CHAPTER 2
DESIGN

PART SD
SYSTEMS DESIGN

SD-1 PURPOSE AND SCOPE

The purpose of Part SD is to establish design guidelines applicable to bioprocessing equipment. Wherever "equipment" is stated in this Part, it shall mean all bioprocessing equipment, components, assemblies, and systems.

The purpose of this Part is to provide requirements for the specification, design, fabrication, and verification of process equipment and systems that are fit for intended use, and to minimize risk to the product. Part SD also provides design guidelines that should be applied at the discretion of the owner/user on the basis of assessed risk to the product. Figures in this Part are intended to illustrate accepted applications of general design principles and are not intended to limit alternate designs.

The scope of Part SD encompasses requirements for equipment, process systems, and utilities that could potentially impact product quality. Specific guidance is provided for bioburden control in manufacturing processes, including design requirements for cleaning, sanitization, and/or sterilization of bioprocess systems.

(19) SD-2 GENERAL GUIDELINES

All equipment and/or systems shall be designed according to the bioprocessing application, requirements, and specifications of the owner/user. It shall be the responsibility of the owner/user to specify the cleaning and/or sanitization requirements of the equipment and/or system.

Following installation, to remove construction debris and/or foreign bodies, process contact liquid-service systems should be flushed with deionized or better-quality water and/or chemically cleaned, per owner/user's requirements, before being placed into service. This does not apply to single-use or precleaned components.

The design shall provide for the removal of components (e.g., pumps, control valves, spray devices, instrumentation) that may be damaged by construction debris during flushing. If removal is not practical, the design shall allow for a temporary strainer installed upstream of the component, sized to catch the debris.

The pipe design and the flushing sequence, including associated variables (e.g., velocity), shall meet the owner/user's requirements.

SD-2.1 Containment

The containment level of the system or individual pieces of equipment should be specified and communicated by the owner/user.

The owner/user shall determine the containment level for the particular type of equipment or system, in accordance with the Centers for Disease Control and Prevention (CDC) and guidelines of the National Institutes of Health (NIH) or directives of the European Union and other applicable local codes or environmental regulations.

SD-2.2 Bioburden Control

[Reserved for future content]

SD-2.3 Bioburden Reduction (19)

SD-2.3.1 Thermal Sanitization. Thermal sanitization is the application of heat to reduce bioburden in a system. Bioburden reduction can be accomplished by the appropriate application of moist heat or dry heat. Specific temperatures and exposure times depend on the objectives. Thermal sanitization includes the following: dry heat treatment, SIP for sanitization, SIP for sterilization, steam out of place (autoclaving), hot liquid sterilization, and hot liquid sanitization.

SD-2.3.1.1 Steam-in-Place. Equipment parts and components subjected to SIP should be designed and constructed to withstand continuous exposure to saturated steam at a minimum temperature of 266°F (130°C; representing 24 psig/1.65 bar under saturated steam conditions) for a duration of at least 100 hr under continuous steady-state conditions. All process contact surfaces subjected to SIP shall reach the required temperatures, under the required saturated steam pressure conditions, during the SIP cycle. Executing SIP operations at temperatures exceeding 266°F (130°C) may cause degradation of elastomers and/or damage to other components, resulting

in reduction of overall equipment life. SIP conditions that are more stringent may be imposed by the owner/user. The use of elastomers (within a piece of equipment or certain process instrumentation) that could thermally degrade during SIP shall be evaluated by the owner/user.

SD-2.3.1.1.1 Requirements. Process systems subject to SIP shall be designed to

(a) provide for air removal within the SIP boundary

(b) provide for condensate drainage within the SIP boundary

(c) be drainable in conformance with SD-2.4.3

(d) have provisions in place for verification of SIP performance

(e) have no dead legs within the SIP boundary

SD-2.3.1.1.2 Recommendations. Process systems subject to SIP should be designed to

(a) avoid concurrent steam supplies from alternate locations to prevent stagnant zones/entrained air

(b) monitor temperature and pressure at appropriate locations (e.g., vessels) that confirm saturated steam conditions within the SIP boundary

(c) monitor temperature at every SIP boundary point during performance verification

(d) enable continuous verification or periodic confirmation of the validated state

(e) maintain the integrity of the system post-SIP

SD-2.3.1.2 Depyrogenation. [Reserved for future content]

SD-2.3.2 Chemical Sanitization. [Reserved for future content]

SD-2.4 Fabrication

Fabrication shall be performed in facilities where the process contact surfaces are protected from contamination. During field welding and assembly, surface contamination shall be prevented.

Systems, equipment, and components shall be cleaned with a suitable cleaning agent and covered for protection before shipment. The use of preservative fluids is not recommended.

Any process contact surfaces that require shipment with preservatives or coatings shall be

(a) mutually agreed to, in advance, by the owner/user and manufacturer

(b) clearly identified to all parties

(c) in compliance with FDA or other applicable regulations, as appropriate for the process

SD-2.4.1 Materials of Construction

(19) **SD-2.4.1.1 General.** Generally, materials such as stainless steels (e.g., 316-type and 316L-type alloys), duplex stainless steels, and higher alloys have proven to be acceptable. The owner/user shall be responsible for the selection of the appropriate materials of construction for the specific process. Metallic materials of construction are listed in Part MM.

When nonmetallic materials are used (e.g., polymeric materials or adhesives), the owner/user shall specify which one of these materials shall carry a Certificate of Compliance. The conformance of material shall be explicitly stated (e.g., conforming to FDA 21 CFR 177 and USP Section <88> Class VI). Polymeric materials and other nonmetallic materials of construction are listed in Part PM.

SD-2.4.1.2 Process Compatibility

(a) Materials of construction shall be capable of withstanding the temperature, pressure, and chemical corrosiveness of the process.

(b) Materials shall be compatible with the stated bioprocessing conditions, cleaning solutions, and SIP conditions, etc., as specified by the owner/user.

(c) Surfaces exposed to bioprocessing fluids, cleaning, and SIP conditions must be

(1) homogeneous in nature

(2) impervious

(3) inert

(4) nonabsorbent

(5) nontoxic

(6) insoluble by process or cleaning fluids

(7) resistant to corrosion, scratching, scoring, and distortion

(d) Materials that are in contact with bioprocessing fluids shall be identified by an industry-recognized standard (see para. MM-4).

SD-2.4.1.3 Surface Coatings. Clad or electroplated surface coatings, plating, and surface preparatory chemicals may be used provided approval from the owner/user has been obtained. All surface coatings shall remain intact and be tolerant to the process, SIP and CIP fluids, and temperatures, without peeling or cracking.

SD-2.4.1.4 Transparent Materials

(a) Transparent materials (e.g., glass, polymer) that are used in viewing ports shall be rated for the applicable pressure, temperature range, and thermal shock.

(b) Internally coated glass shall only be used if the coating complies with FDA regulations or another regulatory authority's regulations and is approved by the owner/user.

SD-2.4.2 Cleanability (19)

(a) The following provisions are applicable to tubing, equipment, or systems intended to be cleaned:

(1) All surfaces shall be cleanable. Surface imperfections (e.g., crevices, gouges, obvious pits) should be eliminated whenever feasible.

(2) All surfaces shall be accessible to the cleaning solutions and shall be accessible to establish and determine efficacy of the cleaning protocol.

Table SD-2.4.3.1-1 Slope Designations for Gravity-Drained Lines

Slope Designation	Minimum Slope, in./ft	Minimum Slope, mm/m	Minimum Slope, %	Minimum Slope, deg
GSD1	1/16	5	0.5	0.29
GSD2	1/8	10	1.0	0.57
GSD3	1/4	20	2.0	1.15
GSD0	Line slope not required			

(3) Fasteners or threads shall not be exposed to the process, steam, or cleaning fluids. The use of threads within the process requires owner/user agreement. Bolted attachments should be eliminated whenever possible.

(4) No engraving or embossing of materials (for identification or traceability reasons) should be made on the process contact side. When markings are required on process contact surfaces, other methods of identification shall be used.

(b) The following provisions are applicable to tubing, equipment, or systems intended to be cleaned in place:

(1) Internal horizontal surfaces should be minimized.

(2) The equipment should be drainable and free of areas where liquids may be retained. The equipment shall be free of areas where soil or contaminants could collect. The equipment should be free of areas of low flow and velocity or impact where soil or contaminants could collect.

(3) Design of corners and radii should meet the following requirements: All internal angles of 135 deg or less on surfaces shall have the maximum radius possible for ease of cleanability. Where possible, these surfaces shall have radii of not less than 1/8 in. (3.2 mm) except where required for functional reasons, such as the bonnet/body connection. For special cases, the radii may be reduced to 1/16 in. (1.6 mm) when agreed to by the owner/user. When the 1/16 in. (1.6 mm) radii cannot be achieved for essential functional reasons such as flat sealing surfaces and flow control apertures, the surfaces of these internal angles shall be readily accessible for cleaning and examination.

SD-2.4.3 Drainability

SD-2.4.3.1 General. For the purpose of bioburden control and cleaning, gravity is an effective way to facilitate drainage. To achieve gravity drainage, lines should be pitched to designated points at a specific slope. Refer to Nonmandatory Appendix C for suggested method of slope measurement. For gravity-drained piping/tubing systems, the owner/user may define the system slope in accordance with one of the designations listed in Table SD-2.4.3.1-1. Gravity-drained piping/tubing systems shall have a continuous pitch that is equal to or greater than the slope designation. Line sections up to 10 in. (25 cm) in length (or longer with advance approval of the owner/user) that are level or have a positive slope less than the slope designation are acceptable if the section is fitting-bound.

SD-2.4.3.2 Drainability Design Considerations. The system's process requirements should be considered in the selection of slope designation.

(a) Process contact lines exposed to liquid should be sloped to minimize pooling in the system.

(b) Lines that are steam sterilized in place should be sloped to facilitate gravity drainage of condensate.

(c) Lines that are cleaned in place should be sloped to facilitate gravity drainage of cleaning fluids.

The physical characteristics of the system (e.g., line size, materials, fluid viscosity, fluid surface tension) will influence drainability at a given slope and should also be considered. The owner/user may apply additional criteria in the selection of slope designation to address issues such as product recovery or maintenance. Fluid retention due to capillary action should be considered when using tubing less than 3/4 in. (20 mm). System leveling should be considered for mobile equipment that is gravity-drained.

SD-2.4.3.3 Slope Considerations. The recommended minimum slope designation for gravity-drained process contact lines is GSD2.

SD-2.4.3.4 Drain Points

(a) Piping and equipment should be installed with designated drain points to maximize self-draining properties. The number of drain points should be minimized. The equipment manufacturer shall indicate the proper orientation to optimize drainability. The owner/user shall ensure that proper orientation is achieved.

(b) Systems or equipment that cannot be gravity-drained shall use forced expulsion with pressurized gas where line drainability is required.

SD-2.4.4 Miscellaneous Design Details

SD-2.4.4.1 Lubricants

(a) Grease and other lubricating fluids that are used in gearboxes, drive assemblies, etc., shall be contained to prevent leakage of the lubricants or process, either directly or indirectly (e.g., through seepage, seal leaks).

(b) The equipment manufacturer shall specify the type of lubricants that are to be used for maintenance. If the specified lubricant is not accepted by the owner/user, the choice of an alternative shall be agreed to by the owner/user and the equipment manufacturer.

(c) The owner/user shall give his approval for the lubricants that could come in contact with the process. These lubricants shall be identified by name, manufacturer, and grade and shall conform to FDA or other applicable regulatory codes.

SD-2.4.4.2 Exterior Design. Equipment located in clean areas is periodically cleaned by wash-down or manually cleaned by wipe-down with harsh cleaning solutions. Such equipment shall conform to the following:

(a) Materials of construction should be corrosion resistant, easily maintained, cleaned, and sanitized without flaking or shedding.

(b) Finishes shall be compatible with the area/room classification as agreed to by the owner/user and manufacturer.

(c) Components shall be capable of being chemically cleaned, steam cleaned, or pressure washed.

(d) All burrs or weld marks shall be removed.

(e) Hinges should be easily removable and/or cleanable.

(f) Equipment mounted on cabinets that are exposed to the environment should be mounted flush.

(g) Skids should have no openings in the frame allowing water retention. Supporting skid frame structures and modules should be constructed from fully sealed tubes or pipes, which are easily cleaned. Frames should have rounded rather than sharp edges.

(h) Motors, gearboxes, and similar equipment should not retain fluids or cleaning solutions on their external surfaces.

(i) Nameplates for tagging equipment should be constructed from corrosion-resistant material, such as stainless steel or polymeric material, and should have minimal crevices. The nameplates should be attached and sealed or attached with a corrosion-resistant wire loop.

(j) There should be adequate clearance below or under the equipment for cleaning, and a clearance for discharge should be provided. Elevated equipment under open frames should have a minimum clearance of 6 in. (150 mm) for wash-down and cleaning. In other cases a minimum of 4 in. (100 mm) would be adequate.

(k) Joints and insulation materials shall be sealed and impervious to moisture and cleaning agents.

(l) Electrical enclosures and conduit should be cleanable and use materials of construction that are compatible with cleaning agents.

(m) Painted surfaces shall be identified by the fabricator and have the advance approval of the owner/user. All paint systems shall be FDA compliant.

SD-2.4.4.3 Surface Finishes. The finishes of process contact surfaces shall be specified by the owner/user in accordance with the definitions of Part SF in this Standard.

(19) SD-2.5 Hygienic System Design

The hygienic design of the system shall incorporate the applicable functionality for passivation, cleaning, sanitization, steam-in-place, process fluid distribution, and process parameter measurement and control. The system's hygienic physical (general arrangement) design shall be integral with its operations including, but not limited to, valve sequencing, parameter measurement, and controls. The owner/user and designer should evaluate the design across all operations to confirm that the design mitigates contamination risk to the product and to identify installation, operational, and performance verification testing requirements.

SD-2.5.1 Tube/Pipe Branches. Tube/pipe branches that are closed (e.g., closed valve, capped branch tee) during an operation should be designed and installed to mitigate contamination risk. Tube/pipe branches closed during CIP/SIP operations, designed to meet the minimal dimensional and orientation criteria detailed in SD-3.1.2.2, are not dead legs if they are operated, cleaned, or sanitized under specified conditions (e.g., velocity, temperature, time). Tube/pipe branches that are open during CIP/SIP shall be designed to enable flow of cleaning/sanitizing fluids under specified conditions. Tube/pipe branches with valves that are cycled during processing operations should be designed to mitigate cross-contamination risk and are not dead legs if they are toggled, cleaned, or sanitized under specified conditions (e.g., flow/impingement, steam penetration, temperature, time).

SD-2.5.2 Tube/Pipe Instruments. Process tubing/piping instrumentation and associated connection points should be designed to mitigate the risk of contamination due to extended ferrule connections and any annular space around the sensor. Instrument tees or short-outlet tees conforming to DT-4.1.2 should be used where feasible, maintaining $L/A < 2$ [see Figure SD-3.4.3-1, illustration (a)]. When an instrument tee or short-outlet tee is not used, the tee should be oriented such that cleaning and sanitization fluids circulate into the branch and annular space around the instrument sensor, and air is not trapped, to avoid the formation of a dead leg. The system designer shall identify instrument locations where L/A or $L/d < 2$ is not met.

SD-2.5.3 Equipment Nozzles. Equipment nozzles used to accommodate agitators, controls, instrumentation, or process fluid transfer should be designed to mitigate contamination risk due to extended connections or the annular space around the inserted appurtenance by meeting the dimensional and orientation criteria detailed in SD-3.5.1 and SD-3.4.3. Equipment nozzles closed during CIP/SIP operations shall be designed to meet the minimal dimensional and orientation criteria detailed in SD-3.4.2 and are not dead legs if they are cleaned or sanitized under specified conditions (e.g., flow/impingement, steam penetration, temperature, time).

SD-3 PROCESS COMPONENTS

SD-3.1 Connections, Fittings, and Piping

(19) SD-3.1.1 General

(a) Design of equipment should minimize the number of connections. Butt-welded connections should be used wherever practical.

(b) Connections to equipment shall use acceptable hygienic design connections, mutually agreeable to the owner/user and manufacturer.

(c) All connections shall be capable of CIP and SIP. Fittings shall be so designed that there will not be any crevices or hard-to-clean areas around the gasketed joint. ASME raised-face or flat-face flanged joints should be avoided where possible (see Figure SD-3.1.1-1).

(d) Ferrules and ferrule connections should not constitute a dead leg. The use of short welding ferrules should be incorporated into the design to promote enhanced cleanability or bioburden reduction of the system.

(e) All process contact fittings exposed to liquid should be self-draining when properly installed.

(f) Threaded fittings, exposed to process fluid, are not recommended (see Figure SG-2.2.2-5).

(g) The use of flat gaskets may be acceptable, when agreed to by the owner/user and manufacturer, for applications where it is considered self-sanitizing (i.e., in pure steam distribution systems).

(h) The centerline radius of factory-bent tubes shall be in accordance with Table DT-3-1, CLR, (*R*).

(i) Piping systems described in Part SD refer to hygienic tubing systems. Caution should be exercised if using pipe (instead of tube) to ensure that the requirements of this Standard are met. The requirements of hygienic tubing (e.g., surface finish, dimensions, and tolerances) are not typically met by pipe.

SD-3.1.2 System Design

SD-3.1.2.1 General

(a) Product holdup volume in the system should be minimized.

(b) Bioprocessing piping and tubing design should have routing and location priority over process and mechanical support systems.

(c) Piping and connections to in-line valves should be of all-welded construction where feasible, practical, and agreed to by the owner/user and manufacturer. To ensure the highest degree of hygienic design, the piping systems should use welded connections except where make-break connections are necessary.

(19) **SD-3.1.2.2 Closed Tube/Pipe Branches.** Closed tube/pipe branches will be measured by the term *L/d*, where *L* is the leg extension from the I.D. wall normal to the flow pattern or direction, and *d* is the I.D. of the extension or leg of a tubing fitting or the nominal dimension of a valve or instrument. For valves, *L* shall be measured to the seal point of the valve. Tables SD-3.1.2.2-1 and SD-3.1.2.2-2 indicate *L/d* values based on the BPE definition for various tubing geometries and configurations.

There is evidence that an *L/d* of 2 or less may prevent the branch from being a dead leg; however, the size and shape of the branch are also important in determining if the branch could lead to contamination. With sufficient flow through a primary pipeline, a branch may not constitute a dead leg.

The orientation of a branch is critical to the cleanability of the system. The branch shall be oriented to avoid a dead leg (e.g., a vertical branch with an *L/d* of 2 or less may still result in a dead leg with trapped gas or residual materials).

For high-purity water systems, an *L/d* of 2 or less is attainable with today's manufacturing and design technology. For other bioprocessing systems, such as purification, filtration, and fermentation having cluster, block, and multiport valves, an *L/d* of 2 or less is achievable. However, it may not be achievable with certain equipment and process configurations as they are currently manufactured. An *L/d* of 2 or less is recommended but shall not be construed to be an absolute requirement. The system designer and manufacturer shall make every attempt to eliminate system branches with an *L/d* greater than 2. It will be the responsibility of the system manufacturer or designer to identify where exceptions exist or where the *L/d* of 2 or less cannot be met.

An *L/d* of 2 or less may not be achievable for weir-type valves clamped to tees and certain sizes of close welded point-of-use valves, as shown in Figure SD-3.1.2.2-1, illustrations (a), (d), (e), (f), and (g). For the header and valve size combinations where the *L/d* of 2 cannot be met using these configurations, a specific isolation valve design, as shown in Figure SD-3.1.2.2-1, illustrations (b) and (c), may be required to achieve the desired ratio.

SD-3.1.2.3 System Piping (19)

(a) Routing of piping should be as direct and short as possible to ensure a minimal quantity of CIP solution to fill a circuit and eliminate excessive piping and fittings.

(b) Cross-contamination of process streams shall be physically prevented. Methods of separation used in industry are

(1) removable spool piece

(2) U-bend transfer panel

(3) double block-and-bleed valve system (see Figure SD-3.1.2.3-1)

(4) mix-proof valving

(c) The use of fluid bypass piping (around traps, control valves, etc.) is not recommended.

(d) The use of redundant in-line equipment is not recommended due to the potential creation of dead legs.

(e) Eccentric reducers shall be used in horizontal piping to eliminate pockets in the system.

Figure SD-3.1.1-1 Flat Gasket Applications

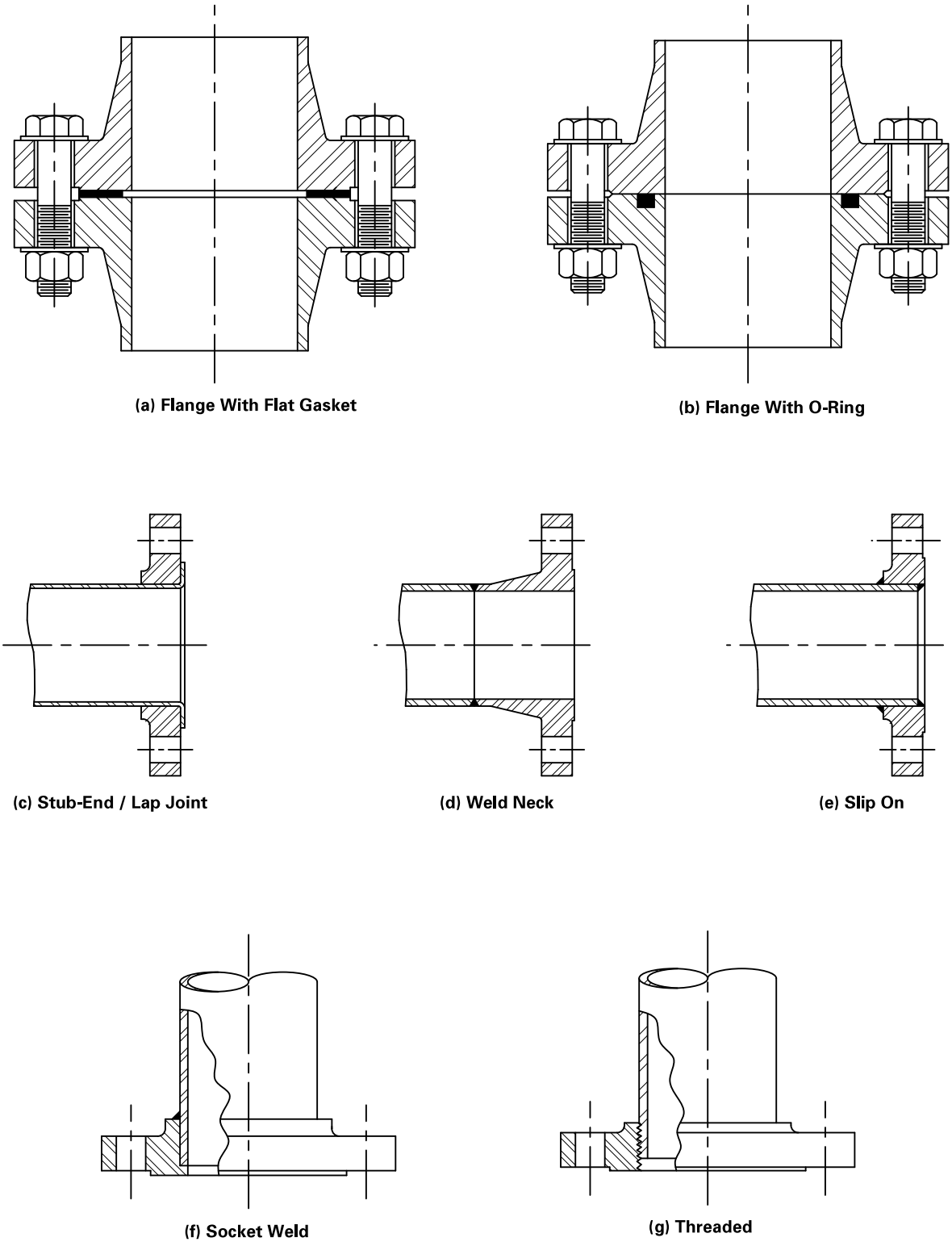
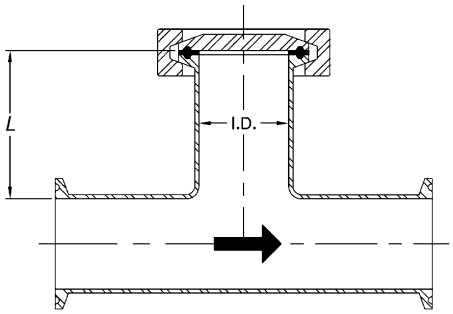
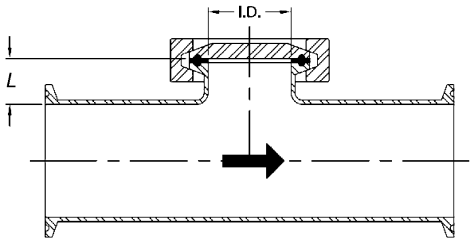


Table SD-3.1.2.2-1 *L/d* Dimensions for Flow-Through Tee: Full-Size Standard Straight Tee With Blind Cap



Nominal Size, in.	Wall Thickness	I.D. (*d*)	Branch, *L*	*L/d* (Branch)
1/4	0.035	0.180	2.16	12.00
3/8	0.035	0.305	2.10	6.88
1/2	0.065	0.370	2.07	5.58
3/4	0.065	0.620	2.07	3.33
1	0.065	0.870	2.19	2.52
1 1/2	0.065	1.370	2.14	1.56
2	0.065	1.870	2.44	1.30
2 1/2	0.065	2.370	2.44	1.03
3	0.065	2.870	2.44	0.85
4	0.083	3.834	2.83	0.74
6	0.109	5.782	4.24	0.73

Table SD-3.1.2.2-2 *L/d* Dimensions for Flow-Through Tee: Short-Outlet Reducing Tee With Blind Cap

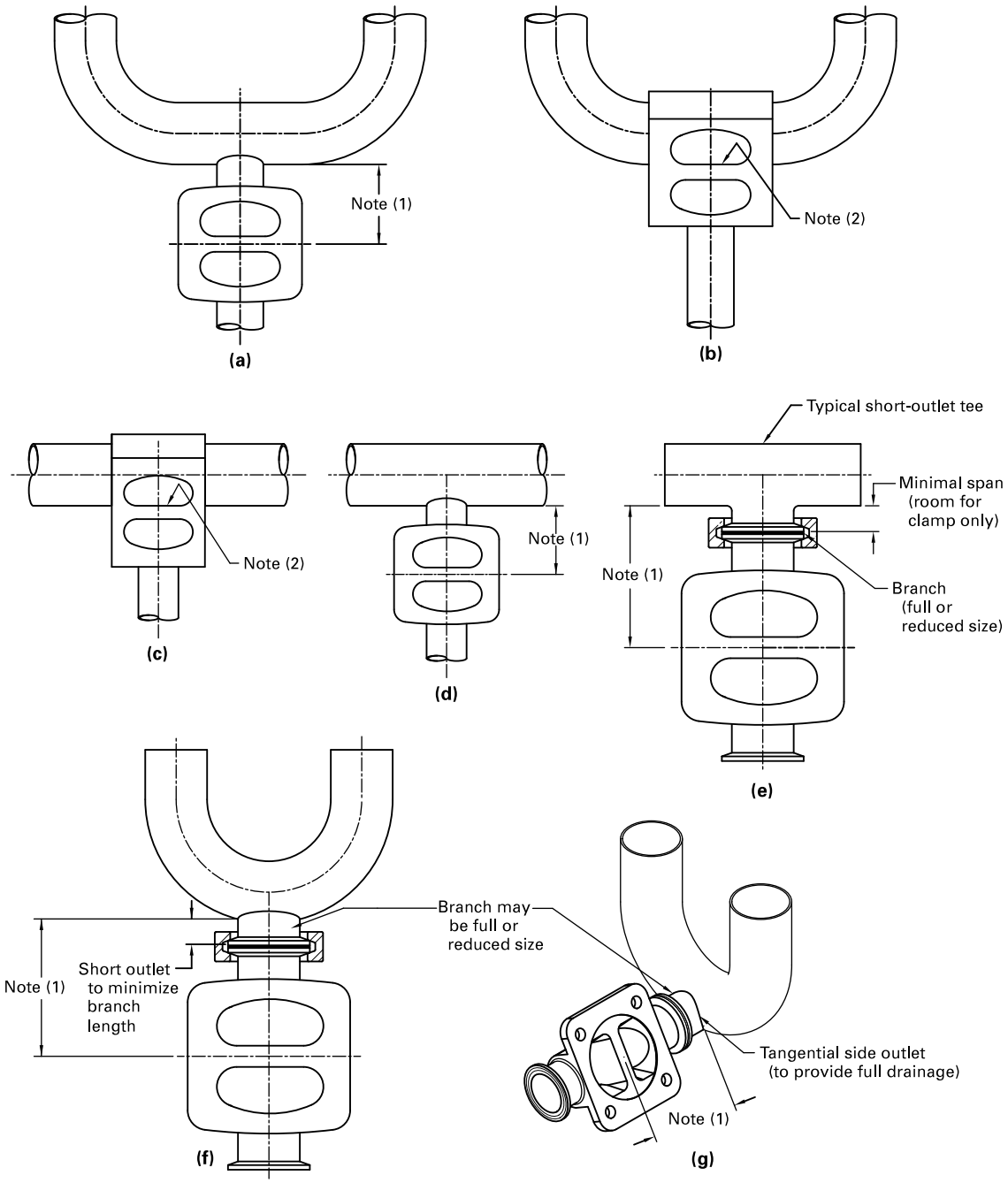


Nominal Tee Size, in.	Nominal Branch Size, in.	Tee Wall Thickness	Branch Wall Thickness	Branch I.D., *d*	Branch, *L*	*L/d* (Branch)
3/8	1/4	0.035	0.035	0.180	0.85	4.71
1/2	1/4	0.065	0.035	0.180	0.82	4.53
1/2	3/8	0.065	0.035	0.305	0.82	2.67
3/4	1/4	0.065	0.035	0.180	0.69	3.83
3/4	3/8	0.065	0.035	0.305	0.69	2.26
3/4	1/2	0.065	0.065	0.370	0.69	1.86
1	1/4	0.065	0.035	0.180	0.69	3.83
1	3/8	0.065	0.035	0.305	0.69	2.26
1	1/2	0.065	0.065	0.370	0.69	1.86
1	3/4	0.065	0.065	0.620	0.69	1.11
1 1/2	1/4	0.065	0.035	0.180	0.69	3.83
1 1/2	3/8	0.065	0.035	0.305	0.69	2.26
1 1/2	1/2	0.065	0.065	0.370	0.69	1.88
1 1/2	3/4	0.065	0.065	0.620	0.69	1.11
1 1/2	1	0.065	0.065	0.870	0.69	0.79
2	1/4	0.065	0.035	0.180	0.69	3.83
2	3/8	0.065	0.035	0.305	0.69	2.26
2	1/2	0.065	0.065	0.370	0.69	1.86
2	3/4	0.065	0.065	0.620	0.69	1.11
2	1	0.065	0.065	0.870	0.69	0.79
2	1 1/2	0.065	0.065	1.370	0.69	0.50
2 1/2	1/4	0.065	0.035	0.180	0.69	3.83
2 1/2	3/8	0.065	0.035	0.305	0.69	2.26
2 1/2	1/2	0.065	0.065	0.370	0.69	1.86
2 1/2	3/4	0.065	0.065	0.620	0.69	1.11
2 1/2	1	0.065	0.065	0.870	0.69	0.79
2 1/2	1 1/2	0.065	0.065	1.370	0.69	0.50
2 1/2	2	0.065	0.065	1.870	0.69	0.37
3	1/4	0.065	0.035	0.180	0.69	3.83
3	3/8	0.065	0.035	0.305	0.69	2.26
3	1/2	0.065	0.065	0.370	0.69	1.86
3	3/4	0.065	0.065	0.620	0.69	1.11
3	1	0.065	0.065	0.870	0.69	0.79
3	1 1/2	0.065	0.065	1.370	0.69	0.50
3	2	0.065	0.065	1.870	0.69	0.37
3	2 1/2	0.065	0.065	2.370	0.69	0.29

Table SD-3.1.2.2-2 *L/d* Dimensions for Flow-Through Tee: Short-Outlet Reducing Tee With Blind Cap (Cont'd)

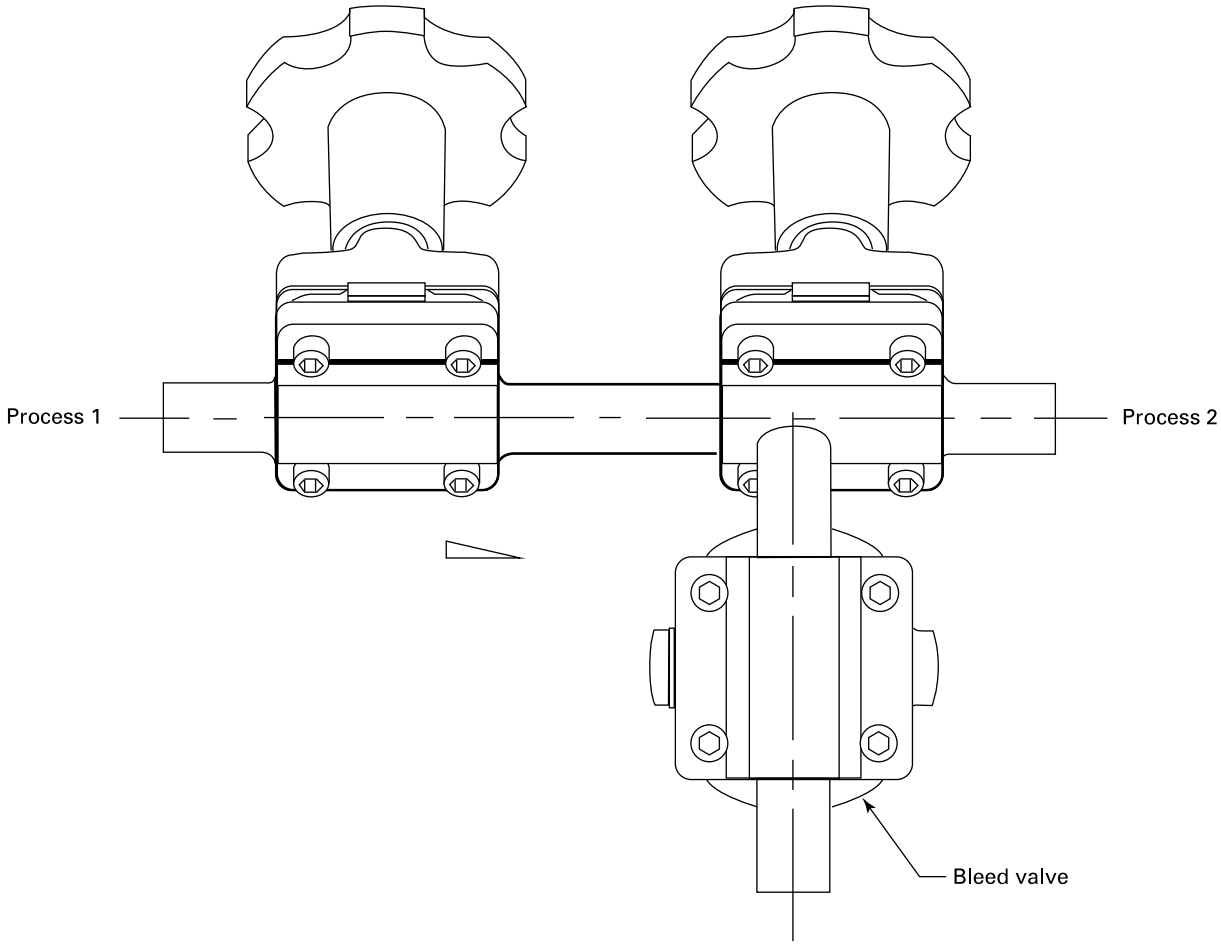
Nominal Tee Size, in.	Nominal Branch Size, in.	Tee Wall Thickness	Branch Wall Thickness	Branch I.D., *d*	Branch, *L*	*L/d* (Branch)
4	1/4	0.083	0.035	0.180	0.71	3.93
4	3/8	0.083	0.035	0.305	0.71	2.32
4	1/2	0.083	0.065	0.370	0.71	1.91
4	3/4	0.083	0.065	0.620	0.71	1.14
4	1	0.083	0.065	0.870	0.71	0.81
4	1 1/2	0.083	0.065	1.370	0.71	0.52
4	2	0.083	0.065	1.870	0.71	0.38
4	2 1/2	0.083	0.065	2.370	0.71	0.30
4	3	0.083	0.065	2.870	0.71	0.25
6	1/4	0.109	0.035	0.180	0.86	4.77
6	3/8	0.109	0.035	0.305	0.86	2.82
6	1/2	0.109	0.065	0.370	0.86	2.32
6	3/4	0.109	0.065	0.620	0.86	1.39
6	1	0.109	0.065	0.870	0.86	0.99
6	1 1/2	0.109	0.065	1.370	0.86	0.63
6	2	0.109	0.065	1.870	0.86	0.46
6	2 1/2	0.109	0.065	2.370	0.86	0.36
6	3	0.109	0.065	2.870	0.86	0.30
6	4	0.109	0.083	3.834	0.86	0.22

Figure SD-3.1.2.2-1 Accepted Point-of-Use Designs



NOTES:
(1) L/d of 2 or less.
(2) L/d = 0 (preferred).

Figure SD-3.1.2.3-1 Double Block-and-Bleed Valve Assembly



(f) The system shall be designed to eliminate air pockets and prevent or minimize air entrainment.

(g) Field bending of tubing is permitted for diameters up to and including ½ in. (15 mm). The centerline radius of field-bent tubes should be not less than 2.5 times the nominal tube diameter to mitigate the risk of interior surface damage (e.g., wrinkles, striations, and cracks). Field bending of tubing in larger diameters or smaller bend radii may be used with the approval of the owner/user when appropriate examination techniques and procedures (e.g., visual, borescope, and sectioning) are used.

(h) Ball valves are not recommended in fluid hygienic piping systems. See SD-4.2.3(b) for further comments.

(i) See SF-2.4 regarding cleaning and passivation. Passivation of electropolished surfaces is not required unless the surface has been altered (e.g., welded or mechanically polished) or exposed to external contamination after electropolishing.

(j) The use of blind welds in piping systems should be avoided. Proper installation sequencing of the piping system can reduce the number of blind welds. See MJ-7.3.3(b) and GR-5.3.4 for further details.

SD-3.1.2.4 Hygienic Support Systems

(a) Hygienic supports should be used within classified spaces. Hygienic support design should incorporate drainable geometry to facilitate cleanability, have no exposed threads, and have minimal potential for collecting and trapping debris or liquids on the hanger. Materials of construction shall be corrosion resistant and compatible with the chemical, thermal, and physical performance requirements of the installed location. The materials shall have adequate strength and durability to withstand the application of continuous and/or cyclic thermal exposure that may be encountered in the designed service.

(b) The piping should maintain proper continuous slope for drainability. Hygienic support systems shall assist in maintaining the required slope and alignment under all operating conditions, taking into account thermal cycling, distortion, settling, moment loads,

fluid specific gravity, etc. The support system should be designed to distribute loads and stresses from any potential movement. The supports shall be installed without adding stress to the tube or pipe in an attempt to achieve a desired slope.

(c) The support systems shall provide for, and control, the intended movement of the system. The designer should take into account system and equipment movement when planning the design. Anchoring systems should be designed to avoid piping motion in any of the three Cartesian axes. Guiding systems should be designed to allow piping axial motion due to thermal or mechanical loads. An anchor serves to secure the piping in place, and a guide will allow axial motion of the piping and is used to allow for thermal expansion.

(d) Supports/hangers should be installed close to each change in direction of piping. The only exception is on short subassemblies using small-diameter tube [<1.000 in. outside diameter (O.D.)] that is installed in a drainable position and does not bear any additional weights or loads from other process equipment. Hangers shall be of adequate strength and durability to withstand the imposed loads per MSS SP-58, Table 1. Per manufacturer's recommendations, supports/hangers should be installed as close as possible to (and on both sides of, if possible) concentrated loads including valves, instrumentation, and filter housings.

SD-3.1.2.4.1 Pipe Hangers and Supports for Metallic Piping. Metallic piping system hangers and supports shall be installed in compliance with MSS SP-58, MSS SP-69, MSS SP-89, and ASME B31.3 standards. The metallic pipe or tube to be installed shall meet the straightness criteria of ASTM A1016 to optimize drainability. The support spacing shall not exceed a distance that will permit the piping to deflect under operating conditions.

SD-3.1.2.4.2 Pipe Hangers and Supports for Nonmetallic Piping

(a) Nonmetallic piping system hangers and supports shall be engineered based on the specific materials selected. When properly installed, stress concentration points will be minimized. Considerations shall be made to ensure drainability and overcome any deflection, such that pooling is minimized. Refer to manufacturer's recommendations for spacing, which is based on calculations that take into consideration the piping material, density, modulus of elasticity, diameter and wall thickness of the pipe, specific gravity of the fluids being transported, operating temperature, and thermal expansion properties.

(b) The requirement of a continuous support shall be determined based on the operating temperatures and the specific gravity of the process fluid being transported. Support channels may be available in a "V" or "U" section and shall be manufactured with no sharp edges that may embed or cause damage to the pipe exterior. These are commonly available in stainless steel or fiberglass reinforced plastic (FRP) materials. These supports cannot restrict axial movement of the piping and shall be approved by the owner/user.

SD-3.2 Hose Assemblies

SD-3.2.1 General

(a) Permanently installed hose assemblies shall be installed and supported to be self-draining [see Figure SD-3.2.1-1, illustrations (a) and (b)]. In temporary runs, hose assemblies may be manually drained after disconnecting.

(b) Hose assemblies shall be installed to avoid strain on end connections. Hose assemblies shall not be used as a substitute for rigid tube fittings or as tension or compression elements.

(c) Hose assembly length should be minimized and fitted for purpose.

(d) Hose assemblies shall be easy to remove for examination and/or cleaning.

(e) Hose assembly shall be clearly marked or tagged with the design-allowable working pressure/vacuum and design temperature range.

(f) Hose assemblies shall be inspected and maintained on a scheduled basis.

SD-3.2.2 Flexible Element

(a) The flexible element of the hose assembly shall be constructed of materials that permit the appropriate degree of movement or drainable offset at installation.

(b) The interior surface of the flexible element shall be cleanable and drainable.

(c) The materials used shall comply with the applicable requirements in Part PM and/or Part SG with regard to biocompatibility. The materials used must also be compatible with cleaning and/or SIP conditions.

SD-3.2.3 End Connections (19)

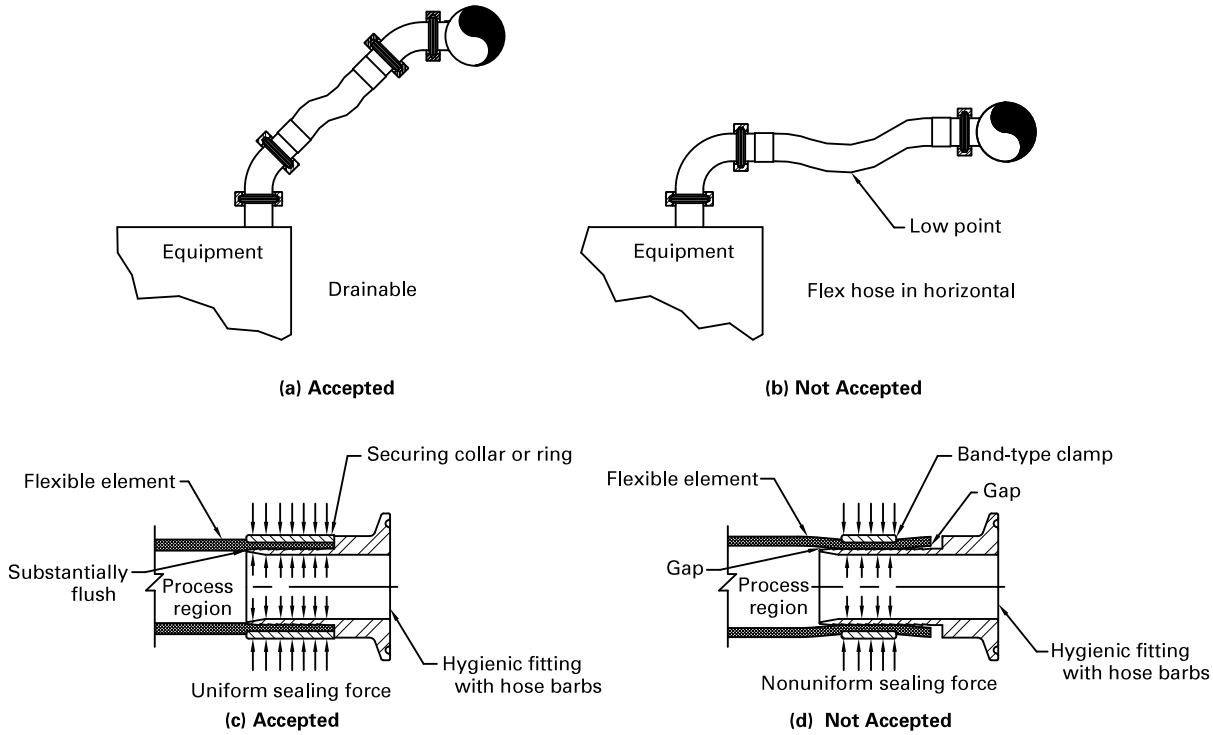
(a) End connections shall be of a material and design sufficiently rigid to withstand the combined forces of the burst pressure rating of the flexible element and the compression forces required to affect the secure assembly with the flexible element. [Refer to Figure SD-3.2.1-1, illustrations (c) and (d).]

(b) End connections shall be of a material compatible with the process fluid, cleaning solutions, and steam where applicable. Materials shall meet the requirements of SD-2.4.1 or Part PM.

(c) End connections shall meet all surface finish requirements of Part SF.

(d) End connections shall be a hygienic connection design per SG-3.3.2.

Figure SD-3.2.1-1 Flexible Hygienic Hose Design



SD-3.3 Pumps

SD-3.3.1 Diaphragm Pumps

(a) Diaphragm pumps may be used in positive displacement pump applications. Some diaphragm pumps are available that provide low shear, constant flow or pressure, low pulsation, high turndown ratio (e.g., 1,000:1), and/or low particle generation.

(b) The owner/user shall evaluate whether holdup volume and drainability characteristics of a diaphragm pump are acceptable for the application. Some process applications require the process system, including the diaphragm pump, to remain continuously flooded with sanitizing solution instead of being drained.

(c) Process contact diaphragms, O-rings, gaskets, and seals shall comply with Part SG. Process contact metallic materials of construction shall comply with Part MM. Nonmetallic process contact surfaces including diaphragms shall comply with Part PM.

(d) Where applicable, check valves shall comply with SD-3.13

(e) Where used, diaphragm fasteners shall be attached within the pump head such that crevices or threads are not exposed to the process fluids.

(f) The owner/user should consider leak detection and/or leak path design of the pump to identify a failure that can lead to process contamination and/or biohazards.

SD-3.3.2 Hygienic Pumps

SD-3.3.2.1 General

(a) Pumps shall be cleanable. Pumps shall be selected according to the operating conditions determined by the owner/user (e.g., process, CIP, SIP, passivation).

(b) All process contact connections to the pump shall be of a hygienic design (see Figures SG-2.2.2-1, SG-2.2.2-2, SG-2.2.2-3, and SG-2.2.2-4).

SD-3.3.2.2 Centrifugal Pumps

(a) Hygienic centrifugal pumps shall be capable of CIP.

(b) All process contact surfaces shall be drainable without pump disassembly or removal.

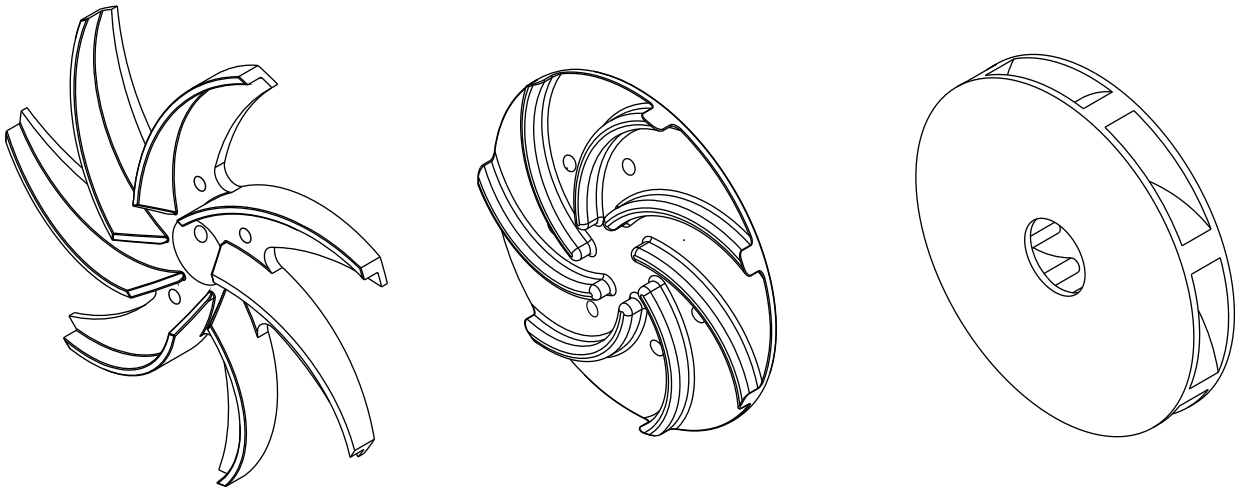
(c) Shrouded/closed impellers should not be used. Figure SD-3.3.2.2-1 illustrates open, semi-open, and closed impeller configurations.

(d) The impeller shall be attached to the shaft in such a way that all crevices and threads are not exposed to the process. Threads, such as in an impeller nut/bolt, shall be sealed by an O-ring or hygienic gasket. Refer to Figure SD-3.3.2.2-2. The use of O-rings or hygienic gaskets shall be consistent with Part SG.

(e) Suction, discharge, and casing drain connections shall be an integral part of the pump casing.

(f) Casing drains shall be at the lowest point of the casing, to ensure drainage (see Figure SD-3.3.2.2-3).

Figure SD-3.3.2.2-1 Pump Impeller Configurations

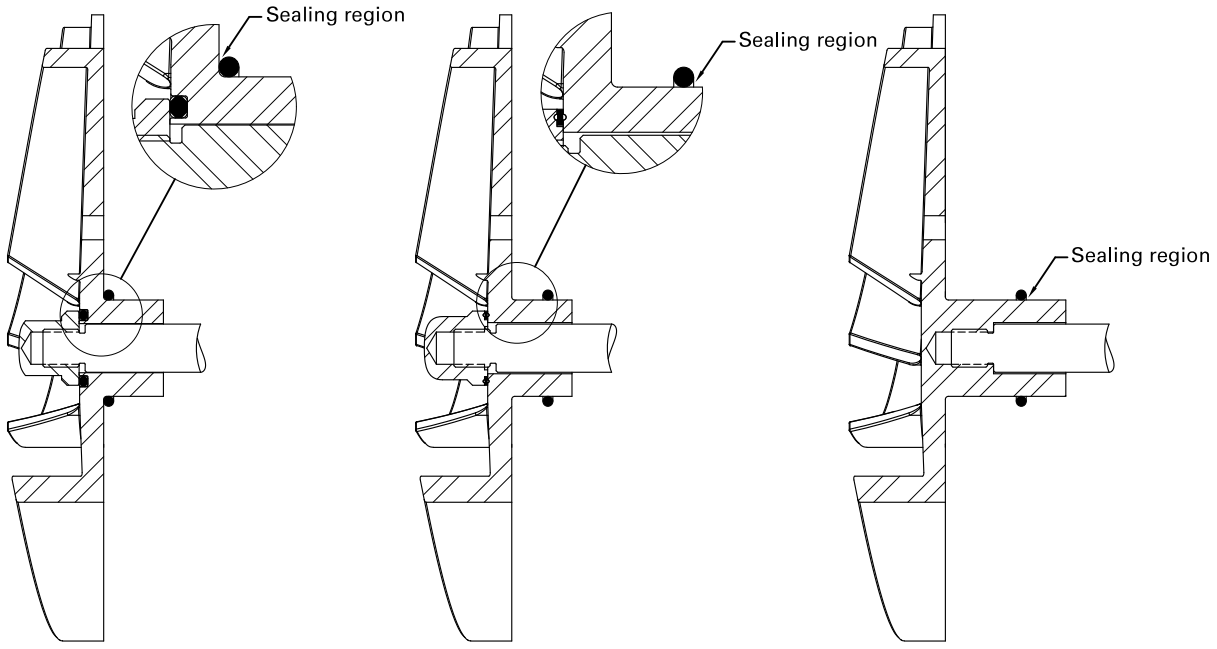


(a) Open

(b) Semi-Open

(c) Shrouded/Closed

Figure SD-3.3.2.2-2 Acceptable Impeller Attachments

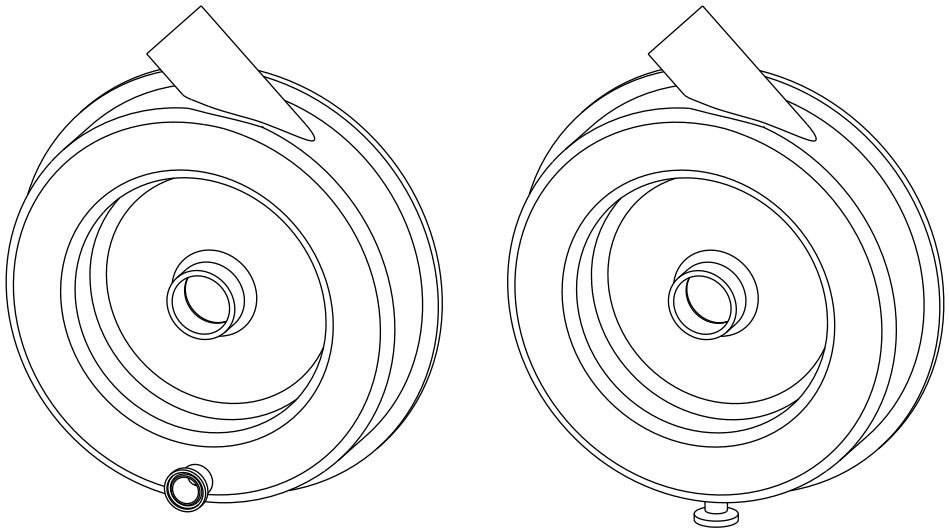


(a) Impeller Nut With O-Ring

(b) Impeller Nut With Hygienic Gasket

(c) No Impeller Nut

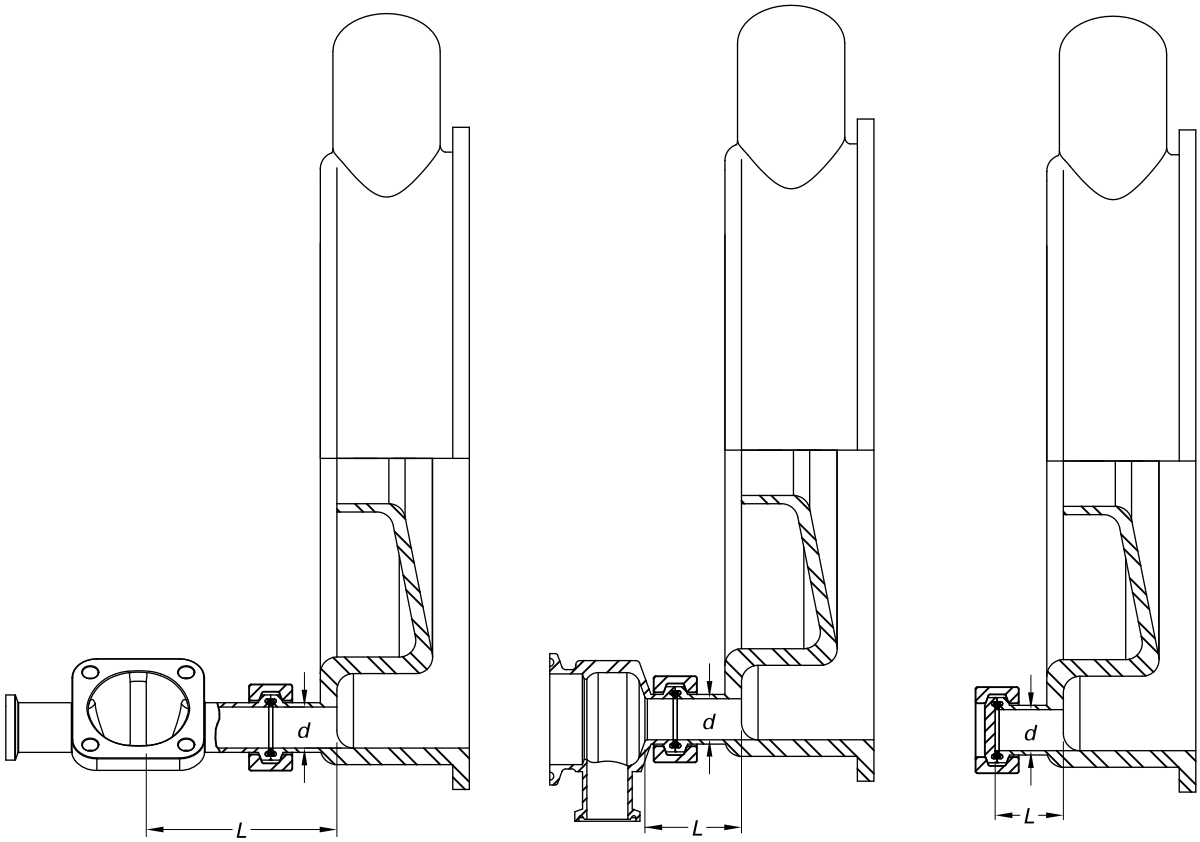
Figure SD-3.3.2.2-3 Casing Drain Configurations



(a) Horizontal

(b) Vertical

Figure SD-3.3.2.2-4 Casing Drain *L/d* Ratios

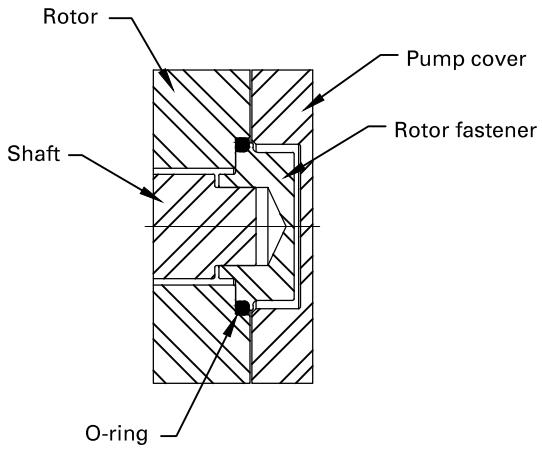


(a) Weir-Style Diaphragm Valve

(b) Radial-Style Diaphragm Valve

(c) Capped

Figure SD-3.3.2.4-1 Rotary Lobe Pump Rotor Attachment



(g) The use of an elbow-type casing drain is not recommended without the use of an automatically controlled drain. The casing drain connection shall be designed to minimize the *L/d* as shown in Figure SD-3.3.2.2-4.

(h) The pump discharge connection should be tilted to allow for full venting of the casing (see Figure SD-3.3.2.2-3).

(i) All pump seals should be designed to minimize seal material degradation.

(j) Shaft seals shall conform to Part SG.

SD-3.3.2.3 Positive Displacement Pumps

(a) When possible, positive displacement pumps should be configured with vertically mounted inlets and outlets to promote drainability and venting.

(b) When using internal bypass pressure relief devices, they shall be of a hygienic design. It is preferred that an external, piping-mounted relief device (hygienic rupture disk) rather than a pump-mounted bypass be used.

SD-3.3.2.4 Rotary Lobe Pumps

(a) The owner/user shall specify the chemical, thermal, and hydraulic operating conditions of the pump (e.g,. process, CIP, SIP) to ensure proper component selection. Hygienic rotary lobe pumps are temperature sensitive (e.g., rotor to casing contact due to thermal expansion).

(b) The pump should be designed and installed to minimize holdup volume.

(c) Rotor fasteners shall be attached to the shaft in a way that crevices and threads are not exposed to the process. Threads and crevices shall be isolated from the process fluid by an appropriate hygienic seal, such as an O-ring or hygienic gasket (see Figure SD-3.3.2.4-1).

(d) The pump cover shall seal against the pump body by means of an O-ring or hygienic gasket.

(e) All process contact O-rings, gaskets, and shaft seals shall comply with Part SG.

(f) If a pressure relief device is used, it shall be of hygienic design in conformance with SD-3.15.

SD-3.4 Vessels

SD-3.4.1 General. This section defines the requirements that should be met in the design, fabrication, and supply of pressurized and nonpressurized biopharmaceutical vessels.

(a) Design and fabrication of vessels and internal parts shall ensure that surfaces are free of ledges, crevices, pockets, and other surface irregularities. If more restrictive tolerances are required, they shall be included as part of the fabrication specifications for the project.

(b) All heat transfer surfaces should be drainable and ventable.

(c) Reinforcing pads, doubler plates, poison pads, etc., should be constructed of the same material as the vessel. If the vessel material of construction is a superaustenitic stainless steel, 316L-type alloys or other higher alloy stainless steels may be used for these components on non-process contact surfaces only. No telltale holes are allowed on process contact surfaces and those that are outside should be cleanable.

(d) Vessels that are to be exposed to temperatures above 176°F (80°C) [e.g., SIP, hot water-for-injection (WFI), hot U.S. Pharmacopeia (USP) waters, and hot CIP solutions] should be designed for full vacuum service [maximum allowable working pressure-external of 15 psig (1 barg)].

(e) Top and bottom heads on vessels that are cleaned in place shall be self-draining. Dished heads such as ASME flanged and dished (F&D), elliptical, and hemispherical are the most common types. Flat or conical heads should slope at not less than $\frac{1}{8}$ in./ft (10 mm/m) to a common drain.

(f) All internal surfaces should be sloped or pitched for drainability.

(g) Test protocols for drainability shall be agreed upon in advance by all the parties (see SD-7.4). All vessels should be checked for drainability during fabrication.

SD-3.4.2 Vessel Openings

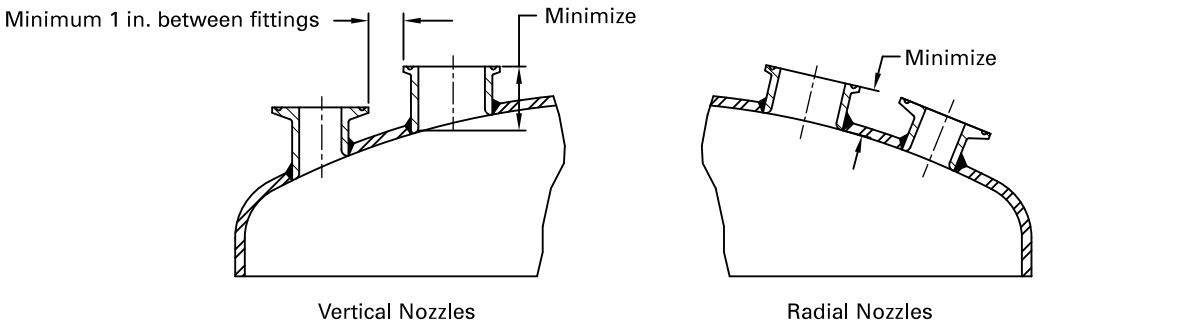
(a) Nozzles that are designed to be cleaned by a spray device should have the smallest *L/d* ratio possible. For non-flow through nozzles, an *L/d* of 2 or less is recommended (see Figure SD-3.4.2-1).

(b) Nozzles less than 1 in. (25 mm) in diameter are not recommended unless the system design provides for SIP and CIP through the nozzle.

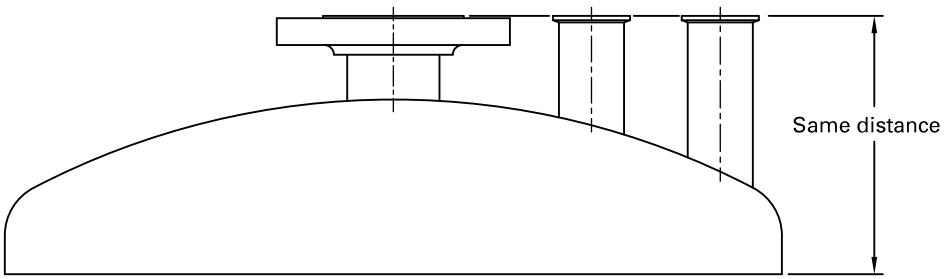
(c) Bottom-mounted agitators, valves, pads, etc., shall not interfere with the drainability of the vessel.

(d) All instrument probes and any sidewall penetrations (see Figure SD-3.4.2-2) shall be sloped for drainage, unless the instruments used require horizontal mounting (see Figure SD-3.4.2-3).

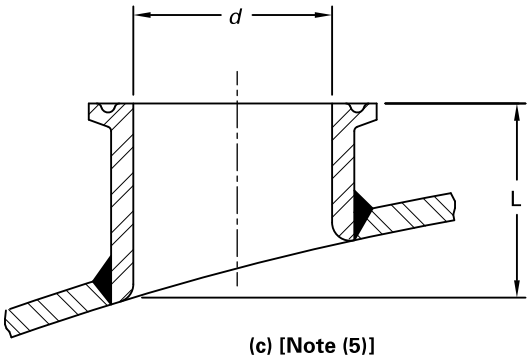
Figure SD-3.4.2-1 Nozzle Design



(a)
Allow for Clamp Access
[Notes (1) and (2)]



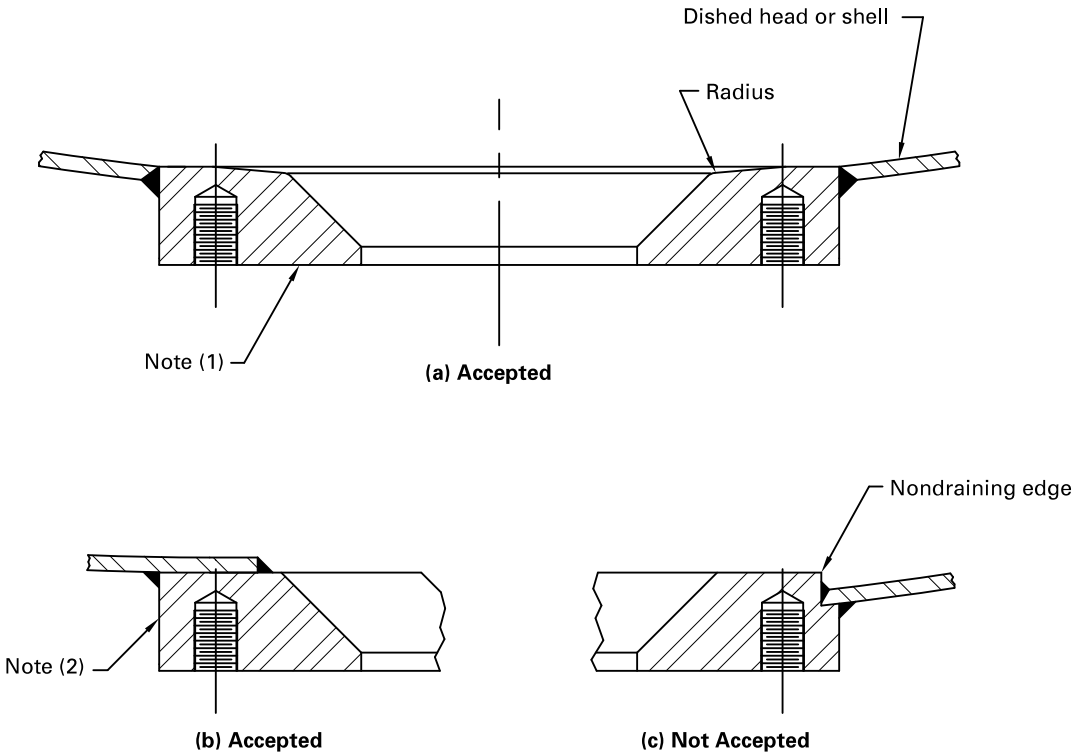
(b)
[Notes (3) and (4)]



(c) [Note (5)]

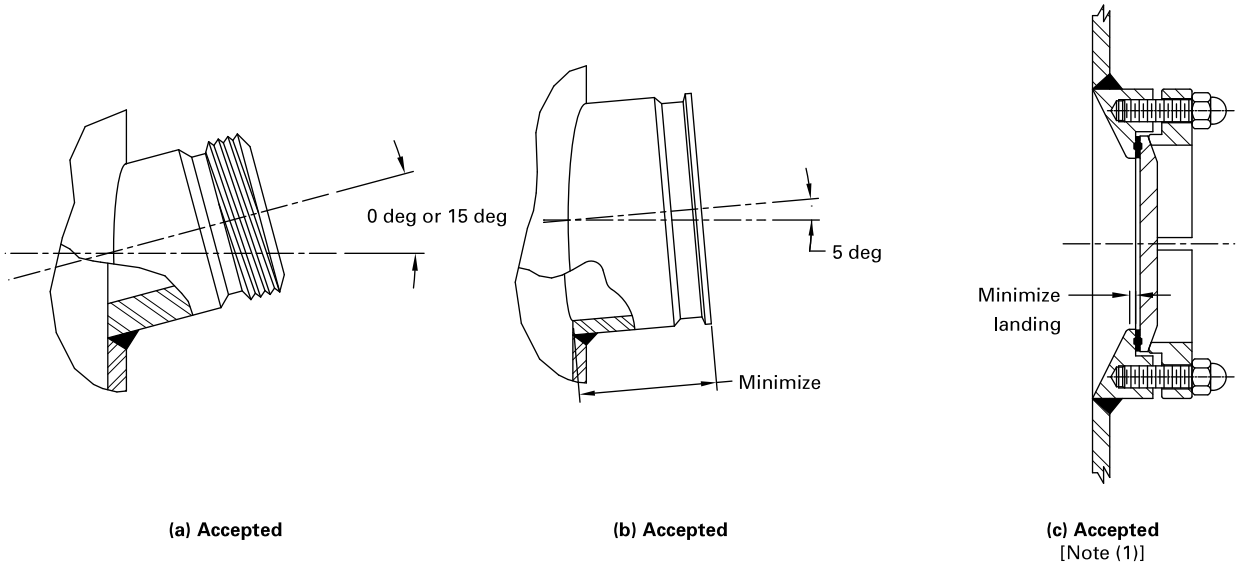
NOTES:
(1) Less dead space.
(2) Better CIP/SIP capabilities.
(3) Potential problems with CIP and SIP with capped connections.
(4) Dead space: stagnant areas.
(5) All L/d ratios to be calculated on long-side dimensions for vessel heads.

Figure SD-3.4.2-2 Side and Bottom Connections



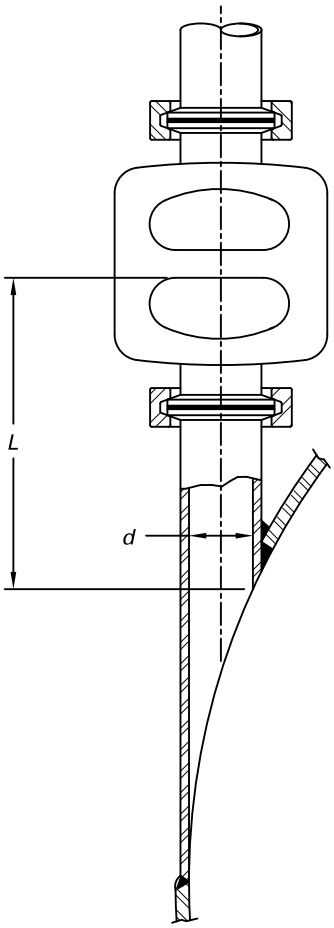
NOTES:
(1) If a flat gasket is used, mismatch of diameters can result in crevices.
(2) Telltale hole required.

Figure SD-3.4.2-3 Sidewall Instrument Ports



NOTE: (1) May also be pitched similar to illustration (b).

Figure SD-3.4.2-4 Vessel Design Tangential Nozzles



Definition of *L/d* for Tangential Inlet: Top Section View

GENERAL NOTE: CIP through nozzle is recommended.

(e) Blank covers or hygienic plugs used in process contact applications shall have the same finish as the vessel internals.

(f) Drain valves should optimize drainability and minimize branch *L/d*.

(g) The number and location of spray devices should be selected to eliminate shadowing at internal parts such as mixer shafts, dip tubes, and baffles.

(h) The number of shell-side nozzles and connections should be minimized.

(i) Manways on the side shell of a vessel shall be installed only by agreement of the owner/user. If side-shell manways are required, they shall be sloped for drainage.

(j) Sample valves shall be designed in accordance with SD-3.11.

(k) Sample valves shall be installed in accordance with SD-3.11.

(l) As required by the process, inlet nozzles tangential to the vessel surface may be used (see Figure SD-3.4.2-4 and Figure PI-9.1.3.3-1).

(m) Manway covers should be dished rather than a flat design.

(n) Flanges that have metal-to-metal contact on the process contact side shall not be used.

(o) All nozzles should be flush with the interior of the vessel except where projections are required to ensure additives are directed into the process fluid (e.g., chemical addition) (see Figure SD-3.4.2-5).

SD-3.4.3 Internal Components

(a) Sparger and dip tubes shall be designed in accordance with SD-3.4.1(a), SD-3.4.1(d), SD-3.4.1(f), and SD-3.4.1(g). Sparger and dip tubes shall incorporate low-point drains [where applicable, i.e., horizontal lines should slope at not less than $\frac{1}{8}$ in./ft (10 mm/m)] and be properly supported to ensure drainability. Refer to Table SD-2.4.3.1-1 to determine the appropriate slope designation.

(b) Dip tubes and spargers mounted in the nozzle neck should have an annular space between the O.D. of the dip tube or sparger and the I.D. of the nozzle neck in accordance with Table SD-3.4.3-1. An *L/A* of 2 or less is recommended (see Figure SD-3.4.3-1). If a larger *L/A* exists, a method for cleaning this space shall be specified. In all cases, sufficient annular space to allow access for CIP coverage shall be provided.

(c) Internal support members shall be solid, rather than hollow, which have a higher risk of fatigue and contamination problems (see Figure SD-3.4.3-2).

(d) Mitered fittings for internal pipe work shall only be fitted with the prior agreement between the owner/user and manufacturer. When mitered joints are used, they shall be designed and fabricated in accordance with the appropriate Codes.

(e) Vessels shall drain to a common point and shall not have multiple draining points, unless agreed to between the owner/user and manufacturer.

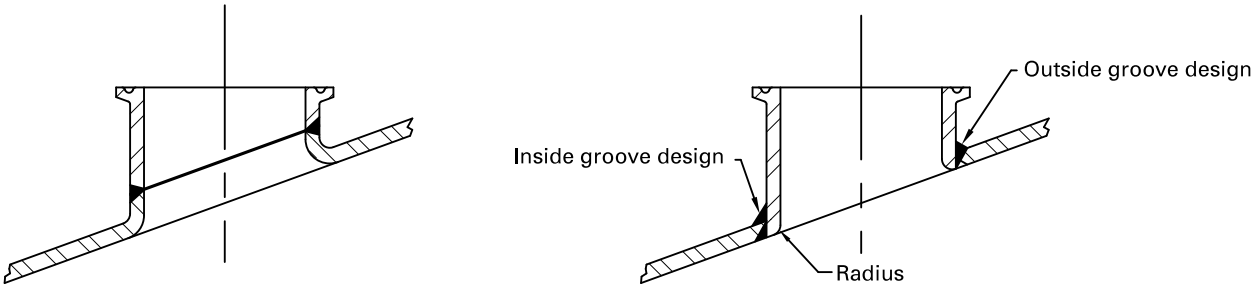
SD-3.4.4 Fabrication (19)

(a) For process contact surfaces, butt welds should be used and the use of lap joint welds should be minimized. Stitch welding shall not be used on process contact surfaces.

(b) Flanges are not recommended, and their use should be minimized. The bore of weld neck flanges shall be the same as the I.D. of the connected pipe or tubing to prevent ledges and nondrainable areas.

(c) Where slip-on nondrainable flanges are used, the bore-side bevel weld shall be designed to eliminate potential drainability and CIP difficulties.

Figure SD-3.4.2-5 Typical Nozzle Detail



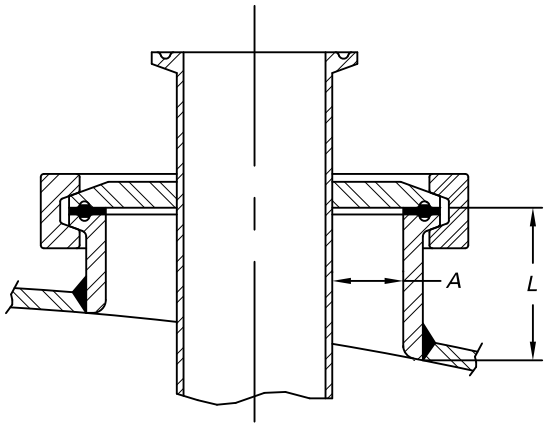
(a) Swage/Butt Weld Design (Accepted: If Vessel Wall Is Thin Enough to Flare)

(b) Full Penetration Groove Weld With Fillet Design (Accepted)

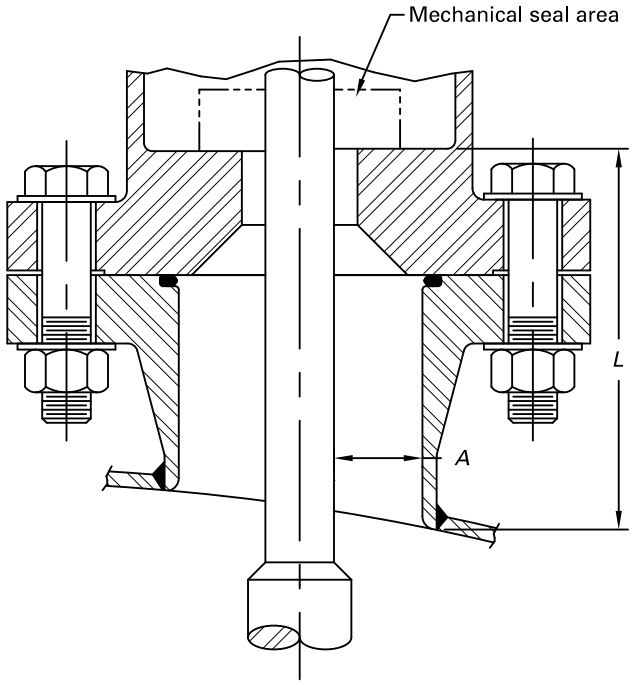
Table SD-3.4.3-1 Annular Spacing Recommendations for Hygienic Dip Tubes

Dip Tube Size Tube O.D.		Mount Nominal Size	
in.	mm	in.	mm
½	12.7	2	50
¾	19.1	2	50
1	25.4	3	75
1½	38.1	3	75
2	50.8	4	100
2½	63.5	4	100
3	76.2	6	150
4	101.6	6	150

Figure SD-3.4.3-1 Accepted Nozzle Penetrations



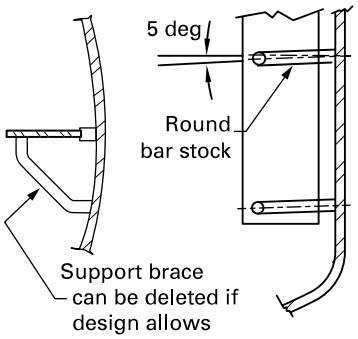
(a) Dip Tube or Sparge
[Notes (1) – (3)]



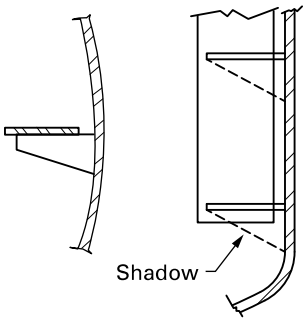
(b) Agitators
[Notes (2) and (4)]

NOTES:
(1) Nozzle and dip tube size per Table SD-3.4.3-1.
(2) *L/A* less than 2:1.
(3) Requirements also apply to nozzles with instrument penetrations.
(4) *A* = 1 in. (25 mm) minimum.

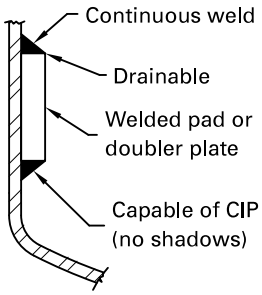
Figure SD-3.4.3-2 Internal Support Members



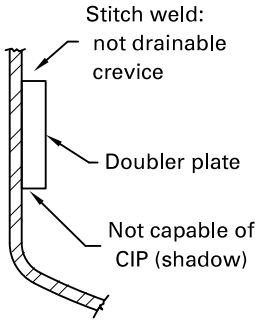
(a) Hygienic Design
(Accepted: Sloped, Minimum Shadow, and Curved Surface)



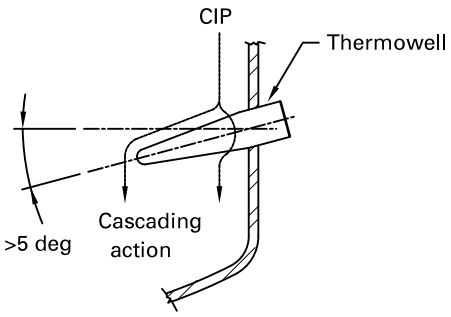
(b) Nonhygienic Design
(Not Accepted: Flat Surfaces, Ledges, and CIP Shadows)



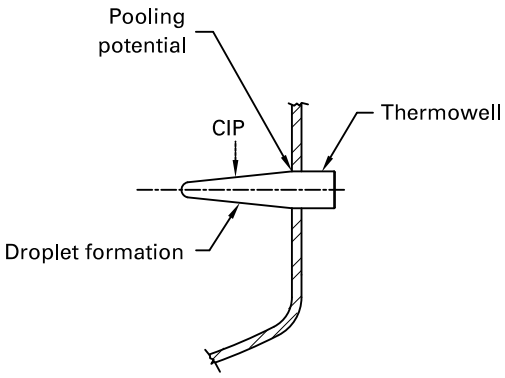
(c) Good Design
(Accepted)



(d) Poor Design
(Not Accepted)



(e) Positive Slope in All Directions
(Accepted)



(f) Positive Slope in Only One Direction
(Accepted)

SD-3.4.5 Finishes

(a) Surface finishes shall be specified in R_a values (see Table SF-2.4.1-1) and measured as required by Part SF. Surface finish coupons shall be submitted when agreed to by the owner/user and manufacturer.

(b) Process contact surface finish specifications shall pertain to all the wetted or potentially wetted surfaces (e.g., vapor space, nozzle necks, agitators, thermowells, dip tubes, baffles).

(c) The polishing of a connection face, body flange, etc., shall extend up to the first seal point.

SD-3.4.6 Sight Glasses

(a) Sight glasses on the vessels should be designed with reference to SD-3.4.2(a). Sight glasses on vessels should be designed with the smallest *L/d* possible and incorporate cleanable O-ring designs when applicable (see Figure SD-3.4.6-1).

(b) Refer to PI-9.1.2.3 for additional sight glass requirements.

(c) Surface finish for the metal frame shall meet the requirements of Part SF in this Standard.

(d) Sight glasses shall be marked with the glass type, maximum pressure, and temperature rating per DT-11.1 and DT-11.1.1.

(e) Part SG requirements shall be met when mounting a sight glass.

(f) Preferred sight glass mountings are shown in Figure SD-3.4.6-1.

SD-3.4.7 Portable Tanks. Portable tanks shall be designed in accordance with SD-3.4.

(a) Casters shall be cleanable and compatible with cleaning solutions used for external cleaning.

(b) Casters should be designed for the environment in which the vessel will be used.

(c) Flexible hoses used to connect portable vessels shall meet the requirements of SD-3.2.

(d) Provisions for static grounding should be evaluated and incorporated into the vessel design, if required. The connections for static grounding should be designed to be cleanable.

SD-3.4.8 Media Bulk Containers. [Reserved for future content]

SD-3.4.9 Cryogenic Containers. [Reserved for future content]

SD-3.5 Agitators and Mixers

(19)

SD-3.5.1 General

(a) All process contact surfaces of agitators and mixers with their associated components shall be accessible to the cleaning fluids as specified by the owner/user for clean-in-place service (CIP; e.g., via spray, directed flow, immersion).

(b) Process contact surfaces should be self-draining and shall not inhibit drainage of the vessel.

(c) Machined transitions (shaft steps, coupling surfaces, wrench flats, etc.) should be smooth, with 15-deg to 45-deg sloped surfaces.

(d) The annular space between the agitator shaft and the agitator nozzle shall, for cleaning purposes, have an *L/A* of 2 or less, or a minimum of 1 in. (25 mm) gap, whichever is larger, to facilitate CIP spray coverage [see Figure SD-3.4.3-1, illustration (b)].

(e) Cleaning and sterilization parameters shall be provided by the owner/user prior to design of the agitator. The manufacturers of agitators and mixers shall verify the cleanability of their equipment as specified and agreed to with the owner/user.

(f) Top-entering mixers with shaft seals are typically mounted to a vessel using a flanged or hygienic clamp connection [see Figure SD-3.5.1-1, illustrations (a), (b), and (c)]. The designer shall ensure that

(1) the use of O-rings or hygienic gaskets to seal between mating surfaces shall be consistent with the current guidance provided in Part SG (see Figure SG-3.3.2.2-1).

(2) the selected mounting arrangement will support the agitator mounting design loads while achieving an appropriate seal.

(3) the flange and nozzle construction is consistent with requirements of other applicable codes and standards (e.g., ASME BPVC, Section VIII; ASME B31.3)

(g) Socket head cap screws shall not be used in process contact applications.

(h) The design of agitator process contact parts should minimize the occurrence of void spaces. All voids should be closed by either fabrication (welding) or approved sealing techniques (O-ring seals, etc.).

(i) The use of in-tank nonwelded connections (shaft couplings, impeller hub-to-shaft, impeller blade-to-hub, etc.) should be avoided to minimize potential cleanability issues.

SD-3.5.2 In-Tank Shaft Couplings

(a) Welded in-tank shaft connections are preferred.

(b) The use of in-tank shaft couplings shall be agreed to by the owner/user.

(c) In-tank couplings shall be of an accepted hygienic design. See examples in Figure SD-3.5.2-1.

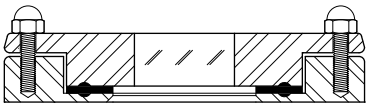
(d) In-tank coupling location should be driven by process and mechanical considerations.

(e) Threaded shaft connections are accepted for in-tank couplings [see Figure SD-3.5.2-1, illustration (a)].

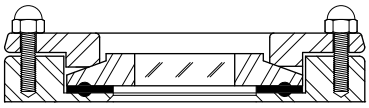
(1) Shaft rotation is limited to a single direction for threaded shaft connections to ensure that shaft sections do not separate.

(2) The designer will ensure that the use of a threaded shaft connection is appropriate for the selected shaft diameter and design loads.

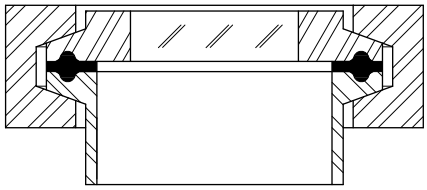
Figure SD-3.4.6-1 Sight Glass Design (Accepted)



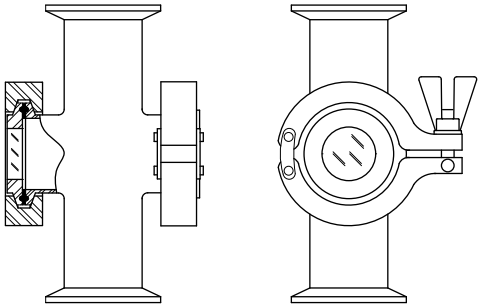
(a) Full Flange Sight Glass on Hygienic Pad Connection



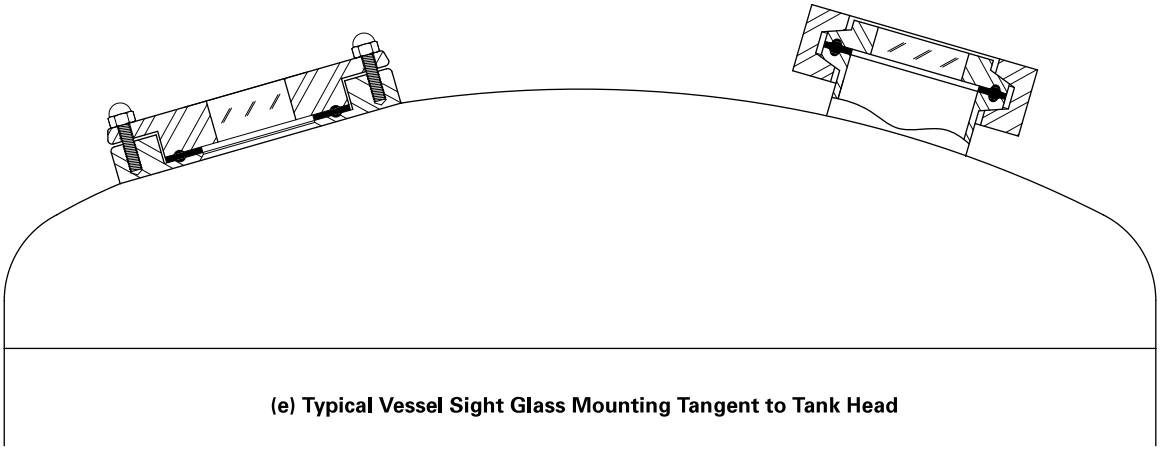
(b) Hygienic Clamp on Hygienic Pad Connection



(c) Hygienic Clamp Sight Glass

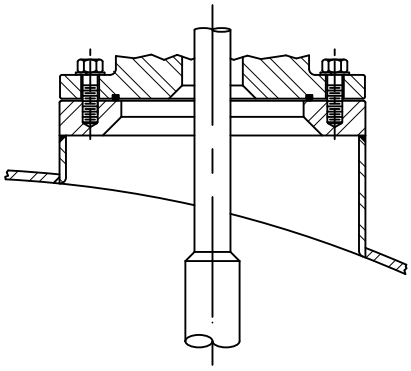


(d) Hygienic Cross Sight Flow Indicator

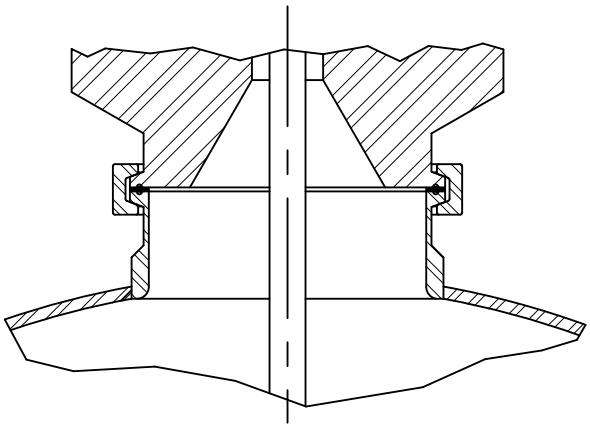


(e) Typical Vessel Sight Glass Mounting Tangent to Tank Head

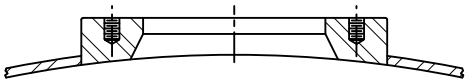
Figure SD-3.5.1-1 Agitator Mounting Flanges



(a) Bolted Flange With O-Ring

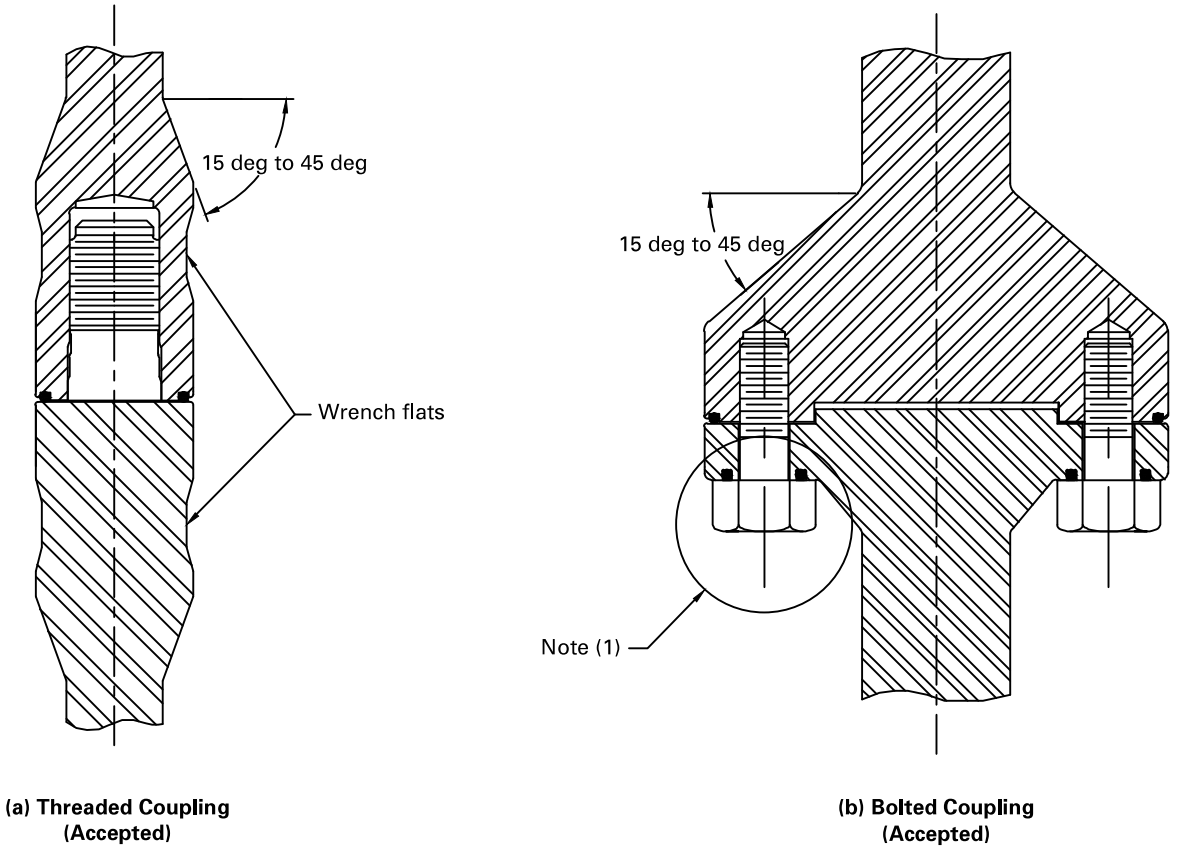


(b) Hygienic Union With Gasket



(c) Pad Flange

Figure SD-3.5.2-1 Shaft Coupling Construction



(a) Threaded Coupling (Accepted)

(b) Bolted Coupling (Accepted)

NOTE: (1) See Figure SD-3.5.2-3 for alternative bolt seals.

(3) Hygienic bolted coupling construction may be used where appropriate for the particular application [see Figure SD-3.5.2-1, illustration (b)].

(f) Threads shall not be exposed in any type of shaft or coupling hardware connection.

(g) The preferred location for fastener hardware is on the underside of couplings. Accepted fastener types include

(1) hex-head cap screws

(2) acorn-head cap screws

(3) threaded studs with acorn nuts

(h) Fastener heads shall be free of raised or engraved markings that might inhibit cleanability.

(i) O-rings rather than flat gaskets are preferred to seal coupling mating surfaces. Figure SD-3.5.2-2 presents the following acceptable approaches for seal applications:

(1) O-ring located in a single groove inboard of the coupling O.D. [see Figure SD-3.5.2-2, illustration (a)]; O-ring compression, internal space to accommodate compression, and outboard clearance space all designed to minimize the intrusion of process fluid between the coupling faces and to facilitate flow of CIP fluid.

(2) Alternate construction for O-ring located in a groove just inboard of the coupling O.D. [see Figure SD-3.5.2-2, illustration (b)]; O-ring restrained by lip at coupling circumference with clearance space provided as above to ensure cleanability of the coupling area.

(3) Alternate construction for O-ring located in grooves in both coupling halves inboard of the coupling O.D. [see Figure SD-3.5.2-2, illustration (c)]; outboard clearance space provided as above to ensure cleanability of the coupling area.

(4) O-ring with attached inboard flat segment located between coupling faces [see Figure SD-3.5.2-2, illustration (d)]; outboard clearance space provided as above to ensure cleanability of the coupling area.

(j) Bolted flanges shall be sealed. Examples of accepted fastener seals are shown in Figure SD-3.5.2-3 as follows:

(1) O-ring seal [illustration (a)]

(2) O-ring seal alternate [illustration (b)]

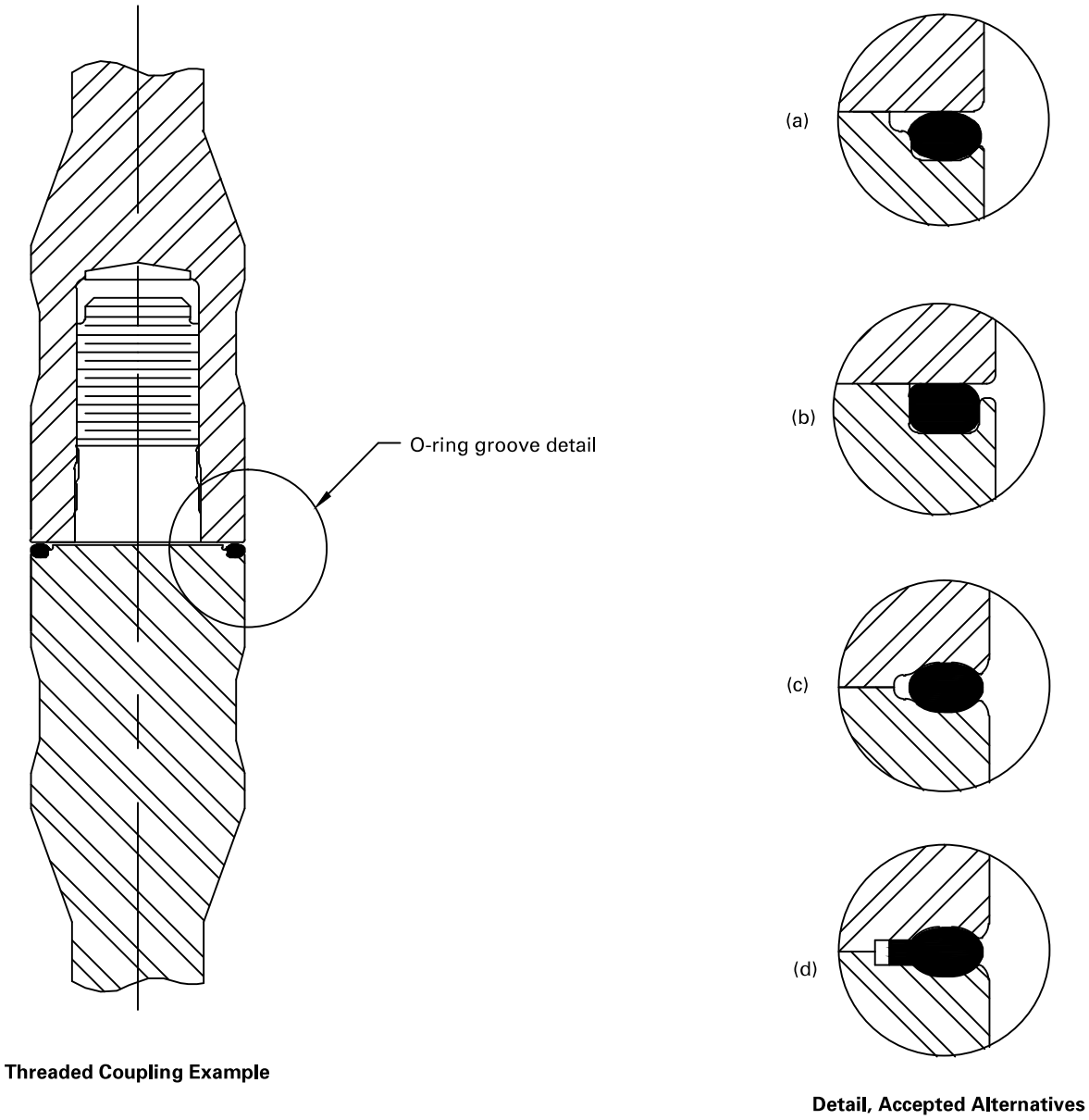
(3) seal washer with metal core [illustration (c)]

SD-3.5.3 Shafts and Keyways

(a) One-piece shaft construction, without mechanical couplings, is preferred.

(b) Solid shafts are preferred over hollow shafts.

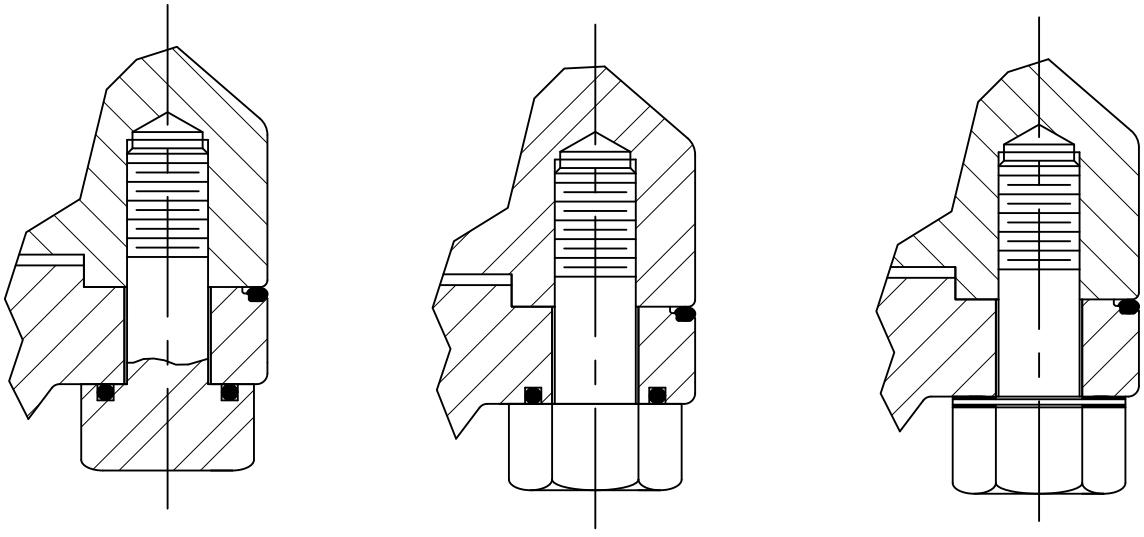
Figure SD-3.5.2-2 Shaft Coupling Seal Arrangements



Threaded Coupling Example

Detail, Accepted Alternatives

Figure SD-3.5.2-3 Fastener Seal Arrangements: Alternative Bolting Designs



(a) Accepted (b) Accepted (c) Accepted

(c) Hollow shafts, if used, shall be of sealed (welded) construction, inspected for integrity, and accepted per criteria given in Part MJ prior to installation.

(d) Keyways exposed to the process are not recommended.

(e) Keyways, where employed due to mechanical design considerations, shall have edge radii as specified by SD-2.4.2(b)(3).

(f) Keyways may require additional design and/or cleaning practice to ensure drainage and cleanability (e.g., spray ball and/or wand additions, increased CIP flow, and adjusted spray coverage).

(g) Permanent shaft hardware, installed on the process contact side, that may be required for routine maintenance (e.g., support collars for mechanical seal installation and removal, lifting eyes for shaft and/or impeller installation and removal) shall be fully drainable and cleanable.

SD-3.5.4 Hubs and Impellers

(a) All-welded impeller assemblies (e.g., hubs, blades) are preferred.

(b) Impeller hubs welded to the shaft are preferred over removable hubs.

(c) Removable, hygienic impellers may be used where impeller adjustment or substitution is required for process reasons or where impeller removal is required due to mechanical design and/or installation considerations.

(1) Removable impellers may be one-piece or split hygienic construction.

(2) Hub-to-shaft clearance for removable impellers shall be sufficient to preclude shaft surface finish damage during installation and removal.

(3) Removable hardware (e.g., impeller hub and shaft, impeller set-screws and hub) should be sealed in a manner consistent with the guidance provided for in-tank couplings (see SD-3.5.2).

(d) Removable impellers and impellers with flat, horizontal surfaces (e.g., flat-blade disk turbines, concave-blade disk turbines) may require additional design and/or cleaning practice to ensure drainage and cleanability, e.g., drain holes, spray ball and/or wand additions, increased CIP flow, adjusted spray coverage, impeller rotation.

SD-3.5.5 Impeller and Shaft Support Bearings (19)

(a) Normal operation of a shaft-steady bearing or a magnetically driven mixer with in-tank impeller or shaft support bearings (see Figures SD-3.5.5-1 and SD-3.5.5-2) generates particulate debris. It is the responsibility of the owner/user to establish compliance with applicable standards (e.g., USP limits for particulate material in injectables) as appropriate.

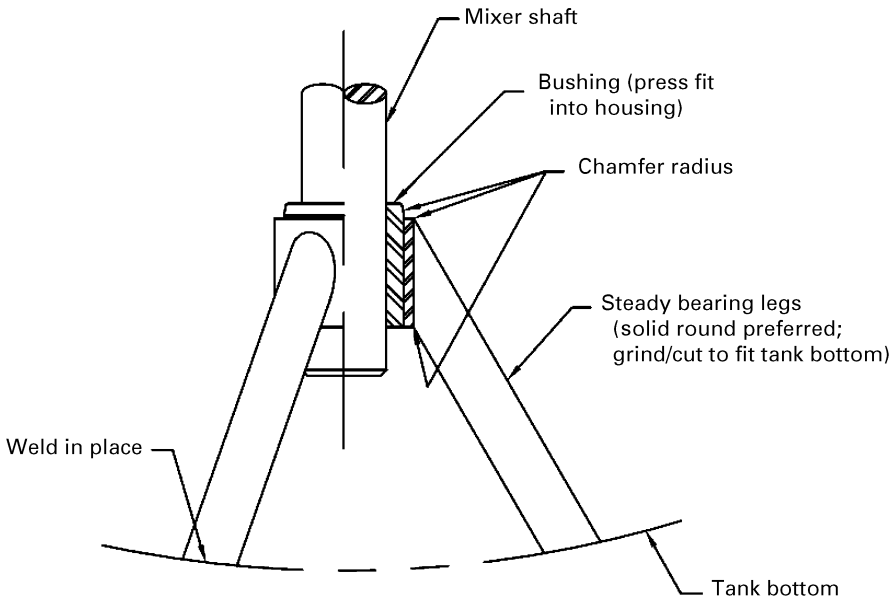
(b) Tank plates that support bottom-mounted magnetically driven mixers shall not interfere with drainage of the vessel.

(c) When an application mandates the use of shaft-steady/foot bearings, design features and/or procedures are required to ensure cleanability (e.g., drain holes, spray ball and/or wand additions, increased CIP flow, operating the steady bearing immersed in CIP fluid).

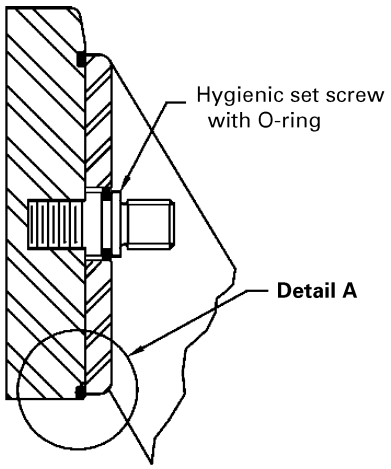
(d) Shaft-steady bearings, where used, shall not interfere with the drainage of the vessel.

(e) Shaft-steady bearing pedestal support members may be of solid or hollow construction. Hollow pedestal supports, if used, shall be of sealed (welded) construction,

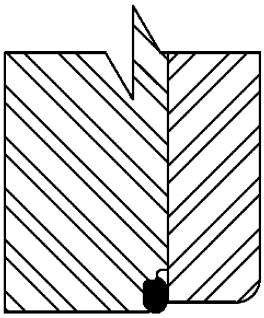
Figure SD-3.5.5-1 Shaft-Steady Bearing



(a) Hygienic Tripod Steady Bearing
(Alternative Design — Flat Bar Legs With Rounded Edges)

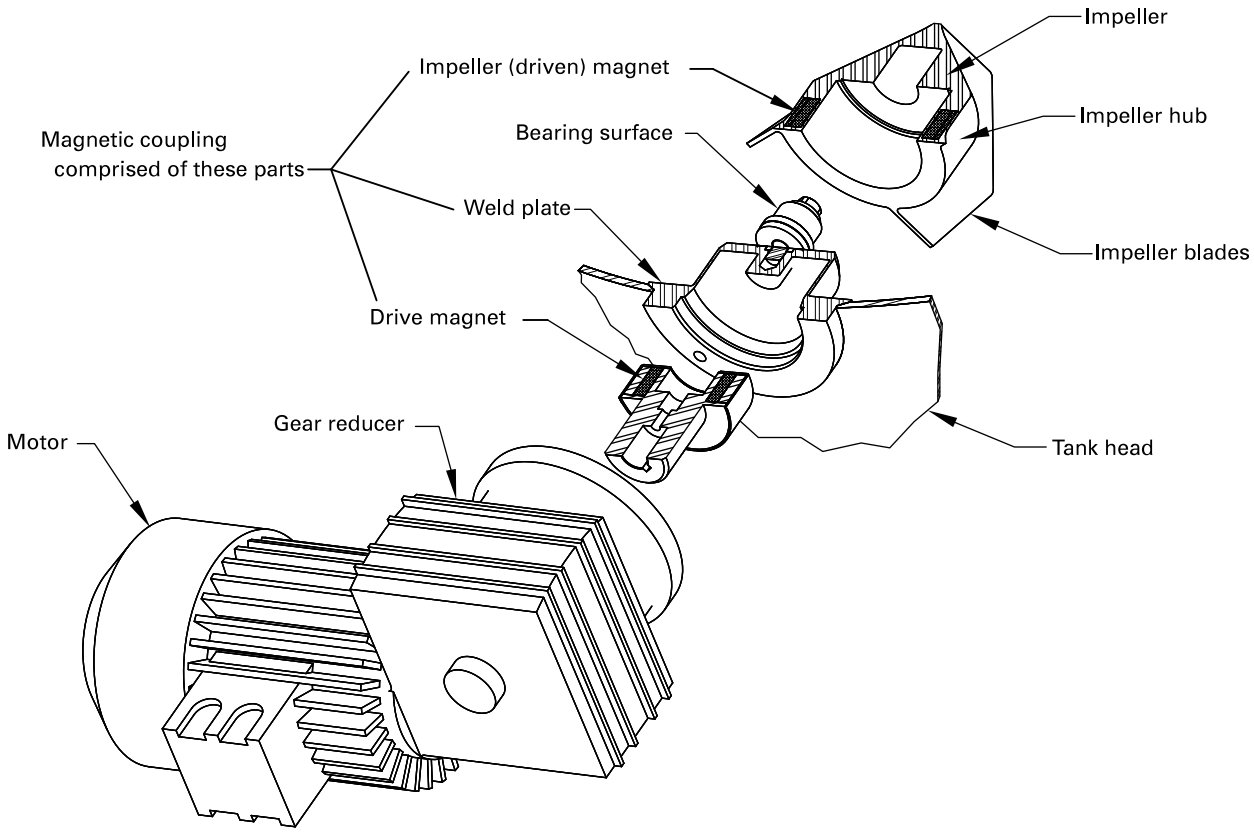


(b) Alternative Bushing Securing Method



Detail A
O-Ring With Groove Exposed for Flushing

Figure SD-3.5.5-2 Magnetically Coupled Mixer (Typical Bottom-Mount)



inspected for integrity, and accepted per criteria given in Part MJ after installation.

(f) Magnetically driven mixers require design features and/or procedures to ensure cleanability (e.g., drain holes, spray ball and/or wand additions, increased CIP flow, operating the agitator with the magnetically driven impeller immersed in CIP fluid).

(g) The arrangement of wear surfaces (bushing, shaft, or shaft sleeve) shall facilitate drainage.

(19) **SD-3.5.6 Mechanical Seals**

(a) Mechanical shaft seals shall incorporate design features for drainability, surface finish, material of construction, etc., as outlined in Part SD, and shall be suitable for the application (e.g., process, CIP, SIP, passivation).

(b) Normal operation of a mechanical seal generates particulate debris. It is the responsibility of the owner/user to establish compliance with applicable standards (e.g., USP limits for particulate material in injectables) as appropriate.

(c) Seal debris wells or traps (see Figure SG-2.3.2.3-2) may be used to prevent ingress of seal face wear particles that could contaminate the process fluid.

(d) Refer to Part SG of this Standard for specific seal design details.

SD-3.6 Heat Exchange Equipment

Plate-and-frame-type heat exchangers should be used only by agreement between owner/user and designer due to the difficulty of CIP and SIP.

SD-3.6.1 General (19)

(a) Straight tube heat exchangers are easier to clean and inspect. The tubes can be seamless or full-finish welded, as agreed to by the owner/user and manufacturer.

(b) The heat exchanger process and non-process contact surface inspection shall be possible by conventional means.

(c) The technique used to form U-bend tubes shall ensure the bending process does not create structural imperfections (e.g., cracks, voids, delaminations). The technique should minimize surface imperfections (e.g., orange peel, rippling). If requested by the owner/user, the manufacturer shall supply a sectioned sample of the bend area.

(1) The sectioned sample should be from the same tube batch or heat that will be used to fabricate the heat exchanger.

(2) The sectioned sample shall be the smallest bend radius in the exchanger.

(3) The sample shall be sectioned so that the bend's centerline is visible.

(d) The internal surface of the U-bends shall be free of relevant liquid penetrant indications, as defined by ASME BPVC, Section VIII.

(e) The I.D. of the U-bends shall be large enough for a borescopic examination.

(f) Minimum recommended bend radii for heat exchangers should be as follows:

Nominal Tube O.D.		Minimum Bend Radius	
in.	mm	in.	mm
0.375	9.5	0.625	15.2
0.500	12.7	0.750	19.1
0.625	15.8	0.938	23.8
0.750	19.1	1.125	28.6
1.000	25.4	1.500	38.1

(g) Welded shell-and-tube heat exchangers shall be of a double tubesheet design to prevent contamination of the process in the event of a tube joint failure (see Figure SD-3.6.1-1).

(1) During fabrication, when the tubes are to be expanded into the inner and outer tubesheets, the process contact surface shall not be scored.

(2) Tubes shall be seal welded to the outer tubesheet.

(3) The distance between inner and outer tubesheets shall be sufficient to allow leak detection.

(4) Tubesheets and channels shall be drainable.

(h) The owner/user shall specify the orientation of the exchanger (i.e., horizontal or vertical), and the manufacturer shall ensure the complete draining of the process liquid from the process contact side of the heat exchanger at the specified orientation, other than the natural cohesive properties of said process liquid. If this holdup is unacceptable, then the manufacturer shall design some type of assist to aid draining, such as an air blowdown.

(1) In the specified orientation, the shell side shall also be drainable (e.g., WFI condensers).

(2) Transverse baffles with notches should be provided, when necessary, to allow for proper draining of the shell.

(3) The heat exchanger bonnet shall be match marked with the outer tubesheet for proper orientation to ensure drainability or cleanability.

(i) Heat exchanger thermal and mechanical calculations shall be performed for both operating and SIP cycles.

(j) In shell-and-tube heat exchangers, the design pressure for the process contact side shall be equal to or greater than the design pressure of the utility side.

(k) The type of connections to the utility side (shell side) shall be agreed to between the owner/user and manufacturer.

SD-3.6.2 Cleaning and Steaming

(a) The process contact surfaces shall be constructed to withstand CIP and SIP or other cleaning/bioburden control methods specified by the owner/user.

(b) The cleaning and steaming conditions shall be provided by the owner/user prior to the design of the heat exchanger.

SD-3.6.3 Gaskets and Seals

(a) Gaskets that are in contact with product shall be removable and self-positioning and shall have readily cleanable grooves.

(b) Channel/bonnet gaskets shall be of a cleanable design.

SD-3.7 Transfer Panels

SD-3.7.1 General

(a) The transfer panel shall be constructed so that the process contact surfaces can be cleaned by a CIP fluid or other method specified by the owner/user. The process contact surfaces shall be free of crevices, pockets, and other surface irregularities.

(b) The transfer panel nozzle elevation shall be properly designed with respect to the connecting equipment such as tank and pump to ensure drainability, cleanability, and bioburden control during process transfer, CIP, and SIP.

(c) Design and fabrication of the transfer panel and associated components must ensure that the piping system can be fully drained when properly installed. This is not to imply that panel nozzles and/or subheaders should be sloped (see Figure SD-3.7.1-1).

(d) Tagging/labeling of the transfer panel and its components shall be per SD-2.4.4.2(i). Tagging nozzles on the back side of panels will help reduce the number of incorrect piping connections during field installation.

SD-3.7.2 Nozzles or Ports (19)

(a) Nozzle construction shall accommodate a design feature that will assist in the elimination of internal surface anomalies caused in part by joining the nozzle to the panel structure.

(b) The method of joining a nozzle into a panel structure shall be of hygienic design. Acceptance criteria for these welds shall meet the requirements of Table MJ-8.5-1.

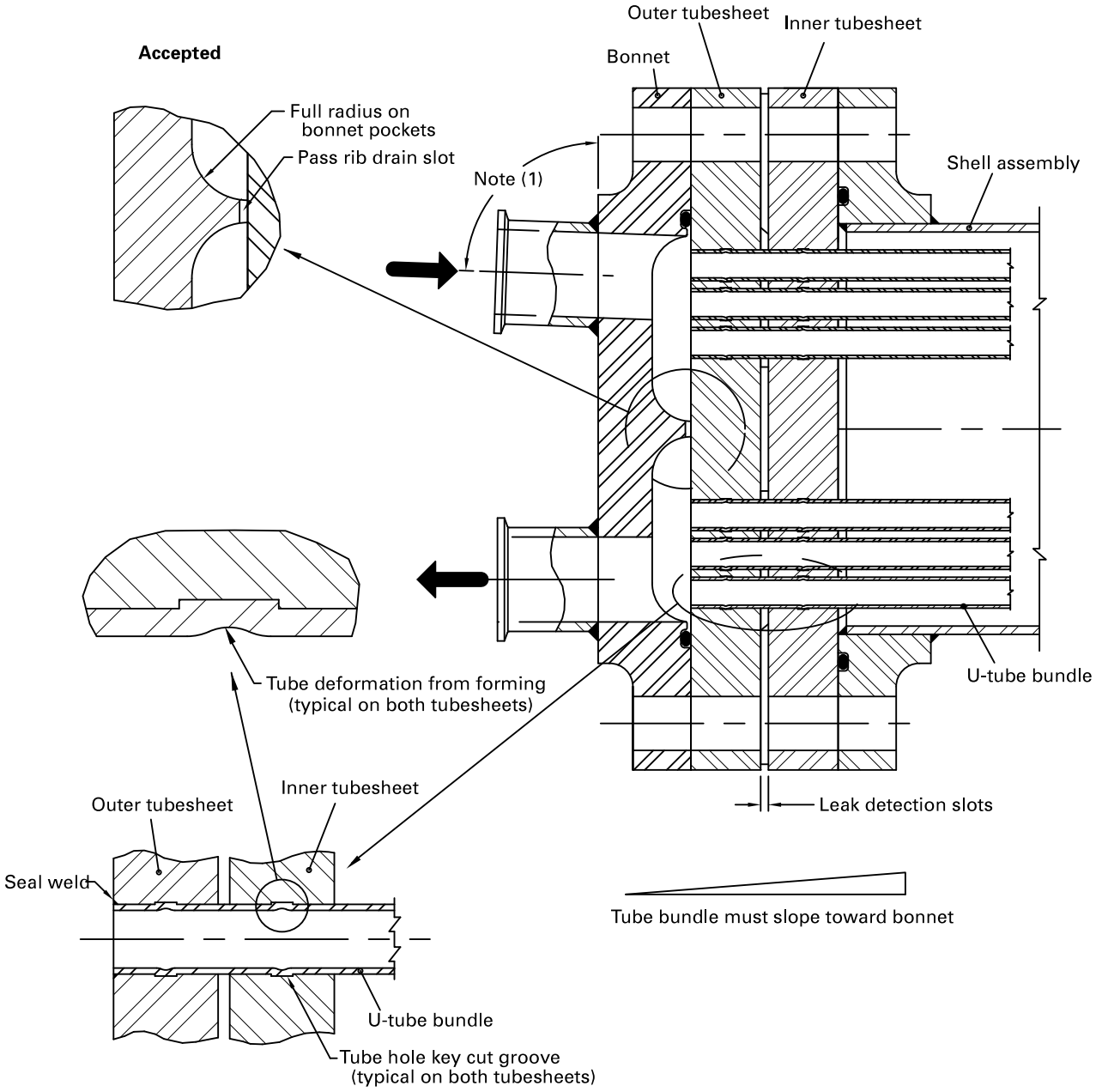
(c) Each front nozzle connection shall be of a hygienic design and the horizontal projection minimized to optimize drainability.

(d) To ensure proper panel functionality and joint connection integrity, panel nozzles shall not be sloped (see Figure SD-3.7.2-1).

(e) Nozzle-to-nozzle clearance shall be such that jumper drain valve interference, if applicable, will not occur when jumpers are connected in all possible operating and cleaning configurations.

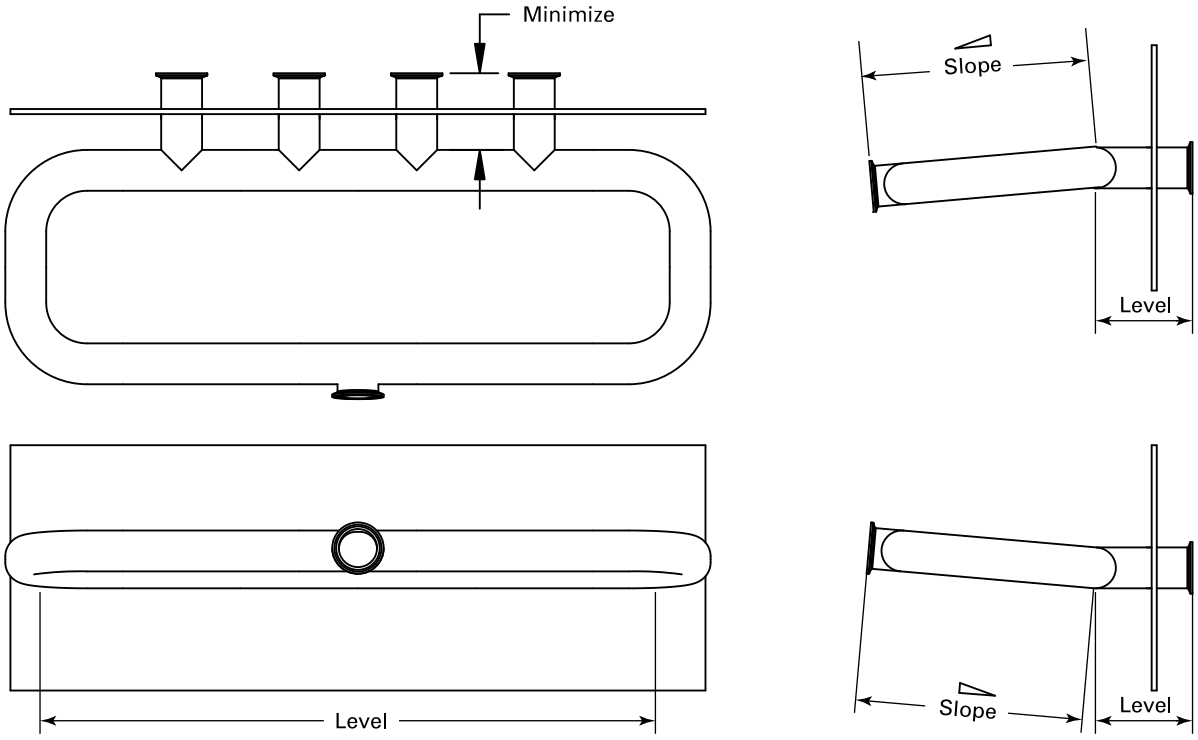
(f) Nozzles shall be capable of being capped. Caps may include bleed valves or pressure indicators for safety or operating purposes.

(19) **Figure SD-3.6.1-1 Double Tubesheet Heat Exchanger Bonnet Design**

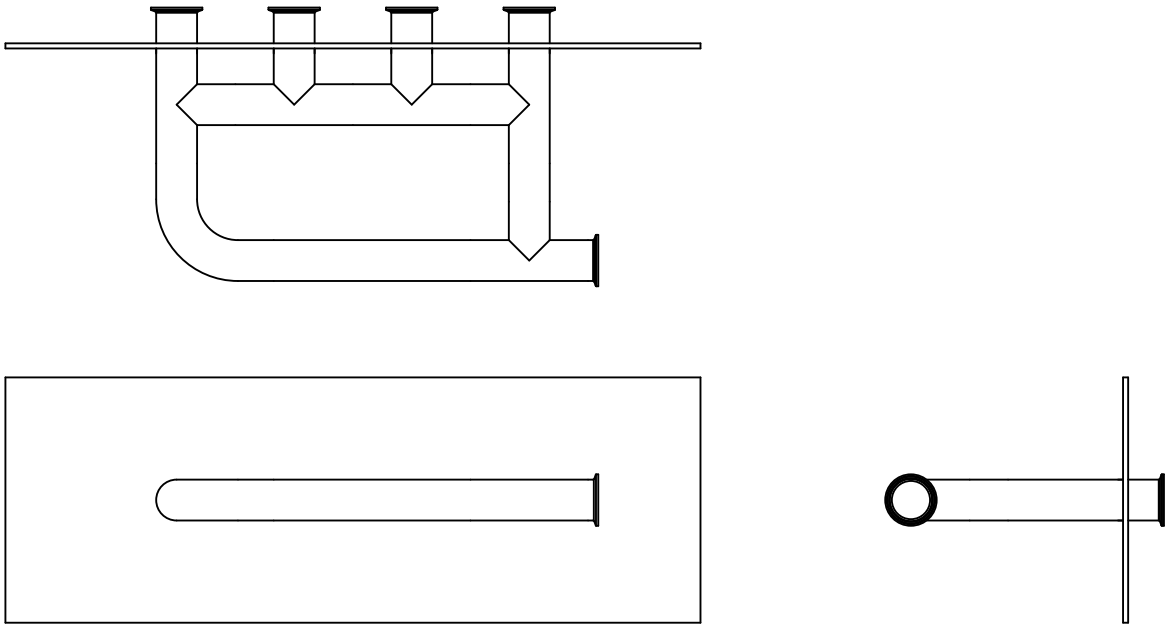


NOTE: (1) Owner/user to specify inlet tubing slope. Heat exchanger manufacturer to slope inlet on bonnet to match inlet tubing slope.

Figure SD-3.7.1-1 Transfer Panel Looped Headers

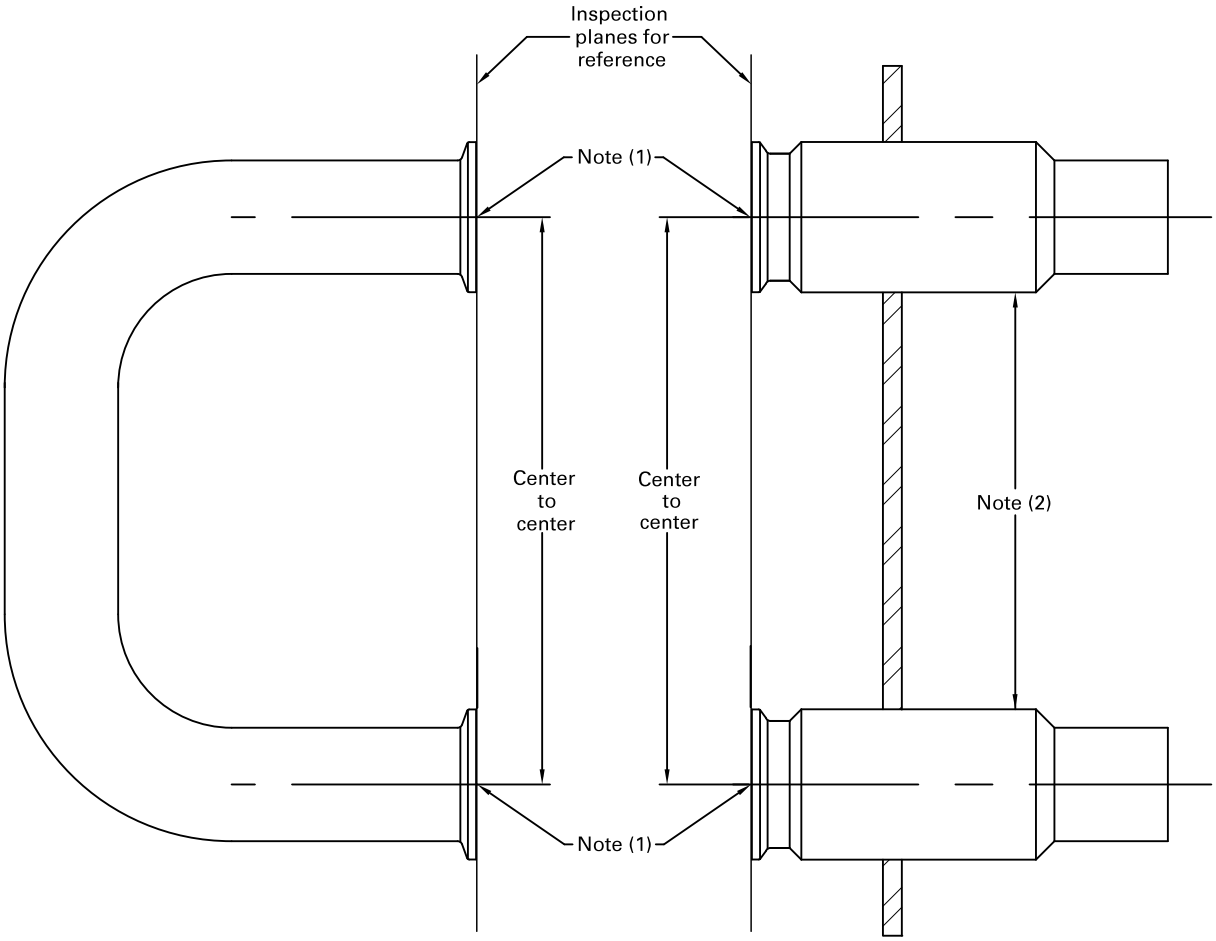


(a) Accepted



(b) Not Accepted

(19) **Figure SD-3.7.2-1 Transfer Panel Tolerances (Reference Table DT-7-3)**



NOTES:
(1) Flatness tolerance defines the maximum gap allowed across the entire sealing surface relative to the inspection planes shown above.
(2) Tolerances applied to related nozzles (defined by jumper paths).

(g) Nozzle center-to-center and flatness tolerances are extremely critical to proper panel functionality and shall be agreed on by the manufacturer and owner/user. Recommended tolerances are per Table DT-7-3 and Figure SD-3.7.2-1.

(19) **SD-3.7.3 Headers or Pre-Piped Manifolds**

(a) When a looped header design is employed, the branch length at capped or unused nozzles, or to the weir of the unused point-of-use valve, should be minimized. The dimension of the subheader leg to the nozzle face should not exceed an *L/d* of 2 (see Figure SD-3.7.1-1). A dead-ended and/or unlooped subheader is not recommended.

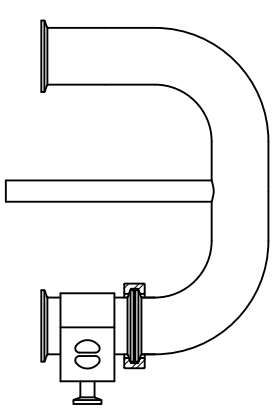
(b) To optimize the drainability at all nozzles, regardless of use, subheaders and pre-piped manifolds shall not be sloped. All-encompassing lines including long runs with the exception of subheaders, manifolds, and nozzles may be sloped as defined in SD-2.4.3.

SD-3.7.4 Jumpers or U-Bends (19)

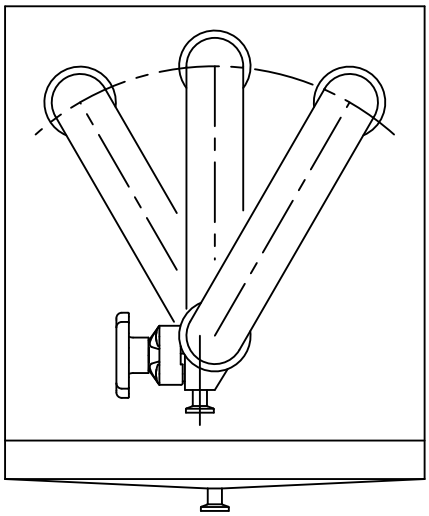
(a) Jumpers shall be constructed with hygienic connections on both ends designed to mate with the panel nozzles.

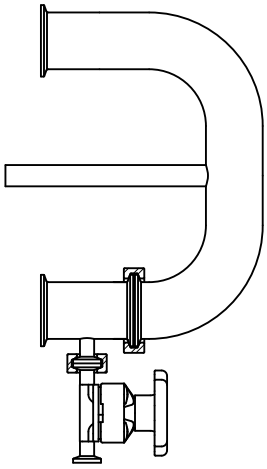
(b) Jumpers may have a low-point drain to provide both complete drainage and vacuum break after the liquid transfer has been completed (see Figure SD-3.7.4-1). The branch *L/d* of a low-point drain connection should be minimized. Zero-static diaphragm valves are recommended for low-point drains if available from the manufacturer [see Figure SD-3.7.4-1, illustrations (a) and (d)]. Low-point drain designs that incorporate a spool piece allow for full rotation of the drain valve [see Figure SD-3.7.4-1, illustrations (a), (b), and (c)]. This design ensures that the drain valve is always at the true low point of the assembled jumper connection in any specified orientation.

Figure SD-3.7.4-1 Transfer Panel Jumpers

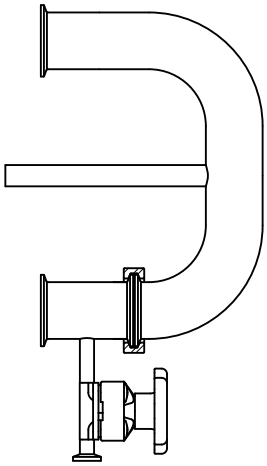


(a) Accepted

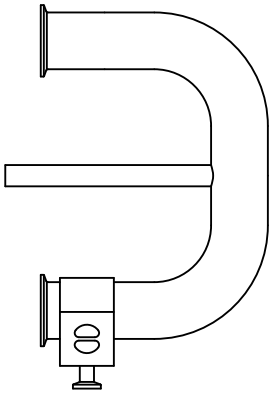




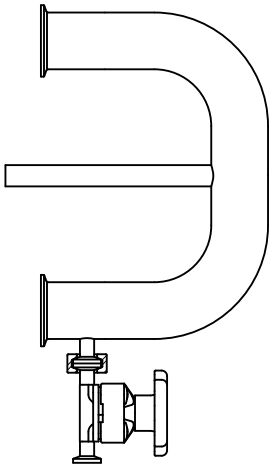
(b) Accepted



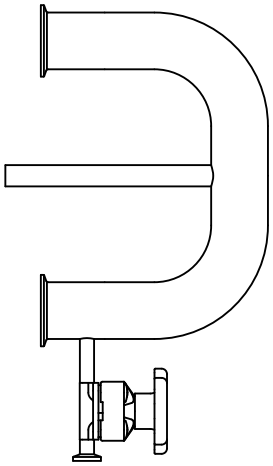
(c) Accepted



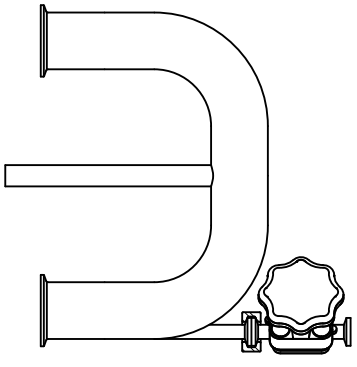
(d) Accepted



(e) Not Accepted



(f) Not Accepted



(g) Not Accepted

(c) Jumper center-to-center and flatness tolerances are extremely critical to proper panel functionality. Recommended tolerances are per Table DT-7-3 and Figure SD-3.7.2-1.

(d) The use of reducing jumpers is not recommended due to drainability concerns based on jumper orientation. Any reduction in line size should be made behind the primary nozzle connection (behind panel structure), thus allowing all connections to be the same size on the front of the panel.

(e) The overall panel design should be such that the quantity of unique jumper centerline dimensions is minimized.

(f) The same jumper should be used for process transfer, CIP, and SIP.

(g) If a pressure indicator is installed on a jumper, it shall be a hygienic design and mounted in a manner that maintains drainability in all jumper positions. The L/d should be 2 or less.

SD-3.7.5 Drain or Drip Pans

(a) Drain pans, if used, shall be built as an integral part of the transfer panel. The intended function is to collect spilled fluids that can occur during jumper or cap removal.

(b) Drain pans shall slope [preferred minimum of $\frac{1}{4}$ in./ft (21 mm/m)] to a low point and be piped to the process drain. The depth of the drain pan is determined by calculating the largest spill volume and accommodating it with a sufficient pan holding volume. Consideration should be given to increasing the drain port connection size in lieu of increasing pan depth. The preferred drain port location is central bottom draining or central back draining.

(c) The elevation of the pan should take into account the clearance required for the jumper drain valve position when a connection is made to the bottom row of nozzles. The pan should extend horizontally to accommodate the furthest connection and/or drain point from the face of the panel.

(19) ### SD-3.7.6 Proximity Switches

(a) Proximity switches are used to detect the presence or absence of a jumper with a stem positioned between selected nozzles.

(b) The use of magnetic proximity switches that are mounted behind the panel structure to avoid penetration of the panel face is preferred. This elimination of structural penetration removes any unnecessary cracks, crevices, or threads at the point of attachment, effectively mitigating risk of process fluid entrapment and/or contamination concerns.

(c) Jumpers will contain a magnetic stem to activate the corresponding proximity switch. The use of a ferrous magnetic material is required; however, it shall be fully encapsulated to ensure that the ferrous material does not contaminate the classified manufacturing area. The acceptance criteria for welds joining the sensor stem to the jumper shall meet the requirements of Table MJ-8.5-1.

(d) The magnet should be of sufficient gauss rating to properly activate the corresponding proximity switch. In addition, the temperature rating of the magnet should withstand the specified temperature ranges for process and SIP without compromising the magnet performance.

(e) The proximity switch mounting shall be structurally sound to maintain the specified design location. The proximity switch shall not interfere with the function, cleaning, or maintenance of the transfer panel to which it is mounted.

SD-3.8 Filters

SD-3.8.1 Code 7 Cartridge Lock Design. The ASME BPE Code 7 lock is designed to be used with filter cartridges using an SAE AS 568-226 double O-ring seal and a two-locking-tab design.

SD-3.8.1.1 Design Features. This design consists of the following features:

(a) a socket bore that is machined into a base or cartridge plate into which the filter cartridge O-ring adapter is inserted.

(b) a locking tab retainer mechanism that captures the cartridge locking tabs when the cartridge is inserted into the socket bore.

(1) Table DT-4.5.1-1 shows a recessed tapered lock retainer design in which the locking tab retainers are machined into a plate and the machined recesses capture the cartridge locking tabs as the cartridge is rotated into position.

(2) Table DT-4.5.2-1 shows an external tapered lock retainer design in which a set of metal cages captures the cartridge locking tabs as the cartridge is rotated into position.

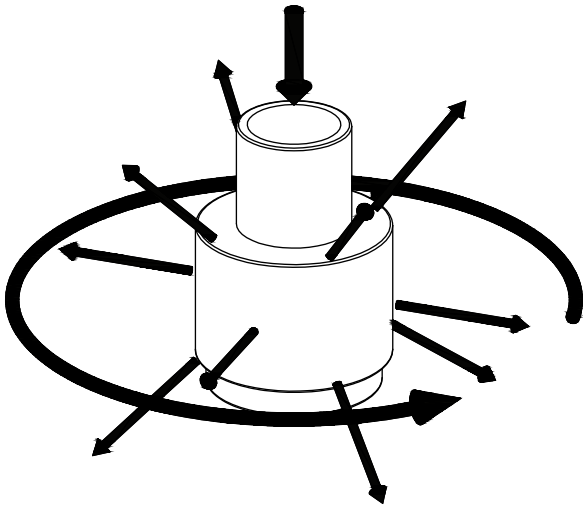
(c) the locking tab retainers shall be designed with a taper to provide a secure lock for the cartridge. The cartridge tabs shall travel through the narrowing tab retainers until a tight fit is achieved. The taper shall be on the upper portion of the tab retainer. Full capture of cartridge tabs by the locking tab retainers is not required to secure cartridges for operation.

(d) all surfaces of the cartridge socket shall meet the required finish for the wetted surfaces as specified by the owner/user.

(e) the cartridge O-ring(s) shall be completely contained within the socket bore.

SD-3.8.1.2 Testing. The cartridge manufacturer shall validate that its cartridge design fits, seals, and remains in place with one of the housing designs shown in Tables DT-4.5.1-1 and DT-4.5.2-1.

Figure SD-3.9.1-1 Dynamic Spray Device: Single Axis



GENERAL NOTE: Spray pattern is for illustration purposes.

SD-3.9 Spray Devices

SD-3.9.1 General. This section covers spray devices intended for use in bioprocessing equipment, intended to remain in place or be removed during production. Recommendations in this section are valid for water-based cleaning solutions. The flow rate recommendations in this section are for metallic vessels.

(a) Spray devices distribute rinse and cleaning solutions to interior surfaces of bioprocessing equipment by direct spray and use sheeting action for remaining targeted areas. Spray devices are also used in other applications [e.g., water systems to maintain coverage of the storage tank head space and in clean-out-of-place (COP) cabinet washers].

(b) The differential pressure across the spray device generates liquid velocity exiting through the spray device orifices, nozzles, or slots. Differential pressure and its resulting flow are key parameters of spray devices. Flow is the recommended control parameter because it is independent of temperature and location of the measurement device.

(c) The spray pattern, as it exits the device, is determined by the spray device design. Spray patterns are typically streams/jets or fans.

(d) The impact pattern is determined by the interaction over time of the spray pattern and the geometry of the equipment.

(e) During design, consideration should be given to the following in the selection of spray device(s):

(1) residue characteristics

(2) equipment geometry and appurtenances

(3) physical location and orientation of spray device(s)

(4) process requirements including air-purge and steaming, if applicable

(5) cleaning system capacity

(6) installation of screen/strainer to protect the functionality of the spray device

(7) cleaning cycle time

(8) cleaning chemistry compatibility with materials of construction

(9) potential orifice erosion (e.g., from CIP and SIP)

(f) Spray devices are either static or dynamic.

(1) Static spray devices continuously produce a defined impact pattern by stationary direct spray. Static spray devices have no moving parts. Examples of static spray devices include static spray balls, stationary nozzles, and spray wands.

(2) Dynamic spray devices are either single axis or multiaxis. Both produce a defined impact pattern by moving multidirectional spray(s). Dynamic spray device rotation is rinse water/cleaning solution driven or motor driven. Dynamic spray devices have moving parts, which may include bearings, gears, and turbines.

(-a) Single-axis dynamic spray devices (see Figure SD-3.9.1-1). When the orifices/nozzles/slots are manufactured at an angle, the resulting force spins the spray head. Rotation can also be turbine or motor driven.

(-b) Multiaxis dynamic spray devices rotate in more than a single plane (see Figure SD-3.9.1-2). When rinse water/cleaning solution driven, the flow through the spray device turns a turbine wheel, which typically turns the body around one axis as well as the nozzle(s) around a second axis, creating a repeatable indexed pattern. When motor driven, the body and nozzles are turned mechanically by the motor.

(g) Spray devices can be designed as removable, retractable, or to remain in place.

(h) Spray device(s) are specific to the application and equipment. Spray devices are generally not interchangeable without considering the specific flow, pressure, equipment design, spray pattern, and drainability of the spray device(s).

SD-3.9.2 Spray Device Requirements

(a) Materials of construction shall comply with SD-2.4.1.2 or as otherwise agreed on with the owner/user.

(b) When installed, spray devices shall be drainable and cleanable inside and outside or otherwise as agreed on with the owner/user.

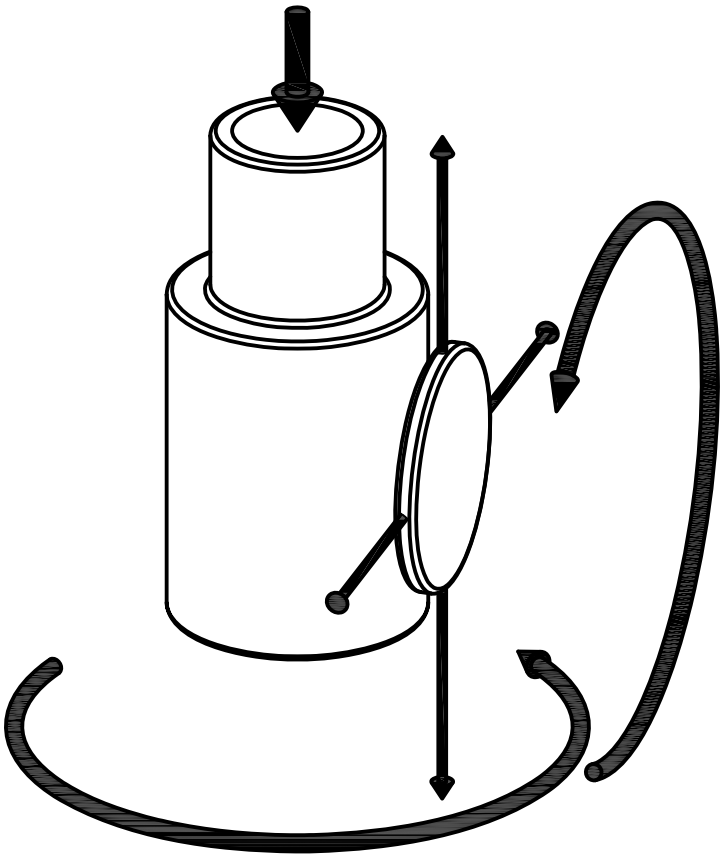
(c) Spray device(s) shall be installed per manufacturer's instructions.

(d) When operated within specification, the spray device(s) shall produce repeatable effective coverage over a defined area of the equipment.

(e) Effective coverage shall not be affected by flow rate variations of 10% or otherwise agreed on by the owner/user.

(f) Spray devices shall be accessible for functionality verification, inspection, and maintenance.

Figure SD-3.9.1-2 Two-Axis Dynamic Spray Device



GENERAL NOTE: Number of jets is for illustration purposes.

(g) Removable spray device(s) shall be capable of being re-installed in a repeatable manner by unique identifiers to ensure proper installation location.

(h) Spray device selection, orientation, and location shall be designed to ensure the equipment and the targeted surfaces of its appurtenances (e.g., manways, dip-tubes, baffles, nozzles, agitator shaft, and impellers) are exposed to rinse water/cleaning solution.

(i) Spray device(s) shall be provided with a level of documentation that is consistent with the equipment for which it is to be installed and in accordance with GR-5 documentation requirements.

(j) Process contact surface finishes of spray devices should be consistent with the equipment for which it is installed or otherwise specified by the owner/user and in accordance with the definitions of Part SF.

(k) Spray devices shall not use lubricants other than the process liquid. Dynamic devices are typically lubricated by the rinse/cleaning solution(s).

SD-3.9.2.1 Static Spray Device Requirements

(a) Static spray devices shall have a positioning device (preferred) or mark to allow for proper orientation during re-installation, as static devices are orientation sensitive (see Figure SD-3.9.2.1-1)

(b) Weld-on or self-cleaning slip-joint/clip-on connections are acceptable. Provision shall be made to ensure proper orientation and location if a slip-joint/clip-on-style static spray device(s) is used.

(c) A portion of the flow is directed toward the specific appurtenances.

(d) The flow rate guideline for vertical cylindrical vessels with dished heads is 2.5 gal/min/ft to 3 gal/min/ft (31 L/min/m to 37 L/min/m) of inner vessel circumference. Reference Figure SD-3.9.2.1-2. The majority of the flow is directed toward the upper head to ensure coverage of appurtenances and provide the sheeting action.

(e) The flow rate guideline for horizontal cylindrical vessels with dished heads is 2 gal/min/ft to 3 gal/min/ft (25 L/min/m to 37 L/min/m) of perimeter ($2L + 2d$). Reference Figure SD-3.9.2.1-3. The majority of the flow is directed toward the upper one-third of the

Figure SD-3.9.2.1-1 Static Spray Device

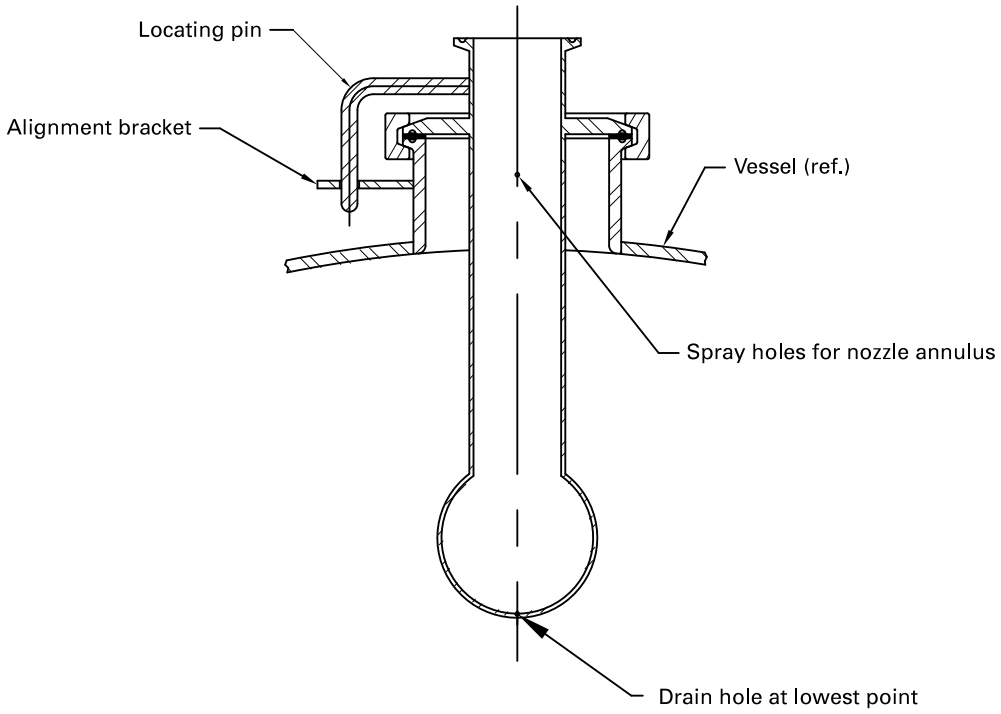


Figure SD-3.9.2.1-2 Flow Rate Guideline for Vertical Cylindrical Vessels

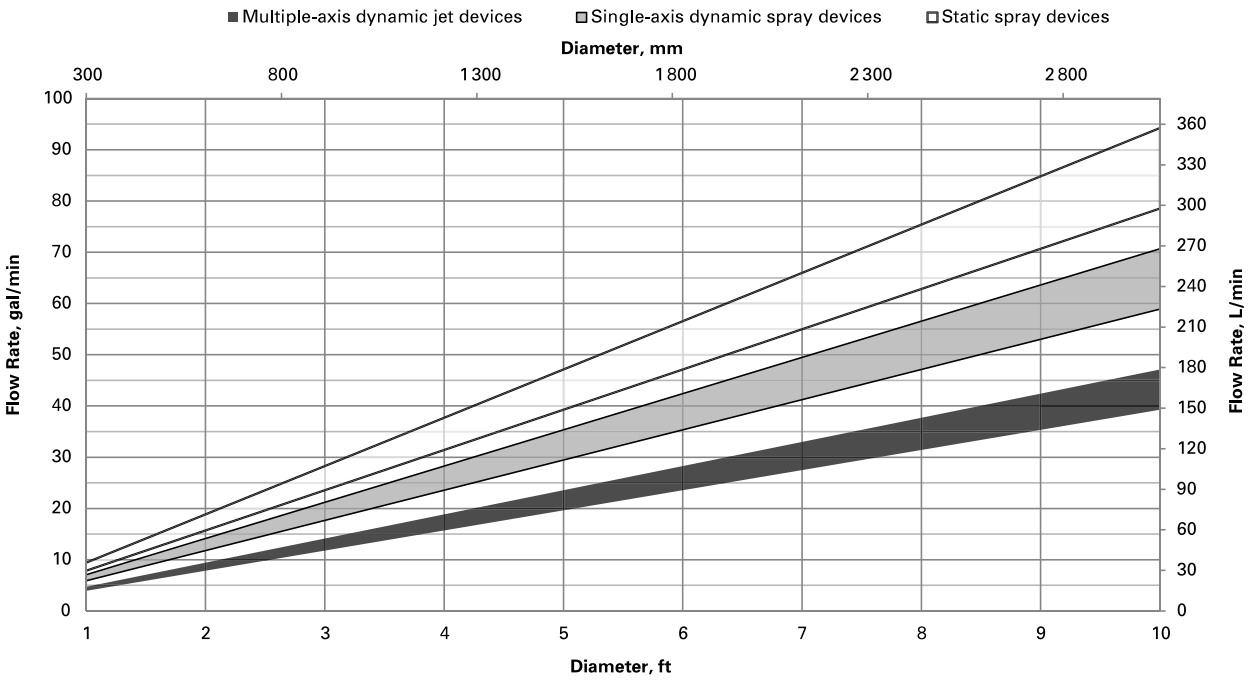
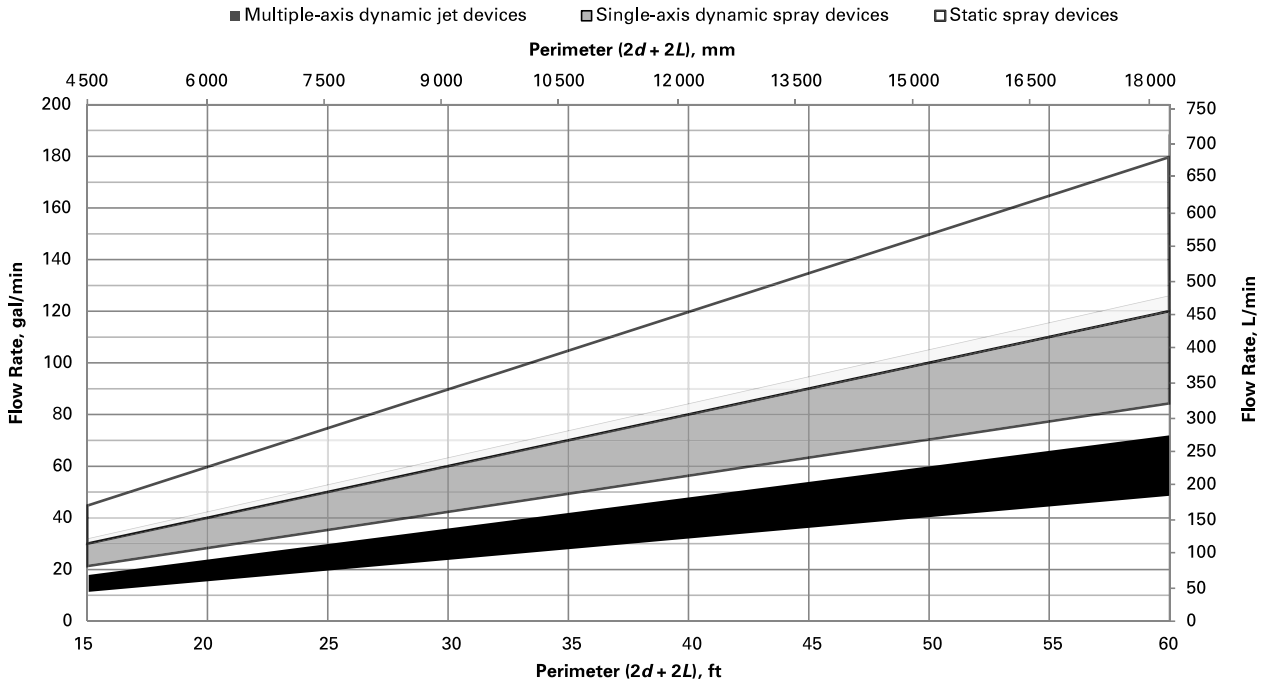


Figure SD-3.9.2.1-3 Flow Rate Guideline for Horizontal Cylindrical Vessels



vessel to ensure coverage of appurtenances and provide the sheeting action.

(f) Flow requirements for the specific application should be confirmed with the spray device and/or equipment manufacturer or other subject matter experts.

SD-3.9.2.2 Single-Axis Dynamic Spray Device Requirements

(a) Rotation and/or frequency verification shall be agreed on with the owner/user.

(b) Weld-on or self-cleaning slip-joint/clip-on connections are acceptable. Other hygienic alternatives shall be agreed on with the owner/user.

(c) The flow rate guideline for vertical cylindrical vessels with dished heads is 1.9 gal/min/ft to 2.3 gal/min/ft (23.6 L/min/m to 28.6 L/min/m) of inner vessel circumference. The majority of the flow is directed toward the upper head to ensure coverage of appurtenances and provide the sheeting action.

(d) The flow rate guideline for horizontal cylindrical vessels with dished heads is 1.4 gal/min/ft to 2.1 gal/min/ft (17.4 L/min/m to 26.1 L/min/m) of perimeter ($2L + 2d$). The majority of the flow is directed toward the upper one-third of the vessel to ensure coverage of appurtenances and provide the sheeting action.

(e) Flow requirements for the specific application should be confirmed with the spray device and/or equipment manufacturer or other subject matter experts.

(f) High-velocity gas flow from air-blows or steam passing through liquid-driven spray devices can result in wear to bearing surfaces. Consideration should be taken to restrict gas flow through the spray device according to the manufacturer's recommendation.

SD-3.9.2.3 Multiaxis Dynamic Spray Device Requirements (19)

(a) Rotation and/or frequency verification shall be agreed on with the owner/user.

(b) The time to complete a full impact pattern (see Figure SD-3.9.2.3-1) at a specified pressure or flow rate shall be provided by the manufacturer.

(c) Weld-on or self-cleaning slip-joint/clip-on connections are acceptable. Other hygienic alternatives shall be agreed upon with the owner/user.

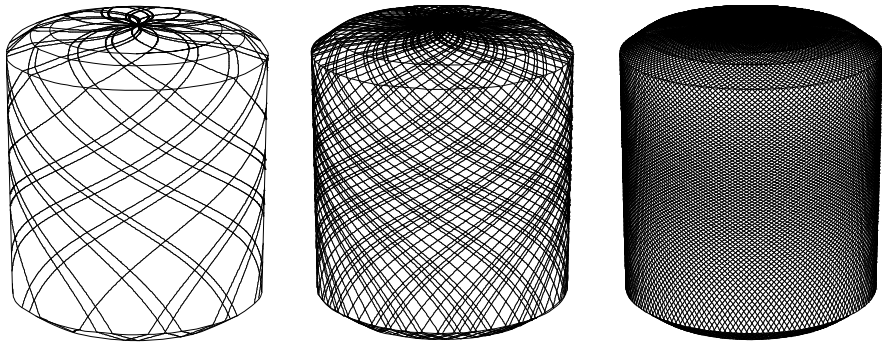
(d) The flow rate guideline for vertical cylindrical vessels with dished heads is 1.3 gal/min/ft to 1.5 gal/min/ft (16.1 L/min/m to 18.6 L/min/m) of inner vessel circumference to ensure coverage of appurtenances and provide the sheeting action.

(e) The flow rate guideline for horizontal cylindrical vessels with dished heads is 0.8 gal/min/ft to 1.2 gal/min/ft (9.9 L/min/m to 14.9 L/min/m) of perimeter ($2L + 2d$) to ensure coverage of appurtenances and provide the sheeting action.

(f) Flow requirements for the specific application should be confirmed with the spray device and/or equipment manufacturer or other subject matter experts.

(g) High-velocity gas flow from air-blows or steam passing through liquid-driven spray devices can result in wear to bearing surfaces. Consideration should be taken to restrict gas flow through the spray device according to the manufacturer's recommendation.

Figure SD-3.9.2.3-1 Impact Pattern Buildup



SD-3.10 Disposables That Require Presterilization or Poststerilization

[Reserved for future content]

SD-3.11 Sampling Systems

SD-3.11.1 General

(a) Sampling equipment in the biopharmaceutical industry is used for the collection of samples that then undergo chemical or microbiological evaluation. Sampling may be either aseptic or nonaseptic.

(b) Sampling systems shall not adulterate the process fluid being sampled nor affect the sample characteristics being tested.

(c) Aseptic sampling systems shall be steamable or presterilized single-use.

(d) Hygienic sampling systems shall either be cleanable or single-use.

(e) Aseptic sampling systems shall be closed to isolate the process; protect the sample, sample container, and sample transfer process from the environment; and obtain representative samples.

SD-3.11.2 Aseptic Sampling Systems

SD-3.11.2.1 Basic Requirements

(a) Steamable sample systems shall meet the relevant requirements of SD-2.3.1.1.

(b) Sampling systems intended for multiple-use shall be cleanable.

(c) Sample valves shall meet the requirement of SG-3.3.2.3.

(d) In septum sample devices, the needles shall be sterilized prior to insertion into the vessel or process line.

(e) Collecting devices shall be designed, connected, and disconnected in ways that maintain the integrity of the sample.

SD-3.11.2.2 Installation. The sampling device shall be installed to maintain the aseptic barrier between the process fluid being sampled and the environment. Consideration should be given to ease of assembly and subsequent handling of the sample.

SD-3.11.2.3 Sample Collecting

(a) When using single-use collecting devices, consideration shall be given to maximum pressure ratings of valves, adaptors, and bags.

(b) Consideration should be given to the impact of absorption and off-gassing that could lead to nonrepresentative samples. Polymeric material requirements for leachables and extractables are listed in Part PM.

SD-3.11.3 Nonaseptic Sampling. [Reserved for future content]

SD-3.12 Steam Traps

(a) Steam traps are not considered hygienic. Steam trap bodies shall have an internal surface finish (excluding the bellows assembly) as agreed to by all parties. Surface finish specification shall match the clean steam condensate tube finish specification unless the condensate downstream of the trap is used in the process or sampled for quality assurance.

(b) Where used in process systems, the traps shall be capable of effectively venting air.

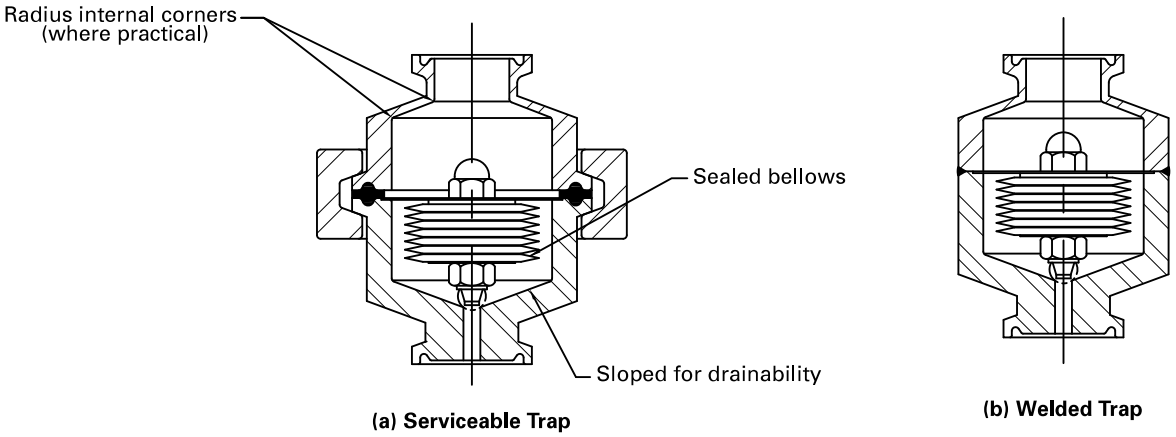
(c) Where installed on process systems, traps shall be maintainable to allow easy examination and cleaning. Welded traps are acceptable if agreed to by the owner/user.

(d) The trap design and mode of operation shall be such that the risk of soil attachment to the wetted surfaces is minimized, especially around the bellows and seat (see Figure SD-3.12-1).

(e) The trap shall be sized and installed to operate such that there is no backup of condensate into the process equipment and clean steam system under operating conditions. Operating conditions include heat-up, hold, and cool down.

(f) The trap shall be designed such that the normal mode of mechanical failure will be in the open position.

Figure SD-3.12-1 Steam Traps for Clean Steam Systems



(g) Thermostatic steam traps, installed in vertical trap legs, are preferred for use in clean steam systems (see Figure SD-3.12-1).

(h) Trap operation/reactivity should be improved by the installation of an uninsulated section of tubing upstream of the trap [suggested 12 in. (30 cm) as recommended by supplier] (see Figure SD-4.2.2-2).

(19) **SD-3.13 Check Valves**

(a) Check valves that are used in product contact applications shall be of hygienic design. They shall be designed for CIP. Crevices and holdup volumes should be minimized.

(b) Check valves in process contact applications should be installed in a manner that permits self-draining. Non-self-draining valves may be used for liquid streams that flow continuously (e.g., a compendial water loop) or where valves are wetted with a sanitizing medium when not in use (e.g., chromatography system that is filled with sodium hydroxide solution between uses).

(c) The flow direction and required orientation for drainability should be clearly identified on the device. Where the valve is integral to equipment (e.g., diaphragm pumps, homogenizers) indication of the flow direction is not required.

(d) The use of check valves with springs in product contact should be avoided. The owner/user should determine whether check valves that use a spring are acceptable for other process contact applications. Applications where spring check valves are typically acceptable include condensate removal lines and dry process gases.

(e) Check valve design shall comply with SG-3.3.2.3.

SD-3.14 Orifice Plates

Orifice plates, when required and used in hygienic piping systems, shall be installed in a drainable position.

SD-3.15 Relief Devices

(a) Rupture disks (or other hygienic pressure relief devices approved by the owner/user) shall be installed in a hygienic manner without compromising the safety or efficiency of the system.

(b) The cleaning system design shall ensure that the rupture disk (or other hygienic pressure relief devices approved by the owner/user) will not be damaged by the cleaning process (e.g., mechanical forces, chemical compatibility).

(c) Rupture disk (or other hygienic pressure relief devices approved by the owner/user) installation shall comply with the *L/d* ratios mentioned in SD-3.1.2.2.

(d) Rupture disks shall be installed in the manufacturer's recommended holder to ensure proper functionality and cleanability.

(e) Relief devices, including discharge piping, shall be installed in compliance with applicable codes (e.g., flammable liquids and combustibles in accordance with NFPA 30).

(f) Pressure relief valves that are used in product contact applications shall be of hygienic design on both sides of the valve seat. Crevices and holdup volumes should be minimized.

(g) Safety pressure relief valves that are used in product contact applications shall be of hygienic design up to the valve seat.

(h) Pressure and safety pressure relief valves shall be installed in a manner that permits self-draining on both the process and discharge sides of the valve seat.

(i) Pressure relief valves that are used in product contact applications shall be CIP capable. If required for CIP or SIP, an override that allows flow through the valve shall be included.

(j) Pressure relief valves that are used in product contact applications shall comply with SG-3.3.2.3.

SD-3.16 Liquid Pressure Regulators

(a) Regulators should be installed to be fully drainable through the outlet and/or inlet ports.

(b) There shall be no voids or crevices within the area wetted by the fluid. Regulator designs, where a portion of the valve stem penetrates the sensing diaphragm, shall be avoided unless provisions are made to avoid entrapment of foreign matter and any leakage through the interface between stem and diaphragm, especially after SIP.

(c) Due to the inherent design characteristics of self-contained regulators, manual means of override may be required to allow full cleanability and drainability.

SD-4 PROCESS UTILITIES

(19) SD-4.1 Compendial Water Systems

(a) Compendial water systems, such as USP Grade Water-for-Injection (WFI), USP Grade Purified Water (PW), and Highly Purified Water (HPW), shall be designed as looped circulatory systems, rather than noncirculating, dead-ended, branched systems.

(b) Loops shall be designed to provide fully developed turbulent flow in the circulating sections and to prevent stagnation up to the weir of each point-of-use valve.

(19) SD-4.1.1 Compendial Water Generation

(a) All surfaces that shall come into direct contact with the compendial water, feed water, or condensate/blowdown produced by the units shall be constructed of 316- or 316L-type stainless steel or other material as specified by the owner/user.

(b) Connections to the compendial water, feed water, or condensate/blowdown compendial water by the units shall be made by the use of hygienic design fittings. All fittings should be constructed in such a manner as to avoid dead legs and crevices.

(c) Units should be completely drainable and should not contain any areas where agents used to clean, descale, and/or passivate the units are trapped or not easily flushed during rinsing operations.

SD-4.1.2 Compendial Water Distribution Systems

SD-4.1.2.1 Point-of-Use Piping Design for Compendial Water Systems. Point-of-use (POU) can be defined as a location in a compendial water loop where water is accessed for processing and/or sampling. Typically, the point-of-use assemblies are composed of the following elements:

(a) piping associated with a compendial water loop at the physical POU

(b) POU valves, equipment, and instruments

Additional process components and equipment may be added to satisfy application and/or system requirements and will be discussed further in this Part (see Figure SD-4.1.2.1-1).

SD-4.1.2.2 Critical Design Criteria for Point-of-Use Assemblies (19)

(a) All point-of-use assemblies should be designed to optimize drainability through the POU valve.

(b) Assemblies should be designed to promote the ability to CIP, SIP, and/or purge with clean gases.

(c) Valves used in POU applications should be welded into the water distribution loop where possible. Current industry designs are available to achieve an L/d of 2 or less (see SD-3.1.2.2).

(d) Sample valves should be integral to the design of the primary valve and should not constitute dead legs.

(e) Sample valves should be installed only as needed on the main loop.

(f) Sample valves should be installed where water is used for the process to demonstrate water quality compliance to compendial monographs.

(g) Any valve used to provide clean utility services to the POU assembly (e.g., steam or clean gas) should be fabricated in such a manner as to achieve an L/d of 2 or less downstream from the primary POU valve [see Figure SD-4.1.2.1-1, illustrations (a) and (c)].

(h) The length of tubing from POU valves to process equipment should be minimized [see Figure SD-4.1.2.1-1, illustrations (a) and (b)].

(i) If evacuating the system is not possible, appropriate porting of the primary POU valve should be accomplished to facilitate sanitization.

(j) When heat exchangers are used as POU coolers [see Figure SD-4.1.2.1-1, illustration (c)], the design shall comply with SD-3.6.

(k) Physical breaks shall be employed between hoses, drain valves, or any other component leading to drains or sinks to avoid back-siphoning into the POU assembly [see Figure SD-4.1.2.1-1, illustrations (d) and (e)]. The distance H of the physical break should be at least twice the inner diameter of the hoses, drain valves, or any other component leading to drains or sinks to avoid back-siphoning into the POU assembly. The break shall be at least 1 in. (25 mm) for hoses, drain valves, or other components with internal diameters less than or equal to $\frac{1}{2}$ in. (13 mm) (see Figure SD-4.1.2.2-1).

(l) Tubing and other piping materials should be a minimum of $\frac{3}{4}$ in. (19 mm) in diameter to facilitate free drainage of water after use.

(m) POU assemblies shall be drainable as indicated in SD-2.4.3.

(n) A POU may include a venturi or orifice plate, if the restriction of water flow is required. Where used, the additions of these components will require a blowdown to ensure drainability.

(o) When compendial water systems are constructed of metallic materials, the surface finish should be less than or equal to 25 μin. R_a or 0.6 μm (see Part SF) and may be internally electropolished. All 316L-type internal surfaces shall be passivated.

Figure SD-4.1.2.1-1 Point-of-Use Piping

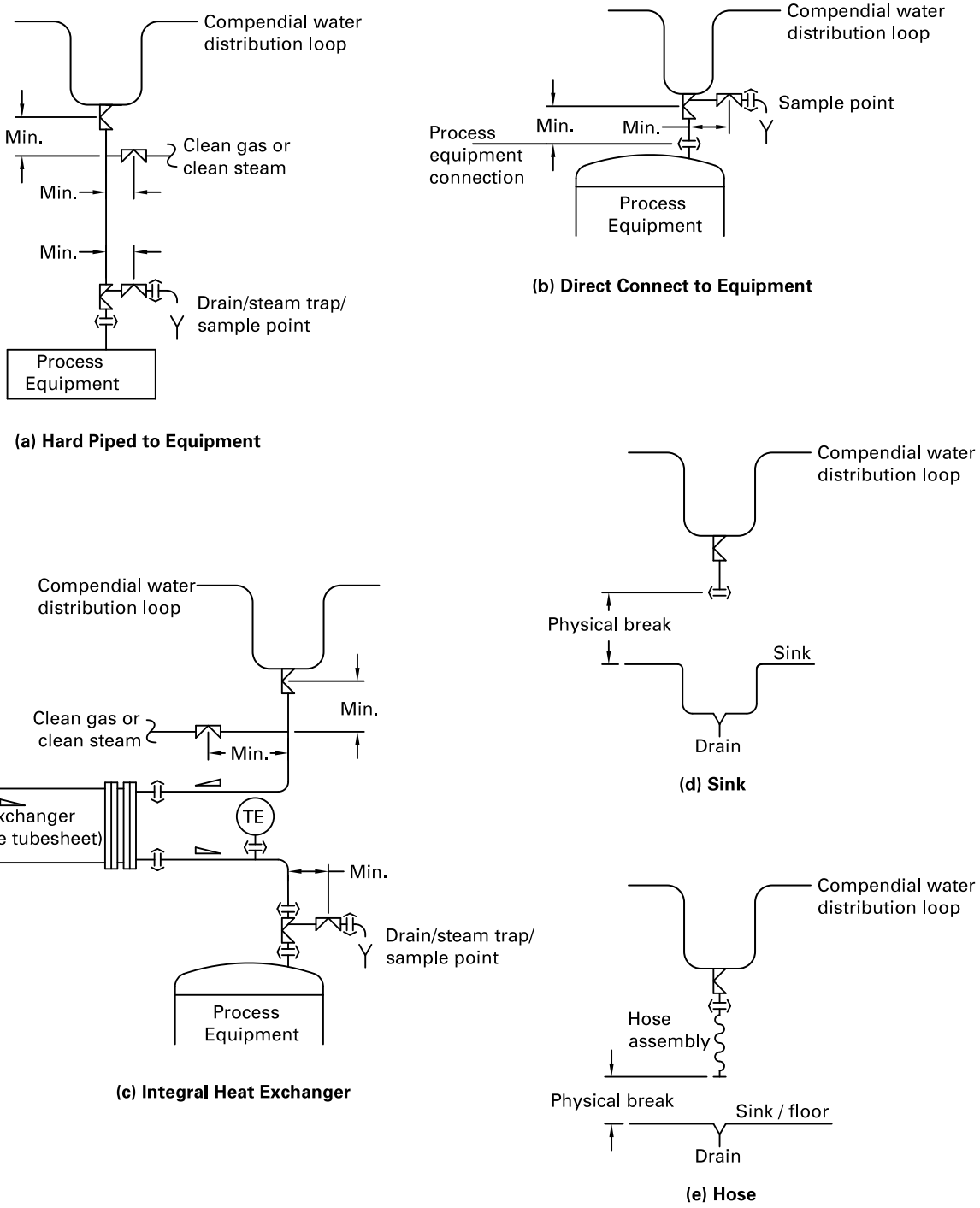
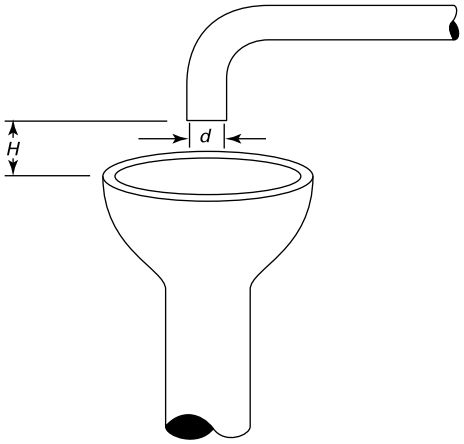


Figure SD-4.1.2.2-1 Physical Break in Point-of-Use Piping



GENERAL NOTE: $H = 2d$ or $H = 1$ in. (25 mm) if $d < \frac{1}{2}$ in. (13 mm).

(p) When compendial water systems are constructed of polymer materials, the surface finish should be less than or equal to 25 µin. R_a or 0.6 µm.

SD-4.2 Clean/Pure Steam Systems

This section is applicable to both clean and pure steam systems.

(19) **SD-4.2.1 Clean/Pure Steam Generation**

(a) All surfaces that come into direct contact with the clean/pure steam, feed water, or condensate/blowdown produced by the units shall be constructed of 316- or 316L-type stainless steel or other material as specified by the owner/user.

(b) Connections to the clean/pure steam, feed water, or condensate/blowdown produced by the units shall be made by the use of hygienic design fittings. All fittings should be constructed to be free of dead legs and crevices.

(c) Units should be completely drainable and should not contain any areas where agents used to clean, descale, and/or passivate the units are trapped or not easily flushed during rinsing operations.

SD-4.2.2 Clean/Pure Steam Distribution System

(a) The distribution system shall have adequate provision to remove air during start-up and normal operations. The use of air vents installed at locations where air is likely to be trapped, such as at the ends of steam headers, can assist in this requirement.

(b) The horizontal distribution lines should be sloped in the direction of flow as indicated in SD-2.4.3. Where necessary, increases in height should be achieved by vertical risers (see Figure SD-4.2.2-1).

(c) Adequate provision should be made to allow for line expansion and to prevent sagging of the distribution lines, so that line drainage is not reduced.

(d) Distribution systems shall not be directly connected to any nonhygienic steam systems (e.g., plant steam systems).

(e) Trap legs for the collection of condensate from the steam distribution system should be of equal size to the distribution line for sizes up to 4 in. (100 mm), and one or two line sizes smaller for lines of 6 in. (150 mm) or larger. These shall be trapped at the bottom. The line size reduction can be made after the branch to the trap leg (see Figure SD-4.2.2-2).

(f) Trap legs should be installed at least every 100 ft (approximately 30 m), upstream of control and isolation valves, at the bottom of vertical risers, and at any other low points.

(g) Condensate shall be allowed to drain to and from steam traps. The use of overhead, direct-coupled, pressurized condensate return systems should be avoided (see Figure SD-4.2.2-2).

(h) Where possible, all components within the distribution system should be self-draining.

(i) Dead legs should be avoided by design of runs and the use of steam traps to remove condensate (see Figures SD-4.2.2-1 and SD-4.2.2-2).

(j) Branches and points-of-use should be routed from the top of the steam header to avoid excessive condensate loads at the branch (see Figure SD-4.2.2-2).

(k) Sampling points for clean/pure steam should be located to collect representative sample(s) of the system (e.g., generator outlet, distribution header ends, critical points-of-use, autoclaves, or SIP stations).

SD-4.2.3 Clean/Pure Steam Valves. This paragraph covers isolation, regulation, and control valves that are part of the steam system and are subject to continuous steam service.

(a) Valves for steam service shall be designed for drainability and should have minimal fluid holdup volumes.

(b) Ball valves are an acceptable industry standard for isolation purposes on continuous steam service. Three-piece-body ball valves should be used instead of single-body designs for both cleanability and maintainability. The bore of the ball valve assembly shall match the inside diameter of the tube (see Figure SG-2.3.1.3-1).

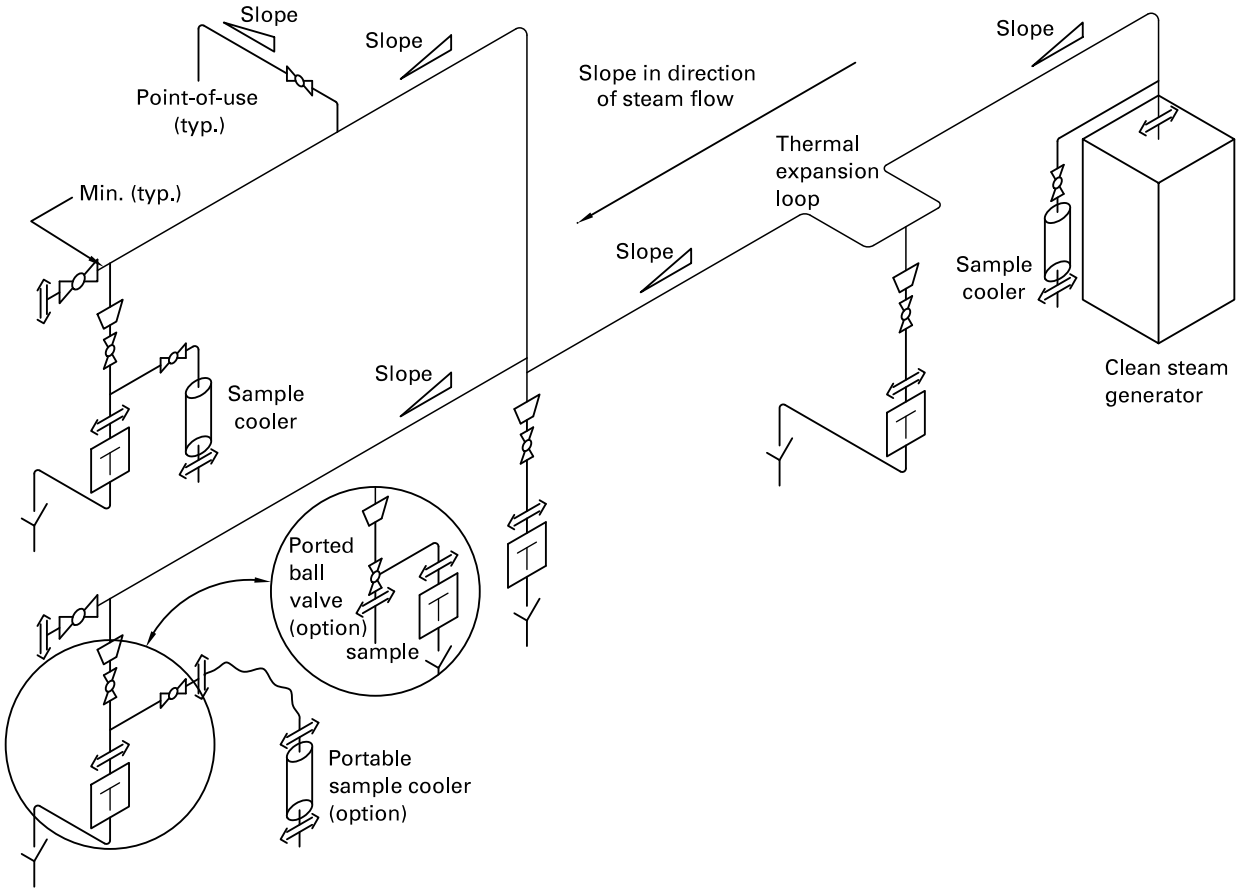
(c) All components shall be suitable for continuous steam service at the temperatures and pressures specified by the owner/user.

(d) Requirements for operation under CIP and SIP conditions [see SG-3.3.2.3(a)(11) and SG-3.3.2.3(a)(13)] can be relaxed when agreed to by the owner/user.

(e) Secondary stem seals with telltale connections are not required for steam service.

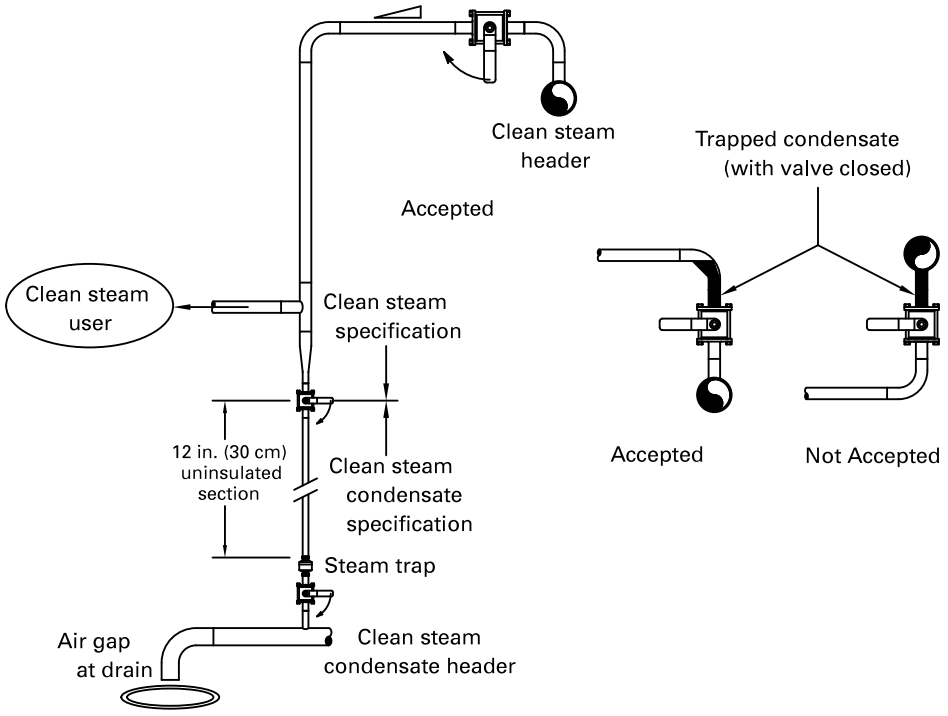
(f) Valves shall be accessible for maintenance.

Figure SD-4.2.2-1 Typical Clean Steam System Isometric



GENERAL NOTE:
Provide steam traps
(a) where line transitions from horizontal to vertical (at the bottom of the vertical riser)
(b) at least every 100 ft (30 m)
(c) at end of each header or branch
(d) at thermal expansion loops or transitions
(e) where steam is sampled

Figure SD-4.2.2-2 Clean Steam Point-of-Use Design



SD-4.3 Process Gases

(19) **SD-4.3.1 Process Gas Distribution Systems.** For this section, a process gas distribution system is one that extends from the bulk supply source (including cylinders) to the points of use as defined by the owner/user.

(a) The installation of process gas delivery and distribution systems for use within the scope of this Standard requires appropriate selection of piping materials. All components shall be supplied or rendered both hydrocarbon free (e.g., oil free) and particulate free prior to installation and/or use.

(b) For materials of construction, the owner/user shall specify all materials. When copper is used, it should be hard drawn and installed in accordance with the current edition of NFPA 99, Chapter 5. When copper is specified in a clean room or area, the owner/user shall confirm that all planned cleaning and sanitizing agents are compatible with copper and all materials of construction. When stainless steel tubing is specified, the materials of choice are 304L-type or 316L-type alloys. Orbital welding is the recommended joining method. Inside clean rooms, the materials of choice are 304L-type or 316L-type stainless steel tubing and fittings. The owner/user and manufacturer shall agree on all joining methods, levels of inspection, and acceptance criteria for all joints prior to installation.

(c) Compression fittings may be used for valves, regulators, mass flow controllers, and other instrumentation systems at the source and/or within system boundaries.

(d) Gas systems are not designed or configured with the intent or provisions to be cleaned, passivated, or chemically treated after installation. Features such as slope, high-point vents, and low-point drains need not be incorporated into these systems.

(e) There shall be no nonvolatile residue. The system design shall ensure that gas will remain pure throughout its delivery.

(f) It is important to select appropriate prefilters and final system filters. The final point-of-use gas purity shall comply with the process requirements.

(g) Gas systems testing and sampling shall comply with 21 CFR 211 and ICH Q7 (International Conference on Harmonization, Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients).

SD-4.4 Process Waste Systems

This section addresses process waste systems because the reliable function of the waste system can reduce the risk of contamination to the process. By designing systems that can be cleaned and rendered safe for access and preventive maintenance, reliable operation may be achieved.

SD-4.4.1 General. The manufacturing of biologics generates liquid waste in various quantities that may or may not contain viable microorganisms. The liquid waste comes directly from the process fluids and may include cleaning solutions mixed with product components, buffers, or media.

The performance of process waste treatment systems may benefit from the sanitary design requirements of Part SD. The design of the process waste transfer line(s) shall prevent process waste backflow to the process system(s), reducing the risk of contamination.

The effectiveness and safety of process waste treatment systems have been shown to benefit from incorporating the design principles of Part SD. This is true of bio-inactivation systems where heat or chemical dosing is used, or where biosafety containment is required.

SD-4.4.2 Bio-Inactivation Systems. Depending on the type of waste, the treatment method is chosen based on effectiveness, efficiency, and jurisdictional requirements. The owner/user shall define the inactivation conditions and verify the effectiveness of the system with respect to these requirements. Bio-inactivation may be designed to be continuous or batch type and is achieved using one or more of the following methods:

(a) thermal
(b) chemical
(c) radiation

The system design should minimize fouling and buildup of solids and films. Bio-inactivation systems should be cleanable to allow safe disassembly and maintenance. Where biosafety containment is a requirement, the system shall be sanitizable.

In bio-inactivation systems, piping design features specified in SD-2 and SD-3 may help in achieving proper and repeatable operation of these process waste systems.

(19) # SD-5 PROCESS SYSTEMS

SD-5.1 Bioreactors and Fermentors

SD-5.1.1 General. For this section, the terms "fermentors" and "bioreactors" are interchangeable. A bioreactor or fermentor shall be defined as a vessel-based system used in the growth of microorganisms or plant, mammalian, or insect cells.

SD-5.1.4 System Design

SD-5.1.4.1 Inlet Gas Assembly. The inlet gas assembly shall be defined as a piping assembly that has the ability to deliver controlled amounts of filtered gases into a bioreactor vessel. The assembly shall include but is not limited to the items in SD-5.1.4.2 through SD-5.1.4.5.

SD-5.1.4.2 Flow Control Devices

(a) Flow control devices (e.g., rotameters, mass flow controllers, and modulating control valves) shall be installed outside of the sterile boundary; therefore, piping requirements within this section may not apply. However, provisions shall be included within the design to prevent instrumentation damage due to SIP procedures and backflow.

(b) Flow control devices should be sized to prevent a vacuum condition, or a provision to bypass the flow control device shall be provided to maintain positive pressure in the vessel.

SD-5.1.4.3 Inlet Filter Assembly

(a) For this section, an inlet filter shall be defined as a filter element installed in a housing of suitable material. The inlet filter assembly shall be defined as the filter(s) local to the bioreactor.

(b) Inlet filter assemblies shall be designed for SIP with provisions to remove entrapped air and condensate.

(c) If multiple inlet filters are used in series, then the filter assembly closest to the bioreactor shall be a sterilizing filter.

(d) Provisions shall be made for integrity testing of the inlet filter assembly in situ or out of place.

(e) If the inlet housing(s) are included in a cleaning circuit, the filter element(s) shall be removed prior to introduction of cleaning solutions.

(f) Gas filters should be installed above the bioreactor liquid level.

SD-5.1.4.4 Gas Sparging Assemblies

(a) Spargers shall be defined as mechanical devices normally located below an impeller used to disperse gases within a charged bioreactor. This section applies to sparge lances, wands, rings, and other devices (see Figures SD-5.1.4.4-1 through SD-5.1.4.4-4) that may be mounted in the bioreactor vessel to introduce various gas streams for process operations. Sparge device assemblies shall meet the requirements of SD-3.4.2.

(b) Spargers shall be designed for SIP with the vessel.

(c) Spargers should be designed for CIP. If the sparge element cannot be CIP'd, provisions shall be made to remove the sparge assembly from the bioreactor for replacement or cleaning out of place.

(d) The removable sparger shall be supplied with the means to ensure that the installation orientation is in compliance with design intent.

(e) If a check valve is installed in the sparge line within the sterile envelope, it shall be designed for CIP and SIP.

SD-5.1.4.5 Inlet Gas Piping

(a) Overlay piping is defined as piping that directs filtered gases to the vessel headspace.

(b) Inlet gas assembly piping (sparge and overlay) within the sterile envelope shall meet the requirements as defined in SD-3.1.2.

SD-5.1.4.6 Exhaust Gas Assembly. The exhaust gas assembly is defined as a piping assembly that maintains the integrity of the sterile boundary with respect to

Figure SD-5.1.4.4-1 Gas Sparging Assembly — Lance

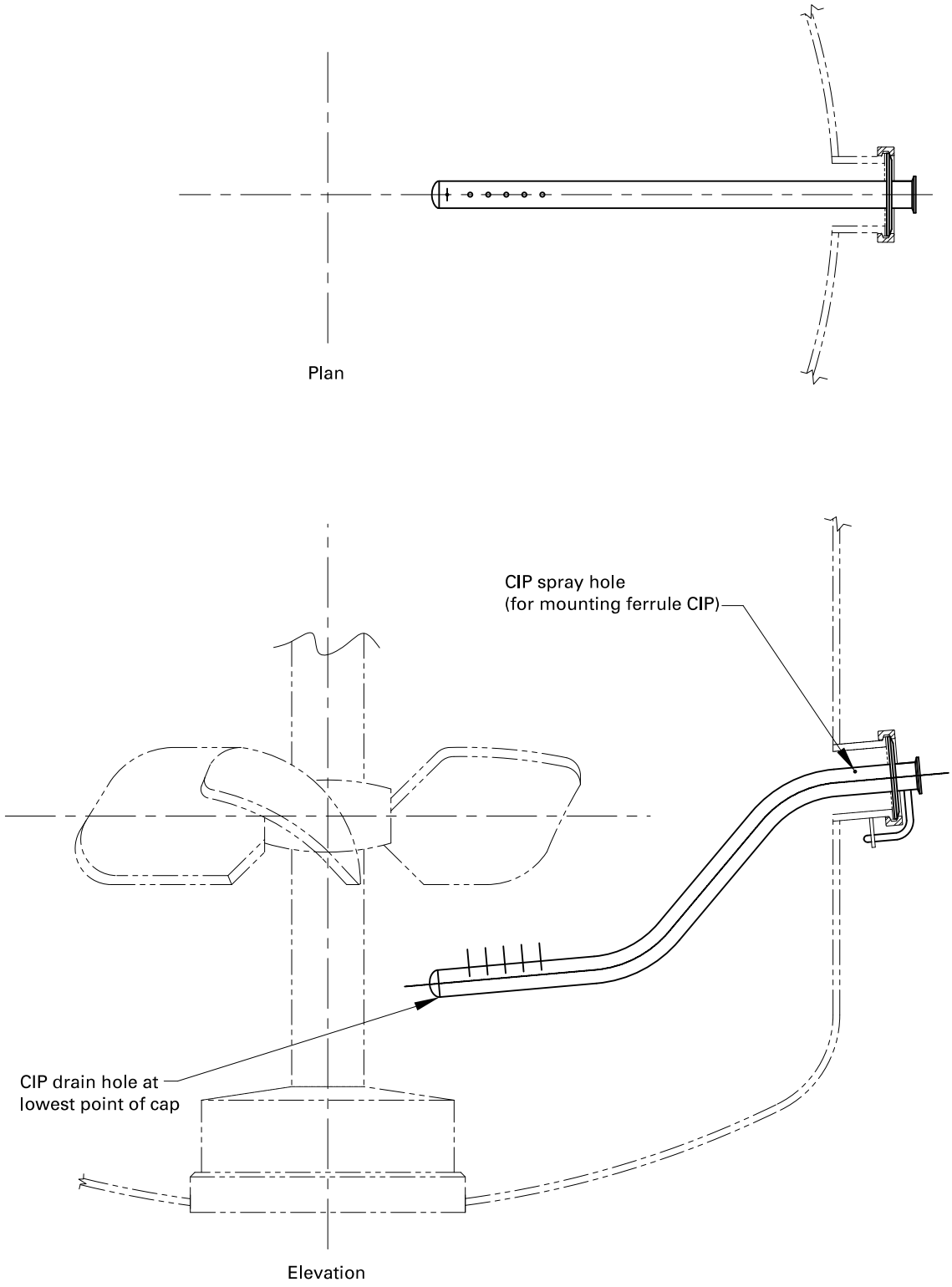


Figure SD-5.1.4.4-2 Gas Sparging Assembly — Sintered

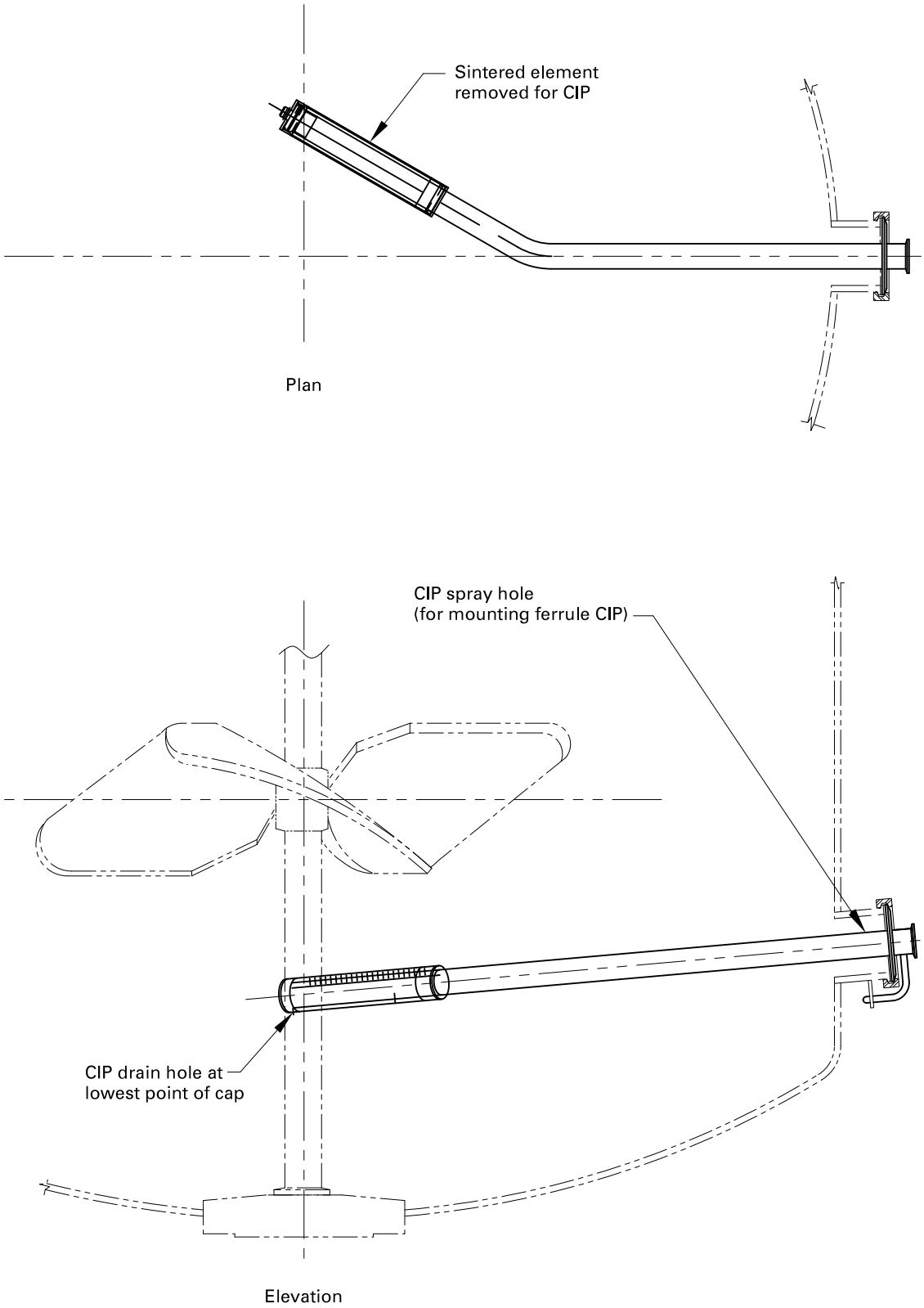


Figure SD-5.1.4.4-3 Gas Sparging Assembly — Ring

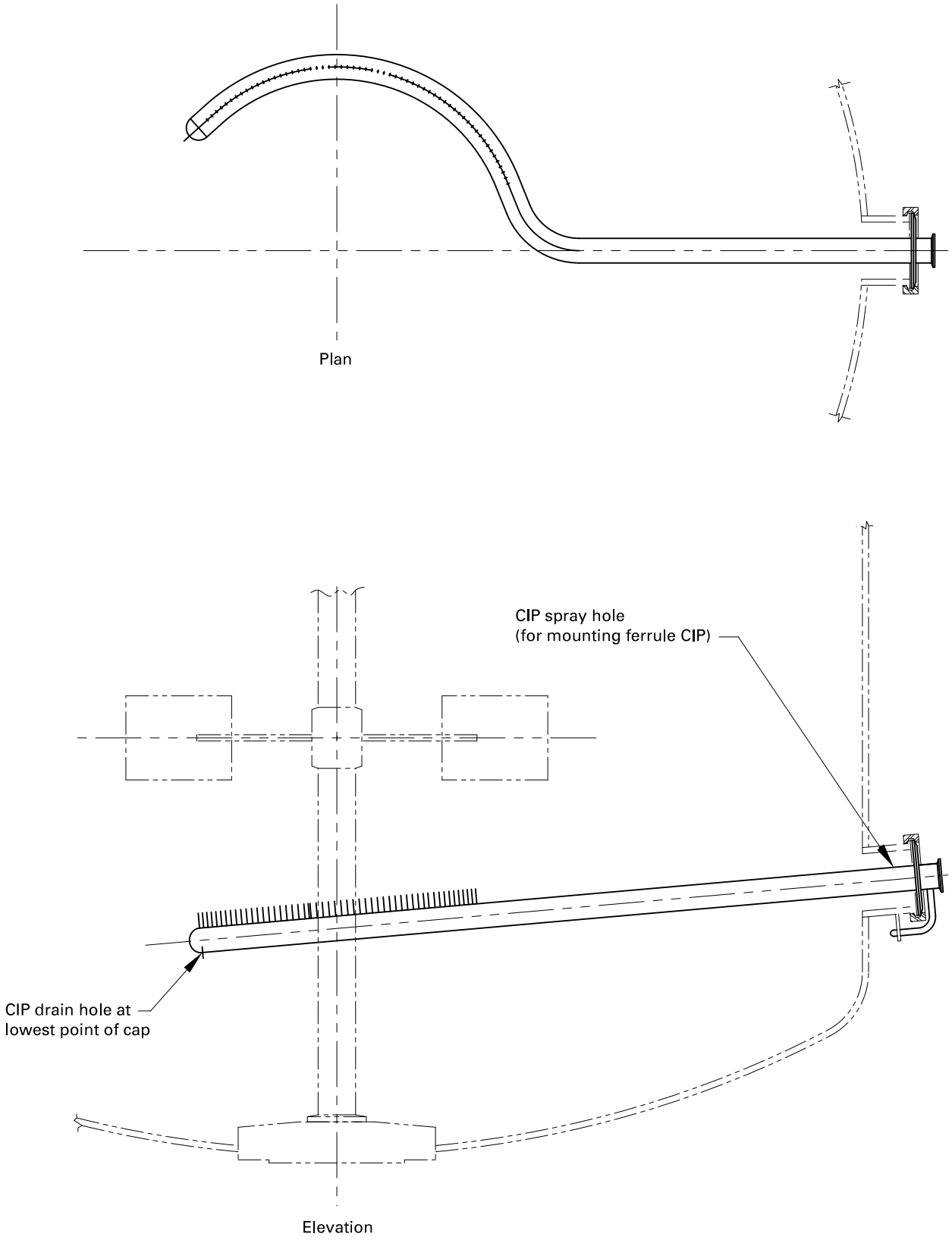
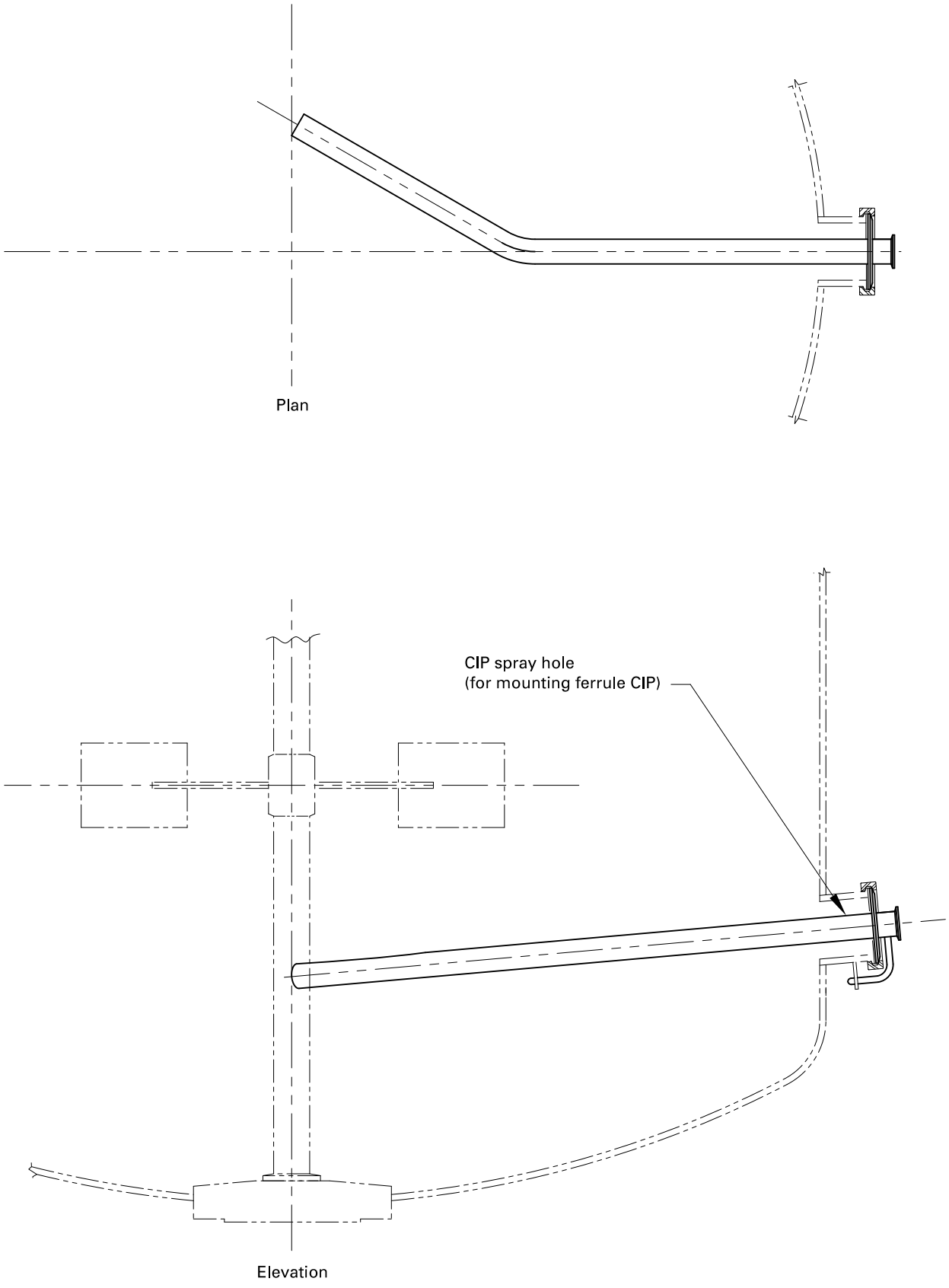


Figure SD-5.1.4.4-4 Gas Sparging Assembly — Single Orifice



sterility and pressure. The assembly shall include but is not limited to the items in SD-5.1.4.7 through SD-5.1.4.9.

SD-5.1.4.7 Exhaust Filter

(a) For this section, an exhaust filter shall be defined as a filter element (as described in Nonmandatory Appendix T) installed in a housing of suitable material.

(b) Exhaust filters shall be designed for SIP. The housings shall be installed in such a way as to prevent the collection of condensate in the elements due to SIP.

(c) If redundant sterilizing-grade exhaust filters are used in series, then the filter farthest from the bioreactor shall have a maximum rating of 0.2 μm absolute. In addition, provisions shall be included for draining condensate from the piping between the filters.

(d) Consideration should be made for CIP or removal in the case of cleaning out of place.

(e) Provisions shall be made for integrity testing of the exhaust filter assembly.

(f) If the exhaust filter housing(s) are included in a cleaning circuit, the filter element(s) shall be removed prior to introduction of a cleaning solution

(g) To prevent the exhaust filters from becoming blinded by condensate saturation during operation, the exhaust gas assembly may include exhaust condensers (Figure SD-5.1.4.7-1), exhaust heaters (Figure SD-5.1.4.7-2), or steam jacketed or electrically heat traced filter housings (Figure SD-5.1.4.7-3). These items shall be designed for SIP and CIP.

SD-5.1.4.8 Exhaust Gas Piping

(a) The exhaust gas assembly within the sterile envelope shall meet the requirements as defined in SD-3.1.2.

(b) The design of exhaust gas piping from the bioreactor should ensure that there is no condensate accumulation in the line downstream of the system.

SD-5.1.4.9 Back Pressure Control Devices

(a) If required, back pressure control devices (e.g., modulating control valves or regulators) should be installed outside of the sterile boundary.

(b) Back pressure control devices shall not hinder the bioreactor's capability of being SIP'd and CIP'd.

(c) If a vapor-liquid separator is used in the exhaust within the sterile envelope, it shall be designed for CIP and SIP.

SD-5.1.4.10 Feed Lines. This section applies to bioreactor piping systems used to feed liquid ingredients (e.g., pH control reagents, antifoam reagents, media, nutrient, and inoculum). Feed lines shall be designed with the appropriate piping system to allow CIP and SIP of the bioreactor vessel and the feed line itself. CIP and SIP of the feed line may be done independently or simultaneously with the bioreactor.

SD-5.1.4.11 Dip Tubes. This section applies to all bioreactor port tube-extensions within the vessel.

(a) Bioreactor dip tubes shall meet the requirements of SD-3.4.2.

(b) Removable dip tubes (see Figure SD-3.4.3-1) shall be inserted through a hygienic fitting. The removable dip tube shall be supplied with the means to ensure that the installation orientation is in compliance with design intent.

(c) Bioreactor dip tubes shall be designed for CIP or cleaning out of place (COP).

SD-5.1.4.12 Harvest Valves/Bottom Outlet Valves. This section applies to all valves installed in the vessel bottom head.

(a) Harvest valves shall meet the requirements of SG-3.3.2.3.

(b) Bioreactor harvest valves shall be designed for SIP and CIP or COP.

SD-5.1.4.13 Agitation Assemblies. This section applies to mechanical agitator assemblies mounted in the bioreactor for achieving one or more mixing-related unit operations (e.g., blending, mass transfer, heat transfer, and solids suspension).

(a) Agitators shall meet the requirements of SD-3.5.

(b) Agitators with double mechanical seals (see Figure SG-2.3.2.3-2) or magnetic couplings (Figure SD-3.5.5-2) are recommended to isolate bioreactor contents from the environment.

(c) Agitator seal or magnetic coupling components shall be designed for CIP and SIP.

SD-5.1.4.14 Mechanical Foam Breaker Assemblies. This section applies to mechanical foam breaker assemblies that may be mounted in the bioreactor for reducing or eliminating foam accumulation in the vapor space of the bioreactor.

(a) Foam breaker assemblies shall meet the requirements of SD-3.5.

(b) Foam breakers with either double mechanical seals (Figure SG-2.3.2.3-2) or magnetic couplings (Figure SD-3.5.5-2) are recommended to isolate bioreactor contents from the environment.

(c) Foam breaker seal or magnetic coupling components shall be designed for CIP and/or SIP as appropriate.

Figure SD-5.1.4.7-1 Exhaust Gas Condenser

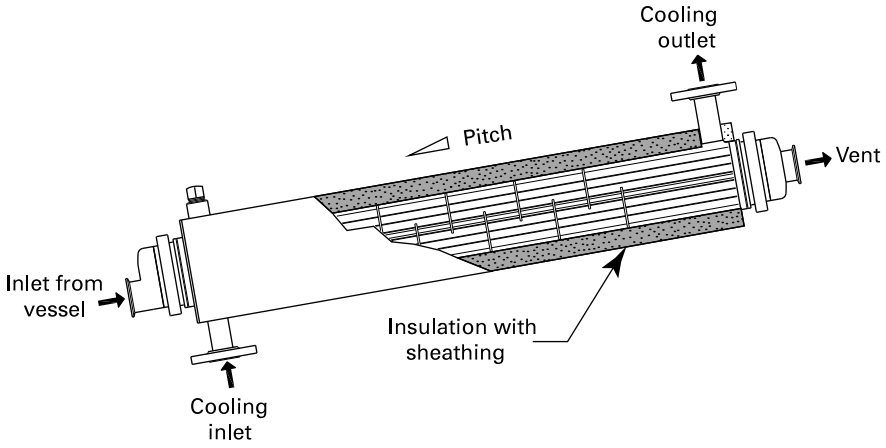


Figure SD-5.1.4.7-2 Exhaust Gas Heater

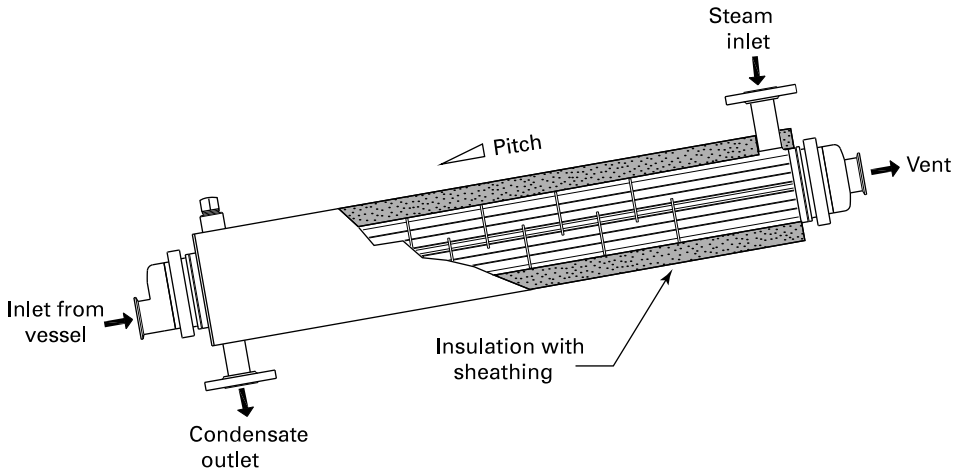
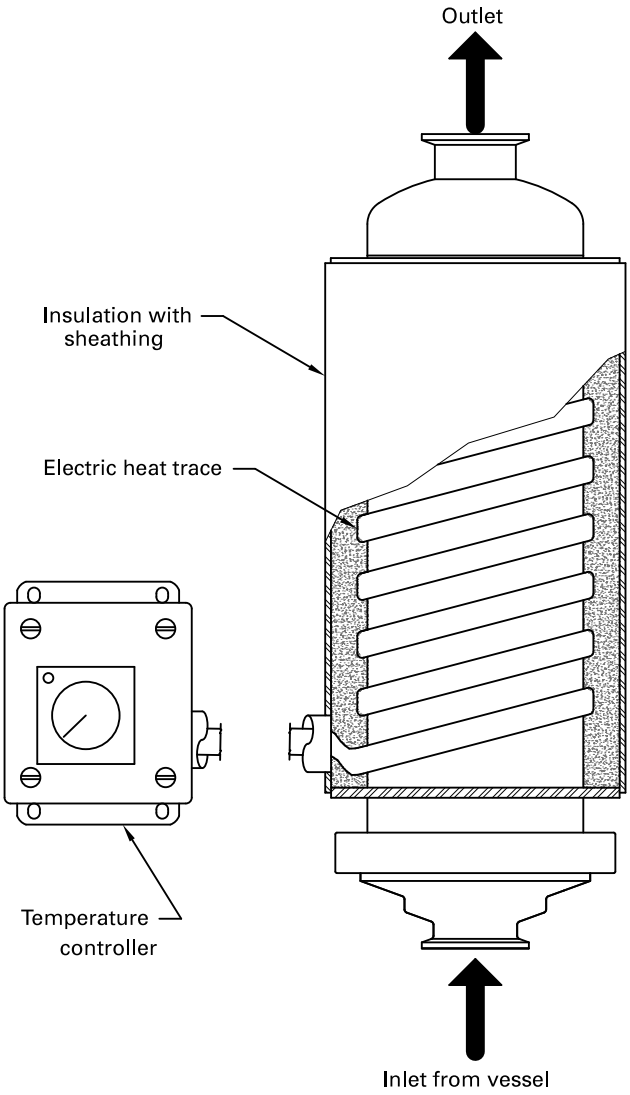


Figure SD-5.1.4.7-3 Electrically Heat Traced Filter Housing



SD-5.1.4.15 Internal Coils

(a) Internal coils should be avoided where possible.

(b) Product contact surfaces of internal coils require provisions for CIP and SIP.

SD-5.1.4.16 Baffles. Baffle assemblies shall meet the requirements of SD-3.4.

SD-5.1.4.17 Spray Devices. This section applies to sprayballs, wands, and other devices (see Figure SD-3.9.2.1-1) that may be mounted in the bioreactor vessel for distributing cleaning solution during CIP operations.

(a) Spray device assemblies shall meet the requirements of SD-3.4.2 and SD-3.9.

(b) If not removed during processing, spray device assemblies shall be designed for SIP.

SD-5.1.4.18 Instrumentation

(a) Instruments installed within the sterile envelope or boundary shall be designed for SIP. Consideration should be made in the design for instrument removal for calibration.

(b) Instruments installed within the sterile envelope or boundary shall be designed for CIP or removed for COP.

(c) Temperature-sensing elements should be installed in thermowells. Piping associated with in-line thermowells shall be sized to allow sufficient steam and condensate flow.

SD-5.1.5 Design for Bioburden Control

(a) The area within the bioreactor sterile envelope or boundary shall be designed for cleanability and bioburden control. As a minimum, the bioreactor sterile envelope or boundary shall include the following (see Figures SD-5.1.5-1 and SD-5.1.5-2):

(1) vessel internals

(2) inlet gas piping from the filter element(s) to the vessel and any installed isolation valving (If redundant sterilizing-grade filters are used in series, the inlet filter element farthest from the reactor vessel shall define the sterile boundary.)

(3) exhaust gas piping from the vessel side of the exhaust filter(s) to the vessel and any installed isolation valving (If redundant sterilizing-grade filters are used in series, the exhaust filter farthest from the reactor vessel shall define the sterile boundary.)

(4) agitation assembly including all internal surfaces of the impellers and the shaft up to the mechanical shaft seal in contact with the product

(5) feed systems from the vessel to the seat of the isolation valve nearest to the bioreactor vessel or if the feed stream is being filter sterilized, the sterilizing-grade filter element

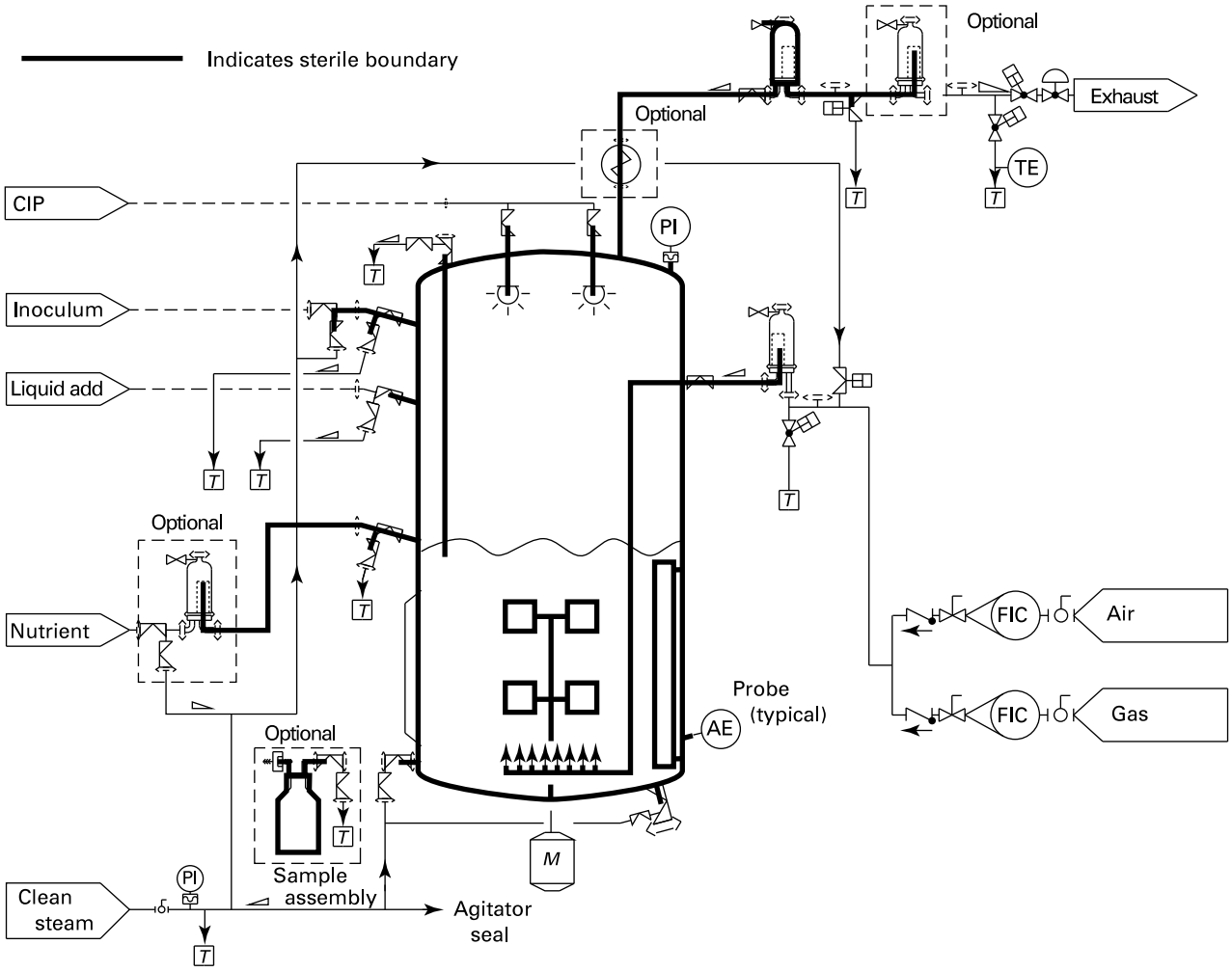
(6) sampling system

(7) product harvesting system from the vessel to the seat of the isolation valve nearest to the bioreactor vessel

(b) A bioreactor is made up of a number of subassemblies. Process-contacting subassemblies require special design consideration for cleaning and bioburden control.

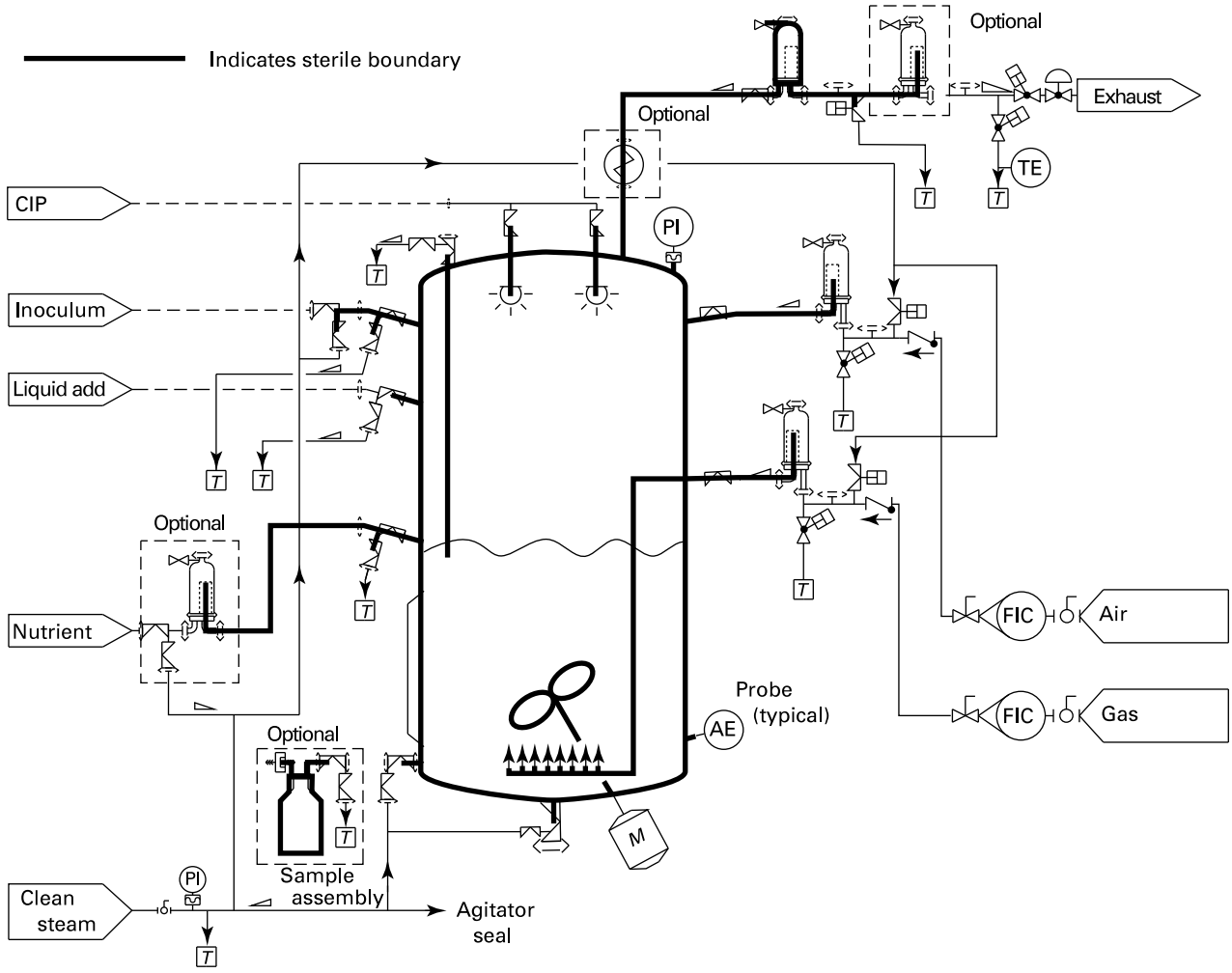
(c) The bioreactor design for cleanability and sterility shall take into consideration the biosafety level requirement for the system. A bioreactor shall be designed in accordance with a biosafety level requirement as defined by the National Institutes of Health or equivalent organization (e.g., BSL-1, BSL-2, BSL-3, or BSL-4). The biosafety level requirement should be determined based on the organism, the process, the product being produced, and/or the owner/user's preferences. To meet a specific biosafety level requirement, special operational considerations (e.g., steam blocks) may have to be addressed within the bioreactors' subassembly designs. If the bioreactor has been used to grow an organism that requires biohazard containment, provision shall be

Figure SD-5.1.5-1 Fermentor Sterile Envelope



GENERAL NOTE:
Design may vary.

Figure SD-5.1.5-2 Bioreactor Sterile Envelope



GENERAL NOTE: Design may vary.

made to decontaminate all surfaces that may have come in contact with the product prior to CIP, or to contain and decontaminate the fluids used for CIP.

SD-5.1.5.1 Drainability

(a) Inlet gas piping within the sterile envelope shall meet slope requirements as defined for GSD3 in Table SD-2.4.3.1-1.

(b) Exhaust gas piping within the sterile envelope shall meet slope requirements as defined for GSD3 in Table SD-2.4.3.1-1.

(c) All wetted surfaces of sparge devices shall be sloped to drain by gravity into the vessel.

(d) Feed line valves and piping orientation shall be designed to provide complete drainage during CIP and SIP.

(e) All wetted surfaces of dip tube(s) shall be sloped to drain by gravity into the vessel.

(f) Bottom outlet valves shall be drainable and installed in such a way as to ensure complete drainage of the bioreactor contents.

(g) Bottom-mounted agitators shall not interfere with free and complete drainage of bioreactor contents.

SD-5.1.5.2 Cleaning

(a) The area within the sterile envelope should be designed for CIP. For components that cannot be CIP'd, the design shall allow removal for replacement or manual cleaning out of place.

(b) If instruments will be cleaned out of place, blind caps or plugs should be provided to maintain the integrity of the bioreactor system.

(c) If CIP of the ingredient feed system is performed during active culture operations, then the design should include provisions to prevent cross-contamination between CIP solutions and product.

(d) If dip tube(s) are cleaned in place with the vessel, both the inside and outside of the dip tube(s) shall be cleaned.

(e) Provisions shall be included in the design to clean the product contact surfaces of impellers. Additional spray elements may be required to achieve coverage.

(f) CIP for sparge devices that use porous material for gas distribution requires particular attention. These devices should be evaluated for CIP cleanability and should be removed from the bioreactor for external cleaning and/or replacement when CIP is not feasible.

SD-5.1.5.4 Thermal Sanitization/Sterilization

(a) The area within the sterile envelope should be designed for SIP. For those components or assemblies that cannot be SIP'd, the design shall allow removal for steam sterilization using an autoclave as long as additional provisions are provided for sterilizing the interface (e.g., steam block) once the components or assemblies are reconnected to the remainder of the bioreactor system. Autoclaved components or assemblies shall be capable of being steam sterilized without degradation to any of the elastomers or polymers that make up the components or assemblies.

(b) If the bioreactor is sterilized with media in the vessel, the SIP operation shall direct steam flow through the sparge device.

(c) If the bioreactor is sterilized with media in the vessel, and dip tube(s) extends below the working level of the media, the SIP operation shall direct steam flow through the dip tube into the vessel.

(d) For dip tube(s), the SIP operation shall direct or balance steam distribution to establish and maintain sterilization temperature within the tube(s) during the sterilization hold period.

(e) Special considerations for spray devices are as follows:

(1) The SIP operation shall direct or balance steam distribution to establish and maintain sterilization temperature within the spray device during the sterilization hold period.

(2) With the exception of a combination sparger/spray device, internal spray devices should be located above the bioreactor operating liquid level.

(3) If the bioreactor is sterilized with media in the vessel, and the spray device assembly extends or is located beneath the working level of the media, the SIP operation shall direct steam flow through the device into the vessel.

SD-5.1.7 Testing. The bioreactor vessel should be pressure/vacuum and temperature rated per the owner/user's design criteria. The vessel shall be constructed, tested, inspected, and stamped in accordance with local ordinances, regulations, and codes.

SD-5.2 Cell Disrupters

SD-5.2.4 System Design

(a) Product contact material shall not affect product quality or integrity.

(b) The design shall incorporate nonshedding components and parts.

SD-5.2.5 Design for Bioburden Control

SD-5.2.5.1 Drainability

(a) The device shall be designed with the ability to optimize drainability.

(b) Safety rupture disks shall be oriented for drainability while maintaining system integrity and safety.

SD-5.2.5.2 Cleaning. The disrupter shall be designed for ease of disassembly to allow for COP.

SD-5.3 Centrifuges

SD-5.3.1 General. Centrifugation is a process used to separate suspended materials of different densities using centrifugal force. Centrifuges may be used for collection of solids such as harvest of cells, inclusion bodies of precipitated protein, or clarification of bioprocess solutions. Different types of centrifuges include disk stack centrifuges, tubular bowl centrifuges, single-use centrifuges, and ultracentrifuges.

SD-5.3.2 Process Parameters. The owner/user should define the following process parameters:

(a) whether the centrifuge will be used for collection of solids, for clarification, or for both

(b) whether the centrifuge is intended for open, closed, or briefly exposed operation(s)

(c) the biosafety level containment and room classification requirements of the process and system

(d) product phase (e.g., supernatant or solids)

(e) cleaning requirements (e.g., CIP or manual cleaning)

(f) sanitization requirements (e.g., SIP)

(g) batch size

(h) process liquid feed flow rate

(i) solids cell type or particle size and distribution

(j) solid concentration [in packed cell volume (PCV)]

(k) feed pressure

(l) process temperature

(m) density difference between solvent and suspended solids

(n) viscosity and surface tension of liquid

(o) physical properties of solids (e.g., shear sensitivity, rheology)

For each parameter, the user may also define warning and alarm tolerances or limits. Additional process requirements may be defined by the owner/user.

SD-5.3.3 Performance Requirements. The owner/user shall define the following system performance requirements:

(a) maximum allowable processing and cleaning/sanitization times

(b) desired purity (e.g., PCV in supernatant or % solids)

For each parameter, the user may also define warning and alarm tolerances or limits. Additional performance requirements may be defined by the owner/user.

SD-5.3.4 Disk Stack Centrifuge. In bioprocessing, the disk stack centrifuge is typically used as a continuous unit operation to separate cells from cell broth, cell debris or acid precipitates from liquid, or to recover inclusion bodies after homogenization of microbial cells. A disk stack centrifuge consists of a cylindrical bowl containing a stack of conical disks separated by spacers, which reduce the distance and increase the surface area for particulate settling when under centrifugal force.

SD-5.3.4.1 Operating Capabilities and System Function. The centrifuge shall be capable of the following functions:

SD-5.3.4.1.1 Cleaning. Centrifuges should be designed for CIP. Different parts within the centrifuge may have different cleaning requirements or procedures. Centrifuges that will be CIP'd shall be constructed of materials compatible with the chemistry and conditions of the cleaning process (SD-2.4.1.2). Centrifuges designed for CIP shall comply with SD-2.4.2. Additional requirements for disk stack centrifuges subject to CIP include the following:

(a) The manufacturer shall ensure that all product contact surfaces are cleanable with the CIP process. This includes adequate velocity of cleaning solutions in piping per SD-6.3.5.2. The use of instrument tees conforming with Tables DT-4.1.2-10 and DT-4.1.2-11 is recommended for instruments. However, all product contact branches (e.g., instrument tee/ports, process branches) shall be exposed to cleaning fluids during CIP.

(b) The manufacturer should design the equipment to include sample collection points that allow for representative cleaning verification/validation of all product contact branches.

(c) Spray devices shall conform with SD-3.9.

(d) The manufacturer shall recommend CIP solution supply rate and pressure requirements for effective cleaning.

(e) Due to fluctuations in flow (e.g., bowl discharge), use of recirculating CIP flow paths may require break-tanks, bypass flows, and pumps that can generate suction when run dry.

(f) The centrifuge manufacturer shall identify all areas of primary and incidental product contact that require manual cleaning in addition to CIP. Centrifuges that are not designed for CIP shall be capable of disassembly and reassembly for cleaning and examination.

SD-5.3.4.1.2 Sterilization/Sanitization. The owner/user shall inform the manufacturer of the sterilization/sanitization and storage requirements (e.g., temperature, pressure, chemistry) and storage condition (e.g., flooded or dry). The owner/user and manufacturer shall define the sterile envelope or boundary.

Centrifuges that will be SIP'd shall be designed in accordance with SD-2.3.1.1, and, in certain jurisdictions, may be considered pressure vessels (see GR-1). The manufacturer shall demonstrate saturated steam penetration across components that define the sterile boundary of the system.

Centrifuges that will be chemically sanitized shall be sanitized with an agent and process that have been proven to achieve the bioburden reduction requirements of the system.

The manufacturer should recommend the operating conditions (e.g., sanitizing agent supply flow rate, bowl speed, discharge rate) required to ensure effective chemical sanitization.

SD-5.4 Filtration Systems

SD-5.4.4 System Design

(a) All wetted surfaces should be accessible for cleaning and examination.

(b) The filter housing shall be designed to allow for complete venting and draining. Liquid tee-type filter housings should be installed vertically, and vent-type in-line filter housings should be installed vertically with the condensate/drain port directed downward (see Figure SD-5.4.4-1).

(c) All nozzle connections shall be of a hygienic design.

(d) Baffle plates, when used, should be cleanable and designed for SIP.

(e) The housing assembly, tube sheets, end plates, and connections should be designed to prevent bypassing of process fluid around the element.

(f) Parts forming internal crevices should be easily disassembled to enable access for cleaning.

(g) Vent filters for hot process services should be heat traced or steam jacketed. Other methods for preventing moisture accumulation in vent filters, such as vent heaters or condensers, could be considered.

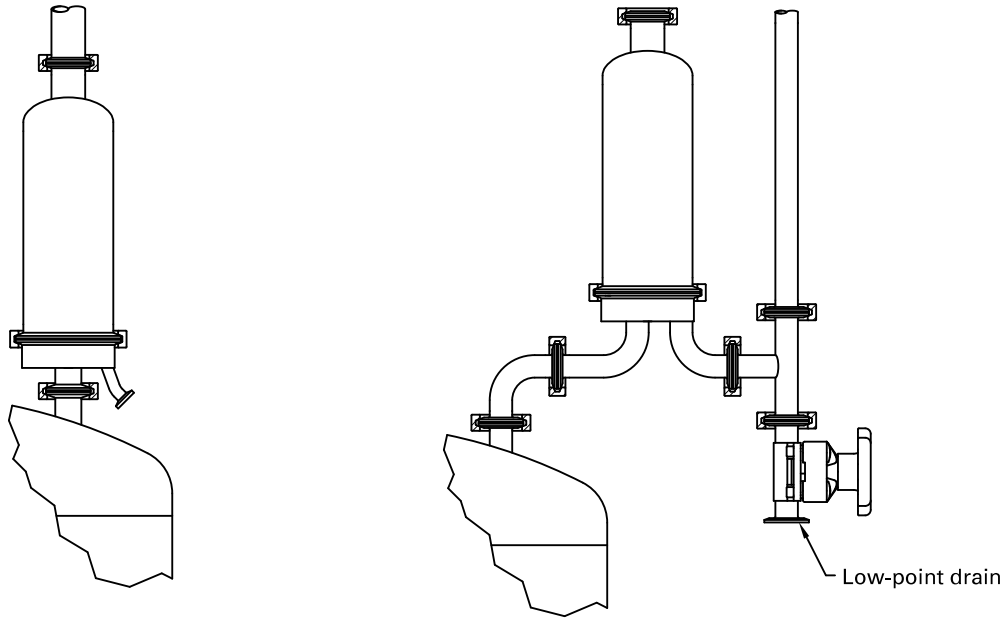
SD-5.4.4.1 Micro/Ultrafiltration Systems

(a) Skid pumps designed for both process and CIP shall be designed to provide turbulent flow for cleaning. All process piping systems that include piping, tubing, and fluidic components shall be sloped for adequate drainage. For all low points in the system, a drain port shall be installed. A common drain port on the skid is preferred.

(b) Piping and equipment holdup volume shall be minimized.

(c) Ultrafiltration cartridge housings shall be designed with connections and covers that will allow the unit to drain completely.

Figure SD-5.4.4-1 Tank/Vessel Vent Fillers



(a) In-Line Design
(Accepted)

(b) T-Type Design
(Accepted)

SD-5.4.5 Design for Bioburden Control. The owner/user is responsible for defining the sanitization requirements based on the level of bioburden control required for the unit operation. All components and filter elements shall be either compatible with the selected sanitization agents and conditions or capable of being removed or isolated prior to the sanitization process while maintaining a flow path through the system.

SD-5.4.5.2 Cleaning

(a) Filtration systems that are designed for CIP shall be designed in accordance with SD-2.4.2 unless otherwise agreed to by the owner/user and manufacturer.

(b) Tangential flow filtration elements may be designed for repeated use and cleaned along with the system. When multiple-use elements are cleaned in place, system design shall ensure suitable conditions (e.g., flow rates) to properly clean the filtration elements.

(c) Direct flow filtration elements are typically not reused and are not installed during the cleaning process.

SD-5.4.5.3 Chemical Sanitization/Sterilization. Equipment intended to be chemically sanitized shall be designed to ensure contact between process contact surfaces and the sanitization solution.

SD-5.4.5.4 Thermal Sanitization/Sterilization. Temperature, flow direction, and differential pressure of the thermal sanitization or sterilization process shall be defined by the owner/user. The properties of the filter elements shall be considered to confirm compatibility of the element with the exposure conditions of a thermal sanitization process.

SD-5.5 Chromatography Systems

For this section, the term "system" is intended to cover the chromatography piping skid, not including the associated column.

SD-5.5.5 Design for Bioburden Control

SD-5.5.5.2 Cleaning. Chromatography systems shall be designed for CIP. Systems should be designed in accordance with SD-3.1 unless otherwise agreed to by the owner/user and manufacturer.

SD-5.5.5.3 Chemical Sanitization/Sterilization. Chemical sanitization processes are used to reduce bioburden. All process contact surfaces of system components shall either be compatible with the selected sanitization agents or be capable of being removed or isolated prior to the sanitization process.

SD-5.5.5.4 Thermal Sanitization/Sterilization. Chromatography systems may be designed for thermal sanitization. If a system is designed for thermal sanitization, components shall be designed for the specified conditions, or shall be removed or isolated prior to the sanitization process. Note that if items are removed for sanitization, they should be sanitized separately and reinstalled in a controlled environment to avoid contaminating the system.

SD-5.5.5.5 Post-Use Storage. Chromatography systems are typically stored flooded with a sanitizing solution to maintain bioburden control.

SD-5.6 Lyophilizers/Freeze Dryers

SD-5.6.1 General. For the purpose of this section, the terms "lyophilizer" and "freeze dryer" may be used synonymously. This section describes the requirements for cleanability and bioburden control of lyophilizers that are used for biopharmaceutical processing. This section applies to lyophilizers in which product is loaded onto shelves. Other designs that use methods and components not described in this section should be evaluated and agreed upon by the owner/user. A lyophilizer comprises a number of interconnected components. Components with process contact surfaces and/or product contact surfaces shall be designed for cleanability and bioburden control.

Lyophilizer surfaces of components, piping, equipment, or systems that are isolated by design from both product and process fluids are not process contact surfaces nor required to be designed for cleanability or bioburden control. Examples of surfaces that are not process contact surfaces include the exterior surfaces of equipment, drain lines, vacuum lines, and systems containing hydronic or hydraulic fluids.

SD-5.6.2 Components. A lyophilizer is comprised of functional components/systems, as shown in Figure 5.6.2-1, which are designed for isolation, cleanability, and/or bioburden control. These components/systems have the potential to affect product quality and include the following:

(a) lyophilizer chamber
(b) condenser vessel
(c) lyophilizer shelves
(d) vacuum systems
(e) isolation bellows
(f) internal moving parts
(g) spray devices
(h) gas filter assemblies
(i) doors and door seals
(j) valves
(k) instruments

SD-5.6.2.1 General

(a) All components shall be rated for the applicable pressure, vacuum, temperature range, thermal shock, and exposure to sanitizing agents [e.g., vaporized hydrogen peroxide (VHP)] when applicable.

(b) Process contact surfaces made from metallic material should comply with SD-2.4.1.1 through SD-2.4.1.3.

(c) Process contact surfaces made from nonmetallic material should comply with SD-2.4.1.1, SD-2.4.1.2, SD-2.4.1.4, and Part PM.

SD-5.6.2.2 Lyophilizer Chamber

(a) The interior surfaces of the lyophilizer chamber (chamber vessel) are considered process contact surfaces.

(b) The lyophilizer chamber includes all necessary fittings and closures (e.g., doors, bellows, isolation valves). The chamber floor shall be self-draining.

(c) The surface finishes of the chamber internal surfaces (i.e., door, walls, ceiling, and floor) shall be specified by the owner/user using the designations in Table SF-2.4.1-1.

(d) Where the chamber interfaces with the clean room or isolator, the surfaces shall meet the owner/user's specified requirements.

SD-5.6.2.3 Condenser Vessel

(a) The condenser vessel, used to contain the condenser heat exchanger, is connected to the chamber vessel and may be separated by a main isolation valve.

(b) All surfaces shall be self-draining.

(c) In systems designed with backstreaming prevention (i.e., prevention of reverse flow from the vacuum pumps), the condenser vessel is downstream of the chamber. The condenser vessel surfaces are not process contact surfaces and do not have surface finish requirements.

(d) In systems not designed with backstreaming prevention, the condenser vessel surfaces are process contact surfaces. The surface finishes of the condenser vessel shall be specified by the owner/user using the designations in Table SF-2.4.1-1.

SD-5.6.2.4 Lyophilizer Shelves

(a) The flat surfaces of shelves supporting containers of product (e.g., vials containing product) are considered process contact surfaces.

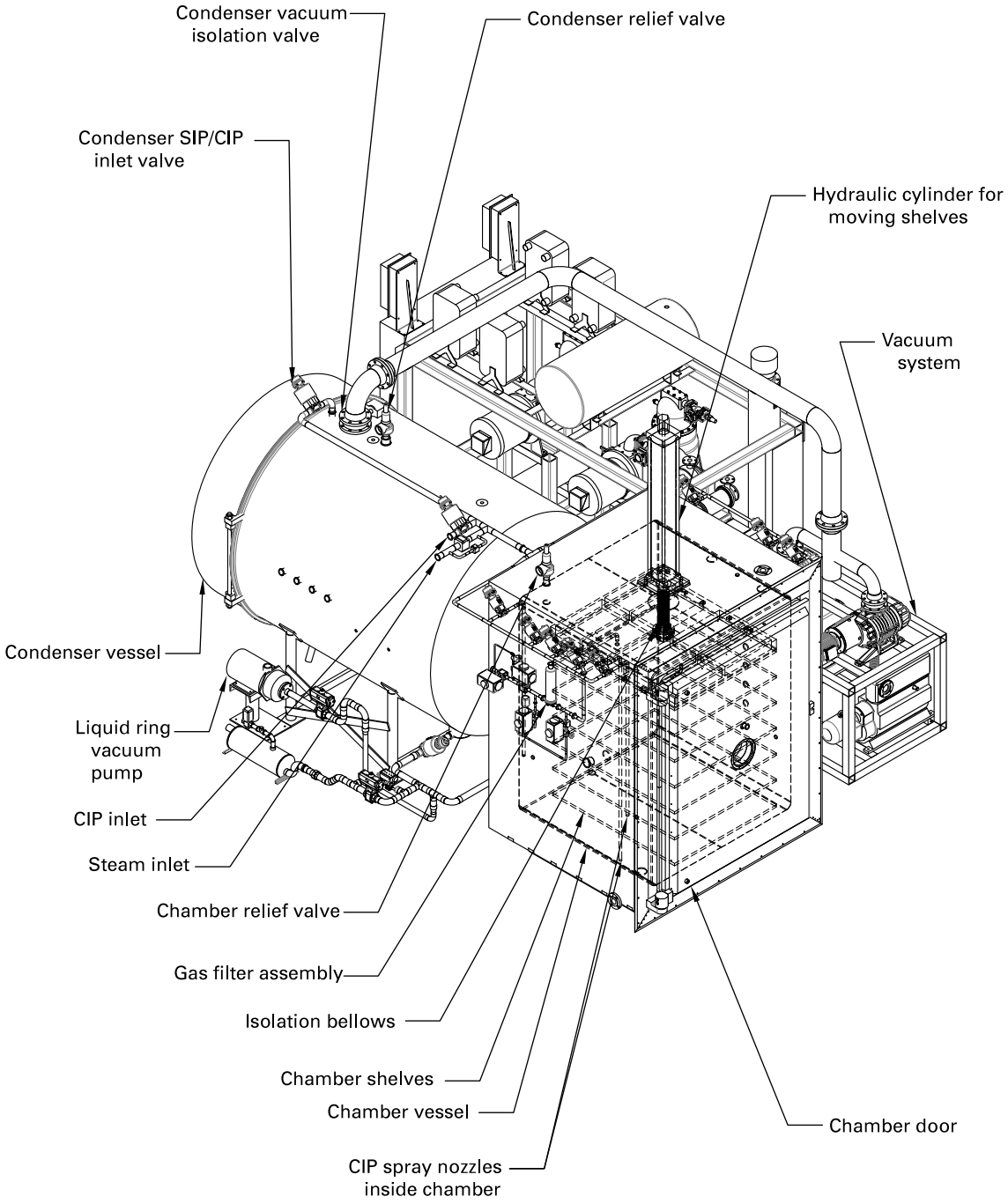
(b) The flat surfaces of shelves are considered product contact surfaces if product without containers is placed directly on the shelves.

(c) Surfaces of the structural components of the shelves are considered process contact surfaces.

(d) The shelf heat transfer performance depends on shelf flatness. The loading/unloading and initial container closure performance require the shelves to be level. Therefore, shelves are not required to be sloped. Methods other than self-draining may be required to remove residual CIP liquid (e.g., collapsible shelves may be contracted to remove residual CIP liquid from shelf surfaces followed by a process that facilitates drying, such as SIP followed by a vacuum hold).

(e) The surface finishes of shelves shall be specified by the owner/user using the designations in Table SF-2.4.1-1. A rougher surface may be specified for the bottom side of the shelves by the owner/user to meet process requirements (e.g., stopper adhesion prevention).

Figure SD-5.6.2-1 Typical Lyophilizer Component Assembly



SD-5.6.2.5 Vacuum Systems

(a) The lyophilizer vacuum pumps and condenser cooler establish a pressure gradient during lyophilization from the chamber vessel through the condenser vessel resulting in single-direction flow toward the lyophilizer vacuum pumps. To maintain an environment appropriate for aseptic processing in the chamber vessel, the vacuum system shall prevent reverse flow (backstreaming).

(b) The lyophilizer vacuum pumps are not hygienic components and should be designed to be outside the sterile boundary.

(c) Where vacuum pumps for wet service (e.g., liquid ring vacuum pumps) are used to evacuate air/vapor from the chamber and condenser vessels, they should be located outside the sterile boundary.

SD-5.6.2.6 Isolation Bellows

(a) Isolation bellows are employed to isolate nonhygienic moving components from the lyophilizer sterile boundary.

(b) The surfaces of the bellows and its mounting connections exposed to the inside of the lyophilizer are considered process contact surfaces and should be assessed for cleanability. The bellows shall be extended during the cleaning cycle to provide access to all exposed process contact surfaces.

(c) The bellows shall be sealed at each end to isolate the inside of the lyophilizer from external conditions. Bellows may be bolted or welded into place. A bellows sealed by a bolted flange connection with an O-ring seal within the chamber vessel facilitates replacement and maintenance. The inside of the bellows may be evacuated, vented, or pressurized to facilitate retraction or extension of the bellows. The lyophilizer may be provided with a leak-test system to ensure the bellows are intact.

(d) When specified, the bellows shall be suitable for sterilization and shall allow for full penetration of the sterilizing agent at all surfaces inside the sterile boundary.

SD-5.6.2.7 Internal Moving Parts. The following should be considered in the design of moving parts (e.g., the raising and lowering of the shelves) within the chamber and/or condenser vessels:

(a) Nonmetallic material (e.g., PTFE, PEEK, UHMWPE) may be used for moving parts in order to reduce friction. The selection of the material should consider minimizing particle generation.

(b) Contact surfaces between moving parts shall be exposed to solutions used for cleaning and bioburden control.

(c) A bellows may be used to isolate the chamber and/or condenser from moving parts that are not of hygienic design.

SD-5.6.2.8 Spray Devices

(a) Spray devices are used in lyophilizers to facilitate the cleaning of surfaces inside the chamber and condenser vessels. Spray devices in the condenser vessel may also be used for directing spray at the condenser cooler to facilitate defrosting of the condenser cooler.

(b) Spray devices designed for cleaning should provide sufficient flow and force to clean flat surfaces (e.g., shelves) by direct spray. Cleaning the internal surfaces of a lyophilizer by direct spray may require a supply pressure and flow rate that are substantially higher than are typical for cleaning an empty vessel. The supply pressure and flow rate should meet the manufacturer's recommendation for these spray devices.

(c) Both static and dynamic spray devices are acceptable for use in lyophilizers. The use and application of a particular spray device design should be agreed upon among the owner/user, lyophilizer manufacturer, and CIP system integrator. The number of spray devices may be reduced if the shelves are allowed to move during cleaning. Spraying of shelves should be designed to avoid the interference of spray streams of opposing directions.

(d) The use of threaded connections for spray devices shall only be used when agreed upon by the owner/user.

(e) Spray devices shall meet the provisions of SD-3.9.2.

(f) Spray device design, location, and orientation shall ensure appurtenances (e.g., nozzles, bellows, shelf supports, and hoses) are exposed to complete spray coverage.

SD-5.6.2.9 Gas Filter Assemblies

(a) For the purpose of this paragraph, the gas filter assembly is defined as those filters installed for the purpose of filtering process gases supplied to the lyophilizer. The filter assembly includes the filter media, seals, housing, and connected tubing.

(b) The last filter in the path of the gas to the lyophilizer (proximal filter) shall be part of the sterile boundary and be designed for the chosen means of bioburden reduction (e.g., SIP or VHP). This filter shall be a sterilizing-grade filter. If a redundant sterilizing filter is used, both filters shall be included within the sterile boundary.

(c) Filter assemblies that are steamed in place shall be designed to

(1) limit the pressure drop across the filter to within the manufacturer's specifications in the specified flow direction

(2) permit temperature monitoring in a location representative of the coldest location

(3) accommodate the integrity testing of the proximal filter, either in situ or out of place

(d) If CIP of the gas filter assembly is specified, provisions shall be made in the design for removal of the filter element(s) prior to the CIP. Filter elements shall be reinstalled prior to sterilization of the filter assembly.

SD-5.6.2.10 Doors and Door Seals

(a) Lyophilizer doors and door seals shall be designed to withstand vacuum, cleaning, and sterilization conditions.

(b) Lyophilizer doors shall be accessible, cleanable, and replaceable and should be capable of undergoing inspection without dismantling.

(c) For multiple-door systems, the doors shall be interlocked to allow the opening of only one door at a time during normal operation.

(d) Doors and locking hardware that interface with the clean room should not be retracted to uncontrolled space.

(e) Both sliding and swing door designs are acceptable.

(f) Door seals can be made with either static or inflatable seals. Static seal grooves that hold the seal may be on either the door or the chamber.

(g) The seal groove may be set back from the chamber flange edge to keep the seal in position during vacuum conditions.

(h) Compression of a single static seal to achieve a metal-to-metal contact is preferred to avoid a gap between door and chamber vessel.

(i) The door static-seal design shall provide access for manual sanitization as the seal face under compression does not permit penetration of sterilizing agents.

(j) A combination (static and inflatable) seal design with the static seal circumscribing the inflatable seal provides for penetration of sterilizing agents across the sealing face of the inflatable seal.

(k) Door seal lubricants shall not be used in aseptic processing applications.

(l) Refer to Part SG for specifications of seals used in bioprocessing.

SD-5.6.2.11 Valves

(a) Valve design and selection for service shall follow SG-3.3.2.3(a) and Part SD as appropriate. The application of a specific valve type for a given service should be agreed on by the manufacturer and owner/user.

(b) Hygienic valves shall be used inside the sterile boundary.

(c) Diaphragm valves are acceptable for hygienic fluid service.

(d) Butterfly valves may be used as part of the sterile boundary when piping/tubing is larger than 2 in. in diameter.

(e) Ball valves may be used outside the sterile boundary to establish positive isolation.

(f) Pressure relief devices or rupture disks of hygienic design may be used as part of the sterile boundary.

(g) If the lyophilizer is designed for isolation between the chamber and condenser, the isolation valve may take the form of a mushroom valve, butterfly valve, or other proprietary valve design.

SD-5.6.2.12 Instruments

(a) All instruments within the sterile boundary should comply with all applicable sections of Part PI, including PI-2.1, PI-2.1.2(c), PI-2.1.2(f), and PI-2.2.2.

(b) Instruments in process contact should be of hygienic design.

(c) Instrument probe surfaces and side port penetrations shall be oriented for self-drainage.

(d) Instruments installed within the sterile boundary should be designed for CIP and sterilization. Instruments not designed for CIP should be removed for cleaning and reinstalled for sterilization.

(e) Locations with product-sensing instruments (e.g., thermocouples and RTDs) and wire lead-throughs should be considered when designing for cleaning and sterilization.

(f) Instrumentation with integral seals or diaphragm seals is preferred within the sterile boundary. The risk of using instrumentation without integral seals or diaphragm seals (e.g., Pirani gauges) should be assessed based on the risk to product quality as determined by the owner/user.

SD-5.6.3 Sterile Boundary. For the purpose of identifying areas that should be exposed to sterilizing agents, the following areas within the chamber and condenser vessels define the sterile boundary as indicated in Figure SD-5.6.3-1:

(a) the inside surfaces of the chamber vessel to the chamber door isolation seal.

(b) the inside surface of the condenser vessel to the condenser door isolation seal.

(c) the chamber and condenser drains to the first isolation drain valve.

(d) the vacuum pump inlet connection in the condenser vessel to the first isolation vacuum valve closest to the condenser vessel.

(e) the vacuum break/gas inlet line to the sterile gas filter. If redundant sterilizing filters in series are used, the sterile boundary ends at the membrane of the filter farthest from the chamber vessel.

(f) the CIP/SIP inlet lines to the first CIP/SIP isolation valve that is closed during the lyophilization process.

(g) the sealing surface on all instruments connected to the chamber and condenser vessels.

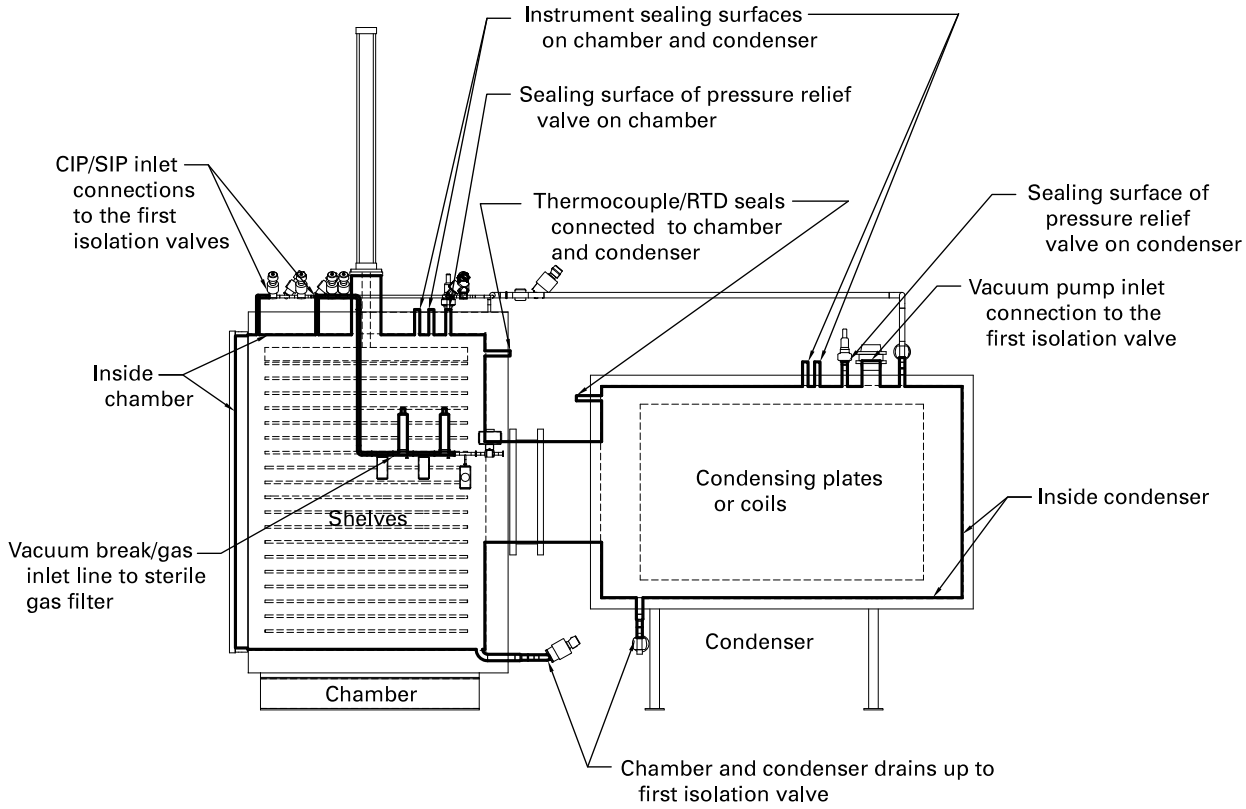
(h) thermocouple/RTD seals connected directly to the chamber and condenser vessels.

(i) the exposed surface of the pressure relief valve or rupture disk.

SD-5.6.4 Internal Connections and Fasteners

(a) Threads sealed by an O-ring or hygienic gasket are acceptable. The use of exposed threads within the lyophilizer sterile boundary should be avoided. If other means of fastening are not practical, the use of exposed threads may be permitted with the agreement of the owner/user. The

Figure SD-5.6.3-1 Lyophilizer Sterile Boundary



surfaces of exposed threads should be among those assessed for cleaning and penetration of sterilizing agents.

(b) For process contact surfaces, the use of pins, clevis rods, snap rings, and clips may be required to mount hardware inside the sterile boundary but should be minimized and only be used if agreed on by the owner/user. The surfaces of these fasteners should be among those assessed for cleaning and penetration of sterilizing agents.

(c) Socket head cap screws and counterbored holes inside the sterile boundary shall only be used with the agreement of the owner/user.

SD-5.6.5 CIP of Lyophilizers

(a) Systems used to clean lyophilizers shall comply with SD-6.3.3(a), SD-6.3.3(b), and SD-6.3.3(c). Cleanability requirements of SD-2.4.2 are applicable to lyophilizers except for SD-2.4.2(b)(1), which does not apply to lyophilizer shelves.

(b) It is accepted practice to use water as the CIP fluid for cleaning water-soluble compounds. Water for injection shall be used for the final rinse in aseptic processing applications.

(c) The chamber vessel, which includes internal shelves, should be cleaned via internal spray devices designed to provide coverage of targeted surfaces. Risk to product quality should be considered when determining the required coverage. The acceptance criteria for coverage shall be agreed to by the manufacturer and owner/user. Nonmandatory Appendix M provides an acceptable procedure for spray device coverage testing.

(d) The process contact surfaces within the condenser vessel may be cleaned via internal spray devices to provide the coverage agreed on between the manufacturer and owner/user.

(e) Internal liquid distribution piping shall be sloped to meet the requirements of GSD2 to facilitate gravity draining.

(f) External liquid distribution piping shall be designed with valve actions that facilitate gravity draining. The pipe slope shall meet the requirements of GSD2.

(g) The liquid level in the chamber and condenser vessels should be minimized during once-through CIP by correct sizing of the drain and by providing slope to the respective drain. A CIP drain pump may be used to assist draining of the chamber and condenser vessels.

(h) When recirculated CIP is used, the following requirements apply:

(1) Recirculated systems, including pump casing(s), shall be drainable.

(2) Recirculated systems shall be capable of removing residual chemicals and debris during the final rinse.

(i) The chamber and condenser vessels shall be self-drainable.

(1) Process contact surfaces shall be sloped to meet the requirements of GSD3 for drainage of CIP fluids and to prevent the collection of condensate during the steaming processes.

(2) Interior surfaces of nozzles penetrating the vertical walls of the vessel shall be sloped to meet the requirements of GSD3.

(3) The floor of the vessel shall be sloped toward the drain connection to meet the requirements of GSD3, unless otherwise agreed to by the manufacturer and owner/user.

SD-5.6.6 Bioburden Reduction in Lyophilizers. Lyophilizers designed for bioburden control should consider the following:

(a) pressure or vacuum hold testing in preparation for the bioburden reduction process. Refer to SD-5.6.7.

(b) evacuation of air from the chamber and condenser vessels to reduce the potential for air to be trapped during the bioburden reduction process. Effective air evacuation may be achieved through the use of a liquid ring vacuum pump or similar.

SD-5.6.6.1 Steam-in-Place. When designing lyophilizers for steam-in-place

(a) steam should enter the lyophilizer at only one point at a time to minimize the potential to trap air or condensate. If steam needs to enter through multiple locations simultaneously, the design should create flow paths that avoid air entrapment. The design should ensure that condensate will freely flow toward low-point drains.

(b) a dual control design may be used to deliver high steam flow rates that are often required during the heating phase and to maintain tight control of temperature and pressure during the exposure phase. For example, one regulator and/or control valve may be used for the heating phase and a separate regulator and/or control valve may be used for tight control during the exposure phase.

(c) a vacuum drying phase should be used to eliminate any condensate remaining within the sterile boundary following SIP.

(d) if cooling and drying are accomplished with the introduction of a process gas with open drains, a positive pressure differential shall be maintained to preserve the sterile boundary during this operation.

(e) temperature monitored throughout the SIP cycle should include coldest (worst-case) locations. If routine monitoring of worst-case locations is not practical, the temperature of locations that have been correlated to the actual worst-case locations may be monitored instead.

(f) to minimize cold locations during SIP, horizontal penetrations should be sloped to allow condensate to drain.

SD-5.6.6.2 Hydrogen Peroxide Sterilization. When designing lyophilizers for sterilization with hydrogen peroxide gas under vacuum

(a) the system should be designed to be dried and have a surface temperature that meets the supplier's specification for the hydrogen peroxide supply system [typically 59°F (15°C) and 176°F (80°C)] prior to the start of the sterilization process.

(b) the system should be designed to verify that the residual hydrogen peroxide levels are below the established thresholds, after the sterilization process has been completed. Threshold levels should be agreed on by the owner/user for both operator's safety and the potential impact on the product quality.

SD-5.6.7 Leak Rate

(a) Lyophilizers designed for aseptic lyophilization processes shall be designed to meet leak-rate testing criteria as agreed to by the owner/user. The sterile boundary should be leak tested before aseptic operations begin. The leak rate is calculated as follows:

$$Q_L = \frac{\Delta PV}{\Delta t} \quad (1)$$

where

Q_L = leak rate, mbar-L/s
V = the lyophilizer system volume subject to the vacuum, adjusted to exclude the volume occupied by internal hardware, L
ΔP = the absolute pressure rise during the test, mbar
Δt = the test duration, sec

(b) Leak-rate testing should be performed on a clean, dry, and fully assembled and insulated system with the condenser cooler in operation to capture residual vapor. Typically, leak rates less than 0.02 mbar-L/s are acceptable for new installations. Leak-rate testing is intended to confirm vacuum integrity of the system.

(c) Leak-rate tests are performed at high vacuum conditions with an absolute pressure typically on the order of 0.01 mbar.

(d) Sufficient stabilization time will avoid misinterpretation of the vacuum leak rate due to virtual leaks. Virtual leaks are identified by a leak rate that stabilizes over time.

(e) Individual component assemblies, which are subjected to vacuum conditions, should be helium leak tested prior to final installation.

SD-5.6.8 Branch Connections

(a) The provisions of SD-3.1.2.2 are applicable to liquid-service process contact piping leading to the lyophilizer.

(b) Nozzles within the sterile boundary should be designed to allow for full exposure to the sterilizing agent.

(c) Nozzles and other appurtenances that are cleaned by liquid spraying should allow complete coverage.

(d) Lyophilizer internals should be designed to avoid low points where fluid can be trapped.

SD-5.7 Solution Preparation Systems

Solution preparation systems are used for the preparation, storage, and distribution of buffer solutions, media solutions, and other reagents used in bioprocessing, formulation, and filling operations. Systems may include components for transfer and mixing of solids and liquids (e.g., agitators, in-line mixers, vacuum transfer equipment, intermediate bulk containers). The systems may also include tanks/vessels for solution preparation and for solution storage. Systems may also include components designed specifically for bioburden reduction or solution conditioning. Examples of these include filtration systems and thermal conditioning systems such as ultra-high-temperature/high-temperature short-time (UHT/HTST) systems.

SD-5.7.1 Operating Capabilities and System Function. The owner/user shall define which process contact surfaces require cleaning and/or sanitization (e.g., vessel internals, solids transfer equipment, solution transfer lines, vent lines) and which cleaning methods (e.g., CIP, COP, water rinses) and/or sanitization methods (e.g., chemical sanitization, SIP, hot-water flush) are to be used. When a solution sterilizing-grade filter is SIP'd with the system, the sterile envelope shall include the filter membrane. In practice, this requires a design that achieves sterilization conditions across the filter membrane.

For systems that require closure, controls to achieve and maintain a functionally closed system after mixing may include

(a) equipment to achieve required bioburden reduction in prepared solutions (e.g., sterilizing-grade filters, HTST, sterilization vessels)

(b) technologies that prepare equipment for use (e.g., CIP, SIP, use of gamma-irradiated single-use components)

(c) procedures and designs to maintain control during processing and holds after bioburden reduction (e.g., system closure after sanitization, drying equipment for holds, and hold and processing time limits)

SD-5.7.2 System Design

SD-5.7.2.1 Contamination Control. Measures should be taken to contain powders that are added to mixing tanks and to contain aerosols that may be generated during solution preparation to mitigate the risk of cross-contamination between operations. The owner/user shall assess the risk of cross-contamination between operations. Controls to mitigate the risk of cross-contamination may include

(a) physical separation (e.g., separate rooms, isolators)

(b) airflow controls (e.g., dust collection systems, filtration of circulated air, flow direction)

(c) use of closed-process systems

(d) temporal separation

(e) procedural separation

The owner/user shall specify requirements for mitigation of risks from environmental contamination and growth of adventitious agents such as bacteria, fungi, and viruses in solutions during processing and hold times.

SD-5.7.3 Design for Bioburden Reduction

SD-5.7.3.1 Filters. Systems used for buffer distribution may require a filter to reduce bioburden during transfers to downstream systems, particularly when the buffer is growth-promoting or is transferred to a holding system before use.

SD-5.7.3.2 Preparation Tanks. Preparation tanks may be designed for operations that are briefly exposed to the room environment (e.g., addition of reagents through an open port) when appropriate measures are exercised for bioburden control and other particulate contamination (e.g., filtration to reduce bioburden after reagents are dissolved).

SD-5.7.3.3 Tanks for Long-Term Storage. Tanks used for long-term storage of solutions should be designed to be sterilized unless the intended solution is bactericidal or bacteriostatic.

SD-5.7.3.4 Thermal Sanitization/Sterilization. Systems used for aseptic processing shall have all surfaces that contact sterile process streams downstream of the bioburden control device capable of being sterilized. This includes interfaces between components that are sterilized separately.

SD-6 PROCESS SUPPORT SYSTEMS (19)

SD-6.1 Cabinet Washers

SD-6.1.1 General. This section describes the requirements for washers that are designed to clean various materials and components such as glassware, drums, containers, hoses, pallets, and accessories (washable items) that are not cleaned in place. Requirements in this section are intended to be applied to cabinet washers, but may be applied to other types of washers as appropriate.

(a) Cabinet washers shall be fully automatic and should be capable of multiple cycle types for various load conditions. Cabinet washers may be designed with an integrated chemical addition system or receive cleaning solutions from a CIP system.

(b) Cabinet washers shall include racks or holding systems designed to enable repeatable exposure of washable items to cleaning solutions.

(c) The documentation requirements of GR-5 are applicable to process contact components/instruments of cabinet washers.

SD-6.1.3 Operating Capabilities and System Function

(a) Cabinet washers shall be capable of delivering cleaning solutions and of the subsequent rinsing of cleaning solutions from washed surfaces.

(b) Cabinet washers should have the ability to perform the following general phases during the cycle:

(1) prewashing
(2) washing
(3) rinsing
(4) final rinsing
(5) drying with heated filtered air
(6) cooling with filtered air

SD-6.1.3.1 Rinse Requirements

(a) The final rinse step may be performed using recirculated water integrated with drain steps or as a single-pass rinse (or series of single-pass rinses) to remove residual cleaning solutions. The final rinse water at the outlet of the washer shall meet the owner/user's acceptance criteria (e.g., conductivity, total organic carbon, cycle time).

(b) The ways of providing a single-pass rinse include

(1) direct connection supply from a utility water system with hygienic safeguards to prevent backflow. If a direct utility connection is used, the design should mitigate the effect of variation in supply pressure (e.g., due to draw by other users) and its impact on the flow rate.

(2) use of a water break-tank. The break-tank shall be self-drainable and vented. Rinse water from the break-tank shall not contribute to the soiling or bioburden load in the cabinet.

(c) The hydraulic conditions (i.e., pressure and flow rate) for the rinsing phases shall be consistent with those established for washing phases to ensure consistent rinsing of the washable items, the chamber interior, and the complete hydraulic circuit.

SD-6.1.4 System Design

(a) Materials of Construction

(1) Process contact surfaces shall comply with the requirements of SD-2.4.1.

(2) All welded metallic process contact surfaces shall be passivated in accordance with SF-2.6.

(3) External surfaces of the washer cabinet shall be fabricated with material that is resistant to cleaning and sanitizing agents as specified by the owner/user.

(4) Process contact polymeric materials shall comply with Part SG and Part PM.

(5) Process contact metallic materials shall comply with Part MM.

(b) Surface Finish. The surface finishes for the interior surfaces of the chamber, wetted process contact tubing, and exterior surfaces exposed to cleaning solutions shall be specified by the owner/user using designations provided in Table SF-2.4.1-1. Electropolishing is not required unless specified by the owner/user.

SD-6.1.4.1 Wash Chamber

(a) The interior surfaces of the chamber are considered process contact surfaces. These surfaces, which have the potential to drip onto washed items, shall have complete spray coverage (see SD-6.1).

(b) The interior of the chamber shall comply with SD-2.4.2. Internal surfaces that may be difficult to clean (e.g., wheels, cabling, external surfaces of exposed hygienic-clamp connections) should be minimized and assessed for the risk to product quality.

(c) All internal surfaces shall be sloped for drainability with a slope agreed on between the owner/user and fabricator. Where possible, a slope of not less than $\frac{1}{8}$ in./ft (10 mm/m) is recommended.

(d) External surfaces should be insulated to minimize heat transmission and promote cleaning and drying.

(e) Breastplates, reinforcing pads, doubler plates, poison pads, etc., which are required for welding dissimilar material to the chamber, should be of the same material as the chamber.

(f) Lubricants shall not be used where they may come in contact with cleaning solutions or washable items.

SD-6.1.4.2 Chamber Openings

(a) Nozzles that are designed to be cleaned by a spray device should have the smallest *L/d* ratio practical. For non-flow through nozzles, an *L/d* of less than 2 is recommended (see Figure SD-3.4.2-1).

(b) Sidewalls and chamber-ceiling nozzles should be flush with the interior of the chamber (see Figure SD-3.4.2-5).

(c) Blank covers shall have the same surface finish as the chamber internals.

(d) Process valves shall meet the requirements of SG-3.3.2.3.

(e) Sample valves shall meet the requirements of SD-3.11.2.1.

(f) Sight glasses on the chamber shall meet the requirements of Figure SD-3.4.6-1. Sight glasses should be designed with the smallest *L/d* practical and should incorporate cleanable seal designs.

SD-6.1.4.3 Washer Door and Door Seals

(a) Washer doors and door seals shall be designed to prevent wash fluid leakage during the entire wash cycle.

(b) For multiple-door systems, the doors shall be interlocked to allow the opening of only one door at a time for loading and unloading.

(c) Both sliding and swing door designs are acceptable.

(d) Doors that interface with classified clean rooms should not be retracted to an uncontrolled space.

(e) Construction of the door shall meet SD-2.4.1.

(f) The internal surface finish of the door shall be the same as specified for the chamber internal surfaces.

(g) Solid or inflatable door seals shall meet the requirements of SD-2.4.1.1 (e.g., conforming to FDA 21 CFR 177 and USP Section <88> Class VI).

(h) Refer to Part SG for specifications of seals.

SD-6.1.4.4 Internal Components

(a) Washer cabinet internal components include loading racks and supports, thermowells, spray manifolds, etc.

(b) Weld-in thermowells [see Figure SD-3.4.3-2, illustrations (e) and (f)] shall have the same finish as the chamber internals.

(c) Loading racks/accessories

(1) The racks are designed to support the cleaning of specific washable items. The rack design should be verified to provide complete spray coverage for washable items defined by the owner/user in an arrangement for which the loading rack is designed.

(2) Loading racks shall secure the washable items during the wash cycle.

(3) Loading racks may be designed to distribute rinse and cleaning solutions to interior and exterior surfaces of the washable items.

(4) Loading racks should have a surface finish that meets the surface finish requirements of the chamber. Surface finish verification may not be possible for all components of the loading rack.

(5) The loading rack manifold fabrication shall comply with SD-3.1.2.3.

(6) Loading rack design considerations should include the disassembly required for inspection and maintenance.

SD-6.1.4.5 Air Drying, Intake, and Exhaust Systems. Where specified by the owner/user to dry washed items, the following provisions are applicable:

(a) The air intake system shall be filtered. A prefilter and HEPA filter system are recommended to protect the washed items.

(b) The drying system shall provide heated, filtered air to the chamber, the hydraulic circuit, and in-line components.

(c) The filtered air used for drying may be supplied from a controlled or uncontrolled environment.

(d) Temperature and humidity variability of intake air should be considered in system design.

(e) The exhaust ducting should be designed to direct condensate to a drain.

SD-6.1.4.6 Spray Systems. Design of spray systems in cabinet washers requires the integration of manifolded spray devices in the chamber with those installed in loading racks. Spray systems in cabinet washers may use both static and dynamic spray devices that comply with SD-3.9.

(a) Loading-rack spray systems may have interchangeable spray devices to accommodate a variety of washable items in a single rack.

(b) Translational/reciprocating spray devices in the cabinet using mechanical devices (e.g., pulleys and PTFE sheathed cables) should be designed for ease of disassembly for inspection and maintenance.

(c) Mechanical devices used in the chamber shall be compatible with the process fluids and shall be cleanable.

SD-6.1.4.7 Chemical Addition Systems. When cleaning solutions are not provided by a CIP system, the following provisions are applicable:

(a) A number of chemicals that function as pH adjusters, emulsifying agents, and/or soil removers may be added during the cabinet washer cycles. The design considerations should include positive identification of each chemical delivery and connection.

(b) Concentrated chemicals may be delivered to the washer from bulk distribution systems or from local holding containers. The design of concentrated chemical delivery and storage systems should consider minimizing human contact.

(c) Design of concentrated chemical storage and distribution components should consider safety provisions enumerated in SD-6.3.4(d).

(d) The design should include monitoring of adequate bulk chemical supply (e.g., level) for the entire wash cycle.

SD-6.1.4.8 Recirculation Pumps

(a) The pump shall have sufficient capacity (flow rate and pressure) for all spray configurations used in the washer.

(b) Pumps shall comply with SD-3.3.2.

(c) Pump seals shall comply with Part SG.

SD-6.1.4.9 Heat Exchangers

(a) Heat exchangers included in cabinet washers to heat cleaning solutions, rinse water, etc., shall comply with SD-3.6.

(b) Heat exchangers using steam or a thermal liquid may include shell-and-tube, coil, or tube types.

(c) Electric heat exchangers may be direct or indirect immersion type heaters.

SD-6.1.4.10 Instrumentation

(a) All process contact instruments should comply with the applicable sections of Part PI.

(b) The design should enable operators to monitor process parameters without having to pass through changes in room classifications.

SD-6.1.4.11 Interfaces. Where the chamber interfaces with the clean room, the external surfaces shall meet the owner/user's specified requirements.

SD-6.1.5 Design for Bioburden Control

(a) Cabinet washers shall comply with the fabrication requirements of SD-2.4.1.

(b) Tubing within the process contact boundary should be orbital-welded tubing where possible and shall comply with Part MJ.

(c) All wetted process contact surfaces shall be of hygienic design per the applicable sections of this Standard.

SD-6.1.5.1 Branch Connections

(a) The provisions of SD-3.1.2.2 are applicable to liquid-service process contact piping leading to the chamber and delivering cleaning solutions to the spray manifolds.

(b) Liquid-service branch connections with an L/d greater than 2 shall be provided with low-point drains that are opened between each phase of the washing cycle to avoid cross-contamination.

SD-6.1.5.2 Drainability

(a) The chamber drainability should be verified during fabrication. Verification methods and acceptance criteria for drainability shall be agreed on in advance by all the parties.

(b) Instrument probes and sidewall penetrations (see Figure SD-3.4.2-2) shall be sloped for drainability, unless the instruments used require horizontal mounting (see Figure SD-3.4.2-3).

(c) Loading racks shall be self-drainable.

SD-6.1.5.3 Cleaning

(a) The design should enable multiple chemical additions during the prewashing and washing processes.

(b) Cleaning solution temperature shall be controlled and monitored during washing and rinsing phases.

(c) The pressure and flow rates of cleaning solutions supplied to dynamic and static spray devices within the chamber and/or loading racks should be monitored.

(d) If cleaning solutions are recirculated during the cycle, the recirculation pump shall meet the requirements of SD-3.3.2.

(e) The design should provide final rinse water at an elevated temperature [e.g., >149°F (65°C)] for sanitization and improved drying efficiency.

(f) The system shall be designed to provide analytical verification of final rinse water quality (e.g., conductivity and/or total organic carbon).

SD-6.1.6 Design for Serviceability, Examination, and Operation

(a) Cabinet washers should be designed to enable access for inspection and service of components that are subject to wear and to allow periodic calibration of instruments.

(b) Mechanical components and instruments that require maintenance may be located in an unclassified space where the maintenance can be performed.

(c) The washer design considerations should include integration with the space where maintenance is performed (e.g., minimizing moisture due to condensation).

(d) Pumps should be designed and configured to enable access for removal, inspection, and maintenance.

SD-6.1.7 Testing. The test requirements shall be defined by the owner/user and agreed to by the manufacturer, and may include tests beyond those described in this section. These tests apply to newly installed systems and to modifications of existing systems (e.g., the addition of a loading rack to an existing system).

SD-6.1.7.1 Spray Device Coverage Test. Cabinet washers should be tested to confirm complete spray coverage of the specified washable items and the interior process contact surfaces of the washer chamber. The spray device coverage testing described in SD-7.1 is applicable to cabinet washers. The spray device coverage test procedure described in Nonmandatory Appendix M may be used for cabinet washers with the following additional considerations:

(a) Testing should include empty configurations (i.e., loading rack only).

(b) Testing should include racks loaded to capacity.

(c) It is acceptable to bypass the drying phase of the cycle to examine the wet conditions. If parts are dry when inspected, they should be gently rewetted with ambient or cold water to observe any residual riboflavin fluorescence.

(d) The sequence in which parts are examined should be documented to prevent false positive results due to transfer of residual riboflavin from one washable item to a clean washable item.

SD-6.1.7.2 Drainability Test. The proposed drainability test procedure in SD-7.4 for vessels may be applied to cabinet washers with the following exceptions/considerations:

(a) It is not necessary to fill the chamber with the outlet closed. The chamber should be wetted by liquid delivered through the spray system.

(b) The chamber drainability test should be performed without drain pump assistance.

SD-6.1.7.3 Cycle Performance Test. The performance test should demonstrate the ability to clean loaded items based on an initial list of washable items agreed to by the owner/user and manufacturer. The test should verify removal of residue from surfaces and that the final rinse meets the specified water quality (e.g., an acceptable compendial water requirement) at the drain within a specified period of time. The test should verify that the process contact surfaces

within the washer are also cleaned to the same specifications used for the washable items.

SD-6.2 Steam Sterilizers/Autoclaves

SD-6.2.1 General. For this section, "autoclaves" and "steam sterilizers" shall be used synonymously. This section describes the requirements of autoclaves that are used in bioprocessing for the steam sterilization of hard, dry-wrapped, and liquid materials.

This section does not pertain to pasteurizers, ETO (ethylene oxide), VHP (vaporized hydrogen peroxide), or ClO_2 (chlorine dioxide) type sterilization equipment. The manufacturer shall define the sterile boundary of the system.

SD-6.2.3 Operating Capabilities and System Function. Autoclaves should be capable of multiple cycle types for various load conditions. Autoclaves shall only be used to sterilize the types of goods for which they are designed. The most common load types are specified in SD-6.2.3.1 through SD-6.2.3.3.

SD-6.2.3.1 Hard Goods Cycles. "Hard goods" refers to goods such as metallic instruments, containers, and glassware. Effective removal of noncondensable gases is required for effective autoclaving of hard goods. Hard goods may be wrapped or unwrapped. Unwrapped goods can often be effectively autoclaved using either a single vacuum pull or gravity air displacement. These goods can sometimes be autoclaved at higher temperatures. Multiple vacuum pulse preconditioning is required for wrapped goods to ensure proper evacuation of noncondensable gases from both the autoclave chamber and autoclaved goods. Steam sterilizers used for the processing of wrapped or porous goods shall be able to pull vacuum to levels below 1 psia [69 mbar] and maintain the vacuum with a maximum leak rate of 0.1 psi/5 min (6.9 mbar/5 min). Cooling, drying (pulse, vacuum) is an optional cycle step used to dry goods at the end of the autoclave cycle. Heated pulse drying is also recommended for the drying of porous goods such as rubber stoppers. Exhaust rates and heating rates should be adjustable for pressure-sensitive materials.

SD-6.2.3.2 Liquid Cycles. Forced air removal preconditioning is an optional cycle used to evacuate the noncondensable gases from the autoclave chamber. Liquid cooling cycles should be provided to efficiently cool the autoclave chamber. Providing the chamber with overpressure helps prevent the liquid goods from boiling over during the cooldown phase. Liquids can also be cooled by slow-rate exhaust. Heating rates should be adjustable to help compensate for differences in heating profiles of items in mixed loads.

SD-6.2.3.3 Air Filter Sterilization. An independent air filter SIP sterilization cycle should be provided for the in situ sterilization of the chamber vent filters ensuring supply of sterile air for cooldown phases of autoclave loads.

SD-6.2.4 System Design. Materials in contact with steam shall resist corrosion from steam and steam condensate. The materials shall not affect steam quality and shall not release any substances known to be toxic or that could adulterate the product. Piping/tubing and fittings shall be pressure and vacuum tight. The piping/tubing layout should be designed to eliminate dead legs within the sterile boundary. Tubing within the sterile boundary should be orbital-welded stainless steel tubing where possible and shall comply with Part MJ (Table MJ-8.4-1) acceptance criteria. All process contact surfaces within the sterile boundary including tubing, chamber, and components shall be passivated.

The autoclave shall be enclosed with paneling that is resistant to corrosion and is cleanable.

The surface finish within the sterile boundary need not exceed 35 µin. R_a (0.89 µm). Electropolishing is not required for steam sterilization systems.

Elastomers shall comply with SG-3.1.1, SG-3.1.2, and SG-3.3. Elastomers shall be resistant to corrosion and to chemical and thermal degradation. Elastomers used in autoclave applications shall be capable of withstanding pressures of a minimum of 25 psig at 266°F (1.7 barg at 130°C). Seals should meet the testing requirements specified in SG-4.2.

SD-6.2.4.1 Chamber. Autoclave chambers are pressure vessels and shall be pressure and temperature rated per the owner/user's design criteria with a minimum pressure rating of 25 psig at 266°F (1.7 barg at 130°C). The chambers shall also be vacuum rated.

For systems used in the processing of materials used in the European market, autoclaves may also be required to comply with Pressure Equipment Directive (PED) 97/23/EC and/or EN-285.

SD-6.2.4.2 Doors. Autoclave door(s) shall be accessible, cleanable, and replaceable, and should be capable of undergoing inspection without dismantling. The door seal shall be resistant to clean steam and clean steam condensate. The door on the nonsterile side shall be capable of reopening after closing without undergoing a cycle. The door(s) shall not be capable of opening during a sterilization cycle. The doors shall be constructed of materials that are resistant to clean steam and clean steam condensate. For multiple-door systems, the doors shall be interlocked to allow the opening of only one door at a time. The unloading ("sterile-side") door shall remain sealed in standby mode. Refer to Part SG for specifications of seals used in bioprocessing.

SD-6.2.4.3 Sterile Air/Vent Filters. Where the sterilization cycle requires admission of air into the chamber, the air should be filtered with a sterilizing filter (0.22 µm or less). The filter element shall be replaceable. Provisions

for the steam in place of the vent filter elements should be provided.

SD-6.2.4.4 Steam Traps. Refer to SD-3.12 for requirements of steam traps.

SD-6.2.4.5 Loading Carts/Trays. Carts and trays exposed to clean steam shall be constructed of materials resistant to clean steam and clean steam condensate. Carts, trays, and chamber shall be accessible or removable and cleanable.

SD-6.2.4.6 Valves. Valves and sealing materials located within the sterile boundary shall comply with SG-3.3.2.3. Valves within the sterile boundary are typically only exposed to clean steam service and chemical(s) used during passivation. Exposure to these conditions should be considered when selecting a valve type for this application.

SD-6.2.4.7 Check Valves. Provisions to prevent back-siphoning into the service feed systems should be considered.

SD-6.2.4.8 Jacket. The jacket shall be constructed using materials that are resistant to corrosion and degradation from steam or clean steam and clean steam condensate, as applicable.

SD-6.2.4.9 Instrumentation. Autoclave pressure and temperature shall be displayed at all doors. All instruments within the sterile boundary should be of hygienic design. Instruments shall be capable of being calibrated and replaced. The instrumentation shall include the following:

(a) Temperature. Independent temperature elements (one or two for monitoring and recording and an independent one for controlling temperature) shall be provided. The chamber temperature recording element should be located in the chamber drain. Each temperature element shall be accurate to ±0.18°F (0.1°C) with a sensor response time <5 sec. The element installation shall not affect the maximum leak rate. The temperature elements shall be temperature and clean steam resistant.

(b) Pressure/Vacuum. Pressure/vacuum instruments shall be provided. The pressure instruments shall monitor the chamber and jacket pressures. Provisions for recording chamber pressure during active autoclave cycles shall be included.

(c) Date/Time. Provisions for recording the date and time during an autoclave cycle shall be included.

(d) Recording. Recording may be achieved by paper or 21 CFR Part 11–compliant electronic means.

SD-6.2.4.10 Interfaces

(a) Drain Temperature. Waste to drain temperature shall comply with owner/user specifications. The owner/user shall specify discharge temperature requirements to the manufacturer.

(b) Insulation. External surfaces should be insulated to minimize heat transmission.

(c) Biocontainment. Special conditions such as bioseals may be required for autoclaves used in BSL-3 and BSL-4 applications. Please refer to the Biosafety in Microbiological and Medical Labs (BMBL) and Centers for Disease Control (CDC) guidelines for these special conditions.

SD-6.3 CIP Systems

SD-6.3.1 General

(a) The following terms are defined for this section:

(1) CIP circuit: the sum of paths within a process unit operation that are cleaned as part of a single CIP cycle (e.g., bioreactor, buffer hold vessel).

(2) CIP cycle: the executed recipe of rinses, washes, and air blows used to clean soiled equipment.

(3) CIP path: the specific destination contacted with cleaning solution/rinse water during a CIP cycle (e.g., spray device path, inoculum line path, addition line path). Multiple paths within a circuit may be cleaned simultaneously.

(4) clean-in-place (CIP) system: a system used in the preparation, distribution, delivery, and subsequent removal of cleaning solutions to soiled equipment.

(b) All in-circuit components of the CIP system (e.g., filter housings, pumps, vessels, heat exchangers, transfer panels, instrumentation, valving, piping) shall be designed to be cleanable, drainable, and of hygienic design appropriate for use in contact with process fluids per the applicable sections of this Standard.

SD-6.3.2 System Performance Requirements

(a) The following cleaning variables should be considered in the design of the CIP system and CIP cycle:

(1) time of exposure (contact time) to wash and rinse solutions

(2) temperature of wash and rinse solutions

(3) chemical concentration of wash solutions

(4) fluid hydraulics

(b) A CIP system should include the capability to control directly or indirectly (monitor and record if applicable) the following CIP variables:

(1) timing of CIP cycle

(2) path being cleaned (e.g., valve position indication, pressure/flow verification, manual setup verification)

(3) CIP supply temperature (or return if applicable)

(4) conductivity, volume of cleaning chemical added, or cleaning chemical concentration for wash solutions

(5) final rinse conductivity or residual cleaning chemical concentration

(6) CIP supply flow rate

(7) totalized flow (if timing not monitored)

(8) CIP supply pressure

(9) spray device rotation (if used)

(10) interruption or unacceptable decrease in flow to a path

(11) pressure of clean compressed air supply (if used in air blow)

SD-6.3.3 Operating Capabilities and System Function

(a) The CIP system shall be capable of delivering and subsequently removing cleaning solutions to soiled equipment in a verifiable and reproducible manner.

(b) The CIP system shall be capable of removing process soils to an owner/user-determined acceptance criteria.

(c) The CIP system shall be capable of removing cleaning chemicals to a verifiable amount characteristic of the final rinse solution.

(d) The CIP skid should be designed to deliver feed water, inject cleaning chemicals, heat, and supply the cleaning solution to the soiled equipment. The skid shall also be designed to remove all residual cleaning chemicals added during the cycle.

(e) The CIP distribution system shall be designed to deliver the cleaning solution to the soiled equipment. The distribution system may also return the solution to the CIP skid, if applicable.

SD-6.3.4 System Design

(a) A CIP system is a distributed system of properly integrated components.

(b) For this section, a CIP skid consists of a wash and/or rinse tank with all requisite valves, pumps, and instrumentation. Provision for separation of feed waters and wash solutions should be considered. CIP skids may be located in a fixed, centralized location or may be portable and used adjacent to the soiled equipment.

(c) The CIP system design should consider the CIP circuit volume for water consumption, location of skid in facility (if fixed), chemical consumption, waste effluent, and energy required to clean a given circuit.

(d) The design should consider hazardous operation of cycle considering choice of cleaning chemicals. Chemical segregation, spill control, addition handling, material compatibility, secondary containment, and personnel safety should be considered.

SD-6.3.4.1 Wash/Rinse Tank

(a) The wash/rinse tank(s) shall be designed and fabricated per SD-3.4. The tank(s) shall be designed for cleanability per SD-6.3.5.3 and shall be equipped with a spray device(s) per SD-3.9.

(b) If used on wash/rinse tanks, a hydrophobic vent filter shall be designed to prevent moisture accumulation in the vent filters and shall be fabricated per SD-5.4.

SD-6.3.4.2 Heat Exchanger. Heat exchange equipment shall be designed and fabricated per SD-3.6.1.

SD-6.3.4.3 Supply Pump

(a) The CIP skid should have flow control, either via pump output or by means of flow control valves.

(b) CIP supply pumps shall be designed and fabricated per SD-3.3.2. The pump design should consider the handling of a gas/liquid mixture.

SD-6.3.4.4 Return Pump

(a) CIP return pumps (if required) shall be designed and fabricated per SD-3.3.2. Centrifugal pumps are preferred for CIP return applications. If a gas/liquid mixture is anticipated, then hygienic liquid ring pumps are recommended.

(b) When a vessel is included in the circuit, CIP return pumps should be placed as close as possible to the vessel bottom outlet and at the low point of the circuit.

(c) Provision shall be made to flush through the casing drain of CIP return pumps.

(d) CIP return pumps shall be designed to maintain hydraulic balance (supply and return flow) of the CIP circuit.

SD-6.3.4.5 CIP Return Eductors

(a) For this section, a CIP "return eductor" is defined as a device that uses a motive fluid to create a pressure differential that returns the CIP solution.

(b) Special design factors shall be considered when using CIP return eductors (e.g., vapor pressure, return line size).

SD-6.3.4.6 CIP Distribution Piping

(a) General

(1) The use and application of a particular distribution design or combination of designs is to be decided by the owner/user.

(2) The use of looped headers, transfer panels, and valve types (e.g., divert, mix-proof, multiport, zero-static, and diaphragm) should all be considered in the design of the CIP distribution system.

(b) Looped Headers (see Figure SD-6.3.4.6-1)

(1) The dimension from the looped header to the isolation valve weir or seat should conform to SD-3.1.2.2 (see Figure SD-3.1.2.2-1 for details). The use of short-outlet tees or zero-static valves should be decided by the owner/user.

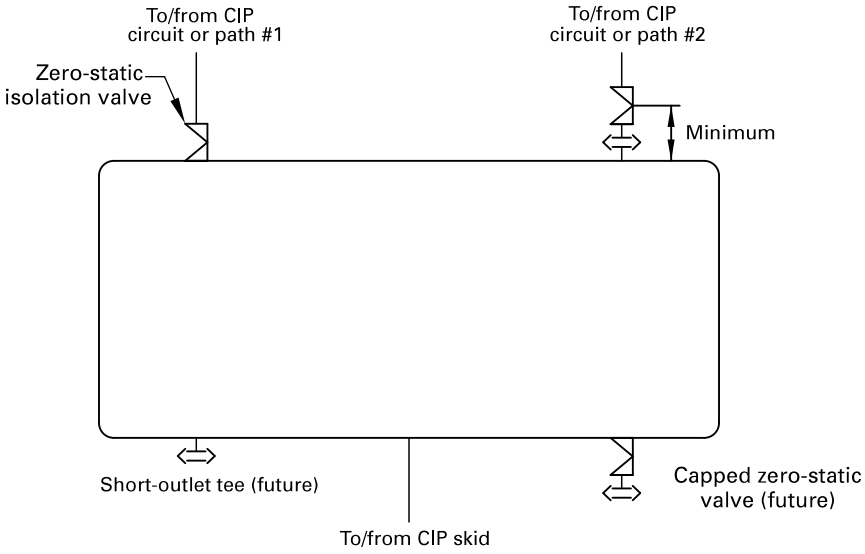
(2) Future connections (if applicable) on the looped header should use capped short-outlet tees or capped installed zero-static valves.

(3) Looped header connections should be oriented horizontally when used in CIP return applications.

(4) CIP supply header design should provide for adequate velocity in parallel cleaning paths (e.g., line size reduction in loop header).

(5) The entire looped header shall be cleaned during a CIP cycle.

Figure SD-6.3.4.6-1 CIP Looped Header (Supply or Return)



(c) Transfer Panels. Transfer panels shall be designed and fabricated per SD-3.7.1.

(d) Multiport Valves. For this section, a CIP distribution "multiport valve" is defined as a multiple valve assembly fabricated as a single body to minimize distances and maximize drainability [see SG-3.3.2.3(a) for details].

(e) Zero-Static Chains (see Figure SD-6.3.4.6-2). For this section, a CIP distribution "zero-static chain" is defined as a manifold of circuit-specific zero-static valves. Provision shall be made to flush the manifold in a zero-static chain.

(f) Swing Elbows and Piping Spools (see Figure SD-6.3.4.6-3). For this section, a "swing elbow" or "piping spool" is defined as a removable section of pipe used to provide a positive break between two paths. Swing elbows or piping spools shall be connected to adequately supported piping to maintain line slope and connection alignment.

(g) The distribution piping and components in a recirculated CIP circuit shall be hygienic for design and fabrication as per SD-3.1.2 and SD-2.4.3 .

(h) The distribution piping and components in a once-through CIP circuit or path (not recirculated) shall be hygienic for design and fabrication as per SD-3.1.2 and SD-2.4.3 upstream of the location of cleaning performance verification.

(i) CIP supply piping should be sized to ensure that the fluid flow meets or exceeds the guidelines stated in SD-6.3.5.2 and SD-6.3.5.3.

(j) The distribution circuits shall be designed such that fluid flow will maintain a positive pressure relative to the process drain, preventing backflow.

(k) CIP return piping shall be designed to maintain hydraulic balance (supply and return flow) of the CIP circuit.

SD-6.3.4.7 Instrumentation. Instrumentation and controls architecture (if applicable) should be designed to communicate, monitor, and synchronize the CIP cycle, and report CIP variables.

SD-6.3.5 Design for Bioburden Control

SD-6.3.5.1 Drainability

(a) Process vessels should be cleaned via internal spray device(s) designed to consistently expose all internal surfaces to the cleaning variables described in SD-6.3.

(b) CIP return eductors shall be designed and installed to be drainable.

SD-6.3.5.2 Cleaning: CIP Flow Rate Guidelines for Process Lines

(a) For effective cleaning, the CIP flow rate shall be sufficient to ensure that the cleaning agent and rinsing solutions wet all targeted surfaces within the CIP boundary. The CIP flow rate should be greater than the process flow rate.

(b) Table SD-6.3.5.2-1 details flow rates that ensure solution contact in straight horizontal and vertical lines for line sizes up to 2 in. (50 mm) without branches, fittings, and other in-line components. These flow rates correspond to a flow velocity of 5 ft/sec (1.5 m/s), which is well into the turbulent range and typical for CIP solutions that are within the scope of this section and all line sizes referenced in Part DT.

(c) CIP flow rate requirements should be considered in conjunction with other CIP process variables (e.g., temperature, chemical concentration, and time).

(d) Air trapped in branches may inhibit full contact of cleaning agent and rinsing solution to those process contact surfaces. The flow direction, line orientation,

Figure SD-6.3.4.6-2 Zero-Static Chain

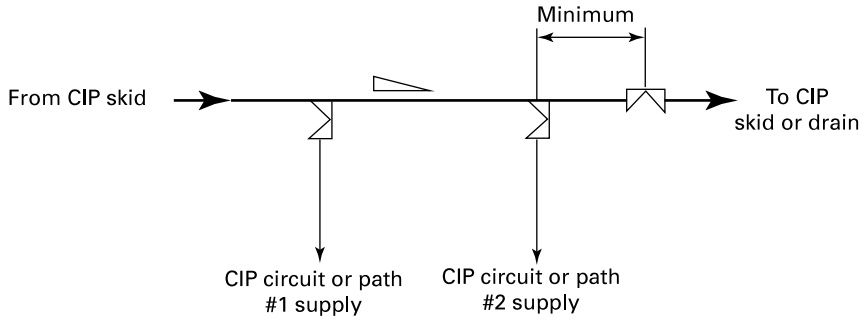


Figure SD-6.3.4.6-3 Swing Elbow Arrangement

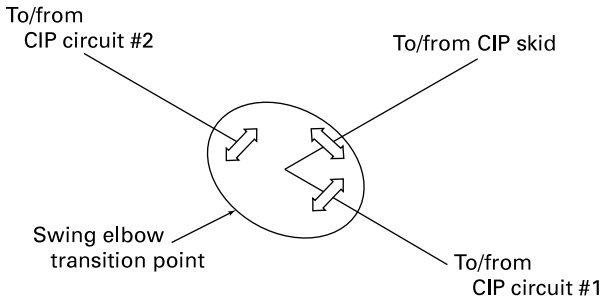


Table SD-6.3.5.2-1 Flow Rates to Achieve 5 ft/sec (1.52 m/s)

Sanitary Tube Size				Flow Rate	
O.D.		I.D.			
in.	mm	in.	mm	gal/min	L/min
0.5	12.7	0.37	9.4	1.7	6.3
0.75	19.1	0.62	15.7	4.7	18
1.0	25.4	0.87	22.1	9.3	35
1.5	38.1	1.37	34.8	23	87
2	50.8	1.87	47.5	42.8	162

line size, and presence and orientation of branches, fittings, and other equipment can have a significant influence on the flow rate required to remove air. Adequate solution contact may be achieved at a flow velocity of 5 ft/sec (1.5 m/s) with 1.5 in. (38 mm) and larger short-outlet tees (Table DT-4.1.2-5). Smaller-diameter short-outlet tees and tees with longer branches may require velocities greater than 5 ft/sec (1.5 m/s) for adequate solution contact. Solution contact in branches can be enhanced in the design by

(1) strategic use of zero-static valves

(2) flow through branch or bleeding air from branch

(3) orienting blocked branches in the horizontal position

(4) use of flush-mounted instrument fittings, short-outlet tees, gauge tees, or minimum *L/d* "instrument cups" for small lines

(5) orienting branches so the flow of the liquid entering the tee is directed toward the blocked branch

(e) Branches with risk of incomplete solution contact should be considered worst-case locations that may require local cleaning verification.

NOTE: Factors that may mitigate the risk of insufficient cleaning due to incomplete air removal from branches include

(a) CIP flow rates higher than process flow rates are likely to wet all surfaces that were soiled.

(b) Instruments or other devices protruding into the flow path may create additional local turbulence.

(c) Condensate generated during hot washes or hot rinses as part of a CIP cycle may provide some additional rinsing of surfaces.

(d) Dynamic flow conditions during route transitions and air blows may assist wetting.

SD-6.3.5.3 Cleaning: Design Guidelines for Cleaning Process Vessels

(a) Process vessels should be cleaned via internal spray device(s) designed to consistently expose all internal surfaces to the cleaning variables described in SD-6.3.

(b) The use and application of a particular spray device design to satisfy these requirements shall be decided by the owner/user. Spray devices shall be designed and fabricated per SD-3.9 (also see Figure SD-3.9.2.1-1 for static spray device design considerations).

(c) Dished-head vertical vessels should have cleaning solutions delivered with the majority of flow directed toward the upper head and sidewall area at the upper knuckle radius. Cylindrical horizontal vessels should have cleaning solutions delivered with the majority of flow directed toward the upper one-third of the vessel.

(1) If a static spray device is used, gravity provides a solution sheeting over the side wall and bottom head (vertical vessels) or lower surfaces (horizontal vessels).

(2) If a dynamic spray device is used, the device may directly spray areas throughout the vessel or rely on sheeting action.

(3) Figure SD-3.9.2.1-2 details ranges of flow recommendations for static spray devices on vertical process vessels under typical cleaning loads. The recommendations in Figure SD-3.9.2.1-2 ensure sufficient coverage.

(4) The criteria to ensure sufficient coverage on horizontal process vessels vary with geometry and size.

(d) Spray device design and location shall ensure appurtenances such as manways, baffles, dip tubes, agitator impellers, and nozzles are contacted with cleaning solution. Some appurtenances may require additional provisions for cleaning.

(e) Spray devices only ensure coverage of the exterior of installed appurtenances and equipment. If not removed during CIP, cleaning solutions shall flow through appurtenances to clean their interior.

(f) The fluid level should be minimized in the process vessel during CIP. Proper hydraulic balance (supply and return flow) of the CIP circuit and sizing of the bottom outlet valve should be considered to minimize fluid level.

(g) Vortex formation during CIP may adversely affect the operation. The installation of a vortex breaker may be required.

(h) Vortex breaker design should be decided by the owner/user. Vortex breaker surfaces shall be sloped to eliminate pooling during CIP and positioned to not adversely affect the hydraulic balance of the CIP circuit.

(i) For process vessels equipped with an agitator, the impeller should be rotated at an appropriate speed during the CIP cycle.

SD-6.3.6 Design for Serviceability, Examination, and Operation. CIP return eductors shall be designed to be removable for examination.

SD-6.3.7 Testing. During the cleaning of process vessels, sufficient exposure shall be confirmed by coverage testing per SD-7.1 at the site of equipment manufacture and/or installation.

SD-6.4 Thermal Treatment Systems

SD-6.4.1 General

SD-6.4.1.1 Terminology. The following terms are used in this section:

average residence time: the volume of the retention tube divided by the volumetric flow rate. (Average residence time should always be greater than the required residence time.)

coil heat exchanger: a coiled tube for process liquid flow, inside a shell or a second tube containing heating/cooling medium.

cooling equipment: heat exchangers and/or a flash cooler used to cool the process liquid after the retention tube.

energy recovery heat exchange system: optional equipment that takes heat from the discharge of the retention tube and uses it to preheat the incoming process liquid. These systems may have process fluid on both sides of a heat exchanger.

heating equipment: heat exchangers and/or direct steam injection equipment. Direct steam injection refers to use of a steam injector valve (typical) or a steam infusion chamber.

high-temperature short time (HTST): processing at a combination of temperature and required residence time that is designed to achieve a desired level of bioburden reduction or viral inactivation. Treatment conditions (i.e., exposure temperatures and residence times) for HTST systems range broadly, depending on the performance goal of the system.

required residence time: the minimum exposure time required at the specified temperature to achieve desired results.

retention tube: a section of tubing used in HTST/UHT systems to retain the process liquid (typically an aqueous solution) at an elevated temperature for a specified time.

ultra-high temperature (UHT): processing at temperatures above 275°F (135°C) with rapid heating and cooling and short exposure times to achieve what is generally accepted as a sterile condition.

Thermal treatment system example configurations are shown in Figures SD-6.4.1.1-1 and SD-6.4.1.1-2.

SD-6.4.1.2 Scope and Purpose. This section addresses thermal treatment systems used in bioprocessing to reduce or eliminate viable microorganisms and viruses in a liquid under continuous flow conditions while minimizing degradation of the product or a product intermediate. Thermal systems may be designed to achieve goals that do not require sterilization of the process liquid, such as inactivation of viruses or a particular bacterial species. Bio-inactivation (waste treatment) systems (SD-4.4.2) and food pasteurization systems are not addressed in the scope of this section.

SD-6.4.2 System Performance Requirements. The following system performance capabilities shall be defined:

(a) treatment temperature range

(b) required residence time at treatment temperature

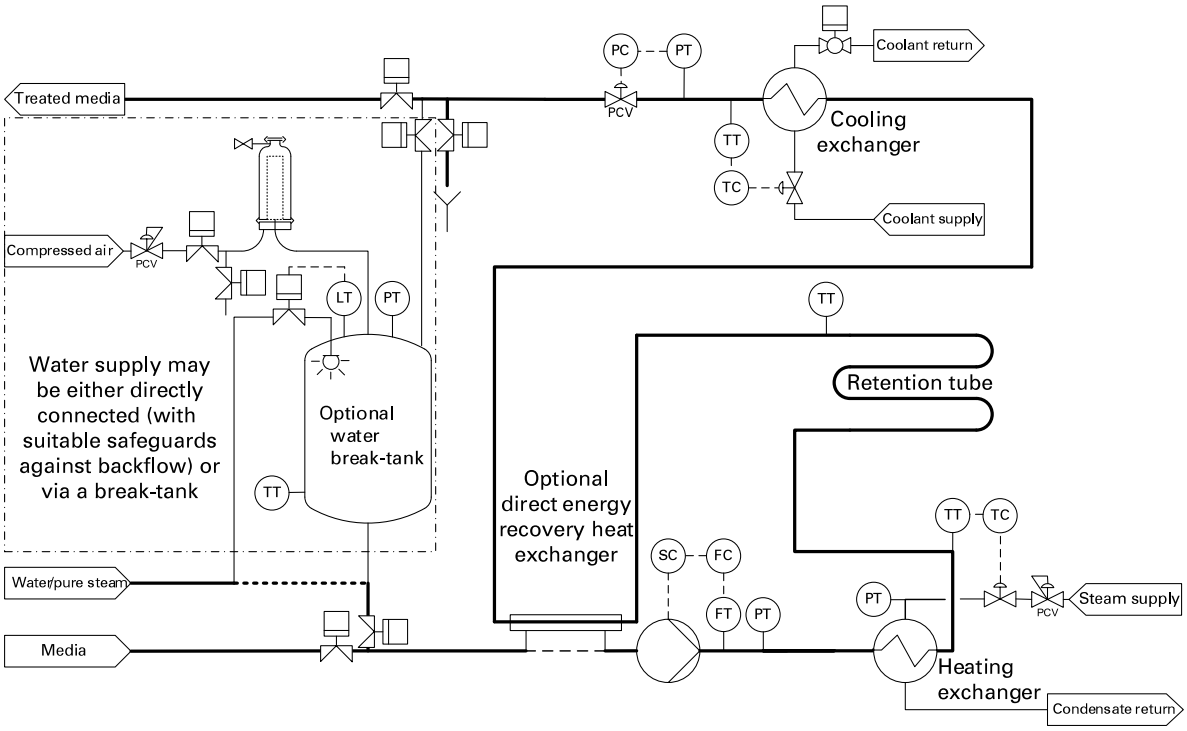
(c) process liquid flow rate

(d) discharge temperature range

(e) maximum heating surface temperature, heat transfer fluid temperature, or process liquid heating rate (°F/sec, °C/s)

Additional performance requirements may be defined by the owner/user. Additional process parameters required to confirm system capabilities, including specifying the process fluid's incoming temperature and other properties, should be provided by the owner/user.

Figure SD-6.4.1.1-1 Example of HTST Process Flow Schematic Diagram



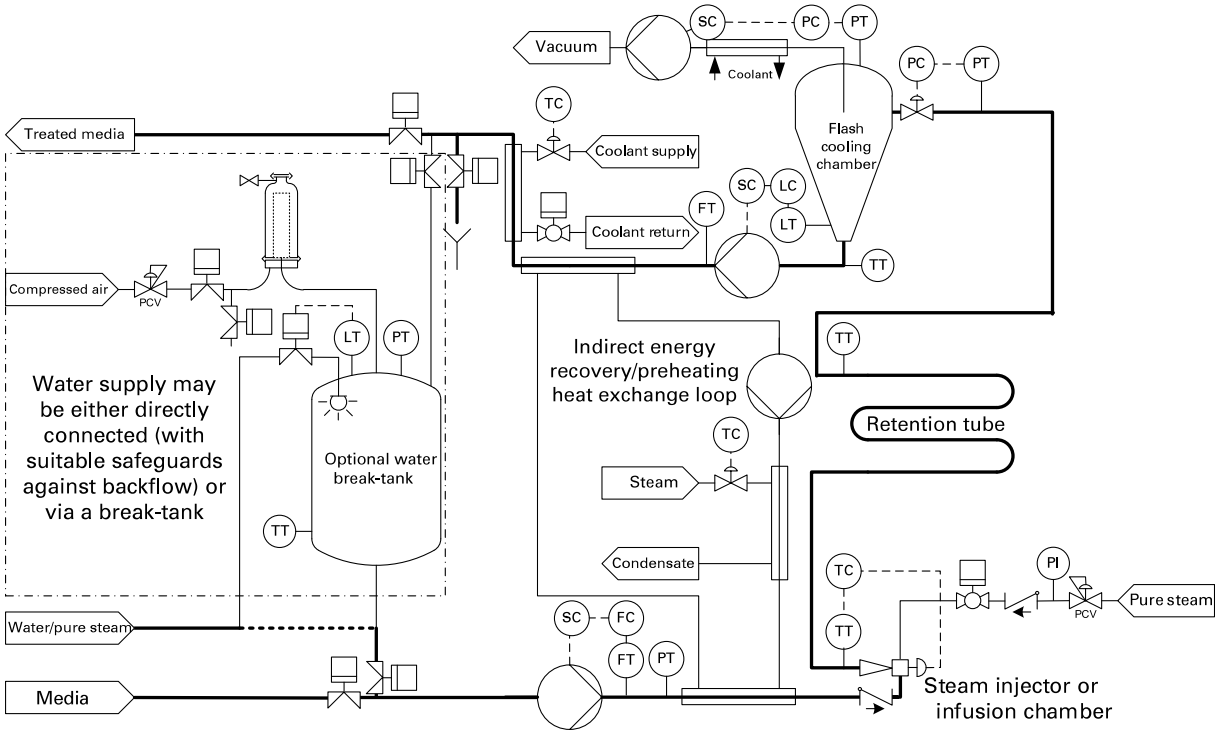
GENERAL NOTES:

(a) Only major piping and instruments are shown.

(b) Additional or alternative piping, valves, instruments, and equipment may be required for the following purposes, including:

(1) pressure safety
(2) media prefiltration with differential pressure monitoring
(3) CIP requirements
(4) SIP or hot water sanitization requirements
(5) alternative skid startup sanitization methods
(6) single-pass media startup sanitization methods
(7) low-pressure condensate return
(8) maintenance and calibration requirements
(9) energy recovery

Figure SD-6.4.1.1-2 Example of Direct Steam Injection UHT Process Flow Schematic Diagram



GENERAL NOTES:
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(3) CIP requirements
(4) SIP or hot water sanitization requirements
(5) alternative skid startup sanitization methods
(6) single-pass media startup sanitization methods
(7) low-pressure condensate return
(8) maintenance and calibration requirements
(9) energy recovery

SD-6.4.3 Operating Capabilities and System Function

SD-6.4.3.1 Priming. The system shall be capable of a priming operation to fill the piping with liquid, remove air, and establish pressure and flow control. The thermal treatment system should be primed by the process liquid to be treated or a priming liquid (e.g., WFI), or both.

SD-6.4.3.2 Thermal Sanitization. The owner/user shall define the sanitization condition (e.g., time and temperature) capabilities required for the system. UHT systems shall be designed to enable sanitization. HTST systems shall be designed to enable sanitization when the treated process liquid has the potential to be compromised by the priming activities. For a functionally closed system, the owner/user shall define which components (e.g., the receiving vessel, cooling exchanger, flash chamber) must be thermally sanitized to meet the functional closure criteria.

SD-6.4.3.3 Temperature Stabilization. Thermal treatment systems shall be designed to stabilize the temperature of the liquid before initiating forward flow to the destination. Heating, cooling, flow rate, and back pressure control loops shall be enabled and allowed to stabilize prior to heat treatment.

If the system uses a priming liquid, such as WFI, the system shall be designed to stabilize the temperature using the priming liquid and then transition to and meet the performance requirements using the process liquid. Stabilization using the process liquid should continue until all the priming liquid has been cleared from the system, at which point the system shall initiate forward flow of the heat-treated process liquid to the destination.

SD-6.4.3.4 Heat Treatment. The system shall be designed to deliver heat-treated process liquid to the destination only if the performance requirements are met. If they are not met, the system shall divert the

liquid to another destination (typically to a drain or a collection vessel). If the heat treatment conditions are not maintained, the owner/user shall specify whether the system resanitizes itself, continues diverting until the temperature and flow requirements are reestablished without resanitization, or performs a shutdown sequence.

The system shall be designed to continue heat treatment until the desired amount of liquid is treated. The owner/user shall specify whether the system flushes residual treated process liquid forward using heat-treated priming liquid to maximize recovery at the conclusion of the process batch.

SD-6.4.3.5 Post-Use Sequence. The owner/user shall specify whether the system shall be designed to perform a cold flush of the HTST or UHT equipment prior to cleaning to minimize soil buildup at the end of processing. The post-use sequence should finish by draining the system or promptly initiating the CIP sequence.

SD-6.4.4 System Design

(a) The following parameters shall be monitored and controlled by the system:

(1) heater outlet temperature

(2) cooler outlet temperature

(3) flow rate

(4) back pressure

(b) The following parameter shall be monitored by the system: retention tube outlet temperature.

(c) The owner/user shall specify whether the system shall be primed using compendial water (from a break-tank or from a backflow-protected direct water system connection) or sanitized and primed using the process liquid.

(d) The following should be considered in selection of materials used in fabrication of HTST/UHT systems:

(1) Cyclic temperature and pressure conditions may shorten the life of materials.

(2) Solutions at high temperature may accelerate the rate of metal corrosion or elastomer/polymer degradation.

(3) High-temperature operating conditions used in UHT systems may exceed the temperature ratings of typical bioprocessing equipment or components.

(e) Although UHT processing conditions are above the temperature limit specified in SD-2.3.1.1, process contact materials used for these systems shall be selected to meet the higher temperature requirements of the process.

SD-6.4.4.1 Heat Exchangers. Heat exchangers shall be designed to meet the performance requirements in SD-6.4.2 and the applicable design criteria of SD-3.6. Heat exchangers shall be designed to achieve fully developed turbulent flow conditions during process and CIP operations, on the process liquid contacting side(s) of the exchanger. Heat exchangers should be designed and operated such that the pressure of the treated process liquid is higher than the pressure of the utility or untreated process liquid during heat treatment to reduce the risk of process liquid contamination, unless the owner/user has assessed the risk of an alternate design. The owner/user should identify any requirements needed to minimize process fouling or enhance cleaning performance (e.g., minimum Reynolds number or velocity and/or maximum process contact surface temperature).

Direct energy recovery heat exchangers with process fluids on both hot and cold sides (Figure SD-6.4.1.1-1) shall be of hygienic design on both sides. Indirect energy recovery heat exchangers (Figure SD-6.4.1.1-2) shall be of hygienic design on the process fluid side.

The following types of heat exchangers may be used in thermal treatment systems:

(a) Shell and Tube. Shell-and-tube heat exchangers may be straight tube or U-tube. The effect of bypass through the bonnet drain slots and slippage between the bonnet and tube sheet shall be considered in thermal design of the heat exchanger.

(b) Coil-in-Shell. Coil-in-shell heat exchangers shall be installed in a self-drainable vertical orientation.

(c) Electric. Electric heat exchangers shall be designed to provide uniform heating (e.g., where electric current is applied directly to the process contact tube).

(d) Tube-in-Tube. Process liquid should flow through the inner tube. Process fluid may also flow through the outer tube in direct energy recovery heat exchangers.

(e) Plate-and-Frame. See cautions in SD-3.6 regarding use of plate-and-frame heat exchangers before considering use in this application.

SD-6.4.4.2 Steam Injectors

(a) Steam injectors shall introduce steam (typically pure steam) directly into process liquids.

(b) Steam injectors shall be installed such that single-phase flow is achieved at the desired outlet temperature. A sight glass installed downstream of the steam injector is recommended to confirm single-phase flow.

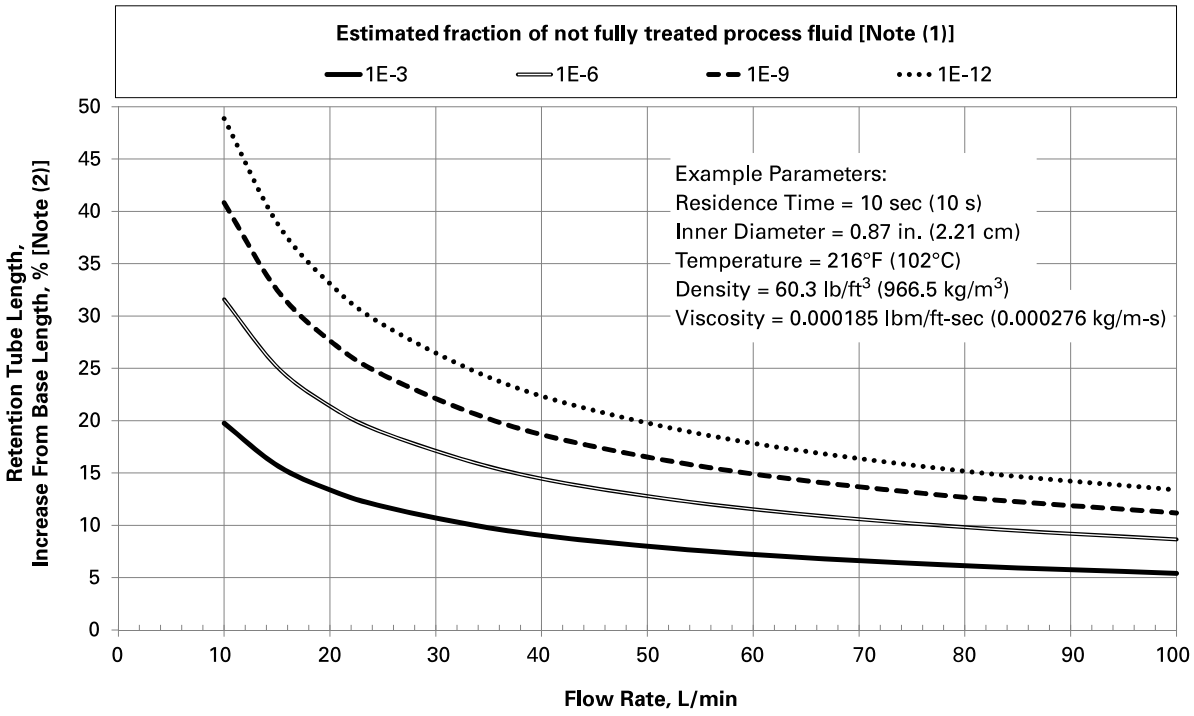
(c) Steam injectors shall be oriented to permit CIP, or designed for disassembly and cleaning out of place (COP), with agreement from the owner/user. Where the steam injection system is designed for CIP, it shall be drainable and exposed to CIP solution across the seat of the steam injection valve.

(d) Media dilution and changes in retention time due to condensate addition shall be accounted for in the system design.

SD-6.4.4.3 Flash Chambers. [Reserved for future content]

SD-6.4.4.4 Pumps. Process contact pumps used in HTST/UHT systems shall be hygienic and shall comply with SD-3.3.

Figure SD-6.4.4.5-1 Example of Additional Retention Tube Length Required to Account for Axial Mixing



NOTES:
(1) "Not fully treated" fluid is defined as fluid whose retention time is less than the required retention time.
(2) "Base length" is the average fluid velocity in the retention tube multiplied by the required retention time.

SD-6.4.4.5 Retention Tube

(a) To account for axial dispersion in the piping, the average residence time necessary to achieve the required residence time shall be defined by the owner/user.

NOTE: The average residence time should be specified so as to meet the owner/user-defined probability that each process fluid particle is retained for the required residence time. As an example, the Taylor equation for axial dispersion in turbulent flow was used to develop Figure SD-6.4.4.5-1 which shows the theoretical additional retention tube length required for a water-like liquid treated at 216°F (102°C) for 10 sec in a 1-in. (25-mm) nominal retention tube to account for axial dispersion, assuming an insignificant number of bends. In the figure, to ensure that less than 1 particle out of 1,012 has less than the 10-sec required residence time at 9.2 gal/min (35 L/min), the retention tube length would have to increase by 24%. Actual retention tube geometry, such as the number and radii of elbows, coils, or U-bends, may impact the results.

(b) The retention tube diameter should be no larger than the main system piping diameter to minimize the residence time range due to axial dispersion.

(c) The retention tube shall be designed to enable visual inspection at its inlet and outlet. The owner/user shall specify whether inspection is required for two-phase flow during operation and/or for cleaning effectiveness.

(d) The retention tube shall be designed to maintain a consistent temperature within the tube during heat treatment (e.g., the tube should be insulated and shall not have branches or tees that could result in low local temperatures).

(e) No device shall be permitted for short-circuiting a portion of the retention tube (e.g., bypass valves) to compensate for changes in the process liquid flow rate.

(f) The retention tube shall have a continuous upward slope toward the discharge complying with Table SD-2.4.3.1-1 category GSD3 to ensure that air is purged from the retention tube during operation. It shall be drainable during cleaning and/or sterilization operations.

(g) No portion of the retention tube between the inlet and the outlet temperature sensors shall be heated.

SD-6.4.4.6 Flow Control. The flow rate shall be controlled and monitored to ensure proper system operation.

SD-6.4.4.7 Back Pressure Control. The system shall be designed to ensure that pressure downstream of the heating exchanger or steam injector is above the process fluid boiling pressure, until the treated fluid has been cooled or until it reaches a flash chamber for cooling. A pressure of at least 10 psi (0.7 bar) above the boiling pressure is recommended.

SD-6.4.4.8 Instrumentation. [Reserved for future content]

SD-6.4.4.9 Interfaces

(a) The owner/user shall specify the maximum allowable discharge temperature for connections to the system outlet and drains.

(b) The owner/user shall specify whether system sanitization/sterilization ends within the system boundary or extends beyond the system boundary to upstream or downstream equipment.

(c) To design appropriate interfaces with source and destination systems, the owner/user shall provide the stated purpose of the system and the functional location within the process (e.g., upstream or downstream of sterilizing filters). The owner/user shall specify whether the thermal treatment system is intended to be implemented as part of an open, functionally closed, or briefly exposed process.

SD-6.4.5 Design for Bioburden Control

SD-6.4.5.1 Drainability. The process contact portions of the system shall be drainable per SD-2.4.3.

SD-6.4.5.2 Cleaning. Thermal treatment systems shall be designed for CIP of process contact surfaces, unless other methods are specified where necessary. Where fouling of heated surfaces may occur, cleaning and operational procedures (e.g., visual inspection) should address potential fouling of those segments of the system. When compendial water from a break-tank is used in nonrecirculating mode to condition and flush the system, provision shall be made for the sanitization of the water tank and its piping at a minimum.

SD-6.4.5.3 Chemical Sanitization/Sterilization. If chemical sanitization or sterilization of the system is required, the area within the sterile envelope or boundary shall be designed for exposure to and removal of the sanitizing agent while maintaining the sanitized state.

SD-6.4.5.4 Thermal Sanitization/Sterilization. If thermal sanitization or sterilization of the system is required, the area within the sterile envelope or boundary shall be designed for SIP or for sanitizing/sterilizing the system with hot liquid.

SD-6.4.5.5 Post-Use Storage. [Reserved for future content]

SD-6.4.6 Design for Serviceability, Examination, and Operation. [Reserved for future content]

SD-6.4.7 Testing. System performance requirements (e.g., residence time at temperature) to be tested for HTST or UHT shall be defined by the owner/user. The system design should accommodate test instrumentation required to verify the system performance and confirm the control/monitoring process performance.

(a) Temperature performance should be verified using temperature measurement devices independent of the system instruments at the inlet and outlet of the retention tube. The independent sensors should be positioned in a manner that allows measurement of the bulk fluid temperature.

(b) Average residence time should be determined. It may be determined by dividing the retention tube volume by the measured flow rate.

(c) If a surface temperature limit has been specified by the owner/user, the heating surface temperature should be verified. For electrically heated tubing, the exterior surface temperature may be measured to provide an indirect, but conservative, measure of the interior surface temperature. For steam-liquid or liquid-liquid heat exchangers, the utility-side (e.g., steam or hot water) inlet temperature may be measured to provide an indirect, but conservative, measure of the tube surface temperature.

(d) Initial testing of new equipment should document the heat supplied to meet the process requirements. The heat supplied can be documented as power input for electrically heated tubes, steam pressure for steam heat exchangers, and non-process liquid inlet and outlet temperatures for liquid-liquid heat exchangers.

(e) Initial testing of system performance should document the steady-state pump speed, pump differential pressure, flow rate, system back pressure, and back pressure control valve position.

SD-6.5 Immersion Washers

SD-6.5.1 General. This section describes the requirements for immersion washers used in bioprocessing that are designed to clean parts out of place from their typical installation. Immersion washers are a subcategory of clean-out-of-place (COP) washers, which includes cabinet washers (see SD-6.1). When using immersion washers, parts are completely submerged within an immersion tank throughout the cleaning cycle. Requirements in this section are intended to be applied to immersion washers, but may be applied to other types of washers where appropriate.

The following terms are defined for this section:

designed load immersion basket/rack: a basket or rack to hold parts that is designed for a specific, repeatable loading configuration. A designed load basket or rack is used for geometrically complex parts where there is concern with cleanability of the part due to it requiring specific orientation or placement, liquid holdup after system draining, or entrapped air during a cleaning cycle.

end nozzle zone: a hydraulic circuit with nozzles or jets that encourages end-to-end flow within an immersion tank.

general load immersion basket/rack: a basket or rack to hold parts that is not designed for any specific loading configuration or orientation of the parts. A general

load basket or rack is used for geometrically simple parts (e.g., gaskets) and/or non-process contact surface components (e.g., clamps, tools) where repeatable orientation is not critical.

immersion tank: the vessel designed to hold and allow delivery of cleaning solutions in which parts are immersed.

parts: any component to be cleaned in the immersion washer, such as pipes, hoses, clamps, gaskets, fittings, and accessories.

side nozzle zone: a hydraulic circuit with nozzles or jets that encourages rotational flow within an immersion tank.

SD-6.5.2 System Performance Requirements. Immersion washers shall be capable of delivering and removing cleaning solutions from surfaces of parts across multiple phases of a cleaning cycle. Immersion washers may be self-contained, or receive cleaning solutions from a CIP system. The following are typical general phases of an immersion washer cleaning cycle:

(a) pre-rinse
(b) wash
(c) rinse
(d) final rinse

The design should allow for multiple chemical additions during washing phases. The hydraulic conditions (i.e., pressure and flow rate) of all rinsing phases should be the same as for wash phases to ensure consistent rinsing of parts, immersion tank interior, and hydraulic circuit. The final rinse may be performed with recirculated final rinse water integrated with drain steps to remove residual cleaning solutions. The design should be capable of providing a final rinse phase at an elevated temperature [e.g., >149°F (65°C)] to improve air-drying efficiency.

SD-6.5.3 Operating Capabilities and System Function

(a) The immersion washer should control and monitor time of exposure (contact time) during wash and rinse phases.

(b) The immersion washer shall control and monitor cleaning solution temperature during all washing and rinsing phases.

(c) The immersion washer should monitor the pressure and/or flow of cleaning solutions supplied to zones within the immersion tank and/or immersion basket/rack.

(d) The immersion washer shall be designed to provide analytical verification of final rinse water quality (e.g., conductivity, TOC, number of final rinse steps).

(e) For immersion washer capabilities for chemical addition, see SD-6.1.4.7.

(f) For immersion washer recirculation pump requirements, see SD-6.1.4.8(b) and SD-6.1.4.8(c).

(g) Immersion washer pumps should have sufficient capacity (flow and/or pressure) for all zones used in the washer.

(h) For immersion washer heat exchanger requirements, see SD-6.1.4.9.

SD-6.5.4 System Design

(a) Immersion baskets/racks (general or designed load) should incorporate thermoplastic or thermoset material components to prevent scratching parts and/or immersion tank I.D.

(b) Materials of construction of immersion washer process contact surfaces shall adhere to the same requirements set forth in the cabinet washers section [see SD-6.1.3(a)].

(c) Materials of construction and general design of the immersion tank shall follow requirements for vessel general design (see SD-3.4.1). The full vacuum service design requirement is not applicable to atmospheric immersion tanks.

(d) The surface finishes for the interior surfaces of the immersion tank, process contact tubing surfaces, and any other process contact surfaces shall be specified by the owner/user using designations provided in Table SF-2.4.1-1. Electropolishing is not required for immersion washers.

(e) The surface finish of baskets/racks, supports, thermowells, guards, and other internal tank components should meet the surface finish requirements of the tank. Surface finish verification may not be possible for all components of an immersion washer's baskets/racks.

(f) The internal surface finish of the immersion tank cover should be the same as specified for the immersion tank internal surfaces.

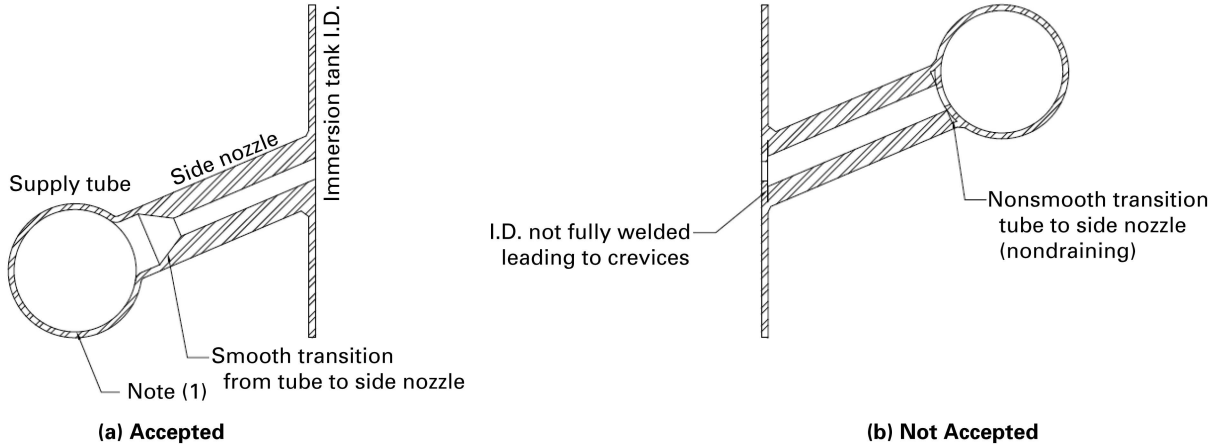
SD-6.5.4.1 Zone Design

(a) Immersion washer design can include multiple zones to clean parts through various methods. Zone piping design shall follow SD-3.1.2.2, with the consideration that zone branch connections shall be opened between each phase to avoid carryover. All zones should be targeted during each phase to provide consistent flushing.

(b) Turbulence is critical for cleaning within an immersion washer, and zone design should provide adequate turbulence to all part surfaces. For example, tubing or similar parts that are not exposed to turbulence on the I.D. from a side nozzle zone would require an end nozzle zone or direct connection to a zone to provide adequate I.D. flow.

(c) For zones with piping manifolds within the immersion tank, baskets, and/or racks, the fabrication of the piping manifolds shall comply with the applicable sections of system piping (see SD-3.1.2.3).

Figure SD-6.5.4.2-1 Immersion Tank Side Nozzle Design



NOTE: (1) Supply tubing and all side nozzles should be drainable, either back through the supply tube header or into the immersion tank.

SD-6.5.4.2 Tank and Cover Openings

(a) Immersion tank and cover opening design shall adhere to the same requirements used for cabinet washers (see SD-6.1.4.1).

(b) Side nozzles shall be of hygienic design (see Figure SD-6.5.4.2-1).

(c) Immersion tank covers should be used and designed to reduce operator exposure to splashing during operation as well as to minimize added humidity to the area around the immersion washer. Both sealed and nonsealed designs are permitted.

(d) Sealed (e.g., gasket or O-ring) immersion tank covers shall be designed to prevent wash fluid from leakage during the wash cycle.

(e) Nonsealed immersion tank covers should be designed to minimize wash fluid leakage during the wash cycle.

(f) Both sealed and nonsealed types should be designed to minimize wash droplet formation above the immersion tank and loaded parts.

(g) Process contact static seals used in immersion washers shall comply with the requirements of Part SG.

(h) The external surfaces (e.g., frame, immersion tank O.D.) shall meet the owner/user's specified requirements of the installed location of the equipment.

(i) External surfaces should be insulated to minimize heat transmission

SD-6.5.4.3 Baskets and Racks

(a) General load immersion baskets/racks should be designed to accommodate variable configurations and load items. Parts used in these baskets/racks do not require a specific orientation for self-drainability or to prevent air entrapment.

(b) Designed load immersion baskets/racks should be designed for repeatable loading and may be subject to verification, if required by the owner/user, to assure removal of entrapped air. Load items as well as the designed load immersion basket/rack shall be self-drainable.

(c) All immersion baskets/racks should be designed for disassembly required for inspection and maintenance.

SD-6.5.4.4 Interfaces. Immersion washers' parts are loaded and unloaded in the same area/room classification. If process flow requires a separation of clean and dirty parts, an immersion washer should not be used.

SD-6.5.5 Design for Bioburden Reduction

SD-6.5.5.1 Drainability

(a) Immersion washer process contact surfaces shall adhere to SD-2.4.3.

(b) For rectangular immersion tanks sloped both to center and along the tank length, a minimum lengthwise slope designation of GSD3 (see Table SD-2.4.3.1-1) should be used to facilitate self-draining. Other surfaces sloping to drain within the tank are also recommended to have a minimum slope of GSD3.

SD-6.5.5.2 Cleaning. The interior surfaces and components of the tank as well as the baskets/racks are considered process contact surfaces and should comply with SD-2.4.2 except for SD-2.4.2(a)(4). These surfaces include the immersion tank wall I.D. above an overflow port and the immersion tank cover I.D. surfaces with the potential to drip onto cleaned parts within the immersion tank.

(a) Engraving or embossing of materials (for identification or traceability) is permitted on exterior process contact surfaces, such as the exterior of process contact tubing in the washer. Engraving or embossing

should be limited to only what is needed for unique identification or traceability.

(b) Adherence to SD-2.4.2(a)(2) for the immersion tank wall I.D. above an overflow port and immersion tank cover I.D. surfaces should be considered by the owner/user depending on the criticality of the parts being cleaned.

(c) Final rinse tank level should be higher than wash solution rinse level to promote quicker achievement of final rinse conditions.

Parts with recessed holes or cavities should not be cleaned in immersion washers. Risk of air entrapment or lack of drainability may impede exposure to and removal of cleaning solution.

SD-6.5.6 Design for Serviceability, Examination, and Operation. Immersion washers should be designed to enable access for inspection and service of components that are subject to wear, and to allow for periodic calibration of instruments.

SD-6.5.7 Testing

SD-6.5.7.1 Flow Coverage. Designed load immersion washer baskets/racks designed for repeatable loading should have flow coverage (e.g., riboflavin) testing performed for verification of liquid coverage of parts' surfaces. The spray coverage testing described in SD-7.1 is applicable to the flow coverage testing for immersion washers. If Nonmandatory Appendix M is used, it is applicable to immersion washers, with the following additional considerations:

(a) The scope of the riboflavin application and expected removal should be documented and agreed to by all parties (e.g., parts and baskets/racks only; parts, baskets/racks, and immersion tank process contact surfaces).

(b) Riboflavin may be applied while parts are loaded in the baskets/racks inside of the immersion tank, or may be applied to parts prior to loading into the basket/rack and/or immersion tank. Application prior to loading may be required for parts with limited access areas such as tubing lengths.

(c) Immersion tank filling should occur as in normal operation and to the normal operating level. As once-through rinsing is not applicable to immersion washers, a complete fill, zone(s) rinsing, and drain should be performed not less than two times. The maximum number of zone rinses (complete fill and drain) during the riboflavin testing shall not exceed the total number of phases with complete fill and drain steps during an owner/user's normal operating wash cycle. Only the zones applicable to the components being tested should be used. Pertinent information such as zones used, time of rinse, and zone sequencing should be recorded.

(d) Riboflavin inspection may occur while parts are still loaded in the immersion tank, outside of the immersion tank, or through a combination of both. Inspection outside of the immersion tank may be needed for parts with limited access areas. Care should be taken while unloading parts from the baskets/racks and/or immersion tank to avoid false results due to transfer of residual riboflavin from other parts.

General load immersion washer baskets/racks are not subject to the same testing due to the nonrepeatable and nondesignated loading conditions and variations in parts being cleaned.

SD-6.5.7.2 Drainability. Drainability testing for immersion tanks should use methods described in SD-7.4 for vessels, with the following additional considerations:

(a) At minimum, the immersion tank should be filled to completely submerge the tank bottom.

(b) Drainability testing intended for ensuring immersion tank drainability should be performed without any baskets/racks loaded.

(c) Any outlet strainer or screen used in normal operation should be installed.

(d) Drainability testing can be performed on designed load baskets/racks and loaded parts to verify draining of surfaces on these components. The baskets/racks and parts loading information and configuration should be recorded, and the immersion tank should be filled to at minimum above the highest component of the basket/rack or loaded part.

SD-6.6 Isolator Systems

SD-6.6.1 General. Isolator systems, hereafter referred to as isolators, are used to create a controlled environment for bioprocessing and quality control testing that is isolated from operators and the background environment. This section describes the design requirements for two types of isolators, as follows:

(a) aseptic isolators, which are designed to protect the process from the environment, enable aseptic processing (e.g., cell bank processing, liquid filling of final product)

(b) containment isolators, which are designed to protect the operator environment from the process and enable safe processing of potent compounds (or other hazards) in an isolated environment

This section does not address equipment/components used inside the isolator. Requirements of the process and process equipment enclosed by the isolator should be provided by the owner/user. This section is not applicable to restricted access barrier systems, which restrict access but do not provide environmental isolation.

SD-6.6.2 System Performance Requirements. The following system performance requirements shall be defined:

(a) environmental classification inside and outside the isolator

(b) airflow conditions as unidirectional or turbulent

(c) pressure differential target to background environment

(d) log reduction for decontamination

(e) overall cycle time limit for decontamination and aeration

(f) temperature operating ranges

(g) humidity operating ranges

(h) recirculation air, make-up air, and total exhaust air flow limitations

(i) allowable decontamination agent (e.g., vapor phase hydrogen peroxide) concentration at the end of aeration for product protection

SD-6.6.3 Operating Capabilities and System Function

SD-6.6.3.1 Differential Pressure Control. Differential pressure set points should be adjustable in the range of 0.06 in. to 0.18 in. (15 Pa to 45 Pa) of the water column. Phase transitions in the isolator system (e.g., re-dosing to aeration, aeration to production) shall be controlled without loss of pressure balance in the surrounding room specified by the owner/user.

It is permissible for the set point to be positive or negative to the surrounding room as defined by the owner/user to meet the product manufacturing requirements. The differential pressure (between the isolator interior and exterior) should be maintained within 0.02 in. (5 Pa) of water column of the set point.

SD-6.6.3.2 Temperature and Humidity. The isolator should be designed to monitor operational, decontamination, and aeration temperatures within the range specified by the owner/user.

Humidification requirements are application dependent and should be agreed to by the owner/user. Consideration should be given to decontamination requirements, product requirements, potential static electricity discharge, and condensation within the isolator or connected equipment (e.g., lyophilizer).

SD-6.6.3.3 Decontamination. Unless otherwise specified by the owner/user, the decontamination cycle shall demonstrate a five log reduction of microorganisms. The complete decontamination cycle includes leak testing, conditioning, decontamination, and aeration of residual decontamination agents. The isolator shall be designed to reduce the level of the residual decontamination agent to a concentration to be specified by the owner/user. If vapor phase hydrogen peroxide is used, the aeration shall reduce the residual vapor phase hydrogen peroxide to <1.0 ppm at the specified operating temperature for operator safety. The isolator should be designed to prevent opening during decontamination (e.g., incorporating door and window interlocks).

SD-6.6.3.4 Venting During Aeration. The isolator shall be designed to safely exhaust decontamination gas though a dedicated exhaust system. For example, if hydrogen peroxide gas is exhausted, a building stack or catalytic filter may be required to safely convert the hydrogen peroxide into water vapor and oxygen as it is released to the environment.

SD-6.6.4 System Design. Isolator systems contain bioprocessing equipment and normally do not have product contact surfaces. The owner/user shall specify

(a) surfaces required to be designed for product contact

(b) isolator designation as aseptic and/or containment

(c) product sensitivity to decontamination agents

(d) specific environmental requirements (e.g., inert gas blanketing)

Process contact surfaces should be impervious, nonreactive, nonadditive, and resistant to cleaning/decontaminating agents. Metallic process contact surfaces shall be fabricated with 316-type or 316L-type stainless steel by welded construction, unless otherwise approved by the owner/user. Exterior non-process contact surfaces may be fabricated with 304-type or 304L-type stainless steel by welded construction.

All equipment should be compatible (chemically resistant, nonpermeable) with cleaning and sanitization agents specified by the owner/user, e.g., sporicidal agents, peracetic acid, hydrogen peroxide gas, or 70% IPA.

Glove ports, comprising a glove and sleeve sealed into the wall or window of an isolator, shall be made with materials resistant to decontamination agents and specified sanitizing/cleaning agents (e.g., hard coated aluminum, stainless steel, UHMWPE).

Unless otherwise specified by the owner/user, process contact surfaces of metal construction should have a surface roughness of 35 μin. R_a (0.89 μm) or less. Unless otherwise specified by the owner/user, the exterior (non-process contact surfaces) of metal construction should have a surface roughness compatible with the associated environmental classification. If the exterior operational environment is ISO class 8, a surface finish of 48 μin. R_a (1.2 μm) or less is recommended for metal construction.

SD-6.6.4.1 Isolator Shell. The isolator shell (the main work chamber of the isolator), which may include windows, lights, and openings, should be designed to integrate internal equipment with ergonomic operations. The isolator shell construction should be designed to accommodate the user-specified pressure differential with limited shell deformation. Isolator shell deformation limits should accommodate openings where brittle material may be used such as glass windows and lights.

To ensure isolator shell seal integrity, tolerances for isolator shell and connection points should accommodate the potential for weld heat distortion. The shell shall be fabricated using welded construction unless otherwise specified by the owner/user.

The isolator shell construction radii of internal corners and seams should be 0.6 in. (15 mm) or greater to facilitate cleanability.

The aseptic isolator design should provide a barrier or sufficient space for the separation of particulate generating operations (e.g., stoppering and capping) from the product filling operations.

SD-6.6.4.2 Isolator Base Plate. The isolator base plate (the lowest part of the isolator interior interfacing with the isolator shell) shall be designed to separate the isolator environment from the area below, which may contain drives, motors, electrical installation, and other components. The isolator base plate surfaces exposed to the isolator environment are considered process contact surfaces. Isolator base plate penetrations shall be designed with integral seals to establish a pressure boundary to avoid contamination. Penetrations should use rounded corners with minimum radii of 0.6 in. (15 mm) to facilitate cleanability.

The isolator base plate thickness shall be designed to support process equipment specified by the owner/user.

Where isolators are designed for CIP or liquid washing, the isolator base plate shall be sloped to one or more drains in the isolator base plate.

When the isolator manufacturer does not fabricate the base plate, dimensions and tolerances for tight integration with the isolator shell shall be provided to the isolator manufacturer by the isolator base plate fabricator or owner/user.

SD-6.6.4.3 Doors/Windows. Doors/windows should be designed, installed, and sealed to maintain the shell integrity and cleanability. The design shall provide access to clean the inside of the windows.

Both fixed and operable window designs are permitted. Door and operable window designs should consider interlocks to prevent opening during decontamination.

SD-6.6.4.4 Lighting. Lights should be designed, installed, and sealed to allow illumination of the isolator interior while maintaining the shell integrity and without compromising cleanability. The owner/user should specify product sensitivities to certain wavelengths (e.g., UV wavelengths) or to light intensity levels. The type and intensity of light at the work location should be specified by the owner/user to meet ergonomic requirements (e.g., fluorescent lighting at 75 foot-candles to 80 foot-candles (0.026 lumens/m^2 to 0.028 lumens/m^2) or LED lighting at 45 foot-candles to 50 foot-candles (0.016 lumens/m^2 to 0.017 lumens/m^2). If specified, the design should accommodate different levels of lighting within the isolator (e.g., at least one for processing and one for cleaning/sanitization). The placement and orientation of the lighting should minimize reflection and glare on the windows.

SD-6.6.4.5 Glove Ports. The design of an isolator should include a mock-up activity to determine the final position of any glove port. The mock-up should include a life-size model of the isolator and the equipment planned for use in the isolator for verifying ergonomics and accessibility. Both oval and circular shapes are permitted. Glove seal construction inside the isolator shall be free of crevices, threaded fasteners, or any areas difficult to clean and decontaminate. The glove port shall be designed to provide an integral seal with the isolator.

For containment isolators, the glove port shall be designed to allow a glove change without exposing the used glove to operators.

SD-6.6.4.6 ULPA/HEPA Filters. For aseptic isolators, the total nonviable particulate concentration shall meet ISO class 5 requirements using ULPA or HEPA filters. For aseptic isolators, the design should be capable of unidirectional (downward) airflow during normal operation with airflow velocity of 90 ft/min (0.46 m/s) ± 20% as measured 6 in. to 12 in. (15.2 cm to 30.5 cm) below the diffuser membrane. Turbulent airflow conditions are permitted during decontamination and aeration.

For containment isolators, ULPA filters are recommended. Airflow breach velocity (e.g., as measured from an open glove port) should be between 100 ft/min and 125 ft/min (0.51 m/s and 0.64 m/s), unless otherwise specified by the owner/user.

SD-6.6.4.7 Transfer Ports. The aseptic isolator design shall provide for aseptic transfer of components required for the operation (e.g., caps, stoppers for filling). The design should accommodate component transfer for initial setup and to replenish supplies during operation.

Connected tubing from a final filter into filling heads in an isolator shall have an integral seal at the isolator shell. The recommended location for the final filter is outside the isolator.

A rapid transfer port (RTP, sometimes referred to as an alpha-beta port) in which mating ports between the isolator and another container or system, whose exposed door surfaces become sealed when interlocked to each other, shall be designed to maintain isolation integrity while transferring materials into and out of an isolator. The mating surfaces of RTPs shall create a seal such that opened ports do not expose the isolator environment to surfaces that have not been decontaminated.

RTPs should be located to accommodate the operator access through glove ports and allow adequate clearance from internal equipment when open. Sizes should be specified to include the beta container seal clearance when docked. In containment applications, a mechanical interlock should be provided to prevent the alpha door from being opened when the beta container is not docked. The use of RTPs for powder transfers that come into direct contact with seals is not permitted.

Split valves that use the same interface technology as RTPs, except that the interlock acts as a butterfly valve, may be used for liquid or solids additions into an isolator. Split valves are permitted for use in both aseptic and containment isolators.

Pass-in/pass-out holes (openings that allow the transfer of material into and/or out of isolators while in operation) shall be designed to be sealed by an external door during a decontamination cycle. The design of aseptic isolators should not permit opened doors of pass-in/pass-out holes to rest in a position above the aseptic operations. The isolator shall be designed to maintain specified pressure differentials and airflow velocities with open pass-in/pass-out holes during normal operation.

SD-6.6.4.8 Airlock/Decontamination Chamber. Airlock/decontamination chambers, compartments with an inner door and outer door used for moving material into and out of the isolator, shall be designed with double-interlocked doors, which prevent the outer door (to room) from being opened while the inner door (to isolator) is open. Both doors should also be interlocked from opening during the decontamination cycle. The inner door shall be interlocked such that it can only be opened after a successful decontamination cycle.

SD-6.6.4.9 Internal Components. For piping/tubing, all wetted process contact tubing shall comply with SD-2.4.2 and shall be sloped and/or provided with an air purge to allow draining of lines per SD-2.4.3 and Nonmandatory Appendix C. Welded joints are preferred. If disassembling of the pipe/tube system is required, hygienic process connections shall be used. Exposed threads (e.g., the exterior of hygienic clamps) should be avoided within the isolator.

Brackets or other equipment shall not be located directly above open containers in aseptic isolator interiors.

SD-6.6.4.10 Instruments

(a) Hydrogen Peroxide Detection. When hydrogen peroxide is used as a decontaminating agent, the system should be designed to detect residual hydrogen peroxide above specified critical levels for product and personnel safety. For personnel safety, residual hydrogen peroxide shall be less than 1 ppm. The owner/user shall specify the residual level limit to protect the product. The measurement principle and detection limit of sensors should be agreed on between the manufacturer and owner/user. The sensor position shall provide for monitoring the worst-case location within the isolator.

(b) Viable Particle Indicators. The isolators designed to create ISO class 5 conditions shall include continuous active air sampling for viable particle monitoring during active processing.

(c) Nonviable Particle Indicators. The isolators designed to create ISO class 5 conditions shall include continuous particle monitoring for nonviable particles.

SD-6.6.4.11 Seals. All elastomer seals shall meet 21 CFR 177.2600 or equivalent. Gaskets and O-ring seals used to seal the isolator are not considered product contact surfaces, but should be nonshedding where exposed to the aseptic environment. Where seals are exposed to cleaning and/or decontamination processes, they are considered process contact surfaces and shall be resistant to cleaning and/or decontamination fluids. Process contact elastomers shall comply with the applicable requirements in Part PM or Part SG. The potential for seal degradation and chemical absorption and subsequent desorption should be considered in the selection of seal materials. For example, silicone and EPDM offer resistance to many cleaning and decontamination agents.

Inflatable seals and static seals are permitted. For example, inflatable seals are acceptable for doors/windows that are designed to be opened during setup and cleaning procedures. The potential for occluded areas should be considered in the design and use of inflatable seals. Inflatable seals shall have a continuous leak check, using either constant pressure or constant flow.

Seals between the isolator shell and mating equipment (e.g., depyrogenation tunnel, lyophilizer) should be designed to accommodate the effects of the thermal dilation/contraction of the mating equipment. The temperature at these interfaces should be considered in the selection of seal material.

When an isolator system comprises multiple connected isolators, seals between isolators shall be designed to expose seal surfaces to decontamination agents during a decontamination cycle. Single or double seals are permitted between isolator chambers.

SD-6.6.4.12 External Surfaces. Exterior design requirements of SD-2.4.4.2 are applicable to isolators. The external surfaces of an aseptic isolator shall be compatible with the environmental classification to which it interfaces. The following design practices should be considered:

(a) All cables should be covered.

(b) Gaps between the isolator and other equipment, such as depyrogenation tunnels or lyophilizers, should be sealed.

SD-6.6.5 Design for Bioburden Control

SD-6.6.5.1 Drainability. Horizontal process contact surfaces of the isolator shall be self-draining. If CIP of the isolator is specified, all permanently installed internal liquid distribution piping (e.g., spray wands) should be sloped to meet the requirements of Table SD-2.4.3.1-1 category GSD2 where possible or supplied with an air purge to allow for draining per SD-2.4.3 and Nonmandatory Appendix C.

SD-6.6.5.2 Cleaning. Selection of cleaning agents should be made with consideration of all process contact materials including elastomer seals and sensors. If CIP of the isolator is specified, all process contact surfaces shall be exposed to cleaning solutions and accessible for visual verification.

SD-6.6.5.3 Chemical Sanitization/Sterilization. All transport systems shall be set in a position (or in motion) such that all process contact surfaces are exposed to the chemical agent used for the decontamination cycle.

SD-6.6.5.4 Thermal Sanitization/Sterilization. [Reserved for future content]

SD-6.6.5.5 Post-Use Storage. Aseptic isolators should be designed to maintain an ISO class 5 environment under dynamic and static conditions for a period of time specified by the owner/user. A post-use storage time under static conditions should be specified by the owner/user and verified through environmental monitoring.

SD-6.6.6 Design for Serviceability, Examination, and Operation. The isolator systems should be designed to enable safe access for inspection and service of components that are subject to wear, and to allow periodic calibration of instruments.

The isolator systems should be designed to provide adequate space for maintenance accessibility of all mechanical components.

SD-6.6.7 Testing

SD-6.6.7.1 Isolator Leak Testing. Both the pressure decay and pressure hold methods of leak-rate testing are acceptable. When choosing a test method, consideration should be given to the size of the isolator, time required for testing, and external influences that may affect testing (e.g., room temperature changes, room pressure changes).

The maximum leak rate shall be no greater than 1% of the isolator volume per hour with all pass-in/pass-out holes and RTP fittings closed and sealed (ISO 14644-7:2004, ISO 10648-2:1994 class 3). Leak-rate test pressures should be selected at 3 times to 5 times the working pressure as agreed to by owner/user. The temperature during the leak test shall not change more than 0.9°F (0.5°C).

SD-6.6.7.2 Glove Leak Testing. System integrity should be confirmed by a glove leak test. A glove port assembly tester is recommended to locate a potential glove leak. It is recommended to test both the installation and the glove sleeve.

Leak testing methods found in ISO 14644-7 are acceptable. Unless otherwise specified by the owner/user, the maximum permissible leak of 0.5% of volume per hour is recommended. The use of a completely automated device that uses pre-assigned test recipes is recommended.

SD-6.6.7.3 ULPA/HEPA Testing. The isolator design shall include integral DOP (dispersed oil particulate) or PAO (polyalphaolefin) ports for HEPA filter integrity testing with dioctyl phthalate or other approved testing aerosol challenge. For aseptic isolators, the methods consistent with the certification standards for an ISO class 5 cleanroom should be applied.

SD-6.6.7.4 Mock-Up. Unless otherwise agreed to by the owner/user, a mock-up at the factory or user site should be conducted prior to fabrication of aseptic isolators to assess aseptic operations through glove ports and associated ergonomics. When possible, the actual equipment or models of the actual equipment should be in place for the mock-up.

SD-6.6.7.5 Airflow Verification and Visualization Testing. The design of airflow in aseptic isolators should be verified to maintain ISO class 5 conditions.

Airflow visualization studies should be conducted under specified conditions (e.g., ISO class 5) to demonstrate that the unidirectional airflow minimizes the risk of contamination during operation. It should demonstrate a sweeping action over and away from the sterilized/decontaminated equipment, product, containers, and closures.

Airflow visualization studies should document the airflow patterns under static conditions, dynamic (operating) conditions, and the airflow during all interventions (e.g., clearing a jammed vial).

SD-7 DESIGN CONFORMANCE TESTING (19)

Design conformance testing shall not result in the formation of any surface anomalies or contamination. All design conformance tests and test results documentation shall have the date and time recorded. Each test document shall include a record of personnel who performed and confirmed the test results.

SD-7.1 Spray Device Coverage Test

An acceptable spray device coverage test procedure is provided in Nonmandatory Appendix M. The purpose of the spray device coverage test is to demonstrate and document liquid coverage of the process contact surfaces. The test provides information about liquid coverage and the conditions necessary to achieve this coverage as a prerequisite for cleaning of the process equipment. Effective coverage shall be visually determined using a fluorescent solution and an ultraviolet lamp or by other verification methods as agreed to by the owner/user and manufacturer. The minimum acceptable water quality is noncompendial purified water (e.g., reverse osmosis or deionized). Acceptance criteria and coverage test protocol should be agreed to by the owner/user and manufacturer.

Spray device coverage tests are not intended to demonstrate system cleanability. System cleanability is achieved through the equipment design, the spray design, knowledge of the soils, cleaning agent selection, and cleaning process parameters. Cleanability is verified using a complete CIP per protocol during cleaning validation.

SD-7.2 Cleaning, Steaming, and Bioburden Control Testing

Cleaning, steaming, and bioburden control testing (in addition to spray device testing) shall be as agreed to by the owner/user and manufacturer, and in accordance with accepted industry standards.

SD-7.3 Fluid Requirements for Leak Testing

Where leak testing is required, the following fluids shall be used:

(a) Hydrostatic testing shall use clean purified or deionized water filtered at 25 μ or better, unless otherwise agreed to by the owner/user.

(b) Pneumatic testing shall use oil-free clean dry air, nitrogen, or inert gas filtered at 25 μ or better, unless otherwise agreed to by the owner/user.

SD-7.4 Vessel Drainability Test

Specific steps or operations in a bioprocess may require vessels to be self-draining. A drainability test for such vessels shall be conducted as agreed to by all parties. As a proposed test procedure, the following should be considered:

(a) The vessel shall be in its intended operating orientation within a tolerance agreed to by the owner/user.

(b) The vessel shall be filled approximately to the weld seam that joins the shell to the bottom head.

(c) The outlet valve shall be opened, the vessel shall be vented to atmosphere, and the vessel shall be allowed to drain by gravity.

(d) There shall be no puddles of water left on the bottom of the vessel greater than as agreed to by the owner/user and manufacturer.

It is generally understood that residual water may be present in the form of droplets that typically do not exceed a diameter of 5 mm. Residual water droplets adhere to process surfaces due to surface tension and are not indicative of a vessel's drainability. Observed puddles that are displaced with a 1.0-in. (25-mm) rubber dowel applied perpendicular to the puddle and re-form at the point of displacement indicate a flat or unintended low point, and that area shall be repaired to the satisfaction of the owner/user. Puddles that are displaced with a 1.0-in. (25-mm) diameter rubber dowel applied perpendicular to the puddle and do not return to the point of displacement are considered to be large droplets and do not constitute a test failure.

NOTE: Filter housings are available in several designs. In some cases, flat-bottom filter housings are specified by the owner/user based on their risk-assessed process and equipment requirements. Flat-bottom cartridge-mount filter housings, including those that will be steamed in place, are exempt from this test, and the equipment shall be installed as agreed by the manufacturer and owner/user.