Heating, Ventilation and Air-conditioning Systems

1. Do manufacturers need an HVAC system in their manufacturing facilities?

Good Manufacturing Practice requires that there should be effective ventilation, with appropriate filtration, to ensure that there is no risk of contamination or cross-contamination. In the absence of an HVAC system, effective (meeting an objective) ventilation (supply and removal of air), with appropriate filtration (meaning that filters must be installed), is impossible. The design of an HVAC system will be influenced by various factors, including the external environment (contaminants), product range being manufactured, re-circulation of air (or not), area classification, processing steps and equipment design and others. Pharmaceutical manufacturers thus need an appropriately designed HVAC system to help them supply appropriate quality air to areas, and to remove contaminants and contaminated air to ensure that there is no risk of contamination and cross-contamination.

2. Can manufacturers of oral solid dosage (OSD) forms re-circulate the air in manufacturing facilities?

Re-circulation of air in OSD manufacturing facilities is allowed, provided that there is no risk of contamination or cross contamination. An appropriate level of filtration is required to ensure that particles generated in one area are not transported into another area, for example, through ducting or from area to area, which may result in cross-contamination. WHO GMP guidelines (WHO Technical Report Series No. 961, 2011, Annex 5) stipulate that at least H13 filters (together with other types of filters before the H13 filter) are needed if air is re-circulated.

3. What is allowed as a percentage of air re-circulated?

The percentage of re-circulated air that is allowed is dependent on national occupational and safety legislation. A certain amount of fresh air has to be supplied to production and control areas and this is normally in the range of 10–20%.

4. Do manufacturers have to have more than one air handling unit (AHU) in manufacturing facilities?

Manufacturers can design their HVAC system depending on need; and using a risk-based approach. One or several AHUs can be installed in a manufacturing suite or site. The design of the AHU should ensure that appropriate components are selected and installed to ensure effective ventilation that will prevent contamination and cross contamination, as well as appropriate environmental conditions (e.g. temperature and relative humidity).

5. What are the general parameters that should be considered in area classification, monitoring and qualification?

Normally, in a multiproduct facility, parameters that should be considered include (but may not be limited to) particle monitoring (non-viable and where appropriate, viable), temperature, relative humidity, air flow direction, installed filter leakage testing, air flow velocity, air volume, and air exchange rate.

6. Which guidelines can be followed for performing different tests such as particle counts, temperature study and air flow direction tests?

ISO14644 is the international standard for cleanrooms and other controlled environments. It provides tests and procedures for all these tests. It is recommended that manufacturers follow the procedures in this guideline.

7. What is the frequency at which these tests have to be performed?

After the initial qualification is completed, manufacturers should determine the frequency of performing these tests based on risk assessment. Some of the factors that may be considered in the risk assessment include (but are not limited to) the type of product, amount of dust generated, type of process, processing step/stage, type and design of equipment, maintenance, and cleaning.

8. Do manufacturers have to do a recovery test for areas classified as ISO 8 (Class D or Class 100 000)?

Recovery rate (also referred to as clean-up rate) can be determined for different area classes. The test can give a good indication of the time it takes to clean a room after it has been contaminated with particles. The test is often performed as part of the initial qualification of a system or area. ISO 14644 does not recommend this test for ISO 8 areas.

9. Do manufacturers have to have a building management system (BMS)? Does the BMS have to be validated?

A BMS, otherwise known as building automation system (BAS), is a computer-based system installed in buildings that controls and monitors the building' mechanical and electrical equipment such as ventilation, lighting, power systems, fire systems and security systems. It is recommended that such a system be used, where appropriate, to ensure continuous monitoring of the performance of the HVAC system. After an initial qualification of a BMS, the BMS should be periodically re-qualified using a risk based approach..

10. Are manufacturers allowed to use mobile dehumidifiers?

Mobile dehumidifiers are generally not recommended. These require additional controls to ensure that they do not become sources of contamination and cross-contamination. It is recommended that appropriately designed and installed dehumidification systems be considered in the initial design of the facility and HVAC system.

11. Are manufacturers allowed to use mobile dust collectors?

Mobile dust collectors are generally not recommended. These require additional controls to ensure that they do not become sources of contamination and cross-contamination. It is recommended that appropriately designed and installed dust-collecting systems be considered in the initial design of the facility and HVAC system

12. What is meant by start-up and shut down sequence?

Pressure cascades and appropriate air flow directions play an important role in containment. Therefore, pressure cascades and air flow direction should be maintained as designed. In cases where AHUs are turned off (e.g. when cleaning or maintenance takes place), a pre-determined sequence of shutting down AHUs should be followed to ensure that there is no risk of contamination or cross contamination due to migration of dust from dirty to clean areas. (The principle also applies when staring AHUs).

13. Are schematic drawings required for AHUs?

Manufacturers should have authorized (signed and dated) schematic drawings of all AHUs. The schematic drawings should reflect all the necessary components and should reflect the currently-installed AHUs, including their distribution to various manufacturing areas.

14. At what frequency do manufacturers have to clean or change filters such as G4, F9 and H13 filters?

Manufacturers should establish the intervals for cleaning, replacement and testing of filters based on risk assessment. Risk assessment should take various factors into consideration, such as suppliers' recommendations, process steps, product range and properties, hours of use, history, maintenance schedule, pressure differentials over filters and outcomes of tests such as installed filter leakage testing.

15. Do manufacturers have to sanitize the AHUs and ducts of the HVAC system?

Manufacturers should ensure that there is no build-up of contaminants including particles such as environmental dust, product dust, microbial and other contaminants in the AHUs and ducts. Dust and moisture accumulating in AHUs, filters and ducts can become areas that support bacterial and mould growth leading to possible contamination of areas. Quality attributes for the HVAC system should be determined and checked at periodic intervals including e.g. ducts, condensate collection trays, filters and filter seals. Cleaning and sanitization may be considered as part of the general approach in the control and preventive maintenance plan of the HVAC system. Cleaning and sanitization should not have a negative impact on the HVAC system and its components including filters.

16. Do manufacturers have to calibrate pressure gauges and other sensors/devices such as temperature probes in HVAC systems?

Manufacturers should identify, based on risk assessment, which sensors / devices need to be included in a calibration schedule. Some sensors / devices are important for ensuring appropriate control / monitoring or operation and performance of a system. These should be included in a calibration schedule. The sensors / devices should be calibrated at a justifiable frequency as determined by the manufacturer. Other sensors / devices may be subjected to Good Engineering Practice and may thus be monitored.

17. Can manufacturers switch AHUs off when there is no production in some areas?

It is generally recommended that AHUs be kept in an operational state at all times (other than the times when they are undergoing maintenance or cleaning) to ensure that the environmental conditions are maintained, areas are clean and meet their classification, and that the pressure cascades and other parameters are within their defined specifications / limits. Manufacturers may turn off selected AHUs only if risk assessment shows that this off will not impact product quality negatively. It is important to note that routine requalification of AHUs should take turning off of AHUs into account, and any precaution required during day-to-day operation of AHUs. Start-up and shut down of AHUs should be carried out in accordance with a standard operating procedure (SOP). (Routine on-off switching of AHUs in sterile product manufacturing facilities is generally not recommended).

18. Can manufacturers specify only upper limits for temperature in the production areas?

Where possible, upper and lower limits should be specified for parameters such as temperature, relative humidity and pressure differentials. Results during normal operation and performance should be monitored and recorded, and fall within these specified limits.

19. Do manufacturers need AHUs for the quality control laboratory, or can they use office type air conditioning systems?

Office type air conditioners are generally not recommended for production and quality control areas. Normally, AHUs of appropriate design should be installed that will ensure that production and quality control and microbiology laboratories have separate air supply, and that there is no risk for contamination or cross-contamination. Quality control laboratories should normally be maintained at appropriate environmental conditions (e.g. temperature and relative humidity); some materials, samples, volumetric glassware and instruments need to be stored and tests performed at specified temperature and/or relative humidity conditions.

20. Do you require continuous or regular monitoring of pressure differentials over primary (e.g. G4), secondary (e.g. F9) and/or HEPA (e.g. H13) filters?

Manufacturers should have systems in place to ensure that the appropriateness of filters is monitored, to prevent problems such as clogging, tears and damage to filters. Monitoring the pressure differential over filters such as secondary and HEPA filters at regular and defined intervals (based on risk assessment that includes historical data) can be helpful, to indicate when filters may be due for cleaning or replacement.

21. Do you require that temperature mapping be carried out for production areas, other than storage areas or warehouses? In temperature mapping, do you expect acquisition of data at 1-, 2-, 5-, 10-, 15- or 20-minute intervals? For how many days will monitoring be required?

Temperature mapping should be undertaken for areas where materials and products (which have specified storage conditions) are stored. A protocol should be prepared, containing procedures, reference to devices to be used, number of points and locations for monitoring, as well as intervals for data acquisition over a defined period of time. The number of points can be calculated based on the area, dividing the area into equal grids based on the square root of the area, and then by determining the number of grids and locations for monitoring based on risk assessment. Data acquisition intervals should be justifiable, using a risk based approach. and should be carried out over a period of 3–5 days. The WHO guideline on temperature mapping of storage areas. (WHO Technical Report Series No. 961, 2011, Annex 9 can usefully be consulted on this topic.) Temperature mapping should be repeated throughout a twelve-month period, to cover all seasons. See also ISO 14644 for temperature tests.

22. How should we do particulate monitoring?

Particulate monitoring should be carried out in accordance with an SOP. The procedure should be based on the test described in ISO 14644. The number of locations is calculated based on the area. The volume of air should be calculated based on the prescribed formula and should be taken over the required minimum time (as appropriate for the specific area and its classification). Information on the preparation for the test, results, calculations (e.g. upper control limit) and test report should be well-documented.

23. What is the maximum allowable time before a H13 filter is replaced?

There is no prescribed timeframe for the replacement of HEPA filters. Manufacturers should define the intervals at which H-type filters are replaced. This may be based on supplier recommendations and other risks identified. Contributing factors may include the overall design of the AHU (with pre-filters), dust loads (as a result of the environment, product type, processing step, type of equipment used such as open or closed systems), pressure differential over the filter, results of installed filter leakage test, preventive maintenance and quality attribute checks. Filter media may also deteriorate over time. The interval defined by a manufacturer should be appropriate and there should be no risk of filter failure (where the filter failure can have a significant negative effect on for example, but not limited to areas, conditions, operations, materials or products) prior to replacement of the filter.