

# Clean and Pure Steam Systems Biopharmaceutical Industry

Technical Reference Guide

1st edition

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Spirax Sarco, Inc. Clean and Pure Steam Systems Biopharmaceutical Industry  
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# Introduction

This guide follows on from the 'Clean steam - Introductory application guide' that outlines the reasons why a higher grade of steam is required, for particular applications, within certain industries and the differences between the different types of 'clean steam', including filtered, clean and pure.

This guide focuses specifically on clean and pure steam systems within the biopharmaceutical industry, including both clean steam for non critical applications and pure steam for those applications that require pyrogen free WFI quality steam. It addresses key issues such as; purity, general design requirements, feedwater concerns, generation, distribution, key applications and validation.

# 2

## Related standards

### 2.1 ISPE

The International Society of Pharmaceutical Engineers (ISPE) has developed a series of baseline guides and documents with the intention to advise engineers on the best practice to employ when designing and operating pharmaceutical systems.

Volume 4 'Water & steam systems' addresses clean steam systems within the pharmaceutical market, and covers the following issues:

- Defines the type of steam that should be used.
- Attempts to readdress the types of steam used for key pharmaceutical manufacturing processes.
- Assists design engineers in selecting / key design requirements for clean steam generators.
- Details key issues concerning clean steam system design.

## 2.2 ASME BPE

The ASME BPE standard covers, directly or by reference, requirements for materials, design, fabrication, examination, inspection, testing, certification and pressure relief of vessels, together with piping for bioprocessing systems. Including sterility and cleanability, dimensions and tolerances, surface finish requirements, and seals for the bioprocessing systems.

In 1990 (approximately) the American Society of Mechanical Engineers' (ASME) Council on Codes and Standards issued a decree to the Board on Pressure Technology Codes and Standards to form a committee to investigate and catalogue the biopharmaceutical industry's concerns about inconsistencies. Consequently, the Bioprocessing Equipment ASME BPE Standards Committee was created. The committee, consists of end users (biofood, biopharmaceutical, and biochemical industries), equipment manufacturers or suppliers, drug manufacturers, distributors, and engineers. The objective of this ASME BPE committee was to create a standard that could bring clarity and consistency to the bioprocessing industry (bioprocessing, biotechnology, biofood, biopharmaceutical and biochemical industries) and end miscommunications, misunderstandings, misinterpretations, and ambiguities in the applicable entities.

The ASME BPE consists of various subcommittees:

1. General requirements
2. Design for sterility and cleaning (Part SD)
3. Dimensions and tolerances for stainless steel automatic welding and hygienic clamp tube fittings (Part DT)
4. Material joining (Part MJ)
5. Stainless steel and higher alloy interior surface finishes (Part SF)
6. Equipment seals (Part SG)
7. Polymers and elastomers
8. Accreditation
9. Metallic materials of construction

The ASME BPE standard gives the biotechnology industries a tool to purchase, specify and manufacture biopharmaceutical, biofood, and biochemical production equipment and systems at an even and comparable level for the benefit of the industry's engineers, manufacturers, and biotechnology end users. The standard also provides a method of ensuring that the design, production and installation of bioprocessing equipment, tubing, fittings, and components are consistent and uniform.



## 2.3 FDA / cGMP

The USA Food and Drug Administration (FDA) is the regulatory body controlling the production and sale of pharmaceutical, food and cosmetics in the USA. The FDA is also active in many other countries. Any pharmaceutical manufacturer who wishes to sell into the USA, the largest single market, must first obtain FDA approval of their facilities and quality control systems. However, the FDA does not approve single manufacturing components or products such as steam traps, but concentrates their attention on the whole facility.

Broadly speaking, FDA regulations are little more than general guide lines, which, from an engineering point of view, leave much to the interpretation of both the pharmaceutical manufacturing company and also to each individual FDA inspector. What is deemed acceptable by one inspector will not necessarily be accepted by another in a different part of the world, or even in the same country. This obviously makes life difficult for the pharmaceutical companies, as the cost of being even only partially shut down by the FDA can run into millions of dollars in only a very short time.

The sections of the regulations which most directly affect the application of our products is the Code of Federal Regulations (CFR) Title 21, part 210 - current Good Manufacturing Practice (cGMP) in manufacturing, process, packaging or holding of drugs; general: and part 211 - cGMP for finished pharmaceuticals. Even those sub-paragraphs of the part concerning equipment that could relate to our products (para 211.65 Equipment construction, and 211.67 Equipment cleaning and maintenance) only say that equipment should be constructed and maintained, cleaned and sanitised as not to alter '... the safety, identity, strength, quality, or purity of the drug product beyond the official or other established requirements'.

Having said that, there is a trend towards higher standards of equipment throughout the pharmaceutical industry, as what is being seen as 'state of the art' today is often being insisted upon as standard for the facilities which are now being designed, installed and updated.

Other sections of the FDA regulations, which could be considered relevant, are those to do with materials of construction, which could come in to contact with the end product. These generally relate to elastomers, boiler feed treatment chemicals and so on.

## 2.4 USP

The United States Pharmacopeia (USP) is the official public standards-setting authority for all prescription and over-the-counter medicines, dietary supplements and other healthcare products manufactured and sold in the United States. USP sets standards for the quality of these products and works with healthcare providers to help them reach the standards. USP's standards are also recognized and used in more than 130 countries. These standards have been helping to ensure good pharmaceutical care for people throughout the world for more than 185 years.

A monograph for pure steam first appeared in USP 32. Steam purity is often defined by the purity of the condensate, and this is often referred to as one of the published water purity standards laid out within the USP - Water For Injection (WFI) or Purified Water (PW).

There is also equivalent European Pharmacopia (EP) and Japanese Pharmacopia (JP), the limitations of which are very similar.

The use of clean steam in the biopharmaceutical industries is covered by Good Manufacturing Practice (GMP). These are general rules applicable to pharmaceutical manufacture, detailed in the code of Federal Regulations (CFR Title 21, Part 211). These regulations 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 processes and end products.

The ISPE baseline guide for steam and water systems and the ASME BPE guidelines are the most directly related and current standards for steam system and related component; design, manufacture, test and inspection, for use in the biopharmaceutical industry. Compliance to these standards therefore can be considered as meeting cGMP for steam systems and related components.

# 3 Purity issues

Before discussing the purity requirements of clean and pure steam, it is first worth covering the requirements for the purity of water used in pharmaceutical manufacturing. This is because 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 which pharmaceutical water quality is measured (conductivity, total organic carbon, endotoxins and microbial content) are those usually used for determining steam purity.

For biopharmaceutical companies operating to FDA standards, there are statutory requirements regulating the purity of water used in pharmaceutical manufacture and two grades of high purity water are defined in international pharmacopeia, namely Purified Water (PW) and Water For Injection (WFI). PW must meet the chemical specification for conductivity, Total Organic Carbon (TOC), and microbial specification. WFI is water of a higher purity; it must meet the same chemical specification as PW, but a much higher microbial specification must be maintained. Additionally, it must meet a specification for endotoxins and must be produced by a defined method (either distillation or reverse osmosis. European pharmacopoeia allows only distillation).

**Table 1 USP specification for water purity**

	Purified water	Water for Injection
<b>Conductivity</b>	<1.1 $\mu\text{S}/\text{cm}$ at 20°C	<1.1 $\mu\text{S}/\text{cm}$ at 20°C
<b>Total Organic Carbon (TOC)</b>	<500 ppm	<500 ppm
<b>Microbial (recommended action limit)</b>	100 cfu/ml	10 cfu/ml
<b>Endotoxin</b>	No requirement	0.25 EU/ml
<b>Production method</b>	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 pharmaceutical manufacturer sets the microbial specification for PW and WFI for each system, but the pharmacopoeia guidelines for PW would be 100 cfu/ml, whereas for WFI it would be 10 cfu/100ml.

Endotoxins are breakdown products of dead microbes. 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 patients.

In contrast to water, there is no biopharmaceutical standard for clean and pure steam. Each manufacturer must prepare a specification for purity of such steam and the specification must be such that they meet the cGMP (current Good Manufacturing Practice) required to avoid contamination of the end product. In theory, there could be a wide range of different steam specifications, applicable to products of different degrees of purity and different stages of manufacture. In practice however, the pharmaceutical industry has tended to consolidate around specifications for PW or WFI.

The most common steam specification is that where 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) and is referred to as **pure steam**. Pure steam is used where strict endotoxin limitations are required including end products such as injectables and intravenous (administered through the vein) products.

Although some biotechnology products may not be intended for intravenous use, pure steam is often used for sterilising the production system, as absolute sterility is demanded to guarantee repeatability of the process.

A specification for **clean steam** may be based on PW specification in so far as the chemical composition (TOC and conductivity). This would be appropriate in facilities producing products which must be sterile, but where endotoxin in the final product is not a concern. An example of this would be non-injectables.

For biopharmaceutical companies who are not operating within FDA standards, these guidelines do not apply, and many installations use clean steam applications where pure steam should be used.

Humidification of clean rooms in the biopharmaceutical industry can be for critical applications, where injectable drugs are exposed to the atmosphere, or non-critical applications, where drugs are not exposed. An FDA approved site should use pure steam for the humidification of critical areas and either pure or clean steam for non-critical applications. Non FDA sites may use clean steam for humidification.

# 4 Fundamentals of system design

When designing clean and pure steam and condensate systems for use in the biopharmaceutical industry, there are two key areas of consideration that must be observed:

## 4.1 Corrosion issues

Clean and pure steam systems have a very low conductivity, resulting in a media that is very aggressive and ion hungry. This, coupled with the fact that unlike plant steam systems, clean and pure steam has no corrosion inhibitors. This means that carbon steel, gunmetal and bronze, all commonly found in plant steam components, would be rapidly corroded. Metal components for these systems are therefore usually 316L stainless steel as a minimum. Non-metallic materials used include EPDM and PTFE.

The need to avoid corrosion is necessary for safeguarding the integrity of the system. In addition, possible corrosion particles entering the system must be eliminated to prevent contamination of the pharmaceutical product, either as chemical or particulate contamination.

Even where 316L stainless steel is used, a particular form of corrosion entitled 'rouging' is often encountered in high purity steam systems. The passive layer of the stainless steel surface is disrupted and a red, brown or black film develops. Often this film is stable and does not pose a threat to the pharmaceutical product. However, sometimes a powdery film develops and this can detach from the surface and cause discoloration of equipment in which the steam contacts. If this occurs and the pharmaceutical manufacturer feels that there is risk of contamination of the product, the steam generator and the system may require cleaning; a process known as 'derouging'.

A variety of methods are used, but they all involve chemical treatment to remove the surface layer, essentially an etching process. After derouging, a process must be used to restore the passive layer on the stainless steel surface, since it is the passive layer that is responsible for the corrosion resistance.

## 4.2 Prevention of microbial growth

Steam, at typical operating pressures, will kill bacteria and their spores, so the parts of a high purity steam system that are continuously exposed to steam will be sterile. However, if condensate collects in the system and is allowed to cool, this stagnant water can provide a suitable environment for bacteria growth. Though these bacteria may be killed when exposed to steam, their breakdown products, including endotoxins, may still be present. Typical clean and pure steam system temperatures do not destroy endotoxins.

# 5

## General design requirements

### 5.1 Materials of construction

The high purity of the feedwater used in clean and pure steam systems makes it extremely corrosive and able to cause the rapid degradation of carbon steel commonly used in plant steam systems.

This would not only damage the components and pipework, but also lead to contamination of the steam. Any corrosion of components within the system can soon spread, leading to the formation of 'rouge'. The products of corrosion will also be carried through the system to the point of use.

To overcome this, components used in high purity steam systems are manufactured from corrosion resistant grades of stainless steel. In order to understand the choice of material, it is important to briefly review the types of stainless steel commonly available.

There are more than 70 standard types of stainless steel and many special alloys. These steels are produced in the wrought form and as cast alloys. Generally, all are iron based with 12% to 30% chromium, 0% to 22% nickel, with minor amounts of carbon, columbium, copper, molybdenum, selenium, tantalum and titanium. Descriptions of the most widely used stainless steels are given in the following sub section:

#### Wrought stainless steels

- **Martensitic** - Characteristically magnetic and hardened by heat treatment; are oxidation resistant. Type 410 is the most notable example. These alloys contain 12% to 20% chromium with controlled amounts of carbon and other additives. Their corrosion resistance is inferior to that of austenitic stainless steels and are generally used in mildly corrosive environments. Used rarely in process applications, martensitic grades are primarily used in cutlery, turbine blades and other high-temperature parts. Martensitic stainless is also used in hardened surfaces in valves and steam traps designed for plant steam systems.
- **Ferritic** - Characteristically magnetic (because of the ferrite structure), but not hardened by heat treatment. Ferritic contains 15% to as much as 30% chromium with low carbon content (0.1%). Its corrosion resistance rating is good due to the higher chromium content. Type 430 is widely used in nitric acid plants.
- **Austenitic** - This material is widely used in the biopharmaceutical industry. Characteristically it is non-metallic, not hardenable by heat treatment and is the most corrosion resistant of the three groups. The many types of austenitic steel include; highly alloyed, the lower alloys in which manganese has been substituted by nickel (the 200 series) and the 188 group which includes Types 304 and 316 and all their variations. Types 304L and 316L are the workhorse materials of the biopharmaceutical industry. They have their carbon content lowered from about 0.08% to a maximum of 0.030% which minimizes the chromium carbide precipitation. These steels do not rust, are easily weldable and machinable and will not corrode.

**Table 2 Typical composition of stainless steel commonly used in clean steam systems**

Element	% by weight		
	AISI 304	AISI 316L	AISI 316Ti
<b>Iron (Fe)</b>	66.4 - 74	65	65
<b>Carbon (C)</b>	Max. 0.08	0.03	0.08
<b>Chromium (Cr)</b>	18 - 20	17	16 - 18
<b>Manganese (Mn)</b>	Max. 2	2	2
<b>Nickel (Ni)</b>	8 - 10.5	12	10 - 14
<b>Phosphorus (P)</b>	Max. 0.045	0.045	0.04
<b>Sulphur (S)</b>	Max. 0.03	0.03	0.03
<b>Silicon (Si)</b>	Max. 1	1	1
<b>Molybdenum (Mo)</b>	-	2.5	2 - 3
<b>Titanium (Ti)</b>	-	-	Max. 0.7

### Cast stainless alloys

Widely used in pumps, valves and fittings. Under ASME standards, all corrosion resistant alloys have the letter C plus a second letter (A to N) denoting the nickel content. Numerals indicate maximum carbon. Typical members of this group are CF-8 similar to 304 stainless; CF-8M, similar to 316; CF3M, similar to 316L and CD4M Cu, which has improved resistance to nitric, sulphuric and phosphoric acids.

Other geographical areas have their own standards and are numbered appropriately.

### Corrosion resistance

The corrosion resistance of stainless steel results from the formulation of a layer of chromium oxide on the surface of the material immediately after it has been pickled at the mill. When this protective layer is removed from the surface, such as by scratching, it will almost instantaneously reform in the presence of oxygen or any other oxidising agent such as water or nitric acid. This means that potential corrosion sites will generally arise from the presence of impurities and other defects on the surface of the material.

To limit the effects of corrosion it is necessary to limit the number of these defects. Which can be achieved by maintaining a high quality surface finish.

Stainless steel components are usually 'finished' after fabrication using one or more of the following processes:

- **Pickling** - The component is immersed into a nitric acid and hydrofluoric acid solution in order to remove a thin surface layer (typically between 5 - 12 microns thick). This removes any impurities and defects embedded in the surface, leaving a roughened surface.
- **Electropolishing** uses an electric current to remove the surface layer. Unlike pickling, electropolishing tends to smooth the surface.
- **Passivation** - In lay terms, the passivation process removes 'free iron' contamination left behind on the surface of the stainless steel from machining and fabricating, by means of a chemical dissolution, most typically by a treatment with an acid solution. These contaminants are potential corrosion sites that result in premature corrosion and ultimately result in deterioration of the component or system if not removed.

In addition, the passivation process facilitates the formation of a thin, transparent oxide film that protects the stainless steel from selective oxidation (corrosion).

## 5.2 Corrosion issues

Corrosion can be divided into two basic types:

- **General corrosion** - The dissolution of the metal at a uniform rate over the entire surface exposed to a corrodent. It is caused by the loss of the protective passive film that forms on the surface in environments where the steel is resistant. General corrosion is usually expressed in corrosion rates as 'mils' (thousandths of an inch) or millimeters per year (mpy or mm/y).
- **Localized corrosion** - The dissolution of the metal in which only a small area is affected, but the rate is relatively high.

Stainless steel in the passive state appears in a relatively noble position in the galvanic series and is usually cathodic, therefore, not subject to attack. However, under certain conditions all or portions of a piece of stainless steel may become active. This active surface becomes anodic to the more noble mass and in the presence of an electrolyte, a galvanic cell is set up and attack will occur. The rate of attack will vary with different electrolytes and the area relationship of the anode and cathode.

Localised corrosion can take the form of various types including, intergranular, pitting, galvanic, stress corrosion etc. These can be further explored in the appendix.

### Factors affecting corrosion

Other than the metal composition and corrodents, some of the factors that influence corrosion are:

- The presence of even minor percentages of impurities in the corrosive medium.
- The temperature of the corrodent (generally, corrosion increases as temperature increases).
- The degree of aeration to which the corrodent is exposed.
- Velocity of corrodent.



## 5.3 Non-metallic materials

For non-metallic materials, (e.g. plastics, elastomers or adhesives) depending upon customer requirements, the material should comply to FDA, 21CFR, 177 and USP Class VI.

FDA 21 CFR 177 - basically dictates that the material used will have no adverse affect if ingested by a human.

Compliance to USP class VI focuses on the safety of materials that could potentially contaminate an injectable drug, typical materials include PTFE (polytetrafluoroethylene)

TFM is a chemically modified PTFE that fills the gap between conventional PTFE and melt-processable PFA. According to ASTM D 4894 and ISO Draft 539-1.5, TFM is classified as PTFE. Compared to conventional PTFE, TFM has the following enhanced properties:

- Much lower deformation under pressure (cold flow) at room temperature and elevated temperatures.
- Lower permeability.
- May be used at higher pressures.

Some of our clean steam products utilise TFM, including the M70i and M80i ball valve range.

## 5.4 Surface finish

The requirements for improved surface finish are predominantly to maintain sterility in the system by reducing the risk of microbial growth in crevices on the surface. Due to the high temperature of steam the majority of bacteria will be killed, however pyrogens, the dead cells of the bacteria, will not be removed and this can lead to unacceptable contamination. Polishing is also performed to improve the corrosion resistance of the material.

Due to the high levels of sterility demanded in the biopharmaceutical industry clean systems (clean and pure steam, water for injection, purified water and clean gases, etc...) piping systems, equipment and components are required to have a particular surface finish. This is typically specified by either a mechanical 'roughness', measured in microns or micro-inches ( $R_a$  = arithmetic mean roughness) or as a 'grit' number e.g. 180 grit.

Table 3, cross-referencing surface roughness with Grit and Polish numbers is given as a guide only. One of the major problems in the Clean industry is that a given surface roughness of, 32 micro-inches for example, can be anywhere between 150 - 240 grit, depending upon who you talk to. There are efforts being made by the Standards Institutes to resolve this problem.

**Table 3 Surface finish comparison**

Polish No.	Grit No.	Micron $\mu$ m Ra	Micro-inch $\mu$ in Ra
<b>Foundry finish (Investment castings)</b>	-	4.25 - 4.5	170 - 180 (Typically)
<b>Satin finish</b>	-	1.8	75 approx.
<b>4</b>	150	0.76 - 0.89	30 - 35
<b>7</b>	180	0.51 - 0.64	20 - 25
<b>7</b>	240	0.38 - 0.51	15 - 20
<b>7</b>	320	0.23 - 0.28	9 - 11

An improved surface finish will result in the following:

- **Reduced surface area** - The smoother the surface, the smaller the microscopic areas available for corrosion sites to be set up and the smaller the surface area. Note that mechanical polishing or machining leaves numerous surface scratches which cause areas of differing electrical potential because of the surface stresses, in turn resulting in local corrosion cells being set up.
- **Cleanability** - One of the key reasons for specifying a smooth surface finish on process systems is to enable any process fluid or product to be easily removed from the equipment or component surface and to reduce potential areas for stagnation and growth of microorganisms.
- **Improved corrosion resistance** - Polishing removes the top layer of the surface exposing passive layer of chromium, which leads to greater corrosion resistance.

The operating temperatures in steam systems are often more than sufficient for inhibiting microbiological growth. Therefore, surface finish is not as critical with steam systems as with, say WFI systems, due to the 'self-sanitising' nature of the steam.

Typically 180 grit or 0.51 - 0.64 micron or 20 - 25 micro-inch surface finish is sufficient for tubing, fittings and components on pure steam systems.

Due to the less critical nature of clean steam systems, surface finish is less of an importance and a finish of 0.8 micron Ra (32 micro inch) or even mill finish can be acceptable.

External surface finish can also be a concern if pipework or components are exposed to atmosphere in a clean room environment.

The ASME BPE has developed its own surface finish designation as follows:

**Table 4**

Surface designation	Mechanically polished	
	Ra Maximum	
	Micro-inch	Micron
<b>SF1</b>	20	0.51
<b>SF2</b>	25	0.64
<b>SF3</b>	30	0.76
Surface designation	Mechanically polished and electropolished	
<b>SF4</b>	15	0.38
<b>SF5</b>	20	0.51
<b>SV6</b>	25	0.64

The required surface finish of high purity steam traps is very much dependent on the customer requirements. A key factor here is in determining where the customer draws the 'sterile boundary'. If this is downstream of the trap, the surface finish of the trap should be the same as the connecting tubing. If the sterile boundary is at the valve prior to the trap, then a trap with a lower quality surface finish may be opted for.

Where traps are used for SIP (sterilisation / steam in place) applications, draining fermentors or bioreactors, then typically a higher quality surface finish is required to overcome the problem of process debris adhering to the internal surfaces of the trap, leading to blockage and possible process failure.

### **Electropolishing**

When higher grades of surface finish are required, then electro-polishing may follow mechanical polishing.

In simple terms, this is a process whereby surface metal is removed by the process of anodic dissolution in a suitable electrolyte under an imposed current potential - in essence the opposite to electroplating.

Electropolishing will further enhance corrosion resistance by increasing the passive, or chromium oxide, layer on the surface. It also improves the overall smoothness of the surface by removing some of the rough 'peaks' formed during the mechanical finishing process. Depending on the specific electropolishing process, this improvement can be between 10% and 25%.

## 5.5 Tubing and connections in the pharmaceutical industry

Austenitic stainless steel tubing is very commonly used in the biopharmaceutical industry in preference to nominal bore piping. This section outlines the reasons behind this use and describes the various types of tubing commonly used, together with preferred methods of connections and fittings.

For many years, the dairy industry has been the forerunner in developing codes, practice and standards for hygienic processing. Although these are often very loosely defined, they have, to a large extent, been adopted by other clean processing industries, including the biopharmaceutical industry. Among these are the use of thin walled tubing for the process and clean utility piping systems, for reasons that include:

1. Relatively low-pressure applications do not require the thicker walls found in most industrial pipes.
2. The thinner wall results in an overall lighter weight, leading to lower cost of material and installation.
3. Dimensions and tolerances are more tightly controlled during manufacture of tubing, resulting in better uniformity of internal sections when joined. This, in turn, leads to a more consistent and smooth internal surface throughout the system.
4. Thin walled tubing lends itself to direct TIG (Tungsten Inert Gas) orbital welding, using straight end preparations and no filler i.e. a fusion of the parent metal. This produces a very high quality weld, with little change in wall thickness.

There are three commonly used standards worldwide, the occurrence of which will depend on the territorial preference. These include Imperial, ISO 1127 and DIN 11850 - details of these can be found in the appendix.

The design of sanitary equipment and systems should minimise the number of connections. Tube weld connections should be used wherever practical. Where connections must be used to facilitate cleaning or maintenance, the sanitary clamp type connection should be used.

Where tube weld end connections are employed, pipeline products typically use Extended Tube O/D ends (ETO). An ETO end is one that permits in-line welding of the component in to the piping system. The dimension of the ETO end matches the tubing system diameter and wall thickness. The extended tube length accommodates orbital welding heads and provides sufficient length to prevent body seal damage due to the heat of the welding. The ASME BPE suggests minimal lengths shown in Table 5.

**Table 5 ASME BPE suggested minimal lengths**

Nominal O/D tube size, inches	Tangent length	
	inches	mm
1/4"	1.5	38.1
3/8"	1.5	38.1
1/2"	1.5	38.1
3/4"	1.5	38.1
1"	1.5	38.1
1 1/2"	1.5	38.1
2"	1.5	38.1
2 1/2"	1.5	38.1
3"	1.75	44.45
4"	2.0	50.8
6"	2.5	63.5

Screwed and flanged connections are not classed as sanitary in design and therefore not the preferred choice for pure steam systems. However, less critical clean steam systems often incorporate these types of connections as well as nominal bore stainless steel pipe.

# 6 Clean and pure steam generation

## 6.1 Feedwater

Clean and pure steam generators will only operate satisfactorily if the feedwater is of appropriate quality. Manufacturers often specify low limits on hardness, particulates and silica concentration (to minimise scaling) and upon chlorine concentration (to minimise corrosion).

Raw water is rarely adequate and will usually require some pre-treatment which is governed by the nature and concentration of contaminants. For good quality potable water, free of colloidal silica and organics, softening may be appropriate. Some deposition of sodium scale inside the generator may occur, but this can be removed easily by acid cleaning. For waters with high salt concentrations, silica or organics, demineralisation or reverse osmosis (RO) may need to be employed.

**Table 6 Typical pure steam generator manufacturers requirement for feedwater**

<b>Source:</b>	Drinking water
<b>Treatment:</b>	Deionisation or reverse osmosis
<b>Amines, chlorines and chlorides:</b>	Free of amines, chlorines and chlorides
<b>Silica:</b>	<1 ppm
<b>Total hardness:</b>	<1 ppm
<b>Micro-organisms</b>	<1 000 CFU/ml
<b>Conductivity:</b>	<10 $\mu$ S/cm

As most facilities using pure steam will also require PW, this is often used as the feedwater source for pure steam generators, even though its purity is higher than that required. For plants that have very large pure steam requirements or do not use PW, RO water is used as the feedwater.

Clean steam generators may also utilise PW as the feed but more often utilise a separate RO water source. This is to keep the cGMP, WFI / PW / Pure steam systems, separate from the often non-validated non-critical clean steam systems.

## 6.2 Key feedwater concerns

### Turbidity and particulates

Particulates are insoluble suspended materials present in the water. Concentrations are measured in mg/l. Sources of particulates are dust, pollen, silica, insoluble minerals and corrosion products.

Turbidity is a cloudy appearance in water caused by the presence of suspended and colloidal materials. Rather than a physical property it is an optical property based on the amount of light reflected by the suspended particles and is measured in Nephelometric Turbidity Units (NTU). The EPA (Environmental Protection Agency) limit for turbidity in drinking water is 1 NTU. Turbidity cannot be related to particulates since it is effected more by particle size, shape and colour rather than concentration. Removal of particulates and turbidity is required to prevent fouling of the later treatment process.

A key method of removal is via **media filtration** - often utilising a depth filter using sand, carbon or manganese to remove particulates down to 10 - 40 µm.

### Hardness

The presence of calcium (Ca) and magnesium (Mg) in a water supply is commonly known as 'hardness'. Hardness in water can result in scale formulation, which is a deposit of minerals left over after the water has been removed or evaporated.

A common method of removing these, scale forming 'salts', is via an ion exchange water softener. In many cases, other multivalent ions such as soluble iron (ferrous) and ionised silica are also removed with softeners.

### Organics and microbial impurities

Organic and microbial contaminants need to be addressed in water treatment systems. The concerns are twofold: contaminants entering the system and contaminants created / growing in the system. Organics usually enter with the feedwater, but may also leach from some non-metallic materials of construction. Microbiological contaminants may enter with the feedwater or grow in the system and are classified as viable and non-viable. Viabiles are those organisms that can proliferate, given specific conditions. Non-viables are derived from a breakdown of or a product of a viable organism.

#### Common organic contaminants include:

- **Bacterial contamination** - Usually expressed as 'total viable microbial counts per ml' or as 'Colony forming units (CFU)' These are determined by counting the growth resulting from incubating samples. Each colony is assumed to form 1 bacterium.
- **Pyrogenic contamination** - Pyrogens are substances that can produce a fever in mammals. The pyrogens are often endotoxins, organic compounds (lipopolysaccharides) that are shed by bacterial cells during growth, or are the residue of dead cells. They are chemically and physically stable and are not necessarily destroyed by conditions that kill bacteria. Pyrogen levels are quantified in Endotoxin units (EU) per millilitre. Pyrogens are of great concern to the pharmaceutical industry since high concentrations may cause responses in humans ranging from fever to shock or death.
- **Total Organic Carbon (TOC)**- TOC is a measure of organic material contaminating the water and is specified in mg/l. TOC is a very fine measurement used in sophisticated water treatment systems where any organic contamination can adversely affect product quality. TOC is not a good measure of microbial contamination.

- **Dissolved organic compounds**- Organics occur both as the product of the decomposition of natural and as synthetic compounds such as oils or pesticides. Naturally occurring organics include: tannin, humic, acid, and fulvic acids. They detract from the aesthetics of water (i.e. colour), but unless they come in contact with certain halogens, they have no known health consequences in normal concentrations. Under conditions of free halogen compounds (principally chlorine and bromine), they form chlorinated hydrocarbons and trihalomethanes (THMs), which are suspected carcinogens.

**Typical methods of removing organics include:**

- **Micro filtration** - filtration capable of removing particles ranging in size from 100 µm down to 0.1 µm and thus capable of capturing bacteria
- **Ultrafiltration** - Can be used to remove organics and bacteria as well as viruses and reduce pyrogens. Filtration rates typically from 0.1 µm down to 0.001 µm
- **Reverse osmosis** - Similar to ultrafiltration, the RO unit will eliminate impurities too large to pass through the RO membrane
- **Periodic heat sanitisation** - Typical procedure involves raising the system temperature to 80°C several times over a 4 - 8 hour period.
- **Ultraviolet light** - Treatment with UV light is a popular method of microbial control - water is exposed to ultraviolet light waves, the UV light deactivates DNA in the microbes preventing duplication and thus leading the bacteria reduction.

Generator manufacturers will often guarantee only a log 3 (1 000 times) to log 4 (10,000 times) reduction in bacteria and endotoxins for pure steam generators. Thus, a low allowable microbial count, or endotoxin concentration, could exceed if the feedwater to the generator becomes heavily contaminated.

## **Volatiles**

Volatiles include any chemical that can present in a gaseous state and therefore become entrained and carried over in the steam

Chloramines are an example of a volatile that is undesirable in a pure steam system, resulting in ammonia and ammonium being present in the system. Ammonia will affect conductivity and pH, making it difficult to meet USP conductivity measurement.

An activated carbon filter removes chloramines and chlorides by absorbing them onto the carbon particles in a carbon bed.

## **Chlorine**

Chlorine must also be removed due to possible corrosion of the stainless steel generator and system. Chlorine is present in city water as biocide, to control the level of microorganisms, and its removal may allow microbial levels to increase. Feedwater treatment must therefore include some other, non-chemical, means of controlling microorganisms, and often the final treatment is a membrane process such as reverse osmosis (RO).



## **Acidification, degasification and feedwater pH**

The control of feedwater pH is very important when designing the pretreatment for a purified water system. Too high a pH (alkaline) will result in increased risks of scaling, while too low a pH (Acid) will result in possible corrosion to pipelines, as well as increase the amount of CO<sub>2</sub> in the system.

Injecting acid to the water to reach a pH of approximately 5.5, will minimise the effect of scaling, however this will maximise the amount of CO<sub>2</sub> in the water.

CO<sub>2</sub> will pass directly through pretreatment and RO membranes and have a direct impact on the conductivity and pH, making it difficult to meet USP conductivity measurement. It will also have a dramatic impact on the levels of non-condensable gas entrained in the steam and thus make compliance with HTM 2031 / EN 285 difficult.

A common method of overcoming high CO<sub>2</sub> levels is via the utilisation of a degasification unit.

## **6.3 Principle pre-treatment equipment**

### **Water softener**

A standard water softener has four major components: a resin tank, resin, a brine tank and a valve or controller. The softener resin tank contains the treated ion exchange resin - small beads of polystyrene. Capacity depends on volume of the resin bead. The resin beads initially absorb sodium ions during the brine regeneration. The resin has a greater affinity for the multi-valence ions such as calcium; magnesium and other multivalent ions such as iron and silica adhere to the resin, releasing the sodium ions until equilibrium is reached. The water softener has exchanged its sodium ions for the calcium, magnesium and iron ions in the water.

Regeneration is achieved by passing a sodium chloride (NaCl) solution through the resin, exchanging the hardness ions for sodium ions. The resin's affinity for the hardness ions is overcome by using a highly concentrated solution of NaCl (brine).

### **Reverse osmosis (RO)**

RO is a pressure driven process utilising a semi-permeable membrane capable of removing dissolved organic and inorganic contaminants from water. A semi-permeable membrane is permeable to some substances such as water, while being impermeable to other substances such as salts, acids, bacteria and endotoxin.

RO membranes are produced commercially for water purification in spiral wound and hollow fibre configurations. Spiral wound elements are much more forgiving in pretreatment protection against fouling. Membranes are available in two basic materials: cellulose acetate and thin film composite (polyamide).

### **Continuous electrodeionisation (CEDI)**

Electrodeionisation removes ionised or ionisable species from water using electrically active media and an electrical potential to effect ion transport.

### **Feedwater pressure**

Generally feedwater should be delivered at approximately 0.7 bar (10 psi) greater than the required steam pressure. If the feedwater originates from a distribution system being run at a pressure lower than this, a feedwater tank and pump should be installed to boost the pressure.

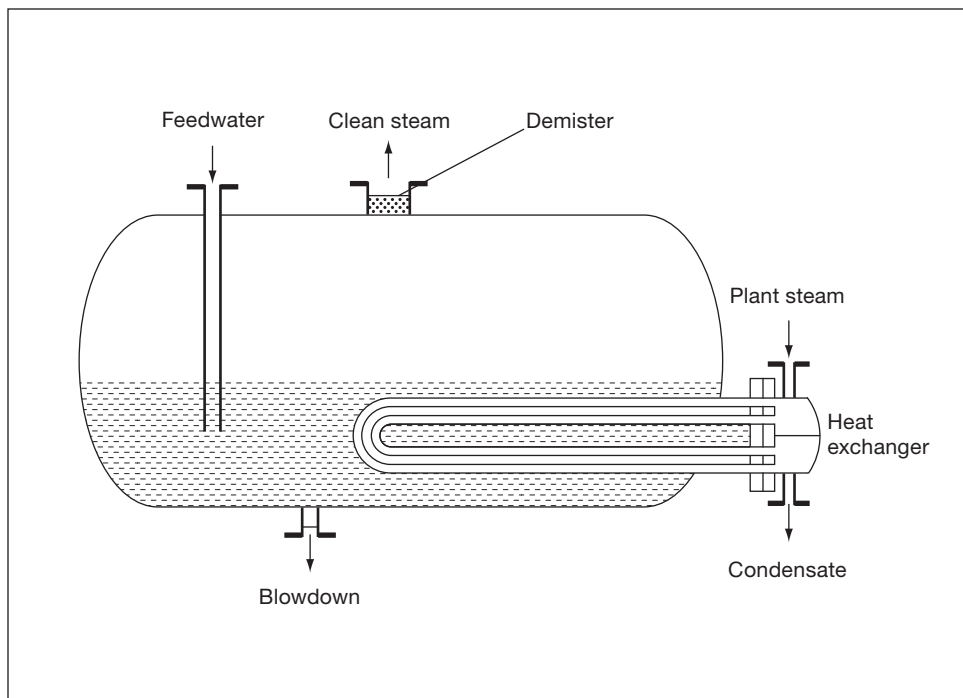
## 6.4 Generator overview

Purifying plant steam is possible to some degree. Filters, for example, can be used to remove particulates such as rust and particles; however, there is no practical method of removing volatile chemical contaminants from steam. Thus clean and pure steam must be generated independently, rather than be produced by the purification of plant steam.

Design of clean and pure steam generators is determined by the need to raise dry, saturated steam from water without added corrosion inhibitors or anti-scaling additives and without carryover of liquid droplets.

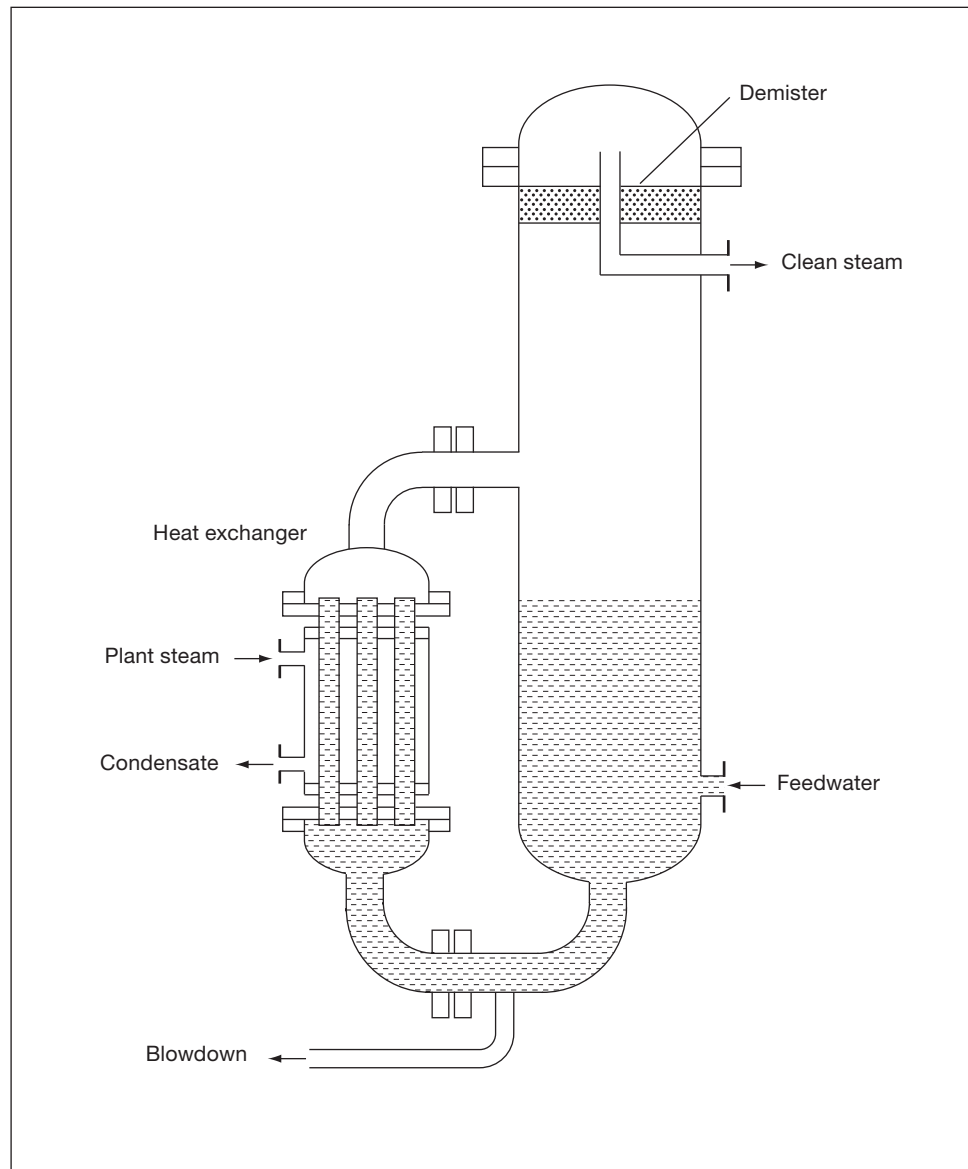
The simplest type of generator is similar to a conventional reboiler in design (Figure 1) and consists of a pressure vessel into which a tube bundle is inserted below the water level. Although this design is acceptable for generating clean steam, the fact that the steam vapour is generated below the liquid surface, causing it to entrain water as it rises, makes it unsuitable for producing pure steam. Also the high hold-up of liquid within the unit, requires a higher degree of blowdown to maintain a given steam quality making it less economic than other types of generators.

**Fig. 1 Reboiler type generator**



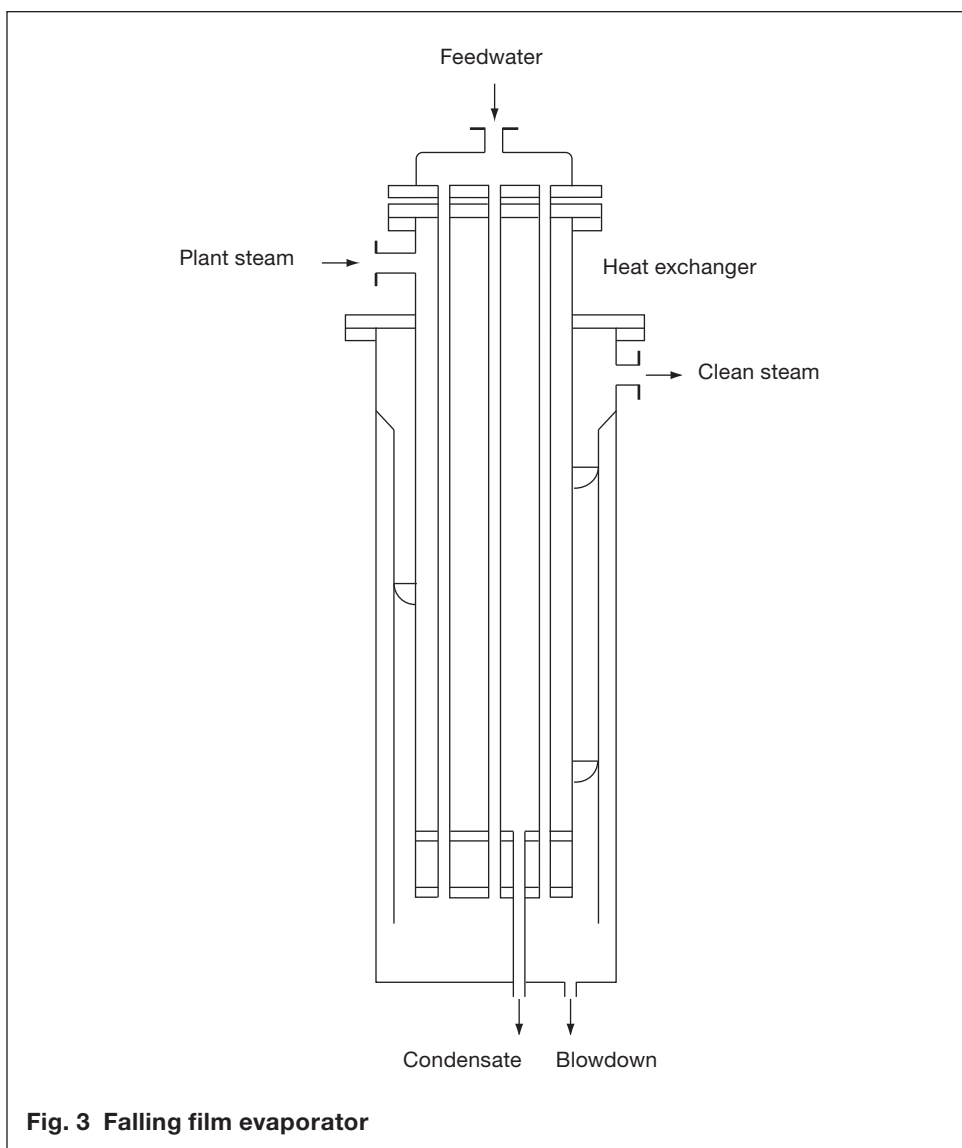
The thermosyphon type generator is one such design (Figure 2). It consists of a vertical pressure vessel connected to a vertical reboiler. Steam is generated on the tube surface of the reboiler and is discharged into the vapour space of the vessel. As steam is generated in the reboiler, a differential head is created which causes more water to flow from the vessel into the reboiler. Since the water in the vessel is close to boiling point, there is some flashing of the liquid to vapour; this can result in the production of some droplets in the clean steam. The pressure vessel is designed to have a relatively large diameter and to be relatively tall, to reduce the steam velocity and thus allow water droplets to separate. Additionally, thermosyphon generators are usually provided with a demister or baffle at the outlet.

**Fig. 2 External rising film evaporator / thermosyphon type generator**



The third type of design is the falling film evaporator (Figure 3). Water flows down through a tube bundle, being heated as it falls. At the base of the bundle the steam is discharged into the base of a jacket that surrounds the tube bundle. Such a design has a low liquid hold up volume, minimising the blowdown requirement and reducing the production of water droplets by flashing. A baffle arrangement between the outer wall of the bundle and the inner wall of the jacket causes the steam to move upwards in a spiral fashion. Any droplets that are entrained in the steam are removed by impingement on the baffles or the wall itself.

In small facilities, equipment costs can be minimized, sometimes by using pure steam bleed from the first effect of a WFI still. Some stills can produce pure steam and WFI simultaneously, while others may only produce pure steam when the production of WFI is stopped.



**Table 7**

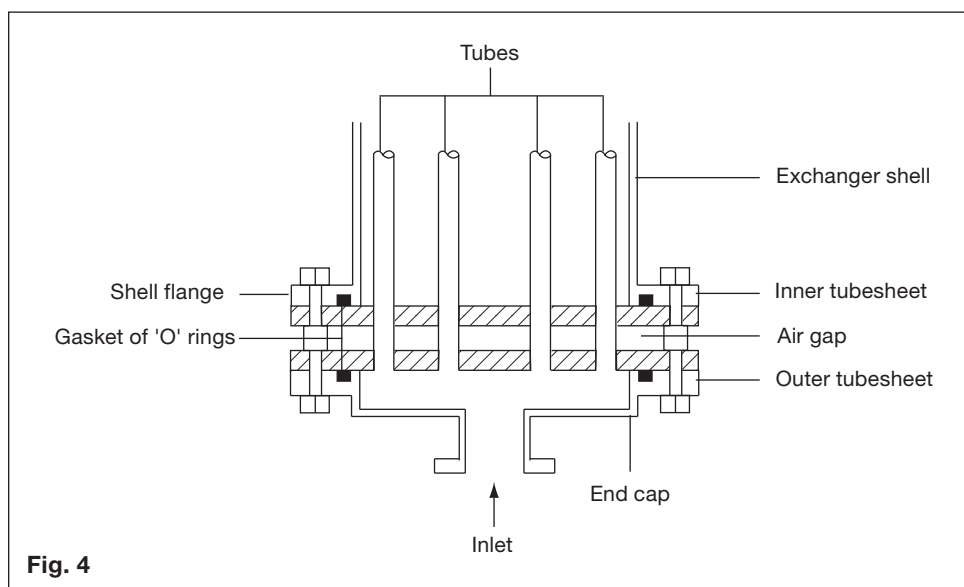
<b>Generator type</b>	<b>Advantages</b>	<b>Disadvantages</b>
<b>Pure steam from WFI still</b>	No need for separate generator	Limited simultaneous production of WFI and pure steam
<b>Evaporator type generator</b>	Low investment cost	No effective separation method  Poor steam quality / purity  High blowdown rates = high running cost
<b>Thermosyphone type - with external evaporator</b>	Quick reaction time  Short evaporator column reducing possible stress fatigue of tubes  Short external evaporator simplified maintenance	Depending on design, can produce poor quality steam
<b>Falling film evaporator</b>	Good steam quality	Long evaporator columns leading to; a. Susceptible to stress fatigue of tubes. b. Difficult to maintain as complete generator must be disassembled c. Large space required for disassembly  Slow reaction time to produce steam  Poor accuracy of steam pressure

## 6.5 Configuration of a pure steam generator

The inability to use corrosion inhibitors and the requirement for high purity, ion hungry feedwater, requires that the generator product contact surface be manufactured from corrosion resistant material, usually 316L stainless steel.

Sanitary construction includes orbital Tungsten Inert Gas (TIG) welding wherever possible or mechanical welding with the inner surface ground smooth after welding. All removable connections should be of sanitary design; tube butt weld or sanitary clamp fittings are preferred. Flanges and threaded connections are not considered sanitary.

To prevent possible cross contamination, heat exchangers using plant steam as the heat source, including evaporators, should be of double tubesheet, tubular design (Figure 4) to prevent contamination of the pure steam by the heating media.



Most pure steam generators, except perhaps those with very small output, are fitted with feedwater heaters, this often utilises the generators blowdown as the heating media. This obviously has the added benefit of cooling the blowdown and thus avoid discharging very hot and flashing water.

A feedpump may be required if the feedwater supply pressure is inadequate. Depending on the system design and the manufacturer, a feed pressure of approximately 0.5 – 0.75 bar g (8 – 10 psi g) above the maximum expected pure steam pressure is required. This allows for pressure drop in piping and valves.

A sample cooler fitted with a conductivity meter and alarm is often used to monitor pure steam condensate purity. Conductivity of the condensate will provide information regarding the suitability and applicability of the distributed steam for its final use.

### **Plant steam pressure**

The plant steam supplied to the generator at typically 7 to 8.5 bar g (100 to 120 psi g) must be at a higher pressure than the required pure steam pressure. In general, for a given size generator, the greater the differential between the plant and the pure steam pressure the higher the pure steam production rate. Plant steam pressure should be at least 2 to 3 bar g (30 to 45 psi g) higher than the pure steam pressure, to optimise the production rate. Plant steam consumption will be approximately 10% to 20% greater than the quantity of pure steam produced.

### **Surface finish**

Mechanical polishing (MP), electropolishing (EP) and passivation processes are implemented in some stainless steel clean and pure steam systems. Chlorine and / or chlorides will damage the generator regardless of the finish.

The operating temperatures of these systems are more than sufficient for inhibiting microbial growth. Therefore, MP is advocated for final finishing of mechanical welds, with mill finishes and final passivation to optimise the formation of the corrosion resistant chromium oxide barrier. Electropolishing will also optimise this barrier, and should be considered if passivation is not an option.

### **Configuration of a clean steam generator**

As previously discussed, there are biopharmaceutical applications that do not require pyrogen free pure steam, but that cannot accept plant steam. In such cases it may be more economical to utilise clean steam, produced in a generator that does not include many of the sanitary features of a pure steam generator. Savings may be worthwhile when the elimination of the internal steam separator is combined with non-sanitary features such as;

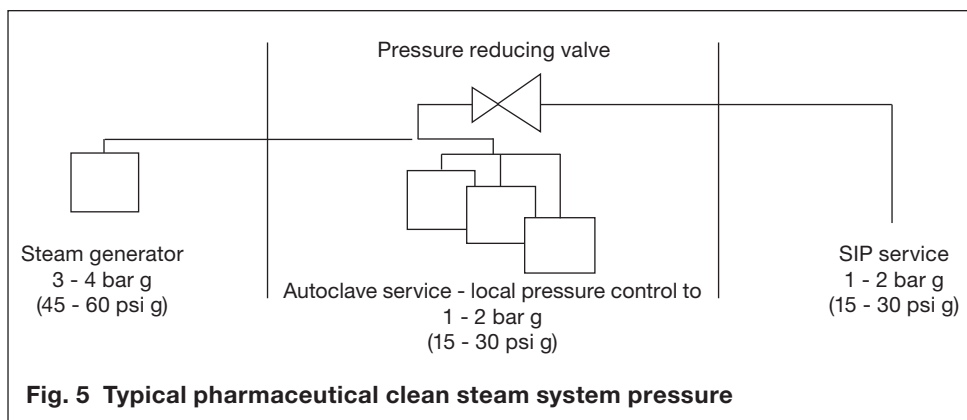
- Non-sanitary pipe and fitting.
- Non-sanitary instruments and valves.
- No polishing.
- Minimal controls.

### **Pure steam pressure**

Pure steam pressure in the biopharmaceutical industry is usually defined by the requirements of the autoclaves. Sterilisation in pharmaceutical manufacturing is usually carried out at 121 - 135°C (equivalent to 1 - 2 bar g or 15 - 30 psi g saturated steam). Typically, autoclaves have their own pressure control valve at the steam inlet, and this will have a related pressure drop. Therefore, autoclave manufacturers typically demand a supply pressure of about 3 - 4 bar g (45 - 60 psi g).

Again 1 - 2 bar g (15 - 30 psi g) saturated steam is used for sterilisation-in-place (SIP) of vessels, equipment and pipelines. These pieces of equipment typically do not have independent pressure control and are dependent on the supply pressure of the steam. In such cases a steam header is usually fed with 3 - 4 bar g (45 - 60 psi g) steam with a pressure regulator provided to reduce the pressure to the required 1 - 2 bar g (15 - 30 psi g)

Clean steam in the biopharmaceutical industry is typically used for non-critical humidification and as such is usually produced at around 1 bar g (15 psi g).



Conventional plant steam boilers are often direct-fired, using gas or oil as the primary heat source. Such an option is not available for clean and pure steam generators as corrosion in the fired tube sheet is unavoidable. Therefore, heating is usually indirect, most commonly by plant steam, but also pressurised hot water or thermal oil. Small capacity generators that use electrical heating are also available.

Treated water is fed to the steam generator, but as the water is evaporated even low levels of feedwater contaminants become concentrated in the liquid hold-up volume of the generator. These contaminants must be discharged, a process known as blowdown. The quality of the feedwater dictates the frequency of this operation. With high-quality feedwater intermittent blowdown may be adequate, but for lower quality water, continuous blowdown of up to 15% of the feedwater flow may be employed. The operation can be automatically controlled from conductivity measurement of the hold up liquid. Blowdown must be cooled to prevent flashing as it is released from the generator pressure. In larger generators the energy efficiency may be increased by using the blowdown to pre heat the incoming feedwater via a heat exchanger.



# 7

## Clean and pure steam distribution

### 7.1 General information

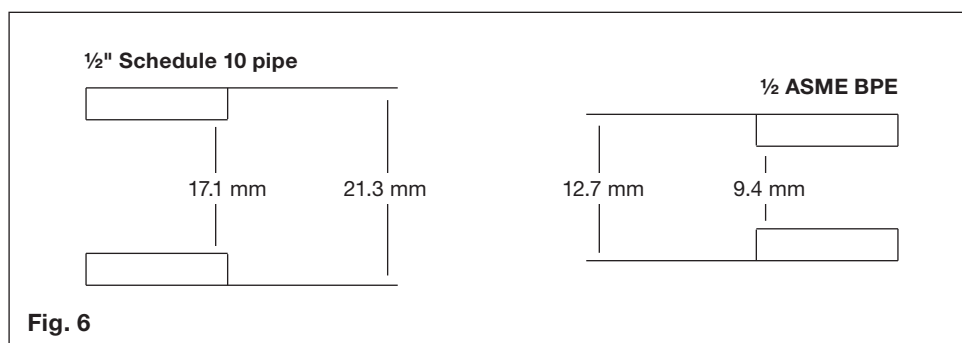
The key requirement of a clean and pure steam distribution system is that it delivers steam to the point of use in an uncontaminated, dry, saturated state without superheat. The general principles of steam distribution that apply to utility steam systems also apply to clean and pure steam, but there are some significant differences, primarily in the materials of construction and the need for sanitary design.

Steam at 121°C kills microorganisms and their spores. In well-designed clean and pure steam systems, adequate removal of air and condensate will allow the steam to contact all surfaces and sanitary design is consequently less important than it is to PW and WFI systems, or in pharmaceutical process piping. However, the following should be observed to ensure a well-designed system:

### 7.2 Line sizing

As with plant steam systems, the distribution system for clean and pure steam should be correctly sized to prevent erosion and noise. Typically generation will be at around 3 - 4 bar g (40 - 60 psi g) to minimise line size, reduce heat loss, lower installation costs and increase dryness fraction of the steam from the generator. Where a generator is used to serve a single point of use or adjacent multi points of use, then generation will often be at the required pressure, which is typically 1 - 2 bar g (15 - 30 psi g), corresponding to temperatures of 121°C - 135°C (250°F - 275°F) for sterilisation.

Whatever the pressure, the line should be sized with maximum recommended velocities of 35 m/s (120 ft/s) for pipe and 30 m/s (100 ft/s) for tube. Note that the sizing criteria for tube and pipe systems are fundamentally different due to the differences in dimensional specifications. For example, a ½" schedule 40 pipe has an internal diameter (I/D) of 15 mm (0.622"); while a ½" imperial pharmaceutical tube with a 0.065" (1.6 mm) wall thickness has an internal bore of only 0.37" (9.4 mm). The cross sectional area of the tube is only 39% of the pipe. A velocity based sizing chart for tubing can be found in the Appendix (Section 10).



### 7.3 Air removal

Air or other non-condensable gases will inevitably be present in a distribution system at start-up or after any period of inoperation of any section. This must be effectively removed to prevent incomplete sterilisation of the process, because air, even if mixed with steam, is an effective insulator. An air film of 1 mm thick has the same thermal resistance as a layer of copper 15 m thick. In real terms, this thin film present at the heat transfer or sterilising surface will reduce the temperature of the condensate film interface; with steam at 121°C (250°F) this reduction will be 5°C (41°F), resulting in incomplete sterilisation.

To effectively and automatically vent air and other non-condensable gases from the distribution system, balanced pressure thermostatic clean air vents should be installed on the following: distribution headers, separators, reactors, autoclaves and other pieces of equipment.

## 7.4 Removal of entrained moisture

Generally speaking, steam produced from a pure steam generator needs to be very dry, as the carryover of water droplets will affect conductivity and purity levels. However, as soon as the steam leaves the generator and passes through the distribution system water vapour starts to form in the steam system due to heat loss reducing the steam quality.

Steam may be dried of moisture by reducing the generated pressure just prior to the point of use to coincide with steam saturation temperature at the required pressure.

Depending on the system design, steam traps alone may not be sufficient to remove this moisture and an inline separator (Figure 7), may be required at the point of use, just prior to, or just after, the regulator. If the separator is located upstream of the regulator, the regulator should be protected from water damage (wire drawing) and impingement damage on the regulator diaphragms.

In-line separators of sanitary design are available in a range of sizes and remove moisture with a series of baffles on which the suspended water droplets impinge and fall out by gravity to the drain, which must be piped to a trap. Spirax Sarco separators have a separation efficiency of better than 99% in the removal of all liquid entrainment.

Sanitary type cyclonic separators are also available, however these have been found to work better at fixed velocities, and under more realistic conditions, where velocities fluctuate, the baffle plate design gives higher efficiencies.



**Fig. 7**

## 7.5 Prevention of superheat

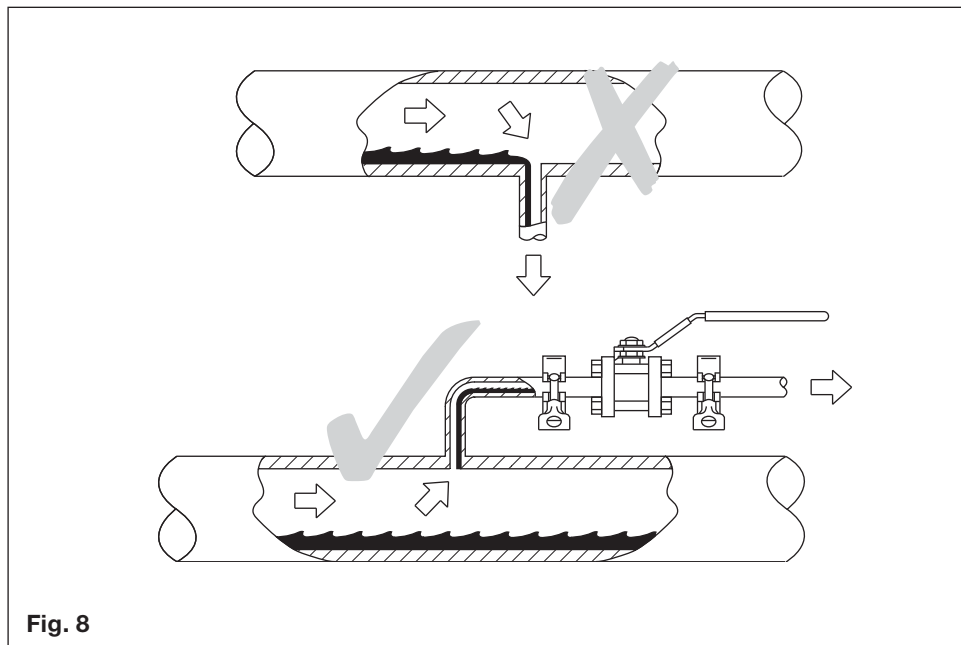
Dry saturated steam becomes superheated when it is reduced in pressure, such as might occur when a low-pressure header is supplied via a pressure reducing valve, or where there is a large pressure drop through piping. Energy from the high pressure steam is released by the pressure reduction process, so raising the steam temperature above its saturation temperature at the lower pressure.

Conversely, there are features in a steam system that act against superheating. The presence of condensate in the high pressure steam reduces the probability of generating superheat, as the excess energy has to evaporate the condensate foremost. The lower pressure steam will either be wet, dry or superheated depending on the degree of wetness in the higher pressure steam and the pressure drop taking place. Also heat losses from piping will cause the steam temperature to fall, causing the steam to revert back to either a saturated or a wet state.

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 46 bar a (60 psi a), then the reduced pressure should not be less than 2 bar a (30 psi a). But each situation must be taken on its own merits.

## 7.6 Steam take-off

Good engineering practice dictates that steam take-offs from main header or distribution lines should be taken from the top of the piping rather than the bottom, as illustrated in Figure 8. This will help ensure the steam remains dry for its transition from main line to branch line.



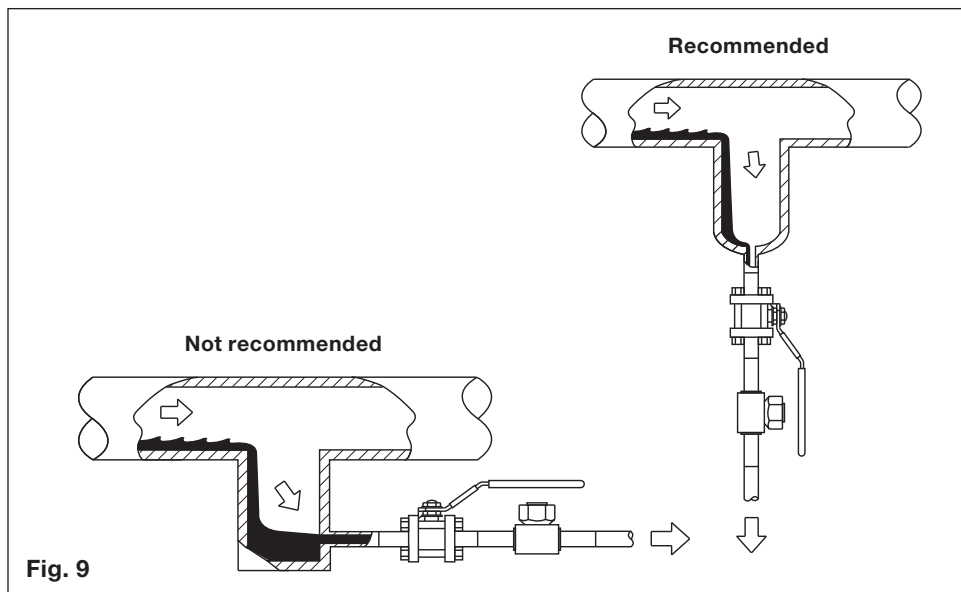
## 7.7 Condensate removal

In any steam distribution system, condensate will form due to radiation losses from the line. Much of this will fall to the bottom of the line resulting in the risk of waterhammer. If not removed, water can damage valves and fittings, and reduce heat transfer capability at the point of use.

When considering clean and pure steam, the additional problem of bio-contamination is of concern. Pockets of stagnant condensate can be an ideal breeding ground for bacteria and microorganisms - these can potentially lead to system failure due to unacceptable levels of endotoxins.

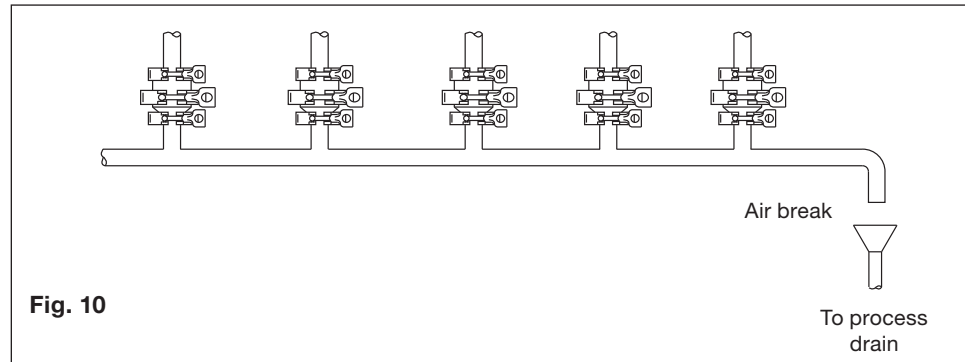
To minimise condensate retention in the distribution system, the following general guidelines should be followed:

- Pipes should be sloped to direct condensate to low levels where steam traps are installed. Typically horizontal lines should have a minimum gradient of 1:100.
- The line should be adequately supported to prevent sagging, thus minimising dead spots where condensate can collect.
- Steam traps should be installed at all points where condensate can collect. For example at least every 30 m (100 ft) intervals, upstream of control valves and isolation valves, at the bottom of vertical risers and at any other system low points.
- Collection pockets should be of equal size to the distribution line for sizes up to 4", and one or two sizes smaller for lines of 6" or larger. These should be trapped at the bottom, again avoiding any risk of condensate retention.
- Steam traps should drain collection pockets vertically downwards to avoid any risk of condensate hold up, as illustrated in Figure 9.



- Wherever possible, the action of gravity should be utilised, and the use of overhead return systems should be avoided.
- The use of air breaks should be used to ensure there is no backpressure downstream of the steam trap. This break should be at least 50 mm or 2 pipeline diameters, whichever is greater. Where steam traps discharge into a local manifold, the air break should be provided at the manifold outlet or the closest convenient location.

Where the air break is in a clean room, using an expansion pot at the end of the manifold, and venting through a filtered vent outside the clean room could prevent the potentially harmful effects of flash steam. The vent filter could alternatively be located at a 'kill' tank, if used.



- Group trapping should be avoided - i.e. always use a single trap for draining each process line, vessel, etc. Failure to do this will invariably cause back-up of condensate in the system.
- Dead legs should be avoided by the careful design of pipeline runs and the use of steam traps to remove condensate - i.e. instrument branches should be installed vertically upwards to avoid condensate retention.
- The system should be designed to minimise condensate formation. Therefore, adequate insulation is important, especially where clean steam lines are run through unheated service areas. Thermostatic type steam traps should not be insulated, as these need to be able to radiate heat to operate.

Condensate from pure steam systems should not be recovered for re-use in generation, due to the potential for contamination from process residues. However, it is sometimes collected and used in the plant steam system (provided it is not contaminated).

Plant steam condensate usually employs mild steel or gunmetal components. The highly corrosive nature of clean and pure steam condensate requires the use of stainless steel piping, traps and fittings. Grade 316L stainless steel is most resistant to corrosion.

In biopharmaceutical plants, employing recombinant or pathogenic organisms under bio-containment conditions, means the pure steam condensate system may potentially contain viable organisms. In such cases, the condensate will be discharged to a disinfection or 'kill' tank for chemical or thermal treatment. The tank will typically have one or two 0.2 micron sterilising filters on its vent to prevent escape of any viable organisms. Flash steam from the condensate can block this filter, causing pressure fluctuations in the condensate system, and thus allowing the possibility of condensate back flow into sterilised process systems. Possible methods for dealing with this are:

- Subcool the condensate upstream of the disinfection tank.
- Install a condenser and drain(s) upstream of the vent filter.
- Heat the vent filter housing by electric tracing or steam jacket.

## 7.8 Steam traps

In simple terms, the purpose of a steam trap is to automatically discharge condensate while maintaining live steam within the system. Steam traps for use on clean and pure steam systems usually fall into two categories:

1. Drip traps to remove condensate from mains distribution systems upstream of the process connections.
2. Process drain traps which remove condensate from the process. For example: SIP applications on the process piping, tanks, reactors etc.

Clearly, drip traps will usually be constantly live and no process fluid should ever find its way into the trap. Process traps however, will typically be used intermittently and will often have process fluids flushed through them during certain cleaning or process operations. The selection criteria for each trap is subsequently quite different.

Two different steam trap types are preferred for these applications:

- **Thermodynamic** traps operate on a velocity principle discharging lower velocity cool condensate and closing when the higher velocity hot condensate or steam impacts them.

They do have poor resistance to blockage and as such should not be used in applications where steam could carry any solid residues, i.e. Bioreactor SIP applications. They usually stay open when they fail. Thermodynamic traps are suitable for clean steam distribution headers and other applications where they are constantly exposed to steam.

- **Balanced pressure thermostatic** traps operate on the temperature differences between steam and condensate. They incorporate an element which is filled with an alcohol / water mix, which expands at a given temperature blocking the flow of steam, but opening to the lower temperature of condensate. There must be a temperature range over which this element closes and therefore these traps do retain some condensate on the upstream side of the trap and allow it to sub cool. An uninsulated length of pipe should be allowed upstream of the trap and this should be of such a length that the condensate cools but does not back-up into the system.

A near-to-steam element allows condensate drainage with minimum sub cooling, typically between 2°C and 5°C below the steam saturation curve. If a temperature measuring device is used to verify sterilisation temperature, as is the case on many SIP applications, then this should be installed with the longest condensate leg possible, typically 300 mm - 450 mm (12" - 18").

Key benefits of thermostatic traps:

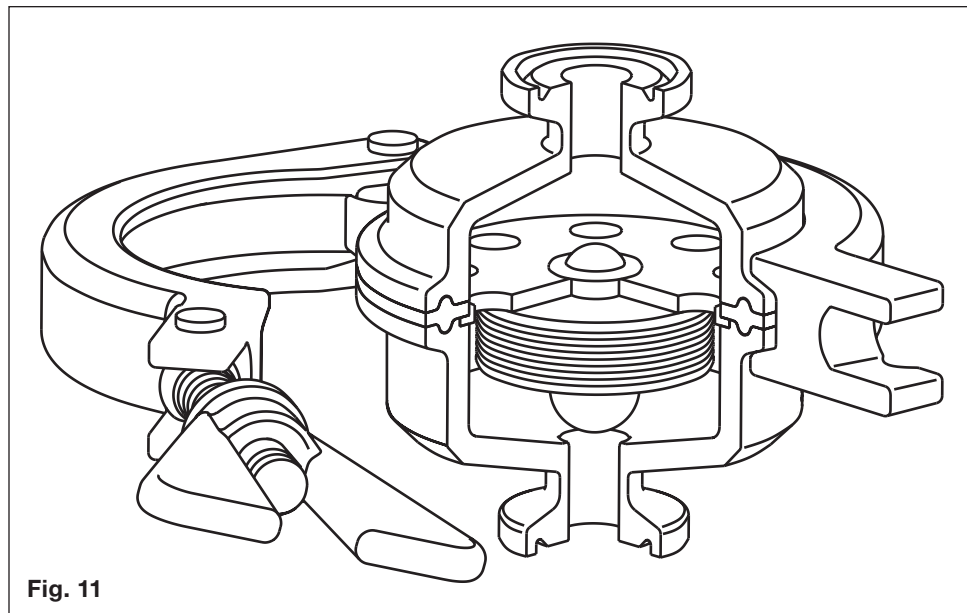
- Normally fail in the open position.
- They have good air-venting capability, so are good for intermittently used steam equipment where rapid air venting is required to decrease heat-up times, i.e. autoclaves, WFI piping and bioreactors.
- Some designs offer complete drainability of the housing.

Thermostatic type traps are the first choice as a clean process drain trap and, depending upon user preference, are often also used as a mains drainage trap.

Process drain traps require the following additional criteria:

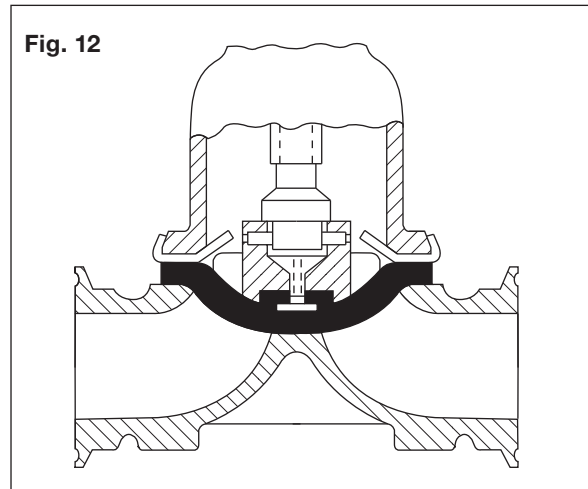
- To allow good drainability / cleanability, an internal surface finish of 180 grit or 0.5 - 0.6 micron Ra (20 - 25 micro inch) is typically required. This will allow any process debris to easily pass through the trap during the SIP cycle.
- A clamped body arrangement is usually desired to allow rapid disassembly of the unit for cleaning and maintenance. This can happen frequently, sometimes after each batch.
- The drain angle at the bottom of the trap should be a minimum of 15° to allow easy drainage.

Mains distribution drip traps do not usually need to have a high quality internal surface finish, as they are constantly exposed to steam and thus sanitized.



## 7.9 Isolation valves

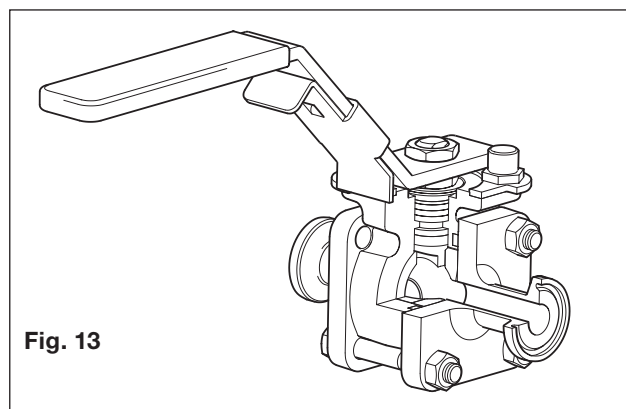
There are two main types of valve, which are used for isolation on pure steam systems: diaphragm and ball. The optimum choice depends on the application, but it is clear that from a sanitary point of view, diaphragm valves (Figure 12) are the better design. However, they are not well suited for continuous use of steam service where pressures exceed 1.5 to 2.0 bar g (20 to 30 psi g) and the valve is normally open. For these applications primarily on the distribution system, ball valves of sanitary design (Figure 13) are the valve of choice since their rugged design lends itself to continuous steam service. As discussed earlier, and provided the supply is constant, the self-sterilising nature of steam should assure aseptic operation.



Ball valves for clean applications differ from traditional ball valves in the following respects:

- **True port design** - The I/D of the ball valve is exactly the same as the connecting tubing. This removes the possibility of having a 'step' in the pipeline and thus ensures the system remains free draining.
- **Cavity filler** - The design of a traditional ball valve means that there is a gap or cavity around the ball - the use of cavity filler eliminates this gap. However there is some debate in the industry as to whether sanitary ball valves should utilise this seat arrangement or not. Some feel that if cavity filler is used then steam can find its way under the seat surface and become an area for bacteria growth. ASME-BPE advise against the use of cavity fillers.
- **Surface finish** - As per pure steam distribution line.
- **FDA / USP compliant seals**

For aseptic reasons, diaphragm valves are usually selected for the final valve in the steam system, i.e. the one that has steam on one side and process on the other. On applications such as this, clean ball valves are sometimes closely coupled upstream of the diaphragm valve to provide a double block arrangement, preventing continuous steaming of the diaphragm valve. Where diaphragm valves are subject to steam service it is important to initiate preventative maintenance programmes to routinely change out diaphragms.

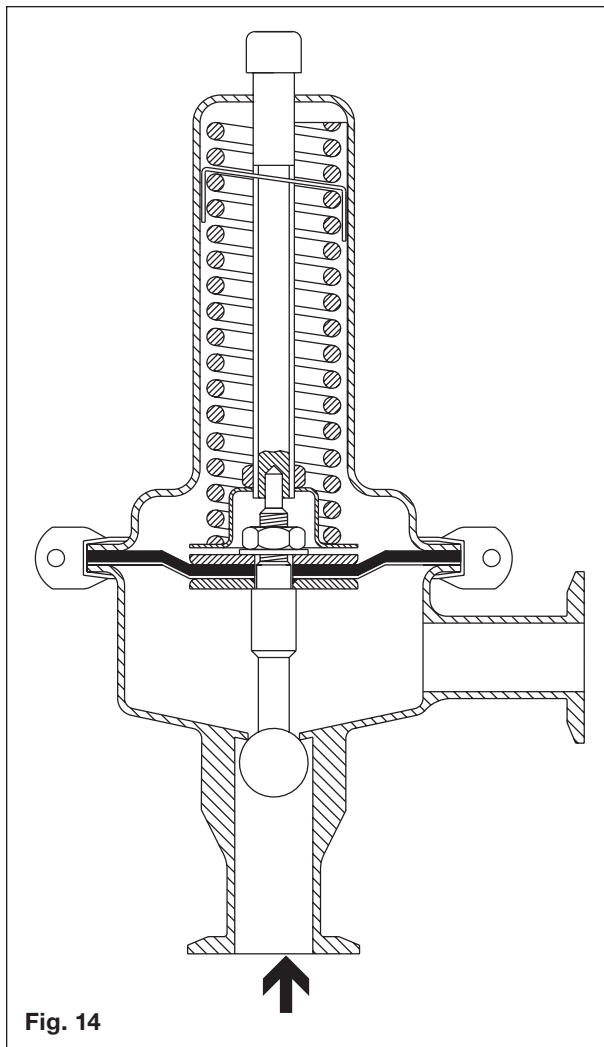




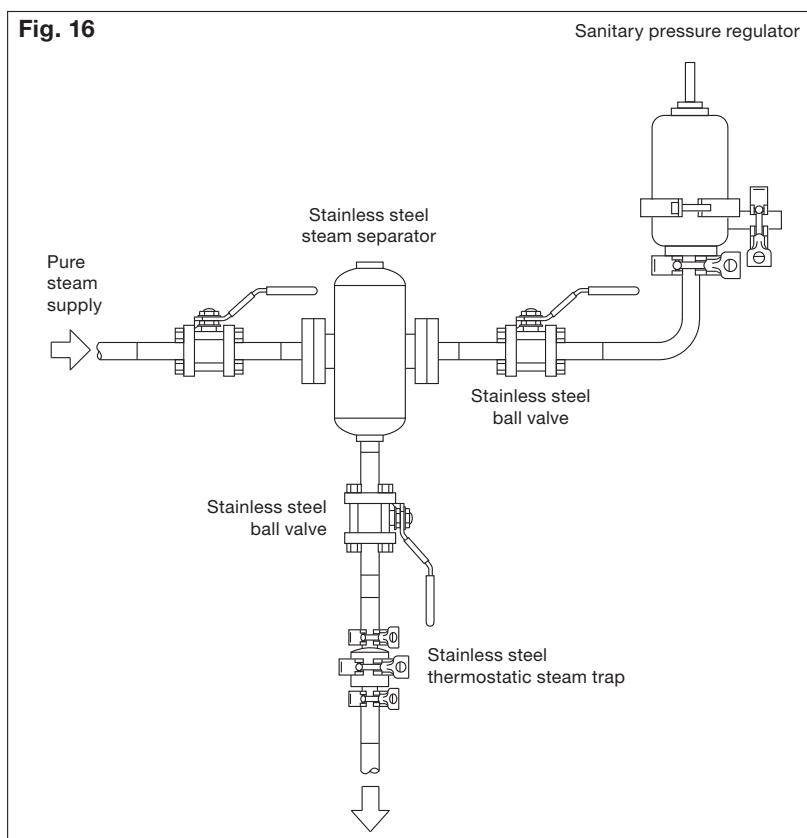
## 7.10 Pressure control

The simplest way to reduce steam pressure at the point of use is with a direct acting pressure regulator of sanitary design as illustrated in Figure 14. Steam enters the inlet at the bottom of the valve and passes through the valve seating arrangement. The pressure acts on the underside of the diaphragm, counteracting the spring force, which is set using the adjustment screw. The valve will modulate to maintain a force equilibrium giving a steady downstream pressure.

For applications that require very fine pressure control or where large pressure turndown is required, an electrically or pneumatically actuated control valve of sanitary design should be utilised, as illustrated in Figure 15.



Any modulating control device such as a pressure regulator used on steam service must be provided with dry steam supply, which is free of entrained water droplets to prevent wire drawing of the valve seating surfaces. A recommended installation is illustrated in Figure 16.



## 7.11 Check valves

The ASME BPE states that the use of check valves for hygienic process piping systems requires caution and is not recommended. This is of course due to the fact that if a check valve is present this will result in a non-free draining system - there will always be a certain amount of fluid backed up behind the check valve.

However, there are instances where the use of a check valve is the lesser of two evils. If steam traps are discharging into a disinfection or kill tank that is under pressure (these tanks are often injected with live steam to raise the temperature and thus sterilise the contents) there is a high risk of back flow through the steam trap into the clean system, resulting in contamination. The use of a check valve in this situation is often considered the best solution to this problem.

## 7.12 Sampling

When required by the process, the steam purity shall be monitored through acceptable sampling techniques. A slipstream of the steam may be passed through a sample cooler, fitted with a sampling valve.

To ensure that the steam does not contribute to the drug product contamination, sampling should be included during commissioning, as a good engineering practice, and / or prior to each time the steam is used.

If the sampling requirement is for endotoxin or pyrogen testing, the sample cooler, tubing and valve should be of sanitary construction.

Sample coolers are typically fitted to the generator, at points in the distribution line and / or at the point of use. It is commonplace to fit sample coolers with conductivity monitors and alarms at the generator.

# 8

## Key application information

### 8.1 SIP process

Biopharmaceutical sterilisation or steam-in-place (SIP) systems are used to sterilise process equipment after a batch of product is completed. Such systems are necessary because equipment such as bioreactors, fermentors, and the accompanying tubing must be cleaned and/or sterilised before a new production cycle begins. These systems are constructed from high grade, stainless steel materials, as well as flexible materials (e.g. teflon-lined piping) approved by the FDA or the USP.

Steam pressures for these systems are typically 1 to 2 bar g (15 to 30 psi g) with corresponding temperatures ranging from 121°C to 135°C. The relationship between pressure and temperature is predictable; however, sterilisation times will depend on the temperature and nature of the item being sterilised. In general, the lower the temperature, the longer it takes to sterilise. The sterilisation time / temperature relationship in a typical SIP process will occur at about 121°C for 30 - 40 minutes. For systems with hard-to-reach components, time may be longer.

Steam quality is very important. Typically, a dedicated steam generator provides the necessary volume; temperature and pressure of steam needed to sterilise each system. To ensure that each component and all piping are completely sterilised, temperature sensors are placed in critical and hard to reach areas to gauge whether the components and piping reach the sterilisation temperature for the required time.

During this entire process, modulating valves are used to maintain the required clean steam pressure, temperature and flowrate.

During the SIP process, condensate generated from the steam must be quickly removed from the system. This is done through proper placement of clean steam traps, which also maintain the high temperatures needed for the sterilisation cycle.

Key considerations for designing an SIP system:

- Process vessels and piping to be sterilised must be fully capable of withstanding the temperature and pressures associated with the steam.
- Provision must be made for adequate condensate removal. The process system should be suitably trapped, and designed to promote drainage of condensate.

An adequate cooling leg should be provided to allow condensate to not back-up into the vessel, resulting in potential cold spots.

In SIP applications, it is likely that process fluid and debris will enter steam traps along with condensate, especially during start-up. In order to reduce the risk of trap blockage, the trap should have a smooth surface finish typically 0.4 micron Ra to 0.8 micron Ra and have a large valve orifice, which allows fluids to pass freely prior to normal steam operation.

- Sufficient air venting should be provided on the process system to prevent the formulation of air pockets, which can lead to cold spots. Inverted thermostatic steam traps or a specifically designed, clean air vent, are the most suitable products for this application.
- Process systems, which incorporate SIP, should be designed to ensure that steam will pass through the entire system, for example narrow restrictions should be avoided. Furthermore, all potential cold spots should be identified and if necessary, the temperature of these areas should be monitored throughout the SIP process.
- Steel structures connected to the process vessel, such as supporting structures, will act as heat sinks and will often be cold spots. Compensating steam may be required to heat these areas to overcome the effects.
- Most vessels will have dead legs, for example, for piping to a pressure gauge or to a valve. Steam will not readily flow into these dead spaces and there may be insufficient heat transfer to sterilise them. The length of dead legs should therefore be minimised. In the pharmaceutical industry, dead legs are typically limited to three pipe diameters in length.

## 8.2 Clean in place (CIP)

Clean-in-place (CIP) is an automatic method for washing tanks, piping and other process equipment using cleaning fluids such as detergents, acids, alkalis and water. A CIP system typically consists of reservoirs of detergents and rinse water together with pumping and heating systems for the solutions.

CIP systems can be used to clean a wide range of equipment used in the process industry. Indeed most equipment in which cleaning solutions can be made to contact the surfaces either by spraying or by circulation of the fluid under pressure can be CIP cleaned. Typically, examples of such equipment include:

1. Process and storage tanks.
2. Piping systems including pumps, valves and other ancillary equipment.
3. Suitably designed process equipment - a wide range of process equipment used in the food, dairy and biopharmaceutical industries can be designed to accommodate CIP systems.

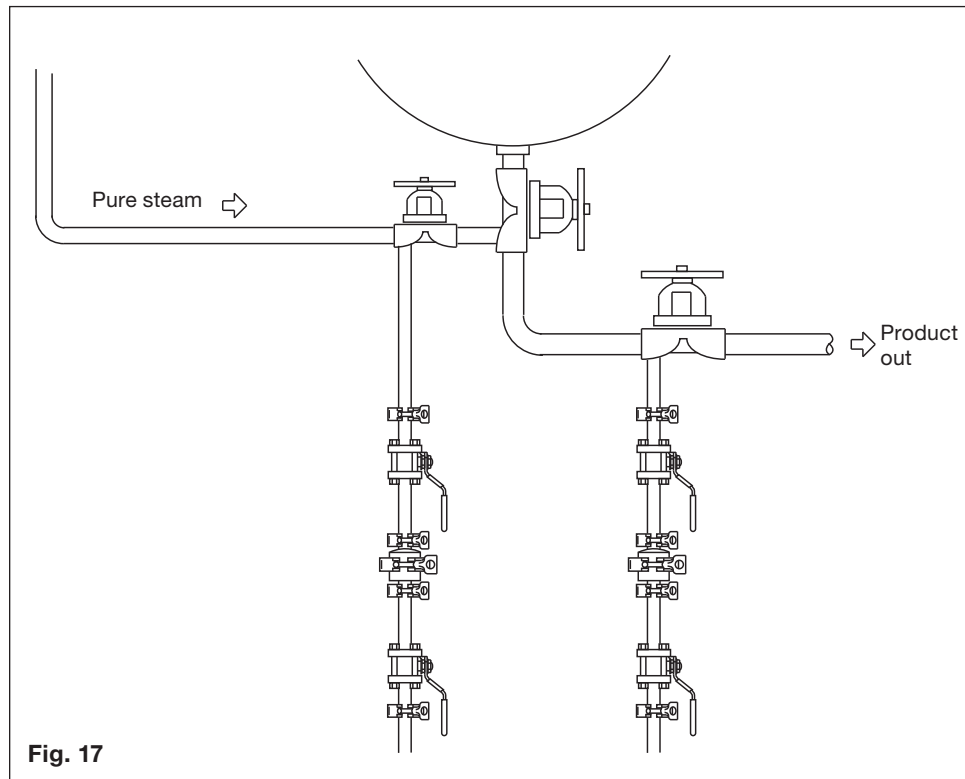
The stages involved in the CIP process will vary depending on the particular application and the relevant standards, but will usually include the following steps:

1. **Pre-rinse** - This involves flushing the systems with low-grade water, often recovered cleaning solution. The water is usually at ambient temperature so as not to 'set' any remaining process fluid on the equipment surface.
2. **Detergent wash** - A heated alkaline solution is passed through the equipment. The solution is typically heated to between 60°C and 80°C.
3. **Post-rinse** - The system is flushed with clean water to remove the detergent.
4. **Acid rinse** - A final rinse is passed through the system to neutralise any remaining traces of the alkali detergent.
5. **Final rinse** - A final rinse using pure water is performed to remove all traces of the chemical solutions.

In applications where sterility is required, the CIP procedure is usually followed by an SIP cycle.

## 8.3 Block and bleed / sterile barriers

Sterile barriers, or block and bleed systems, are used extensively in the biopharmaceutical industry to prevent contaminating organisms from entering the process and, for some applications, to prevent possible contamination of the 'outside environment'. A simple example is shown in Figure 17.



Due to piping arrangements, process fluids will often be flushed through the trap. This can often result in plugging if standard industrial designs of traps are used. Therefore traps with large self-draining design should be selected. Quick release sanitary clamps are also preferable to facilitate periodic cleaning

## 8.4 Steam steriliser / autoclave

The steam sterilisation process will include some or all of the following steps:

- 1. Loading** - Sterilisers may have a single or double door design. The double door (or pass through) type is used in clean room or biohazard situations; the load is inserted into the steriliser through one end (dirty room) and then removed from the other (clean room). This helps prevent contamination or recontamination of the goods and the environment.
- 2. Preheating** - Some sterilisers include a steam jacket which surrounds the sterilisation chamber. When the steriliser is first started, the jacket is filled with steam, heating up the chamber and acting as a steam reservoir. This can help reduce the time taken by the steriliser to reach the required temperature and pressure, particularly if the steriliser is to be used repeatedly or when liquids are to be sterilised.
- 3. Exhaust/purge cycle** - An important consideration when using steam sterilisation is the removal of the air from the system. If air is present, it will act as a thermal insulator, preventing proper sterilisation of the load. However, it should be noted that some sterilisers deliberately include a proportion of air in the steriliser to reduce the temperature, in which case, a longer sterilisation cycle is required.

The successful removal of air is indicated by the Bowie Dick test and air detector tests (see BS EN 285).

There are two methods of removing the air:

- Downward (gravity) displacement - since steam is lighter than air, if the steam is injected through the top of the steriliser, the air will tend to accumulate at the bottom of the chamber, from where it can be vented.
- Vacuum - a vacuum pump is used to remove air from within the chamber, before steam is allowed to fill it. This process may be repeated several times to ensure that as much air as possible has been removed.

Evacuation of the chamber is essential where the load is packaged in porous materials or where the devices incorporate areas where air may become trapped, for example, instruments with narrow lumens such as suctions, cannulas etc. Care needs to be taken when 'disposing' of the evacuated air as it may contain the hazardous substances that sterilisation is intended to destroy. The purged air should be filtered or heated sufficiently before it is discharged to the atmosphere. Discharge of untreated air has been linked to an increased rate of nosocomial infections in hospitals (nosocomial infections are those that are contracted whilst in the environs of the hospital).

- 4. Steam injection** - Steam at the required pressure is then injected into the steriliser; it will take some time for the entire chamber and load to reach the sterilisation temperature - known as the 'equilibration time'.

Having reached this temperature, the entire chamber is maintained at the sterilisation temperature band for a period of time related to the temperature - known as the 'holding time' (Table 8).

**Table 8 Sterilisation temperature and holding times**

Sterilisation temperature (°C)	115	121	126	134
Minimum holding time (minutes)	30	15	10	3

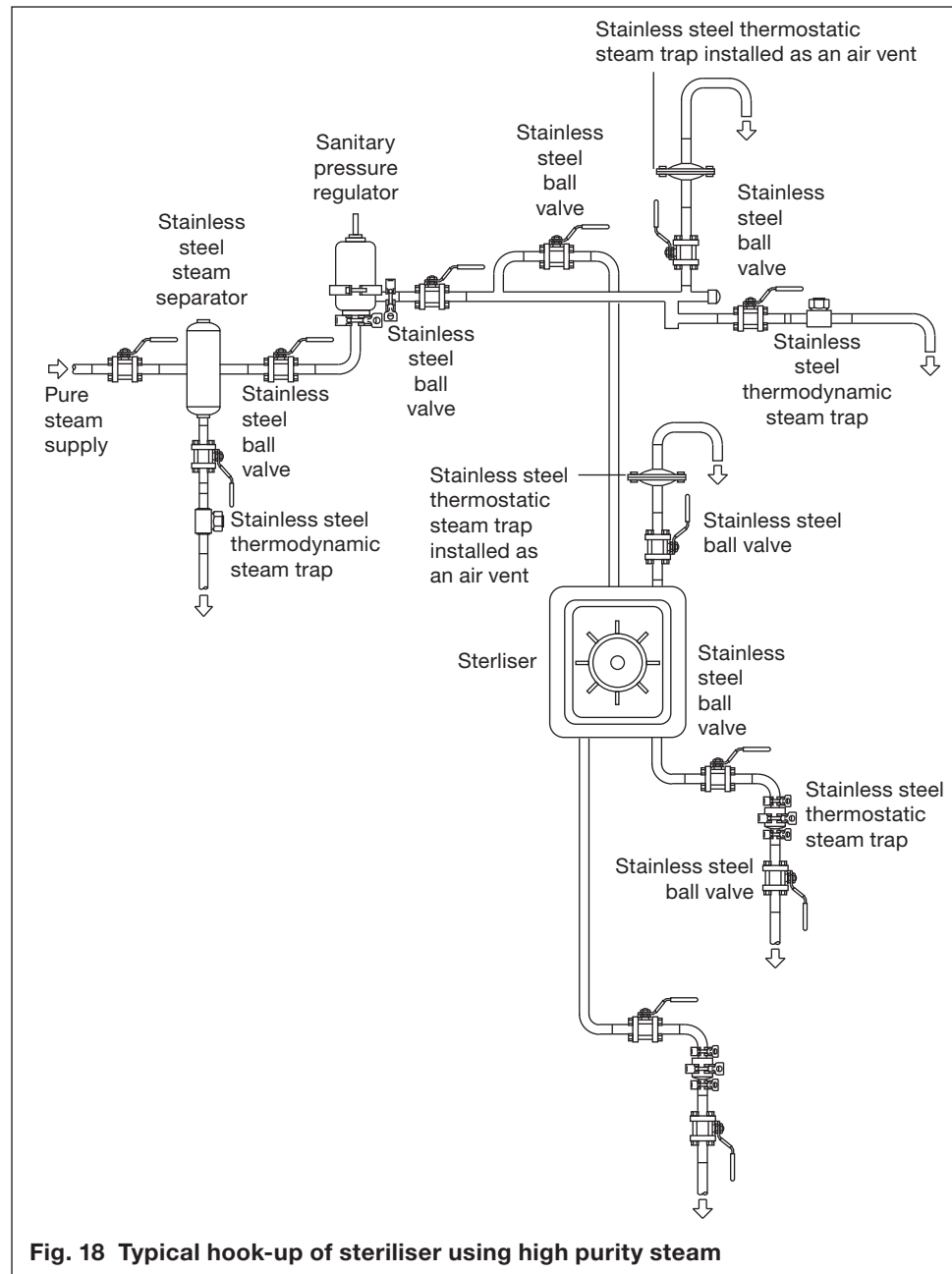
- 5. Collapsing of the steam (cooling)** - The steam is then condensed and drained from the chamber via a steam trap. Condensation may be performed by spraying the chamber with sterile water; alternatively, compressed air may be used. Additional cooling of the load to room temperature may also be required.
- 6. Drying** - evacuating the chamber will cause water remaining on the surface of the load to boil off. Alternatively, a cooling fan or compressed air may be used to dry the products.

The following points should be considered when designing the steam supply system for a steriliser:

- The distribution system between the generator and the steriliser should be sized to carry the sum of the peak steriliser demands.
- Adequate trapping and venting of the upstream supply system should be provided to ensure the removal of condensate, air and other non-condensable gases.
- The steam service to the steriliser plant room should terminate in a header, which should be adequately trapped and vented. This will facilitate the removal of air and condensate during start up and during periods of light or no load. The header is not intended to provide a steam reservoir, nor is it intended to facilitate the removal of non-condensable gases, entrained in the steam supply to the steriliser during its cycle.

- Figure 18 illustrates a typical clean steam system supplying a steam steriliser. A separator fitted with a suitable trap should be installed upstream of the reducing valve. This not only helps to prevent wiredrawing of the valve and waterhammer, but also increases the dryness fraction of the steam entering the steriliser.

Careful sizing of the reducing valve is required; an undersized valve will result in failure to achieve the sterilising temperature within the cycle time, an oversized valve can cause excessive pressure fluctuations, affecting the quality of the control provided by the valve.



## **Steam quality**

The quality of the steam used in a steriliser depends on the particular application and the associated standards. However, the presence of entrained water, non-condensable gases and superheat is undesirable and every effort should be made to reduce their levels. EN 285, HTM 2031 and HTM 2010 put limitations on these as follows:

- Non-condensable gases should be less than 3.5 ml/100 ml of steam.
- The degrees of superheat in free steam at atmospheric pressure should be less than 25°C.
- The dryness fraction should be greater than 0.9.

## **Background**

It is widely accepted that the original source for the test limits came from the British National Health Service with the first references appearing in HTM 101 (subsequently superseded by HTM 20102). In addition to their adoption by European standards, the same limits may be found in ISO 111343. At the outset, the limits were established pragmatically and further information may be found in 'The Derivation of United Kingdom Physical Steam Quality Test Limits 4'.

While HTM 2010, ISO 11134 and EN 2855 contain the same limits; no clear guidance is provided on the location of the sample points or interpretation of the results. In the case of both dryness value and superheat tests this is an important factor.

## **Application**

Steam quality test limits should only be applied to the porous load or equipment sterilisation process. Not to the terminal bottled fluid sterilisation or steam / sterilisation in place (SIP) applications. Explanations for this approach will be found later.

## **Introduction**

Steam for sterilisation requires a number of attributes in order to be an effective sterilant. Steam provides the moisture that allows the coagulation of cell wall proteins and supplies the energy that heats the components and maintains their temperature, the combination of temperature and moisture resulting in sterilisation. The higher the temperature, the shorter the sterilisation time required. Where steam comes into intimate contact with components that are either medical devices or that will come into contact with parenteral products, it should not add chemical or endotoxin contamination.

The following will concentrate on the engineering aspects and intends to provide an appreciation of the potentially complex nature of what is often assumed to be a simple heating process.



## **Dryness fraction / value**

The dryness fraction of steam is the measure of the moisture carried within steam. A measured value of 0 denotes 100% water and the value of 1 represents dry saturated steam, i.e. steam as a vapour having no entrained water. Therefore steam with a dryness fraction of 0.95 will be a mixture of 95% dry saturated steam and 5% water.

The dryness fraction of steam is inextricably linked with the latent heat that it possesses. Steam having an energy level equal to 50% of the latent heat for its saturation pressure will have a dryness fraction of 0.5 indicating a 50:50 water/steam mixture. Therefore, only when steam has its full quotient of latent heat will it be dry saturated and have a dryness fraction of 1.

## **Measurement of dryness value**

By using simple calorimetry, the energy that steam possesses at a particular pressure may be measured and therefore its dryness assessed. When we use the methods described in EN 285 to measure the latent heat there is a significant error present. The steam sample is taken from the center of the steriliser steam supply pipe and as such takes no account of moisture present either as a film on the pipe wall or any condensate at the bottom of the steam pipe. As a result the calculated latent heat and therefore dryness fraction will not be accurate but be an approximation. It is for this reason that the calculations quote results in terms of dryness values and not dryness fractions.

EN 285 states - The test method described should be regarded not as measuring the true content of moisture in the steam, but as a method by which the provision of acceptable quality steam can be demonstrated.

While more accurate results may be obtained, the linkage between these and the pragmatically established limits will have been lost, while at the same time increasing the scale, complexity and therefore the disruptive aspects of the test.

## **The impact of wet steam**

At the end of a sterilisation cycle, packaging materials should be sufficiently dry to maintain their sterile barrier properties (EN 554 - A.2.5). The correct steam quality combined with proper loading and packing techniques should ensure that dry loads are consistently achieved.

Because the heating process within a steriliser inevitably results in condensation being generated, it is easily assumed that variations in the dryness value of the steam to be inconsequential. This indicates a failure to appreciate the fundamentals of the process and in particular misunderstands how the drying process works.

## **The drying of loads**

When we heat a component with steam, it condenses and gives up its latent heat. If all the water associated with this heating process were to somehow remain on the component, when the chamber is under drying vacuum conditions the boiling point is reduced (to 32.9°C at 50 mbar a). A reduction in pressure from 3 bar a to 50 mbar a will result in the water on the component having an excess of sensible heat at the lower pressure of  $561 - 138 = 423$  kJ/kg. This excess energy is sufficient to cause only some 15% of the water to be turned to steam. The balance of the energy required to evaporate the remaining 85% of the condensate must come from the only available source, the component i.e. the energy used to heat a component is also used to dry it.

Should surplus condensate settle on the component either as a result of water entrained in steam or by condensate dripping from another component, it may not dry. In practice, as steam condenses, much of

the water generated will drain by gravity (provided the load is correctly loaded and configured) and reduce the need for the latent heat contribution from the component. In this example any component having more than 15% of the condensate present at the end of the sterilising stage that is needed to heat it, will be much slower to dry. The drying time will be dependent upon the location of the condensate, its surface contact area and the specific heat of the component, i.e. large quantities of condensate in contact with a small surface area of a component will be slow to evaporate and that insulators will dry more slowly than good conductors of heat.

This brief explanation serves to explain why if a wet component is loaded into a steriliser, at the end of the process it will remain wet. A reduction in pressure alone is insufficient to dry components.

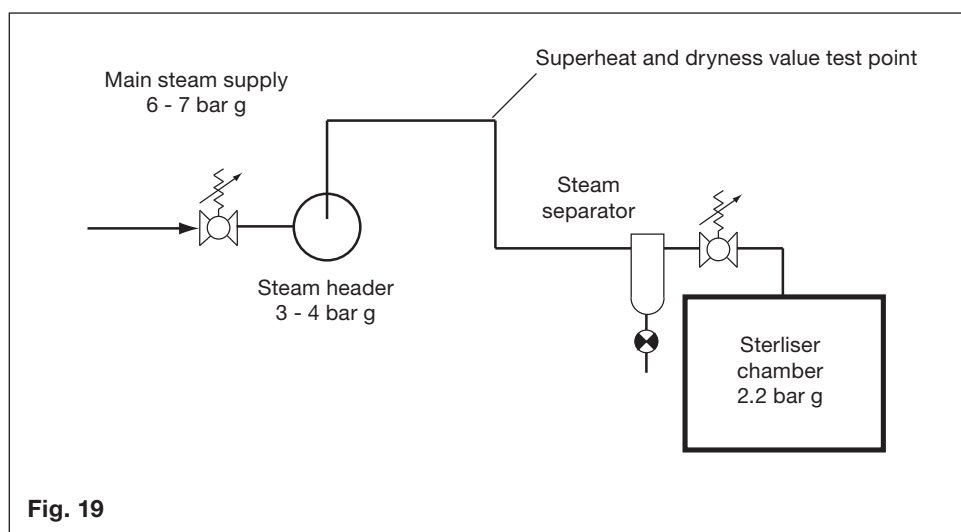
It will be seen that the impact of wet steam will depend upon specific components and their loading methods. The dryness values quoted in EN 285 are  $> 0.9$  for porous loads and  $> 0.95$  for metal loads - the higher quality requirement being for loads typically used in the pharmaceutical industry.

### Water as an insulator

In addition to the risk of wet loads, water can act as an insulator and prevent good heat transfer to component surfaces causing locations that are slow to heat. A static film of water 1 mm thick is equivalent to a layer of copper 500 - 600 mm thick. Obviously the effects of turbulence and convection reduce the impact, but in any event standing water should be avoided by correct loading techniques.

### Sample point location

It should be noted that in EN 285 the measurement point for the dryness value test is not defined. If we use the combination of HTM 2010 and standard UK hospital design practices for guidance, it will be seen that the test point is assumed to be located as shown in Figure 19. This assumes a further 2 bar pressure drop will occur after the test point, before the steam enters the chamber and that a steam separator will be fitted to the steriliser. Given that a pressure drop will tend to improve the dryness of steam, these design aspects must be taken into consideration when conducting dryness value tests and interpreting the results. The ability to maintain the limits in the standards need not be a guarantee of dry loads and should be used as guidance and corrected if the conditions at the test point differ from that shown in Figure 19.



Pragmatically, if loads are not wet, the steam has a sufficiently high dryness value, though ideally, the steam should be in a dry saturated condition when it enters the steriliser as to present the load with the absolute minimum entrained water possible and the maximum amount of available energy. While the reduced energy content of wet steam will have an impact on the heating effect, this is likely to be minimal.

Where a pure or clean steam generator is utilised having a well engineered separator and is controlled to prevent moisture and therefore endotoxin carryover, under all demand conditions, it will produce steam that is dry saturated. Its condition can only deteriorate within the steam distribution system as a result of heat loss causing condensation (unless excessive pressure drops are present, which will tend to dry the steam). Good pipeline design, insulation and trapping practices combined with the use of steam separators should ensure the condition of steam is maintained at the point of use.

Pipeline component design has a large part to play in the elimination of wet loads as components must be capable of being drained and this is a fundamental aspect of the purchasing/validation process for a steriliser. Components should be of self-draining design.

### **Steriliser jackets at reduced temperatures**

Operating a steriliser with its jacket at a colder temperature than the sterilising temperature is often cited as good practice in some countries to prevent / eliminate the threat of superheat. While superheat will be dealt with later, it is self evident that this will result in extraneous water dripping onto the load, having the same effect as wet steam. Given that wet loads may be a greater threat to sterility than superheat (where metal loads are concerned), this practice is not recommended.

### **Dryness value and steam/sterilise in place**

Where steam is used in steam / sterilise in place (SIP) applications, the dryness value (and any superheat) will have little or no impact on the efficacy of the process. Pipes and/or vessels will often not be insulated and large quantities of condensate will be generated in any event. Unlike a variety of components offered for processing within a steriliser, process vessels and pipework will have been designed specifically to self-drain. Provided the combination of moisture and temperature are present, sterilisation will occur. This is not to suggest that well designed and engineered steam systems are not required for such systems, but that point of use testing is not necessary.

### **Superheat**

Superheated steam is steam that is at an elevated temperature for its saturation pressure. It cannot be generated at source by a conventional pure or clean steam generator, as energy would have to be applied to the steam once it was in a dry saturated condition. Superheated steam is usually generated as the result of pressure drops through either pressure reducing valves or orifices. The impact of the pressure drop is to modify the pressure of the steam while its energy content remains the same. The excess of energy for the pressure present will result in any excess moisture turning to steam. If the steam is already dry saturated or if excess energy is still present after turning what moisture is present to steam, an increase in temperature will be evident. Once steam is dry saturated only a small amount of energy is required to create high temperatures. Table 9 below provides some examples of the effects of a pressure reduction from 5 bar a on the dryness fraction.

**Table 9 The effect of pressure reduction**

Before pressure drop		After pressure drop	
Pressure fraction	Dryness fraction	Pressure fraction	Dryness fraction
5 bar a	0.95%	3.2 bar a	0.96%
5 bar a	0.98%	3.2 bar a	0.99%
5 bar a	0.95%	2.1 bar a	0.97%
5 bar a	0.98%	2.1 bar a	1.00%
5 bar a	0.98%	1.0 bar a @ 10°C of superheat	

**Risks of superheat**

The risk to the sterilisation process of superheated steam is that the steam will not condense and provide moisture until the steam temperature has reduced to the saturation temperature. Until this occurs, the steam will act as hot air and at the temperatures present will have little or no sterilising effect. The excessive temperatures generated can result in damage to both components and packaging.

The rate at which superheat will decay is dependent upon the nature of the load and will be present for longer where loads have a low heat capacity. The worst-case condition usually experienced is where small quantities of batches are processed and will have a greater impact where short sterilising times are utilised. While the pharmaceutical industry generally uses sterilisation cycles at 121°C for greater than 15 minutes, hospitals generally use 134°C for 3 minute cycles, where there is a very short time for the heat exchange and therefore loss of superheat to occur. The risk cause by superheat is therefore greater under these conditions and can pose a very real threat.

**Superheat and water**

It is often assumed that superheat and the presence of condensate are mutually exclusive.

Indeed, in the description above it is indicated that the impact of surplus energy is to evaporate excess moisture. What must be considered however is that the process takes a finite time and it is perfectly possible for the two conditions to co-exist. In this respect, the concept may be considered to be similar to the presence of ice at room temperature.

Whilst thermodynamic tables indicate that ice cannot exist under these conditions, it plainly does until the heat exchange process is completed.

**Pressure drop ratio**

To reduce the impact of excessive pressure drops, EN 285 indicates the need to have pressure drops not exceeding a ratio of 2:1. Another important aspect is the length of pipe between pressure drops, which will allow superheat to decay through the evaporation of excess moisture and conduction through the pipe wall. In practice, the pressure drop ratio may be exceeded, provided the drop occurs sufficiently far away from the steriliser.

**Sample point location**

The superheat test in EN 285 is designed to measure the condition of the steam between the 4 and 2 bar g pressure drops as shown in Figure 19. It is an inferential test and seeks to establish if the result will cause more or less than 5°C of superheat in the chamber, following a separator and a further pressure drop of 2 bar. Once more, this important assumption is not stated in EN 285 and as with the dryness value test, care needs to be taken with the location of the sample point and the interpretation of the results obtained.

## **Overheat**

Where superheat is measured even where the pressure drop ratios and superheat tests are satisfactory, the cause may be due to a phenomenon known as overheat and is due to the velocity of the steam entering the chamber. The process may be considered similar to waterhammer. In the case of steam, the flow is brought to an abrupt halt as it enters a comparatively small chamber. Instead of the mechanical action with the water pipe, the effect of the kinetic energy is to increase the temperature. Provided the pipework design and steam quality entering the chamber is satisfactory, the phenomenon indicates a design problem with the steam port sizing. The calculation for overheat may be simplified to: -

$$\text{Overheat} = V^2/2C_p$$

Where  $V$  is the velocity of the steam in m/s and  $C_p$  is the specific heat at constant pressure (@ 1900 at 2 bar g).

It will be seen that a steam velocity of 200 m/s will result in an excess of temperature of 10.5°C.

Overheat is not seen to pose the same threat to the process as superheat, as it automatically reduces with the steam flow, as the load is heated to the sterilising temperature. As with genuine superheat and exothermic superheat, detailed below, the phenomena can result in damage to components and packaging. Devices and baffles fitted to the steam entry ports can effectively reduce the steam velocity and sometimes eliminate overheat.

## **Exothermic superheat and gassing**

Another cause of the superheat phenomena is due to an exothermic reaction and occurs where condensing steam rehydrates previously dehydrated materials with a resulting increase in temperature. This phenomenon is evident where paper products are processed, wipes, sponges, mop heads etc. or filters that have been dried in a cabinet. It is probable that the products themselves will be sterilised, as the phenomenon can only exist when they have been rehydrated.

## **Non-condensable gases**

Non-condensable gases are liberated by steam when it condenses. The source of such gases is usually from the steam generator feedwater and the impact of such gases is that they modify the steam from being pure water vapour to a mixture of steam and gas and are therefore an unwanted contaminant.

If we consider the heating of a single component by steam it will be seen that as steam condenses on the item its volume will reduce by a factor to 1/841 of the original value (for steam at 122°C). This rapid reduction in volume causes a low-pressure area, which in turn is refilled with more steam. Until the product is heated, this process will continue.

The flow of steam is always towards the component. As any gases are liberated at the point of condensation, they will be forced by the flow of steam towards the product. If the component is hollow or porous, any liberated gases will be forced to the center. There is little difference in the specific mass of air and steam at the sterilisation temperature and therefore no real gravitational effect to cause the air to leave the component. Air is approximately 12 000 times more resistant to heat transfer than copper and whether present as a film or a pocket, may prevent direct steam contact or insulate the component. Such conditions are identical to inadequate air removal, where very small quantities of air remain.

To what extent are non-condensable gases an issue? The limit in EN 285 is 3.5% and is expressed in terms of ml of gas collected per 100 ml of condensate. This is often misinterpreted to be 3.5% by volume. In practice the percentage by volume is  $3.5 \text{ ml} / 169.4 \text{ l} = 0.002066\%$  (20.66 ml per kg of steam). When homogeneously mixed with steam, such levels are unlikely to have any impact, as the molecules are so widely dispersed as not to prevent the sterilisation of simple surfaces. This would be the case for a fluid sterilisation process, for example.

The design of the component, its mass and the amount of non-condensable gases in the steam will determine the extent of any problem and the limit in EN 285 and HTM 2010 should be easily satisfied by a well designed and installed generation plant. As with both the dryness value and superheat tests EN 285 applies a caveat - The test method described should be regarded not as measuring the exact level of non-condensable gases but a method by which the provision of acceptable quality steam can be demonstrated. Unlike the former tests, the location of the sample point with respect upstream and downstream pressures will not have an impact on the non-condensable gas test result.

### **Air vents**

While air vents are particularly successful in removing large quantities of air when systems are started up, they are less effective in dealing with air that tends to be homogeneously mixed with the steam. Air will collect and may be removed by vents under no/low flow conditions, but when traveling at speeds of 25 m/s or faster, gases are more likely to be carried to the point of use than removed.

Non-condensable gases may be evident either as continuous levels or intermittently and this will be the result of feedpump operation etc.

### **Pure / clean steam versus plant steam generators**

While the perception in the industry is that we design and construct high quality steam generation and distribution systems, this aspect is often restricted to the measures we take to eliminate chemical contamination and endotoxin. In fact the presence of high levels of such gases in clean steam systems is more likely than in plant or utility steam systems for the following reasons:

1. Feedwater for clean / pure steam generators is often not heated to a satisfactory level, and the solubility of gas in water reduces with increased temperature. While the water may be heated as an energy conservation measure immediately before it enters the generator, no means of eliminating the gas will be evident on most standard systems. By contrast, a well designed utility steam system uses a large proportion of condensate return for its feedwater which will naturally be hot and is often heated, where necessary, to maintain temperatures in excess of 80°C.
2. Gases are liberated at the point steam condenses. Where this occurs in a steam main, the low mass gases will be carried with the flow of steam and need not necessarily leave the system by means of steam traps. The condensate return is therefore essentially deaerated and in plant steam will be reused to feed the boiler. As pure or clean steam is rarely returned and reused and therefore 100% feedwater make-up is required.
3. The impact of feedwater systems incorporating numerous stages, each with storage and recirculation systems result in water delivered to the pure or clean steam generator being excessively aerated. This does not occur to the same extent with simpler systems on plant steam. Even where preheaters are used on pure and clean steam systems, bubble size, convection currents and direction of water flow can all combine to prevent gases easily and quickly leaving the water.
4. Plant steam systems utilise chemicals such as hydrazine to scavenge oxygen from the water in order to minimise corrosion. Where corrosion is a major issue, as in the case of high-pressure systems, water make up may be mechanically degassed and the feedwater deaerated.

5. Where sterilisers are supplied with plant steam, the distribution systems tend to be much larger and have plant demands much greater than from sterilisers. This results in large quantities of steam being used for space, water and process heating which ensures that the systems are continually being purged of non-condensable gases.

To this end, deaerators should be employed, to ensure any gases are driven off prior to steam generation. Deaerators atomise water to present a large surface area and the resulting aerosol is heated with a contraflow of low-pressure steam. The steam heats the water close to the saturation temperature (boiling point for the pressure present) and physically strips away the resulting air bubbles on the water surface. Often a vacuum pump will be fitted to draw off the resulting steam/gas mixture.

Where steam systems are either routinely or irregularly shut down, large quantities of air will be present in the distribution system on restarting. It is recommended that in such circumstances a comprehensive venting procedure should be applied and testing for non-condensable gases may be appropriate.

### **Steam/sterilise in place systems**

Unless active air removal systems are utilised in steam/sterilise in place systems of an effectiveness equivalent to an equipment steriliser, non-condensable gases are unlikely to have a measurable impact on the process, i.e. the amount of residual air following free steaming, will probably exceed the amount of non-condensable gases present in steam by several orders of difference.

### **Testing frequency**

The only references to the frequency of steam, quality testing are to be found in HTM 2010, where it is indicated that steam quality should be tested as part of the annual validation exercise for each steriliser. Where steam systems are either routinely or irregularly shut down, large quantities of air will be present in the distribution system on restarting. It is recommended that in such circumstances a comprehensive and validated venting procedure should be applied and testing for non-condensable gases may be appropriate.

### **Conclusions**

Wet steam, superheated steam or non-condensable gases all have the potential to adversely affect the sterilisation of equipment loads in the pharmaceutical industry. The extent to which the process is affected will be dependent on the extent of the problem and the nature of the load. Understanding the condition of the steam used for sterilisation both confirms that the design requirements of the steam raising plant have been satisfied and assists with any troubleshooting. While routine testing at an annual frequency at the point of use is indicated by HTM 2010, the period between tests may be inadequate to detect any transient or seasonal problems that exist. Furthermore, it is implicit in HTM 2010 that daily Bowie Dick tests are conducted and equipment is fitted with air detectors, both of which may under certain conditions detect non-condensable gases.

A suitable test frequency for the pharmaceutical industry will be determined by a number of aspects:

1. Extensive testing of the steam generator when initially validated, so that suitable actions can be taken to ensure poor quality steam production is eliminated.
2. A good understanding of the distribution system and how it performs under different demand conditions may allow sampling at certain locations to provide valid data for more than one steriliser. If the pressure drops in a system are known and monitored, superheat from this cause can be avoided.
3. The use of supporting data from Bowie Dick tests and the use of air detectors.
4. Procedures that provide high levels of assurance that wet loads will be detected by operators.



5. If a deaerator is fitted, a temperature logger or recorder can provide assurance that the feedwater temperature is maintained at a minimum temperature and can continuously monitor its performance. This could reduce the need for non-condensable gas tests.

The key to minimising the impact of testing is knowledge of both the cause and effects of poor steam quality. Unless a system has been designed to avoid the problems described, a more extensive testing regime is indicated. Properly designed and constructed steam generation plant and distribution systems should have no difficulties in meeting the pragmatically established limits.

### **Bowie Dick test**

The Bowie Dick test was conceived as a test for successful air removal for so-called high-vacuum porous load sterilisers. A successful Bowie Dick test indicates rapid and even penetration of steam into the test pack. Retention of air within the pack due to;

- An inefficient air removal stage.
- The presence of an air leak during the air removal stage.
- The presence of non-condensable gases in the steam supply are circumstances, which can lead to failure of the test.

The result of the test can also be affected by other factors, which inhibit steam penetration. A failure of the test is therefore not conclusive proof that a fault is due to air retention, air leakage or non-condensable gases, and other causes of failure may need to be eliminated.

The test pack is typically a pack of sheets 220 mm x 300 mm x 250 mm high, with a heat sensitive indicator at the centre. If air is present in the system this will be forced to the centre of the pack and thus the indicator will not be exposed to the required heat.

### **Biological indicators**

Despite being able to get an accurate prediction of the efficiency of a steam steriliser from measurements of steriliser temperature and pressure, and of steam quality and purity, it is sometimes necessary to test the 'microbial efficacy' (efficiency in destroying microorganisms) of the steriliser. This may be particularly important if an unusual type or size of load is being placed in the steriliser, or after any modification to the cycle or to the steriliser itself. Testing is usually carried out using biological indicators and testing procedures outlined in relevant standards.

A biological indicator (BI) is a test device that contains a quantity of a microorganism similar to that being destroyed in the steriliser. The BI is placed in the sterilising chamber along with the load and should be in the same condition as the devices to be sterilised. For example, if medical devices wrapped in linen are being sterilised, the BI should be wrapped in a similar fashion.

At the end of the sterilising cycle, the BI and the load are removed from the steriliser. The BI is then incubated, typically for up to 48 hours, before it is tested for the presence of viable microorganisms. The absence of microorganisms will validate the efficacy of the sterilisation cycle.



## 8.5 Humidification

The purity of steam used for the humidification within a clean room is dictated by the manufacturing process undertaken within the clean room. The ISPE's base line guide for pharmaceutical steam and water systems gives the following statement regarding humidification;

“ When steam is used for indirect humidification, such as injection into HVAC air streams prior to final air filtration, the steam does not need to be purer than the air that is being mixed with. However, when humidifying process areas, the potential levels of impurities, including amines and hydrazines should be evaluated in order to ascertain the impact on the final drug product. This is particularly important in areas where open processing takes place, such as aseptic filling suites and formulation areas. If diluted water vapour is found to contribute significantly to the contamination of the drug, a purer grade of steam should be selected.”

Generally speaking, chemically free, clean steam is used for humidification within the pharmaceutical manufacturing areas, as a minimum. Pure steam is used where open processing takes place.

# 9

# Validation of pure steam systems

## 9.1 General information

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

There is no universal system of nomenclature, but the following example includes all the principle 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 (PQ).

## 9.2 User requirement specification (URS)

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

For the pure 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-condensable gases.
- 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 e.g. GAMP or 21 CFR part 11 requirements for automation systems.
- Sampling requirements.

Sometimes the URS 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.

## 9.3 Functional specification (FS)

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

- 'The pure steam system shall be constructed of materials that are inert, non-absorbent, resistant to corrosion and do not contaminate the system'
- The then FS might answer that with a statement listing the product contact materials to be used and any specification with which they must comply, for example:
- 'Piping will be 316L stainless steel, to ASME BPE standard etc... '

## 9.4 Design qualification (DQ)

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 pure steam system the documents reviewed would typically include:

- The piping and instrumentation diagram.
- The functional specification.
- The specification for the major equipment items (the pure steam generator) piping and valves.
- Control system specification.
- Documentation requirements for supplier.

## 9.5 Installation qualification (IQ)

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 the 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, dead legs, and instrumentation orientation.

## 9.6 Operational qualification (OQ)

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 SOPs.

For pure steam systems 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 SOPs for use.

## 9.7 Performance qualification (PQ)

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

For example, a pure steam PQ might include the requirements 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 the PQ the SOPs will be approved from use.



# 10

## Appendix

### 10.1 Localised corrosion

The dissolution of the metal in which only a small area is affected, but the rate is relatively high.

Stainless steel in the passive state appears in a relatively noble position in the galvanic series and is usually cathodic, therefore, not subject to attack. However, under certain conditions all or portions of a piece of stainless steel may become active. This active surface becomes anodic to the more noble mass and in the presence of an electrolyte, a galvanic cell is set up and attack will occur. The rate of attack will vary with different electrolytes and the area relationship of the anode and cathode.

#### **Intergranular corrosion**

This type of localised corrosion is rarely a problem if the stainless steel is used in the 'mill annealed' condition. Austenitic stainless steel becomes susceptible to intergranular corrosion in some environments after being heated for short times in the range of about 480°C - 815°C (900°F - 1500°F). This can be avoided by either using only stainless steel in the annealed condition, using alloys that have low carbon, or using 'stabilised' alloys by adding carbides such as titanium or columbium.

#### **Pitting corrosion**

A type of localised corrosion can occur for several reasons, and probably the most common reason is the lack of cleanliness. If scale, dust etc., are allowed to deposit on a stainless steel surface, the metal underneath these deposits will not have ready access to oxygen which is required to maintain the corrosion-resistant film that gives stainless steel its corrosion resistance. This corrosion may be accelerated by chemical changes in the corrodent beneath the deposit. Other common causes of pitting corrosion are the presence of chlorides and stagnant conditions where deposits may become lodged on the metal surface thus permitting the concentration of damaging elements.

#### **Contact or crevice corrosion**

Contact or crevice corrosion is the most common cause of pitting of stainless steels. Wherever a solid or semi solid material adheres or lies against a stainless steel surface in contact with an electrolyte, pitting may occur. The relative anode and cathode areas and the type of electrolyte will influence the rate of attack. This type of corrosion will spread as product of corrosion deposits on other areas of the metal form new cells which cause further pitting. Regular and efficient cleaning with correct cleaning agents will minimise these types of attack.

### **Galvanic corrosion**

Galvanic corrosion or bi-metal attack is a type of localised corrosion that occurs when two different metals come in contact in the presence of an electrolyte. The least noble metal in the galvanic series becomes sacrificial to the more noble. In general, the corrosion resistance of stainless steel is reduced when in contact with lead, nickel, copper, copper alloys or graphite. On the other hand, it is improved at the expense of the other metal when in contact with iron, steel, aluminum, zinc and cadmium. The solution to this problem is to use metals of the same composition for complete system assemblies or to use flange gasket sets and/or dielectric unions to form a separation of the metals at the point of contact.

### **Stress corrosion and corrosion fatigue**

This type of localised corrosion is the result of combined residual or applied stresses a corrosive environment and temperatures above 50°C (120°F). Metal under stress is slightly anodic in relation to the unstressed metal of the same analysis. Austenitic steels under stress are subject to attack when exposed to certain corrosive agents. The halogen salts are probably the most serious offenders. It is important to design installations that eliminate sources of stress such as applied loads, vibration, flexing and excessive expansion and contraction due to temperature changes.

### **Electrolyte or stray current corrosion**

Stray electric current may produce pitting attack on stainless steel. The rate of attack with an AC current is considerable less than DC and in most cases insufficient to be considered.

### **Chemical corrosion**

Austenitic stainless steels are resistant to most chemicals; however, there are compounds such as halogen and sulphur that are notorious for attack on stainless steels. In general, acidic solutions will cause more severe attacks than basic solutions of the same elements. The use of inhibitors may render these solutions less harmful.

### **Erosion corrosion**

Certain liquids or gases moving at high speeds may cause erosion corrosion; however, if these same materials remain motionless, they would not affect the stainless steel. It is believed that the attack is due in part to the destruction of the passive layer on the surfaces. The action of fluids in rapid motion is not always destructive, and in some cases, the scouring effect keeps the stainless steel free of deposits and sludge that may cause other types of corrosion.

## 10.2 Tubing and connections in the pharmaceutical industry

### Imperial

Imperial OD tubes have an exact outside dimension and a specified wall thickness such that for any given size, there are a number of different internal diameters. Wall thicknesses are usually given in thousandths of an inch, or sometimes in the corresponding gauge. The most commonly used sizes and wall thicknesses up to 6' are listed in Table 10:

**Table 10 Imperial O/D tubing sizes**

Nominal Size	Tube O/D		Tube wall thickness		Hygienic clamp size
	Inches	mm	Inches	mm	
¼"	0.250	6.35	0.035	0.89	¾"
⅜"	0.375	9.53	0.035	0.89	¾"
½"	0.500	12.70	0.065	1.65	¾"
¾"	0.750	19.05	0.065	1.65	¾"
1"	1.000	25.40	0.065	1.65	1½"
1½"	1.500	38.10	0.065	1.65	1½"
2"	2.000	50.80	0.065	1.65	2"
2½"	2.500	63.50	0.065	1.65	2½"
3"	3.000	76.20	0.065	1.65	3"
4"	4.000	101.60	0.083	2.11	4"
6"	6.000	152.40	0.109	2.77	6"

Tolerances on dimensions and ovality are covered in specifications such as ASTM A-269 and A-270, with details varying with tube size. For example, A-269 allows a variation of + 0.005" (0.13 mm) on O/D and +/- 15% on wall thickness for tubes up to ½". This standard has been adopted by the ASME BPE, and is generally the most common tubing globally.



## ISO 1127

This standard again specifies O/D with a variety of preferred wall thicknesses. In the range of sizes which we are interested, the most common preferred wall thicknesses are 1.6, 2.0 or 2.3 mm, according to Table 11.

**Table 11 ISO 1127 tubing sizes**

Nominal size	Tube O/D (mm)	Tube wall thickness (mm)
<b>DN8</b>	13.5	1.6
<b>DN10</b>	17.2	1.6
<b>DN15</b>	21.3	1.6
<b>DN20</b>	26.9	1.6
<b>DN25</b>	33.7	1.6
		2.0 (Most common)
<b>DN40</b>	48.3	1.6
		2.0 (Most common)
<b>DN50</b>	60.3	1.6
		2.0 (Most common)
<b>DN65</b>	76.1	1.6
		2.3 (Most common)
<b>DN80</b>	88.9	2.0
		2.3 (Most common)

**Notes:**

1. The DN designated against the tube O/D is not defined in the standard, but the correlation given is as commonly accepted in the industry.
2. Other wall thicknesses in each size are available, but are not very popular or common.

## DIN 11850

This standard is for dairy industry tubes, and for each DN there are three different series of O/D and thickness combinations, all giving rise to the same I/D.

For example:

DN10 Series 1 has O/D 12 mm, thickness 1.0 mm (I/D = 10).

DN10 Series 2 has O/D 13mm, thickness 1.5mm (I/D 10).

DN10 Series 3 has O/D 14, thickness 2.0mm (I/D = 10).

However, due to the large number of permutations and combinations that this gives rise to, a set of 'hybrid' dimensions are used by manufacturers or fittings, as outlined in Table 12:

**Table 12 DIN 11850 tubing sizes**

Nominal size	Tube O/D (mm)	Tube wall thickness (mm)
<b>DN8</b>	10.0	1.0
<b>DN10</b>	12.0	1.0
<b>DN15</b>	18.0	1.5
<b>DN20</b>	22.0	1.5
<b>DN25</b>	28.0	1.5
<b>DN40</b>	40.0	1.5
<b>DN50</b>	52.0	1.5
<b>DN65</b>	70.0	2.0
<b>DN80</b>	85.0	2.0

## 10.3 Velocity sizing charts for pharmaceutical stainless steel tubing

**Table 13 Metric - Velocity sizing chart (kg/h)**

Pressure bar g	Velocity m/s	Tube size (O/D x 1.651 inch wall thickness)									
		8 mm	10 mm	15 mm	20 mm	25 mm	40 mm	50 mm	65 mm	80 mm	100 mm
<b>0.3</b>	15	0.6	1	2	9	16	41	77	123	179	326
	24	0.9	1	4	14	27	66	123	195	288	524
	30	1.1	2	5	18	32	82	154	245	358	652
<b>0.7</b>	36	1.7	2	7	20	39	98	184	295	431	784
	15	1.1	2	5	11	20	50	95	152	222	405
	24	1.7	4	7	16	32	82	150	243	356	648
	30	2.3	5	9	23	41	100	191	304	445	809
<b>1.4</b>	36	2.7	5	11	25	50	123	227	363	533	970
	15	1.2	3	5	14	27	70	129	209	306	557
	24	1.8	4	7	23	45	111	209	333	490	892
	30	2.5	5	10	27	54	141	259	417	613	1,115
<b>2</b>	36	2.8	6	11	34	68	168	311	501	735	1,338
	15	1.7	3	7	18	36	88	166	265	388	706
	24	2.8	5	11	29	57	141	263	424	622	1,131
	30	3.4	5	14	36	73	177	331	531	776	1,412
<b>2.8</b>	36	4.0	7	16	43	86	211	395	635	930	1,693
	15	1.8	3	7	23	43	107	200	320	470	855
	24	2.8	5	11	34	68	170	318	510	755	1,375
	30	3.6	6	15	45	86	213	399	640	939	1,709
<b>3.4</b>	36	4.5	9	18	52	104	252	476	767	1,125	2,048
	15	2.3	4	9	25	50	125	234	374	549	999
	24	3.4	6	14	41	82	200	372	599	878	1,598
	30	4.5	8	18	50	100	250	467	749	1,098	1,998
<b>4.1</b>	36	5.7	9	23	61	120	299	560	898	1,318	2,399
	15	2.8	5	11	29	57	143	268	429	628	1,144
	24	4.0	7	16	48	93	229	426	685	1,005	1,829
	30	5.7	9	23	59	113	286	535	858	1,257	2,287
<b>5.5</b>	36	6.2	11	25	70	138	343	640	1,028	1,509	2,746
	15	3.4	7	14	36	73	179	333	535	785	1,429
	24	5.1	9	20	59	116	286	533	858	1,257	2,287
	30	6.8	14	27	73	145	358	667	1,071	1,570	2,857
<b>6.9</b>	36	7.9	16	32	88	172	431	800	1,286	1,885	3,431
	15	4.0	8	16	43	86	213	399	642	941	1,713
	24	6.2	11	25	70	138	343	640	1,028	1,506	2,742
	30	7.9	15	32	86	172	426	799	1,284	1,883	3,427
<b>8.3</b>	36	9.6	18	39	104	206	515	960	1,540	2,257	4,108
	15	4.5	9	18	52	100	250	467	749	1,098	1,998
	24	7.4	15	29	82	161	402	746	1,198	1,758	3,200
	30	9.1	18	36	104	200	499	935	1,497	2,196	3,997
	36	10.8	20	43	123	243	601	1,118	1,799	2,636	4,798

**Table 14 Imperial - Velocity sizing chart (lb/h)**

Pressure psi g	Velocity ft/ sec	Tube size (O/D x 0.065 inch wall thickness)									
		¼"	⅜"	½"	¾"	1"	1½"	2"	2½"	3"	4"
5	50	1.3	2	5	20	35	90	170	270	395	719
	80	2.0	3	8	30	60	145	270	430	635	1,156
	100	2.5	4	10	40	70	180	340	540	790	1,438
10	120	3.8	5	15	45	85	215	405	650	950	1,729
	50	3	5	10	25	45	110	210	335	490	892
	80	4	8	15	35	70	180	330	535	785	1,429
	100	5	10	20	50	90	220	420	670	980	1,784
20	120	6	12	24	55	110	270	500	800	1,175	2,139
	50	3	6	11	30	60	155	285	460	675	1,229
	80	4	9	16	50	100	245	460	735	1,080	1,966
	100	6	11	22	60	120	310	570	920	1,350	2,457
30	120	6	13	25	75	150	370	685	1,105	1,620	2,948
	50	4	6	15	40	80	195	365	585	855	1,556
	80	6	11	25	65	125	310	580	935	1,370	2,493
	100	8	12	30	80	160	390	730	1,170	1,710	3,112
40	120	9	15	35	95	190	465	870	1,400	2,050	3,731
	50	4	7	16	50	95	235	440	705	1,035	1,884
	80	6	10	25	75	150	375	700	1,125	1,665	3,030
	100	8	14	32	100	190	470	880	1,410	2,070	3,767
50	120	10	20	40	115	230	556	1,050	1,690	2,480	4,514
	50	5	9	20	55	110	275	515	825	1,210	2,202
	80	8	13	30	90	180	440	820	1,320	1,935	3,522
	100	10	18	40	110	220	550	1,030	1,650	2,420	4,404
60	120	13	20	50	135	265	660	1,235	1,980	2,905	5,287
	50	6	10	25	65	125	315	590	945	1,385	2,521
	80	9	16	35	105	205	505	940	1,510	2,215	4,031
	100	13	20	50	130	250	630	1,180	1,890	2,770	5,041
80	120	14	25	55	155	305	755	1,411	2,265	3,325	6,052
	50	8	15	30	80	160	395	735	1,180	1,730	3,149
	80	11	20	45	130	255	630	1,175	1,890	2,770	5,041
	100	15	30	60	160	320	790	1,470	2,360	3,460	6,297
100	120	18	35	70	195	380	950	1,764	2,835	4,155	7,562
	50	9	17	35	95	190	470	880	1,415	2,075	3,777
	80	14	25	55	155	305	755	1,410	2,265	3,320	6,042
	100	18	34	70	190	380	940	1,760	2,830	4,150	7,553
120	120	21	40	85	230	455	1,135	2,115	3,395	4,975	9,055
	50	10	20	40	115	220	550	1,030	1,650	2,420	4,404
	80	16	32	65	180	355	885	1,645	2,640	3,875	7,053
	100	20	40	80	230	440	1100	2,060	3,300	4,840	8,809
	120	24	45	95	270	535	1,325	2,465	3,965	5,810	10,574

## 10.4 Rouging

Rouging is seen in many water systems, usually, high temperature (80°C) distilled water and clean / pure steam systems. Rouge is not limited to storage and distribution systems; it can also be found in distillation and clean steam generating equipment. The main constituent of the rouge film is ferric oxide, but it can contain iron, chromium, and nickel of different forms. From Auger Electron Spectroscopy, it has been found that the outer layer of a rouge film is carbon rich, and the underlying region is iron and oxygen rich, probably iron oxide. Over time, the film uniformly distributes itself throughout the system; the exact mechanism of the rouge formulation and proliferation is unknown. Because the phenomenon occurs in systems that offer the most corrosive environment, it is thought that low molecular weight ions of stainless steel, such as iron, are drawn to the metal surface or are dissolved and uniformly re-deposited throughout the system. Others feel the rouge is an external contaminant probably colloidal in nature that once in the system, uniformly deposits itself.

Rouging would seem to be very site (facility) specific because of the variety in appearance and texture. Rouge can be observed in a variety of colours including; orange, light red, red, reddish-brown, purple, blue, grey and black. It can be a very loose film, dust-like in appearance and texture that can be readily wiped off to a tight tenacious film that requires scraping with a sharp instrument to be removed. In addition to the diversification already discussed, rouge can be multi-layered, exhibiting different colours and textures. Traditionally the red rouges are most common in high purity high temperature water systems, while the blue / black rouges are typically found in clean / pure steam systems.

Evidence of the migration of rouging in distribution systems can be demonstrated by monitoring a system over a period of time. Key places to look for rouging are WFI still and clean / pure steam generation discharge lines, tank water / vapour interface, pump heads, Teflon diaphragms on diaphragm valves, interior surface of tank spray balls, and the heat effected area of welds. Rouge deposition seems to have an affinity to Teflon and would be one of the first places to look for signs of system rouging.

In some cases, the rouging appears as quickly as a month or two after system start-up. In other cases, it is several years before rouging is observed. In either case rouging is an industry wide phenomenon. In specific cases, a facility cold WFI system would re-rouge within a week of being derouged and passivated.

The presence of rouge in high purity water systems has not been proven to effect water quality. The FDA has no written position addressing rouging, its existence, or presence in high temperature high purity water and steam systems. Their criterion has and remains to be meeting established USP standards for water quality. There is some fear that as the unwanted film develops, it might eventually slough off and be dispersed throughout the system. This, in fact, does occur and is manifested in systems with filtered use points. Filters become discoloured with the typical reddish-brown rouge colour.

Depending on the severity of the problem, phosphoric, citric, oxalic acids are ammonium citrates can be flushed through the system to remove the rouge. Oxalic acid solutions are used for the worst cases, with passivation required after the flushing.

## References

1. ISPE Baseline Pharmaceutical Engineering Guide:  
Volume 4 'water & Steam systems' (2001)
2. ASME BPE 2005 Guide
3. 'Clean steam system', Tim Latham, in Pharmaceutical Engineering Volume. 15,  
No.2, March/April 1995
4. 'Clean steam in the pharmaceutical industry', Tim Latham, PDH course.
5. 'The application of steam quality test limits', Keith Shuttleworth
6. Health Technical Memorandum (HTM) 2031
7. HTM 2010 Sterilisation (1994) Part 3 validation and verification
8. EN 285 Sterilisation - steam sterilisers - large Sterilisers (1996)



# 11

## Glossary of terms

Annealing	Generic engineering	Profilometer
Antibody	GMP facility	Pure steam
Antigen	GTAW	Purge gas
Aseptic	Guideline	Pyrogen
Aseptic processing	Heat number	Ra
Audit	Hold-up volume	Recombinant DNA (rDNA)
Automatic welding	Hydrotest	Resistivity
Bioprocessing	Hygienic	Rmax
Bioprocessing equipment	Hygienic clamp joint	RMS
Bioreactor	Inclusions	Roughness
Biotechnology	Inspection	Rouging
Cavitation	Inspector	Sanitation
Certification	Intergranular corrosion	Seamed tubing
CGMPs	In-vitro	Seamless tubing
Clean	Liquid penetrant indication	Self-draining
Clean In Place (CIP)	Lyophilisation	Shield gas
Clean room	Machine welding	SIP
Clean steam	Mammalian cell culture	Spore
Cloudiness	Material Test Reports (MTR's)	Square cut
Concavity	Media	Steam In Place (SIP)
Containment	Microinch	Sterile
Convexity	Micrometre or micron ( $\mu\text{m}$ )	Sterility
Dead leg	Monoclonal Antibodies (MAbs)	Surface inclusion
Demarcation	Nominal	Surface residual
Diagnostics	Occlusions	Therapeutics
Disinfection	Orange peel	T.I.G.
Documentation	Orbital butt weld	T.O.C.
Downstream processing	Parenterals	Tube
Electropolishing	Passivation	USP
ETO	Passive layer	Wall thickness
Fermentation	Pathogen	Weld discoloration
Fermentor (fermenter)	Penetration	WFI
Full penetration	Pitch	
Gene	Porosity	



# A

**Annealing:** a treatment process for steel for the purpose of reducing hardness, improving machinability, facilitating cold working, or producing a desired mechanical physical, or other property.

**Antibody:** a protein produced by humans and higher animals in response to exposure to a specific antigen, and characterised by specific reactivity with its complementary antigen.

**Antigen:** a substance, usually a protein or a carbohydrate, which when introduced into a human or higher animal, stimulates the production of an antibody, which will specifically react with it.

**Aseptic:** free of pathogenic (causing or capable of causing disease) micro-organisms.

**Aseptic processing:** operating in a manner that prevents contamination of the process.

**Audit:** the evaluation of a system or procedure to verify its effectiveness.

**Automatic welding:** welding with equipment that performs the welding operation without adjustment of the controls by a welding operator. The equipment may or may not perform the loading and unloading of the work (see machine welding).

# B

**Bioprocessing:** the creation of a product utilising living organisms.

**Bioprocessing equipment:** equipment, systems, or facilities used in the creation of products utilising living organisms.

**Bioreactor:** vessel in which a bioprocess takes place.

**Biotechnology:** commercial techniques that use living organisms or substances from these organisms, to make or modify a product. 'New' biotechnology is the sector, which uses novel biological techniques, such as RDNA and cell fusion, and new bio-processes for commercial production.

# C

**Cavitation:** a condition of liquid flow where, after vaporisation of the liquid, the subsequent collapse of vapour bubbles can produce surface damage.

**Certification:** documented testimony by qualified authorities that a system qualification, calibration, validation, or revalidation has been performed appropriately and that the results are acceptable.

**cGMPs:** current Good Manufacturing Practices. Current design and operating practices developed by the pharmaceutical industry to meet FDA requirements as published in the Code of Federal Regulations, Chapter 1, Title 21, Parts 210 and 211.

**Clean:** free of dirt, residues, detergents, or any contaminants that may affect or adulterate the product or process.

**Clean In Place (CIP):** internally cleaning a piece of equipment without relocation or disassembly. The equipment is cleaned but not necessarily sterilised. The cleaning is normally done by acid, caustic, or a combination of both, with Water-For-Injection (WFI) rinse.

**Clean room:** a processing area in which the levels and size of airborne particulates are strictly controlled to below predetermined levels.

**Clean steam:** steam free from boiler additives that may be purified, filtered, or separated. Usually used for incidental heating in pharmaceutical applications.

**Cloudiness:** the appearance of a milky white hue across some portion of a surface, resulting from the electropolish process.

**Concavity:** as viewed from the outside of the tube, this would be viewed as a depression of the weld.

**Containment:** the retention of all potentially harmful organisms or materials within a processing system.

**Convexity:** as viewed from the outside of the tube, this would be a raised area of the weld.

# D

**Dead leg:** an area of entrapment in a vessel or piping run that could lead to contamination of the product.

**Demarcation:** a localised area that is dissimilar to the surrounding areas with a defined boundary after electropolishing.

**Diagnostics:** products that recognise molecules associated with disease or other biological conditions and are used to diagnose these conditions.

**Disinfection:** the removal of undesirable microbes using chemical agents. This does not imply the removal of all microbes or spores.

**Documentation:** evidence in verification of facts, proof (or writing) to support a test or inspection.

**Downstream processing:** the separation and purification of a product after fermentation.

# E

**Electropolishing:** process that involves the chromium enrichment of the surface in stainless steel materials. This process uses mild acids (usually phosphoric, sulphuric and surfactants) with an electrode to facilitate the removal of metals from the surface of the material.

**ETO:** Extended Tube O/D

# F

**Fermentation:** the biochemical synthesis of organic compounds by micro-organisms or cultivated cells.

**Fermentor (fermenter):** a vessel for carrying out fermentation.

**Full penetration:** a weld joint is said to be fully penetrated when the depth of the weld extends from its face into the weld joint so that the joint is fully fused. For a tube-to-tube weld, no unused portions of the weld joint shall be visible on the inside diameter of a fully penetrated weld.

# G

**Gene:** the basic unit of inheritance; a sequence of DNA coding that can be translated by the cell machinery into a sequence of amino acids linked to form a protein.

**Generic engineering:** the international production of new genes, and alteration of generic endowment of a species, by the substitution/additional/new generic material through in-vitro chemical reactions.

**GMP facility:** a facility designed, constructed, and operated in accordance with cGMP guidelines established by the FDA.

**GTAW:** hand executed Gas Tungsten Arc Welding: Note: Since the advent of the automatic orbital welding equipment, the use of 316L grade stainless steel with SF, the orbital welding is the usual method of welding.

**Guideline:** a suggested practice that is not mandatory.

# H

**Heat number:** an alphanumeric identification of a stated tonnage of metal obtained from a continuous melting in a furnace.

**Hold-up volume:** the volume of liquid remaining in a vessel or piping system after it has been allowed to drain.

**Hydrotest:** a pressure test of piping, pressure vessels, or pressure-containing parts, usually performed by pressurising the internal volume with water at a pressure determined by the applicable code.

**Hygienic:** of or pertaining to equipment and piping systems that by design, materials of construction and operation provided for the maintenance of cleanliness so that products produced by these systems will not adversely affect human or animal health.

**Hygienic clamp joint:** a tube outside the diameter union consisting of two neutered ferrules having flat faces with a concentric groove and mating gasket that is secured with a clamp, providing a non protruding, recess-less product contact surface.

# I

**Inclusions:** impurities on and into the surface. Metal carbides are a typical problem.

**Inspection:** the performance of examination, testing, measuring, verifying, witnessing or reviewing to determine conformance to specified requirements.

**Inspector:** personnel certified to verify conformance to specific requirements.

**Intergranular corrosion:** (Etching) when an excessively aggressive electropolishing procedure is performed on the surface of a tube, the area between the grains can be corroded. This will cause a non-preferential corrosion, which leads to additional corrosion. Typically, corrosion products can be observed on SEM micrographs and identified with EDX or Auger spectroscopy

**In-vitro:** in artificial equipment.

# L

**Liquid penetrant indication:** refer to ASME BPVC, Section V, Article 6, para T-600, for testing an anomaly or an indication.

**Lyophilisation:** The process used for the preservation of material for long-term storage, usually by freeze-drying.

# M

**Machine welding:** welding with equipment that performs the welding operation under the constant observation and control of a welding operator. The equipment may or may not perform the loading and unloading of the works (see automatic welding).

**Mammalian cell culture:** the in-vitro growth of cells isolated from a mammal. These cells are normally of one type.

**Material Test Reports (MTR's):** these reports are generated by the steel mill that produces the stainless steel and show the chemical make-up of the steel as well as many of the physical properties of the steel. An analysis is made for each batch of the steel, which could cover as much as 100 tons. Some of this steel is made into tubes and some is made into other materials. All of the batch will have the same heat number. The (MTR) or Material Test Report will contain all of this information.

**Media:** a nutrient system for the artificial cultivation of cells or organisms, especially bacteria yeast of fungi.

**Microinch:** one millionth of an inch.

**Micrometre or micron ( $\mu\text{m}$ ):** one-millionth of a metre. Micron is now a defunct metric unit.

**Monoclonal Antibodies (MAbs):** homogeneous antibodies derived from a single clone of cells, which recognise only one chemical structure.

# N

**Nominal:** refers to the designed wall thickness, NOT the actual wall thickness.

# O

**Occlusions:** voids in the metal.

**Orange peel:** an appearance of a pebbly surface.

**Orbital butt weld:** a weld made by a machine without the addition of filler metal. The automatic orbital welder is used to fusion weld thin wall tubes and fittings together in a totally inert environment, without the use of filler materials or special weld preparation.

# P

**Parenterals:** drugs destined to be administered to patients by other means than orally. Usually applied to injectable medicines.

**Passivation:** a final treatment / cleaning process used to remove free iron or other anodic contaminants from the surfaces of corrosion-resistant steel parts such that uniform formation of a passive layer is obtained.

**Passive layer:** a passive oxidized film that forms naturally on the stainless steel surface when exposed to air or a similar oxidizing environment, protecting the underlying base metal from corrosion.

**Pathogen:** a disease-producing agent, usually restricted to a living agent such as a bacterium or a virus.

**Penetration:** this refers to the complete melt of the steel at the butted sight during the welding process.

**Pitch:** To be set at a particular angle or slope. Degree of slope or elevation.

**Porosity:** cavity-type discontinuities formed by gas entrapment during solidification.

**Profilometer:** this is a tool that measures the roughness of a surface. It uses a stylus that is dragged over the surface. The up and down movement is recorded as roughness. The profilometers have a limit as to their LDL because of the physical size of the stylus. The following are (2) types of Profilometers: Surphometer and Perthometer.

**Pure steam:** steam that is produced by a steam generator which, when condensed, meets requirements for Water-for-Injection (WFI).

**Purge gas:** refers to Argon and is used to prevent oxidation at the weld side.

**Pyrogen:** substances which, when injected, cause fever or inflammatory reactions. These are most often proteins, bacterial cells or parts of cells etc.

# R

**Ra:** surface roughness measuring the average value for the mean to peak height.

**Recombinant DNA (rDNA):** the hybrid DNA produced by joining pieces of DNA from different organisms together in-vitro.

**Resistivity:** the resistance of a material to allow a flow of electricity, used to describe the inorganic concentration in ultra pure water systems. The maximum resistivity attainable for water is 18.5 million ohms (megohm). Salts added to water will decrease its resistivity. Just a few ppb of sodium will degrade the resistivity to below 10 (megohm).

**Rmax:** The maximum roughness measurement within the stroke of the measuring tool.

**RMS:** the 'Root Mean Square' of the roughness average.

**Roughness:** the unevenness of a flat surface. This is usually expressed in values of Ra, Rmax. The units are in microinches or micrometres.

**Rouging:** the formation of a thin layer of red, brown or black rust on stainless steel.



# S

**Sanitation:** the reduction of microbial loads to low, acceptable levels, usually achieved by heat at lower temperatures or applied for shortened periods as opposed to sterilisation, or by chemical disinfectants.

**Seamed tubing:** tubing made from a flat sheet that is rolled into a cylinder and welded.

**Seamless tubing:** tube made by forcing a hollow over a mandrel, creating the desired wall thickness and outside diameter.

**Self-draining:** the elimination of all fluid from the system due to the force of gravity alone.

**Shield gas:** this purge gas protects the tungsten from oxidation.

**SIP:** Sterilise (or steam) In Place; the process of sterilising plant and equipment without dismantling, usually flowing CIP procedures.

**Spore:** A uni or multicellular, asexual, reproductive or resting body that is resistant to unfavourable environmental conditions and which produces a new vegetative individual when the environment is favourable.

**Square cut:** a tube end cut perpendicular to the tangent plane.

**Steam In Place (SIP):** the use of steam to sanitise or sterilise a piece of equipment without the use of an autoclave.

**Sterile:** free from living organisms.

**Sterility:** the absence of all viable organisms.

**Surface inclusion:** particles of foreign material in a metallic matrix. The particles are usually compounds such as oxides, sulphides, or silicates, but may be a substance foreign to and essentially insoluble in the matrix.

**Surface residual:** a foreign substance that adheres to a surface by chemical reaction, adhesion, adsorption or ionic bonding (for example, corrosion, rouging, and staining).

# T

**Therapeutics:** pharmaceutical products used in the treatment of disease.

**T.I.G.:** Tungsten Inert Gas, used in arc welding.

**T.O.C.:** Total Organic Carbon, used to qualify the cleanliness levels of D.I. water systems. This measurement is an indication of the amount of microbiological activity in a UPW system.

**Tube:** tube is sized by its nominal outside diameter. For bioprocessing equipment, tube does not include pipe.

# U

**USP:** United States Pharmacopoeia.

# W

**Wall thickness:** thickness of tube or fitting, normally measured in thousandths of an inch.

**Weld discolouration:** this refers to discolouration or oxidation in the heat-affected zone of the weld. The heat-affected zone is an area about 1 to 2 millimetres to both sides of the weld. Normally, the colour referred to is a light blue or yellow. Often, it takes a proper light and angle to distinguish the colour. Apparently, the colour is caused by light refraction and is not an actual 'blue' or 'yellow'.

**WFI:** Water For Injection; high purity water which is suitable for use in parenteral drug production.