Understanding Pharmaceutical Cleanroom Design

By John Zhang

A prop3er HVAC system is a critical part of pharmaceutical cleanroom design. Even though various design guidelines and standards are available, there is no clear-cut guidance for many crucial HVAC design parameters, particularly air changes per hour for a specific class of cleanrooms. FDA guidelines[1] only specify a minimum of 20 air changes per hour for controlled areas without providing any specifics.

A recently published ISO Standard[2] does provide some guidelines on the air change rates, but only for the microelectronic industry. This standard-specified air-change rate is 10 to 20 for Class 8 (equivalent to Class 100,000 in Fed 209E,[4] which has been repealed and replaced with ISO 14644-1), a deviation from the earlier FDA guideline, furthering the confusion.

The ISPE Baseline Guide for sterile facilities[3] did try to cover this important design aspect by devoting Section 15.4 to address the calculation of air-change rate. Unfortunately, this section has only a subtitle and not the actual equation.

As a result, different pharmaceutical and biotech companies are using their own guidelines to approach cleanroom HVAC design, leading to a range of scattered design parameters. For example, some use100 air changes per hour for all ISO 7 (Class 10,000) cleanrooms while others use as low as 30 for the same classification. The question naturally arises: how can a design professional reach proper parameters with a set of given conditions when designing a cleanroom HVAC system? This article attempts to address this question by looking into the fundamentals of cleanroom HVAC systems.

A cleanroom is defined in the new ISO standard 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 in-

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side the room, and in which other relevant parameters, e.g., temperature, humidity, and pressure, are controlled as necessary."[2] For example, an ISO 7 cleanroom is controlled to allow not more than 10,000 particles of 0.5 µm or larger per ft^3 (0.02832 m^3) of air volume. The particle count in a cleanroom is periodically tested to maintain the validity of a cleanroom.

Cleanroom Fundamentals

The fundamentals of cleanroom design are to control the concentration of airborne particles. The particulate matter come from several sources: the supply air; the internal particle generation; and infiltration from adjacent spaces. To control these airborne particles, all three sources need to be controlled.

Supply Air Controls

Particles from the supply air are easily controlled by using HEPA (high-efficiency particulate air) filters. Most HEPA filters have a minimum efficiency of 99.97% tested on 0.3 micron particles. In other words, only less than 0.03% of all particles of 0.3 microns or larger can get through such a filter. So if the return air contains 10,000 particles per ft^3 (353000 particles per m^3), its concentration would be reduced down to three particles per ft^3 (106 particles per m^3) after it goes through the filter. Therefore, the supply air can be considered almost particulate-free.

Infiltration Controls

Particles from adjacent spaces also are easy to control. If the adjacent area is less clean than the cleanroom of concern, particle infiltration can be minimized by controlling the airflow direction, so that air flows from the cleanroom to its adjacent space. This can be easily accomplished by supplying more air than returning air, thus slightly pressurizing the room.

Internal Generation Controls

The internal particulate generation always is the focus of any cleanroom design. The internal generation consists of those from building elements such as walls, floor, ceiling, etc., from equipment, and most importantly from operators. The internal generation from building elements can be minimized by using hard-surfaced, non-porous materials such as polyvinyl panels, epoxy painted walls, and glass board ceilings. The internal generation from operators can be minimized with proper gowning to shield the human body and street clothing from the surroundings.

Particles from Operators

As mentioned earlier, the operators are the main source of internal generation. It is well-known that thousands of dead cells are shed from the human body every minute. That would contribute millions of particulate counts into a cleanroom. As the cleanroom class becomes more stringent, so do the room finish and gowning requirements. Nevertheless, a typically cleanroom-gowned operator would still generate approximately 10,000 particles of 0.5 µm or larger per second per ft^3 (353 000 particles per m^3) of air volume (Reference 3, Chart A3-1). Assuming a cleanroom of 20 ft × 20 ft × 9 ft (6 m × 6 m × 2.75 m) high with four operators, the particle generation rate due to the operators would be 670 per minute per ft^3 (23 660 per minute per m^3), assumed with perfect mixing.

However, even though a high air-change rate is provided, a completely even spread of these particulate matters is highly unlikely. The zones immediately around operators will have much higher concentrations than those far away from them. With this in mind, a reasonable estimate for internal generation due to operators would be around 5,000 particles per minute per ft^3 (177 000 particles per minute per m^3) in a typical cleanroom.

Cleanroom Controls

Although ISO 1 through ISO 5 cleanrooms use unidirectional flow designs, most pharmaceutical cleanrooms depend on the principle of dilution to control their particles. For wellmixed air, at any given moment, the particle concentration x can be expressed in the following equation, assuming no infiltration as the room is pressurized:

$$dx(s–x) \times v \times dt + g \times dt \qquad (1)$$

where

- s is the supply air particulate concentration in particles per ft^3 (m^3);
- v is the supply air volume flow rate in terms of air-change rate per hour;
- g is the internal generation rate in particles per ft^3 (m^3) per hour; and
- x is room or return air concentration in particles per ft^3 (m^3).

Assuming the initial room concentration is Xo and neglecting the variation of g with time t, the above differential equation can be solved as:

$$x = (Xo – s – g/v)\ exp\ (–vt) + s + g/v \qquad (2)$$

As time t goes on and the system reaches the steady state, the room final concentration x simply becomes:

$$x = s + g/v \qquad (3)$$

or

$$v = g/(x–s) \qquad (4)$$

With Equation 4, the air-change rate can be easily calculated as a function of g, s, and x.

Examples

A Typical ISO 7 (Class 10,000) Cleanroom

Using a specific example, when the aforementioned

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ISO 7 cleanroom (x=10,000) using 99.97% HEPA filters (s=3) with a typical internal generation (g = 5,000 × 60), the supply airchange rate v would be approximately 30 per hour.

By the same token, if the rate is increased to 50, the actual particle count in the room would be approximately 6,003. (In reality, particle counter readings would scatter within a certain range.)

209E	ISO 14644	0.1㎜	0.2㎜	0.3㎜	0.5㎜*	1㎜	5㎜
—	Class 1	10	2				
	Class 2	100	24	10	—		
1	Class 3	1,000	237	102	(1)	8	
10	Class 4	10,000	2,370	1,020	(10)	83	
100	Class 5	100,000	23,700	10,200	(100)	832	29
1,000	Class 6	1,000,000	237,000	102,000	(1,000)	8,320	293
10,000	Class 7				(10,000)	83,200	2,930
100,000	Class 8				(100,000)	832,000	29,300
	Class 9				(1,000,000)	8,320,000	293,000

* Particulate count for this particular size is per ft³ (for illustration purposes)while all others are per m³

Table 1: Selected airborne particulate cleanliness classes.

Filtration Effects

Proper air filtration is crucial for cleanroom controls. Nevertheless, once standard pharmaceutical grade HEPA filters are used, the supply air can be considered practically particle-free. This statement is in total agreement with ISPE's guide[3] Therefore, further improving supply HEPA filter's efficiency does not help improve the cleanliness of a cleanroom. This can be easily illustrated in the following example.

In the same cleanroom, when double HEPA filters are used, as some of pharmaceutical engineers advocate (s = 0.0009), with the same air-change rate (50) and internal generation rate (5,000 × 60), the actual particle count would be improved from the previous 6,003 to 6,000, a meaningless amount.

Design Hints

From the previous analysis, it is obvious that the most effective way of controlling the cleanroom quality is to minimize the internal generation and to supply adequate HEPA air to limit the actual particle counts under the ISO standard-specified limit. According to FDA guidelines,[1] a minimum of 20 air changes per hour should be used. While this is quite enough for a typical ISO 8 (Class 100,000) cleanroom, it may not be so for an ISO 7 cleanroom. Therefore, for ISO 7 or under, more analyses are required before an optimal air-change rate can be decided.

Regardless, a design professional should keep in mind that a high air-change rate cannot be substituted by using extremely high-efficiency HEPA. That would be a fundamental mistake for a cleanroom design.

Air-Change Rate for a Typical ISO 7 Space

For a typical ISO 7 space with a typical internal generation of approximately 5,000 per cfm (10600 per L/s), and supply air through 99.97% HEPA filters, the required air-change rate would be

$$v = g/(x–s) = 60 \times 5{,}000/(10{,}000 – 3)$$
$$= 30 \text{ air changes per hour}$$

	At Rest		In Operation	
Grade	Maximum permitted number of particles per cubic meter (per cubic foot) equal to or above:			
	0.5 ㎜	5 ㎜	0.5 ㎜	5 ㎜
A	3,500(100)	0	3,500(100)	0
B	3,500(100)	0	350,000(10K)	2,000
B	350,000(10K)	2,000	3,500,000(100K)	20,000
D	3,500,000(100K)	20,000	Not Defined	Not Defined

Table 2: EU/MCA airborne particulate classification.

Of course, in the case that internal generation is significantly higher, more air changes would be required.

Air-Change Rate for an ISO 6 Space

With identical conditions, an ISO 6 (Class 1,000) space would require almost 10 times as many air changes as an ISO 7 space. However, in reality, it does not. For one thing, very few pharmaceutical spaces are classified as ISO 6 (there is no ISO 6 classification in EU/MCA). For those that do, they are typically either an airlock or a buffer zone separating an aseptic filling room (typically an ISO 5 zone) and its adjacent ISO 7 spaces. (It is absolutely acceptable to have an ISO 5 unidirectional flow zone within an ISO 7 room; they do not need to be separated by an intermediate ISO 6 airlock.) In this case, the internal particle generation is very small due to the absence of operators. To be conservative, assume g = 1,000 × 60 (per hour). Therefore, the required air-change rate would be

$$v = g/(x–s) = 60 \times 5{,}000/(10{,}000 – 3)$$
$$= 60 \text{ air changes per hour}$$

When operators are present and the space has to be validated as operational, an ISO 6 room requires much higher air changes than 60 as discussed here.

Air-Change Rate for an ISO 5 Space

The analyses so far were based purely on the dilution principle that is applicable to only ISO 6 and beyond. For ISO 5 spaces, the displacement principle applies, and

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that renders the previous equations irrelevant. Normally, an ISO 5 space/zone is entirely covered by a HEPA ceiling or hood. In other words, the entire space is flooded by particle-free supply air that is unidirectional. The key to maintain such unidirectional flow is to have sufficiently high velocity out of the HEPA filters, typically at 90 fpm (0.5 m/s), providing unidirectional momentum to prevent contaminated air outside the ISO 5 space from crossing this flooded zone boundary. Therefore, the air-change rate is not a design parameter for an ISO 5 space in most cases.

Nevertheless, a rule of thumb can be derived if one wishes to relate air change rates with an ISO 5 space. Typically, such a space is 100% covered by HEPA filters. Also, actual filter sizes are normally only 80% of the nominal ceiling space, and HEPA filter design face velocity is 90 fpm (0.5 m/s). Therefore, the supply air volume is typically 72 cfm/ft^2 (366 L/s per m^2). An ISO 5 space rarely has a high ceiling. Assuming a 9 ft (2.75 m) ceiling, this design setup would translate into 480 air changes per hour. If the ceiling height is only 8 ft (2.5 m), then the airchange rate would be increased to 540. In the light of this analysis, a typical ISO 5 space has roughly 500 air changes per hour.

Impact of Pressurization

One of the most important parameters in cleanroom HVAC design is room differential pressure. It is easily understood that by maintaining positive pressure over its adjacent space, the infiltration of less clean air into a cleanroom is minimized.All guidelines recommend a 0.05 in. (12.5 Pa) differential across doors separating rooms with different classification. Absolutely nothing is wrong with this design philosophy and close attention should be paid to it.

Let's look at how differential pressure reversal affects a typical cleanroom performance. Again, the example is an ISO 7 space adjacent to an ISO 8 airlock. As is well-known, the airlock, since it is normally unoccupied, is usually cleaner than the ISO 7 space. Nevertheless, for the sake of argument, we would still treat it as an ISO 8 space with a particulate concentration of 95,000 per ft^3 (3.4 million per m^3). Also, assume a typical 3 ft × 7 ft (0.9 m × 2.1 m) door with a typical crack of 1/8 in. (3 mm). This crack results in an opening of 0.21 ft^2 (0.02 m^2). When a serious differential reversal takes place, say, 0.05 in. (12.5 Pa) the other way, the infiltration from the airlock into the ISO 7 space is approximately 200 cfm (94 L/s). This would contribute about 19 million 0.5 µm or larger particles per minute into ISO 7 space. Assuming again perfect mixing with the room air (20 × 20 × 9 = 3,600 ft^3 [102 m^3]), this infiltration would require

$$v = g/(x–s) = 60\times(19{,}000{,}000/3{,}600)/(10{,}000–3) = 32$$

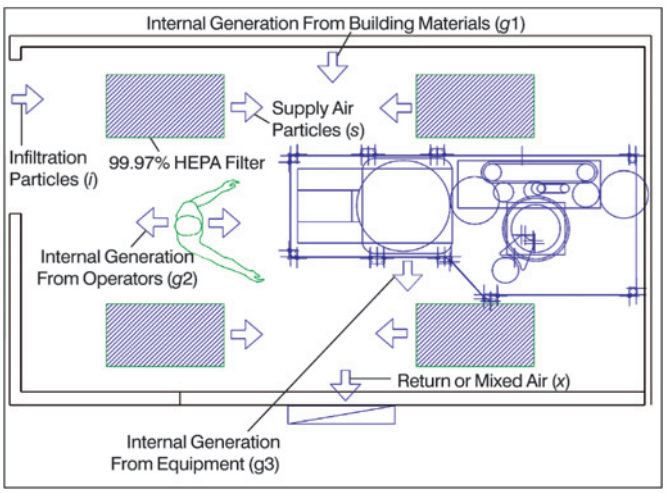

Figure 1 : Typical cleanroom with HEPA supply, internal generation and infiltration

Thirty-two additional air changes per hour are needed just to deal with this pressure reversal. It is little wonder that quality assurance personnel in many companies tend to react strongly when the differential is not maintained or somehow is accidentally reversed, resulting in shutting productions down, alarming the entire manufacturing facility, or even dumping good products.

Is It Really So Bad?

To maintain design pressure differentials is a daunting task for HVAC professionals as many seasoned engineers in pharmaceutical industry can testify. In reality, the damages caused by a pressure reversal are much less than what was illustrated earlier. First, as mentioned before, the adjacent airlock is more often than not cleaner than the cleanroom of concern. Even if it is not, the cleanliness is rarely as bad as near the 100,000 level. Second, doors are normally sealed with sweeping rubber blades, resulting in very small cracks. Third, the pressure reversal when it happens is always very slight, hardly more than –0.02 in. (–5 Pa).

Now let's examine such a more realistic condition: The airlock actual cleanness level is 30,000 (three times dirtier than 10,000, which is unusually high); the actual door crack is half the previous example, or 0.1 ft^2 (0.01 m^2); and the pressure reversal is –0.02 in. (–5 Pa). Thus, the resultant airflow reversal is 57 cfm (27 L/s). The 0.5 µm or larger infiltration into this 3,600 ft^3 (102 m^3) room is then merely 475/cfm (1007 per L/s). Assuming the internal generation is 6,000 per minute and the design air-change rate is 50, the average cleanliness of this ISO 7 room is:

$$x = s + g/v = 3 + 60 \times 6{,}475/50 = 7{,}773$$

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an acceptable level. Without airflow reversal, the level is:

$$x = s + g/v = 3 + 60 \times 6{,}000/50 = 7{,}200$$

This is about 8% better. In the light of this analysis, one may wonder if it is warranted to dump all products out simply due to a very minor degree of airflow reversal.

Validating Cleanroom With Reversed Air Airflow

Obviously no one is willing to place his or her job on the line to say the pressure reversal is no big deal. But, many safe rectification measures exist. In addition to tightening up the door cracks, the most effective way to ensure quality is to validate the cleanroom under the deliberate condition of airflow reversal. That is, test the space cleanness under the worst condition. If the space passes the particulate count test protocol when the airflow is reversed, no one should need to shut down production when the problem is merely inability to maintain designed 0.05 in. (12.5 Pa) differential. This will solve many problems facing maintenance personnel in the pharmaceutical industry.

Validating Airlock as the Same Class as the Cleanroom

If this approach seems unorthodox, another approach can be taken: make the airlock as clean as the cleanroom and validate it as such. As a matter of fact, this has become a recent trend. As EU/MCA[5] states, "The final stage of the changing room (designed as an airlock) should, in the at-rest state, be the same grade as the area into which it leads." The air-change rate for the airlock does not have to be increased significantly since almost no internal particulate generation exists as the space is normally unoccupied. In other words, no design parameters need to be changed. Simply validate the airlock to the same class as the cleanroom.

Recovery Time

Another consideration in cleanroom HVAC design is so-called recovery time. The recovery time is inversely proportional to the air-change rate. In other words, the higher the air changes, the faster the recovery. The recovery time from one class up (say, from ISO 8 to ISO 7) can be estimated using the following formula:

$$t = 2.5/v \qquad (5)$$

For example, the time for an ISO 7 room to recover from a shutdown condition of 100,000 level to an operational 10,000 level, assuming 30 air changes, takes approximately 0.083 hours or 5 minutes. If the air-change rate doubles to 60, then only 2.5 minutes is required. If an ISO 6 room is to recover from ISO 8 condition with the same air-change rate, twice as much time would be required. However, an ISO 6 is likely to have at least twice as many air changes and, thus, the recovery time is about the same. It is noteworthy that the recovery time for an ISO 5 zone or room is almost instant since the entire zone is covered by particulate-free supply air and no dilution but displacement process is involved. It is obvious that most cleanrooms can recover in a reasonably short time.

Conclusion

Three main particulate contamination sources exist: supply air, infiltration air, and internal generation. Of various internal generations, operators are the main contamination source and proper gowning and operating procedure prove to be critical.

Once a reasonable estimate for internal generation can be secured, the air change rates for a dilution-based cleanroom design can be achieved using the equation: $v=g/x$ for all practical purpose. It couldn't be emphasized more that higher efficiency HEPA filters cannot serve to reduce the designed air-change rate. More often than not, the other way around is possible.

Maintaining proper pressurization is important to maintain cleanliness in a cleanroom. It is recommended that the protective airlock be validated at the same class as the cleanroom itself without significantly increasing the supply air to the airlock. If feasible, cleanrooms should be tested with a slight pressure reversal but *operated with proper pressurization*.

This article also offers a rule of thumb for estimating the recovery time using a simple formula: $t = 2.5/v$ per class recovery. Most cleanrooms can recover from shutdown in less than 10 minutes, if they are designed properly.

The suggested air changes for various cleanroom classes are based on common practice only. Extensive research would be required to reach optimal design parameters such as air changes and differential pressures. It is this author's hope that ASHRAE and other engineering organizations such as ISPE would come up with funding to support this type of research and millions of dollars can be saved by designing better and more efficient cleanroom facilities.

References

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