Life Sciences Industry Solution Blueprint for Environmental Monitoring Systems (EMS)
ISPE Guidance and Best Practices

Author: Roberto Zerbi, Global Industries Solutions – Life Sciences, Invensys

What’s Inside:
1. Introduction
2. ISPE Good Practice Guide - HVAC
3. ISPE Baseline® Guide: Active Pharmaceutical Ingredients
4. ISPE Baseline® Guide: Oral Solid Dosage Forms
5. ISPE Baseline® Guide: Sterile Manufacturing Facilities
1. Introduction

The International Society for Pharmaceutical Engineering (ISPE) is the world's largest not-for-profit association dedicated to educating and advancing pharmaceutical manufacturing professionals and their industry. Founded in 1980, ISPE serves 25,000 members in 90 countries. Members work together to improve the industry while helping one another make more educated decisions, more quickly.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. Often, an EMS is mixed/embedded within HVAC systems or within Building Management Systems/Building Automation Systems (BMS/BAS). Over the last five years, it has been common practice to consider BMS/BAS as the sum of a ‘validated’ EMS plus a ‘Good Engineering Practice’ HVAC (with Access and Fire controls considered as ‘options’).² To understand how these guides are addressed by Invensys’ Industry Solution Blueprint for Environmental Monitoring Systems, refer to Invensys’ EMS brochure.

This document provides direct, limited selections from several ISPE Guides pertinent to Invensys’ Industry Solution Blueprint for Environmental Monitoring Systems. All ISPE material is © International Society for Pharmaceutical Engineering and is used here with permission. The very comprehensive source documents are available through ISPE and www.ispe.org.

² For the latest information, visit the ISPE website at www.ispe.org and/or consider joining ISPE and the ISPE HVAC Community of Practice (CoP).
1. Introduction

1.6 – Key Concepts

1.6.17 – HVAC Controls and Monitoring

“It is common practice to qualify monitoring systems (sensors, transmitters, indicators, recorders, alarms, etc.) for those parameters defined as critical and to use GEP [Good Engineering Practices] to ensure the development and maintenance of a robust control system. … A common alternative approach is to employ an independent system for alarming and managing critical data. The HVAC control system is limited to control and maintenance information.”

2. Design Process

2.2 – Developing User Requirements

2.2.1 – Introduction

“Critical HVAC parameters often associated with qualification (e.g., temperature, humidity, DP, air quality, etc.) are treated differently from non-critical HVAC parameters. Critical HVAC parameters are part of direct impact systems, while systems providing only non-critical HVAC parameters are either indirect or no impact systems as defined in the ISPE Baseline® Guide for Commissioning and Qualification.”

“Once user requirements are established, design strategies and their effects should be considered. It may be desirable to segregate HVAC systems, such that only one system deals with critical parameters, and therefore, has direct impact (e.g., processing areas on one HVAC system, support areas on another HVAC system). This may help simplify the scope of qualification.”

“An alternative approach is to define systems by function, rather than by AHU. For example, monitoring systems for critical HVAC parameters are direct impact. If all the room DP monitors were grouped as the DP monitoring system they could be qualified as a single system, the air handlers themselves being indirect impact systems. Should any AHU fail to deliver the correct quantity of air, the direct impact system (the DP monitoring system) would detect it. Other grouped systems can be temperature monitoring, HEPA filtration (periodic testing), airflow monitoring (to verify air changes and recovery), RH monitoring, etc.”

8. Appendix 2 – HVAC Applications and Equipment

8.5 – HVAC Controls and Monitoring

8.5.1 – Introduction

“A common alternative approach is to employ an independent system for alarming and managing critical data, such as a data logger, process control system, or LIMS. The HVAC control system is limited to control and maintenance information required to manage a facility.”

“Where critical parameter logging, indication, recording, and alarming take place, critical field data may be collected by a separate standalone process computer (e.g. DCS or PLC), instead of ‘validating’ a BMS for process HVAC recording and alarming.”

“The various functionalities, as well as critical versus non-critical parameters handled in the BMS, can be assessed for risk and tested and documented accordingly.”
“The critical parameter data may originate from a common device and be relayed to the BMS/BAS 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 common data being provided 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.”

“The various functionalities, as well as critical versus non-critical parameters handled in the BMS, can be assessed for risk and tested and documented accordingly.”

“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 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).”

8.5.4 – Critical Parameter Controls

“Industrial grade instruments/sensors usually are employed, as they usually are more reliable, more robust, but more expensive. For some instruments, accuracy and repeatability are important, e.g., measuring room temperature. For others, accuracy is not as important as repeatability, e.g., measuring a system’s flow rate in order to maintain constant flow using a variable speed fan. ‘Three point’ calibration may be required, but single point calibration may be justifiable.”

8.5.6 – Monitoring of Critical HVAC Parameters

“It is common practice to qualify monitoring systems (sensors, transmitters, indicators, recorders, alarms, etc.) for those parameters defined as critical (usually handled in the process monitoring computer system) and to use GEP to ensure the development and maintenance of a robust control system (via the HVAC control system,…).”
3. ISPE Baseline® Guide: Active Pharmaceutical Ingredients, Revision to Bulk Pharmaceutical Chemicals (2nd Ed. June ’07)

8. HVAC

8.2 – HVAC System Parameters

“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.”

“Room parameters that may affect products or materials include…”

8.2.1 – Temperature

“Room temperature may be a critical parameter for both open and closed systems.”

8.2.2 – Relative Humidity

“Room relative humidity, dew point, or absolute moisture level may affect exposed intermediate, or product, that are sensitive to air moisture…”

8.2.3 – Airborne Particulates

“Airborne particulates should be controlled in a manner to prevent contamination and cross contamination from both the facility internal environment and from the outdoors…”

8.2.4 – Room Relative Pressure

“The velocity, or mass, and direction of transfer air flow between spaces helps to prevent airborne contaminants and products from passing from one space to another…”

8.2.5 – Air Changes

“Currently, there is no minimum cGMP [Current Good Manufacturing Practice] requirement for air changes per hour, except for aseptic or sterile processing…”

8.2.6 – Monitoring

“Regular monitoring of critical parameters should indicate to the user when acceptance criteria are not met. Established alert values should indicate when a monitored parameter is beginning to drift out of control. The Qualification Plan should address sensors, alarms, and recording systems for critical parameters.”

8.2.7 – Special Processes

“...The use of an isolator or barrier, such as a glovebox or glovebag, reduces the volume of the environment to which the process would be exposed…”

8.2.8 – Worker Comfort

This section describes T, RH, and Air Filtration requirements to preserve working conditions.
8.3 – HVAC Controls and Monitors

“Instrumentation should be provided to monitor and record critical room parameters and alarms, according to the User Requirements specification. It is often desirable to monitor, record, and/or alarm with commissioned and qualified portable or other instrumentation that is not a part of the HVAC control system. In this case, the HVAC control system should then need only to be commissioned. It is good practice to monitor the performance of equipment such as fans and coils and control components, but it is not a regulatory requirement, as long as critical parameters meet acceptance criteria...”

“Sensors, monitoring, recording, and alarming for critical parameters should be part of the qualification and ongoing validation and change control program.”

“Critical parameters should be monitored, recorded, and alarmed either continuously via commissioned and qualified automated monitoring systems, or frequently by manual methods using qualified instruments.”

“Critical sensors monitoring critical parameters should be calibrated to National Institute of Standards and Technology (NIST) or equivalent reference standards.”

10. Instrumentation and Control

10.2 – Principles

“...instruments and control systems are considered critical and should be qualified when they measure or control critical parameters.”

“All instruments and control systems should be designed, installed, calibrated, and maintained appropriately, according to Good Engineering Practices. All critical instruments and control require qualification and change control...”


10.4 – Calibration and Preventive Maintenance

“The calibration of instruments 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 standards...”
3. Product Protection

3.1 – Potential Product Protection Requirements

3.1.1 – Levels of Protection

“Level 1 – General: an area within the facility that has no potential for product or product contact surface exposure to the environment or personnel. Such areas include secondary packaging where environmental conditions are determined to have no direct or indirect impact on the product. Environmental control may be provided for staff comfort, and these systems should be designed, specified, and commissioned following GEP.

Level 2 – Protected: an area within the facility that has no potential for product exposure to the environment or personnel; however, the environment or activities in this area may directly and/or indirectly impact the product. In these areas, design considerations or procedural controls are utilized to protect the product and materials or components, which will contact or become part of the product. Examples include:

- Secondary Packing where control and monitoring of temperature is a GMP [Good Manufacturing Practice] requirement (direct impact). Personnel may need protection against potential exposure to product following damage to primary packaging.
- Warehouse where control and monitoring of temperature is a GMP requirement (direct impact)...

Level 3 – Controlled: an area within the facility in which specific environmental/facility conditions and procedures are defined, controlled, and monitored to prevent degradation or cross contamination of the product. The areas include all sampling, dispensing, manufacturing, and primary packing areas where the product, raw materials, or components are exposed to the room environment, plus equipment wash and storage areas for equipment product contact parts. Within controlled areas, environmental conditions, including temperature, humidity, and air filtration quality will be specified and validated...”

3.1.2 – Protection against Contamination

3.1.2.3 HVAC

“HVAC systems should maintain the specified environmental conditions of air quality, temperature, humidity, and room pressurization critical to the product in controlled areas and some protected areas. Note that hygroscopic products could require special low humidity conditions...”

3.1.3 – Protection against Product Cross Contamination

“...HVAC systems, which protect against cross contamination through use of differential pressure regimes to control air flow direction...”
6. Process Support and Utilities

6.3 – OSD Process Support Systems and Utilities

6.3.6 – Facility and Process HVAC Systems

6.3.6.1 Facility HVAC Systems

“Facility HVAC systems typically have direct contact with product. However, most OSD facilities are under continuous monitoring by an Environmental Monitoring System (EMS) for temperature and relative humidity. For compounds that are highly sensitive to temperature and humidity conditions, appropriate design and qualification of the control system should ensure product quality...”

7. HVAC

7.1 – Introduction

“HVAC systems can help mitigate risks to both the product and the people who work around it. Their contributions include:

GMP Risks

• protecting the product with quality room air delivered at temperature, humidity, and particulate per user requirements
• protecting the product from cross contamination from other areas by providing pressurization patterns and preventing entrainment of particulate into the distribution system”

7.4 – Design Considerations

“...The key to the design of the HVAC system is providing an overall positive pressurization to the entire building, while maintaining negative pressure within critical areas...”

7.4.1 – Critical Parameters

“To design an HVAC system, key parameters should be defined, including:

• temperature and humidity levels within the room with a level of operating tolerance
• outside air design conditions (ASHRAE Standard 90.1...)
• filtration requirements
• space pressurization requirements
• control requirements

Microbial contamination also should be considered. The relative direction of airflow between spaces may be a critical parameter if airborne particulates or vapors could have a detrimental effect on the product or the material in another space.

Acceptable operating ranges should be considered in establishing the design criteria. Temperature excursions outside the defined parameters over specific time duration can result in either an Alert or Action condition. These conditions are highly applicable to the HVAC control and monitoring system.”

7.4.2 – Monitoring and Control

“Regular monitoring of critical points should indicate when parameters exceed operational limits. Instrumentation should monitor GMP critical room parameters and alarms. It is possible to monitor, record, and/or alarm with portable or other instrumentation, which is not part of the HVAC control system. Alert points can indicate when a monitored parameter is beginning to drift out of control. It is considered good practice to monitor the performance of equipment, such as fans and coils and control components.
Instruments for critical room parameters should be part of the qualification, ongoing validation, and change control program. Qualification plans should address sensors, alarms, and recording systems for critical parameters.

Control devices have an accuracy range which can affect the design tolerance. Care should be taken to ensure that sensors and monitors fall within the level of operating tolerance required for the space. Sensors, transmitters, indicators, records, alarms, etc., used for monitoring critical parameters should be periodically calibrated to National Institute of Standards and Technology (NIST) reference standards... The location of controls and sensors should be carefully considered to allow access for regular maintenance and calibration.

Critical parameters should be monitored, either through the HVAC control system, process control automation, or by manual methods. If manual monitoring is selected, the frequency of monitoring should be sufficient to show that critical parameters were maintained within acceptable operating ranges, and that any deviations were of duration not impacting either product, or material. Commercial HVAC (Building Management System (BMS)) control systems may provide adequate control, data handling, and alarming capability, as long as the system can be validated for critical parameters. However, some commercial grade sensors often are less desirable than industrial grade sensors for critical parameters, from a life cycle cost standpoint, driven by reliability, drift, repeatability, and maintenance cost.

Hazardous environments and duct airstreams may require special selection and location of sensors and controls.

Pneumatic controls should be considered for use for actuation of various control devices, such as control valves, humidifiers, or dampers where fast acting response is required. Pneumatics sensors and transmitters should not be used for critical space sensing due to their sensitivity to dust and their limited accuracy for sensing.

7.5 – Non-GMP Considerations

7.5.1 – Worker Comfort

This section describes T and RH requirements to preserve working conditions.

10. Other Considerations

10.2 – Strategies to Control Employee Exposures to Hazardous Materials

10.2.5 – Administrative Controls and Work Practices

10.2.5.3 Air Monitoring

“Air monitoring techniques are used to confirm that airborne contaminants are less than set occupational exposure limits or within set occupational exposure bands, either for ongoing monitoring or for commissioning...”

10.5 – Environmental

Table 10.5: Environmental Issues Comparison

<table>
<thead>
<tr>
<th>Environmental Issues Comparison</th>
<th>Issues for Industrial Sources to Address</th>
<th>Typical Risk Mitigation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Air Emissions: public air quality should be maintained below national air concentration standards for pollutants, such as:</td>
<td>Controlling air emissions from process and utility systems operations, whether continuous, intermittent, or fugitive to meet regulatory requirements</td>
<td>Process vents or local exhaust ventilation systems to contain and collect pollutants at the sources for treatment by Air Pollution Control Devices, such as:</td>
</tr>
<tr>
<td>• Particulate Matter (PM)</td>
<td></td>
<td>• PM: fabric filters, wet scrubbers,</td>
</tr>
<tr>
<td>• Carbon Monoxide (CO)</td>
<td></td>
<td>• Mechanical collectors, HEPA filters</td>
</tr>
<tr>
<td>• Nitrogen Oxides (NOx)</td>
<td></td>
<td>• Hazardous solvents: Thermal oxidation, gas absorbing scrubbers, adsorption</td>
</tr>
<tr>
<td>• Ozone</td>
<td></td>
<td>• Combustion by products, such as NOx, SOx, CO: selective catalytic reduction</td>
</tr>
<tr>
<td>• Sulfur Dioxide (SOx)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IMPORTANT NOTE: Although this ISPE Baseline® Guide is the most currently available at the time of preparing this White Paper, the document is being updated, and a new edition is scheduled to be released in September 2011. This White Paper will be appropriately updated following ISPE’s release of the new 2nd Edition.

1. Introduction

1.3 – Key Features of This Guide

“One of the most fundamental issues, in regard to facilities for aseptic manufacture, are HVAC principles. In particular, engineers should understand that regulators are particularly interested in the environment during in operation conditions, as this is the time when the product may be exposed. HVAC design and clean area classifications should relate to this situation. Engineers should understand sources of particulate and microbial contamination, and the various ways that air quality can be maintained during manufacturing, for example, by filtration, cleanliness cascades, etc...”

2. Concepts and Regulatory Philosophy

2.5 – Aseptic Processing Area

“The aseptic process areas are those where the product is likely to be exposed to the atmosphere. The point- of-fill is at least a Class 100 environment, protected under unidirectional air flow...

...Having established the required environmental standards through air filtration, air flows, appropriate pressure differentials, etc., it is important that this quality is not compromised by entry of potential contamination via such items as clothing or containers...

...The design of each element of the manufacturing facility should contribute to minimizing the contamination risk. For instance, extraneous contamination is minimized by using a changing regime for personnel, or pretreatment of components. The manufacturing environment is controlled by means of air filtration, air flow and pressurization...

5. HVAC

5.4 – Environmental Standards and GMP

5.4.2 – GMP Critical Parameters

“The following environmental parameters typically are critical to maintaining a sterile manufacturing facility in compliance:

• Product specific parameters
• Environmental conditions...
• Acceptable unidirectional air flow patterns and velocities for critical areas
• Air flow patterns within sterile rooms to show protection of critical operations
• Temperatures
• Humidity
• Differential pressures to provide assurance against contamination from lower grade environments
• Air change rates in classified rooms"
5.5 – Manufacturing Layout and HVAC Principles

5.5.2 – Differential Pressures

“The integrity of differing environmental standards is maintained by cascading air flows from higher to lower classifications. It is of prime importance that ‘dirty’ air does not contaminate ‘cleaner air’...

...In practice, ...air flow requirements are set up using a differential pressure cascade. Differential pressure provides a useful, quantifiable design tool, and measurable performance objectives for the designer...

...The industry-accepted normal design figure is 0.05 inches water gauge (12.5 Pa) between air classes...

...There is a cost benefit in keeping the pressure differentials as low as practical (within regulatory guidelines). Air leaking to lower grade areas means more fresh air has to be ‘cleaned’ to replace it. This results in greater capital costs for filters, fans, etc., and increased operating costs, due to filter blocking requiring greater fan power and more regular replacement. Alternatively, smaller pressure differentials will require more sophisticated controls and pressure stabilizing equipment, resulting in high capital and maintenance costs.”

5.8 – Monitoring

5.8.1 – Air System Monitoring

“It is not possible to assess product sterility on-line. The level of sterility assurance required for sterile products, means it is unlikely that random sampling of the finished product will detect any sterility failure resulting from processing. Such techniques as particle counting, active air sampling, or settle and contact plates provide useful data.

Even with this essential and informative data, final product sterility cannot be assured. Hence, aseptic operations, particularly for products that cannot be terminally sterilized, rely upon validated procedures carried out in strictly controlled environments for all critical stages, to minimize potential product risk.

As mentioned...certain environmental parameters may be considered ‘GMP Critical’. These parameters must be monitored and documented, but it is not always possible to do so continuously. Therefore, aseptic manufacturing needs a robust design, to minimize potential problems, and a well-considered and qualified monitoring/documenting program.

For example:

a) Differential Pressures

All differential pressures within a sterile area environmental cascade should be measured, indicated, alarmed, and documented regularly during a shift...

...Typically, periodic monitoring may repeat some tests carried out as part of the original Process/Equipment Qualification exercise...

...The test frequency will depend upon plant operating experience and the Process/Equipment Qualification findings. It also may vary from area to area...

...The importance of this routine environmental monitoring, from an engineering viewpoint, is that the tests provide feedback on the HVAC system’s overall performance. It tests the design and will highlight lack of performance in an individual system, not only the ‘Direct Impact Systems’. It is important that the results are compared carefully to Qualification test results to look for any change in performance...”
5.8.2 – HVAC Controls

“When considering the HVAC controls system, it is important to consider it as another service supporting environmental condition control. Automatic controls need not have ‘Direct Impact.’

…it is the monitoring and documenting systems that provide ‘GMP Critical Parameter’ data to production staff, hence these systems are direct impact and require qualification studies.

It may be preferable that the monitoring and documenting of these ‘GMP Critical Parameters’ should be isolated from any HVAC (Building Management System; BMS) control systems, to avoid qualification complications…”

5.10 – Qualification of HVAC Systems

“By its nature, the HVAC system serving an aseptic manufacturing suite must be a ‘Direct Impact System,’ e.g., its failure to perform may directly affect final product quality. Therefore, qualification, testing, and commissioning, in line with Good Engineering Practice, needs to be considered carefully. Chapter 12 gives guidance on this subject.”

8. Control and Instrumentation

8.2 – GMP Critical Environmental Parameters

8.2.1 – Environmental Conditions within the Production Area

“The production of sterile products requires a cleanroom environment. Processes and products will vary, however it is likely that all will require specified conditions for the following parameters:

• Temperature
• Percent relative humidity (or moisture content)
• Differential pressure
• Particle count
• Airborne microbiological levels
• Air velocity for Class 100 areas

These are examples of ‘GMP Critical Parameters’…”

8.2.2 – Monitoring and Documenting

“‘GMP Critical Parameters’ should be monitored and documented.

Monitoring means that a parameter is periodically (or continuously) checked to ensure it is within its required limits. This can be accomplished with either permanently installed or portable instruments.

Documented means that the parameter value (or that it is within limits) is recorded at some predefined frequency for future reference. The frequency should be based upon a rationale that should reflect:

• the consequences of manufacturing outside required (process) limits
• the probability of temporary parameter control loss
• the probability that parameter control loss will depend largely upon the control mechanism’s degree of dynamics and/or complexity (e.g., is it Actively or Passively controlled)...

For Room Temperature, Room percent RH, and Room Differential Pressure ‘Continuous recording’ is recommended.

Particle count is controlled passively, through such means as filters, low leakage ductwork, personnel control, air change rates. Continuous recording may not be necessary…”
8.2.3 – Alerts & Alarms

“‘GMP Critical Parameters’ are required to remain within Process Limits. Where continuous monitoring or documenting is necessary, the C&I system should provide:

• an Alert to indicate that the parameter has deviated from the normal operating range (e.g., outside the Normal Operating Conditions - a possible control problem)
• an Alarm to indicate that the parameter has deviated from Process Limits (e.g., a product quality issue)

It is recommended that alarms be latched (e.g., the alarm remains active even after the condition has been corrected) until acknowledged by a user, or operator.

Where momentary parameter deviation outside Alert Limits is acceptable to QA, appropriate ‘delay-on’ intervals could be incorporated into the alarm logic.”

8.2.4 – Process Limits, Design Limits and Normal Operating Conditions

“Process Limits are the upper and lower limits demanded by the production process(es). The Design Limits are used to calculate HVAC plant capacity, and are based upon a number of factors, such as:

• Operator comfort
• Energy conservation
• Regulatory requirements
• Process limits
• What is possible

Normal Operating Conditions usually are within Design Limits and become apparent during operation; the extremes of these conditions are defined by the Alert Limits.”

8.4 – Instrumentation

8.4.2 – Performance: Accuracy

“For each ‘GMP Critical Parameter’, there usually are Process Limits within which a product must be produced or a process operate. These limits should be defined in pharmacopoeias, product registration documents, company standards, or process validation documents.”

8.4.3 – Location

“ Instruments measuring a manufactured product or excipient ‘GMP Critical Parameter’ should be located at a point representative of the product or excipient.

Instruments measuring a manufacturing process ‘GMP Critical Parameter’ should be located at points in the process that represent its worst case conditions.

Instruments used to control and monitor ‘GMP Critical Parameters’, respectively, (if not the same instrument) should be mounted at the same location.”

8.4.4 – Calibration

“The calibration method and cost should be considered when selecting any instrument. Instrument suppliers should be asked to provide comprehensive calibration guidance for their instruments before one is chosen.”
8.7 – HVAC

8.7.1 – Controls System Choice

“When specifying systems to control HVAC, the following should be considered:

HVAC’s industrial nature in cleanroom applications may not justify use of PLC- or DCS-based solutions. Pharmaceutical HVAC can be controlled satisfactorily using HVAC industry control systems. Other factors that may support use of PLC- or DCS-based systems; however, these are unlikely to offer baseline solutions.”

8.7.2 – HVAC Control Systems

“…As the application’s scale, complexity, and remote monitoring demands increase, the use of BMSs rapidly becomes more cost-effective.”

8.7.3 – Particle Counting

“Particle monitoring systems may be used to measure non-viable particle concentration near-continuously, at multiple points throughout a cleanroom or cleanroom complex. However such particle monitoring within a cleanroom does not eliminate the need for periodic room scans with a portable instrument,…”

12. Commissioning and Qualification

12.1 – Introduction

12.1.2 – Definitions

12.1.2.1 Examples:

a) HVAC system serving the aseptic area:

• Whole system is a ‘Direct Impact System’
• Terminal HEPAs are ‘Critical Devices’
• Differential pressure and room air change rate are examples of ‘GMP Critical Parameters’
• Whole system is qualified as part of Facility Qualification
• Final performance testing (e.g., maintaining differential pressure within limits during simulated operation), is part of Process/Equipment Qualification, etc.

b) Environmental monitoring/documenting system:

• Whole system is a ‘Direct Impact System’
• Differential pressure sensors are typical ‘Critical Instruments’
• Parameters measured are normally ‘GMP Critical Parameters’
• Whole system is qualified as part of Facility Qualification
• Final performance testing (e.g., the accuracy of the system in documenting ‘GMP Critical Parameters’ during simulated operation, etc.), is part of Process/Equipment Qualification…”
12.2 – Qualification of HVAC Systems

“By its nature the HVAC system that serves an aseptic manufacturing suite must be a ‘Direct Impact System’, (e.g., its failure to perform may affect final product quality). However, the HVAC system relies on ‘Indirect Impact Systems’ to achieve its optimum performance, for example, chilled water, electricity distribution, etc. Therefore, when qualifying an HVAC system, boundaries must be established where enhanced documentation will be applied.

Within ‘Direct Impact Systems’, ‘Critical Devices’ should be identified. In a conventional HVAC system supplying an aseptic area, the ‘Critical Devices’ typically would be:

- Terminal HEPA filters
- Unidirectional air flow units

Monitoring of environmental ‘GMP Critical Parameters’ indicates if the system, as a whole, is performing. For example, the main supply fan may fail for any number of reasons, but it is the loss of differential pressure, temperature and humidity changes that alert the production supervisors to the problem. Therefore, it is the monitoring system that is ‘critical’.

There also is some overlap with the Process/Equipment Qualification, and proving of HVAC environmental performance. In the case of sterile production the performance of the HVAC system is central to being able to produce aseptic conditions and hence is part of Process/Equipment Qualification.”

12.2.1 – Facility Qualification Tests

“The following are examples of qualification tests on a ‘Direct Impact’ HVAC. They are intended to ensure that the system as a whole performs within acceptable and designed limits, to maintain the desired environmental ‘GMP Critical Parameters’:

- Air change rates (clean and simulated dirty filter conditions)
- Differential pressure cascades (clean and simulated dirty filter conditions)
- Air flow paths, in the ‘at rest’ state (room to room, and critical zones)
- Area classification as FS 209E (in the ‘at rest’ state…)
- Temperature and humidity ranges (under varying internal and external load conditions)
- Integrity testing (terminal/unidirectional HEPA filters)
- Accuracy of ‘GMP Critical Parameter’ monitoring, recording equipment to reflect parameters within the suite
- Unidirectional air flow velocities over critical areas…”