MANUFACTURING & QUALITY AUDIT DIVISION
CENTRE FOR DRUG ADMINISTRATION

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GUIDANCE NOTES ON

HEATING, VENTILATING AND AIR CONDITIONING (HVAC) SYSTEM FOR MANUFACTURING PREMISES

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GUIDANCE NOTES

Subject: HEATING, VENTILATING AND AIR CONDITIONING (HVAC) SYSTEM FOR MANUFACTURING PREMISES

1 Introduction

The quality of air and its flow in a facility are crucial to containment and protection of the product. Air in a manufacturing facility is handled by the heating, ventilating and air-conditioning (HVAC) system, sometimes referred to simply as the air-handling unit. Production operations are generally conducted in controlled environments or Clean Rooms. The HVAC system contributes a large part to the maintenance of these controlled environments.

This document is intended as a guide for the design and construction of HVAC system. This guidance note serves as a document facilitating effective communication between the user and the engineering service provider. The qualification of the HVAC system is outside the scope of this document.

1. Basis of Design

The basis of design of a HVAC system must be developed by the engineering staff in a joint effort with other users of the manufacturing facility. The design must take into consideration room temperature and humidity, room classifications, and the operations within the facility. Heat recovery from exhaust systems or thermal storage are examples of other potential areas for study. Any unusual or unique facility requirements, such as emergency backup or redundancy for HVAC systems, must also be designed into the HVAC system. Airlocks are used to isolate the contained areas and those with critical cleanliness from other zones.

1.1 User requirements

At the onset of a project, the user must provide sufficient information to the engineering service provider to enable the development and assessment of specific options. User requirements should focus on what is needed. Operation considerations such as plant operating schedule, planned staffing, potential or allowable impact on existing operations should be communicated.

1.2 Temperature and Humidity

Generally areas are maintained at suitable temperature and humidity to keep people comfortable, to prevent corrosion, to control microbial growth and to reduce the possibility of static electricity. Internal heat

gains from lights, people and equipment must be calculated, along with transmission gains from adjacent spaces, to ensure sufficient air-flow so that the required temperature conditions are met.

It is necessary to establish these criteria early in the design process, to allow the engineer to select suitable equipment. The lower the required temperatures and humidities, the more sophisticated the HVAC equipment becomes.

1.3 Adjacency of Spaces

It is desirable to keep similarly classified areas physically close together, so that they can be connected to the same air-handling unit. thereby minimising duct runs and air system complexity. Adequate spaces must also be allocated so that people can move between them. In general, air-flow should be from 'clean' to 'dirty' areas. Where major demarcations of pressure are required, air locks are used. Air-locks are small rooms with controlled air-flows acting as barriers between spaces.

Ultimately, as the layout develops, suites or groups of spaces are established and grouping of rooms can be made for assignment to separate air-handling systems. It is undesirable to mix dirty and clean systems, or suites which may be a source of contamination to each other.

1.4 Classification of rooms

During the initial stages of design, each room must be assigned a cleanliness classification, according to its function. The classification adopted by Pharmaceutical Inspection Convention/Co-operation Scheme (PIC/S) Guide to Good Manufacturing Practice (GMP) for Medicinal products is reproduced below:

Grade A: The local zone for high risk operations, e.g. filling zone, stopper bowls, open ampoules and vials, making aseptic connections. Normally such conditions are provided by a laminar air flow work station. Laminar air flow systems should provide an homogeneous air speed of 0.45 m/s +/- 20% (guidance value) at the working position.

Grade B: In case of aseptic preparation and filling the background environment for Grade A zone.

Grade C and D: Clean areas for carrying out less critical stages in the manufacture of sterile products.

The airborne particulate classification for these grades is given in the following table.

	At rest[b]		In operation	
Grade	Maximum permitted number of particles/m^3 equal to or above			
	0,5μm	5μm	0,5μm	5μ
A	3 500	0	3 500	0
B[a]	3 500	0	350 000	2 000
C[a]	350 000	2 000	3 500 000	20 000
D[a]	3 500 000	20 000	not defined[c]	Not defined[c]

Notes:

(a) In order to reach the B, C and D air grades, the number of air changes should be related to the size of the room and the equipment and personnel present in the room. The air system should be provided with appropriate filters such as HEPA for grades A, B and C.

(b) The guidance given for the maximum permitted number of particles in the "at rest" condition corresponds approximately to the US Federal Standard 209 E and the ISO classifications as follows: grades A and B correspond with class 100, M 3.5, ISO 5; grade C with class 10 000, M 5.5, ISO 7 and grade D with class 100 000, M 6.5, ISO 8.

(c) The requirement and limit for this area will depend on the nature of the operations carried out.

2. Pressurisation

Rooms should be made as air-tight as possible, so that the air-handling system can build pressure or reduce pressure in particular rooms. Although

air pressure differentials diminishes when doors are opened, the air must still continue to flow from the higher to the lower pressure space. A pressure differential of 10 to 15 Pascals (Pa) should be set during design. The pressure difference exerts a force on the door which can be calculated. In order to obtain a pressure difference of 12 Pa, a velocity of approximately 2.8m/s must be maintained through all openings or leaks in the room. If the openings are large, higher air velocities will be required. A warning system should be provided to indicate failure in air supply.

Where differential pressures are required between adjacent areas, suitable monitoring equipment (i.e. manometers) must be installed. The pressure differences should be recorded regularly or otherwise documented.

2.1 Room seals and Doors

Rooms are made tight by sealing any openings with a proper sealant that does not promote growth of organisms and are easily cleanable. Areas to be sealed include ceiling tiles, lighting fixtures, pipe and telephone outlet penetrations, and any cracks or openings that appear in the structure.

2.2 HVAC Components for Pressurisation

All supply, exhaust, in-filtration, ex-filtration and air that is returned to the system must be accounted for when the pressurisation for a room is calculated. Air-flows in rooms and systems must be balanced. Balance is a term for the procedure which is used to ensure that all air-flow quantities add up; for a complex project, balancing is by no means a simple task.

3. Air-Handling Systems

Air handling systems commonly used include constant- and variable-volume types, with or without reheat coils for control. Combinations of system may be used.

For controlled spaces, the most reliable system is a constant-volume system with terminal re-heat (CVRH). The advantages of re-heat systems are the

controlled humidity and constant air-flow, which makes balancing and pressurisation easy to achieve in most cases.

A variable air-volume system (VAV) is generally used in administrative areas and some storage spaces, if pressure control is not critical, humidity control is not essential and where some variations in room temperatures can be accepted.

3.1 Dehumidifiers

Low relative humidities are required in many cases, such as drying or powder areas, where hygroscopic materials are handled. In order to obtain sufficiently low humidity, a chemical dehumidifier may be required.

Depending on the amount of dehumidification required and the amount of outdoor air (usually with a high moisture content), it may be best to combine the dehumidifier with a conventional air-handling unit and dehumidify only a small portion of the air. Knowledgeable vendors should be consulted to select the best combination of equipment and to specify a proper system for the application.

3.2 Selection and Location of the Air-Handling Unit

Conventional air-handling units consist of filters, coils and fans in a metal casing, with an insulating liner inside the casing. The casing must be a sandwich of metal, with insulation between metal sheets and a smooth, cleanable interior surface that does not foster growth of micro-organisms. The casings should be tightly sealed and designed for pressure higher that those used in commercial applications, due to generally high system air pressures. All sealants and lubricants exposed to the air stream should be food-grade, to minimise the chance of air contamination.

Air-flow measuring devices and dehumidifiers must also be installed and the location of a unit should allow enough straight run of ducts for installation and proper operation of these devices. Location of inlet louvers for outdoor air must be carefully considered. Intakes are generally located high on the side of the building to keep dust intake low. The direction of the prevailing winds should be taken into account

when an inlet is positioned; any nearby (upwind) exhausts or fume concentrations should be avoided.

3.3 Return and Exhaust Fans

Return and exhaust fans are integral parts of the air-handling systems which should be shown on air-flow diagrams. Return fans are used on systems that have long duct returns. Their use allows proper and total system balance and minimises the suction pressure required from the supply fan. Return fans are also needed to provide a negative pressure in some contained rooms. For example, solid manufacturing areas are usually maintained at a negative pressure in relation to adjacent rooms and corridors in order to minimise the possibility of dust migration to these other areas.

3.4 System Operating Procedure

As with all systems, operating requirements should be defined and monitored at appropriate frequency to ensure compliance. This is usually a written document stating how systems are turned on or off, along with a description of the frequency of operation. Time required for operating the air system for purging before the start of production or use of the space shall be determined and documented. In some cases it is necessary to operate a system continuously to ensure that pressurisation or containment is always maintained.

An analysis of system operation must also assess how a shutdown or flow reduction in the system affects an adjacent system or areas. This entire step of establishing operating procedures should ask as many "what if?" questions as possible. System operation should assure that the HVAC systems can maintain cleanliness and containment requirements. These conditions must be maintained while operations are as close to normal as possible, in addition to those periods of unexpected scenarios.

4. HVAC System Components

4.1 HEPA and High-Efficiency Filters

HEPA is an acronym that stands for high-efficiency particulate air filter. It is used in the final stages of air cleaning, to remove very fine particles. A HEPA filter, by definition, removes 99.97% of particles of 0.3 μm size.

HEPA filters are usually located downstream of heating and cooling coils in air-handling systems. They are used in Class 100 work stations, in single or double filtration of air, to provide sufficient cleaning before the distribution of laminar air to the work space. Attention should be paid to the seal between the filter element and its frame, which is a major source of leaks and failures in the system.

4.2 Air Terminal Outlets

In clean spaces, the desired distribution of air is unidirectional; the air acts as a piston, with little turbulence and few eddy currents in the air flow. This piston of air carries particulate to the floor and to the return, and helps to prevent airborne particulate matter from re-circulating and contaminating the work space. In most cases it is desirable to re-circulate air within a space through a filter since the return air has a lower level of particulate than does outdoor air and does not require extensive heating or cooling. Air terminals should be selected of materials that are non-flaking, non-oxidising and easily cleaned.

Outlets are generally located above work areas while return terminals are generally located low in the walls.

4.3 Duct Materials, Pressure and Cleanability

Stainless steel should be used for ducts downstream of the filters since galvanised ducts can flake off or rust and contamination from the duct system itself could result. Many systems are also fumigated or cleaned in place, so the duct material chosen should not be affected by the cleaning agent.

Ductwork systems in clean rooms tend to have higher system pressure requirements than commercial systems. The duct system pressures must be calculated and clearly stated on the contract documents to allow the fabricator to provide metal thickness and construction methods for the required system pressures.

A duct system that might get dirty or contaminated must be cleanable. The design should include carefully located access doors in the duct for future cleaning. Access panels and doors must be in easily serviceable areas, preferably outside the clean space. Ducts should be minimised in clean areas.

4.4 Considerations of Insulation and Sound

Duct insulation should be externally applied since the fibres used in the insulating material offer breeding grounds for microbial growth that are not cleanable and may break loose to become particulate contaminants. Any ducts in areas where the air around the duct might be humid or above the dew point temperature of the duct surface should be insulated to preclude the possibility of sweating.

Sound becomes a consideration in all air-handling systems. Every component of the HVAC system should be evaluated for its noise generating potential. A sound analysis should be made. When noise reduction is required, the use of sound attenuators in the ductwork is not recommended. Since commercial attenuators use porous material exposed to the air stream, they are not acceptable. System attenuation may be obtained by locating air-handling equipment away from occupied space and using natural attenuation from duct runs and elbows.

5. Redundancy Requirement

Total redundancy provides a dedicated piece of standby equipment that is of the same type and capacity of the piece of equipment it must replace in the case of failure.

Shared redundancy provides a dedicated piece of standby equipment that serves more than one purpose. The standby unit normally has the capacity to replace the largest piece of equipment it serves. However, if more than one piece of equipment fails, service to certain areas is lost.

Partial redundancy provides a system where services to areas are manifolded together and served by more than one prime mover, but no extra equipment is

provided. When a prime mover fails, all areas served share the loss in equal proportions providing partial service.

5.1 Redundancy Applications

Each project is unique and redundancy requirements must be evaluated. The company, with advice from engineering staff and various staff members, must determine the degree of safety required and the impacts on facility operation for each project.

6. Testing, Balancing and Cleaning

Air balancing consists of setting terminal devices and air-handling units to deliver the proper quantities of air. Also the additional requirement of establishing pressure differences between adjacent spaces must be set. As part of the balancing, it may be discovered that duct systems or rooms are not as tight as designed and require sealing to obtain the required pressure differences.

Before the system is turned over to the owner, the rooms and ductwork system must be thoroughly cleaned. During the construction, the work areas should be broom-cleaned after each day's work and open duct systems kept closed. These procedures, if followed during construction, result in an easier final cleanup before turnover.

7. Commissioning

Confirmation that all parts of the HVAC system have been provided and installed correctly is the starting point. The company verifies the actual system operation against design values and intent. Air-flow measurements are made at supply and exhaust outlets to verify proper flows. Filters are physically tested or challenged to find leaks in the filter media or at spaces between elements. Samples of air are also taken by the company to assure that the specified cleanliness requirement in maintained by the installed operating air system.

Also important at this stage is the calibration of air flow monitors, which should be installed in systems that supply critical areas, to assure that air flow rates

are as designed. Temperature and humidity sensors at critical areas should also be checked for accuracy.

8. Summary

The HVAC system is an essential element in the successful operation of a facility and must be given proper attention during the planning and design stages. It is essential that the owner and the relevant manufacturing personnel work closely with the architect/engineer design team to establish the philosophy of the HVAC system as well as the proposed operation of the system.

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