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## Distribution of Particles Within the Cleanroom: A Review of Contamination Control Considerations

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### Introduction

Cleanrooms (and controlled environments) provide the working space for the preparation of medicinal products. This 'space' is an area within which the concentration of airborne particles is controlled against a defined maximum level. A primary concern is with particles that are microorganisms or particles carrying microorganisms, especially those that might settle out onto critical areas. To achieve the necessary level of control the cleanroom is designed and constructed in a manner to minimize the introduction, generation, and retention of particles inside the room. As well as good design principles, part of this control relates to the way the room is used (such as operator gowning and cleaning and disinfection). In addition to the control of particles, other relevant parameters such as temperature, humidity, and pressure, are controlled as necessary in relation to a given pharmaceutical process.

'Particle' in the context of a cleanroom is a general term for all sub-visible matter. From this definition, 'airborne particle' simply refers to particles suspended in air. Air contains a variety of different particles of a range of different sizes. These include particles of dust, dirt, skin, microorganisms and so on. While there are multiple sources for particle generation, personnel are the main contributors of particles in cleanrooms as well as the primary source of microorganisms (1). Hence, while a risk can arise from the influx of contaminated air into a cleanroom this is less likely to occur within a correctly functioning cleanroom with effective air filtration; the greater risk is with what happens to particles shed from people working within the cleanroom when such particles enter the air stream (2).

The most important contamination control issue within cleanrooms is air, given that air can distribute contamination around the cleanroom, as well as the way that particles behave in air in relation to a tendency to settle. With this regard particles should not be thought of as 'passive' contaminants. Hence the essential part of cleanroom design is through established principles designed to control airborne particles. These are (3):

#### a) Air filtration

To ensure the air coming into a cleanroom has minimal levels of particles (at least above a specific cut-off size), air entering the cleanroom passes through a terminal filter. Most typically this is a HEPA (High Efficiency Particulate Air) filter. The inner part of the HEPA filter uses three different mechanisms to catch particles as they pass through in the moving airstream (4). These mechanisms are:

- Impaction, where larger particles are unable to avoid fibers by following the curving contours of the air stream and are forced to embed in one of them directly; this effect increases with diminishing fiber separation and higher air flow velocity. Thus at high air speeds, some particles are caught and trapped as they smash directly into the fibers.
- Interception, where particles following a line of flow in the air stream come within one radius of a fiber and adhere to it.
- Diffusion, an enhancing mechanism that is a result of the collision with gas molecules by the smallest particles, especially those below 0.1  $\mu\text{m}$  in diameter, which are thereby impeded and delayed in their path through the filter (via Brownian motion). This occurs at lower air speeds.

#### b) Air movement

In cleanrooms the air is normally operating at a multiple flow or turbulent flow (this is where air enters the room with non-uniform velocity). Here, air is driven in through grilles and ducts at ceiling height and removed through low level ducts (5).

Whilst the air is in the room its initial supply velocity is sufficient to keep it in constant turbulence. This prevents particles and microorganisms from settling (this is an ideal scenario because dead air can occur beneath tables and with other items of equipment).

With clean air devices there is a different requirement with air direction. Here the object is to have unidirectional airflow. To achieve this air is introduced evenly from one entire surface of the area through HEPA filters, which means the air flows at constant velocity across the area and is removed through the entire area, or expelled from the area.

#### c) Air exchange rates

Each cleanroom grade should have a set number of air changes per hour. Air changes are provided in order to dilute any particles present to an acceptable concentration. Any contamination produced in the cleanroom is theoretically removed within the required time appropriate to the room grade. For example, if a cleanroom is designed to have 20 air-changes per hour this means that every three minutes the room air volume is replaced (a factor of 60 minutes divided by 20). This is important because particles would otherwise build up in enclosed spaces if there is no ventilation.

Connected to air changes is the time taken for a clean area to return to the static condition, appropriate to its grade, in terms of particulates following a high particle generating event. Clean-up times are sometimes referred to as 'recovery tests'. This is assessed by the room being subject to a level of particles above the room class and then measuring, through the use of an optical particle counter, how long the room takes to return to the level of particles required for the room class.

#### d) Pressure differentials

Connected to the measurement of airflow is the maintenance of positive pressure. In order to maintain air quality in a cleanroom the pressure of a given room must be greater relative to a room of a lower grade. This is to ensure that air does not pass from "dirtier" adjacent areas into the higher grade cleanroom. Generally this pressure differential is set at 15-20 Pascals, although some areas of the same grade will also have differential pressure requirements due to specific activities, such as where dust is generated through the weighting of powders.

Pressurization is defined as a method by-which air pressure differences are created mechanically between rooms to introduce intentional air movement paths through room leakage openings. With this the relative quantities of air that are delivered and removed from each space by the ducted air system, air transfer system and losses. These openings could be either designated, such as doorways, or undesignated, such as air gaps around doorframes or other cracks.

The above four control areas are not mutually exclusive and need to be considered holistically. This is especially with the amount of air entering the cleanroom, the degree of mixing (and resultant air patterns), and the rate of air extraction. While airborne cleanliness of a non-unidirectional cleanroom is determined by the volume of air supplied to it, but the local cleanliness is determined by the air flow within the room. Thus there is a need to go beyond the measurement of airborne particles alone to determine the risk factors associated with cleanroom operations. It stands that when a cleanroom is tested and particle concentrations are measured particles can be focused in one area due to poor air-mixing; it also stands that some areas are subject to additional factors that can increase the possibility of particles settling out onto critical surfaces. It is with this latter issue that this paper is concerned.

While the mechanisms of particle control are, with reference to cleanroom design, well described and limits are in place for the permitted maximum concentration of particles in a defined volume of air (a cubic meter) (6), the distribution of particles within a cleanroom and the likelihood of particles settling is not so well described. Moreover, measuring the concentration of particles in the air and calculating these as the cumulative number does not inform the cleanroom user as to what proportion of these particles are likely to settle out from the air onto a surface. In discussing particles, this paper is not so much concerned with sources of particle generation; instead the focus is on a less discussed subject: particle distribution within the cleanroom environment and the risks of particles settling onto surfaces.

### **Particles in Cleanrooms**

Particles in cleanrooms are derived from several sources. In general, particles larger than 1  $\mu\text{m}$  originate from mechanical processes (such as two glass bottles colliding, mechanical abrasion or grinding), or particles of this size are produced from personnel in the form of skin matter shed from the body. Particles smaller than 1  $\mu\text{m}$  tend to be liquid droplets, such as the condensation of water, although they could also be from personnel sneezing or depositing spittle in situations where there is not good gown control. Most microorganisms in cleanrooms are not free-floating; instead they are carried on rafts of matter

such as skin flakes.

In cleanrooms particles behave in different ways, where behavior is governed by a range of factors. These factors will determine the likelihood of particles in the air settling out onto cleanroom surfaces. With multidirectional design cleanrooms (that is turbulent flow areas) air currents do not follow a predictable path. The result of this design configuration is that particles can move in any direction. This variation in movement can mean some particles can be re-entrained from a surface or, in poorly designed cleanrooms, from the floor. This leads to an increase in airborne particle concentration. Other particles may be deposited from the air-stream and remain on a surface due to physicochemical forces creating semi-permanent attachment. Disposition from the air is more likely as air moves around objects. Depending upon the shape of an object eddying or 'recirculation zones' can form, as might occur with the underside of a desk.

In a unidirectional flow clean zone (vertical or horizontal) the air flows, at a relatively high velocity, through the area following a predictable path. The increased flow will dilute and carry away any particles generated as soon they appear. This is one reason why unidirectional airflow is required for aseptic processing (as with an ISO 14644 class 5 or EU GMP Grade A area).

In ideal situations particles, in both turbulent flow and unidirectional airflow spaces, follow the streamlines of the airflow. This theoretical assumption is more likely when predicting the diffusion characteristics of small-diameter particles; however, this ideal state is less likely to occur with larger particles (7). Moreover, some particles will inevitably settle out from the air-stream, either due to their size or from collisions with other particles or with objects. In pharmaceutical and healthcare environments microbial carrying particles present the greatest risk. The settling out of particles is examined next.

#### *How do particles settle out in cleanrooms?*

Whether particles settle is partly a factor relating to a particle itself and partly due to the influence of physical forces (which can be classed as deposition mechanisms). The likelihood of the deposition mechanisms actually leading to particle deposition is in part related to the effectiveness of the cleanroom design.

Considering the nature of the particle itself, particles vary by (8):

- Size (including density and surface area);
- Composition (physical, biological, or a combination);
- Concentration (the overall numbers of particles in a given space affects the interactions that might predictably occur between the particles);
- Coagulation of particles (the degree to which particles come together to form larger particles, due to temporary or permanent aggregations).

Each of these factors can influence the likelihood of deposition, with density being perhaps the greatest contributor (9). Here particles of larger density are more likely to be deposited and particles of lower density are more likely to remain suspended in air (or until an event like Brownian diffusion occurs, as discussed later) (10).

How do particles in the air end up on a cleanroom surface? The factors that cause this have been described by Whyte et al (2015a), where deposition is presented as a two-step process (11). First, airborne particles are transferred from an area of the cleanroom onto to the layer of air next to a surface. Second, the particles are transferred through the layer to the actual surface. This happens as air passes over a surface and the surface drag slows down the air velocity. This reduction in air velocity occurs when air reaches the 'boundary layer'. This locale varies from surface to surface although typically it is no more than a few centimeters in thickness from the surface. For particles in the air within the boundary layer, there is a risk of deposition. Crossing the boundary layer, at the point of the surface, the air velocity reduces to zero (it therefore stands that away from the surface the air velocity will increase to a given point where it will match the air velocity of the cleanroom, which is commonly termed the 'free flow' area.

The position of the boundary layer can alter through the additional complexity of the presence of an operator (for instance if a cleanroom operator moves his or her hand close the layer). Research by Yang and Fu reveals the mechanics of these so-termed 'recirculation zones' form around the operator and workbench and how they alter due to the movement of the operator (12). The recirculation zones are not favorable to the cleanroom because they induce a local turbulent flow and entrain and trap contaminants.

There are multiple mechanisms through which particles can settle out onto the surface by crossing the free flow area and on entering the boundary layer. These mechanisms are summarized in a paper by Whyte, Agricola and Derks (13). In the paper

the airborne deposition mechanisms were listed as: gravitational deposition, turbulent deposition, impaction, interception, Brownian diffusion, and electrostatic attraction. These what physicists described as 'dry deposition mechanisms' (given the controlled nature of the as built environment where the air is relatively dry to the outside environment). Research indicates that very large particles will settle out quickly through sedimentation (settling) or impaction processes, while Brownian diffusion has the greatest influence on smaller particles (14).

Looking at these mechanisms further:

- Impaction.

This describes the process when small particles interfacing a bigger obstacle are not able to follow the curved streamlines of the flow due to their inertia. This can occur when the particles hit or impact the droplet. The larger the masses of a small particle facing a larger one, then the greater the chance of displacement of the particle from the flow streamline.

- Gravitational deposition

This is sometimes referred to as gravitational sedimentation. The term refers to the settling of particles which fall down at a given point due to the exertion of the force of gravity.

- Interception.

This factor describes what happens when small particles follow the streamlines. Here if smaller particles flow too close to an obstacle, they may collide leading to deposition.

- Turbulent deposition.

Turbulent eddies in the air transfers particles along streamlines. The crisscrossing of these streamlines means particles can collide. With a collision, particles can be deposited onto surfaces through inertia. The more turbulence and the greater the concentration of larger-size particles, then the greater the likelihood of particles being deposited onto surfaces.

- Brownian diffusion

Brownian motion, in the cleanroom air context, describes the random motion of particles suspended in air resulting from their collision with the fast-moving atoms or molecules in the air. The physical process by which a particle has a tendency to spread steadily from a region of high particle concentration to a region of lower particle concentration is called diffusion. Thus Brownian diffusion refers to the diffusion of particles in the air and particles can collide with surfaces through random movement, with some of the particles remaining on the surface (15).

- Electrostatic attraction

Most surfaces have an opposition charge in relation to the particles found in the air. The presence of a net electrical charge on a surface can create an electrostatic field that accelerates the deposition of particles onto the surface as differently charged particles move close to the surface. Particle deposition velocity (which is equal to the surface particle flux divided by the aerosol particle concentration) increases with growing surface charge (16).

While this phenomenon has traditionally been of more concern to cleanrooms used in the electronics sector, it can exert an influence within cleanrooms used for pharmaceutical use. As a result cleanroom surfaces are often designed to have a low electrostatic charge.

Each of these factors varies according to aerosol particle concentration in the ambient area, and to the exposure time. In addition to Whyte and colleagues' list of deposition factors, other authors cite additional deposition factors. These are turbophoresis (the tendency for particles to migrate in the direction of decreasing turbulence level) (17) and thermophoresis (different particle types exhibit different responses to the force of a temperature gradient) (18) as deposition mechanisms.

In terms of the most common mechanisms, a further paper by Whyte and colleagues, based on experimental data, showed that with particles of a size equal to or greater than 10µm, gravitational settling accounted for over 80 percent of surface deposition (19). Larger particles are affected more greatly than smaller ones to gravitational forces since deposition velocity increases in proportion to the square of the particle diameter. Simply put, larger particles are more likely to settle onto surfaces than smaller ones. This point about larger size particles are important, given that, within the pharmaceutical and healthcare setting, the particles of concern are microbial carrying particles (that is, microorganisms attached to rafts of matter, such as

skin detritus) and these tend to be of a larger size (20). Gravitational settling is also predominant for particles at 5.0µm and above (an important measure in Europe for cleanroom classification and operation); gravity is also influential for many particles at 0.5 µm and larger (the cut-off value for pharmaceutical particle classification according to FDA and European medicines regulators). Therefore, the mechanism of particle deposition of greatest concern for cleanroom users is gravitational settling.

Defining the size of the particle is not straightforward since particles in the air can take on a different shape to particles on a surface, and such particles, despite the ideal assumption of optical particle counters, are rarely spherical. Instead particles are cuboid, fibrous, or irregular (as with skin matter) (21).

#### *How can particle deposition be assessed?*

The degree (time and quantity) at which particles leave the air and fall onto a surface is known as the 'particle deposition rate'. The deposition rate can be quantified by taking an area, such as square decimeter (dm<sup>2</sup> equivalent to 0.01 square meters) or square meter (m<sup>2</sup>) and examining the number of particles landing onto this area over time (seconds, minutes or hours). Thus it is possible for a particle deposition rate per hour can be calculated for a given particle size.

This is not straightforward since, firstly, the surface selected for any assessment needs to be representative; the air around the surface needs to be typical of the cleanroom (which is difficult, given that this would assume that particles in the air are distributed homogeneously, when they are not) (22); and the surface may also need to be of sufficient importance (such as a critical area; in the pharmaceutical context this could be an area of exposed product). Secondly, such an approach might well assume that the surface is horizontal. Complications are introduced for vertical, diagonally raised, curved and other surface positions and to use such spatially positioned surfaces a correction factor needs to be introduced. Thirdly, the shape and the density of particles in cleanroom air will vary and this will affect deposition. The main factor here is in relation to the aerodynamic diameter of the particles (to an extent standard measurements for the density of skin particles, previously assessed as 1100kg/m<sup>3</sup> (23) and the polyester commonly used in cleanroom garments - 1380kg/m<sup>3</sup> (24) - can be used). A fourth factor to consider is airborne velocity. It is possible, according to Whyte et al to calculate the deposition velocity of discrete sizes of particles, as they settle through the air (13). For this a series of equations can be used (although to use these, a series of measurements taken from within the cleanroom are required).

Such modeling should be orientated towards the particle size cut-off values of concern for pharmaceutical cleanrooms (0.5 and 5.0µm), since the size distribution of the particles influences the rate and level of particles that will be deposited on surfaces, all other factors considered.

The above approach is not easy to reproduce in the typical cleanroom. Alternatively, information about particle deposition, in relation to microbial carrying particles, can be derived from reviewing data in relation to the exposure of settle plates. For this, Whyte and Eaton pose the following equation (24):

Number of airborne microorganisms deposited onto the product in a given time (no.) =

Deposition rate (no./cm<sup>2</sup>.s) × area of product exposed (cm<sup>2</sup>) × time of exposure (s)

By knowing how long a settle plate has been exposed for provides the answer to "no./cm<sup>2</sup>

.s)". The usefulness of this approach comes down to the positioning of settle plates in meaningful locations, such as close to exposed product. The predictability of where to position settle plates is clearer in unidirectional airflow paths than in turbulent flow rooms.

#### *How can particle movement and deposition be controlled?*

As can be inferred from the above discussion simply pumping more air into a cleanroom will not necessarily reduce the risk of particle deposition, especially where larger particles are present like skin flakes, unless the factors affecting air distribution are adequately controlled. This control is the product of several cleanroom operational parameters since the value of the deposition velocity of particles and the degree to which they might settle out due to gravitational forces is influenced by a cleanroom's air supply rate and turbulent intensity of the air. Understanding these factors should influence the design of the cleanroom air supply rate and with designing the level of turbulence. This understanding allows for modifications to be made, as required to:

- Cleanroom air inlets;

- The air velocity (of the air entering the cleanroom - the total circulation airflow rate divided by primary cleanroom floor area);
- The amount of air entering the cleanroom over a given time;
- The distribution of air within the cleanroom (and factors like velocities);
- The length of time air remains within the cleanroom (the total cleanroom airflow circulation rate divided by the cleanroom volume);
- The number of air-extracts;
- The 'pull' of the extracts.

The necessary assessments can be made using tools like computational fluid dynamics and then assessed through airflow visualization studies. Computational fluid dynamics (CFD) refers to the application of applied mathematics, physics and computational software to model how air moves, based on Navier-Stokes equations (equations that describe the motion of viscous fluid substances). These equations describe how the velocity, pressure, temperature, and density of a moving fluid (in this case, air) are related and allow for a review of forces associated with small particles and basic hydrodynamics to be made (25). The CFD process allows air patterns to be rendered as three-dimensional graphics, which show particulate concentrations, particle tracks, streamlines and velocity fields. Studying these models can indicate potential locations of vortices, recirculation regions, and adverse interactions between higher and lower cleanroom classification zones and thus help identify cleanroom designs that minimize the transport of particle contamination (26).

An example of the application of CFD is described by Whyte et al (2009) (27). This research showed an important influence to be the method of air supply into the cleanroom, centered on the type of diffuser around the air supply inlet. The diffuser affects the airflow intensity and the direction in which the air first travels (28). The study showed a four-way diffuser produced optimal air mixing and a more even airborne particle concentration throughout the cleanroom. The research noted other variables to consider, including such as air inlet supply velocity, temperature difference between air supplied and the room air temperature. A further variable was the release position of any contamination (such as where a person was positioned in the cleanroom or where the main activity took place).

Once measures have been taken to minimize particle deposition, by airflow design, verification of the airflow can be undertaken through airflow visualization patterns (29). Here a water-carrying substance can be used to create a dense vapor so that air direction can be tracked and the time taken for the air to dissipate measured (30). Understanding air movement can help to understand the path of particle flow and to pinpoint areas at risk (31, 32).

Where problems cannot be fully resolved, or in relation to critical surfaces close to exposed product or by product contact parts, locations of environmental monitoring can be selected (both viable methods, such as settle plates, and particle counters).

## Summary

This article has assessed literature relating to particle distribution within cleanrooms. The purpose of the article was to turn the attention of cleanroom users beyond the simple monitoring of particle concentration in the air and to consider the likelihood of these particles being deposited onto surfaces (with special attention paid to critical surfaces). Data gathered from particle counting as part of cleanroom classification or on-going assessment may be insufficient if relatively high levels of particles are settling out in critical areas. Therefore, further assessment is required.

The assessment of this settling risk is not straightforward and particle deposition, which mainly derives from gravitational settling, a product of many variables. The most significant variable is the relative size of the particle, the velocity of the particle, and the degree of turbulence within the cleanroom.

While the equations required to undertake an assessment of a cleanroom are complex, useful information can be gathered from exposing settle plates in appropriate areas or from methods like computational fluid dynamics, which allows for corrective actions to be taken. Once control has been established airflow visualization can be used as a verification tool. Data from this can help to inform as the best locations for environmental monitoring samples.

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