Life Sciences Automated Environmental Monitoring Systems: ISPE Guidance and Best Practices by Topics

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Eurotherm®

Executive Summary

This document provides direct, limited selections from several ISPE Guides pertinent to the Eurotherm Environmental Monitoring System Digital Engineered Solution

Index

Introduction

"The International Society for Pharmaceutical Engineering is a nonprofit association serving its members by leading scientific, technical, and regulatory advancements throughout the entire pharmaceutical lifecycle." [1]

ISPE Baseline® Guides and Good Practice Guides provide detailed information and recommended practices for, among other things, implementing Environmental Monitoring Systems (EMS) and Heating, Ventilation, and Air Conditioning (HVAC) systems in pharmaceutical facilities. To understand how these guides are addressed by the Eurotherm Environmental Monitoring Systems Digital Engineered Solution, please refer to the Eurotherm EMS page where you can download the Eurotherm EMS brochure.

About this document

This white paper reviews the different topics of interest to consider when developing an Environmental Monitoring System. The content is based on the relevant ISPE guides noted in the "sources" section.

Relevant paragraphs and subparagraphs from these ISPE guides have been gathered based on each specific topic of interest.

Sources

[A] ISPE Good Practice Guide - Heating, Ventilation, and Air Conditioning (HVAC) (1st Ed. Sep '09)

[B] ISPE Baseline® Guide - Volume 1: Active Pharmaceutical Ingredients, Revision to Bulk Pharmaceutical Chemicals (2nd Ed. Jun '07)

[C] ISPE Baseline® Guide – Volume 2: Oral Solid Dosage Forms (3rd Ed. Nov '16)

[D] ISPE Baseline® Guide – Volume 3: Sterile Product Manufacturing Facilities (3rd Ed. Apr '18)

Referencing is structured as follows:

[Guide, Chapter.Paragraph.Subparagraph.Sub-subparagraph]

For example:

[A, 1.3.5.7] references "ISPE Good Practice Guide - Heating, Ventilation, and Air Conditioning (HVAC) (1st Ed. Sep '09), Chapter 1, Paragraph 3, Subparagraph 5, Sub-subparagraph 7"

[1] About ISPE, www.ispe.org/about

Topics of interest

Monitoring of environmental parameters

A Qualification Plan should describe the critical environmental parameters to be "monitored, recorded, and alarmed continuously via commissioned and qualified automated monitoring systems or frequently by manual methods using qualified instruments." [B, 8.3]

In the User Requirement Specification, each critical process parameter is identified and defined through the limits for:

- Design space (as defined in the International Council on Harmonisation "Q8 (R2) Pharmaceutical development" guideline), if different from the normal operating range
- Normal operating range
- Process validated range

The limits of the normal operating range specify the alert alarms.
The limits of the process validated range specify the action alarms.

"The Environmental Monitoring System (EMS) is recommended to provide a GMP *(A/N: Good Manufacturing Practice)* record of the critical environmental parameters." [D, 5.8.3]

"Main factors to consider for a monitoring system:

- Accuracy and repeatability required
- Long-term stability and failure modes
- Sensor location/locations
- Alarm requirements
- Record requirements
- Ease of maintenance and calibration" [A, 8.5.6]

"Sustainability factors are becoming required in some regions." [A, 1.6.25]

Monitoring should consider the different process phases or "states" i.e., occupancy states: in operation, at rest/as-built, and clean-up/purge (sterile/aseptic processes).

"From an engineering perspective, automated environmental monitoring should provide feedback on the HVAC system's overall performance (fans, coils, and control components). The HVAC system's output must be compared carefully to qualification test results to evaluate any change in performance." [D, 5.8.3]

For aseptic or sterile facilities (clean space), it is recommended that the monitoring system notifies the occupants through audible sounds and colored warning lights when any critical parameter is out of a specified range for more than a predetermined time. See [D, 5.8.3] and [D, 5.8.4].

Control of environmental conditions

"Commercially available Building Management Systems/Building Automation Systems (BMS/BAS) are encouraged to be installed in all facilities to *control* Pharmaceutical HVAC." [D, 8.6.1]

(A/N: the source refers to "monitoring" but we consider it more appropriate to refer to "control". Note also that the preferred system is a BAS, not Programmable Logic Controller (PLC) nor Distributed Control System (DCS)).

"When considering the HVAC control system, it is important to consider it as another service supporting environmental condition control (…).

HVAC automatic controls may be employed to control variables, such as:

- Temperature
- Humidity

In more complex designs, other variables may also be controlled actively (or passively with periodic manual adjustment):

- Room DP *(A/N: Differential Pressure)* (especially where airflows to/from rooms are expected to vary)
- Constant supply and extract (or return) fan volume control (usually to compensate for air filter loading)
- Filter blinding condition (pressure drop) monitoring (where the challenge to air filters is high, as in terminal HEPA filters with insufficient pre-filters)
- Active room pressure control" [D, 5.8.5]

EMS and BMS segregation (GMP versus GEP)

It is common practice to qualify an independent, dedicated monitoring system for alarming and managing GMP critical parameters and to use GEP (Good Engineering Practices) to develop and maintain a robust BMS/HVAC system to control a facility. This may help simplify the scope of qualification. (See ISPE Position Paper: Use of Building Management Systems and Environmental Monitoring Systems in Regulated Environments, Pharmaceutical Engineering, Volume 25, Number 5, September/October 2005).

"This approach provides the quality unit with a record from a validated system of room conditions during process operations, without the need for a formal change control process for the BMS/HVAC control system (an engineering change control system is still required, which typically is more manageable and less extensive in its scope, e.g., it may include only some set points and some hardware in the system)." [A, 8.5.1]

EMS to relay parameters to the BMS

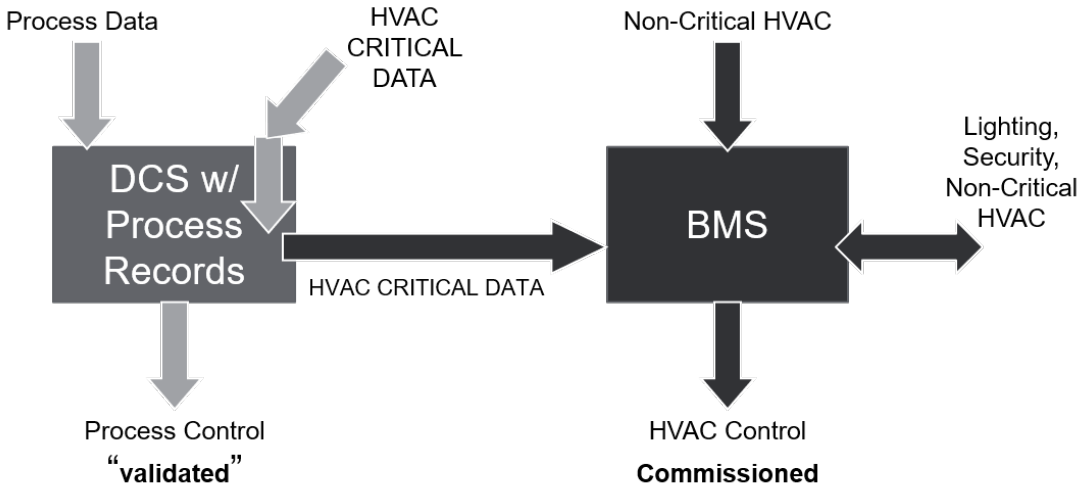
"Where critical parameter logging, indication, recording, and alarming take place, critical field data may be collected *(A/N: monitored)* by a separate standalone process computer (e.g., DCS or PLC), instead of "validating" a BMS for process HVAC recording and alarming.

The critical parameter data may originate from a common device and be relayed to the BMS/BAS (*through the monitoring system*) or the output may go to both systems. The BMS is commissioned to perform the actual control function and to deal with non-critical data and control.

Using a common device has the advantage of providing common data to both systems with one device to calibrate. Systems using two parallel sensors are likely to suffer from different readings because of, e.g., sensor calibration/location." [A, 8.5.1]

Figure 1

BMS and Process Control/Logging Relationship [A, 8.5.1]



Risk management

"Before an HVAC risk assessment can be performed, process and product *(critical)* parameters should be defined." [D, 5.1.5.2]

Risk assessments should focus on identifying, analyzing, and evaluating risks and their associated failure scenarios. Risk assessments may also include GMP (e.g., product quality, compliance) and non-GMP (e.g., production personnel safety, business impact) considerations.

Risk control (e.g., reduction, mitigation, acceptance) should primarily focus on reducing the risk to product quality or personnel safety to an acceptable level.

"Because HVAC processes are well defined, and the failure modes are predictable, two approaches to risk assessment are very well suited to HVAC and environmental control:

- Hazard Analysis and Critical Control Points (HACCP) (…)
- Failure Modes and Effects Analysis (FMEA) (…)

Risk assessment (and subsequent testing/qualification plans) should address expected failure and transitional states (e.g., loss of power, loss of controls, shut down, restart, etc.). The expected conditions for pressurization, cleanliness and other critical parameters should be planned and tested to ensure proper environmental control." [D, 5.1.5.2]

"The appropriate response to the alarm condition should be determined as part of the risk assessment, and the duration of the alarm condition should be considered part of the mitigation strategy." [D, 8.2.2]

Critical Control Points in HVAC Risk Assessment

"Typical critical parameter/control points where a risk assessment might indicate that drug product quality could be affected include:

- Room temperature monitoring system
- Room humidity monitoring system
- Room DP monitoring system
- Environmental monitoring for total and viable airborne particulate
- Continuous airborne particulate monitoring system (expected for ISO 5/Grade A, optional for lower grades)

  Note: The use of automated continuous particle monitoring is recommended. Automated particle monitoring systems provide extensive relevant data on the state of the environment and are generally more reliable than manual monitoring.

- Periodic final HEPA filter integrity (as proven by regularly scheduled filter integrity testing)
- Periodic verification of airflow and/or the airflow monitoring system (for air handler or rooms or unidirectional flow areas)
- Periodic verification of ISO 5/Grade A filter face velocity and air velocity proximate to work height

  Note: The velocity near work height will not be the same as the velocity near the filter face; these measurements should correlate to the measures taken during airflow pattern testing.

- Periodic verification of airflow patterns in ISO 5/Grade A (unidirectional) and general room airflow patterns in ISO 7/Grade B or at interfaces, airlocks, pass-throughs, etc.

Items which only indirectly affect the process environment—and, therefore, have no direct patient safety and product quality impact—usually include Air Handling Units (AHU) pre-filters, fans, coils, humidifiers, and dehumidifiers; ductwork; chilled water; and steam." [D, 5.1.5.2]

Instrumentation

"Industrial *(A/N: not commercial)* grade instruments/sensors usually are employed, as they usually are more reliable, more robust, but more expensive." [A, 8.5.4]

Physical design

"Instruments in process areas should be located to allow cleaning and sanitization of exposed surfaces and should be designed and installed to prevent the accumulation of particulate matter.

Computer screens and keyboards in processing areas should be cleanable, such by utilizing touch membrane technology.

Instruments in direct contact with the product, its components, or associated with a critical manufacturing process should be designed and installed to:

- Prevent accumulation of any matter (including product)
- Withstand required cleaning/sanitization processes and agents without degradation

- Not present a contamination risk to the product or its components
- Not be degraded (physically or in performance) by contact with the product, its components, or the processes to which it is subjected

Many instruments have sensing elements remote from their data processing components. Such devices allow isolation, separation, or remote location of the processing components. This may simplify cleaning and reduce contamination risk." [D, 8.3.1]

Temperature and Humidity

"Room temperature and humidity (...) rarely change measurably in less than a few minutes, so monitoring and data collection at short intervals (minutes instead of seconds) should provide adequate data without creating data overload. Larger rooms may be temperature mapped to determine variations in room temperature and to help determine the most representative location for monitoring (…).

Platinum RTDs *(A/N: Resistance Temperature Detectors)* are preferred for temperature reading, and capacitance sensors are preferred for RH." [D, 5.8.4]

Differential pressure

Where negative DP (pressure reversal) can be expected, "DP sensors should be capable of sensing negative pressures." [D, 5.8.4]

Doors interlocks

Electronic access control should be provided "for rooms that require restricted access for aseptic operations (e.g., ISO 5/Grade A). It is recommended that door interlocks are verified as part of facility commissioning/qualification per GEP." [D, 7.8]

Airborne Particle Counting

"Particle counting instruments (used to measure the airborne non-viable particle concentration) operate by taking a sample of the air in the space and measuring the particle concentration by evaluating scattered light in an optical chamber. Such instruments can count the number and measure the size of particles from 0.1 µm to 5.0 µm. Particle counting systems can be configured in different ways:

- Single portable instruments are usually located close to the environment being classified or monitored. These instruments can be used for both classification and monitoring. Such instruments are suitable for evaluating particles from 0.1 µm to 5.0 µm.
- Single fixed instruments are connected to multiple sample locations through tubing arrays and a manifold system. Each location is sampled in turn. The counter is connected to a data acquisition system. These systems are used for monitoring only. Such instruments are suitable for evaluating particles only in from 0.1 µm to 5.0 µm due to the potential drop-out of larger particles in the transport tubing.

- Multiple miniature point-of-use particle counters are each located close to a location to be monitored and connected to a data acquisition system. These systems only monitor particles from 0.1 µm to 5.0 µm.

Major points to consider when evaluating particle monitoring systems include:

- The difficulty of correlating the data from the relatively small number of sample points of a monitoring system compared to the larger number of data points used to carry out classification in the “at rest” or “in operation” states
- Identifying the room “worst-case” points and relating them to overall room conditions
- Determination of an appropriate sampling frequency for monitoring systems
- Management and interpretation of potentially large amounts of data acquired from automated monitoring systems to identify problems
- Determination of alert and action levels
- Procedures to be followed in the event of excursion beyond alert and action levels
- Re-evaluation of the sample points if there is a change in the layout of the room
- Special attention to be paid to the distance between the air collection point and the counter, in terms of:
  - The inner diameter of connecting tubing
  - Airflow throughput and the occurrence of turbulences (Reynold numbers)
  - Impact on the drop out of particles
  - Material of the tubing (inner surface roughness, electrostatic charge)
  - The geometry of the flow paths (kinks, obstructions, sharp curves)

(…)

The 2004 FDA Guidance for Industry: Sterile Drug Products Produced by Aseptic Processing states:

“Regular monitoring should be performed during each production shift. We recommend conducting non-viable particle monitoring with a remote counting system. These systems can collect more comprehensive data and are generally less invasive than portable particle counters.”

The 2009 EU Annex 1 states:

‘For Grade A zone, particle monitoring should be undertaken for the full duration of critical processing, including equipment assembly, except where justified by contaminants in the process that would damage the particle counter or present a hazard, e.g. live organisms or radiological hazards) ... It is recommended that a similar system be used in Grade B zones although the sample frequency may decrease.’” [D, 8.6.2]

Instrument performances

The project teams should consider “reliability and redundancy of equipment and systems” [A, 2.1.2] during the development of the qualification and the functional design.

“Instrument performance is defined using such terms as:

- Accuracy
- Uncertainty
- Resolution
- Repeatability
- Hysteresis
- Response time
- Stability

(…)

When assessing an instrument's accuracy, several factors should be considered:

- Fitness for purpose
- Instrument cost increases with accuracy
- How misleading the instrument can be without threatening product quality
- Higher accuracy installments reduce the risk of manufacture under unsuitable conditions because of instrument drift

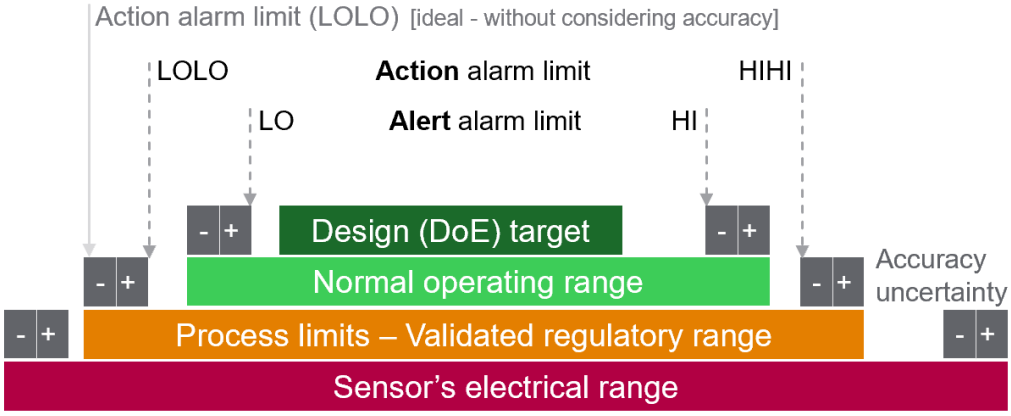
For each CPP, there are usually process limits within which a product should be produced or a process operates. These limits should be defined in pharmacopeias, product registration documents, company standards, or process validation documents.

C&I *(A/N: Control and Instrumentation)* systems should be designed to control conditions to a set point within the Process Limits, usually with a margin of safety or reserve; these are the Normal Operating Conditions.

An indicated value on an instrument is subject to uncertainty (i.e., subject to the instrument's accuracy). For the true condition to remain within Process Limits, at the indicated extremes of the Alert Limits, the instrument's accuracy should give a measurement whose uncertainty is no greater than the difference between the Process and Alert Limits. This difference defines the instrument’s minimum accuracy requirement and is the Instrument Permitted Limit.” [D, 8.3.2]

Figure 2

Impact of accuracy over process ranges

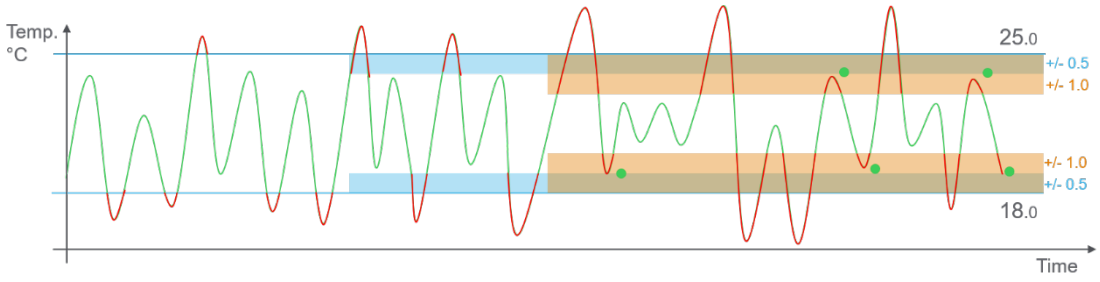


"Using an instrument with an accuracy greater than the Instrument Permitted Limit allows instrument drift while still remaining within Process Limits." [D, 8.3.2]

For example, if the acceptance criteria are 64.4 to 77°F (18 to 25°C) and the monitoring system has an accuracy of +/- 0.9°F (+/- 0.5°C), the action limits should be set at 65.3 to 76.1°F (18.5 to 24.5°C); if the monitoring sensor has an accuracy of +/- 3,6°F (+/- 2°C). the limits should be set between 68 to 73.4°F (20°C and 23°C). See figure 3.

Figure 3

Impact of accuracy on temperature profile for adverse events: reduction of out-of-conformity events reported in the exception batch record



"When using the minimum (i.e., poorest) accuracy, calibration may need to be checked more frequently or a higher risk of operating outside the Process Limits may need to be accepted, consequently risking product quality. Both options have cost implications that often justify using a more accurate instrument. This selection process may be executed under a formal risk assessment where the criticality of instruments is addressed.

For example, instruments of higher accuracy may be selected for equipment deemed part of a critical support system, whereas instruments of lower accuracy may be selected for equipment as HVAC that is non-critical.

The instrument manufacturer's performance claims should be verified. In general, selecting commonly used instruments from internationally known suppliers should provide a satisfactory confidence level." [D, 8.3.2]

Differential Pressures

"Room-to-room and room-to-common reference point are two methods commonly used to monitor room pressure relationships." [A, 1.6.16]

"The accuracy of differential measurement devices is critical. The smallest applicable range should be used with instruments of accuracy sufficient to assure that error is a fraction (generally 10%) of the desired resolution. For example, for control to ± 2.5 Pa, an accuracy of 0.25 Pa is desirable. Drift can also negatively impact sensor accuracy, and the calibration frequency should be sufficient to control this factor." [D, 5.8.4]

Temperature and Humidity

"The accuracy of temperature and humidity instruments is critical." [D, 5.8.4]

Alarm and alert management

"Rapidly changing parameters, such as room pressure, have the potential to create frequent (nuisance) alarms." [A, 1.6.18]

"Where momentary parameter deviation outside specified limits is acceptable, appropriate time delay intervals can be incorporated into the alarm logic. These should

be thoroughly tested, with the rationale documented as part of the system qualification." [D, 8.2.3]

"Alarms should latch and not self-cancel (i.e., the alarm remains active even after the condition has been corrected) until acknowledged by the user/operator. An alarm conditions should be documented and corrective actions recorded." [D, 8.2.3]

Airflow measurements change rapidly and "may require filtering to avoid nuisance alarms. A commonly used filter uses a rolling time-weighted average signal with a rolling average of readings from 4 to 10 seconds typically." [A, 1.6.19]

"Manufactures may apply "Alert" and "Action" alarms. Action alarms should be at the limits of the regulatory range. Alert alarms are typically set between the limits of the operating range and the regulatory range and are used to initiate corrective measures before reaching an Action alarm." [B, 8.2]

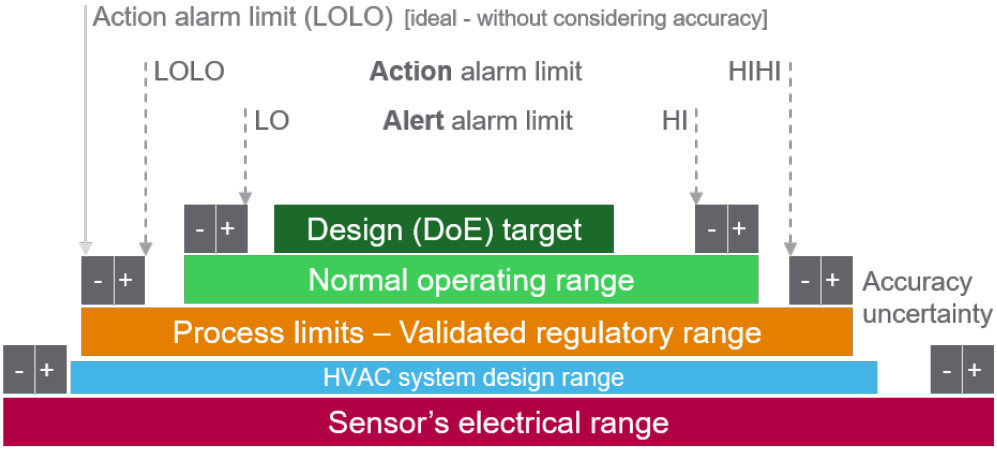


Figure 4

Impact of accuracy over process ranges, including HVAC system design

"Alarm types are either permanent or phase dependent:

- Permanent alarms are always active and do not depend upon the current recipe or phase under execution. These include status alarms, which are independent of batch critical parameters
- Phase dependent alarm triggers should be activated on phase start and then de-activated on phase completion. This includes process alarms, which are dependent on critical process variables". [C, 10.3.1]

Aseptic and sterile facilities

Where the facility design is not based on constant volume supply, "an airflow monitor should be fitted to indicate and alarm a reduction of airflow (and therefore air changes) to rooms. The airflow monitor could be located on the supply fan, in the main air supply duct (and possibly resetting the supply air fan), or at local control boxes/dampers." [D, 5.7.2]

"It is recommended that the environmental monitoring system notify the occupants when any critical parameter is out of specified range for more than a predetermined period of time.

The system should be equipped with colored warning lights to indicate the state of the HVAC system and environmental control to personnel entering clean space and those working within clean spaces." [D, 5.8.3]

Differential pressures

"All DPs within a sterile area environmental cascade should be continuously measured, indicated, recorded, and alarmed (…).

- Monitor DP across airlocks; DP should not go to zero as long as one door in the contamination path remains closed. Door interlocks and audible alarms can help ensure that one door remains closed." [D, 5.8.4]

Door interlocks

Electrical interlocks for the doors of airlocks or changing rooms assist in maintaining pressure regimes and GMP practices. Alternatively, an audible local alarm could be generated to indicate if more than one airlock door is open at the same time. If interlocks are provided, override features should be included in case of emergency." [D, 7.8]

Airborne Particle Counting

Where particle concentrations are very low, monitoring system alert and action levels may be better expressed using frequency (pattern) of seeing low counts rather than trying to discriminate between very low numbers." [D, 8.6.2]

Critical process parameters (CPPs)

A critical control parameter is a parameter that is known to have a direct effect on product quality. The parameters should be controlled and process values captured and recorded. Critical control parameters should be provided with an identification tag and documented on the process and instrumentation diagrams (P&IDs). An acceptable operating range and alarm limits should be set for each parameter, to notify operators when the acceptable process range tolerance is about to be exceeded, or if it has been exceeded. Where a critical control parameter is phase specific, the acceptable operating conditions should be based only on that specific phase.

Table 1

Typical HVAC Critical Parameters by Facility Type [A, 2.2.2]

	Temp.	*Relative Humidity*	*Room Relative Pressure*	*Airborne Particles*	*Air Changes*
Pharmaceutical Ingredients	X	Final API Powder	Low Bioburden API	Low Bioburden API	Low Bioburden API
Oral Solid Dosage Forms	X	X	Air Direction	Cross Contamination	
Sterile Mfg. Facilities	X	X	X	X	X
BioPharma	X	X	Classified Space	See ISPE Baseline Guide	Classified Space
Packaging, Labeling, and Warehousing	X	Exposed Product			
Quality Laboratories	X	X			

Notes:

- Shaded areas represent HVAC parameters that commonly have a product impact or are required for operator comfort to keep airborne contamination low. Some products may not have temperature, humidity, or particulate limits, but USP (A/N: United States Pharmacopeia) temperature and humidity limits may apply.
- Non-shaded areas are HVAC parameters that normally do not have product impact. However, there may be other requirements, such as local codes or regulations that may require specific parameters be considered in the design. For example, room relative pressure may not have product impact in an API facility where processes operate closed, but because of governing codes, the design may include room negative pressurization in order to meet fire safety requirements because of the presence of flammable liquids or vapors." [A, 2.2.2]

"There is no GMP requirement that differential pressure (DP) or airflow direction be automatically controlled. Satisfactory designs using "static" air balance to achieve desired DP values are common in the pharmaceutical industry." [A, 1.6.14]

"Typical HVAC performance parameters that may affect CPPs include the following:

- Temperature
- RH
- Particle count at rest
- Total particle count in use (area classification)
- Clean up and room recovery time from in-use to at-rest
- Supply air HEPA filter performance (capture of contaminants)
- Air change rates/airflow volumes (affecting particle counts and recovery)
- Area DPs (room protection)
- Airflow patterns at critical site
- Microbial viable particulate test results - in air (related to total airborne particles)
- Microbial viable particulate test results - swab tests (indirectly affected by HVAC)" [A, 2.3.1]

Oral Solid Dosage (OSD) facilities

For OSD facilities "filtration may also be a key parameter to assure that the environment is sufficiently clean, this may done in lieu of counting particles since "in-operation" particle counting is not typically practical in facilities where powders are handled.

(…) the following citation from WHO TRS 961 Annex 5 suggests a long list of parameters that may need to be qualified in an OSD forms manufacturing facility:

"8.2.13 For a pharmaceutical facility, based on a risk assessment, some of the typical HVAC system parameters that may be qualified can include:

- *Temperature*
- *Relative humidity*
- *Supply air quantities for all diffusers*
- *Return air or exhaust air quantities*
- *Room air change rates*
- *Room pressures (pressure differentials)*
- *Room airflow patterns*
- *Unidirectional flow velocities*
- *Containment system velocities*
- *HEPA filter penetration tests*
- *Room particle counts*
- *Room clean-up rates*
- *Microbiological air and surface counts where appropriate*
- *Operation of de-dusting*
- *Warning/alarm systems, where applicable.*

For OSD forms manufacturing facilities that class 100,000 (ISO 8) in the “at rest” state (similar to EU Grade D) is a suitable background environment for OSD forms manufacture. As an example, the following is a citation from WHO TRS 961 Annex 5:

“Many open product zones of OSD facilities are capable of meeting ISO 14644-1 Class 8 or Grade D, “at- rest” condition, measured against particle sizes of 0.5 µm & 5 µm...”

Note: The required degree of air cleanliness in most OSD forms manufacturing facilities can normally be achieved without the use of HEPA filters provided the air is not recirculated.” [C, 8.2.2.2]

Temperature

“The USP excursion limits for Controlled Room Temperature (CRT) finished product storage are 59°F to 86°F (15°C to 30°C) with a maximum Mean Kinetic Temperature (MKT) of 77°F (25°C). However, individual products may differ and require a more stringently controlled environment. Product temperature monitoring may be performed as an alternative to room temperature monitoring.

Room temperature can be monitored by return/exhaust duct mounted sensors or wall mounted sensors that relay information to the Building Automation System (BAS) and/or to an independent Environmental Monitoring System (EMS). Typically, a relatively tight control range is specified (i.e., 20°C to 22°C (68°F to 72°F)), with an “Alert alarm” occurring when a wider range is exceeded (i.e., 18°C to 24°C (65°F to 75°F)), before an “Action alarm” occurs when a maximum range is exceeded (16°C to 26°C (60°F to 79°F)). All values being equal to the USP excursion limits, corrected for instrument error.

Note: Temperature and room Relative Humidity (RH) are interdependent and an excessive value in one may adversely affect the other (i.e., a room designed for 21°C (70°F)/50% RH but being maintained at 17°C (62°F) will actually be at > 62% RH).” [C, 8.2.4.1]

Relative Humidity

“Room RH will be a critical parameter for both the operating personnel working in the space and the product present in the room (opened or closed). Depending on the type of product (solid, powder, liquid) varying moisture content in the room will cause different reactions (…).

Typically, room RH is maintained in the 30% to 60% range. Room RH above this level will promote problems with the occupants as well as the product:

- High viable contaminant growth is typically observed above 80% RH (see ASHRAE Systems 2012)
- Occupants will generate particulate as they are likely to perspire in high humidity areas (> 60% RH)
- Powder clumping, improper flow characteristics, and poor machinability may be observed at lower RH depending on product composition
- Hygroscopic products may absorb water causing incorrect formulation or negatively impacting physical characteristics at > 30% RH
- Highly moisture sensitive products, such as effervescent and rapid dissolving tablets, may be negatively impacted by > 10 to 15% RH

For these reasons, room RH may need to be controlled in the 15 to 45% RH range, depending on the product. This will usually require a medium better than mechanical cooling (i.e., chilled water, Direct Expansion (DX), etc.) such as brine, low temperature glycol water, or desiccant.

RH below 20 to 30% greatly increases the risk due to electrostatic discharge (ESD). Static electricity charges can also cause damage to electronics and provide a spark leading to fire or explosion due to ignition of gasses, explosive dusts and/or volatile liquids. The dust deflagration index (Kst) and Minimum Ignition Energy (MIE) of powders being handled impact this risk." [B, 8.2.4.2]

Classification

"The term "Classification" within HVAC and environmental control of pharmaceutical facilities refers to ISO 14644. This standard defines classifications by the count and size of airborne particulate found in the space. For pharmaceutical facilities, we typically focus on particles with a mass mean of 0.5 µm and 5.0 µm. (…) guidance documents (such as WHO TRS 961) suggest that classification according to ISO 14644 as ISO 8 for 0.5 µm and 5.0 µm airborne particles in the "at-rest" state is appropriate for OSD forms.

The use of an ISO 14644 classification of room performance for the design of OSD forms manufacturing facilities provides an independent and verifiable standard for acceptance of designs and eliminates the need for highly suspect and limited acceptance criteria such as air exchange rates (air change rates)." [B, 8.2.4.3]

Differential Pressure and Flow Direction

"Where airborne contamination, cross-contamination, or potent/hazardous material containment are a concern, one tool for control of airborne particulate is to control the differential pressure or direction of airflow between spaces.

The velocity and direction of airflow between spaces should be satisfactory to reduce the transfer of airborne particulates or vapor. While there is not a numerical value for pressurization required in regulation, several suggestions do exist in guidance documents.

Where mass flow is used for control, a velocity of 100 to 200 fpm is desirable to control light powders moving across a work area. This principle is used for containment in weighing booths, dryer discharges, and similar open containment devices.

Where direction of airflow across a door is used for control, a velocity of 100 to 200 fpm is desirable to control light powders moving across the opening. Generally, smoke tests and Baulin tubes may be used as indication in this type of control.

Where airflows are variable, higher levels of containment are required, or containment requires continuous monitoring, differential pressure measurement can be used. In these cases, a minimum pressure difference of 5.0 Pa (0.02"WC) is suggested to allow for repeatable control. For better control and higher containment, a value of 12.5 Pa (0.05"WC) is common." [B, 8.2.4.4]

Air Change Rate

"While air exchange rates (air change rates) are a common design parameter, it has little value as an acceptance criterion for OSD facilities (…).

In lieu of utilizing ACH *(A/N: Air Changes per Hour)* as an acceptance criterion for oral product production spaces, we recommend utilizing ISO Standards 14644-1, 2, 3 to establish HVAC acceptance criteria and proof of environmental control." [B, 8.2.4.5]

Aseptic and sterile facilities

All critical parameters within a sterile area environmental cascade should be continuously measured, indicated, recorded, and alarmed.

Table 2

Typical environmental process parameters, how they are controlled, and monitoring recommendations [D, 8.2.2]

Environmental Process Parameter	Active or Passive Control	Monitoring Recommendation
Room temperature	Always active	Continuous recording is recommended
Room RH	Always active	Continuous recording is recommended
Room differential pressure	Active	• Active control of pressure differences using actuated control dampers is not recommended by this Guide (see Chapter 5). • Where this approach is taken, continuous recording of each pressure differential is recommended.
	Passive	• Where pressure differences are passively controlled via proportional air volume balancing and room pressure relief dampers, they could be documented less frequently (i.e., less than continuously for ancillary aseptic processing area rooms). • Excursions should be recorded.
Particle count	Passive	• Particle count is controlled passively, through means such as filters, low leakage ductwork, personnel control, and air change rates. • Continuous recording may not be necessary; however, it is recommended to set and maintain particle monitoring schedules based on the classification of the environment that is claimed. • See Section 8,6,2 for particle monitoring in critical classified spaces.
Temperature of process environment	Always active	Continuous recording is recommended.
Relative humidity of process environment	Specifically controlled or limited by the HVAC psychrometrics	Continuous recording is recommended.
Room/enclosure pressure differential	Both active control and passive (static air balancing) techniques can be deployed.	• Where the pressure differential is an essential part of space separation for different cleanliness classes or contamination risk, then the pressure differential should be continuously monitored, recorded, and alarmed. • The frequency of monitoring can be related to the criticality of the controlled space. For example, aseptic processing areas are considered more important then clean preparation or formulation areas and, therefore, should be continuously monitored and recorded. • Passive (locked damper) control with continuous monitoring is considered to be the technical baseline for room pressure differentials.

Differential Pressures

"It is suggested that the system provide indication of room-to-room differentials as well as room reference values. Additional considerations for monitoring of DPs include:

- Monitor DP across airlocks; DP should not go to zero as long as one door in the contamination path remains closed. Door interlocks and audible alarms can help ensure that one door remains closed.
- DP sensors can be employed to detect door opening and thus control the time that doors remain open, as required by regulation. The maximum time that a door may be open can be determined by open door testing (which quantifies the impact of an open door on room environmental conditions) and a survey of the duration of door opening required to support activities.

- Only one DP sensor is needed per room, but it should be located to minimize impact of air currents at the sensor.
- The monitoring system should document the duration of an unexpected loss (reduction) in pressure differential.
- Reversed direction of airflow across a door is undesirable and should only occur for brief intervals (e.g., due to the velocity of the door opening). DP sensors should be capable of detecting negative DP and incorporate the calibration tolerances of the measuring devices.
- The accuracy of differential measurement devices is critical. The smallest applicable range should be used with instruments of accuracy sufficient to assure that error is a fraction (generally 10%) of the desired resolution. For example, for control to ± 2.5 Pa, an accuracy of 0.25 Pa is desirable. Drift can also negatively impact sensor accuracy and the frequency of calibration should be sufficient to control this factor.
- The reference point selected for DP measurements is also critical. If measurements are made to a central reference, this reference point should be located in a large stable space, preferably with few doors and ideally without mechanical ventilation or with fixed ventilation. Interstitial areas are often excellent references.
  - Outdoor areas are generally poor reference points due to the velocity pressure of local winds.
  - Mechanical rooms are often poor reference points due to thermostatic ventilation.
  - Large corridors can be good reference points if doors do not open to a large space of different pressure.
- Room and reference terminal devices should be relatively insensitive to drafts and located away from doors and air supplies/returns." [D, 5.8.4]

Airflow to Rooms

"While continuous measurement of airflow is not required, assurance of a consistent airflow supply is an indirect indicator of the ability to dilute contaminants and, therefore, of room environmental control. Airflow monitoring is usually continuous (since an airflow volume/velocity monitor is often installed to adjust fan delivery to compensate for air filter loading). Usually one sensor in a supply duct is sufficient to show overall system airflow unless constant volume controls are implemented at each room or zone.

If a variable airflow scheme (such as idle airflow setback) is utilized, room airflow measurement is recommended to assure that room airflow is appropriate for the particulate generation rate present. Idle airflow setback schemes reduce airflow to rooms which are not in use (unoccupied and not in use for production, setup or cleaning). These schemes typically are not implemented until 15-20 minutes after cessation of use to allow for recovery. These schemes typically maintain room pressurization as well as temperature and humidity control to maintain aseptic conditions. The performance in the setback state and the time required to return to service should be validated." [D, 5.8.4]

"An airflow cascade should be set up using a DP cascade. Considerations include:

- The minimum suggested guidance DP is 10 - 15 Pascals (Pa) between air classes with doors closed. This translates into a typical design pressure of 12.5 ± 2.5 Pa per step. Larger steps are sometimes used to allow for adjacent spaces to reach alert or alarm limits prior to pressure reversal.
- Rooms of differing criticality within an air class may be separated by less pressure, as long as DP can be reliably maintained (with doors closed) and monitored.
- The minimum suggested DP value is 5 Pa between areas of like classification.
- Pressure differentials should be measured in situ using suitably accurate and calibrated equipment, especially for critical areas.
- Where DP less than zero (pressure reversal) is possible, DP sensors should be capable of sensing negative pressures and triggering alarms (regardless of whether a correct cascade is quickly re-established).
- With regards to compounded pressures within the cascade:
  - Excessive pressure may create problems with the fabric of the highest pressure room, with materials transferred across the boundary or doors.
  - For simple facilities, a typical maximum room pressure is usually less than 45 Pa relative to the building, whereas larger complex operations with more layers may require somewhat higher relative pressure.
  - Re-thinking traffic patterns and layout may help avoid expensive high pressure rooms.
- With regards to opening of doors:
  - There is no mandate to maintain pressurization between spaces while the door between them is open; attempting to do this generally results in oversized mechanical systems and unstable control.
  - An overall flow of air in the desired direction when the door(s) between spaces are open should be maintained. The pressurization air should be sufficient to produce the intended velocity across the open door." [D, 5.8.4]

Temperature and Humidity

"Temperature and humidity for rooms with critical operations should be monitored to ensure control of operator comfort, product temperature, humidity requirements, and bioburden. Since critical rooms/zones typically have temperature and humidity sensors (for the controllers), continuous monitoring is possible." [D, 5.8.4]

Airborne Particle Count (Total or Non-viable)

"In critical zones (e.g., ISO 5/Grade A and at ISO 5/Grade A to ISO 7/Grade B interface), the use of automated continuous particle monitoring is recommended. Automated particle monitoring systems provide extensive relevant data on the state of the environment and are generally more reliable than manual monitoring. See Section 8.6.2 for additional information." [D, 5.8.4]

Airlocks

"Airlocks are usually small and should be highly ventilated rooms (for quick recovery), with doors interlocked and/or alarmed to prevent more than one being opened at a time, thereby keeping some resistance to airflow and preserving a measurable pressure differential. Local alarms should be employed if a door remains open for more than a preset period, if both doors are opened simultaneously, or if the DP across an airlock (between the two classified rooms) should go to zero (…). Regardless of the airlock classification, there is no need to design for 10 - 15 Pa per door; it is more appropriate to divide the target pressurization across the number of doors present." [D, 5.6.3]

Data integrity

"If a part of the system requires commissioning and qualification to meet regulatory requirements, functionality for specific common attributes, such as data integrity, may need to be tested to a higher standard." [A, 8.5.1]

"The field devices controlling and monitoring these critical process parameters (…) should be monitored by an approved incorruptible data historian." [C, 10.4]

Note: for further information on how to achieve Data Integrity in the Life Sciences industry visit the Data Integrity in the Life Sciences Industry web pages

Mean kinetic temperature (MKT)

"The USP excursion limits for Controlled Room Temperature (CRT) OSD finished product storage are 59°F to 86°F (15°C to 30°C) with a maximum Mean Kinetic Temperature (MKT) of 77°F (25°C)." [C, 8.2.4.1]

Calibration

The calibration of sensors monitoring critical parameters "should follow a regular program, which provides evidence of consistently acceptable performance. Calibration should follow approved written procedures and the results should be documented. All calibrations should be traceable to certified reference standards" [B, 10.4] like the National Institute of Standards and Technology (NIST) or equivalent.

"Three point calibration may be required, but single point calibration may be justifiable." [A, 8.5.4]

"Comprehensive calibration guidance should be obtained from the suppliers before an instrument is chosen." [D, 8.3.4]

Differential Pressures

"The accuracy of differential measurement devices is critical (…). Drift can also negatively impact sensor accuracy and the frequency of calibration should be sufficient to control this factor." [D, 5.8.4]

Temperature and Humidity

"These instruments should support multi-point calibration and be of sufficient accuracy to provide the desired resolution and control range." [D, 5.8.4]

Electrical

"Electrical power distribution systems are not considered critical systems and are not subject to regulatory oversight and validation requirements, as they do not directly affect the quality of pharmaceutical products (…).

A properly designed electrical distribution system should provide reliable electricity to pharmaceutical equipment." [C, 9.1]

"Both reliability and stability of the power supply are important.

The impact of surges, dips, or total power loss on the overall manufacturing process, HVAC/mechanical services, or individual equipment items, should be studied to determine risk and effects. Generally, the impact is economic (loss of production capacity). If these impacts are considerable, then a standby generator or UPS *(A/N: Uninterruptible Power Supply)* should be considered.

For HVAC systems, momentary power losses may be significant; impact could be mediated if there are provisions for fan rotation to continue and room pressures are maintained within acceptance criteria for short periods. The impact of any power loss potentially affecting the product should be evaluated.

Power for monitoring of DP is a critical issue, as loss of differential or the ability to monitor differential pressure during outages may result in significant product quality impact.

Consideration for UPS or emergency generators can be considered for critical processes, equipment, and systems that may provide, maintain, or record critical parameters as part of GMP operations.

Power quality is equally important as precision equipment has a narrow bandwidth to operate within. Special consideration should be given to:

- Power factor correction
- Phase balance
- Harmonics from digital equipment" [D, 7.4]

Wireless

"Wireless technology is also used for the connectivity of specific devices." [C, 10.4]

Reports

"Reports showing existing alarms, operator logs, trouble conditions, out-of-service devices, etc., are usually either automatically generated as determined by the administrator level operator or can be manually downloaded by the operator." [C, 10.4]

21 CFR Part 11

“Automated monitoring systems for critical process parameters should comply with US FDA 21 CFR Part 11 and be subject to validation to assure the accuracy of the readings and records produced by the system.

EU Annex 1 requires that HVAC monitoring systems notify occupants when the HVAC has failed.” [D, 5.8.3]

Sustainability

“For a facility that is aiming to be considered as “green” or sustainable, HVAC systems are an important component. Compliance with sustainability guidelines has been optional and considered progressive, and provided market differentiation for the building owners. Compliance with sustainability guidelines and standards is becoming required in some regions.” [A, 1.6.25]

About Eurotherm

With a long history in precision process control, automation, and high integrity data management, Eurotherm has a broad range of knowledge and expertise in regulated industries, including food and beverage, helping customers to comply with data integrity related standards and guidelines, such as:

- U.S. FDA 21 CFR Part 11
- EU EudraLex Annex 11
- GxP
- Data Integrity ALCOA+

As well as providing a range of control and data acquisition products, and engineered systems, Eurotherm provides a wealth of expertise in food and beverage applications, offering comprehensive engineering support and services, including data management, energy management, and cybersecurity services.

From discrete products to full automation solutions and industrial reporting packages Eurotherm can help you get the most from your process.

Find out how Eurotherm products, solutions and services have been used in Food and Beverage applications.

About the author

Roberto Zerbi has spent more than 25 years at Eurotherm, covering various roles: project management, sales, marketing, nurturing partnerships with OEM machine builders, strategy, and digital innovation. His experience ranges from continuous to batch processes, covering the life cycle from detailed design to predictive maintenance. In recent years Roberto has been involved in digital transformation, the impact of innovation on business processes, Quality by Design, and risk management. He is passionate about robotics, artificial intelligence, and cognitive processes. Roberto is a member of the Alumni of the Politecnico di Milano and of the International Society for Pharmaceutical Engineering (ISPE).).

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