

Auditing Utilities System

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Audit Training Manual: 011

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Manometer: A device that measures the difference in pressure between two points.



Passivation: The chemical treatment of stainless steel with a mild oxidant, such as a nitric acid solution, for the purpose of enhancing the spontaneous formation of the protective passive film. This process is designed to remove foreign metals, oxides and corrosion from the surface of stainless steel and corrosion resistant steels which allows water to move through the pipes and improves corrosion resistance.

Piping and installation drawings (P & ID): Mechanical drawing or blueprints of the required piping system for installation of equipment. If authorized changes are made, they are indicated as red lines on the drawing.

Potable Water: Water, that as a minimum, meets national standards for water intended for human consumption that have been documented as at least equivalent to World Health Organization (WHO) guidelines, the national standards for the USA, Europe and Japan meet or exceed the WHO guidelines. Potable Water is also known as Drinking Water.

Purified Water: Water produced by a suitable method (e.g., deionization, reverse osmosis, distillation, etc.) from potable water to meet specifications as defined by a compendial monograph.

Pyrogen: A substance that can produce a fever in an animal system.

Ultra low particulate air filter (ULPA): A filter rated at 99.99% efficient in removal of particles to 0.12 microns. Each filter must be labeled with the model number, serial number, efficiency and resistance at tested airflow.

Water for Injection: Water produced by a suitable method (e.g., distillation) from potable water, usually with an intermediate purification step(s), to meet specifications as defined by a compendial monograph.

Explanation of Topic

Introduction

To produce either a finished pharmaceutical, an API, an excipient, a medical device or packaging materials the environment within the plant has to be considered. One of the least noticed but important parts of producing a product free of contamination is the plant utility system. The system includes the heating, ventilation and air conditioning system (HVAC), the water system, the compressed gas system and the steam system, if used in the plant. Each of these systems must be qualified/validated.

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General Characteristics of a Good HVAC System

A well-designed air handling system should start with a good design, be installed properly, qualified, and maintained. At a minimum, it should have sealed ducts to prevent unfiltered air from entering the system, and tight filters for the same reason.

Different areas with different air cleanliness requirements should have separate air handling systems. The level of filtration should be appropriate for the level of air cleanliness that is to be achieved. The percentage of recirculation air to make up air will vary depending on the level of cleanliness desired. Risks for cross contamination should also be considered. No recirculation of air minimizes the risk for cross contamination and should be used, when handling some types of substances or products.

Air filtration, dust collection, and exhaust systems should be used in production areas where the product may be exposed and according to regulatory requirements. The filter should be located in the system where it will do the most good. Intake and air returns should not be located next to each other. Dust extractors and bag filters should be located up stream of the final filters. Temperature and humidity requirements should be established to keep the product free from contamination. Depending on the product and the environment to be achieved, air changes should be consistent with industry standard with more air changes for cleaner environments. (See *ISO 14644, Cleanrooms and associated controlled environments – Part 1: Classification of air cleanliness* for cleanroom standards.)

Pressure differences between cleanrooms and areas of different cleanliness are means of maintaining the environment and the principle is to have higher pressure in cleaner areas. To minimize the risk for cross contamination, which is important in dust generating activities such as for example in tablet manufacturing and when containment is desirable the principle will be to have the highest pressure in the corridor or in the air locks and a lower pressure in the cleanroom to ensure the air is not spread to the environment.

Pressure differentials should be maintained according to design criteria and tested and/or monitored on a frequent basis. An approved procedure and back up power supply should be in place for responding to HVAC failures or loss of power. Duct work should run in long straight sections which allow the air to flow freely. The ducts should be designed so that they can be easily and effectively cleaned. An alarm system should be in place to notify the site if there are unexpected drops in pressure. Depending on the environment, there should be an established airflow direction. There should be adequate controls and monitoring devices for air pressure, microorganisms, dust, humidity, and temperature in finishing areas. Air handling units for dry processing areas (i.e. drying, milling and packaging areas) should be independent.

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Item	Problem	Resulting in
Flow rate controller	Blocked	No control of pressure differentials
Control damper	Poorly adjusted	Bad pressure differential systems
Humidifier	Bad water/steam quality	Risks of microbial contamination
Cooling Unit	No elimination of condensed water	Risks of microbial contamination
Filters	Incorrect retention rate	Risks of contamination (particles, micro-organisms) Filter integrity fails
	Damaged Badly installed	Risks of contamination (particles, micro-organisms)
Ducts	Inappropriate material	Danger of corrosion
	Leaking duct work	Intake of unfiltered air
	Internal insulation	Inability to properly clean

Maintenance

The air system should be on a preventive maintenance (PM) schedule. If HEPA or ULPA filters are replaced, they should be substituted on a "like for like" basis. Testing for both filter integrity (leak testing) and efficiency (filter flow rating) should be performed once the filters are replaced as well as on a regular basis.

The cooling unit or condenser should be placed on a PM schedule. Stagnant water (condensed water) can breed bacteria, which contaminates the filters by passing through them (depending on their retention properties) and contaminating production areas. If the air is not properly desiccated (dried) it can also provide a growth media for mold.

Pressure control can be regulated by automatic air or fixed flow control dampers and/or fan speed control. As filters get dirty, the airflow decreases and pressure differentials change. This could lead to a flow reversal within the area and cross-contamination. Pressure differentials must be defined, monitored, and alarmed in critical cases. The overpressure of each room is measured against a reference point in the factory (point zero). Variable speed drives for fan motors are also commonly used to control airflow.

Objects in the room can significantly disturb the flow of air, and even block it, so that there might be air pockets without air circulation. Machinery or furniture blocking the outgoing air into the room can create unflushed zones, where particle counts and micro-organisms could increase. It is therefore important to consider the content of a clean room, when planning the HVAC system. One of the main points in the design of production rooms is the pressure differentials concept.

During the qualification phase, the airflow is visualized through smoke studies to ensure correct airflow. Air samples are taken at different point to ensure air quality complies with the design. If deviations are found adjustments to the layout or to the air handling systems must be made.

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There should be an SOP for replacing filter units and the testing that should be performed upon replacement. These tests may include, in the case of ULPA and HEPA filters, filter integrity testing, velocity, and leak testing.

Maintenance should have an SOP for the maintenance that needs to be performed on air handling systems. This SOP should include the frequency of maintenance, the activities that should be performed, information on what part should be used, etc.

There should be an SOP that lists the activities that should happen if the HVAC system exceeds its established limits (action limits).

Qualification documents for the air handling system should be complete. Documents that should be reviewed to ensure good GMP operation of an air handling plant should include:

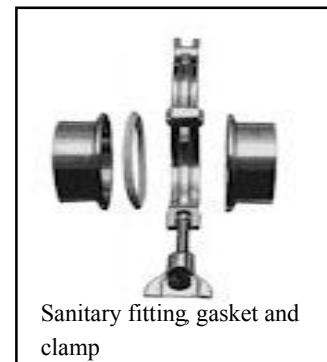
- A complete description of installation (drawings, installed elements, description, etc.).
- Specification of the requirements: What is the system supposed to do? Which values is it supposed to reach?
- Standard Operating Procedures on how to operate the system.
- Performance control with information on how to judge if everything is operating perfectly (fan, filters, etc.).
- Instructions on how to maintain the system.
- Maintenance records showing that the system has been properly maintained.
- Personnel training records.
- Records of environmental testing.

Water Systems

Water is the most widely used starting ingredient or raw material in the manufacture of active pharmaceutical ingredients and medicinal products. Its uses in the production environment range from starting material to cleaning agent to steam source for sterilization processes. Because of this, controlling the chemical and microbiological quality of water and steam is critical. Special care should be taken in the processing, storage, and distribution of water. The higher the risk to the pharmaceutical product, the purer the water should be.

General considerations for water systems

The rationale for appropriate water quality for each process should be documented. The water quality depends on the stage of its use in the manufacturing process, and intended route of administration for the finished product. Water used in production must be routinely sampled and tested according to a predefined and approved plan. This includes the potable water supply. For any water treated to achieve an established quality level, a validated, qualified, and maintained treatment process and distribution system must be used. Water should circulate in a closed loop system, not open to the external environment. Fittings and valves should be of a sanitary type. There should be no threaded pieces where bacteria can enter and multiply. Fittings and valves can be taken apart and sterilized if needed. Water that is held in tanks should either be used within 24 hours of manufacture or circulated.



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Training

All personnel required to maintain, sample, and test the water system should be trained in GMP and the duties of their job function. They should also be trained to respond to alarms in the water system.

Types of Water

The type of water used will depend on the requirements of the product during various stages of production, e.g. purified water for tablets, water for injection (WFI) for sterile products. The way the medicine will be used in the body actually determines which water will be used. Sterile products like injectables need to be produced with the highest quality water (WFI) since these products go directly into the body bypassing the body's defense system.

Water has unique chemical properties, and is able to dissolve, adsorb, absorb or suspend many compounds. These contaminants need to be removed before water can be used as an ingredient.

Four different categories of water are common. They are:

- Potable
- Purified
- Highly purified water
- Water for Injection

Potable water

Potable water is water that, at a minimum, meets national standards for potable water that have been documented as at least equivalent to World Health Organization guidelines. Potable water is usually the starting material for other waters that may be generated at the plant. In this use it may not receive further treatment or purification.

Sampling and Testing

Testing for the full analytical requirements for potable water is usually outside the scope of the typical pharmaceutical laboratory. The recommended practice is to receive Analytical Reports and/or Certificates of Analysis from the municipality/supply company providing the water. If borehole (well) water is the source of water it may be possible to arrange for the local municipality or a contract water-testing laboratory to sample and test the water against the appropriate standard. The local site may choose to perform a limited number of analytical monitoring tests. Appropriate test methods and specifications for potable water requiring higher quality attributes should be established.

Potable water should contain not more than 500 colony-forming units per milliliter (= 500 cfu/ml). If tighter water standards are necessary then total microbial count, objectionable microorganisms and/or endotoxin limits should be established.

Potable water that is used as source water only (i.e., not used in production) may be tested for total aerobic count on a monthly or quarterly basis. This data should be combined with Municipal/supply Company testing data. Potable water that is used in manufacturing (e.g., API intermediates) should have a point of use tested weekly with all points of use being tested within a month.

Materials and construction

Potable water is normally kept in a buffer or break tank to provide a uniform flow and working pressure. If it is necessary to hold larger quantities of potable water then an anti-microbial treatment step is likely to be required. UV lights, ozone treatment, or

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pharmaceutical systems. It must meet the most stringent requirements of all water used in pharmaceutical manufacturing. It should be free from microbial contaminants, and meet a strict level of endotoxin and chemical criteria.

Sampling and Testing

The tests, methodology and specifications for Water for Injection can be found in respective pharmacopeias.

Requirements for total microbial count are not more than 10 cfu/100ml. WFI systems are typically operated hot (70 - 80 C). The isolation of vegative microorganisms should be a rare event. Repeated isolation of any microorganisms would require an investigation to determine the cause with corrective action being taken.

Analytical testing of a WFI system would typically be performed weekly. However, as with Purified Water systems it is now common to install in-line meters to perform TOC and Conductivity measurements.

The WFI system, through one point in the WFI loop should be tested each week. All points of use should be tested weekly. Alternating sampling points in a way that microbiological testing is performed each day is a typical way to sample. Other less frequent sampling programs may be applied but should be based on usage of water, historical data and risk assessment.

The source water should also be tested on a weekly basis. WFI that is used to clean but not used in final rinses should be tested on a monthly basis.

Storage conditions

Water for Injection is held and distributed in stainless steel tanks and distribution systems. It is typically maintained at an elevated temperature (70 -80 C) and cooled at the point of use just prior to use. It should be monitored for Total Organic Carbon and conductivity. These may be monitored through an in-line system connected to an alarm system.

The tanks should also have vent filters on them that should be monitored on a routine basis.

Use of Water for Injection in Manufacturing

WFI is intended as the ingredient water used in sterile product manufacturing. It is used as the final rinse for containers, closures and equipment used in sterile product manufacture. It may also be used as a product diluent.

Steam

Pure, pyrogen-free steam (called Clean Steam) must be used where steam can come into contact with product, or "product contact surfaces", e.g. sterilization-in-place (SIP) equipment. It must:

- Have the same chemical quality as water for injections
- Have no pyrogens or endotoxins
- Have no volatile additives such as amines or hydrazines
- Be produced by stills without condensation
- Have a limit on non-condensable gases

Clean steam should be tested periodically.

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Computer control systems for utilities

Computer systems may be used to control and monitor utility systems. They should be validated.

Summary

The plant utility system must be reliable and properly installed, maintained and qualified or validated to ensure the quality of the product. Computers that may control a utility system should be validated. The plant utility system should be part of the site change control system.

Key Parameters in Auditing a Utilities System

Prior to the Audit

- Determine the relevant utilities to be covered
- Determine if there are any risks of cross contamination needing specific attention
- Request drawings for the site's water systems, steam systems (if applicable), HVAC systems, and compressed gas distribution systems (if applicable).

During the audit

- For *any* utility system, ensure that:
 - All piping or duct work is correctly labeled with the utility name (clean steam, distilled water, compressed air, etc.).
 - Directional arrows are in place to indicate flow.
 - Valves, pressure gauges, sampling points, etc. are identified with unique IDs.
 - Minimum and maximum operating rates are shown.

HVAC

- For a walk through specifically focused on the HVAC system, ensure that:
 - The room air returns are not blocked.
 - The room air supplies are not blocked.
 - The pressure differential gauges and/or manometers are operating properly
 - Cross contamination is minimized by not recirculating air if required, correct pressure differences as designed
- Ensure that each heating, air conditioning and ventilation system has been qualified and operates according to the necessary requirements and specifications.
 - Verify that preventive maintenance is scheduled on a regular basis and that:
 - Pressure differential manometers on AHUs are monitored.
 - Fans and motors are checked on a scheduled basis to determine if they are operating properly.
 - Ducts are checked for leaks from the external environment
 - ULPA filters are monitored through pressure differential measurements and that the system is alarmed if an overlimit is obtained.
- Ensure that critical filters within the HVAC are monitored for drops in pressure.
- Ensure that the following documentation is in place.
 - A complete description of installation (drawings, installed elements, description of the elements, etc.).
 - An SOP that establishes action and alert levels and what actions to take when these are reached.