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Ventilation efficiency improvement in pharmaceutical cleanrooms for energy demand reduction

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ABSTRACT

Cleanrooms are large energy consuming facilities due to their high air change rates. This research elaborates on three ventilation energy efficient measures for pharmaceutical cleanrooms: Finetuning, Demand Controlled Filtration (DCF) and an optimal airflow pattern. To study the possibilities for finetuning and DCF, two case studies and multiple simulations were performed. Results show that DCF could lead to substantial energy savings of up to 93.6% in the specific case study facilities. Besides this, DCF based on occupancy could be implemented with a negligible effect on the environmental cleanliness. To study how an ideal airflow pattern in the cleanroom can be reached, resulting in a high contaminant removal efficiency, experiments were performed in a demonstration cleanroom. The best results for ACR in the range of $16h^{-1}$ - $38h^{-1}$, were obtained when air was supplied without a diffuser above the product area and when the work position was located closely to the air extract grilles.

1. INTRODUCTION

Cleanrooms consume large amounts of energy in comparison with average commercial buildings [1]–[4]. Pharmaceutical cleanrooms can consume up to 25.3 times more energy than non-classified rooms, 1.52 kW/m^2 versus 0.06 kW/m^2 [2]. The heating, ventilation and air conditioning (HVAC) system typically accounts for 50–75% of the total cleanrooms electrical energy use [5], [6]. This is caused by the high air change rates (ACRs) that are necessary in order to achieve the required cleanliness classification, as defined in the European Union Good Manufacturing Practice (EU-GMP) [7]. In the EU, those large amount of ACRs are often supplied by swirl diffusers that provide good mixing throughout the room [8].

Today's normative documents do not specify exact numbers for ACR for non-unidirectional ventilation, leaving it to the designers. Designers often use design guides from the International Society for Pharmaceutical Engineering (ISPE) [9] for sterile processes [2], [10]. However, appropriate airflow design depends on many variables. Design charts like ISPE do not take the impact of these variables into account [10]. Besides that, real particle generation is often unknown during the design process. This results in an over dimensioned HVAC system, in order to make sure that environmental cleanliness is not compromised [1], [2], [5], [11]. (Environmental cleanliness can be expressed by particle concentration throughout the room.) Because production is of more economic importance than energy savings, cleanroom operators have put product safety and product yields on top of their agenda for years, giving energy efficiency a lower priority [12]. This results in cleanroom facilities often operating 24/7 with the same ACR [12], [13].

Intensive energy consuming cleanrooms provide the opportunity to save large amounts of energy. Due to the fact that the cleanroom industry is growing rapidly, there are even more opportunities to save large amounts of energy [4]. In order to reduce potential energy consumption, 16 possibilities are defined in previous research [14]. One of these possibilities is a design specifically based on the real particle concentration present in the cleanroom (so called "*Fitted design*"). Together with the ACR, the amount of particle generation is the most important factor that determines particle cleanliness in the cleanroom [15]. The cleanroom's ACR should be based on the specific particle generation of each cleanroom. This can be applied in existing facilities, so called *finetuning*. A second possibility of reducing energy consumption is controlling the ACR based on demand. This is called demand controlled filtration (DCF). In theory, the ACR can be lowered when no particle generation is present. Controlling of the ACR can be done based on a night/weekend reduction, occupancy, or particle concentration in the cleanroom. A reduction of 33% fan speed contributes, for example, to a reduction in power consumption by 66% [16]. Previous studies have shown that DCF resulted in energy savings from 28% up to 72% over a year [13], [17]–[19]. A third possibility to reduce potential energy consumption is to have an optimal airflow pattern throughout the cleanroom. This can be expressed in a high contaminant removal efficiency (ε) [20] in the cleanroom. A higher contaminant removal efficiency can be achieved by an improved airflow pattern that removes particles more efficient from the cleanroom. This leads to a lower particle concentration throughout the room, which provides the possibility to reduce the ACR. The contaminant removal efficiency (ε) is formulated as:

Equation 1 [20]

$$\varepsilon = \frac{C_{exit} - C_s}{C(t) - C_s}$$

Where: ε is the contaminant removal efficiency, C_{exit} the particle concentration at the exit of the room [p/m^3], C_s the particle concentration at the inlet of the room [p/m^3] and C(t) the mean particle concentration in the room [p/m^3].

For well-known positions and intensities of contaminant sources, the contamination removal efficiency provides a good indication of the air quality [21]. A high ε contributes to a lower particle concentration in the cleanroom. Results of a Computation Fluid Dynamics (CFD) study indicate that ε can vary from 0.68 up to 9.4, when air supply, exhaust position and diffuser type are changed [22]. The performance indicator **ε** is also influenced by the location of the source. This in contrast to other performance indicators, as for example the air change effectiveness (ACE) [23], which is more frequently calculated by recovery time measurements.

In this study, these three aspects of improving ventilation efficiency in cleanrooms, and thereby reducing energy consumption, are researched.
The main underlying research question is: *"How can the ventilation efficiency in pharmaceutical cleanrooms be improved in order to reduce potential energy consumption?"*

1. First, the operating cleanliness of two pharmaceutical facilities with GMP demands (both designed following the ISPE guidelines) is investigated. The sub research question for this field of research is: "*What is the degree of overdesigning in both facilities, and to what extent can finetuning be applied?"*

2. These facilities were also used to determine the applicability of DCF. The sub research question for this field of research is*: "In what way should DCF be applied, and how does this effect the potential energy savings and the environmental cleanliness?"*

3. Finally, in order to obtain an optimal airflow pattern in pharmaceutical cleanrooms, experiments are performed in a mock-up of a cleanroom. The sub research question for this field of research is*: "How can the contamination removal efficiency be improved by considering the room's layout and ventilation design, in order to realise potential energy saving?"*

2. METHODS

Figure 2 shows an overview on how these three fields of research (aspects of improving ventilation efficiency in cleanrooms) contribute to the goal of saving energy. Additionally, this scheme shows the used methods for these aspects. This paper starts with reflecting on the methods that have been developed and applied for these three aspects. Thereafter, the results and discussion of these three studies are presented. A final conclusion will complete the paper.

2.1. Monitoring

For the analysis of the degree of overdesigning and applicability of DCF two different pharmaceutical cleanroom facilities were monitored. One pharmaceutical facility is situated in a hospital (facility H) and one is a radioactive pharmaceutical facility (facility R). They were both monitored on their particle concentration and occupancy during a period of three weeks. Figure 1 shows the two investigated rooms of facility H: a GMP classified B room (30.6m³) and a GMP classified C room (65.1m³). These rooms were monitored for a period from 12 until 30 September 2016. Room B is exclusively used for aseptic preparations in a LAF cabinet. In room C the ampoules machine is primarily used for filling ampoules that will be terminally sterilized later on. Room B is ventilated with an ACR of 42h^{-1} with an according flow rate of 1276 m^3/h, using a perforated plate mounted at the HEPA filter. In Room C the air is supplied by swirl diffusers with an ACR of 21h^{-1}, which is equal to a flow rate of 1351 m^3/h. Facility R is monitored from 14 November until 2 December 2016. This cleanroom is larger (192m^3) and is equipped with four LAF cabinets. The cleanroom is ventilated with swirl diffusers with an ACR of 20h^{-1}

In facility R, the particle concentration was only measured at one location. This location is based on the area where the highest microbes are measured using settle plates. Measurements were performed with a

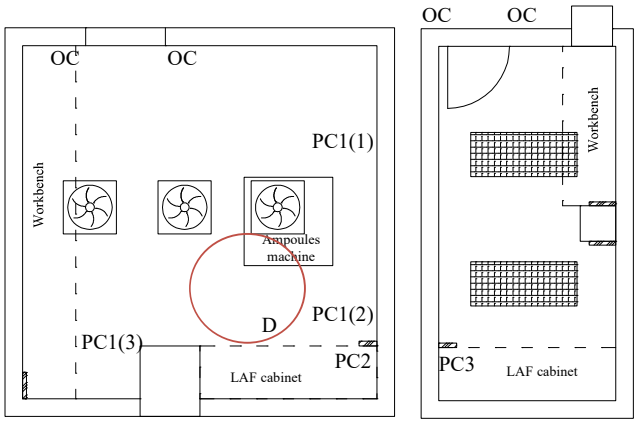

Figure 1 Floor plan of GMP room C (left) and GMP room B (right) of facility H. PC shows particle counter positions and OC the occupation sensors. The red circle indicates the defined working area.

Lighthouse Remote 2014 (1.0 l/min) for a particle size ≥0.5µm in facility R. In facility H, the Remote 2014 was used on the location of particle counter 1 (PC1) (see Figure 1). In order to see if specific areas had a relation with PC2, the location of PC1 was changed every week. During week 1 the Remote 2014 was situated at PC1(1), during week 2 at PC1(2) and during week 3 at PC1(3) (see Figure 1). At PC2 and PC3 a Lighthouse Remote 5104 (28.3 l/min) was used. All particle counters have an accuracy of 5% [24].

In both facilities, Sensor Development (SD) people counters registered people entering or leaving the room. These counters were positioned at the entrance (OC in Figure 1 for facility H). In room C of facility H an additional movement sensor was installed that measured movement in the defined working area (marked by a red circle in Figure 1). This way, the percentage of time the employee is present in the working area, compared to the total time that they are present in the cleanroom, can be calculated. All measuring devices logged their data per minute.

Recorded data should provide information about: the degree of overdesigning of the facilities, the applicability of DCF based on occupancy or particle concentration, the ratio of particle concentration between different measuring points in room C and the amount of contamination generated over time in the rooms of facility H.

2.2. Simulations

Simulations were performed to show the effects of finetuning and different DCF strategies based on both case studies H and R. A model in MATLAB (version R2015a) [25] is made, based on ordinary differential equations (ODEs). The model is able to calculate the particle concentration based on the actual contamination source and ACR. The ODEs are based on the equation of Whyte for a homogeneous cleanroom [15].

Equation 2 [15]

$$C(t) = \left(\frac{D}{Q} + C_B\right) * \left(1 - e^{-\left(\frac{Qt}{V}\right)}\right) + C_i * e^{-\left(\frac{Qt}{V}\right)}$$

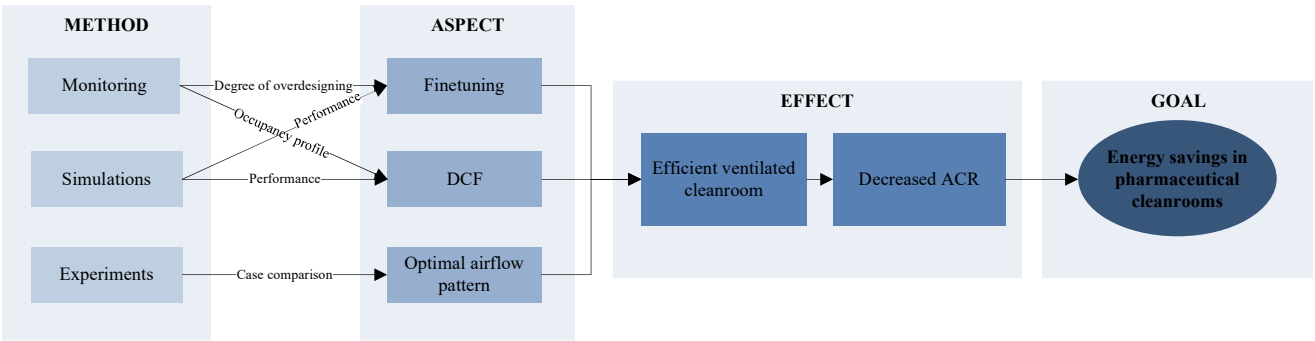

Figure 2 Methodology scheme

Where D is the source rate [p/s], Q the air volume supply rate [m^3/s] and C_B the background concentration of contamination /m^3 entering the room in the air supply.

Converting the above equation to ODEs, provides the ability to keep the ACR and source rate variable in time. In the model an assumption is made that perfect mixing in the cleanroom is achieved. However, in practise, this will never be the case [26].

Two different types of simulations were performed for facilities H and R:

1. *Continuously lowered ACR (finetuning):* For facility H, the ACR is lowered based on the amount of particle concentration during the monitoring time of three weeks. The chosen ACR is ten times lower than the current situation, resulting in an ACR of 2.1h^{-1}
2. *DCF based on occupancy*: For facility H and R the ACR is controlled based on occupancy. No distinction is made between the amount of people in the cleanroom. The ACR of 21h^{-1} and 20h^{-1} for facility H and R respectively, is lowered to an ACR of 6h^{-1} when the cleanroom is unoccupied for 30 minutes or longer. In the model, a reaction time of 150 seconds is considered when moving the air supply actuator to another position [27].

The simulations were performed with a contamination source rate that was estimated from the monitored data for both cases and calculated using Equation 3. In this equation, it is assumed that the filter efficiency is 100%.

Equation 3

$$D(t) = \frac{dC}{dt}V + Q * C$$

Where D is the source rate, and C the particle concentration in the room [p/m^3].

A validation study was conducted prior to the DCF analysis. For that study, a steady state calculation was performed and a validation analysis was done with data obtained from the case study H. The contamination source from the case study H was calculated following Equation 3. Together with the current facility's ACR, this contamination source was implemented in the model. Perfect alignment was shown between the model and the case study.

In order to determine energy savings, fan speed savings are calculated by Equation 4.

Equation 4

$$P = \frac{\phi_v \Delta p}{\eta}$$

Where P is the applied power for the fan [W], ϕv the volume flow [m^3/s] and Δp the total pressure [Pa].

2.3. Experiments

Experiments were performed to provide more insight in contaminant removal efficiency. A high contaminant removal efficiency contributes to a lower particle concentration in the cleanroom when the particle generation from the source is equal. The cleanroom used for the experiments (6.1x4.3x2.7m (LxWxH)) (see Figure 3) has 9 fan filter units (FFUs) (type: Envirco MAC 10® Original Fan Filter Unit [28]) with HEPA filters (H13 filter class). The fan filter units can be controlled on 50% or 80% capacity. This corresponds to approximately 611 m^3/h and 897 m^3/h respectively for each FFU. Air can be extracted at 5 extraction points (A-E). In the cleanroom, a LAF cabinet is present with an appropriate cleanroom chair in front of it. Also, a workbench is situated in a corner.

In the cleanroom, there are 6 calibrated light scattering airborne particle counters situated. These particle counters comply with ISO 21501-4 [29]. In the experiment 4 different types of counters are used: A Lighthouse Remote 2014 (1 l/min) on PC1 (height 1.0m) and PC2 (height 0.2m), a Lighthouse Handheld 3016-IAQ (2.83 l/min) on PC3 (height 0.8m) and PC4 (height 0.8m), a Lighthouse Remote 5104 (28.3 l/min) on PC5 (height 1.0m) and a Lighthouse Remote 5010 (2.83 l/min) on PC6 (height 2.0m). All particle counters logged their data per minute and have an accuracy of 5% [24]. Even though all particle counters used were officially calibrated, a deviation is noticeable between the counters. To make sure that the different particle counters can be compared, all counters have been set side to side for one hour, to make sure they would measure the same particle concentration. The deviations that have been detected are used to correct the outcomes (correction factors in the range of 0.8 till 1.2 were used). A generator (Atomizer Aerosol Generator ATM 226) is used as source (S) (height 0.8m) to regularly disperse particles in the air. The used aerosol liquid is Di-Ethyl-Hexyl-Sebacat (DEHS) [30]. The exact disperse rate of the generator is unknown. This is however not that important, because all cases have the same disperse rate. An estimation based on the extracted particle concentration, shows that the disperse rate is somewhere between 6.4*10^5 and 9.4*10^5 particles per second for particle size ≥0.5µm.

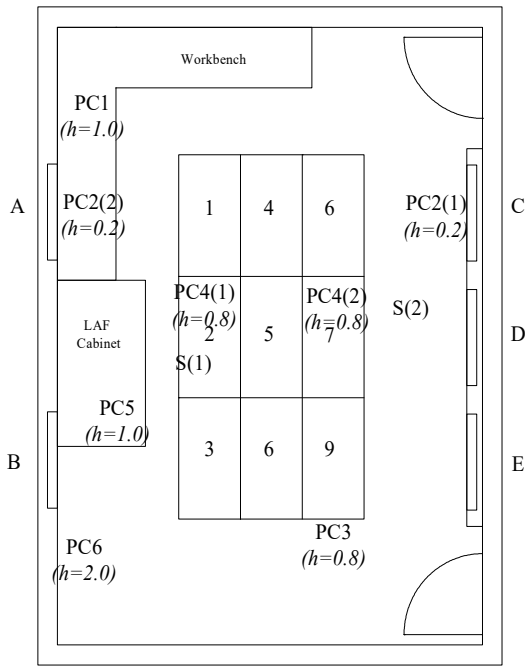

Figure 3 Experimental cleanroom lay-out, in which the locations of the particle counters (PC), fan filter units (1-9), extract grilles (A-E) and source positions (S) are shown. h indicates the distance from the ground.

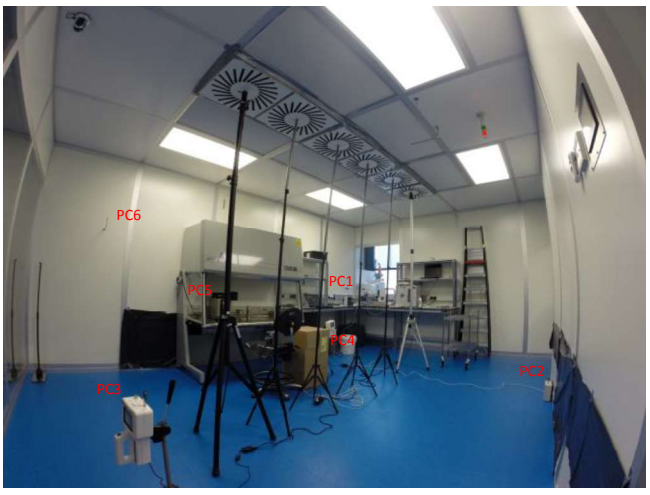

Figure 4 Experimental cleanroom setup with PC(1-6) the position of particle counters

Cases

The experiments considered 13 different cases. These different cases are formed using 6 different variables, that were, amongst others, studied in previous research [14]. One of these variables is the difference between using no diffuser or using a swirl diffuser (TROX VDW QZVM 600-24). Another variable is the difference in swirl angle, using the adjustable blades. The swirl angle can be turned outside or vertical. The third variable is based on the ACR. The amount of ventilation can be set to two different ACRs based on GMP classification B and C, around ~38h^{-1} and ~16h^{-1} respectively. This is considered to be at the low end of the range for both classifications. When the ACR is set to 38h^{-1}, 3 FFUs are activated on 80%. When the ACR is set to 16h^{-1} 2 FFUs are activated on 50%. The supply air position is another variable in the cases. The supply air FFU can be located in position 1 till 9 (see Figure 3). There are always two or three FFU positions in use, depending on the ACR. The fifth variable is the extract air grille position. Air can be extracted at 5 extraction grilles, but there are always two different extraction grilles in use. When an ACR of 16h^{-1} is applied, both air extract grilles are for 50% covered in order to maintain appropriate overpressure in the cleanroom. The last variable is the position of the source. The counter of PC2 may switch between two positons (see Figure 3) depending on which extract grille is open. PC2 is always located in front of an open extract grille. The position of PC4 and S (the location of the source) depends on the case that is performed. An overview of the performed cases with their according variables is shown in Table 1. The codes that have been used for the cases are composed out of the characteristics of the different variables. The first letter stands for the type of diffuser that is used: where the S stands for Swirl and the N stands for None. The next letter indicates the swirl angle: O for Outside, V for Vertical, N for Not Applicable. The first number in the code indicates the ACR. Thereafter the Supply Air Position is coded: M (middle row 4-6), R (right row 6-9), L (left row 1-3) or C (combined left and right row) (See Figure 3). The last letter indicates the Extract Air Position: where R indicates the Right positions (C and E), L indicates the Left positions (A and B) and C indicates a Combination of left and right positions. The final number 1 or 2 indicates the position of PC4 and the source.

Table 1 Experimental cases with different design variables (diffuser, swirl angle, ACR, supply air position, extract air position and source position)

Case	Diffuser	Swirl angle	ACR	Supply Air Position	Extract Air Position	Position of PC4 and S
1.SO38MR1	Swirl VDW	Outside	38h^{-1}	4,5,6	C,E	PC4(1),S(1)
2.SO16MR1	Swirl VDW	Outside	16h^{-1}	4,6	C,E	PC4(1),S(1)
3.SV38MR1	Swirl VDW	Vertical	38h^{-1}	4,5,6	C,E	PC4(1),S(1)
4.SV16MR1	Swirl VDW	Vertical	16h^{-1}	4,6	C,E	PC4(1),S(1)
5.NN38LL1	None	N/A	38h^{-1}	1,2,3	A,B	PC4(1),S(1)
6.NN38LR1	None	N/A	38h^{-1}	1,2,3	C,E	PC4(1),S(1)
7.NN38RL1	None	N/A	38h^{-1}	7,8,9	A,B	PC4(1),S(1)
8.NN16RR1	None	N/A	16h^{-1}	7,9	C,E	PC4(1),S(1)
9.NN38MR1	None	N/A	38h^{-1}	4,5,6	C,E	PC4(1),S(1)
10.SO16MC1	Swirl VDW	Outside	16h^{-1}	4,6	A,E	PC4(1),S(1)
11.NN16CC1	None	N/A	16h^{-1}	3,7	A,E	PC4(1),S(1)
12.SO38MR2	Swirl VDW	Outside	38h^{-1}	4,5,6	C,E	PC4(2),S(2)
13.NN38RR2	None	N/A	38h^{-1}	7,8,9	C,E	PC4(2),S(2)

In order to investigate the influence of all variables, 13 cases were performed. Case 1 and 2 function as a reference case. Their setup is the most common setup in pharmaceutical cleanrooms. In case 3 and 4 the effects of changing the swirl angle to vertical is studied. Case 5 till 9 are cases without diffuser creating a pronounced air flow underneath the HEPA filter. In order to find the case that has the lowest particle concentration throughout the room, air supply and extract position are variables in these cases. For case 10 and 11 the effects, when extracting the air at both sides of the room, are studied. In case 12 and 13 the contamination source is moved to another position. In both these cases it is located closer to the extract position. Besides that, no workbench or LAF cabinet is located in-between the air extract grilles and the contamination source (which is the case in case 5 and 7).

Procedure

The first week several cases were performed with a very high emission rate of the aerosol generator. This resulted in very high unrealistic cleanroom particle concentrations. In week 2 and 3 the emission rate was lowered. These results are represented in this paper. With this 'lower' emission rate, every case is performed at least twice, except for cases 3 and 4. Every session lasted 60 minutes. During the entire session, the aerosol generator was continuously on. The LAF cabinet was off and had its protection screen shoved upward, so that it functioned just like a work bench. Nobody entered the cleanroom during the tests.

Every day, the ground and workbench surfaces were cleaned with appropriate cleanroom cleaning materials. The ground was cleaned with Ecolab klerwipes and the surfaces with Medipal Alcohol IPA Wipes. The cleanroom was entered wearing cleanroom boots and further normal clothes.

Data processing

The data of the last 40 minutes of a session was used for the analysis. In this time range the particle concentration is in steady state. This is shown in Figure 5, in which the red line indicates the theoretical process and the blue line is obtained from actual data from a particle counter of a test. The average particle concentration of each counter, and the according standard deviation of this time range, is calculated. When a case is performed multiple times, the average particle concentrations and standard deviation is calculated using all tests from the same case. When determining the contaminant removal efficiency (see Equation 1, in this paper referred to as *overall particle concentration* or *overall* $\boldsymbol{\varepsilon}$), PC2 is assumed representative as the exit particle concentration. C_s is assumed zero. The averages of PC1 and PC3-PC6 (of the 40min period) together function as average particle concentration of the room. In this paper this is being referred to as *overall average particle concentration* (see Equation 5). In order to tell if a significant overall better particle concentration is reached throughout the room, Mann Whitney [31] tests are performed with SPSS [32] version 20 for PC1, PC3-PC6. Besides that, the particle concentration and contaminant removal efficiency (*local* $\boldsymbol{\varepsilon}$) are also compared locally. The local $\boldsymbol{\varepsilon}$ is calculated by dividing the particle concentration at a certain point by the exit particle concentration at the extract grille (PC2) (see Equation 6). One of the benefits of calculating the local $\boldsymbol{\varepsilon}$, is that the results can more easily be compared, because only the airflow pattern is considered and not the source rate and applied ACR. This is in contrast to particle concentration, that is effected by source rate and applied ACR. Note that, in most cases, the airflow pattern will probably change when the ACR is changed.

Equation 5 Overall $\boldsymbol{\varepsilon}$

$$overall\ \varepsilon = \frac{PC2}{(PC1 + PC3 + PC4 + PC5 + PC6)/5}$$

Equation 6 Local $\boldsymbol{\varepsilon}$

$$local\ \varepsilon = \frac{PC2}{PCi}$$

Finally, an energy savings study is performed, in which all cases are compared to reference case 2. The results show how much ACR is needed in all other cases, in order to obtain the same particle concentration at the most critical point in the room (location PC where the local $\boldsymbol{\varepsilon}$ is the lowest), in comparison to the most critical point of case 2 (PC1). In case 12 and 13 the local $\boldsymbol{\varepsilon}$ at PC4 is not considered in the calculations, because PC4 is moved specifically for these two cases.

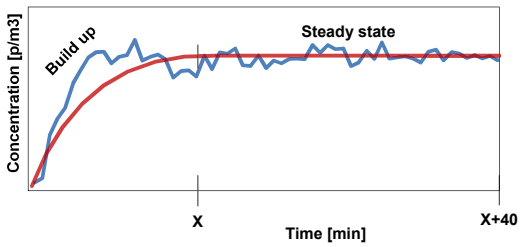

Figure 5 Schematic representation of concentration levels during a case (red line: theoretical, blue line: in practice based on a test of case 10)

3. RESULTS

This chapter shows the results of the three methods for the three ventilation efficient aspects. Due to the fact that the methods monitoring and simulations are used to examine the aspects finetuning as well as DCF, both will be described per method.

3.1. Monitoring

Figure 6 and Figure 8 show the measured particle concentration for case study facility H room C, and facility R during a period of three weeks. Facility R shows higher particle concentration levels. This higher particle concentration level is measured for a longer period of time than in facility H. The amount of time that facility R is in operation is considerably higher than facility H. The time that Room B and C of facility H were occupied during the three weeks of the study is estimated at 1.8% and 3.2% (respectively) of the total time the cases were performed. When Room B was occupied, the employee remained 55% of the time in the defined working area (see Figure 1). The cleanroom of facility R was occupied approximately 22.5% of the time.

The measured particle concentration is never constant for a long period of time; no continuous increase or decrease longer than 10 minutes is observed, due to the high ACRs. Also, rapid rises are visible without a gradual increase. In facility H, particle concentration is measured at different locations. The best correlation is noticeable between location PC1(3) and PC2 (with a correlation coefficient R=0.82). At the other PC1 locations the correlation is not that strong. PC1(2) has a weak correlation compared to PC2 (R=0.19). PC2 is located in the upper extract grille and PC1(2) in front of the lower extract grille. A continuously lower concentration is measured at PC1(2) than PC2. However, it is calculated that more contamination is extracted through the lower extract grille (PC1(2)), because of the higher extract volume rate in the lower extract grille (370 versus 160 m^3/h). It is no exception that a three times higher concentration is measured between one area in the cleanroom and another area. When measuring a particle concentration of less than 10,000 p/m^3 for ≥0.5µm at a certain location, it is possible that at the same time, at another measuring location, 0 p/m^3 is measured.

In general, both facilities operate far below the desired GMP limits for particle size ≥0.5µm. However, the degree of overdesigning in facility H, for room B is not that high as for room C. In both rooms, similar concentrations are measured. Room B has an even higher average particle concentration then room C, when the room was occupied; 13669 p/m^3 and 10976 p/m^3 respectively for particle size ≥0.5µm. Because room C has less strict requirements (factor 10), it has therefore a higher degree of overdesigning than room B.

Finetuning

Room C of facility H has GMP C demands, but approaches GMP B cleanliness almost all the time, except for 6 minutes in total during the 3 weeks of monitoring. Sometimes there are outliers noticeable that are substantially higher than the average concentration in a time period. These peak moments are often 1 minute samples. If we do not consider these outliers, facility R is operating most of the time (99.2%) on GMP B cleanliness when the cleanroom is in use.

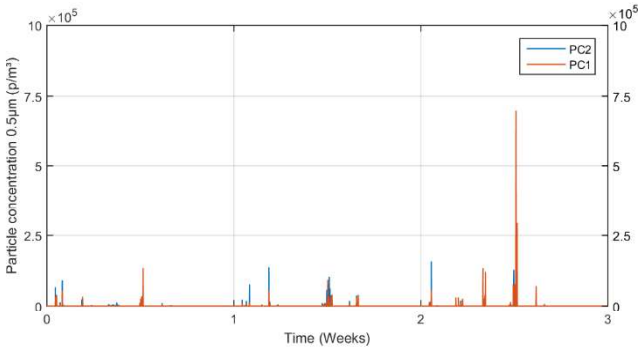

Figure 6 Measured particle concentration in room C for particle size ≥0.5µm for a period of 3 weeks, at facility H

DCF

There is a visible relation between occupancy in the cleanroom and particle concentration. When there are no employees present in the cleanroom, and therefore no source for contamination, a particle concentration of zero will be achieved. As soon as employees enter the rooms of facility H the particle concentration starts rising. The detection of particles in facility R is often later (~3min), due to the fact that this cleanroom has a larger volume than the rooms in facility H. A decrease in particle concentration can be noticed in all situations within 3 minutes after leaving the cleanroom unoccupied. A specific relation between the particle concentration and the occupancy is substantially harder to conclude. It is, for example, also possible to obtain high particle concentrations if only one person is present. In facility R, there is a rising overall average particle concentration for the first four persons in the cleanroom (see Figure 7). The rise in particle concentration is significant for the first three persons (estimated by Mann Whitney tests). There is however, no increase noticeable in the particle concentration operating range when the cleanroom is occupied by 3 till 6 persons.

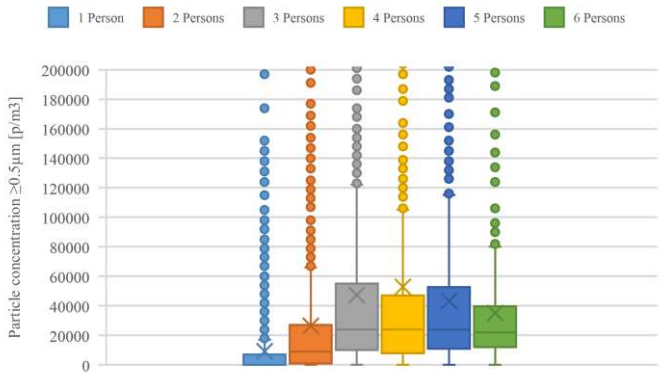

Figure 7 Boxplot of measured particle concentration range in relation to the number of employees in the cleanroom (facility R)

3.2 Simulations

Finetuning

The effects of a reduced ACR for particle concentration ≥0.5µm have been studied for the cleanroom of facility R and room C of facility H. Theoretically, the results show that the ACR can be lowered by a factor 10 in both facilities without having an increased amount of exceeding's of the GMP C ≥0.5µm concentration limit. These results are based on an ACR of approximately $2h^{-1}$ for both cleanrooms.

DCF

It turns out that DCF is applicable without having an effect on the environmental cleanliness, because the particle concentration in the room has already reached zero, when lowering the ACR after the room is unoccupied for 30 minutes. Besides this, in facility R, in most situations, an increase in particle concentration is noticeable after 3 minutes or more. Due to the fact that the desired ACR is reached after

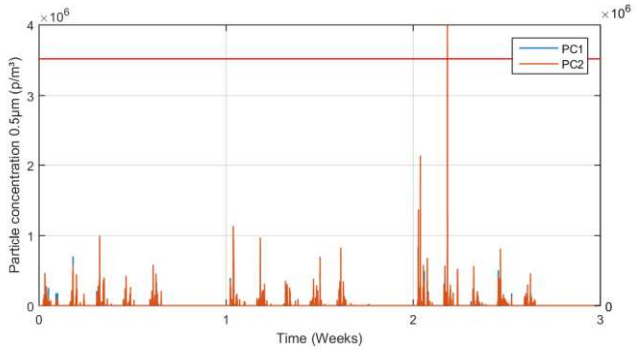

Figure 8 Measured particle concentration in facility R for particle size ≥0.5µm for a period of 3 weeks. Red line shows GMP limit

150 seconds (the time it takes to switch in ACR for the HVAC installation) after an employee enters the room, there is no difference in cleanliness in the simulations. In Room C of facility H an increase in particle concentration is noticeable faster, due to the smaller capacity of the room. This generates a neglectable higher particle concentration sometimes in the first couple of minutes. This is illustrated in Figure 9.

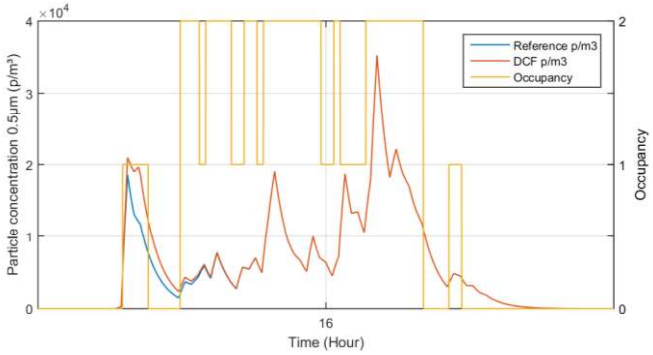

Figure 9 DCF vs. Reference for 15:15-16:45 22th September. Room C Facility H. Shown is particle concentration and occupancy.

Table 2 shows the possibilities for saving energy when applying DCF in the investigated cleanrooms. The shown energy savings are based on Equation 4. In the calculations, the same ventilator efficiency is assumed for a different ventilator speed that is controlled by a Variable Speed Driven (VSD) motor.

Table 2 DCF energy saving possibilities

Cleanroom	% of time occupied	ACR setback % of time	Overall fan speed energy savings
Facility H: Room B	1.8%	96.1%	93.6%
Facility H: Room C	3.2%	88.9%	86.8%
Facility R:	22.5%	70.0%	68.1%

3.3 Experiments

The average particle concentration and the standard deviation of the final 40 minutes of all counters in all cases is shown in Table 3. An estimate for the overall contaminant removal efficiency is also given. A 2D visualization of the airflows of all cases is given in Figure 12.

To put the particle concentrations of Table 3 in perspective, the particle concentration values are ranked by the corresponding ISO class [33] that would be achieved in Table 4. The local **ε** values from the particle concentration are shown in Table 5. The values of a single test are presented separately when a case is performed multiple times. Because these values are easy to compare, it is possible to observe the reliability of the experiments.

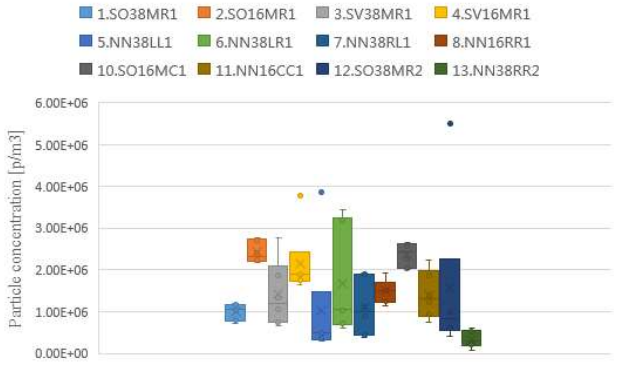

Figure 10 Box plot of the 6 PC measuring points for all cases showing the particle concentration distribution throughout the cleanroom

Reference case 1 and 2 show similar ratios in particle concentration between the different PC locations. Case 1 and 2 provide the most equal (homogeneous) particle concentrations throughout the cleanroom (see Figure 10). In case 1, the average lowest concentration location (PC6) is 1.7 times lower than the average highest concentration location (PC1). In case 2 the average lowest concentration location is 1.2 times lower that the average highest concentration location. The 2.4 times higher ACR in case 1, also generates a ~2.4 times lower particle concentration in case 1 than in case 2, on all PC locations (see Figure 13). This results in a significant (p=0.009) overall cleaner environment in case 1 than in case 2, which is logical because of the higher applied ACR. A relative high local **ε** is achieved at PC6 due to the coanda flow of the swirl diffuser. It seems that the swirl diffuser with an outside swirl angle generates a cleaner environment in the upper part of the cleanroom.

The airflow in case 3 and 4, that is directed more downwards, results in a lower particle concentration in PC1, PC2 and PC4 compared to the reference cases. However, a high particle concentration is noticeable at PC5 (LAF cabinet), because the contamination is now pushed into the LAF cabinet from the source position (see Figure 12 and Figure 13). The local **ε** at PC5 is also very low for case 3 and 4; 0.24 and 0.52 respectively. When PC5 is not considered for the calculation of the overall average concentration, case 4 provides a significantly (p=0.021) cleaner room than reference case 2. For case 3, in comparison to reference case 1, this is not significant (p=0.386).

In case 5 and 6, where the air is supplied above the source position without a diffuser, contamination is also blown towards PC5. This results in a high particle concentration at PC5, just as in cases 3 and 4 (see Figure 12 and Figure 14). Apart from PC5, a lower concentration is achieved on all other measuring locations. When PC5 is not considered, case 5 performs better on all aspects than case 6, in which the extract air grilles are located further from the source. When PC5 is not considered, case 5 results in a 51% significant (p=0.021) lower overall average particle concentration at the measuring points compared to case 1. However, when considering the local **ε**, case 1 generates the best results at PC1 in comparison to case 5.

In case 7 and 8 the air supply is located at the other side of the cleanroom (position 7,8,9) compared to case 5 and 6. In case 7, this seems to generate bigger differences in concentration levels in the cleanroom (less homogeneous) compared to the reference case 1. In case 8 a 27% lower particle concentration is measured at PC2, compared to case 2. Case 8 results in an overall significant (p=0.009) cleaner environment than case 2.

Case 10 (with swirl diffusers) and 11 (without swirl diffusers) were meant to investigate the effects of two air extraction points on opposite sides of the room. Case 10 performs slightly better than case 2 (see Figure 15), however no significant (p=0.465) lower overall concentration is reached. The approximation of the overall contaminant removal efficiency is in case 10 somewhat better than case 2 (0.96 versus 0.90 respectively). Case 11 has a significant (p=0.016) lower overall particle concentration in the cleanroom.

In case 12 and 13 the location of the source and the location of PC4 is changed compared to the other cases. Apart from the location of the source and PC4, case 12 is exactly the same as reference case 1. This way, the effects of relocating the source become apparent. In case 12 the source is located closer to the extract grilles, resulting in a positive effect on the particle concentration in the room. In case 12, all PCs, except PC3 (which, in this case, is closer to the source) have a lower particle concentration. PC4 is not considered because the location differs in both cases. In case 13 the supplied air from above collides on the workbench and is then, for a large part, directed towards the air extract grilles (see Figure 12). This principle was visualized in previous research [14]. Because the source is located in between the workbench and the air extract grilles, contamination is removed efficiently. This results in the highest overall contaminant removal efficiency (1.83) of all cases. Case 13 also results in an overall significant (p=0.016) lower particle concentration in the room

compared to case 12. Especially at PC4, there are big differences between case 12 and 13 (see Figure 16). In case 12 a very high concentration is measured at PC4, because PC4 is located close to the source. In case 13 there exists an airflow from the workbench to the air extract grilles, reducing the contamination flow from the source towards PC4 enormously. This results in a lower concentration at PC4 in case 13 in comparison to case 12 (in this specific setup this results in a 75 times cleaner area at PC4).

Figure 11 shows the percentage of ACR that is needed in order to obtain the same particle concentration at the most critical point in the room of the case, in comparison to the most critical point of case 2 (blue columns). Because many cases are influenced by a high measured particle concentration at PC5, the percentage ACR is also given when considering only PC1. PC1 is located on the corner of a workbench and therefore indicates the cleanliness of a possible product area. This percentage ACR compared to case 2 is shown in the red columns. Case 13 requires the lowest ACR to obtain the minimum environmental cleanliness in the room, if all PCs are taken into account and saves 11% ACR compared to case 2. Many cases (3,4,5,6) require a larger ACR than reference case 2, because of the contamination that is pushed into the LAF cabinet, which results in a local disadvantage at PC5. As shown in the figure, this disadvantage has disappeared, when only PC1 is taken into account (red columns).

4. DISCUSSION

In this research three different methods were used to investigate how to improve the ventilation efficiency in pharmaceutical cleanrooms. This chapter discusses the applied methods.

Monitoring

The rapid rises in particle concentration in all investigated cleanrooms, are making control based on particle concentration less straightforward due to the unpredictability. For the lower measured particle concentration (< 5000 p/m3 for particle size 0.5 µm) the results may be inaccurate due to the low flow rate of the Remote 2014 (1 l/min). In room B and C from facility H, there were similar concentrations measured while they have a different GMP classification. It is not strange that in both rooms similar concentrations are measured. Besides the fact that both rooms are regularly occupied by 2 persons, room B (that is twice as small as room C) has an ACR of $42h^{-1}$ compared to $21h^{-1}$ in room C. This results in approximately the same amount of ventilated air per hour (1276 m3/h and 1351 m3/h respectively). Therefore, with approximately the same source and supplied air volume, the same concentration was reached in both rooms. This shows that designing based on the prescribed ACR does not immediately classify the room's cleanliness, also stated by Birks [12].

The investigated GMP C rooms operate on a 10 times cleaner particle concentration level than required. This degree of overdesigning was also found in previous research in the at-rest state [14]. Based on these measurements, the ACR in both investigated GMP C classified rooms can be lowered without having a negative effect on the indoor climate. However, before drawing definitive conclusions, the particle size of ≥5.0µm and microbial contamination should be considered as well. Although the research was focused on particle size ≥0.5µm, the equipment does provide an indication that the concentration of particle size ≥5.0µm sometimes almost reaches the limits of the GMP C demands. Due to the low flow rate (1 l/min) of the particle counters, no accurate estimation can be given.

Table 4 Average particle concentration of all cases converted to the related ISO classification [33]

Case	PC1	PC2	PC3	PC4	PC5	PC6
	ISO	ISO	ISO	ISO	ISO	ISO
1.SO38MR1	7.5	7.5	7.4	7.5	7.5	7.3
2.SO16MR1	7.9	7.8	7.8	7.8	7.9	7.8
3.SV38MR1	7.3	7.3	7.6	7.5	7.9	7.7
4.SV16MR1	7.7	7.7	7.7	7.7	8.0	7.7
5.NN38LL1	7.3	7.1	7.0	7.2	8.0	6.9
6.NN38LR1	7.5	7.2	7.3	7.5	8.0	8.0
7.NN38RL1	7.7	7.4	7.0	7.5	7.7	7.1
8.NN16RR1	7.6	7.7	7.5	7.6	7.7	7.6
10.SO16MC1	7.9	7.8	7.8	7.9	7.9	7.8
11.NN16CC1	7.7	7.6	7.4	7.8	7.5	7.3
12.SO38MR2	7.1	7.2	7.5	8.2	7.5	7.3
13.NN38RR2	7.2	7.2	6.8	6.3	7.0	6.9

Table 5 Local ε of all PC and overall ε of all performed tests, most cases were performed twice as shown.

Case	PC1	PC3	PC4	PC5	PC6	Overall ε
1.SO38MR1	0.92 / 0.78	1.13 / 1.44	0.96 / 0.94	0.79 / 0.98	1.30 / 1.62	0.99 / 1.07
2.SO16MR1	0.80 / 0.81	0.94 / 1.10	0.92 / 0.93	0.88 / 0.75	0.92 / 1.05	0.86 / 0.94
3.SV38MR1	0.86	0.49	0.61	0.24	0.35	0.42
4.SV16MR1	1.04	1.12	1.03	0.52	1.19	0.90
5.NN38LL1	0.70 / 0.76	1.18 / 1.61	1.06 / 0.89	0.13 / 0.13	1.56 / 1.88	0.43 / 0.44
6.NN38LR1	0.63 / 0.52	0.85 / 0.90	0.49 / 0.81	0.19 / 0.18	0.19 / 0.20	0.33 / 0.33
7.NN38RL1	0.43 / 0.50	1.67 / 3.80	1.74 / 0.51	0.48 / 0.44	1.66 / 2.54	0.81 / 0.73
8.NN16RR1	1.05 / 1.10	1.45 / 1.37	1.07 / 1.05	0.77 / 0.91	1.18 / 1.39	1.06 / 1.13
10.SO16MC1	0.83 / 0.93	1.19 / 1.07	0.91 / 0.84	0.82 / 0.91	1.02 / 1.24	0.94 / 0.98
11.NN16CC1	0.88 / 0.61	1.40 / 1.58	0.57 / 0.69	1.08 / 1.25	2.15 / 1.54	1.00 / 0.97
12.SO38MR2	1.76 / 1.29	0.63 / 0.43	0.11 / 0.11	0.71 / 0.51	1.06 / 0.77	0.36 / 0.32
13.NN38RR2	0.77 / 1.03	2.26 / 2.68	7.01 / 7.58	1.44 / 1.87	1.93 / 2.31	1.62 / 2.05

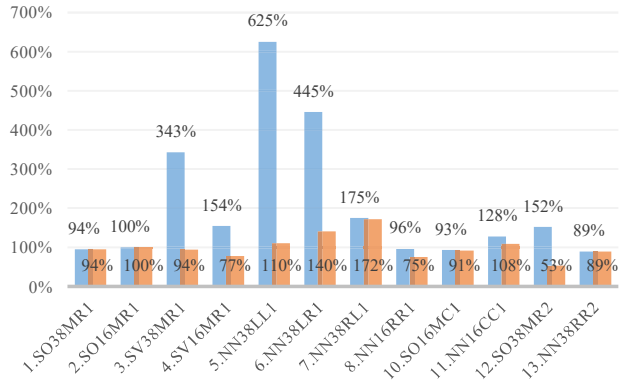

Figure 11 The blue columns (percentage above columns) indicate the percentage of needed ACR in order to obtain the same particle concentration at the most critical point in comparison to the most critical point of case 2. The red columns (percentage on columns) indicate the percentage of needed ACR in comparison to case 2, when only considering PC1.

Table 3 Average measured particle concentration (≥0.5µm) with standard deviation and an estimation of the average overall contaminant removal efficiency

CASE	PC1		PC2		PC3		PC4		PC5		PC6		Overall ε
	p/m³	SD	p/m³	SD	p/m³	SD	p/m³	SD	p/m³	SD	p/m³	SD	
1.SO38MR1	1.20E+06	1.40E+05	1.02E+06	7.42E+04	8.07E+05	1.20E+05	1.07E+06	7.58E+04	1.17E+06	2.74E+05	7.08E+05	3.71E+04	1.03
2.SO16MR1	2.75E+06	1.62E+05	2.22E+06	1.31E+05	2.17E+06	8.35E+04	2.39E+06	1.51E+05	2.71E+06	2.66E+05	2.25E+06	1.85E+05	0.90
3.SV38MR1	7.61E+05	6.24E+04	6.52E+05	5.21E+04	1.33E+06	1.79E+05	1.06E+06	1.49E+05	2.78E+06	4.48E+05	1.87E+06	7.67E+04	0.42
4.SV16MR1	1.89E+06	1.21E+05	1.97E+06	8.87E+04	1.76E+06	1.13E+05	1.92E+06	1.01E+05	3.77E+06	1.02E+06	1.65E+06	8.63E+04	0.90
5.NN38LL1	6.76E+05	1.29E+05	4.95E+05	1.39E+05	3.57E+05	9.61E+04	5.19E+05	2.69E+05	3.85E+06	1.32E+06	2.87E+05	1.40E+04	0.44
6.NN38LR1	1.09E+06	2.59E+05	6.20E+05	4.68E+04	7.12E+05	5.75E+04	1.02E+06	2.32E+05	3.43E+06	1.01E+06	3.20E+06	1.22E+05	0.33
7.NN38RL1	1.90E+06	2.92E+05	8.84E+05	5.35E+04	3.84E+05	5.09E+04	1.11E+06	3.22E+05	1.92E+06	5.19E+05	4.43E+05	7.15E+04	0.77
8.NN16RR1	1.50E+06	9.14E+04	1.61E+06	1.40E+05	1.14E+06	1.55E+05	1.52E+06	9.89E+04	1.94E+06	6.52E+05	1.26E+06	8.61E+04	1.09
10.SO16MC1	2.60E+06	2.30E+05	2.27E+06	1.11E+05	2.00E+06	1.13E+05	2.58E+06	2.00E+05	2.65E+06	2.83E+05	2.05E+06	8.19E+04	0.96
11.NN16CC1	1.88E+06	2.27E+05	1.39E+06	1.04E+05	9.42E+05	6.84E+04	2.24E+06	4.62E+05	1.21E+06	2.71E+05	7.55E+05	4.13E+04	0.99
12.SO38MR2	4.02E+05	5.92E+04	5.94E+05	1.25E+05	1.17E+06	2.05E+05	5.51E+06	4.21E+06	1.00E+06	1.58E+05	6.70E+05	6.40E+04	0.34
13.NN38RR2	5.95E+05	1.75E+05	5.33E+05	9.38E+04	2.15E+05	3.78E+04	7.29E+04	1.92E+04	3.22E+05	5.74E+04	2.51E+05	1.88E+04	1.83

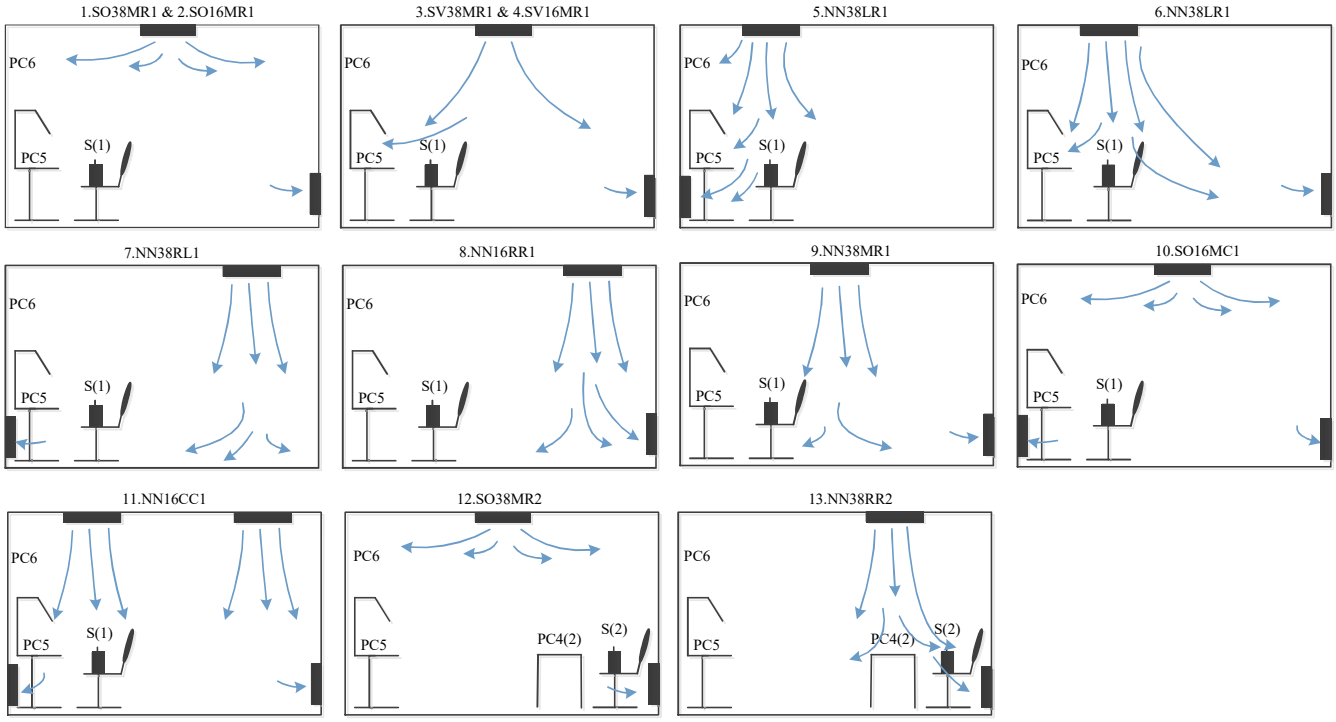

Figure 12 2D Airflow pattern visualization of all cases

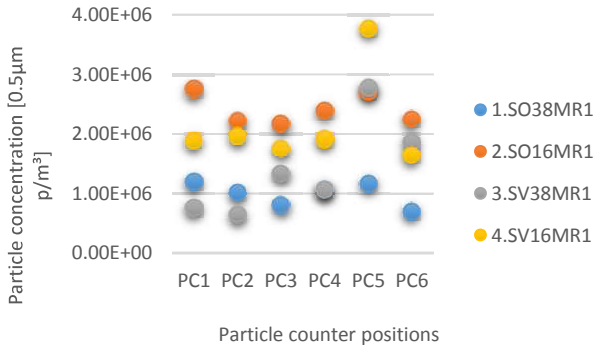

Figure 13 Comparison between case 1-4 in average particle concentration

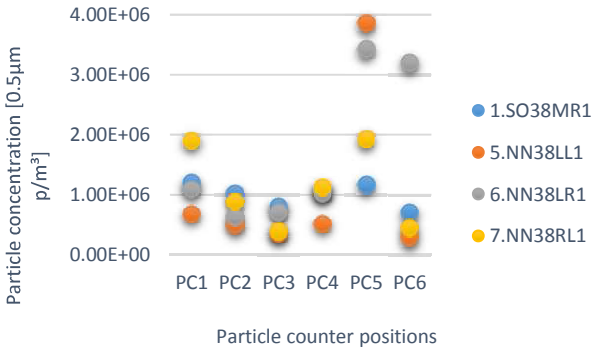

Figure 14 Comparison between case 1,5,6 & 7 in average particle concentration

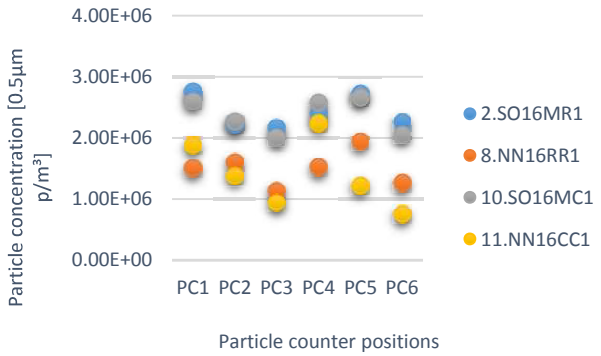

Figure 15 Comparison between case 2,8,10 & 11 in average particle concentration

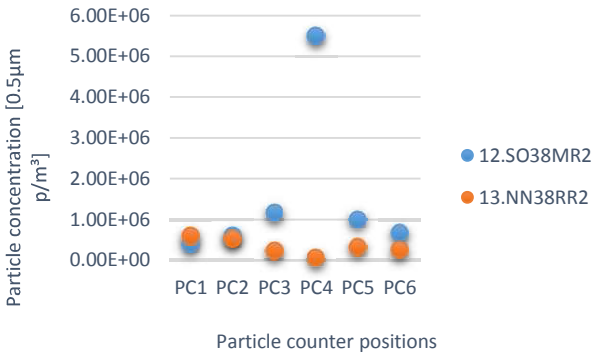

Figure 16 Comparison between case 12 and 13 in average particle concentration

It should be noted that, outside the monitor period of facility H, there was one day at which some exceedings in particle concentration occurred a couple of times. (This was shown in data from the monitoring system of the facility itself.) It remains unexplainable what happened that day since it was outside the research period.

As mentioned before, the rapid changes in particle concentration makes applying DCF control based on particle concentration less applicable. Based on these findings, control based on occupancy seems to be more suitable. This way there is no distinction made between the number of people present in the cleanroom. There is only a distinction made between occupied and unoccupied, resulting in a simple ON/OFF control in the cleanroom, which is considerably lower in price [17].

Simulations

Finetuning in the simulations show that the ACR in the GMP C classified rooms can be lowered by a factor 10 to an ACR of ~2h^{-1}. It is however, not recommended to apply these ACRs in the existing situation, because this would cause problems for the airflow pattern, for the heat loads that need to be cooled and for the overpressure that should be maintained. A minimum ACR of 6h^{-1} is needed to maintain these factors [2]. Lowering the ACR continuously from 20h^{-1} to 6h^{-1} results in fan speed savings of 97.3%.

The calculated DCF energy savings for facility H are high compared to other studies [13], [17]–[19]. The main reason for this is that the two rooms of facility H are barely in use, as presented in Table 2. This is in contrast with facility R, that has a more regular occupation pattern. The energy savings for facility R, are more representative and therefore more in line with DCF particle counting studies from Faulkner (60%) [13] and Tschudi (72%) [18].

Although results for DCF were solely based on particle size ≥0.5µm, this will not cause any problems for particle concentration size ≥5.0µm and microbial contamination. That is because, if a particle concentration of zero is measured for particle size ≥0.5µm, the particle concentration for particle size ≥5.0µm and microbial contamination is also zero.

Experiments

As expected, the EU swirl diffuser setup provided the most homogeneous particle concentration throughout the room, this was also found by Lenegan [8] that used ACE as a performance indicator. The fact that the 2.4 higher ACR in case 1 in comparison to case 2 also led to a 2.4 lower particle concentration when the airflow pattern is consistent, corresponds with the theory [15]. The calculated values for the overall $\boldsymbol{\varepsilon}$ are in a lower range than the CFD study of Villafruela [22]. One of the reasons that certainly contributes hereto, are the high local $\boldsymbol{\varepsilon}$ values at PC5 for some cases, that influence the overall $\boldsymbol{\varepsilon}$ calculations. The assumption that turbulent ventilated cleanrooms have an $\boldsymbol{\varepsilon}$ of 0.7 according to some design guidelines [34], seems to imprecise, based on the found results.

In case 3,4,5 and 6 contamination is blown towards PC5 inside the LAF cabinet. This may not be an issue when the LAF cabinet is turned on, creating a barrier between the inside and outside of the LAF cabinet. However, this might be troublesome when the LAF cabinet is considered to be a normal workbench. Since the contamination removal efficiency is only based on the average of five PCs (including PC5), the approximation for the overall contamination removal efficiency is not representative for case 3,4,5 and 6.

In case 8, the particle concentration at PC2 is 27% lower than in case 2. Because the particle concentration in the cleanroom is not increasing or decreasing the last 40 minutes of the experiments, the current source rate [p/s] should also leave the cleanroom at the same rate (measured at PC2). Due to the fact that the source rate is almost equal in all cases, approximately the same concentration must be measured at PC2. When the particle concentration at PC2 deviates, this indicates a different ACR. The 27% lower particle concentration at PC2 in case 8, indicates a 27% higher ACR. The reason for this higher ACR is that the swirl diffusers provide a resistance in the reference case. By removing this resistance, amongst others, a lower particle concentration is measured on all PC positions. In all other cases without swirl diffusers there is also a lower particle concentration noticeable in PC2 compared to the reference case. The exact amount of ACR reduction delivered by the swirl diffusers can't be estimated since there are always two extract grilles, and particle concentration is only measured at one of them.

The different cases are compared by (local) particle concentration and (local) contaminant removal efficiency. When comparing particle concentration, only cases with the same applied ACR can be compared. When determining $\boldsymbol{\varepsilon}$, the ACR becomes irrelevant and all cases can be compared with each other. A main difference is that cases with a swirl diffuser experience a drop in ACR, due to the resistance of the grille. This is a disadvantage in the particle concentration comparisons. However, when comparing using $\boldsymbol{\varepsilon}$, this disadvantage is removed. It should however, be taken into account that a case with a swirl diffuser has a larger pressure loss that has to be overcome by the HVAC Fan.

Case 7 is the only case in which the results show great deviations between the performed tests. This is shown in Table 5. Therefore, the results are considered as not representative. One of the possible reasons could be that PC2 was located at a wrong location during one of the tests.

The percentage of needed ACR in comparison to case 2 is presented in Figure 11 (in the blue columns). This percentage is in some cases higher than the reference case 2 due to the local $\boldsymbol{\varepsilon}$ at PC5 (case 3,4,5 and 6). Due to the fact that, in order to determine the needed ACR, only the most critical location is taken into account, it does not matter that it is cleaner at other locations in the room. The two references cases, 1 and 2, provide equal particle concentrations throughout the room. This is a benefit, because these cases do not have a measuring point with a much higher concentration. When improving the airflow pattern throughout the room, it is important to improve all areas in the cleanroom, including the most critical areas. This is because, according to the ISO norms [33], all measuring points need to meet the required particle concentration. In the red columns, an ACR comparison to case 2 is made based on PC1 only. In this case, case 3,4,5 and 6 do not have the disadvantage of the high particle concentration at PC5. Especially case 5, 6 and 7 perform better. For product quality, it is important that the product area has a low particle concentration, because it is exposed to the environment for the longest period of time. PC2 provides an indication for the possible product area.

In some cases, additional tests were performed with the LAF cabinet on. Because the LAF cabinet has a HEPA filter in it, it also removes particles from the room. Although it was not the initial purpose of the experiments, the effect this has on the particle concentration in room was also studied. In all cases the overall particle concentration throughout the room was considered significantly lower with the LAF cabinet on. Therefore, having a LAF cabinet turned on in the cleanroom, generates a cleaner environment. This is often not considered in the design phase.

It should be noted that limiting the source's particle emission plays a more important role for environmental cleanliness than the ACR. This is well shown in Table 4. This table shows that, when an ACR is applied that corresponds with a higher ISO classification (for example case 1 versus case 2), this does not immediately mean that a higher ISO class is achieved when the amount of particle emission from the source is the same. This is due to the fact that, in order to achieve a stricter ISO class, the particle concentration has to be a factor 10 times lower. Adding 2 times as much air (which is recommended to get from GMP C to GMP B) leads to a 2 times lower particle concentration when the sources particle emission is the same. Therefore, it is of utmost importance to limit the emission of particles from the source, in order to achieve a lower particle concentration in the room.

5. CONCLUSION

Based on the findings, the GMP C classified cleanrooms are overdesigned to a large extent and operating on GMP B 'at operation' level. This results in a 10 times cleaner environment than required for particle size ≥0.5µm. Theoretically, the ACR of the GMP C cleanrooms can be lowered by a factor 10 based on the findings for particle size ≥0.5µm. This is however not recommended to implement in practise, because this would cause problems for the airflow pattern, heat loads and overpressure. The degree of overdesigning for room B (with GMP B demands) is substantially lower than room C (with GMP C demands), because the ratio between particle generation and the volume of air supply is almost equal in both rooms. The degree of overdesigning for particle size ≥5.0µm seems to be less in facility R. Before drawing conclusions on how much the ACR of facility R can be lowered exactly, the degree of overdesigning together with the limits for microbial contamination should be investigated precisely.

For now, it is recommended to follow the ISPE design guidelines for ACR, because predicting the amount of particle generation from the source in advance, seems to be complicated. This depends to a large extent on the working methods in the cleanroom, the cleaning procedure and the equipment (LAF cabinets). To investigate the exact amount of source generation for certain activities, a lot of data should be obtained or a lot of experiments should be performed. This was however, not the purpose of this research.

That is why it is now advised that, particle concentration for size 0.5 and 5.0 and microbial contamination should be monitored for one month of normal use of the cleanroom. Based on these findings, recommendations can be done on the degree to which the ACR can be lowered exactly. Another solution may be to design with a lower prescribed ACR and, when it turns out that the cleanroom does not meet the standards, solve the shortage by placing a local filter unit in the room. This is possible when the supplied air does not have to be 100% make-up air. Based on the performed experiments, it is possible to assume that, for swirl ventilated cleanrooms, the particle concentration somewhere in the room does not exceed twice the monitored particle concentration and is near mixing.

DCF should be implemented in cleanroom design at all times. It is recommended to maintain a ISPE guideline ACR when the cleanroom is occupied and a lowered ACR when the cleanroom is left unoccupied for a period of 30 minutes or longer. This way of DCF control does not affect the environmental cleanliness. Another beneficial aspect is that DCF based on occupancy is more cost effective than other DCF strategies like control based on particle concentration. The results for facility R, that has a representative occupation pattern, show that 68.1% energy fan speed savings can be obtained when DCF based on occupancy is incorporated.

The airflow pattern throughout the cleanroom has a significant effect on the cleanliness level of the cleanroom. Caution must be taken not to blow contamination from the employee's working area towards the product area. In the standard EU design strategy, in which swirl diffusers are used, this is not a problem due to the coanda flow that exists. When comparing cases with swirl diffusers to cases where no diffusers are applied, a noticeable ACR reduction is present through pressure loss of the diffusers. This has a negative effect on the environmental cleanliness. When rooms need to stay flexible and the working area and product area are changing on a regular basis, it is still advised to apply swirl diffusers in the room because these diffusers approach a homogenous cleanroom the most. However, when the lay-out of the cleanroom is known during the design process, air should be supplied above the product area without a diffuser, creating a very clean local area at the product area. If possible, the employee's working area should be located close to an extract grille, so that the airflow from the product area towards the extract grille takes most contamination that is on its path. This results in a high contaminant removal efficiency, and therefore in a lower particle concentration throughout the room. This gives the possibility to lower the ACR by 11%.

To summarize, the results show that finetuning, DCF based on occupancy and an improved airflow pattern in the cleanroom can contribute to a more efficient operating cleanroom.

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