

# Pharmacy Cleanroom Project Management Considerations: An Experience-Based Perspective

During the last 25 years, many pharmacy professionals installed cleanrooms before they were recommended by the pharmacy profession or even deemed necessary by the Food and Drug Administration (FDA) for drug and medical device manufacturers. Today, many state boards of pharmacy do not specifically mandate that cleanrooms or other controlled environments be used for the preparation of sterile products. In the *ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products*,<sup>1</sup> the American Society of Health-System Pharmacists (ASHP) has outlined recommendations about the facility and environment in which sterile products should be prepared to ensure their highest quality. Pharmacists as a profession continue the struggle to assess whether the cleanroom management process, which includes staff, procedures, a facility, equipment, and materials, affects the quality of pharmacy-prepared sterile products. Controversial issues include:

- The lack of professional requirements and/or regulations issued by state boards of pharmacy that require pharmacists to use cleanrooms or controlled environments for the preparation of sterile products
- The belief that contamination-control procedures are unnecessary because the incidence of contaminated pharmacy-prepared sterile products is negligible<sup>2,3</sup>
- Concerns about cleanroom construction that result from the many operating configurations that may or may not meet the regulatory, operational, and/or fiscal requirements of the pharmacy
- Ignorance about cleanroom construction and project management, which can result in a lack of professional or qualified design input, construction guidance, or support

In this article, some of the mysteries associated with the design, construction, and project management of cleanrooms are examined to provide guidance for those who oversee the installation of their own cleanroom.

Author and pharmacist Lawrence Trissel<sup>2</sup> states that “Within the pharmacy profession, drug product-related issues, including sterile-product preparation and the associated necessary technologies, have been de-emphasized or eliminated from most pharmacy schools’ curricula.” Viable or nonviable contamination can affect the product quality as well as the health and well-being of patients. As pharmacists, we must use the strategies of industries that emphasize and successfully manage issues concerning contamination.

## Contamination Control and Cleanroom Standards

The need to control the quality of critical operating environments dates back more than a century, when the etiologic role of bacteria in infection was discovered. Cleanrooms were developed to

minimize or eliminate bacteria and to control the incidence of infection in hospitals (especially in operating rooms). It was realized that by providing proper ventilation to critical areas in hospitals, the incidence of airborne infections could be greatly reduced. It was also observed that the airborne particles generated from the environment (dust, dirt, pollen, viable and nonviable microorganisms) and from people (skin flakes, lint, cosmetics, respiratory gases) negatively influenced patient outcomes and the quality and reliability of the electronics manufactured for and used in aircraft and tanks during World War II.<sup>4</sup>

Not until the space race between the Soviet Union and the United States in the 1960s was the concept of laminar flow clearly articulated, and the first standard (*Federal Standard [FS] 209*) for determining the cleanliness of cleanrooms by the number of airborne particles was subsequently published.<sup>5</sup> The most current version of that standard is *FS 209E*. Over the years, *FS 209* has evolved and has served as a benchmark of cleanliness for many industries, including the National Aeronautics and Space Administration (NASA); manufacturers of semiconductors, electrical equipment, computers, or pharmaceuticals; and various companies in the hospital and homecare industries.

The world has become an international marketplace, and the use of controlled environments in which environmentally sensitive components are manufactured has increased dramatically. Many international companies have recognized the lack of standardization and consistency in cleanroom standards.<sup>6</sup> To establish a worldwide standard for cleanroom practices and at the request of the American National Standards Institute (ANSI), the International Standards Organization (ISO) developed contamination control and cleanroom standards that were adopted internationally. In 1991, the Institute of Environmental Sciences and Technology (IEST) in the United States established the ISO Technical Committee 209 (ISO TC 209). The ISO TC 209 created eight working groups (WGs) for the development of elements of the standards for cleanrooms that, when approved, will be published as a guideline.

In 1999, the Committee for European Normalization (CEN) and the ISO published *EN/ISO 14644-1 (Classification of Airborne Cleanliness)*. This document was the first of a family of new worldwide standards for contamination control and airborne cleanliness. *ISO 14644-1* establishes the particle classification system that is to be applied to cleanrooms and clean-air devices (laminar flow hoods, biosafety cabinets, glove boxes, etc.). *ISO 14644-2 (Specification for*

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**Table 1. Cleanliness Classifications: ISO Versus FS 209E.**

Airborne Particulate Cleanliness Class Comparisons for Cleanroom Classification			Maximum Concentration for Particles 0.5 $\mu$ in Size			
ISO	FS 209E		ISO	ISO 14644-1 (Particles/m <sup>3</sup> )	FS 209E (Particles/ft <sup>3</sup> )	FS 209E (Particles/m <sup>3</sup> )
1			1			
2			2	4		4
3	1	M 1.5	3	35	1	35
4	10	M 2.5	4	352	10	353
5	100	M 3.5	5	3520	100	3530
6	1000	M 4.5	6	35,200	1000	35,300
7	10,000	M 5.5	7	352,000	10,000	353,000
8	100,000	M 6.5	8	3,520,000	100,000	3,530,000
9			9	35,200,000		

Source: EN/ISO 14644-1, *Classification of Air Cleanliness*, 1999.

*Testing Cleanrooms and Associated Controlled Environments to Prove Continued Compliance* establishes the basic requirements for the initial certification, monitoring, and testing of cleanrooms to demonstrate continued compliance with the initial cleanliness classification specified in ISO 14644-1.

Federal Standard 209E (1992) provides the particle count sampling requirements and the statistical methodology or formula for calculating the upper confidence limit associated with measured particle counts used to establish the cleanliness classification.<sup>7</sup> Cleanroom cleanliness is usually expressed in terms of areas; for example, Class 100 or Class 100,000. Those classifications denote that there were no more than 100 or 100,000 particles larger than 0.5  $\mu$ m per cubic foot of air during the sampling period.

FS 209E was used as a reference in the development of ISO-14644-1 and will, when approved by the United States government, be replaced by ISO-14644-1. The methodology defined in FS 209E is still recognized as an acceptable standard for defining cleanroom design requirements and for defining one of the certification requirements for an owner's final acceptance of a cleanroom constructed by an independent cleanroom contractor or builder. A cross-reference of the FS 209E standard with the new ISO standard is presented in Table 1.

The ISO standards will provide a more comprehensive set of requirements for all industries using cleanrooms than did the standards of FS 209E. The ISO 14644-X series, when approved and published, will provide the definitive family of standards

that will define all certification requirements for any new cleanroom construction project as well as ongoing control and operating requirements for cleanroom operations.

### Design Criteria Parameters

There are several cleanroom performance parameters that are important in the development of design criteria for a new and/or existing cleanroom. They include but are not limited to:

**Particle count (cleanroom classification).** The particle count is the maximum number of particles 0.5  $\mu$  in size per cubic foot or meter of sampled air.

**Airflow velocity and/or volume (cubic feet per minute [CFM]).** These terms refer to the speed of air at 90 feet per minute (average), with uniformity within  $\pm 20\%$  across the entire area of the air exit. This has been interpreted to mean that the air velocity averages between 72 and 108 feet per minute.

**Pressurization.** Pressurization is the measurement of air pressures between two adjoining areas in which the air pressure in the more stringently classified area is higher than that of the next classified area. The pressures are said to "cascade" where air from the cleanest area flows into a dirtier area. Average pressure differentials between two adjoining areas (ie, Class 100 area to Class 10,000 area) are typically +0.05" WC (water column).

**Installed filter leakage.** In-place filter testing for a high-efficiency particulate air

(HEPA) filter with no penetrations to exceed 0.01% of upstream smoke (Emery-3004) concentration is important. Emery-3004 is the compound used to test air filter efficiency and integrity. When heated, it consistently generates particles that are about 0.3  $\mu$  in size.

**Airflow visualization.** A smoke-stick test is used to observe airflow patterns over critical work surfaces and areas of air turbulence that could be reservoirs of excessive particles or bioburden.

**Containment or leakage.** Depending on the environment or the equipment being tested, leaks usually are not desirable; for example, in type II B biological safety cabinets (BSCs) used during the preparation of antineoplastic agents or in HEPA filters.

## Pharmacy Cleanroom Project Requirements

A properly designed, constructed, and maintained cleanroom contributes to the facility-related quality assurance measures of pharmacy-prepared sterile products. It is unreasonable to believe that proper aseptic technique alone can be the primary method of contamination control when laminar flow hoods are placed in uncontrolled areas.<sup>8</sup> Given the extensive and complex body of standards, guidelines, and recommendations (FS 209E, ASHP guidelines, USP recommendations, EN/ISO standards, etc.) that are used to reference the operating conditions of a cleanroom, it is essential to gain an appreciation and a general understanding of how those applicable standards and references apply to the design and ongoing operation of a pharmacy cleanroom. It is *very important* to recognize that to design and build a pharmacy cleanroom without considering critical quality system factors such as policies and procedures, employee training, aseptic technique and process validation, ongoing environmental monitoring, facility maintenance, and compliance auditing *will* result in problems of quality, operation, or maintenance. It may be prudent to identify an independent consultant who can serve as the project manager of the pharmacy cleanroom project.

## The Project Team

The purpose of the pharmacy cleanroom

**Table 2. Anteroom or Gowning Room – Class 10,000 – 100,000 or ISO 7- 8.**

	<b>Material Requirements</b>	<b>Recommended Design Specification</b>
Ceilings	Drywall-epoxy painted Cleanroom ceiling tile with anodized aluminum T-bar grid	Cleanroom ceiling tile with anodized aluminum T-bar grid
Floors	Monolithic vinyl Monolithic epoxy	Seamless vinyl sheet with minimum 4" - 6" cove to the wall
Walls	Monolithic vinyl FRP laminate panel Tempered safety glass Drywall-epoxy painted Melamine panel	FRP laminate panel
Doors	Stainless steel Anodized aluminum Epoxy-painted metal door	Anodized aluminum door frame
Light fixtures	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish
Windows	Tempered safety glass with no sills and stainless steel or anodized aluminum frame	Tempered safety glass with no sills and stainless steel or anodized aluminum frame
Air changes	40 air changes per hour	40 to 60 air changes per hour
Air pressure	Anteroom must be negative to the compounding room and positive + 0.02" WC to the general area	Anteroom must be negative to the compounding room and positive + 0.02" WC to the general area
Air filtration	99.97% HEPA filter or better with a 30% efficiency ASHRAE or better prefilter	99.97% HEPA filter or better with a 30% efficiency ASHRAE or better prefilter
Particulate control	Class 10,000 per <i>FS 209E</i>	Class 10,000 per <i>FS 209E</i>
Temperature	70°F ± 4°F	70°F ± 4°F
Relative humidity	25% to 50% RH	25% to 50% RH
ASHRAE, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc FRP, fiberglass-reinforced plastic	RTV, room-temperature vulcanizing HEPA, high-efficiency particulate air <i>FS 209, Federal Standard 209</i> RH, relative humidity	F, degrees Fahrenheit WC, water column

should be understood before budgets are established and construction is begun. The outcome of the project depends on the ability of the project manager to lead the team and to identify weaknesses in design, engineering, construction, or postconstruction operational requirements. Each member of the project team, which includes outside contractors and suppliers, should understand the importance of his or her role in and contribution to the project.

## Design Criteria and Construction Documents

Cleanroom construction requires specialized knowledge. Choosing the most qualified person and/or contractor to manage the design, construction, and certification of

the cleanroom is critical to the successful outcome of the cleanroom project.

The contractor(s) and cleanroom project manager should work cooperatively to establish the best-cost design solution that will meet all applicable cleanroom and pharmacy operating standards (eg, those of the ASHP, the ISO, the state board, etc.) and the day-to-day requirements determined by the compounding activities that will occur (ie, risk level I, II, or III). Design criteria that demonstrate an understanding of cleanroom requirements must be developed. Examples of such criteria are featured in Tables 2 and 3.

The design criteria document specifies critical construction material requirements, preliminary blueprints or facility layout, and environmental control specifications. Those criteria, which should be clearly doc-

umented in the construction contract and should be approved by all team members, will guide the contractors during all phases of the project and can be used to define certification requirements for the final acceptance of the cleanroom by the owner. All operating parameters should be tested to confirm that the cleanroom was constructed properly so that the owner of the facility can hold the contractor accountable before final payment.

Approval of the design criteria (the owner-driven document) should precede approval of the construction documents, which are supplied by the design, engineering, and/or construction vendor(s). Those documents, such as detailed construction specifications and drawings, are required to satisfy preconstruction code and building permit requirements. The construction documents

**Table 3. Aseptic Processing Room - Class 100/ISO 4 or CLASS 1000/ISO 5\* (Class 100 Laminar Flow Hoods Can Be Used in lieu of a Class 100 Aseptic Processing Room).**

	<b>Material Requirements</b>	<b>Recommended Design Specification</b>
Ceilings	Drywall-epoxy painted Cleanroom ceiling tile with anodized aluminum T-bar grid	Cleanroom ceiling tile with anodized aluminum T-bar grid
Floors	Seamless vinyl sheet Monolithic epoxy	Seamless vinyl sheet with minimum 4" to 6" cove to the wall
Walls	Monolithic vinyl FRP laminate panel Tempered glass Drywall-epoxy painted Melamine panel	FRP laminate panel
Doors	Stainless steel Anodized aluminum Epoxy painted metal door	Anodized aluminum door frame
Light fixtures	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish	Standard construction recessed cleanroom fixture; RTV sealed to anodized aluminum T-bar ceiling grid; acrylic lens with baked enamel finish
Windows	Tempered safety glass with no sills and stainless steel or anodized aluminum frame	Tempered safety glass with no sills and stainless steel or anodized aluminum frame
Air changes	60 air changes per hour (minimum)	80 to 100 air changes per hour
Air pressure	Compounding room + 0.07" WC to the anteroom	Compounding room + 0.07" WC to the anteroom
Air filtration	99.97% HEPA filter or better with a 30% efficiency ASHRAE or better prefilter	99.97% HEPA filter or better with a 30% efficiency ASHRAE or better prefilter
Particulate control	Class 100 per <i>FS 209E</i>	Class 100 per <i>FS 209E</i>
Temperature	70°F ± 4°F	70°F ± 4°F
Relative humidity	25% to 50% RH	25% to 50% RH
Gauges should be installed to monitor the pressure differentials between the cleanroom and the general preparation area. This will ensure that proper operating conditions are being maintained at all times and are routinely monitored.		
* The New Jersey State Board of Pharmacy has mandated that all sterile products be prepared in a class 100 hood/clean zone within a class 1000 cleanroom.		
ASHRAE, American Society of Heating, Refrigerating and Air-Conditioning Engineers, Inc FRP, fiberglass-reinforced plastic	RTV, room-temperature vulcanizing HEPA, high-efficiency particulate air <i>FS 209, Federal Standard 209</i> RH, relative humidity	F, degrees Fahrenheit WC, water column

should be reviewed and approved by the project team members, who should verify that the level of detail and the information on the construction documents are sufficient to meet approved design criteria. Construction documents should specify items such as the location of the control panel that monitors pressurization requirements; ports for measuring room pressures, temperature, and relative humidity; Emery test ports for and the locations and distribution of HEPA filters; flow-monitoring stations; locations of return-air grilles; etc.

## Certification

Constant environmental control is necessary to control airborne contamination. Airflow rates and direction, room pressurization relationships, temperature, humidity, and specialized filtration (HEPA filters) must be tightly controlled and monitored. HEPA filters,

which can remove a minimum of 99.97% of particles 0.3 μ in size or larger, are essential for the creation and certification of a cleanroom environment. These requirements should be specified in the design criteria and construction documents and should be tested after construction has been completed to confirm that the cleanroom meets the design criteria. A qualified, certified, cleanroom certification vendor should perform the certification process.

## Postcertification, Precompounding

After the cleanroom has been certified and before compounding activities are begun, the following three activities should be undertaken:

**Extensive cleaning.** Cleanroom construction and certification will expose the cleanroom to a significant amount of particulate matter and bioburden from equipment, people, and materials. Three

separate cleaning processes should be performed to establish environmental and microbiologic control in the cleanroom. Every surface of the cleanroom, from the ceiling to the floor and all points between, should be washed twice with a bactericidal, virucidal, phenolic, or quaternary ammonium compound (QUAT) detergent such as Vesphene or Hi-Tor. The third cleaning should involve the use of a dilute bleach solution. This three-step process removes particulate and bioburden matter from the cleanroom.

**Environmental testing.** After the three-step cleaning process has been completed, the cleanroom should undergo environmental microbial air and surface testing to ensure that the cleaning was effective in eradicating all microorganisms. An excellent environmental monitoring program that can be used as a template for initial and ongoing environmental monitoring programs is outlined in *USP* chapter <1206>.

**Aseptic technique validation.** All those entering the cleanroom during the cleaning and environmental monitoring processes must adhere strictly to proper handwashing, gowning, and gloving procedures. All personnel (pharmacists or technicians) who prepare sterile products should participate in an aseptic technique validation process to ensure that sterile products devoid of microbial contamination will be prepared.

## Maintaining the Benefits of the Cleanroom

Cleanrooms must be used and maintained properly. According to Richard A. Matthews,<sup>9</sup> chairman of the International Organization for Standardization Technical Committee ISO/TC209, founder of Filtration Technology, Inc, and president of Micron Video International, there are three myths about cleanrooms:

**Positive pressure prevents airborne contamination.** Positive pressure is just one of the many factors that maintain the integrity of the cleanroom environment, which in turn helps to prevent contamination. The amount of positive pressure between adjoining areas also contributes significantly to the prevention of contamination in the cleanroom.

**Cleanroom HEPA filters never need to be changed.** HEPA filters are subject to normal wear and tear and must be replaced. A HEPA filter is usually effective for about 8 to 10 years. Routine testing can be used to monitor the function of HEPA filters.

**The cleanroom will decontaminate itself.** Only properly trained and garbed personnel can decontaminate a cleanroom. The airflow patterns of a properly constructed cleanroom can maintain only a level of stability. The movement of people, equipment, and compounding ingredients and supplies contributes to the total environmental viable bioburden (living bacteria) and to nonviable particle loads. Thorough routine cleaning procedures are required to decontaminate the cleanroom.

Providing employee training and overseeing the management of all cleanroom activities can help to ensure the ongoing integrity and effective operation of a cleanroom.

## Conclusion

A pharmacy cleanroom project is not to be feared, but it must be understood and managed correctly. Never be too wise or too sure to consult with an expert. Solicit proposals or bids from at least three

cleanroom vendors so that the best cost and operational solution can be obtained. Be sure that your knowledge of cleanrooms and their operation is fact based. Cleanroom construction and operation are highly specialized activities, and working with experts will minimize short-term frustration and maximize long-term return. Know your aseptic process needs and be sure that they are consistent with current ASHP, *USP*, and/or state Board of Pharmacy requirements *before* you build your cleanroom. Pharmacists and technicians who work in cleanrooms should read the *ASHP Guidelines on Quality Assurance for Pharmacy-Prepared Sterile Products* in addition to *USP* Chapter <1206>. Those publications provide excellent information about sterile-product preparation practices and cleanroom operating and maintenance requirements.

The cleanroom should be built to enable the processes that will be performed. Pharmacists should consider the operations of other industries that specialize in aerospace projects, semiconductors, electronics, medical devices, or the manufacture of pharmaceuticals and ask the following questions: Why aren't *we* working in cleanrooms or controlled environments? Isn't contamination control or infection control also our responsibility when we prepare sterile products?

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