

# Properly Select Equipment for SIP Systems

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Sterilization-in-place (SIP) systems are essential to the operation of many pharmaceutical and biotech facilities. This article reviews design considerations, selection criteria and performance expectations for control valves, regulators, isolation valves and steam traps.

In today's pharmaceutical and biotech plants, sterilization-in-place (SIP) processes are becoming more and more critical. The nature of batch processing and the relationship between time and temperature for sterilization demand highly efficient SIP systems. The associated valves and steam traps must perform with high efficiency while meeting stringent cleanliness requirements.

SIP systems are designed to sterilize a collection of process equipment after a batch of product is completed. Equipment such as bioreactors, fermentors and the accompanying tubing must be cleaned and/or sterilized before a new production cycle can begin. These systems are constructed from high-grade stainless steel materials and approved flexible materials (*e.g.*, Teflon-lined piping).

Steam pressures are typically in the 20–30 psi range, with corresponding temperatures ranging from 121°C to 135°C. The relationship between pressure and temperature is fixed and known. Sterilization times will vary, and depend on the temperature and the nature of the item being sterilized. In general, the lower the temperature, the longer it takes to sterilize. The sterilization time/temperature relationship in a typical SIP process is about 121°C for 30–40 minutes. For equipment with hard-to-reach regions, sterilization times can be longer.

Steam quality is also an important consideration. Typically, a dedicated clean-steam generator is used to provide the necessary volume of steam at the required temperature

and pressure needed to sterilize each piece of equipment.

To ensure that each component and all areas of the piping remain at the sterilization temperature for the requisite time, temperature sensors are placed in critical areas and in hard-to-reach locations in order to effect complete sterilization. During this entire process, modulating valves maintain the required clean steam pressure, temperature and flow levels.

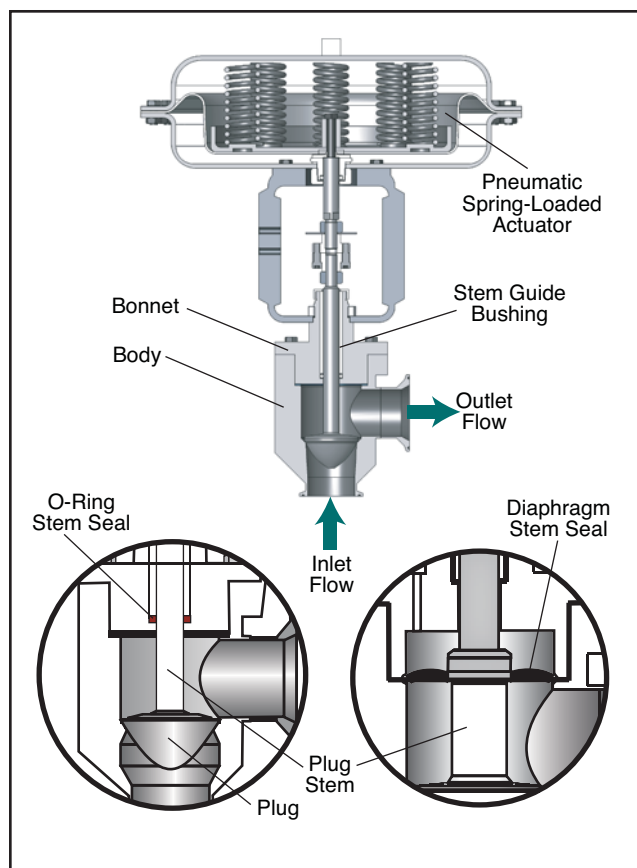
During the SIP process, condensate is generated from the steam and must be quickly removed. Proper placement of clean steam traps will ensure timely and adequate removal of the condensate, which, in turn, will help to maintain the high temperatures needed for the sterilization cycle.

## General equipment design criteria

The ASME BioProcessing Equipment (BPE) Code (1) is the guiding standard for the design, configuration, material selection and surface finish requirements for components used in steam sterilization systems. The following features are important and should be considered when evaluating components for use in SIP systems:

*Corrosion-resistant body and trim* — Typically, Type 316L stainless steel is used. This material is an excellent choice for the aggressive nature of clean steam. It is also used for its enhanced welding properties.

*Food- and/or pharmaceutical-grade soft goods* — The sealing materials should be approved by the local food and drug agencies. Most manufacturers provide elastomers con-



■ Figure 1. Valve stems may be sealed by an O-ring stem seal or by a diaphragm.

forming to the U.S. Food and Drug Administration (FDA) Code Title 21, Paragraph 177, which permits repeated use in contact with food. Often, these materials must also comply with U.S. Pharmacopeia (USP) Code Class VI, Section 88, which is concerned specifically with pharmaceutical and biotechnology products. The equipment and testing requirements for USP Class VI elastomers are frequently considered more stringent than those for FDA-approved materials.

**Self-draining design** — This requires the absence of threads within the components and the elimination of hold-up volumes in the media-contact areas. Threads and hold-up volumes can prevent complete draining or make cleaning and sterilizing more difficult, creating opportunities for bacterial growth that can contaminate the process fluid.

**Sanitary process connections** — These differ from common industrial threaded or flanged connections. Various connection types include male threads, sanitary flanges, tube-weld (or butt-weld) fittings, and clamp fittings. Clamp designs are usually preferred, because they are easier to install and can be removed more quickly for cleaning, repair or replacement.

**Surface finish** — A smooth, mechanically polished inter-

nal surface is typically required. A common surface finish specification is 20 R<sub>A</sub> (20 micro-inches). Electropolishing or passivation may be required.

Since steam is a sterilizing fluid, some steam-system design criteria are less stringent than the requirements for process components. For example, components with sliding or rotating stems seals are normally prohibited in product manufacturing equipment. Ball valves incorporating rotary stem seals and a hold-up volume between the seats are, however, often used as isolation valves in SIP systems. Typically, such ball valves include provisions for easy cleaning and/or for purging the hold-up volume.

The temperature and flow of the steam can be controlled by a control valve and its associated components and controller. Alternatively, a pressure regulator can be employed, since there is a direct correlation between temperature and pressure for the dry, saturated sterilizing steam.

## Sanitary control valves

The use of sanitary control valves typically involves modulating the flow to control either the pressure or the temperature of the steam, depending on the type of controller. The most accurate means of controlling pressure or temperature is the rising-stem globe-style control valve, which can use one of two methods to seal the stem — a sliding stem O-ring seal, or a hermetic diaphragm seal (Figure 1).

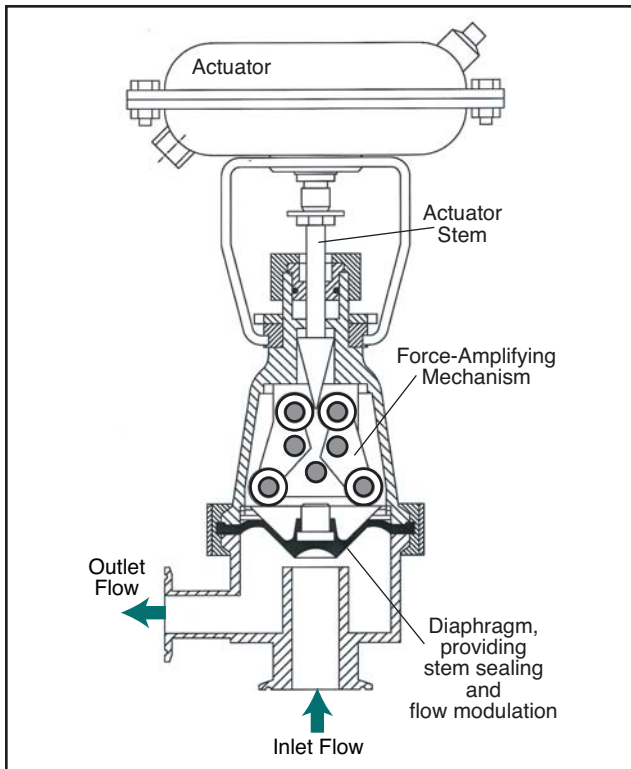
The primary benefit of the O-ring stem seal is that a lower actuation force is needed. Since the pressure of the medium in an O-ring-sealed valve does not act on a large diaphragm area, smaller actuators and lower air-supply pressures can be used. Furthermore, a variety of O-ring materials are readily available to allow the valve configuration to be customized for a specific process. For steam service, the use of perfluoroelastomers is rapidly increasing due to their high temperature resistance.

The drawback to the O-ring seal is that the stem reciprocates through the O-ring. During SIP cycles, the valve must be open, which means portions of the stem will move above the sterilizing medium. For gas and steam services, this may be acceptable, depending on the product being manufactured. Additionally, steam ports above the O-ring seal can be employed to ensure sterilization of the upper stem area.

In the two-piece stem-and-plug valve assembly with a diaphragm stem seal, the diaphragm forms a hermetic seal to the environment. While the trend among users is clearly moving toward the diaphragm seal for process systems, the use of O-ring stem seals in clean steam systems remains an option.

Once the proper valve design has been determined, several performance criteria should be considered prior to selection, including:

**Continuous steam ratings** — For some diaphragm control



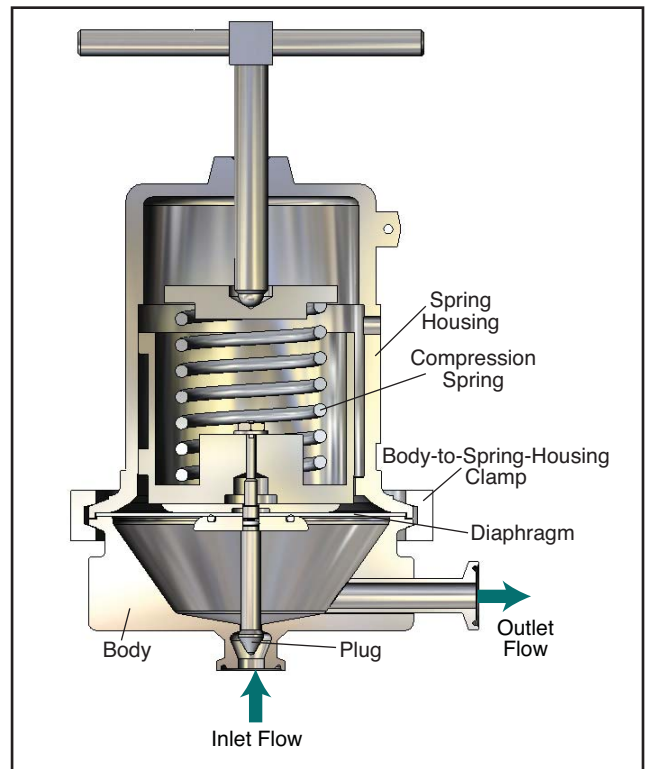
■ Figure 2. A diaphragm serves as this valve's closing member, which could lead to faster wear.

valves, continuous steam service is limited to a range of 30–60 min with 20–30-psi steam. While this is sufficient to cover the demands of the SIP cycle, a better choice is to select a diaphragm that has broader continuous steam-service ratings. The diaphragm material in combination with the valve internal design will dictate diaphragm life.

**Seat leakage and diaphragm performance** — In the stem-and-plug design shown in Figure 1, the plug closes against the valve orifice. Selecting a design that offers a dedicated seat seal and a separate stem seal (for external sealing) can enhance trim life. Designs that feature a diaphragm as the closing member at the orifice (Figure 2) could be subject to faster wear.

**Flow characteristic** — A dedicated plug seal and dedicated diaphragm seal help to ensure a specific and consistent flow characteristic. The lower plug is contoured to yield an equal percentage or linear flow characteristic as required. Designs are also available with soft seats for Class VI shut-off. Globe-style designs utilizing a diaphragm as the seat seal can have a non-linear or non-equal percentage characteristic or a characteristic that changes at various points in the stroke.

**Positioners** — In diaphragm-sealed valves, the diaphragm seal area subjected to the downstream pressure will require a larger actuator force and the use of a positioner to ensure an accurate response to the controller signal. Intel-



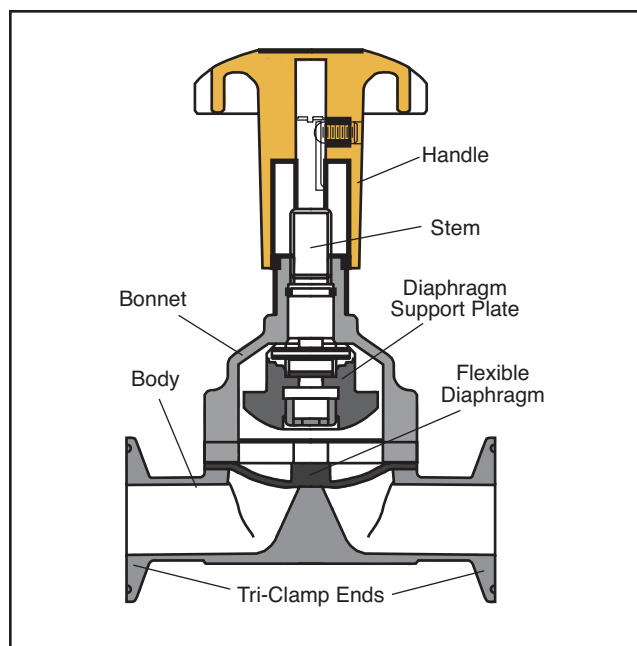
■ Figure 3. A self-operated pressure regulator requires no external control signal.

ligent positioners are becoming increasingly common due to their superior accuracy, diagnostic feedback and self-commissioning capabilities. In modern Hart or fieldbus systems, a variety of positioners can be installed regardless of the control system brand without compromising communication or diagnostic functionality.

### Sanitary pressure regulators

Self-operated pressure-regulating valves (PRVs) are found in most SIP systems. Their simplicity in function is appealing, as no external control signal is required. A typical sanitary regulator is shown in Figure 3.

Several design features must be incorporated for clean-in-place/sterilize-in-place (CIP/SIP) applicability, including corrosion-resistant materials, temperature compatibility of elastomers, and self-draining design. Of particular importance for pressure regulators (and back-pressure regulators) is the ability to ensure that the valve remains open during SIP cycles. When pressure regulators operate with low setpoints (below 20 psi), normal sterilizing pressures may cause the valve to close and prevent the cleaning/sterilizing medium from reaching downstream piping. Various methods for ensuring that the valves stay open in these cases are available, such as manual locking pins, automated mechanical locking pins, and automated pneumatic chambers in the actuator.



■ Figure 4. Sanitary isolation functions can be handled by a weir-style diaphragm valve ...

Inherent to any spring-loaded regulator is a deviation from setpoint as the valve capacity increases. This phenomenon is called droop or offset, which is expressed as a percentage of the setpoint. (For example, if the spring is set at 100 psi but the actual observed outlet pressure is only 90 psi, the droop is 10%.) As the valve capacity is progressively increased, the outlet pressure typically falls. This droop in outlet pressure occurs as a result of the set spring relaxing as the valve opens.

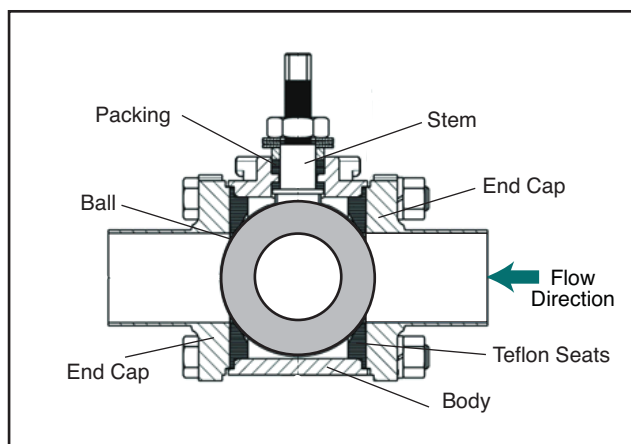
A well-designed, properly sized sanitary pressure regulator should experience no more than 10%–20% droop. Tabulations of operating characteristics listing flow coefficient ( $C_V$ ) or flow at various droop percentages for a range of service conditions based on tests are available from manufacturers. These should be evaluated when selecting regulators.

For a given flow requirement, it is important to select the valve that offers the highest  $C_V$  at the lowest droop percentage. Regulators that display significant droop will result in lower downstream pressures and thus lower temperatures. This, in turn, results in longer sterilization times, the potential for incomplete sterilization, and ultimately perhaps fewer production batches per year.

## Sanitary isolation valves

Isolation valves used in sanitary systems are required to be in compliance with the ASME BPE Code.

In process systems, the weir-style diaphragm valve (Figure 4) is commonly used to provide drainability and a hermetic stem seal.



■ Figure 5. ... or by a ball valve.

For clean steam systems, however, ball valves offer a robust design with high flow capacity and tight shutoff, and thus, are a viable and economic alternative. These three-piece ball valves (Figure 5) are easy to disassemble for cleaning and have ports for steam purging and draining of the hold-up volume between the seats. A “true bore” design is used with closely matching bores in the ball and end connections.

## Sanitary steam traps

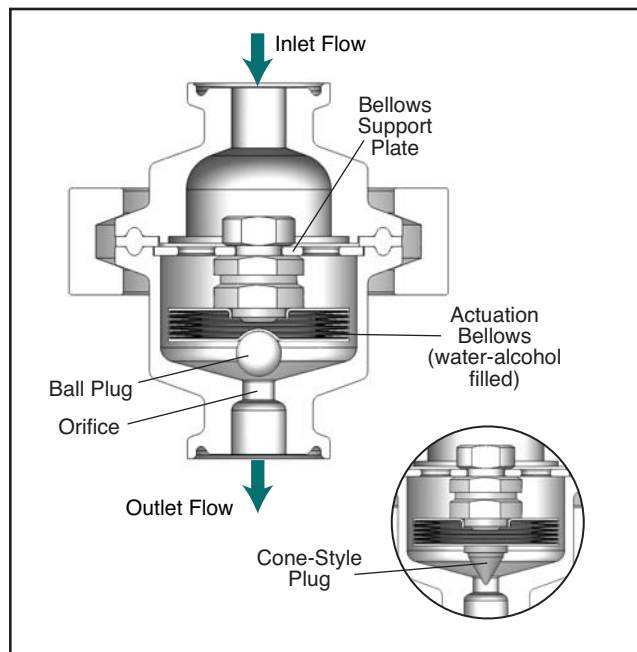
In older SIP systems, standard industrial stainless steel traps (or modified stainless steel traps) were often the primary choice for condensate removal. The rationale was that the condensate was vented to a drain header and not further introduced to downstream process equipment. Subsequently, sanitary steam traps, also known as clean steam traps, have become more prevalent and are the subject of greater scrutiny.

Many of the previously discussed design criteria for valves apply to clean steam traps as regards materials of construction, surface finishes and drainability.

Various types of clean steam traps exist on the market today, including thermodynamic disc traps, float traps, fixed-orifice traps, and thermostatic element traps. Of these, the most common is the thermostatic steam trap, which incorporates a bellows actuator and either a ball plug or a cone-style plug and seat design (Figure 6).

If the bellows assembly and orifice size are optimized, a ball-type plug with a quick opening flow characteristic will permit higher flows at the same amount of sub-cooling. (Sub-cooling is the difference between the temperature at which the steam condenses and the temperature at which the trap will discharge the required flow.)

Bellows assemblies are proprietary to each trap manufacturer. Capacity and sub-cooling charts based on actual testing should be obtained from the manufacturer and evaluated to ensure the best trap performance.



■ Figure 6. Thermostatic steam traps can feature a ball plug or a cone-style plug.

### Closing thoughts

Component designs must adhere to the ASME BPE Code. Due to the self-sterilizing characteristics of steam, some design latitude is permissible, such that sliding or rotating stem seals and hold-up volumes in components can be tolerated, provided there are provisions for cleaning, purging and draining.

The critical issues for optimum performance of clean steam systems are the control of the inlet pressure combined with the necessity for removing condensate with minimum sub-cooling. Control valves can offer benefits over regulators in terms of maintaining a set pressure over a wide flow range together with the capability for remote changes in setpoint and operating parameters during operation. Positioners will also permit communication and diagnostics. However, regulators are often used and are generally considered to provide sufficient accuracy with significant reductions in capital costs.

Thermostatic sanitary steam traps are the predominant choice in SIP systems, and considerable R&D efforts have been expended on obtaining the required condensate removal with minimum sub-cooling.

Some in the pharmaceutical industry have begun to embark on higher-temperature sterilization cycles than the typical 121°C–135°C range. High-temperature, short-time (HTST) sterilization systems, with temperatures ranging from 140°C to 160°C, are becoming more common.

Another trend is the move toward more continuous processing in the pharmaceutical industry. The FDA is begin-

ning to address this movement through its Process Analytical Technology (PAT) initiative. PAT is “a system for designing, analyzing and controlling manufacturing through timely measurements (*i.e.*, during processing) of critical quality and performance attributes of raw and in-process materials and processes, with the goal of ensuring final product quality” (2). The potential evolution toward more continuous processing (and potentially more-demanding sterilization cycles) requires higher-duty-cycle diaphragm control valves for steam. Larger valves for continuous service will also be required, as will smaller valves for such equipment as mobile, modular clean-steam generators and sterilizers.

Valve and trap designs have evolved significantly since their inception two decades ago. Enhanced designs, new materials and demanding applications continue to emerge in the biotech and pharmaceutical arenas.

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