Clean Steam in the Pharmaceutical Industry

Tim Latham, M.Sc., C.Eng., MIChemE.

COURSE CONTENT

1. What is Clean Steam ?

Clean steam is used in the pharmaceutical and healthcare industries in processes where the steam or its condensate can come into contact with a pharmaceutical or medical product and cause contamination. In such cases, steam from a conventional boiler (often called utility or plant steam) is unsuitable because it may contain boiler additives, rust or other undesirable materials.

The use of clean steam is determined by the rules of Good Manufacturing Practice (GMP). These are general rules applicable to pharmaceutical manufacture, detailed in the Code of Federal Regulations (CFR Title 21, Part 211). They do not provide any specific recommendations regarding steam, but do present the general requirements of facilities, systems, equipment and operation needed to prevent contamination of pharmaceutical products during their manufacture.

2. Uses of Clean Steam

The main use of clean steam in pharmaceutical manufacturing is for the sterilization of products or, more usually, equipment. Steam sterilzation is encountered in the following processes :

- Manufacture of injectable or parenteral solutions, which are always sterile.
- Biopharmaceutical manufacturing, where a sterile environment must be created to grow the biological production organism (bacterium, yeast or animal cell).
- Manufacture of sterile solutions, such as ophthalmic products.

Typically in these processes, clean steam is injected into equipment or piping to create a sterile environment, or into autoclaves where loose

equipment, components (such as vials and ampoules) or products are sterilized.

Clean steam may be used for some other functions where conventional utility steam might cause contamination, such as :

- Humidification in some clean rooms.
- Injection into high purity water for heating prior to Clean-in-Place (CIP) operations.

3. Clean Steam purity

Before discussing the purity required of clean steam, it is first worth discussing the requirements for the purity of water used in pharmaceutical manufacturing. This is because clean steam purity is often defined by the purity of the condensate, and this is often referenced to one of the published water purity standards. Additionally, the parameters by which pharmaceutical water purity is measured (conductivity, total organic carbon, endotoxins and microbial content) are those usually used for defining clean steam purity.

There are statutory requirements regulating the purity of water used in pharmaceutical manufacture, and two grades of high purity water are defined in the US Pharmacopoeia, namely Purified Water (PW) and Water for Injection (WFI). PW must meet a chemical specification for conductivity and total organic carbon (TOC), and a microbial specification. WFI is a higher purity water. It must meet the same chemical specification as PW, but a much higher microbial specification. Additionally, it must meet a specification for endotoxins, and must be produced by a defined method (either distillation or reverse osmosis).

TABLE 1 : USP 24 Specification for Water Purity

	Purified Water	Water for Injection
Conductivity	< 2.1 µ S/cm at 25 ^{0}C	< 2.1 µ S/cm at 25 ^{0}C
Total Organic Carbon (TOC)	<500 ppm	<500 ppm
Microbial (recommended Action Limit)	100 cfu/ml	10 cfu/100 ml
Endotoxin	No requirement	< 0.25 EU/ml
Production Method	Not Specified	Either distillation or reverse osmosis

Microbial content is measured in “colony forming units”, or cfu – this reflects the test method, in which water samples are spread on plates of growth medium and incubated, the number of microbial colonies that develop then being counted under a microscope. The microbial specification for PW and WFI is set for each system by the pharmaceutical manufacturer, but the pharmacopoeia guidelines for PW would be 100 cfu/ml, whereas for WFI it would be 10 cfu/100 ml.

Endotoxins are breakdown products of dead microbes, often lipopolysaccharides from the cell walls of Gram negative bacteria. They are also called pyrogens, which is indicative of the main problem that they cause in patients – pyrexia, or fever. The avoidance of endotoxins is therefore mainly of concern for parenteral pharmaceutical products, which are injected into the patients.

In contrast to water, there is no pharmacopoeia standard for clean steam (or any type of steam for use in pharmaceutical manufacturing). A specification for the purity of such steam must be prepared by each manufacturer, and the specification must be such that they meet the GMP requirement to avoid contamination of the product. In theory, there could be a wide range of different clean steam specifications, applicable to products of different degrees of purity and different stages of manufacture. In practice, the pharmaceutical industry has tended to consolidate around specifications where the steam condensate meets the pharmacopoeia specification for PW or WFI.

Probably the commonest clean steam specification is that the condensate meets WFI requirements for conductivity, TOC and endotoxin (The microbial limit is normally excluded as it is acknowledged that viable micro-organisms cannot survive, indeed are killed, in steam systems). The WFI-based specification is used where an endotoxin limit is required, and this is important for injectables and parenteral products. These are produced as sterile solutions and, since clean steam is primarily used for sterilization, they make-up the majority of manufacturing facilities where clean steam is used.

A specification for clean steam may be based on the PW specification, and will thus be confined to chemical composition (TOC and conductivity). This would be appropriate in facilities producing products, or using processes,

which must be sterile, but where endotoxin in the final product is not a concern. Example might include some biopharmaceutical processes, or the production of sterile ophthalmic solutions. Increasingly, processes of some bulk ingested liquids, such as mouthwashes, is undertaken in steam-sterilized plant.

Finally in this section, it is important to discuss nomenclature. Although “Clean Steam” has been used throughout this course, and is used in the ISPE Baseline Guide, it is not used universally, and can have different meaning to different people. Terms such as “Pure Steam”, “Pyrogen-free Steam” and “Low Endotoxin Steam” are encountered in the pharmaceutical industry, and may have specifications that are the same or different to those of Clean Steam used on other sites. The important point is that each site or facility must have its own written specification for a grade of steam used in its processes, and that that specification is appropriate to the manufacturing process in which it is used.

In March 2000 the Water & Parenterals Subcommittee of the United States Pharmacopeia established definitions for “Pure Steam” and “Pure Steam for Injection” and recommended inclusion of these definitions in the "Water for Pharmaceutical Purposes" section of the USP. At the time of writing this course, that recommendation had not yet been enacted.

You may also encounter the term “Clean Steam” used for some types of utility steam – for example, it may be used for a type of steam used in food manufacture, where the boiler additives used are approved by the FDA for food processing.

Where nomenclature becomes confusing, concentrate on the purity specification, and from that develop the type of feedwater, generator and distribution system needed to meet that requirement.

4. Fundamentals of Clean Steam system design

Before describing the details of generator and distribution design, it is worth reviewing some of the fundamental principles upon which their design is based.

Avoidance of corrosion

Unlike utility steam, clean steam has no corrosion inhibitors. Also, low conductivity water or condensate is hungry for ions, causing it to be

corrosive to many materials commonly used in utility steam systems. Carbon steel, gunmetal and bronze, all commonly found in utility steam components, would all be rapidly corroded. Metal components for clean steam systems are therefore usually AISI 316L stainless steel, or sometimes titanium. Non-metallic materials used include EPDM and PTFE.

The need to avoid corrosion is not only necessary for safeguarding the integrity of equipment. Corrosion products entering the clean steam could potentially cause contamination of the pharmaceutical product, either as chemical or particulate contamination.

Even where 316l stainless steel is used, a particular form of corrosion, called “rouging”, is often encountered in clean steam systems. The passive layer on the steel surface is disrupted and a red/brown/black film develops over time. Often this film is stable and does not pose a threat to the pharmaceutical product. Sometimes a powdery film develops and this can detach from the steel surface and cause discoloration of equipment which the steam contacts. If this occurs, and the manufacturer feels that there is a risk of contamination or discoloration of the product, then the clean steam generator or even the full distribution system may be cleaned (“derouging”). A variety of of methods are used, but they all involve a chemical treatment to remove the surface layer of steel – this is essentially an etching process. After derouging, a passivation process must be used to restore the passive layer on the steel surface, since it is the passive layer that is responsible for corrosion resistance.

Preventing entry of contaminants into the system

Clean steam must be free of contaminants at the point of use. Chemical and microbial contaminants can enter steam systems in a variety of ways, and in the design of clean steam systems this must be avoided. Pathways for contamination include leakage, air being piulled into the system and “grow through” from a contaminated external environment.

Preventing microbial growth in the system

Steam at typical operating pressures will kill bacteria and their spores, so the parts of a clean steam system that are continuously exposed to steam will be sterile. However, if condensate is allowed to collect in the system, and it cools, then stagnant water can provide a suitable environment for bacterial growth. Though these bacteria may be killed when the condensate is discharged into equipment, followed by steam, their breakdown products,

including endotoxins, may still be present. Endotoxins are not destroyed by typical clean steam system temperatures.

5. Clean Steam generation

Generation of clean steam relies on the evaporation of good quality feedwater. Contaminants remain in the concentrated feedwater within the generator, and are periodically removed by "blowdown". Clean steam generators are designed to prevent droplets (which may contain contaminants) being carried forward with the clean steam. Fig. 1 shows an example of one type of clean steam generator.

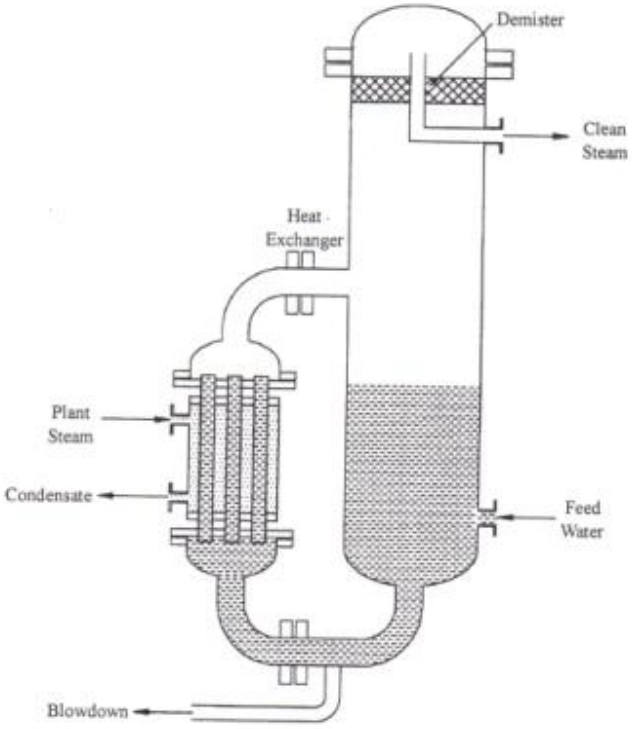

FIGURE 1 : Clean Steam Generator (Thermosyphon)

Feedwater

Feedwater must be pumped into the generator, typically at 10 psig above the operating pressure. The flow is usually controlled by level.

For pharmaceutical manufacturing, it is a regulatory requirement that feedwater must be derived from water that is drinking quality. It is treated to remove the bulk of dissolved solids and any hardness and silica, which could

cause scaling of the generator. A typical manufacturer's specification for feedwater is defined in Table 2.

TABLE 2 : Typical generator manufacturer's requirement for feedwater

Source :	Drinking Water
Treatment :	Deionisation or Reverse Osmosis
Amines, chlorine and chlorides	Free of amines, chlorine and chlorides
Silica	< 1ppm
Total hardness	< 1ppm
Conductivity	< 5 µ S/cm

Amines must be removed because they are volatile and could be carried forward with the steam.

Chlorine must also be removed because it could cause corrosion of a stainless steel generator. Chlorine is present in water as a biocide, to control the level of micro-organisms, and its removal may allow microbial levels to increase. Feedwater treatment must therefore include some other, non-chemical, means of controlling micro-organisms, and often the final treatment is a membrane process such as reverse osmosis (RO). The acceptable microbial level in the feedwater is debatable, but clearly gross contamination could overwhelm the generator. In practice, a microbial content of less than 500 cfu/ml (the recommended maximum limit for drinking water) should allow a generator to produce clean steam with condensate meeting the WFI specification for endotoxin. The ISPE Baseline Guide states that a typical generator can make a 3 to 4 $\log_{10}$ reduction in endotoxin from the feedwater level.

It is probably the case that most clean steam generators used in pharmaceutical facilities are fed with Purified Water. This is a matter of convenience rather than necessity. PW is much higher purity, both in chemical and microbial terms, than is required. However, most facilities using clean steam also need a PW system, the water and steam plant is often located in the same utility room and the capacity and daily usage of steam generators is usually much lower than that of the PW system. In some plants with large steam usage, or which only use WFI, there may be an economic case for providing a separate feedwater system of lower purity than PW, and often RO water is used in those situations.

Heating

Most clean steam generators use utility steam for heating, though for low capacity systems electric heating may be used.

The utility steam must be at higher pressure than the required clean steam pressure, in order to provide the temperature differential for heat transfer. Typically utility steam will be at least 30 psi higher for economic reasons.

The generator design must prevent contamination from the utility steam, which might occur by leakage at the tubesheet. Usually a double tubesheet exchanger is provided (see Fig. 2).

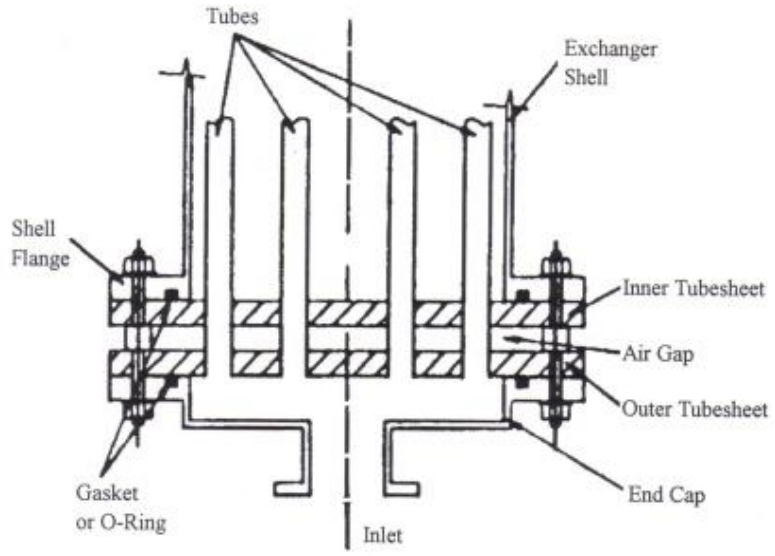

FIGURE 2 : Double tubesheet exchanger construction

Generation Pressure

Clean steam pressure is usually defined by the requirements of autoclaves. Sterilisation in pharmaceutical manufacturing is usually carried out at 121 ^{0}C (equivalent to 15 psig for saturated steam). Typically autoclaves have their own pressure control valve at the steam inlet, and this has a pressure drop. Therefore autoclave manufacturers typically demand a supply pressure of 40 psig or thereabouts.

Lower pressure steam is used for sterilization-in-place (SIP) of vessels, equipment and pipelines, where there is often no pressure control and achieving sterilization temperature is entirely dependent on the supply

pressure of the clean steam. In such cases a clean steam header at 25 psig is provided (higher pressure/temperature is not only wasteful of energy, but may have an adverse effect on valve diaphragms and other equipment components).

Since most facilities using SIP also have autoclaves, often the clean steam is generated at 40 to 50 psig and a sub-header, supplied through a pressure reducing valve, is provided at about 25 psig g.

Droplet Removal

The ability of a clean steam generator to remove contaminants is dependent on preventing droplets of liquid being carried forward in the steam. Different types of generator use different mechanisms to achieve this.

One type uses a disengagement space and a demister. The evaporation vessel is made wide (to reduce steam velocity) and long (to allow droplets to separate) – see Fig. 1.

Another type of generator employs a thin film evaporator (Fig.3), in which the clean steam is channelled through a cyclonic arrangement of baffles in the annulus of the evaporator. The cyclone increase the distance the steam must travel and also provides a centrifugal effect, enhancing droplet separation.

Since droplet removal is essential to generator function and steam is produced dry and saturated, a separator is not required on the steam distribution piping.

Filtration is not essential in a clean steam system, as there are no particulates in the generated steam and correct choice of materials and a suitable maintenance program should eliminate the risk of corrosion. Some pharmaceutical manufacturers, fearing the consequence of a damaged gasket or O-ring contaminating their products, will install a filter at the point of use.

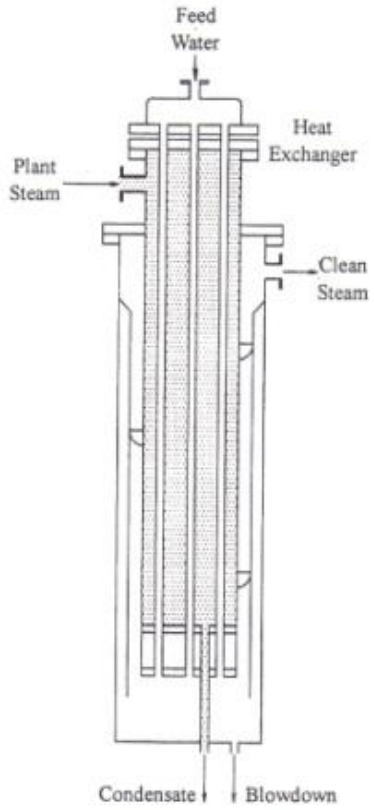

FIGURE 3 : Clean Steam Generator (Evaporator with cyclone)

Materials of Construction

Most generators have AISI 316L stainless steel contact parts to avoid corrosion. Titanium is sometimes used.

Blowdown

The concentrated contaminants from the feedwater are removed from the generator by periodic blowdown. This is usually done on a timed basis, or may be triggered by conductivity measurement. Typically 10 to 15% of the feedwater is discharged in this way. The blowdown is hot and may be used to preheat the feedwater.

6. Clean Steam distribution

They key requirements of a distribution system for clean steam is that it delivers uncontaminated, dry, saturated steam, without superheat, to the point of use. The general principles of steam distribution that apply to utility steam system also apply to clean steam, but there are some significant

differences, primarily in the materials of construction and, to a degree, the need for sanitary design.

Materials of Construction

Invariably piping and other contact materials are AISI 316L stainless steel, to resist corrosion. Lower grades of stainless steel such as 304L are will suffer more quickly from rouging and may even be subject to other forms of corrosion. To enhance the corrosion resistance of stainless steel itneeds to be passivated by a procedure such as that described in ASTM380. Whilst electropolishing has been shown to reduce the rate of rouging, it is otherwise of doubtful benefit for a clean steam system.

Removal of Condensate

In utility steam systems, condensate must be removed because it leads to water hammer, and because it reduces the efficiency of the steam's function, usually heating. In clean steam systems the same factors are present, but additionally cold condensate can allow the growth of micro-organisms, which may cause a failure to meet the endotoxin specification.

Removal of condensate relies on :

- Pipes sloped to direct the condensate to low points where steam traps are used to remove the condensate from the system. Typically horizontal pipes are sloped with a minimum gradient of 1:100. For long pipe runs, one trap manufacturer recommends placing traps at no greater than 100 feet apart.

- Pipes must be properly supported to prevent sagging, should be regularly trapped, and steam traps should be placed at the bottom of vertical risers.

- Traps are also placed on branches to user points if these are at a low point, and especially if they are infrequently used. One neat way of reducing the number of these traps is to run the clean steam header at low level, thus allowing condensate that forms in the rising branch to the user to drain back to the main header, which is itself trapped.

- Other deadlegs where condensate could accumulate are designed out, such as placing instrument branches vertically upwards.

- Traps are used which efficiently remove condensate at or near the steam temperature. Traps which rely on the physical difference between steam and water (float traps, thermodynamic traps) are therefore suitable. That said, there is a particular type of thermostatic trap, the balanced pressure thermostatic trap, which has been developed for clean steam systems. It requires only a small temperture difference to operate, and because of other advantages (good air removal, resistance to blockage, fails open) it seems to have become the preferrred choice for clean steam systems.

- The system should also be designed to reduce condensate formation, so adequate insulation is important, especially where clean steam pipes are run through unheated service areas.

- Separators are not essential for clean steam systems, unless some aspect of poor design has to be addressed. A properly functioning generator will produce saturated steam without droplet carryover, and good pipe insulation should prevent excessive condensate formation.

Removal of Air

Air in steam systems should be avoided. If it mixes with steam it reduces the effective temperature at any given pressure, and consequently could lead to sterilization failures.

In clean steam systems usually air is removed through the steam traps. For removal of large amounts of air at start-up, an air vent or air eliminator (effectively an inverted steam trap) can be installed at the high point on a distribution system.

Prevention of Superheat

Steam becomes superheated when it is reduced in pressure, such as might occur when a low pressure header is supplied through a pressure reducer, or where there is large pressure drop through piping. Energy from the higher temperature steam released by the pressure reduction raises the steam above its saturation temperature.

Conversely, there are features in a steam system that act against superheating. The presence of condensate reduces the tendency to superheat, as steam endeavours to evaporate the condensate and move back towards a

saturated state. Also, heat losses from piping cause the steam temperature to fall, again allowing the steam to move back towards saturation.

In practice, a rule of thumb that pressure should not drop to below 50% of the absolute supply pressure seems to avoid adverse superheat (for example, if steam is supplied at 65 psia (50 psig), then the reduced pressure should not be less than 33 psia (18 psig).

Sanitary Design

Steam at 121 ^{0}C kills micro-organisms and their spores. In a well-designed clean steam system adequate removal of air and condensate will allow the steam to contact all surfaces, and sanitary design is therefore less important than it is in PW and WFI systems, or in pharmaceutical process piping. Historically, clean steam systems were once built using conventional flanged piping, unpolished, and with conventional stainless steel components. Many of these systems functioned perfectly adequately.

Modern clean steam systems are usually fabricated from sanitary tubing (ASME BPE-2002) using orbitally welded joints. Bolted Triclamp connections are often used for instrument connections or other situations where welded joints are inappropriate. It could be argued that such a degree of sanitary design is unnecessary, but tubing is usually less expensive than pipe, and it is usually convenient to use a standard that is consistent with the piping used for process and water systems.

A high degree of internal polish is unnecessary for clean steam systems. The ISPE Baseline Guide recommends mill finish or 180 grit mechanical polish.

Diaphragm valves have achieved almost universal acceptance for PW and WFI systems, but ball valves are usually used for clean steam. They have crevices in their internal construction (which may retain contaminants) and they can retain condensate in their internal cavities. Whilst unsuitable therefore for sanitary process and water systems, they are adequate for use where steam provides a constant sterilising effect. A perceived advantage of ball valves is that their handle position is an obvious indication of valve position (open or closed), whilst this is less so for diaphragm valves.

Whilst ball valves are considered to be safer and more reliable in steam applications than diaphragm valves, appropriate PTFE/EPDM diaphragms are available and some systems utilise these. The diaphragms have to be regularly inspected and are changed when they degrade, but there are several

advantages over ball valves – diaphragm valves are lighter and require less support, they are cheaper, and it is often convenient that they can be maintained by plant operators rather than mechanical fitters.

Sanitary butterfly valves are sometimes used for clean steam. Valves which hold up condensate or which have many internal crevices or screw threads, such as gate and globe valves, are usually avoided.

Special components of sanitary design, such as pressure reducers, instruments and relief valves, are available for use in clean steam systems.

Instrumentation

There are normal operating/maintenance requirments for installing pressure and temperature instruments in clean steam systems, usually at or near the point of generation and at pressure reducing stations. Validation of the system may also demand that these are also placed at the end of long headers, or at other critical points.

Examples of sanitary components

Line Sizing

Normal economic pipe sizing criteria apply, and often a maximum velocity criterion of 120 ft/sec is suitable. Pressure drops should be checked on very long distribution headers to ensure that superheat is not generated, and that the rquired delivery pressure at the point of use is maintained.

7. Clean Steam Sampling

Sampling of clean steam is achieved by condensing the steam with cold water. The sampling device may be portable, connected to the steam system by a hose, or may be permanently installed.

Example of a Portable Sampling Device

Example of Permanent Sampler Installations

8. Condensate systems

The function of the condensate system is primarily to remove condensate quickly from the system, and it also has a part to play in the removal of air.

Care must be taken to prevent contamination flowing back from the condensate system to the clean steam system. Often an air break is used after the trap to prevent backflow. If an open air break is used, this should be located where flash steam will not be a problem.

Condensate from clean steam systems is often discharged as waste water, and is never recycled, untreated, to the generator (it would create a contamination risk). Heat recovery may be used if the condensate is produced consistently and at sufficient capacity.

9. Impact of Foreign Regulations

The preceding part of this course has concentrated on US requirements. For a pharmaceutical facility located in the US producing products for the US market, or for the small number of countries with which the US has bilateral agreements, then this is all that is required. However, pharmaceutical manufacturing typically is aimed at multinational markets and the facility then must meet the equivalent regulations of those markets. It may also be subject to inspection by foreign regulatory authorities. In practice, this should not create many problems with a well-designed clean steam system, but there are a few points worth noting.

Other national pharmacopoeias exist, and may have differences in their purity requirements for PW or WFI. For example, the European Pharmacopoeia, applicable to the countries of the European Community, has slightly different chemical standards for PW and WFI. They both must meet specifications for heavy metals and nitrates, and the conductivity specification is slightly different. These differences should be included in a clean steam purity specification.

In Europe there is a standard for steam supply to autoclaves (EN285). This standard gives limits and testing methods for three physical characteristics of steam, namely dryness factor, superheat and non-condensible gases. A well-designed pharmaceutical clean steam system should have no problem meeting these requirements (which were originally defined for hospital autoclaves using utility steam), but the requirements should be included in a clean steam specification. Whilst EN285 is only variably enforced in some European countries, it is a key concern in others. In particular, inspectors from the United Kingdom will demand that it is met.

The use of US engineering standards, for piping, pressure vessels etc. would not be an issue with which the regulatory authorities would be concerned.

10. Validation of Clean Steam systems

A clean steam system in a pharmaceutical manufacturing facility would normally be classified as a critical system ie. it can have a direct impact on the purity of the pharmaceutical product. As it a critical system, it needs to be validated.

There is no universal system of nomenclature, but the following example includes all the principal activities needed for qualification.

The typical activities of a validation process can be described sequentially as follows :

Develop a User Requirement Specification (URS)
Develop a Functional Specification (FS)
Undergo Design Qualification (DQ)
Installation Qualification (IQ)
Operational Qualification (OQ)
Performance Qualification (PfQ)

User Requirement Specification

This document defines the user's requirements for the system, and is usually generated by the pharmaceutical manufacturing company and approved by their QA team.

For a clean steam system the user requirements would include :

- The steam purity required, usually defined in terms of condensate purity (TOC, conductivity, endotoxins), and sometimes including requirements for saturation, dryness and non-condensables.

- Flow, pressure and temperature requirements at point of use.

- Relevant standards and legislation which must be met, such as which national GMP's need to be met, and requirements to comply with GAMP or 21 CFR Part 11 requirements for automation systems.

- Sampling requirements

Sometimes URS's will include significant detail on the design of a system, such as valve types to be used, surface finish of piping etc. However, these items are better included in the FS, which defines how the URS is going to be met in engineering terms.

Functional Specification

The FS defines how each requirement of the URS is to be met. It is usually generated by the system designer or supplier. For example, if the URS included a requirement that :

The clean steam system shall be constructed of materials that are inert, non-adsorbent, resistant to corrosion and do not contaminate the steam.

Then the FS might answer that with a statement listing the product contact materials to be used, and any specifications with which they must comply, for example :

Piping will be 316L stainless steel, to ASME BPE-2002 standard etc.

Gaskets will be EPDM, complying with USP requirements for biocompatability and Code of Federal Regulations requirements for elastomers (21 CFR 177.2600).

Design Qualification

DQ is a review process, held once the system has been designed and specified. It allows the design, and particularly the FS, to be reviewed for compliance with the URS. It is often conducted as a meeting, and is attended and approved by the QA team of the pharmaceutical manufacturer.

For DQ of a clean steam system the documents reviewed would typically include :

- The Piping & Instrumentation Diagram
- The Functional Specification
- The specifications for major equipment items (the clean steam generator), piping and valves
- Control System specifications
- Documentation requirements for suppliers

Installation Qualification

IQ is the process of proving that the system has been supplied and installed correctly, and meets the requirements of the URS and the standards identified in the FS and approved at DQ. It usually involves the generation of an IQ protocol, effectively a test and inspection plan for the system.

For a clean steam system IQ the following would be typical :

- Assemble documentation on system components, including materials data, welding documentation, calibration certificates.

- Verify compliance of the installation with the P & ID and assembly drawings, including pipe slopes, valve and trap orientation, deadlegs, instrument orientation.

Operational Qualification

OQ is the process of demonstrating the correct operation of the system. It tests not only the correct operation of the system, but also the adequacy of SOP's

For a clean steam system OQ the following would be typical :

- Determine system pressure and temperature at points of use, including fluctuation between minimum and maximum capacity.

- Demonstrate acceptable system capacity.

- Modify (if found necessary) and issue initial SOP's for use.

Performance Qualification

PfQ is the process of demonstrating that the system performance is acceptable when being operated by initial SOP's. It is usually achieved by testing of the steam and condensate. It is often performed by the QA/QC team from the pharmaceutical manufacturing organistion. The PfQ protocol will include sampling requirements (location, frequency and tests to be undertaken). Specific acceptance criteria will be included.

For example, a clean steam PfQ might include the requirement to test condensate from all traps and sampling points, by testing each point once per week over a period of two weeks. The tests might be defined to include conductivity, TOC and endotoxin, and the acceptance criteria would be that all tests meet the relevant USP requirements for WFI.

At the end of PfQ the SOP's will be approved for use.

10. Operation & maintenance of Clean Steam systems

As a critical system in pharmaceutical manufacturing a clean steam system must be subject to a regular scheme of maintenance and supervision. Key aspects of this scheme would include :

- Ongoing revalidation of the system, including regular confirmation that the system meets the user requirements. Typically a revalidation exercise would be undertaken every two years.
- Inspection requirements to meet national standards for pressure systems.
- Instrument recalibration
- Verification of correct functioning of steam traps
- Inspection for rouging, and possible derouging of the generator or the complete system.

References

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