Understanding Pharmacy Cleanroom Design Requirements

By James T. Wagner and
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Image courtesy of Modular Cleanrooms Inc

PRIOR TO THE RECENT PUBLICATION OF USP CHAPTER <797> BY THE UNITED States Pharmacopeia, pharmacists were never required to work in a cleanroom when compounding sterile preparations. Although the mandate to use a cleanroom in pharmacy is new, the need to control the quality of critical operating environments dates over 100 years ago, to the discovery of bacteria. The need to minimize bacterial presence and to control the incidence of infection in hospitals, especially in operating rooms, was the scientific basis for cleanrooms, since it was noted that proper ventilation could greatly reduce the incidence of airborne infection.

A cleanroom is defined in ISO standard 14644 (Cleanrooms and associated controlled environments, 1999) as "a room in which the concentration of airborne particles is controlled, and which is constructed and used in a manner to minimize the introduction, generation, and retention of particles inside the room, and in which other relevant parameters, e.g., temperature, humidity, and pressure, are controlled as necessary."

It is critical to understand how your pharmacy cleanroom is impacted by the myriad of standards and references for cleanroom design and operation, including USP Chapter <797> requirements, ISO standard 14644, and Institute for Environmental Sciences and Technology (IEST) recommended practices (RP).

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Before you begin designing your cleanroom, you need to understand the performance parameters that measure HEPA filters, cleanroom classification, air changes, and pressurization. A written set of specifications for these environmental controls, as well as a list of desired construction materials, are critical steps in the process of designing a certifiable cleanroom. A sample design criteria covering these specifications can be found on page 18.

Air Filtration

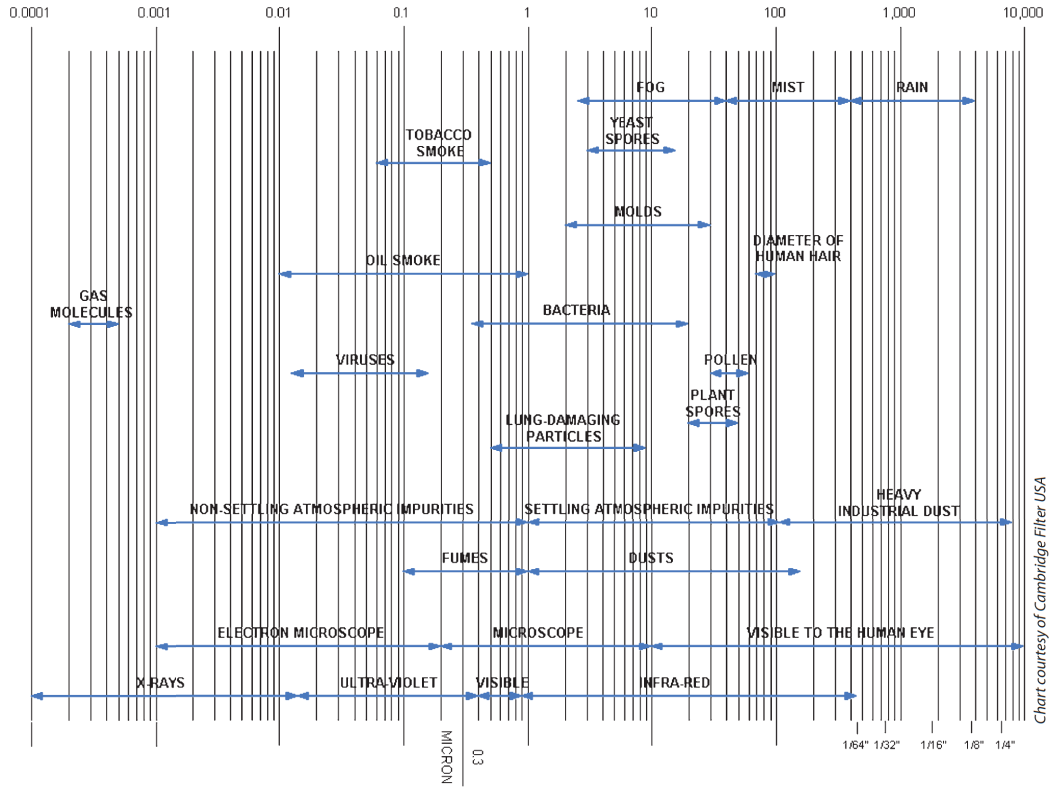
The HEPA (high-efficiency particulate air) filter is the cornerstone to any effective engineering control. There is often conflicting information regarding the rating of HEPA filters. We recommend you review the IEST recommended practice IEST-RP-CC001.3, which is the current national guide for purchasing and specifying HEPA filters. This document defines a HEPA filter as: "A throwaway, extended-medium, drytype filter in a rigid frame, having a minimum particle collection efficiency of 99.97% (that is, a maximum particle penetration of 0.03%) for 0.3-micrometer particles of thermally generated DOP or specified alternative aerosol." It is important to understand that the 0.3-micron size rating is for a "mass median" diameter particle. Traditionally HEPA filters have been tested with mass-concentration devices (photometers) that measure light scattered by all particles and the response is proportional to aerosol volume or mass.

Some European filter manufacturers and recently some domestic manufacturers have been rating HEPA filters with discrete particle counters. When particle counters are used, the rating should refer to a "count median" particle size. HEPA filters are rated by their ability to filter out the most penetrating particle size. When filter manufacturers efficiency-test their filters, they test at what is referred to as the Most Penetrating Particle Size (MPPS). The most penetrating particle size when using particle counter technology is generally referred to as being "between 0.1 and 0.2 micron count median diameter." It is easy to envision how particles larger than the most penetrating size are filtered more effectively through impaction, interception, and sieving. What people generally do not understand is that particle collection through diffusion actually favors particles smaller than the most penetrating particle size. Therefore, HEPA filters are rated at the size where penetration is at its worst case (MPPS). It is not accurate to state "down to 0.3 micron" because particles below that size are generally removed at a higher efficiency than the filter rating.

While HEPA filters have proved effective in removing most particulate contamination (see chart on page 17), they are not effective in filtering gases and vapors. This is why NIOSH requires that biological safety cabinets (BSCs) and isolators used for volatile drugs be externally vented.

There are no specific guidance documents that dictate specifications for type of HEPA filter. The current version of IEST-RP-CC001 lists six filter types, A through F. (This particular RP is expected to be voted on and changed within the next few months.) We recommend a Type C fil-

ter, per IEST-RP-CC001, for hospital pharmacy cleanrooms, as this filter is 99.99% efficient against 0.3 mass median particles and leak-tested using poly-dispersed aerosol. Because all HEPA filters are not created equal, it is very important to specify which filter you want. For example, although an 85% efficient filter is a HEPA filter according to the International Standard, EN 1822, it is not sufficiently effective for a hospital pharmacy cleanroom.



Relative Size Chart of Common Air Contaminants
(particle diameter in microns, logarithmic scale)

Cleanroom Classification

Cleanroom classification is based upon the maximum number of particles that are 0.5 micron size per cubic meter of sampled air, as expressed in the various ISO classifications, for example ISO Class 7, formerly known as Federal Standard (FS) 209 E Class 10,000. Cleanroom particle count is achieved by filtering supply air through HEPA filters. (See chart at left.)

Air Changes

When designing an ISO Class 7 or 8 cleanroom, it is critical to consider how many times per hour you will change the air with HEPA-filtered inflow air (air changes per hour, or ACPH). More critical than the velocity of this incoming air, the amount of air entering the room, or air volume, is expressed in cubic feet per minute (cfm). USP <797> does not specify a minimum number of air changes to use, but the minimum ACPH value will be based on two factors. One is the need to satisfy potential regulatory expectations from an air cleaning perspective. For these values, the FDA looks for a minimum of 20 ACPH in their Guidance for Industry–Sterile Drug Products Produced by Aseptic Processing–Current Good Manufacturing Practice. ISO 14644-4 does not mention air change requirements for health care cleanrooms, but it does specify 30 to

Photo courtesy of Terra Universal, Inc.

70 ACPH for microelectronics cleanrooms. Neither of these references is specific to sterile compounding, but they should be considered good general guidance. The second factor is the amount of air required to condition the space, which must be determined by a qualified HVAC engineer. Factors to be considered include heat loads from people, lighting, fan energy, process equipment, etc. Once the room ACPH requirement is established, the volume of air needed can be calculated (desired ACPH ÷ 60 x room volume in cubic feet = total airflow volume needed in cfm).

Pressurization (Air Pressure)

Pressurization is the measurement of air pressures between two adjoining areas, whereby the air pressure in the more stringently classified area is higher than the pressure of the next classified area. The pressures are said to "cascade," or in other words, air from the cleanest area will flow into the dirtier area. Average pressure differentials between two adjoining areas (i.e., ISO Class 7 area to ISO Class 8 area) are typically +0.05 inch wc. Pressure gradients between rooms of equal cleanliness classification may in some cases be less than 0.05 inch, possibly as low as 0.02 inch.

Construction Materials

In choosing any and all materials, you must take into consideration a given material's ability to contribute to the cleanliness of the environment as well as its capacity to withstand personnel use and abuse, frequent cleaning and disinfection, and the passage of time. Choosing the material used to construct the room (along with understanding its operating conditions) is very similar to knowing what you want when you buy a car. Like a car, a cleanroom is a significant fiscal investment, and as such the materials that are used in the construction of the cleanroom will determine its life cycle. Cheaper material for the floors, walls, and ceiling will not stand up to the use and cleaning required to maintain the proper operating environment. In general the number of joints, cracks, and crevices should be reduced. Additionally, it is critical to avoid material that will deteriorate with use, hence negatively affecting particle control and contributing to contamination.

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Design Criteria

When building a cleanroom to meet the volume of your specific compounding activities, consideration must be given to the design criteria of this facility. Before meeting with cleanroom vendors, it is important to put together a design criteria document that, at minimum, contains a rough floor plan of the existing space, an ideal workflow pattern, a general list of desired construction material, and environmental-control specifications. These criteria should be clearly documented in written form and be approved by all parties involved in the construction of the cleanroom. Additionally, these criteria should be part of the construction contract, which will guide the contractors during all phases of the project. These specifications will also provide a means for defining certification requirements for the final acceptance of the cleanroom by the owner. During the cleanroom testing and certification process, all of these operating parameters should be realized. This validates that the cleanroom was properly constructed. The design criteria document establishes preapproved and acknowledged (signed)

Sample Design Criteria for Cleanroom or Buffer Room- ISO Class 7 (Class 10,000)

	SUGGESTED SPECIFICATIONS
CEILINGS	• Drywall—epoxy painted • Clean room ceiling tile with anodized aluminum T-Bar grid
FLOORS	• Monolithic vinyl • Monolithic epoxy
WALLS	• Monolithic vinyl • FRP laminate panel • Tempered safety glass • Drywall—epoxy painted • Melamine panel
DOORS	• Stainless steel • Anodized aluminum • Epoxy painted metal door
LIGHT FIXTURES	• Standard construction recessed clean room 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 frames
AIR CHANGES	• An adequate number of air changes to properly condition the space with no less than 30 air changes per hour
AIR PRESSURE	• Anteroom must be negative to the compounding room and positive +0.02 wc to the general area
AIR FILTRATION	• IEST-RP-CC001 Type C HEPA filter with a 30% Efficiency ASHRAE* or better prefilter
PARTICULATE CONTROL	• ISO Class 7 per ISO 14644
TEMPERATURE	• 66˚F +/- 4˚F (these values are for employee comfort when properly garbed)
RELATIVE HUMIDITY	• 35 - 65 % RH (these ranges are optimized for employee comfort, suppression of microbial growth, and component functionality)

*The American Society of Heating, Refrigerating, and Air-Conditioning Engineers, www.ashrae.org.

expectations of the cleanroom contractor's final constructed cleanroom, so that the owner can hold the contractor accountable for delivering prior to final payment. Having this understanding and a clearly articulated set of requirements will help to ensure that the cleanroom will comply with USP Chapter <797> now and into the future.

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Non-Engineering Controls

Selecting the appropriate engineering controls is not the only consideration in meeting USP <797> standards. Equally important is assuring compliance with USP <797> standards for the following non-engineering controls:

- Employee training
- Policies and procedures
- Aseptic technique and process verification
- On-going environmental monitoring
- Facility maintenance
- Compliance auditing

These requirements will be the subject of in-depth studies in future issues of *Pharmacy Purchasing & Products*. For important information on facility maintenance, see page 33 of this issue.

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Further Reading:

Kastango, ES, DeMarco, S. Pharmacy cleanroom project management considerations: an experience-based perspective. Int J Pharm Compd. 2001; 5:221-225

Resources:

Institute of Environmental Sciences & Technology .....www.iest.org
International Organization for Standardization .....www.iso.org
United States Pharmacopeia .....www.usp.org