Smart Cleanroom: the innovative solution to reduce HVAC energy consumption in classified areas

A new HVAC control system intensifies efficiency in aseptic pharmaceutical cleanrooms

By Ana Fernández, CRS Pharmaceutical Technology Manager, and Xavier Barrera, CRS Electricity & Control Manager, respectively, at Telstar

WHITE PAPER

ABSTRACT

Pharmaceutical companies face the challenge of reducing production costs without negatively affecting the quality of the finished products. HVAC systems are one of the main energy consumers in pharma facilities especially in sterile manufacturing. Therefore energy savings are particularly noticeable in this area.

The Smart Cleanroom is an innovative flexible solution for cleanrooms that adjusts the supply airflow by means of inline particle counters connected to the HVAC control system, reducing energy consumption and operation costs, providing an excellent payback for pharmaceutical companies.

What is a Cleanroom?

The manufacture of pharmaceuticals and in particular sterile products requires installations, solutions and procedures that fulfil high quality, safety and production controls. It must be carried out in clean areas that should be maintained to an appropriate cleanliness standard. Each manufacturing operation requires an appropriate environmental cleanliness level in order to minimise the risks of particulate or microbial contamination of the product or materials being handled. EU GMP establishes 4 grades and refers to the EN ISO 14644-1 standard. Airborne particles shall be controlled in classified cleanrooms.

According to the specifications stated in the Annex 1 of the EU GMP and ISO 14644-1 standard, the maximum permitted airborne particle concentration in the process room for each grade are:

EU GMP Classification Annex 1	Classification Number ISO 14644-1	Maximum permitted number of particles per m³ equal to or greater than the tabulated size			
		At rest (1)		In operation (2)	
Grade		0.5 µm	5.0µm	0.5 µm	5.0µm
A	ISO 4.8	3 520	20	3 520	20
B	ISO 5	3 520	29	352 000	2 900
C	ISO 7	352 000	2 900	3 520 000	29 000
D	ISO 8	3 520 000	29 000	Not defined	Not defined

Table 1: Maximum permitted number of particles
(1) The "at rest" state is the condition where the manufacturing area is installed and operating, including production equipment but with no operating personnel present.
(2) The "in operation" state is the condition where the installation is functioning in the defined operating mode with the specified number of operators working.

While the FDA in its Guidance for Industry Sterile Drug Products Produced by Aseptic Processing establishes:

Clean Area Classification (0.5 um particles/ft³)	ISO Designation	≥ 0.5 µm particles/m³	Microbiological Active Air Action Levels (cfu/m³)	Microbiological Settling Plates Action Levels (diam. 90mm; cfu/4 hours)
100	5	3 520	1	1
1000	6	35 200	7	3
10 000	7	352 000	10	5
100 000	8	3 520 000	100	50

Table 2: Air Classifications

In addition, cross-contamination should be prevented for all products by appropriate design and operation of manufacturing facilities, creating air patterns with room differential pressures.

Even if the trend of the industry is the use of barrier technology (RABS and isolators) for aseptic processing in the new or renovated facilities, conventional cleanroom technology is used in background environments in all pharma facilities.

Critical Parameters in Cleanrooms

Environmental control is achieved by means of several mechanisms that usually include design, construction and operation aspects.

Dilution of internally generated contaminants by air filtration

Particles generated inside the process room where sterile materials and products are exposed may come from operators, raw materials and product or containers and closures as well as equipment. The use of high airflow rates to dilute airborne particles is the common practice.
In conventional installations in the pharmaceutical industry, HVAC is designed setting a number of minimum air changes per hour (hereinafter referred to as ACH) calculated in order to ensure the room classification and taking into account the required fresh air, heat loads and local exhausts.

These values are based on experience and recommendations. Guidance is provided by several institutions such as the FDA or the ISPE.

ACH are usually equal to and above 20 per hour for classified areas. There is no minimum air change rates specifically defined for non-sterile product facilities and non-classified area, except values defined in local Building Codes for ventilation purposes. For sterile facilities, the 2004 FDA "Guidance for Industry for Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice" gives the following guidance: "For Class 100,000 (ISO 8) supporting rooms, airflow sufficient to achieve at least 20 air changes per hour is typically

acceptable. Significantly higher air change rates are normally needed for Class 10,000 and Class 100 areas."

The ISPE's Good Practice Guide for HVAC gives some "rules of the thumb" for design at early stages:

- 6 to 20 ACH for CNC to ISO 8 (EU Grade D) spaces
- 20 to 40 ACH for ISO 7 (EU Grade C) spaces
- 40 to 60 ACH for ISO 5 (EU Grade B) spaces

It also suggests a later ACH reduction to optimize HVAC investment and operation costs. However, the particulate level is the critical parameter to maintain within the limits defined by regulations (and the only one with set limits) and not the ACH.

The recovery time from in-use to at-rest conditions is the time the process room needs to recover if it gets contaminated. The dilution efficiency and ACH are directly related to recovery time of the classified room: the higher the ACH, the quicker the recovery. The European GMP regulation establishes a "clean up" time of 15 to 20 minutes in a sterile product processing facility. Therefore, the requirement has to be taken into account for airflow design.

Airflow patterns and airflow direction control

According to EU GMP, "adjacent rooms of different grades should have a pressure differential of 10 - 15 pascals (guidance values)". The control of the room pressure is normally achieved through the installation of pressure controlled actuated dampers or automatic variable airflow boxes in the return ducting of the HVAC system. These devices shall be sized and selected to modulate within a certain airflow range and with a specific accuracy and speed of reaction.

Airflow direction in some cases is very important. That is why GMP Annex 1 establishes that critical operations in aseptic processing shall be carried out in A-grade under laminar flow. In unidirectional air flow spaces, the critical parameter is the air velocity. As for the ACH in turbulent ventilated cleanrooms, guidance values are provided. The FDA recommends a velocity of 0.45 m/s ±20% while the EU GMP provides a range of 0.36-0.54 m/s.

Temperature and relative humidity control

Controlling temperature and relative humidity within a certain range is necessary not only to protect product but also to provide adequate conditions to operators present in the process room. Contamination from operators can be reduced with appropriate gowning but cooler temperature and lower relative humidity may be needed for their comfort. Temperature and relative humidity should not interfere with the defined cleanliness standard.

When the cleanroom environment is under control, the air supplied to the cleanroom is enough to dilute or remove the contaminants created inside with the adequate temperature and relative humidity control. The air is clean to ensure that it does not add contamination and follows a correct pattern from clean to less clean areas. The control system shall maintain the continuity of the required levels of critical parameters, shall be robust and in case of failure save the production without operator's safety risk.

Operational Process Environmental Continuous Monitoring

For classification purposes the EN/ISO 14644-1 methodology defines both the minimum number of sample locations and the sample size. Once the process room is classified, a routine monitoring and maintenance plan must be established to ensure the installation remains within the validated limits. Particle counting testing is the most important parameter to analyse to demonstrate that the cleanroom remains EN/ISO 14644-1 compliant.

The recent changes in GMP Annex 1 revision for the manufacture of sterile medicinal products distinguish clearly cleanroom classification and operational process environmental monitoring. For grade A zones, there should be an inline particle monitoring during all critical operations and a similar system is recommended for grade B zone. Therefore due to the concern of the product quality, the importance of the installation of a particle monitoring system in Grade B zones has increased in the last years in the pharmaceutical industry, to achieve the highest requirements of cleanliness during the entire duration of critical processing.

The location of the clean air monitoring devices should be the result of a formal risk analysis study. Monitoring should be at such a frequency and with suitable sample size that changes in levels of contamination and any system deterioration would be captured and alarms triggered if alert

limits are exceeded. Tubbing lengths and radio of bends must be taken into consideration during installation since they can become a source of particle accumulation.

It is recommended to consider previous monitoring data and data obtained for classification and re-qualification for continuous improvement and system reliability. An automated inline system allows a fast detection and recording of potential problems in operating conditions, reducing time product is out of specifications and inline monitoring records in SCADA historian database can be used to justify re-qualification frequencies (analysing long term trends in operating conditions) and provide all benefits of the automatic data capture.

Operating Cost Reduction without Compromising Product Quality

The demand for energy saving solutions whilst preserving high quality standards is continuously increasing while quality requirements become stricter. Market demands, cost reduction and pharmaceutical companies need to find ways to reduce production costs. Energy efficient technologies reduce production costs but may also offer process efficiency opportunities and quality improvement.

HVAC systems are fundamental to the pharma industry as high air change rates are used to ensure a low viable and non-viable particle contamination. As a consequence, the HVAC system is one of the main energy consumers in pharma facilities especially in sterile manufacturing. Therefore energy savings are particularly noticeable in this area.

To reduce HVAC consumption, many solutions have been implemented in the industry:

- Optimization of classified room surface (without compromising the process operations, e.g. spacious change rooms for appropriate gowning of the personnel, staging spaces for equipment, tools, waste... will be always needed).
- Establishing operation modes (e.g. Production mode / Non-production mode, adjusting temperature and relative humidity ranges).
- Free-cooling, heat recovery use or air recirculation, if cross contamination issues are not compromised.
- Use of low pressure drop HEPA filters.
- Use of energy-efficient engines. Electronically-commutated (referred to as EC) fans in AHU units control the direction and speed of the motor with a significant consumption reduction and heat losses.
- Extending the acceptance interval for temperature and /or relative humidity avoiding unnecessary too-narrow tolerances.
- Avoiding over-specifying grades, air flow rates or recovery times.
- Use of barrier technology. Since human contamination is one of the main sources of contamination in controlled environments, the industry tends to replace manual activities with automated processes or to physically isolate them from operators.
- Optimization of laminar flow air velocities.

Smart Cleanroom

Smart Cleanroom (hereafter SmartCR) is a flexible solution for cleanroom control based on the idea of reducing the power consumption of the HVAC system, decreasing the air changes in turbulently ventilated cleanrooms, working always inside the ranges that ensure the classification air quality, and following the regulations stated in EU GMP Annex 1 and ISO Standard 14644-1.

SmartCR uses the data collected by the airborne particle counters installed for the inline environment monitoring system to act on the only parameter in the cleanroom design that remained fixed and constant: airflow rate.

In the normal HVAC systems the ACH are calculated in the design phase and then fixed. Normally the particles counters are not installed permanently, for this reason the renovations ensuring the room classification are oversized and not controlled. SmartCR is a specific HVAC control system that adjusts the airflow rate to provide the optimized airflow required to ensure room temperature, relative humidity, room differential pressure / airflow direction and number of particles under control, meaning important savings in HVAC consumption.

SmartCR software has been specifically developed for the high quality demanding pharmaceutical industry. It has been conceived with a conservative functioning to ensure the stability of the critical parameters of the controlled environment at all times.

The benefits of the ACH optimization are:

- Reduction of capital costs: Lower airflows result in smaller fans, which reduce both the initial investment and construction cost. A 20 percent decrease in ACH will enable close to a 50 percent reduction in fan size. Nevertheless, ACH optimization requires a complex and more efficient control system with the integration of air particle counters monitoring system.

- Reduction of energy consumption:The energy saving opportunities are comparable to the potential fan size reductions. According to the fan affinity laws, the fan power is proportional to the cube of air changes rates or airflow. A reduction in the air change rate by 30% results in a power reduction of approximately 66%.

How does Smart Cleanroom work?

The SmartCR is an engineering solution for cleanroom environmental control composed of an automatic HVAC system with the following elements:

- AHU provided with EC fan (for energy saving and to have better control of the fan speed).
- Fan flow control.
- Room temperature and humidity control (temperature and relative humidity transmitters controlling the cooling and the heating regulation valves in the AHU coils).
- Airbone Particles Counters (hereafter APC) for continuous airborne particle counting and monitoring.
- Motorized dampers (Variable Air Volume type) in supply air net to maintain the airflow constant in the rooms.
- Motorized dampers in return air net for room differential pressure control.
- Pressure transmitters for room differential pressure control.

The environmental cleanliness grade can be configured in the system:

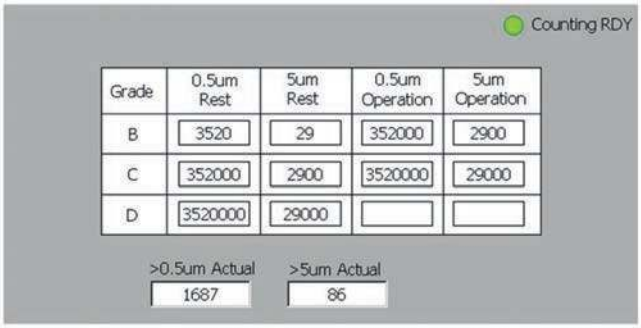

Figure 1. Configuration screen in the HMI: maximum particles allowed in the room. If regulatory limits change, the system can be configured with different values.

The SmartCR solution provides 2 operating modes:

- Conventional Mode: constant supply airflow by setting the ACH according to the design.

- ECO Mode: variable supply flow adjusted by APC captures.

Conventional mode sets the ACH in a pre-defined design value. The room air changes are controlled by a PID loop with a fixed airflow set point. When the system starts, the HVAC system provides ACH design value until reaching a permanent regime.

If the ECO Mode option is selected ("ECO ON" button) the APC will start running automatically when system starts.
Once the system is stabilized in conventional mode working within the limits of temperature,

Figure 2. ECO Mode selection button.

relative humidity and differential pressures, the ECO mode starts reducing the AHU fan speed gradually in controlled steps until finding the upper limit of number of particles admitted in the standards and regulations.

Regulation is made with the>0.5µm particle

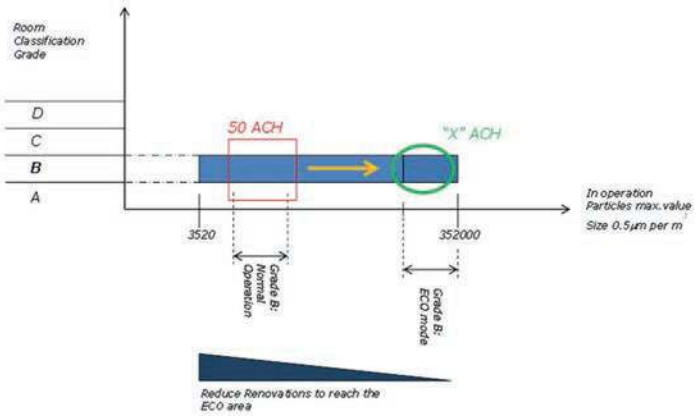

Figure 3. Air changes rate reduction inside the particle limits.

count measures but if the >0.5µm particle count measure exceeds limits, regulation made by APC is stopped. While the system is working under real-time monitoring ECO mode, if an alarm event that drives the cleanroom out of specifications occurs, the SmartCR automatically switches to conventional mode to use the maximum theoretical ACH to return fast within the specified

limits, ensuring the same recovery time as in conventional systems. Alarms are recorded and stored.

The user can also limit the range established in regulations, setting a number of particles as a target:

SmartCR is provided with a setup option to select the type of particles regulation to be performed

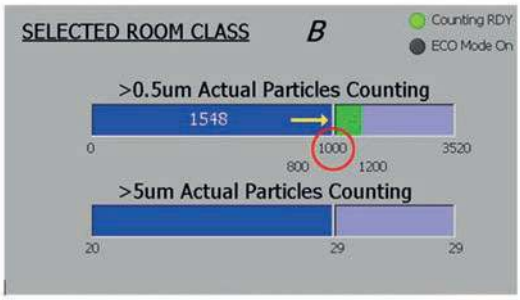

Figure 4. In the configuration screen, 3520 limit for >0.5µm particle has been limited to 1000 by user.

by the control loop: At rest or in operation.

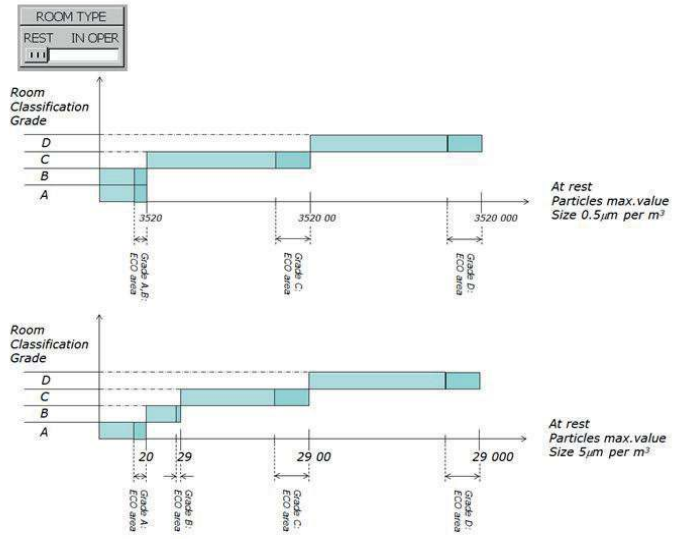

Figure 5. At rest limits.

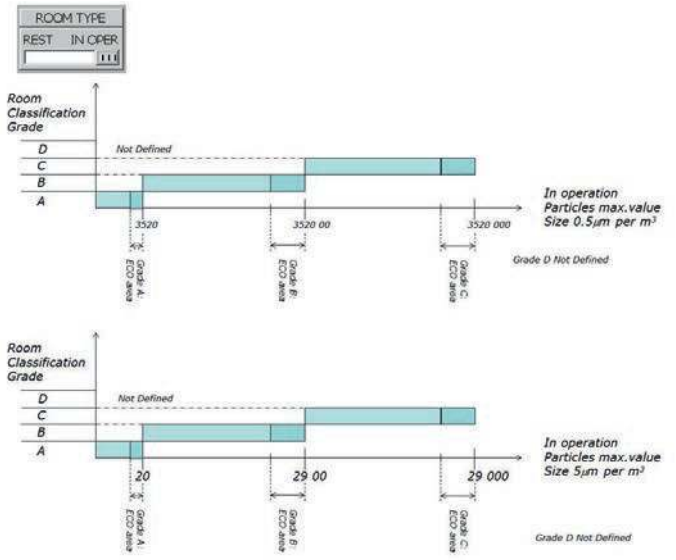

Figure 6. In operation limits.

During the commissioning of the system, the minimum airflow to achieve the correct room cleanliness classification in "at rest" conditions is set. The maintenance of the environmental conditions within the specified limits is verified during at least 12 hours. Then the system is challenged to recover room conditions out of specifications, generating temperature and relative humidity excursions.

Finally, the stability of differential pressures is tested at the minimum airflow previously set. When opening the doors, the pressure differential changes, a reversal of the direction of the airflow is possible and contamination could enter the cleanroom. It is therefore necessary to achieve and maintain a stable pressure under all circumstances. Every change in the room or reference pressure causes the control system to respond and vary the airflow to or from the controlled space.

Commissioning tests reveals that the ACH when no operations are carried out can be significantly reduced achieving very low airflows with a remarkable energy saving. In some cases, airflow is even limited by ventilation requirements. However, in small rooms the limiting factor that appears is pressure control: the minimum airflow may be defined as the minimum needed to prevent backflows or to keep cascades.

The SmartCR solution has been implemented on two different control systems both 21CFR Part 11 and data integrity compliant:

- Controller and touch screen with corresponding audit license.
- Controller with a SCADA application with historian database and audit license: centralized BMS control system with all data registers stored and recorded in a unique database, all parameter settings audited and all configurations GAMP V, and 21CFR Part 11 compliant

Need more information? Please, contact us:
pr@telstar.com

From Telstar we express our gratitude for your interest and your feedback

Conclusion

It can be concluded that the new HVAC control system reduces airflows ensuring environmental conditions within specifications. This reduction on the ACH decreases the power consumption significantly not only on HVAC fans, but also the cooling and heating water. The system is robust, conservative and allows the user several configurations (grades, working conditions, maximum admissible number of particles, etc). Specially developed for the pharmaceutical industry, the control system is CFR21 Part 11 compliant.

References

ISPE Good Practice Guide: Heating, Ventilation, and Air Conditioning

ISO Standards for Cleanrooms and Associated Controlled Environments, www.iso.org.

- ISO 14644-1 Part 1: Classification of Air Cleanliness
- ISO 14644-2:200 Part 2: Specifications for Testing and Monitoring to Prove Continued Compliance with ISO14644-1

EU GMP Volume 4 "EU Guidelines to Good Manufacturing Practice", www.ec.europa.eu.

US FDA CFR Title 21 Food and Drugs, www.fda.gov.

About the authors

Ana Fernández García

Ana Fernández García, Pharmaceutical Technology Manager at Telstar's CRS Engineering, holds a MEng in Industrial Engineering from the UPM (Madrid, Spain) together with a MEng in Chemical Engineering from CPE (Lyon, France). After some years working in the Pharmaceutical industry, Ana jointed the Engineering Department at Telstar in 2007, participating in and managing a wide variety of cleanroom engineering, construction and turnkey projects. Since 2017, Ana is in charge of Conceptual Designs.

Xavier Barrera

Xavier Barrera studied Industrial Technical Engineering and specialized in Industrial electronics at the EUSS University in Barcelona. After finishing his studies in 2004 he worked for several companies focused in different industries; automotive, aeronautics and printing. He gained extensive experience in the automation field during this time. In 2014, Xavier joined Telstar Projects as a Control Engineer, participating in a wide variety of projects related to the Life Science industry. Xavier is currently CRS Electricity & Control Manager at Telstar leading his team to develop pharma engineering and turnkey projects.

About Telstar

Telstar, part of the azbil Group, is a company specialized in the development of engineering & construction projects, integrated process equipment and GMP consultancy solutions, including turnkey projects and critical installations, for companies associated with Life & Health Sciences (pharmaceutical & biotechnology, healthcare, cosmetic, veterinary and food & beverage industries, hospitals, laboratories & research centers). Acknowledged as one of the 10 major suppliers for the pharmaceutical industry, Telstar is one of the few international manufacturers able to offer integrated process solutions for the biopharmaceutical industry with in-house sterilization, freeze drying, containment, process water & waste treatment, clean air and cold storage technologies.