organization (WHO), www.who.int

19.4.2 PUBLICATIONS

- 21 CFR Part 11
- 21 CFR Part 210 and Part 211
- *2015 International Building Code® Illustrated Handbook*
- AHIA/ASSE Z9.5, *Laboratory Ventilation*
- *Cleanroom Magazine*, https://issuu.com/cleanroommagazin/docs/layout_crmagazin_21_englisch_rgb_al
- *Controlled Environments*, www.cemag.us
- Decision Making Confidence, http://www.decision-making-confidence.com/kepner-tregoe-decision-making.html

- *Design Requirements Manual for Biomedical Laboratories and Animal Research Facilities*
- *EU Guidelines to Good Manufacturing Practice—Medicinal Products for Human and Veterinary Use*, Volume 4 of *EudraLex—The Rules Governing Medicinal Products in the European Union*
  - Annex 1: Manufacture of Sterile Medicinal Products
  - Annex 2: Manufacture of Biological Active Substances and Medicinal Products for Human Use
- *Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing—Current Good Manufacturing Practice*
- Guide Q7, *Good Manufacturing Practice Guide for Active Pharmaceutical Ingredients*
- *Guidelines for Planning and Design of Biomedical Research Laboratory Facilities*
- ISO 14644, *Cleanrooms and Associated Controlled Environments*
- ISPE's *Baseline® Pharmaceutical Engineering Guides for New and Renovated Facilities*
  - Volume 1: *Active Pharmaceutical Ingredients*
  - Volume 2: *Oral Solid Dosage Forms*
  - Volume 3: *Sterile Product Manufacturing Facilities*
  - Volume 4: *Water and Steam Systems*
  - Volume 5: *Commissioning and Qualification*
  - Volume 6: *Biopharmaceuticals*
  - Volume 7: *Risk-Based Manufacture of Pharmaceutical Products*
- *ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning (HVAC)*
- *ISPE Good Practice Guide: Quality Laboratory Facilities*
- *Laboratories for the 21st Century: Best Practice Guide—Commissioning Ventilated Containment Systems in the Laboratory*
- *Laboratory Control and Safety Solutions Application Guide*
- *NFPA 45: Standard on Fire Protection for Laboratories Using Chemicals*
- *PDA Journal of Pharmaceutical Science and Technology*, http://journal.pda.org/
- *Phoenix Controls Laboratory Sourcebook*
- "Position Paper: Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments"
- *Problem Seeking: An Architectural Programming Primer*

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20 Cleanrooms in Biotechnology and Health Care Facilities

20.1 GENERAL REQUIREMENTS FOR BIOTECHNOLOGY FACILITIES

Biopharmaceutical or biological medical product manufacturing processes and environments must be engineered to ensure safe and dependable and repeatable processes following principles applicable to pharmaceutical facilities (see Chapter 19). The U.S. Food and Drug Administration (FDA) and similar governing bodies, such as the European Medicines Agency (EMA) in Europe and Health Canada, are responsible for ensuring that safe and effective drugs are licensed and produced. FDA licensing is based on clinical trial data, and the resultant manufacturing process must replicate the specific fabrication technique and methodology of the clinical trials in a repeatable and reliable manner. This aspect is critical to biopharmaceutical drug production because the quality, effectiveness, and safety of biopharmaceutical drugs are dependent on the specific production processes rather than solely on the final chemical composition of the product. As biopharmaceutical processes are enlarged from laboratory scale to manufacturing levels, process and environmental controls are needed to supplement the operational procedures and responsibilities to ensure consistent and repeatable processing steps and overall drug production results. Proper operating conditions and reliable facility designs minimize potential health risks for patients and associated liabilities for manufacturers.

Quality-based manufacturing procedures and policies provide a philosophy and methodology that ensures pharmaceutical products are manufactured safely and repeatedly in compliance within the specifics identified during the drug licensing process. Collectively, the set of procedures and practices that deliver pharmaceutical manufacturing consistency and safety are known as Current Good Manufacturing Practices (CGMPs) (see Section 19.1.2 of Chapter 19 for a detailed discussion of CGMPs). It is critical that these CGMPs are kept up to date to reflect industry lessons learned and to incorporate new technologies and techniques that address inherent challenges more effectively. Operational savings yield more funding for scientific research and new drug development, so careful adherence to CGMPs promote the growth of life-saving technologies that are the basis of the pharmaceutical industry.

The FDA and other pharmaceutical manufacturing regulating agencies have established minimum requirements to ensure public safety. These requirements provide a framework for manufacturers to establish quality policies that ensure safety and consistency. The overall goal of engineering operations is to establish methods and procedures

that incorporate compliance with CGMPs and corporate policies and deliver reliable systems at the least total cost of ownership.

Biopharmaceutical manufacturing facilities are designed to support the pharmaceutical process requirements using the best allocation of capital. Mechanical systems require careful design and installation for successful manufacturing operations and the prevention of contamination, including the control and alarming of the environment for processing drug products and drug substances. A longer and more realistic view of the costs and value of facility investments usually improves the design goals and outcomes. Attention to design details pays big dividends when it comes to facility siting, layout, equipment sizing, capacity, flexibility, sustainability, reliability, redundancy, and longevity considerations. In an ever-growing drug market, flexible and expandable facility and utility system configurations support efficient and economical operations. With modern technological developments, there is often a need to use designs that are more appropriate and effective than those previously used for diverse pharmaceutical applications and challenging requirements, such as powder or hazard handling in a cleanroom environment. Additionally, there are advanced design strategies that enable equipment size reductions and capital cost savings that compensate for the additional controls and monitoring needed for best operations.

HVAC systems must provide well defined, consistent, and controlled environments with sufficient monitoring points to demonstrate continuous compliance with specific process requirements. Monitoring and alarms must provide documentation of continuous proper system operations and must notify system operators of any and all deviations from specified operating parameters. This applies equally to specific manufacturing processes, the environment that supports the manufacturing equipment, raw material handling, filling, packaging, labeling, and transportation of the final drug product.

Cross-contamination potential exists whenever there is a pathway between areas processing different compounds. Facilities and systems must be designed to minimize potential opportunities for contact with foreign airborne or surface compounds. This applies to compounds from different product lines and from different portions of the same pharmaceutical manufacturing process and has a large impact on proper facility and HVAC system design.

In biopharmaceutical plants, work-flow-based layouts, operational area segregation, properly conditioned and high-efficiency particulate air (HEPA) filtered airflows, room pressurization strategies, routine cleaning, and environmental monitoring, along with employee work procedures, are essential factors that ensure contamination control for safe drug manufacturing.

20.2 BIOTECHNOLOGY FACILITIES DESIGN GUIDELINES

Biopharmaceutical manufacturing facilities are commonly designated by the governing organization, such as the FDA or EMA, as drug substance or drug product facilities, depending on their output. Drug substance facilities are involved with creating, inoculating, fermenting, and incorporating the raw materials and processes that enable a drug to be produced, refined, isolated and purified. Drug product facilities process the finished drug through operations for filling, capping, sealing, labeling, and distribution.

Most drug substance operations involve the growth of biological entities and are carried out in sealed containers, such as temperature- and pressure-controlled fermentation tanks. Where there is no pathway for the ambient air to impact or interact with the drug

substance, this is deemed a *closed process*. In closed processes, the surrounding environment has no pathway to impact the growth or processing of the drugs, so a relaxed state of environmental control may be warranted. However, even in this relaxed state there is a need to provide documentation that environmental control exists sufficient to support safe and repeatable manufacturing operations.

Many process steps involve an *open process*, which refers to an operation where the drug or its processing ingredients are exposed to the air in a cleanroom. Many applications require sampling and in-process testing to ensure compliance, which may expose drug substances or components to the ambient environment. Areas where these open operations are required, and often the entire room where they are carried out, must have specific HVAC measures implemented to ensure that there is no resulting contamination from the ambient environment. These design measures are often more stringent than those required for closed processing steps depending on the specific challenges, including localized containment devices, elevated room pressurization levels, vestibules, or air locks.

Aseptic processing involves a higher level of environmental control than any other closed or open processes because it refers to portions of the drug manufacturing process where the finished product is exposed to the ambient cleanroom air and there are no other inspection points available to confirm that no contamination has occurred. This level of cleanroom environment is common where drugs are dispensed into their final containers (vials, ampules, or other sealed packaging). To prevent contamination and procedural errors, aseptic processing regions are established within specifically defined areas using sufficient environmental control and monitoring systems to ensure and document that all critical parameters are continuously maintained, using terminal HEPA filters in all available ceiling areas and glass or plastic airflow-guiding barriers to deliver consistent and unidirectional airflow patterns that do not allow any upwelling (air traveling upwards from below the surface). Common aseptic application practice is to provide double HEPA filtration, usually an in-line HEPA filter bank in the air handler and additional terminal HEPA filtration at the room level.

A common open processing step in biopharmaceutical applications is inoculation, where specific living organisms begin their growth and fermentation stage. This is an aseptic processing step where double HEPA filtration is achieved using a protective HEPA-filtered recirculated laminar flow hood. A contamination problem encountered during this operation does not have the same extreme cost impact as a contamination problem discovered during final fill operations as long as there are subsequent downstream inspection or testing opportunities; therefore, extreme levels of contamination protection redundancy may not be justifiable.

Other challenging biopharmaceutical HVAC applications include powder handling and hazardous compound containment within cleanrooms. Cleanliness concerns drive the designs of most drug processing cleanrooms to be positively pressurized with respect to adjacent rooms. Alternatively, where hazardous, pharmaceutically active, or potent compounds are used, rooms are usually designed to be negative to adjacent spaces. This apparent dilemma between containment and cleanliness, or process purity versus operator safety, is a challenge to creative designers and a common source of conflicting design requirements. Design solutions are available that do not sacrifice containment for cleanliness concerns and do not limit operational work flow optimizations. An optimized solution may result from designing a portion of the cleanroom with a directional room-level airflow toward the containment device or region. Whether the containment device is a slot hood for powder handling or a fume hood, arranging the HVAC supply outlets at one end of a short region, hallway, or vestibule to create a room-level average airflow veloc-

ity of approximately 40 fpm (0.2 m/s) or more may be sufficient to supplement the contained area so the overall room can remain positive to adjacent areas while providing enhanced containment. This measure, with properly designed slot hoods or barrel slot exhausts, has proven effectiveness without requiring a separate room for segregating processing activities.

20.3 CONTROL OF PARTICLE AND MICROBIOLOGICAL CONTAMINATION

The control of both particulate and microbial contamination is of great concern for biopharmaceutical manufacturing operations. In addition to particulate contaminants, viable contaminants (microbes, spores, and anything that can exhibit biological growth) must be controlled and monitored throughout biopharmaceutical manufacturing operations. Due to the inherent biological nature of the processes in biopharmaceutical facilities, there is the potential for more harm from biological contamination than in traditional pharmaceutical applications. For these reasons, biopharmaceutical manufacturing facilities are designed with features that provide enhanced protection against biological contamination.

Cleanroom contaminants are introduced through particulate sources within a cleanroom and ambient airborne contaminants that pass through the HVAC filtration. Both contaminant pathways can introduce viable as well as nonviable particulates.

HVAC system designs that mitigate these particulate sources are implemented as determined by risk-based design processes. Outdoor sources of contamination can be minimized with corrosion-resistant air handler components; crevice-free, nonshedding, cleanable HVAC equipment interiors; effective air filtration with tight-sealing no-leak filter frames; proper airflow and air register locations for good room air circulation patterns; and stable operational controls to maintain the validated state effectively.

Indoor contamination sources are controlled through controlled personnel procedures; proper processing equipment designs; and strategic air supply, return, and exhaust register locations to enhance containment. The control of the room airflow patterns and, therefore, the specific airflow quantities through each register are important to demonstrate consistency and persistence of the validated state. Once a facility design is implemented, a qualification process is necessary for compliance with regulations (see Chapter 17 for further discussion on qualification). The HVAC system and overall facility design must have sufficient controls to demonstrate that all licensing agreements will be maintained in a robust state that matches the conditions during the qualification period. Control strategies and equipment must be designed to provide records that all critical operating parameters are held within acceptable ranges during the qualification period and during all times of subsequent facility operations. This implies that all variable loads (such as HVAC filters) must be addressed with compensating utility generation and distribution technologies so room-level conditions are held consistently within the ranges qualified during the validation process. If an HVAC design is implemented without the ability to compensate for filter loading, the qualification must be done over the full range of resulting field conditions. This usually involves excessive execution time and complications, so variable-frequency drives (VFDs) and energy-efficient distribution system controls are often the best approach. There are other operational benefits to using stable VFD-based and similar HVAC controls, including reduced project implementation timelines due to simplified air balancing, improved energy efficiency, reduced system shutdown requirements, power monitoring, rapid diagnostics, and thorough system alarming.

For biopharmaceutical applications, contamination potential involving biological or chemically reactive compounds poses great concerns because of the increased susceptibility of biological processes. Potent or reactive compounds need to be segregated from the controlled processes through cross-contamination control. One compound used during upstream processing may be harmful to subsequent processing steps, so cross-contamination even within one product line can lead to a lost batch. In facilities running multiple pharmaceutical manufacturing products, cross-contamination concerns drive designers to segregate processing areas, work flows, and HVAC systems by processing stage using HEPA filters or a monitored differential pressure as a barrier across potential contamination pathways.

In many cases, the most effective method of contamination control is the localized exhaust of undesirable particulates at or near the generation sources. These may be best addressed through directed exhausts and minienvironments formed by hard walls and contaminant-capturing equipment such as exhaust canopies, slots, or fume hoods. In these designs, a demonstration of stable process control and consistent environmental conditions is critical to providing the engineering defendability necessary for facility licensing efforts.

Nonprocessing areas within a biopharmaceutical manufacturing facility require careful designs because they are often adjacent to controlled processing areas. Even areas outside the controlled areas need consistency in HVAC control because their resulting room pressurization fluctuations may impact the processing room pressurizations. Care must be taken in design strategies and choices to provide effective environmental control in all areas of a drug manufacturing plant to avoid unanticipated interactions between controlled and noncontrolled areas.

20.4 ENGINEERING DESIGN CONSIDERATIONS FOR VALIDATED SYSTEMS

All engineered installations for pharmaceutical and biotechnology manufacturing must be designed for control and alarming of critical parameters. Validation is a quality-based process that confirms that proper designs, installations, operations, and maintenance have been achieved.

Inherent in the validation process is a confirmation that the facility and operational procedures will result in safe and consistent drug manufacturing. The following features of the validation process must be reflected in the facility and process design to provide an effective drug manufacturing operation:

- The impact of a properly qualified system is correct and repeatable operational steps that result in manufactured products for human consumption. It is critical that all processes be reviewed and documented for independent verification. If it is not documented, it did not occur.
- Validation activities monitor and record system parameters and variables determined to be critical to the specific process.
- Validation activities usually occur over a limited time period.
- Validation activities must be repeated in response to significant changes or process deviations when appropriate to ensure drug manufacturing quality and consistency. This is referred to as *revalidation*.
- The implication of a properly validated system is that the critical parameters are maintained at the acceptable levels between periods of revalidation.

- If a system is not designed to control the critical parameters precisely, appropriate alarming or routine system monitoring must be included to verify that everything is operating within the acceptable ranges.
- If it is discovered that the system is not controlling a critical parameter appropriately, the medicine manufactured during that time period cannot be used for human consumption.
- If a system does not deliver the appropriate stability or if the critical parameters are not continuously monitored, there may not be sufficient documentation that everything was manufactured properly.

Often for marketed products, the impact of a batch that was not manufactured exactly as the process requires results in a loss of product in the distribution pipeline. This loss must be made up quickly enough so the impact is a reduction of stockroom supplies and not a shortage of medicine.

For clinical products, a loss or shortage of product may impact patient health, market timing for new product launches, market share, or overall market due to competition from other manufacturers.

20.5 ROOM PRESSURE AND VENTILATION REQUIREMENTS

20.5.1 FACILITY DESIGN

As stated previously, contamination control is a key requirement of pharmaceutical manufacturing facility design, and mechanical system designs are driven by specific indoor environmental control requirements. The layout of the manufacturing facility and associated utility generation and distribution system designs must be guided by CGMP contamination control principles (GPO 2015).

For successful biological drug manufacturing operations, precautions must be implemented to prevent process and product contamination from foreign agents originating outside the facility, from compounds associated with other drug manufacturing processes taking place within the same facility, and from compounds associated with other steps within the same drug campaign.

The most effective contamination control measures involve personnel procedures such as proper cleanroom gowning, CGMP processing procedures, personal hygiene, routine facility and equipment cleaning practices, and appropriately designed HVAC systems. Additionally, personnel work flow, facility layout, finishes, and utility system designs are essential contributors to safe and repeatable pharmaceutical manufacturing.

20.5.2 SEALED FACILITIES AND HVAC SYSTEM ZONING CONSIDERATIONS

The manufacturing facility is an integral part of the environmental control system and must be designed specifically to enhance contamination control. This involves proper siting and landscaping to minimize opportunities for pest intrusion as well as sealing the facility to eliminate environmental contamination pathways that may impact manufacturing operations. It is a common design approach to avoid combining controlled and noncontrolled areas within a single air handler service area to minimize pest intrusion pathways, enable the highest reliability to be focused on the manufacturing HVAC systems, and minimize unplanned manufacturing shutdowns.

After the establishment of proper air handler zoning to meet project requirements, rightsizing of each HVAC system is critical to good facility design. Oversized HVAC systems

may result in reduced internal room cleanliness if the interior airflow patterns do not match specific processing requirements. Room-level eddies and vortexes may extend the time that particles remain airborne prior to being removed by the HVAC system, which may be recorded as elevated room particulate levels. Operations involving manipulations of powders or small samples may be impossible to execute if the localized airflow is too strong. Containment of potent compounds within a room requires careful design analysis to ensure that no room-level airflow pattern is disruptive to the region dedicated to containment. Even personnel movement and work flows may have a negative impact on the containment effectiveness within a clean area. A thorough understanding of the operational requirements and criticality are necessary components of proper facility and utility system designs.

20.5.3 ROOM-LEVEL DESIGN CONSIDERATIONS

Cleanrooms function best with gypsum wallboard or other inherently sealed ceilings compared to products designed for less critical applications. T-bar ceilings have many seams that are challenging to seal and difficult to maintain. Clipping and gasketing are essential for best performance, but maintenance activities sometimes impair the effectiveness of items requiring personal labor to ensure a seal. (See Section 7.4.1.6.3 of Chapter 7 for further discussion on materials of construction for cleanrooms.) The leakage between the clean space and the interstitial space is driven by the pressure differential across the ceiling. The pressurization in the interstitial space above the ceiling is often uncontrolled and not monitored; however, this pressure may be impacted by facility modifications or by opening access doors. Activities in one room may affect the interstitial pressurization in rooms that are far apart. Also, some HVAC systems in rooms that are not critical may not have precise pressure control, and this may impact interstitial space pressurization. All these conditions may impact the leakage rate through a t-bar ceiling. In addition, whenever air travels up through a t-bar ceiling driven by proper pressurization, small-scale eddies may bring small amounts of interstitial air into the cleanroom, presenting a path for contaminants. If the pressurization between the interstitial space and the cleanroom changes over time, floating ceiling tiles may result if clipped tiles are not used. Even with clipped tiles, if above-ceiling space is accessed and the clips are not repositioned precisely, the leakage rate may change, which will impact the room pressurization. These conditions often are encountered as unexplained room differential pressure fluctuations and can provide operational challenges and cause cleanroom contamination.

Equipment for pharmaceutical cleanrooms must be selected and designed considering their impact on room pressurization. Autoclaves and other equipment that are made to fit between rooms must be selected with bioseal gasketing to prevent contamination from clean to less-clean areas.

The layout of the air supply registers is critical for best cleanroom performance. Even and symmetric layouts can be beneficial in most cases, but care must be taken to avoid supply air velocities that disrupt areas that require stable airflow patterns. Air return and exhaust register locations have a great impact also, often playing a more critical role in room cleanliness than is obvious. The return outlets draw the air across the room and tend to pull contaminants along also. Return or exhaust registers should be placed at the end of the room or in areas where cleanliness is least necessary.

In an air lock, placing the supply registers on the cleaner side and returns on the entering, or less clean, side is good engineering practice. However, precautions must be taken to avoid air supplies too close to doors that may create a localized pressurizing that forces air to move opposite to the direction of room pressurization through cracks around doors. Smaller rooms can present airflow problems when the supply air velocity drives air down to the floor and then back up the walls. This can lead to contamination problems

and is usually discovered through smoke studies in higher classification areas. This common problem is one of the many reasons computational fluid dynamics (CFD) simulations can streamline and improve the pharmaceutical design process by minimizing cleanroom design challenges (see Chapter 13 for a discussion of using CFD for cleanroom design).

In higher room classifications, the use of low wall returns provides performance improvements for cleanrooms. Return or exhaust air registers located near the floor elevation tend to draw contaminants towards them and downwards, which minimizes the impact of particulates on work surfaces. Room airflow patterns can be influenced by the supply air layouts, room and wall configurations, equipment sizes and locations, equipment that impacts airflows, and return/exhaust air register locations. All of these impacts must be considered for optimized airflow pattern control.

20.5.4 ROOM PRESSURIZATION STRATEGIES

Biopharmaceutical processing rooms must be designed to minimize the potential for process and product contamination. All rooms and areas used during drug manufacturing are provided with clean environments, with the cleanest using room pressurization for contaminant control. When doors or other openings between manufacturing areas are opened, pressure-driven airflow helps provide clean environments by maintaining the overall direction of the flow of particles. With this technique, processing rooms are designed for a general cleanliness gradient within each room, with the specific processing areas on the cleaner side.

Contamination control for rooms where drugs are processed is based on maintaining a sufficient differential pressure between adjoining rooms. Room differential pressures are required between areas of different classifications, as well as other areas where specific process contamination or containment concerns are present. To fulfill continuous room differential pressure documentation requirements, room differential pressures must monitored, trended, and retained for potential future reviews. This is accomplished with room pressure sensors transduced to electronic data for processing and storage. In most designs, a pneumatic system is used to directly measure the difference between room pressures. Alternatively, room pressure measurements from each room are compared electronically to derive room differential pressure values. With either strategy, the difference between the room pressures is the key information to monitor and retain as opposed to the absolute value of each room's pressure levels. Measurements based on each room's pressure level may create problems if room pressure fluctuations exceed process requirements. With an appropriately designed CGMP HVAC system, the pressurization of adjacent rooms within each processing stage tend to move together. As a result, the precise room differential pressures may have significantly fewer fluctuations than each individual room's pressure, resulting in fewer room pressure problems encountered.

With pneumatic systems, great care must be taken to eliminate the potential for pneumatic tubing leakage by minimizing junctions (barbed hose connections can present fewer leakage problems than quick-disconnect types) and potential damage points (control panel doors, contact with threaded rods or other sharp edges, and unsecured overhead ceiling routings). Often there is a minimum room differential pressure value required based on gauge accuracy to confirm that proper room differential pressures are achieved.

Many biopharmaceutical facilities are designed with constant-pressure-control HVAC strategies. Alternatively, HVAC control systems often make use of dynamic pressure control strategies where the room pressurization levels or differential pressure levels are used to drive zone-level HVAC control parameters. Often there are increased operational benefits with dynamic pressure control systems that must be balanced with the

potential for increased first costs and commissioning costs. Any equipment that impacts air pressurization with variable exhaust or supply must be addressed with dynamic pressure control for stable room pressurizations. Equipment releasing compressed air, such as vial or glassware washing equipment, and exhaust containment devices that do not run continuously may result in unexpected room pressurization excursions unless the room is sufficiently large to minimize the impact of the fluctuations.

It is critical to ensure that the room differential pressure tolerances and associated alarm levels are coordinated to ensure room pressure alarms are triggered prior to room pressure reversals. It is important for CGMP defendability to account for the accuracy of the pressure-sensing instrumentation when determining room pressure alarm levels.

20.6 FACILITY-LEVEL BIOPHARMACEUTICAL DESIGN CONSIDERATIONS

Air handler systems serving biopharmaceutical operations should be arranged to minimize the frequency and impact of shutdowns. The high cost of restarting cleanroom operations after an HVAC shutdown warrants care and precision in system design strategies. It is common to save more operating costs through minimizing shutdowns than through energy savings, though in many cases the reduced shutdown benefits are only available after incorporating energy efficiency measures.

Many common air handler features may lead to excessive system shutdown requirements unless redundant air handlers are provided. Bearing and moving part lubrication, fan belt replacement, air filter replacement, drain pan cleaning, sensor calibration, and conditional diagnostics all can contribute to increased HVAC system shutdown frequencies. Similar considerations in exhaust, return, recirculation, and other HVAC fans also may lead to increased system shutdown requirements. In many cases, the inclusion of one item on one piece of equipment that requires increased maintenance shutdown frequencies can have extreme facility operational impacts and costly production throughput consequences.

Alternative HVAC equipment design details such as sealed bearings, direct-drive fans, long-life low-pressure-drop air filters, no-bypass filter frames, and noncorrosive and nonshedding interiors can provide longer service intervals between system shutdowns. When incorporating these features, all parts of the HVAC system must be included for best value. An HVAC system with additional features included in the air handler design may not provide shutdown frequency reductions unless the exhaust fans and other system components are designed for extended operation. The high cost of shutdowns, including those for equipment service, cleaning, facility inspections, system restart and stabilization, work flow restart, and the resultant risk of complications usually makes shutdown reduction or elimination worth the additional design and capital costs. These same considerations have sustainability and environmental impact reduction potential due to fewer cleaning chemicals and fewer filters and belts in the waste stream.

Biopharmaceutical manufacturing facilities usually include important noncritical areas that are necessary to support manufacturing operations. Though these support areas do not need as high a level of cleanliness, they do require important design analysis to deliver a well-functioning facility. A sufficient level of work-flow separation and pressure differential between critical and support areas must be maintained to ensure product and process quality. The following design considerations are important for the creation of FDA-compliant biological drug manufacturing facilities:

- **Mechanical/Electrical Rooms and Gray Spaces**
  - A common design practice for gray spaces it to ventilate and provide 100% exhaust airflow with a monitored pressure differential.
  - In many cases, air can be drawn from an adjacent cleaner area and passed through a gray-space room for ventilation. Calculate the air change rate based on total supply to the adjacent room where air is drawn from and add the adjacent room's volume to the overall room volume. Then verity that the incoming rate of transfer air and the exhaust air can be measured. A properly designed system prevents air infiltration from interstitial spaces through careful consideration of system stability, differential pressures, and airflow quantity documentation.
- **Interstitial Spaces**
  - Interstitial spaces must be maintained at a negative pressure to the operating cleanrooms while maintaining a positive pressure to the ambient atmosphere if the area includes any exterior perimeter exposure. Contamination control must include avoiding the introduction of environmental contaminants, including moisture and spores.
- **Laboratory Spaces**
  - Design of laboratory spaces may involve the following items and considerations:
    - Containment hoods and specialized environments along walls
    - Center area work benchtops and scientific instruments
    - Control temperature even after hours for instruments
    - Night setbacks for airflow and temperature requirements
    - Containment exhaust for instruments
    - Room pressurization with flow rate offset
    - Pressure cascade from laboratory containment device to laboratory to corridor to areas where air is recirculated
    - Low-flow hoods

20.6.1 OPERATIONALLY EFFICIENT DESIGN

Design of biopharmaceutical engineering systems must be defendable upon future reviews by independent parties—one must be able to explain the rationale behind the design choices to an independent inspector years later. Sufficient testing, monitoring, and documentation are essential to providing a defendable facility design. If an inspector does not agree with the design approach or execution, he or she may investigate other items further, so engineering consistency between installations and facilities is critical. Review with such independent inspectors early in the design process is also a helpful tool for potentially mitigating concerns during these later inspections.

Facilities and process designs must provide confidence of precise repeatability and safe pharmaceutical production. Good facility designs optimize capital effectiveness, energy and resource efficiency, maintenance efficiency, reliability, operational efficiency, and compliance effectiveness. Good engineering is creating the most value from the least capital, using designs driven by evaluating the total cost of ownership impact of each decision.

A well thought-out user requirements specification (URS) identifies critical and less critical criteria and their relationships to the functions of the cleanroom. The layouts of HVAC systems for environmental control should be guided by CGMP risk-based analysis (ASTM 2016) including contamination control, room pressurization and process requirements, total cost of ownership, rapid diagnostics and recovery from unexpected events,

flexibility, and sustainability. Risk analysis should never be used to justify deviations from existing rules and regulations, and it should not be based on expectations of regulating agency inspection oversights or lack of scrutiny. While these considerations are applicable to all pharmaceutical facilities, they are extremely important to biological drug manufacturing because of the potential impact to drug safety and efficacy from a wide variety of possible factors.

Validation is best executed after commissioning because validation documents that good designs have been implemented. Validation provides independent documentation of quality, but does not add quality; quality comes from good engineering.

It is critical to design HVAC systems that will accommodate an accurate system boundary that captures all elements that may have an impact on the product or process. The following critical design considerations must be incorporated early to prevent difficult or impossible validation challenges:

- Separate air-handling systems commonly serve portions of manufacturing facilities that correspond to stages of biological processing such as inoculation, fermentation, isolation, purification, packaging, and labeling.
- Exhaust systems should match air handler zones and room classifications to avoid risks of contamination through duct connections. Increasing system energy efficiency drives towards lower pressure drops in duct systems and a resultant increased likelihood of contamination if dissimilar areas share an exhaust system. Implications of shutdowns also drive designs to avoid interconnecting air handler systems through the exhaust ducting.
- All items that may impact process or product must be considered for proper risk-based designs. If classified cleanrooms are combined with noncontrolled areas through supply, return, or exhaust ductwork, potential system impacts multiply or the noncontrolled areas must be subjected to additional personnel procedural control. Blanking off or modifying ductwork or registers in noncontrolled areas can impact the HVAC system performance in more critical areas.
- Using a barrier concept creates a separation between cleanliness classes for contamination control. Terminal HEPA filters, monitored differential pressure, or personal procedural and workflow controls can be used to maintain segregation between different classifications or areas.
- Constant duct pressure control strategies require the air handler discharge pressure to be set high enough to achieve the design airflow rates with fully loaded filters, and the terminal boxes provide the required control over airflow at the zone level. This requires initial air balancing duct pressure adjustments to be sufficiently high to handle the expected increase in terminal HEPA filter loading. An air handler discharge static pressure reset control strategy based on terminal box position for systems with terminal HEPA filters can save approximately 0.5 in. w.c. (125 Pa) of total system static pressure over the life of the system without significant added first costs.
- Identifying and controlling critical parameters is required for repeatable and safe pharmaceutical manufacturing process control. Facilities with specific airflow and/or room pressurization requirements need appropriate system controls to ensure reliable environmental control performance. An air handler dedicated to one area or room may provide the system stability necessary, but operational reliability may be impaired when servicing multiple rooms. Zone controls are needed to provide more reliability when multiple areas are serviced by one air handler. Zone-level building automation system (BAS) airflow controls are commonly used along with duct pressure controls at the air handler level. This

combination minimizes system instabilities associated with controlling the same parameter at different duct locations. Careful design consideration must ensure that alarms for zone airflows, room differential pressurization, and other critical parameters are triggered before the process or product quality is impacted.

- VFDs and direct-drive HVAC equipment can provide additional total cost of ownership benefits even considering likely first-cost increases. Additional ease of alarming and monitoring equipment performance and system capacities brings more value through a reduction of unplanned shutdowns. System expandability, facility flexibility, and energy efficiency are enhanced with VFDs and low-pressure-drop components and layouts. The added costs of VFDs can be mitigated through air balancing streamlining and the reduced manufacturing shutdowns. In addition, many fans require fan belt drives and associated maintenance and shutdown cost impacts unless VFDs are used.
- Systems designed with recirculation fans at the zone level can be used with terminal HEPA filters to provide a no-shutdown design. If the air handlers dedicated to multiple areas within one processing stage need shutdowns, well-designed recirculation fans can remain in operation so HEPA-filtered room airflow is not disrupted. Room pressurization would be lost, but the facility restart and cleaning requirements could be reduced through proper consideration of the entire HVAC system and facility designs.
- Avoid controlling to the same parameters in series. Examples of stable control strategies are controlling the air handler discharge by duct static pressure and controlling zones based on airflow. Even though both airflow and static pressure are measurements of pressure, these two parameters have different dynamic characteristics that are less likely to result in unstable control interferences. Controlling the air handler and zones by flow causes unstable loops that may fight for control. This consideration becomes more important with complicated systems serving many zones simultaneously with control of duct static pressure at the upstream level, then the next level by flow, and alternating for subsequent levels. Usually, best results are associated with controlling the lowest-level zone with airflow, especially if terminal HEPA filters are used.

20.6.2 ENVIRONMENTAL QUALITY CHALLENGES

Biotechnology operations usually involve highly specialized equipment cleaning to ensure product and process quality. Often tanks, centrifuges, and other biotechnology processing equipment require cleaning after use, through steaming operations, rinsing, and chemical treatment. Residual products of fermentation and other processing materials need to be removed after use, and many times there are associated odors and fumes. These should be processed, filtered, or treated before dispensing or discharging them, as they may be sources of airborne contaminants. Proper exhaust considerations and room pressurizations will prevent contaminant challenges that may be hazardous or noxious.

20.7 CLEANROOM AREAS FOR HEALTH CARE FACILITIES

In keeping consistent with ASHRAE principles, the energy use, maintainability, and safety of the HVAC systems should also be considered when designing. It is clearly understood that the purpose of the HVAC system is to provide a comfortable environment that reduces the risk of airborne contamination and that not meeting that goal subverts the

purpose of providing the HVAC systems in the first place; however, meeting these goals without regard for the cost of the installation, maintenance, and energy use or the safety of those operating or maintaining the equipment is equally imprudent.

The successful design of the HVAC systems is often directly related to the successful design of the physical spaces themselves. The national standard for ventilation, room pressure, and filtration requirements in health care facilities is ASHRAE/ASHE Standard 170 (ASHRAE 2013). This comprehensive standard was developed over decades, starting with the mechanical sections of *Guidelines for Design and Construction of Hospital and Health Care Facilities* (FGI 2001). It is now an American National Standards Institute (ANSI) standard undergoing continuous maintenance as a result of significant research into the proper ventilation, temperature, and humidity requirements for health care facilities. The designer of these spaces must consult and properly apply this standard.

In general, the airflows should be designed to flow from the cleanest spaces to the dirtiest and then exhaust from the facility in a safe location and direction. Air from many spaces is perfectly safe to recirculate either within the space itself or through a central air-handling unit (AHU). Oftentimes this air is cleaner than outdoors (in terms of both particulates and gaseous contaminants) and it has already been conditioned to proper temperature and humidity levels. Outdoor air will need to be introduced to dilute contaminants and to make up for air that is exhausted from the facility. Particular care should be taken where sources of high contamination, such as decontamination rooms, infectious isolation rooms, or construction are located near clean spaces.

Space pressurization as well as overall building pressurization should be considered during design. It is generally accepted, although no direct science exists to support the value, that controlled pressures should be maintained at a differential of 0.01 in. w.c. (2.5 Pa) and a minimum design differential of 50 cfm (23.6 L/s) of airflow or 10% of the total space airflow. Some standards or guidelines have higher recommendations. The construction of the space itself, including sealing of all penetrations and the envelope, will have a significant impact on the pressure relationship with adjacent spaces and to the outdoors as well. It is possible that a room designed and operated with a specific pressure relationship and monitored to have such a relationship at one point may actually have differing relationships at locations where the envelope is not sufficiently tight.

Mechanical air filtration is used to remove particles from the airstream before delivering it into the space. Filters are rated based on the reduction in particle counts after the filter when a specific quantity and size of particle is introduced upstream and allowed to be carried at a specific volumetric flow rate across a specific cross-sectional area thorough the filter in accordance with ASHRAE Standard 52.2 (ASHRAE 2012). While this should approximate the function in a real application, the conditions of the actual installation can affect the number of particles in the supply air. Fortunately, clean spaces in health care facilities are not usually required to meet ISO 14644-1 (ISO 2015) standards for cleanrooms, where a single particle could foul a process. Rather, they are intended to reduce the concentration of contaminants to a level that will minimize the risk of infecting a patient. Some installations use ultraviolet germicidal irradiation (UVGI) to further break down organisms that are or could get into the airstream or space. Gas-phase filtration is not currently discussed in the design of health care environments, except in relation to gaseous nuclear or compounding agents, which are specifically dealt with in safety hoods. ASHRAE/ASHE Standard 170 (ASHRAE 2013) requires a minimum efficiency reporting value (MERV) 7 prefilter that is upstream of all coils and equipment and a MERV 14 final filter that is downstream of all wet coils and equipment. Reheat coils may be located downstream of the final filters.

20.7.1 COMPOUNDING AREAS

Over the last 10 years, much discussion has been had about compounding in the health care environment. Little regulation or governance had been provided for the compounding of sterile preparations within health care facilities. In the wake of some highly publicized sentinel events (Arnold and Hepler 1971; Duma et al. 1971; Felts et al. 1972), Centers for Medicare and Medicaid Services (CMS), The Joint Commission (TJC), United States Pharmacopeial Convention (USP), American Society for Healthcare Engineering (ASHE), the Health Guidelines Revision Committee (HGRC) of Facility Guidelines Institute (FGI), The National Institute for Occupational Safety and Health (NIOSH), ASHRAE, and others began looking into the requirements for compounding in health care facilities. USP published <797>, which provided guidance for the physical environment inside and outside of the compounding site itself (USP 2012). HGRC, which is responsible for the content of *Guidelines for Design and Construction of Hospital and Health Care Facilities* (FGI 2001), already had some guidance on the physical environments, and ASHRAE and ASHE were working on Standard 170 (ASHRAE 2008), which would further develop the requirements for the HVAC for these spaces.

Some pharmaceutical boards in some states have adopted various editions of USP <797>. However, CMS and TJC refer to the FGI guidelines and to the facility's policies on compounding. The FGI guidelines, which now incorporates ASHRAE/ASHE Standard 170, requires 4 ach of total circulation.

In any case, the compounding itself must follow the USP rules (USP 2012). An ISO Class 5 (ISO 2015) laminar airflow workbench or biological safety cabinet should be provided and properly designed into the HVAC system. Temperature and humidity should be maintained such that the occupants, with protective clothing, are comfortable and can work effectively and the compounds are not spoiled.

Although there are no specific standards that address this, compounding of cytotoxic or other potentially hazardous preparations should be made within a Class II Type B2 biological safety cabinet (NSF 2014) that is exhausted directly to outdoors. that is ducted to outdoors for exhaust. The room or space itself should be negative to its surrounding spaces and have a total air change rate of 10 ach, with all air being exhausted through the hood or otherwise.

20.7.2 PROTECTIVE ENVIRONMENTS

Protective environment rooms in health care facilities are provided for immunocompromised patients. The purpose of these clean spaces is to provide an environment with reduced contaminants, including those that are airborne. These rooms are controlled with HEPA-filtered supply air at 12 ach and maintain a positive pressure in relationship to the spaces around them. The HEPA filters should be placed after all wet surfaces (such as cooling coils) but not necessarily after any heating coils. The HEPA filters may be in the AHUs or at the terminals or anywhere in between. All supply air should flow through the HEPA filters. Thought should be given to the maintenance of the AHUs and replacement of the filters. When changing filters in AHUs, the fans must be shut down, which will compromise pressurization; when changing filters in patient rooms, the room must be shut down and requires bringing filters and personnel into the room as well as removing dirty filters from the room—all of which can produce particles in a room that is to be kept clean.

It is desirable for the supply air to be delivered into the breathing zone of the patient and then swept away to the returns. Often, the patient is fully mobile and does not sit in bed. Placing the supply near the center of the patient area and the returns near the perime-

ter or door should be sufficient to maintain a low level of particulates in the patient's breathing zone. With the return near the door, a local area of low pressure can make keeping the pressure across the door monitor positive difficult. Furthermore, while these patients should be in clean environments, they do not always want to be isolated.

In many cases, the room door is left open, which further makes pressurizing the room a challenge. It is important to discuss with the hospital staff, planner, or other clinical authority how the room will be used, how severely the patient's immune system has been compromised, and how the space will be enclosed. Then, the proper HVAC controls can be designed. Where the door will remain open, it will be virtually impossible to monitor the pressure relationship and, therefore, monitors will not provide any value. In addition, where the pressure relationship is not absolutely critical, monitoring might also be unnecessary.

In such cases where a patient in a protective environment room also requires airborne infection isolation, additional special provisions must be included. The most important of these is an anteroom at the entrance to the space. This anteroom acts as the buffer between the protective environment and the isolation requirements. The anteroom may either have all of its air exhausted and pull air into it from both the protective environment and the surrounding spaces or have all of its air HEPA supplied and push air into the protective environment and into the surrounding spaces. In either case, the protective environment is supplied with only HEPA air and is kept negative to the surrounding space via the anteroom.

20.7.3 OPERATING ROOMS

Operating rooms in health care facilities have also received recent attention and study. While these rooms, like the others spaces discussed in this chapter, are not required to meet an ISO classification, they are clean spaces. Existing codes and standards such as ASHRAE/ASHE Standard 170 (ASHRAE 2013) have been written to require the designer to provide high air changes (20 ach) in the rooms with well-filtered (MERV 14) supply air over the patient and returns low at the perimeter. ASHRAE/ASHE Standard 170 requires a certain amount of the ceiling space directly above the surgical table to be used for air supply. The designer must carefully coordinate this with the other design professionals, because this space is often in high demand for booms, lights, and other equipment. Terminal filters are not required for operating rooms.

The risks to human safety as a result of contamination in health care operating rooms make understanding the requirements for design of their HVAC systems of particular importance. While contact contamination is more likely than airborne contamination, we as HVAC designers can use good design practices to reduce the overall risk by reducing the risk of airborne contamination.

The airflow within the operating room itself has been studied by Memarzadeh and Manning (2002). ASHRAE/ASHE Standard 170 (ASHRAE 2013a) requires the airflow in an operating room to be laminar over 70% of the table and extending 12 in. (305 mm) out on all sides with low wall returns in two remote locations. The velocity of the air is required to be between 25 and 30 fpm (0.127 and 0.152 m/s) leaving the face of the diffuser. Total air changes within the operating room are to be a minimum of 20 per hour. This is thought to provide a clean environment at the wound site.

20.7.4 CENTRAL STERILE SUPPLY

Sterile processing departments within health care facilities are typically divided into four major areas to accomplish the functions of decontamination, assembly and sterile processing, sterile storage, and distribution:

- **Decontamination Area.** Reusable equipment, instruments, and supplies are cleaned and decontaminated by means of manual or mechanical cleaning processes and chemical disinfection. The decontamination area is a dirty space that must be maintained negative to surrounding spaces with all air exhausted directly to the outdoors.
- **Assembly and Packaging Area.** Clean items are received in the assembly and packaging area from the decontamination area and are then assembled and prepared for issue, storage, or further processing (such as sterilization).
- **Sterile Storage Area.** After assembly or sterilization, items are transferred to the sterile storage area until it is time for them to be issued.
- **Distribution Area.** Several major functions are carried out in the distribution area: case cart preparation and delivery; exchange cart inventory, replenishment, and delivery; telephone-order and requisition-order filling; and, sometimes, patient care equipment delivery.

Although assembly and packaging, sterile storage, and distribution areas do not have ISO 14644-1 (ISO 2015) classifications, they are clean areas, and the temperature and humidity conditions are important to ensure and maintain the sterility and cleanliness of their operations. Humidity that is too high can allow for enhanced microbial growth. Humidity that is too low or too high can damage packaging or seals or indicators, thus making the verification of the sterility uncertain.

Additional information on central sterile supply rooms can be found through the Certification Board for Sterile Processing and Distribution (CBSPD), International Association of Healthcare Central Service Material Management (IAHCSMM), Association of periOperative Registered Nurses (AORN), Association for the Advancement of Medical Instrumentation (AAMI), and Association for Professionals in Infection Control and Epidemiology (APIC).

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21 Cleanrooms in Food Processing Industries

21.1 DESIGN CONSIDERATIONS

In designing a cleanroom for a food processing facility it is important to minimize bacterial growth and to consider Current Good Manufacturing Practice (CGMP) and the U.S. Food and Drug Administration (FDA) Hazard Analysis Critical Control Point (HACCP) management system standards for food processing (FDA 2017). Table 21.1 shows the design considerations of note.

The refrigeration systems that can be used in food processing cleanrooms are as follows:

- **Direct Refrigerant Cooled**
  - Heavy-duty industrial food processing plant
    - Ammonia refrigeration system using pump recirculation for more than two air-handling units (AHUs) or air coolers
    - Ammonia-flooded refrigeration system with less than three AHUs or air coolers
  - Commercial food processing plant
    - Halocarbon packaged refrigeration using flooded AHUs or air coolers
    - Halocarbon packaged refrigeration using direct-expansion (DX) AHUs or air coolers
- **Secondary Refrigerant Cooled**
  - Heavy-duty industrial food processing plant
    - Ammonia refrigeration system using secondary refrigerant, either chilled water or glycol, to cool the AHUs or air coolers
    - Ammonia packaged plate heat exchanger chillers using secondary refrigerant, either chilled water or glycol, to cool the AHUs or air coolers
    - Halocarbon packaged chillers using secondary refrigerant, either chilled water or glycol, to cool the AHUs or air coolers
  - Commercial food processing plant
    - Halocarbon packaged chillers using secondary refrigerant, either chilled water or glycol, to cool the AHUs or air coolers
    - Ammonia packaged plate heat exchanger chillers using secondary refrigerant, either chilled water or glycol, to cool the AHUs or air coolers

Table 21.1 Design Considerations for Cleanrooms in Food Processing Facilities

Cleanroom	Room Temperature	Relative Humidity	Coil Temperature Differential
Non-ready-to-eat cleanroom, frozen raw materials	40°F (4.4°C)	60% rh	Forced air: 9°F to 12°F (12.8°C to 11.1°C) Gravity: 14°F to 18°F (–10°C to –7.8°C)
Ready-to-eat cleanroom, frozen raw materials	46°F (7.8°C)	60% rh	Forced air: 9°F to 12°F (12.8°C to 11.1°C) Gravity: 14°F to 18°F (–10°C to –7.8°C)
Ready-to-eat cleanroom, ambient and chilled raw materials	65°F (18.3°C)	60% rh	Forced air: 9°F to 12°F (12.8°C to 11.1°C) Gravity: 14°F to 18°F (–10°C to –7.8°C)

Non-cleanroom areas for food processing facilities generally consist of epoxy-coated walls and ceilings. Floor are most often epoxy coated as well, although, depending on the function of the area, sealed concrete may also be adequate. Paint spraying applications should conform to the U.S. Environmental Protection Agency (EPA) requirements for lead-free paint (EPA n.d.). The paint used should have antibacterial properties (with biocide) to ensure that the room will be germ free and comply with CGMP and the HACCP (FDA 2017) requirements. Floor coating products should be of the same nature.

Airborne particulate filtration must be on the supply and return air mixing box. Temperature and humidity control is a must, as this will affect the quality of the food product being processed in the cleanroom. The room should have an electronic refrigerant leak and carbon dioxide (CO_2) detection system complete with an exhaust fan ventilation system. The facility can be hooked up to a food processing supervisory control and data acquisition (SCADA) system to automate its operation.

21.2 FACILITY CONFIGURATIONS AND PLANNING

The location of a food processing cleanroom should be adjacent to the raw material storage to ensure that the raw materials being processed into finished products, whether frozen, chilled, or at ambient temperature, do not rise above 40°F (4.4°C) to prevent rapid bacterial growth.

Architectural and structural considerations for food processing cleanrooms must be the same as those for standard food processing plants, with considerations to the locations of process and material-handling equipment. For example, if there are any overhead cranes, they should be supported from the floor to avoid wall or ceiling penetrations that are difficult if not impossible to appropriately seal.

The cleanroom building envelope should be made of either polyisocyanurate or extruded polystyrene (XPS) insulated panel with stainless steel 304 skin on the interior (process room side) and prepainted galvanized iron (PPGI) skin on the exterior side, complete with cam locking device.

The heat transfer coefficient of a polyisocyanurate insulated panel should be 0.16 Btu/h·ft^2 (0.909 W/m^2·°C) and of an XPS insulated panel should be 0.185 Btu/h·ft^2 (1.051 W/m^2·°C). The density of the insulation for polyisocyanurate is 2.4 lb/ft^3 (38.4 kg/m^3) and for XPS is 2 lb/ft^3 (32 kg/m^3). The thickness of both types of insulated panel should be 3 in. (76.2 mm).

Floors should be provided with an epoxy coating with antimicrobial properties and a slip-resistant surface, be resistant to impact and thermal shock, and have the capability to withstand exposure to harsh cleaning chemicals, pressure washing, and steam cleaning.

21.3 DESIGN CRITERIA AND INDOOR AIR QUALITY

The AHU should have an electronic thermostat and humidity controller to ensure that moisture formation in the ceiling panel is eliminated.

The cooling systems that can be used in cooling the cleanroom should either be direct refrigerant cooled or use a secondary refrigerant such as chilled water or inhibited propylene glycol. For an industrial plant setting, the preferred cooling system is direct ammonia-cooled using glycol or chilled water as the secondary refrigerant. For small commercial food processing plants, typically halocarbon refrigerant is used.

Indoor air requirements for food processing facilities are the same as those in other cleanrooms but must comply with the CGMP and HACCP (FDA 2017) standards. The AHU should have at least 15% fresh air introduced into the mixing box to ensure that there is always a positive pressure inside the room to prevent ambient air migration into the cleanroom. The return air and fresh air intakes should pass through a washable filter, a bag filter, and a high-efficiency particulate air (HEPA) Filter Type A at 99.97% at 0.3 μm. The room should have a minimum cleanroom rating of ISO Class 8 (ISO 2015). Figure 21.1 illustrates some examples of air-handling systems in a food processing facility.

The supply air duct must be fabric and approved by the United States Department of Agriculture (USDA) and can be machine washable. The cleanroom should have at least one spare fabric duct in order to minimize production downtime when the fabric duct is out for washing and cleaning. Stainless steel or food-grade plastic return grilles should be used for air circulation. Supply airflow should be laminar in order to reduce the wind chill effect for personnel working inside the cleanroom.

A foot bath with a sanitizing agent and a hand wash with soap and sanitizing dispenser are required for personnel entering the cleanroom area. In regard to protective clothing, plant production areas must be set up so that there is a barrier between the employee and the product itself. Items used for this purpose are typically provided by the company and include coats or smocks, plastic aprons or sleeves, hairnets or snoods, and gloves. This protective clothing should never be worn outside of the plant but should always be worn in the plant production areas, and it should be regularly changed (Frederick 2005).

21.4 CLEANROOM QUALIFICATION

A food processing cleanroom is classified as an ISO Class 8 (ISO 2015) cleanroom. The qualification plan and acceptance criteria should be similar to those of other cleanroom facilities, with the exception that a food processing cleanroom should have a lower room temperature to prevent rapid bacterial growth inside the facility. See Chapter 17 for a detailed discussion of qualification for cleanrooms.

21.5 ABOUT HACCP

Hazard Analysis Critical Control Point (HACCP) is an FDA (2017) process control system that identifies where hazards might occur in the food production process and puts

into place stringent actions to prevent the hazards from occurring. By strictly monitoring and controlling each step of the process, there is less chance for hazards to occur. By controlling major food risks, such as microbiological, chemical, and physical contaminants, the industry can better assure consumers that its products are as safe as good science and technology allows. By reducing food-borne hazards, public health protection is strengthened. While many public opinion studies report that consumers are concerned primarily about chemical residues, such as those from pesticides and antibiotics, these hazards are nearly nonexistent. The more significant hazards facing the food industry today are microbiological contaminants, such as salmonella, E. coli O157:H7, listeria, campylobacter, and clostridium botulinum. HACCP is designed to focus on and control the most significant hazards.

HACCP is not new. It was first used in the 1960s by the Pillsbury Company to produce the safest and highest quality food possible for astronauts in the space program. The National Academy of Sciences (NAS), National Advisory Committee on Microbiological Criteria for Foods (NACMCF) of the USDA, and the Codex Alimentarius have endorsed HACCP as the best process control system available today. HACCP is based on a "see, smell, and touch" approach that relies more on detection of potential hazards than prevention. Furthermore, HACCP was designed in the 1930s when the threat of diseased animals and physical contaminants were the main concerns. Today, microbiological and chemical contamination, which cannot be seen, are of greater interest. The USDA requires HACCP for the United States' 7000 meat and poultry plants. Many companies have also provided HACCP training to management and in-plant workforce.

The USDA is pursuing a farm-to-table approach to food safety by taking steps to improve the safety of meat and poultry at each step in the food production, processing, distribution, and marketing chain. On July 25, 1996, the USDA released its Pathogen Reduction/HACCP final rule (USDA 1996). The final rule further targets pathogens that cause food-borne illnesses, strengthen industry responsibility to produce safe food, and focus inspection and plant activities on prevention objectives.

There are seven HACCP principles that must be followed to implement HACCP. Every food production process in a plant needs an individual HACCP plan that directly impacts the specifics of the product and process. Government and industry groups have developed some generic HACCP models that provide guidelines and directions for developing plant-, process-, and product-specific HACCP programs. The International HACCP Alliance has developed a training curriculum to assist the meat and poultry industry (International HACCP Alliance 2017).

The seven HACCP principles developed by the NACMCF that serve as the foundation for a HACCP program are as follows:

- Conduct a hazard analysis to identify potential hazards that could occur in the food production process.
- Identify the critical control points (CCPs)—those points in the process where the potential hazards could occur and can be prevented and/or controlled.
- Establish critical limits for preventive measures associated with each CCP. A critical limit is a criterion that must be met for each CCP. Where appropriate, critical limits may reflect relevant USDA Food Safety and Inspection Service (FSIS) regulations (GPO 2017) and FDA tolerances (FDA 2017).
- Establish CCP monitoring requirements to ensure each CCP stays within its limit. Monitoring may require materials or devices to measure or otherwise evaluate the process at the CCP.

- Establish corrective actions if monitoring determines a CCP is not within the established limits. In case a problem occurs, corrective actions must be in place to ensure no public health hazard occurs.
- Establish effective record-keeping procedures that document the HACCP system is working properly. Records should document CCP monitoring, verification activities, and deviation records.
- Establish procedures for verifying that the HACCP system is working properly. Verification procedures may include reviewing the HACCP plan, CCP records, and critical limits as well as conducting microbial sampling. Both plant personnel and FSIS inspectors conduct verification activities.

Microbiological testing throughout the production process can play a valuable role in HACCP programs as a means for verifying the HACCP system is working properly and for tracking trends and profiles of products. By tracking microbiological data, plants can identify when the production process is not being properly controlled or verify that prevention efforts are successfully reducing bacterial levels. End-product microbiological testing, however, is less effective. There is not sufficient data to determine what is considered an "acceptable" level of bacteria on raw meat and poultry, so end-product tests do not provide useful data other than for trends analysis. While end-product testing may indicate bacteria are present, it does not solve the problem of identifying and eliminating the contamination.

New technologies will play critical roles in HACCP programs because HACCP is designed to institute practices that reduce or eliminate harmful contamination. If new technologies are developed that prevent or eliminate hazards throughout the production process, they will be widely accepted and adopted.

For the most successful implementation of HACCP, it should be applied from farm to table—starting on the farm and ending with the individual preparing the food, whether in a restaurant or at home. On the farm, there are actions that can be taken to prevent contamination from occurring, such as monitoring feed, maintaining farm sanitation, and practicing good animal health management practices. In the plant, contamination must be prevented during slaughter and processing. Once meat and poultry products leave the plant, there should be controls in place during transportation, storage, and distribution. In retail stores, proper sanitation, refrigeration, storage, and handling practices prevent contamination. Finally, in restaurants, in food service facilities that process ready-to-eat food, and in homes, food handlers must store, handle, and cook foods properly to ensure food safety.

Consumers can implement HACCP-like practices in the home by following proper storage, handling, cooking, and cleaning procedures. From the time a consumer purchases meat or poultry from the grocery store to the time they cook and serve a meal, there are many steps to take to ensure food safety. Examples include properly refrigerating meat and poultry, keeping raw meat and poultry separate from cooked and ready-to-eat foods, thoroughly cooking meat and poultry, and refrigerating and cooking leftovers to prevent bacterial growth.

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