

Auditing Utilities System

Goals

When you have completed this training module, you should be able to:

- Perform an audit of a site utilities system
- Use a range of tools and information, including the contents of this unit and the Internet, in support of auditing a utilities system
- Understand and apply applicable GMP standards to an audit of a utilities system recognize compliance or non-compliance of a utility system to applicable regulations

Definitions

Action Levels: A level or a range that, when exceeded, indicate that a process has drifted from its normal operating range. Exceeding an Action Level indicates that corrective action should be taken to bring the process back into its normal operating range.

Air diffuser: A plate in the ceiling where the air is forced through. A diffuser may direct the air throughout the room.

Air handling unit (AHU): An integrated piece of equipment consisting of fans, heating and cooling coils, air-control dampers, filters and silencers.

Alert Levels: A level or a range that, when exceeded, indicate that a process may have drifted from its normal operating condition. Alert levels constitute a warning and do not necessarily require a corrective action.

Deadlegs: Drops in the piping system where water is not circulating.

Dead spots: Lengths of piping where water stays and does not move.

Endotoxin test: A test designed to determine if there are fever producing substances in the drug product. This substance can be produced by the degradation of gram negative bacteria from their cell walls. Endotoxin is harmful to humans.

High efficiency particulate air (HEPA) filter: Retentive matrix designed to remove a defined percentage of particulate matter of a defined size.

Highly Purified Water (HPW): Water produced from Potable Water by methods including, for example, double-pass reverse osmosis coupled with other suitable techniques such as ultrafiltration or deionisation. HPW (Highly Purified Water) meets the same quality standards as WFI (Water for Injections) but the production methods are considered less reliable than distillation and thus it is considered unacceptable for use as WFI. The specification for HPW is defined in the European Pharmacopoeia (EP) and HPW is a consideration only for certain products supplied to the European Union (EU).

Auditing Utilities System

Filtration

The HVAC system must be constructed to prevent contamination. This can be achieved by installing filters in the system. These filters should be included on a routine preventive maintenance schedule. There should be established procedures for replacing the filters as well as procedures detailing the testing that should take place after the replacement. These filters may vary from ULPA high efficiency filters to dust or bag filters. Each should be monitored. It is important to monitor filter pressure drops as an increased pressure drop may lead to a decreased retention rate for the filter. Appropriate limits should be established.

Air intakes/supplies and returns should be separated and designed to not suck in the return air. Exhausts should vent away from the intakes.

Each fan and motor and its ductwork should be labeled and the direction of the airflow indicated. Each should be independently controlled, not interlocked, so if there is a problem it can be isolated.

Air pressure differentials

In areas where air changes and differential pressure are critical, the system must be monitored and documented. Air pressure must be measured and correct pressure differentials maintained. If the pressure differentials are not maintained, there should be a procedure in place defining what action to take.

Blowers and fans should be on a routine preventive maintenance schedule. Ductwork should be checked at an established interval for leaks. Preventive maintenance must be established based on written specifications.

Filters are one of the main components of an HVAC system, since they determine the size of airborne particles that pass through them, and thus the hygiene class. Depending on the type of room air requirements, different filters will be used. In an area where there are powders, often the exhaust will have a bag filter attached to it to catch the escaping powder.



Potential problems

There can be conditions within the HVAC system that can cause the system to malfunction and increase the risk of contamination. A few of these are listed below.

Auditing Utilities System

Validation of water systems

Water systems should take a full year to validate because seasonal environmental conditions will affect the quality of the feed water coming into the plant. Validation should follow the same criteria and produce equivalent documents as other types of validation.

Water processing and purification

Before water can be used in the pharmaceutical industry, it needs to be processed. Environmental pollutants and microbial contaminants need to be removed. Water used in manufacturing product should start as potable water, meeting WHO and other regulatory agency requirements. This “feed water” may be received from a municipality or supply company or undergo treatment at the plant site. If water is purchased from a supplier, it should be accompanied by analytical reports or Certificates of Analysis.

Once the water is received it may need to be softened or deionized. This removes calcium and magnesium ions, which can cause “scale”, or carbonates to form. Water passes through a mixed resin bed or separate cation and anion exchangers. In this first treatment step, bacteria can grow in the bed or resins. It is important to monitor or regenerate the resins on a frequent basis.

When the water has been deionized, then it is ready to be processed for either purified water or WFI. It may be purified through reverse osmosis, deionisation or distillation. The European Pharmacopoeia requires WFI to be produced through distillation.

If reverse osmosis is used, the water is passed through a membrane, leaving behind undesirable contaminants. Reverse osmosis pushes pure water back through a semi-permeable membrane leaving ions and particles in the reject water. Water is continuously passed over the membrane with the reject water being recycled or sent to drain.

If the water is distilled, the water is heated and then condensed, leaving behind organics and microbial contaminants. “Clean steam” is also generated using a distillation process.

Contamination in water

Water can support microbial growth. Water is susceptible to bacterial contamination for many reasons. Causes of contamination in water can be:

- Stagnant or non-circulating water
- Improperly processed water
- Water circulating at too low a temperature
- Water circulating too slowly
- Dead spots or deadlegs in the system

However, a significant part of good water system design is ensuring that microbial contamination is minimized. Microbial contamination can occur as a result of colonization of surfaces and stagnant areas by aquatic bacteria with the formation of biofilm. If the bacteria can be prevented from sticking to the surfaces, the battle is almost won. Smooth surfaces, high temperatures, moving water and no dead spots, are all good design elements.

Auditing Utilities System

Maintenance

Water systems should be scheduled for routine maintenance. Parts of the system that should be included are:

- Replacement of resins for deionizer/softener
- Inspection and replacement of heat exchanger parts, stills, vent filters, fittings, membranes, valves

Compressed Gases

Compressed gases such as nitrogen (N₂), argon (Ar), and compressed air (CA) may be used in the production of drug product and contact the product. Depending on the use of the gas, qualification may be required. Gases may be

- 1) Manufactured and distributed by the site, 2) purchased from an outside vendor and distributed
- 2) Through a site distribution system, or
- 3) Purchased from an outside vendor and used at point of source (gas cylinders). In all cases the gas must meet specifications.

These specifications are determined based on the use of the gas and the environment in which it is used. If the gas is supplied by an outside vendor a Certificate of Analysis should be required to prove that the gas meets identity and other specifications.

If the gas is to be circulated throughout a plant distribution system, the system should be qualified both at the source and points of use. Qualification should include testing of points of use farthest from the source, identification of the gas, testing for hydrocarbons, and particulate and microbial monitoring. A qualification program should demonstrate that the distribution system for the gas does not adulterate the quality of the gas from the controlled source to the point of contact in manufacture. If the gas will be used within a controlled environment, it should meet both the particulate and microbial requirements of that environment. Qualification samples should be taken when the system is in use by multiple users, at various points of use, “worse case” points of use where the system does **not** have long stretches of straight piping. The system should be checked for leaks.

If the site is manufacturing its own compressed air (CA) and/or nitrogen for use in a controlled environment, it should use an oil-free compressor.

A monitoring program should be based on the criticality of the gas to the product. The monitoring program should provide information on the quality of the gas being monitored, and serve to demonstrate that the distribution system has not deteriorated or degraded the quality of gas being distributed. Monitoring frequency should be based on the variability of the gas supply to demonstrate that the supply at point of use is consistent across a period of time.

Test samples taken for the monitoring program should be taken under identical conditions as used in the process. If production flushes the point of use for 3 minutes, the sample should be taken after a flush of 3 minutes. If a filter is installed at point of use, the sample should be taken from a point of use filter. If maintenance work is performed on the system, test samples should be taken to verify that the system has not been compromised through the work. All routine monitoring should be documented as appropriate.

The system should be placed on a routine maintenance schedule.