TABLE 1. BOIL-UP RATES		
Vapor	lb/min	gal/min
Boil-up rate	13.0	2.1
Condensing in the top head	0.6	0.1
Condensing in the riser	0.7	0.12

TABLE 2. CIP WASH RATES		
1,000-gal reactor	lb/min	gal/min
Top head	434	70
Vapor riser	312	50
Condensers	370	60

Making the Case for Clean in Place

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Boil-up methods are no longer the standard for cleaning high-purity process reactors

Clean-in-place (CIP) technology provides a repeatable, automated process for cleaning process equipment and fluid-flow systems [1]. During the CIP process, developed more than 50 years ago for the dairy industry, cleaning solutions are applied to the surfaces of process systems to effectively remove a soil or contaminant without disassembling the process system. Contact time, temperature and concentration of the cleaning agent are tightly controlled.

The use of CIP technology has since been embraced by the finished pharmaceutical and biotechnology sectors, and is rapidly becoming standard practice. Over the last decade, many companies involved in the production of active pharmaceutical ingredients (APIs) have incorporated CIP into the design of their plants. However, there is still resistance to CIP technology.

Some of this resistance is attributed to the capital costs for implementing CIP in a new facility or retrofitting an existing plant to accommodate the technology [2]. Another factor is the complexity of software designed to handle frequent changeouts of a variety of products, as may be the case in plants built for custom synthesis [2]. Also at issue are the safety concerns associated with spraying solvents. Perhaps the most influential factor hindering CIP, however, is the assumption that traditional cleaning methods are equally effective, in terms of both cost and performance. Upon closer examination, neither of these assumptions holds true.

CIP vs. boil-up methods

For years, the typical method for cleaning batch reactors in bulk chemical facilities has been to perform "boil-ups." This method consists of introducing a solvent in which the product residue, or soil, is soluble. The solvent is then heated to reflux. Solvent vapor condenses in the overhead system and on the top head of the reactor vessel. The expectation is that, given enough time, the condensing vapor will dissolve any chemical contaminants.

Boil-up is augmented by line flushing, which is effective for cleaning piping 3 in. or smaller (larger lines require inordinate amounts of fluid to produce the required velocities). The advantages of boil-up are that it is straightforward and requires no additional piping or spray devices beyond those required for the process.

However, API facilities that use boil-up methods may spend as much as 30% of their time cleaning process trains [3]. In addition to being time and energy intensive, boil-ups do not make the most effective use of aqueous cleaning solutions; the technique is virtually impossible to make repeatable; and most importantly, the results may be inconsistent or unsatisfactory.

A major shortcoming of boil-ups is that the condensing vapor only acts where it condenses. Soil actually inhibits the condensation of vapor and therefore, cleaning. Most of the vapor is condensed in the overhead condenser, while dead legs, like valved or blinded nozzles, receive little of the cleaning solution. This also applies to ducts and chutes, as the rate of condensing does not provide adequate run-down over vertical surfaces.

Consider, for example, a 1,000-gal reactor undergoing an atmospheric boil-up with acetone, a common cleaning solvent. By assuming that the reactor's wetted heat-transfer area is limited to the bottom head, the top head and vapor riser are uninsulated, and a generous value for natural convection is used, then a vapor generation and condensate rate can be approximated as shown in Table 1.

By comparison, the CIP method introduces many times more cleaning fluid per unit time, as shown in Table 2. This intense rate of solution application can shorten cleaning cycles. Fluid can be distributed evenly, or more solution can be applied to highly soiled areas while less-soiled areas can be treated less aggressively.

Aqueous cleaning solution applied via spray devices can be used to supplement organic solvent rinses. Although some are acidic, these aqueous solutions are primarily alkaline in nature, and because they are non-volatile, they cannot be distributed via reflux methods. Typically applied at low concentrations of 0.15–0.5%, they are cost effective for cleaning many types of soil, and can be used at concentrations as high as 5% for heavily fouled heat-exchange surfaces [1].

Many companies have developed cleaning protocols that specify that reactor systems be cleaned to a level deemed acceptable with traditional boil-up methods. Many of these cleaning procedures rely on a "test until clean" philosophy. That is, the boil-up or flush solution is analyzed, and the equipment is subjected to additional cleaning cycles if required. According to the Inspection Guide on Cleaning Validation by the U.S. Food and Drug Administration (FDA; Washington, D.C.; fda.gov), testing for cleanliness in this manner may not be acceptable. Retesting until an acceptable residue level is attained is "acceptable only in rare cases" [4].

What is required is a validated cleaning method — a system that is "qualified" for its ability to wet a

Key for Figures 1 and 2

A = Reactor vessels
B = Condensers
C = Emergency vent lines
D = Vapor risers & instrumentation
E = Baffles and unlashed nozzles
F = Solids-charge ports
G = Bottom outlets
M = Manway
LI = Level indicator
LT = Level transmitter
PI = Pressure instrument
TI = Temperature instrument
TC = Temperature controller
TT = Temperature transmitter
SG = Sight glass
XV= On/off valves

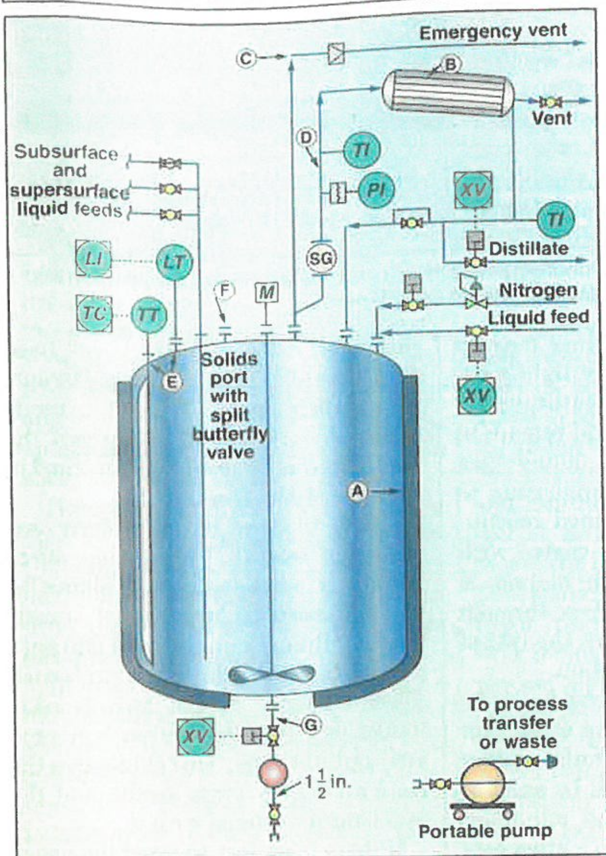


FIGURE 1. For effective cleaning of a nominally non-CIP reactor, it is necessary to wet all surfaces. Fluids are directed at at areas where soil is likely to accumulate

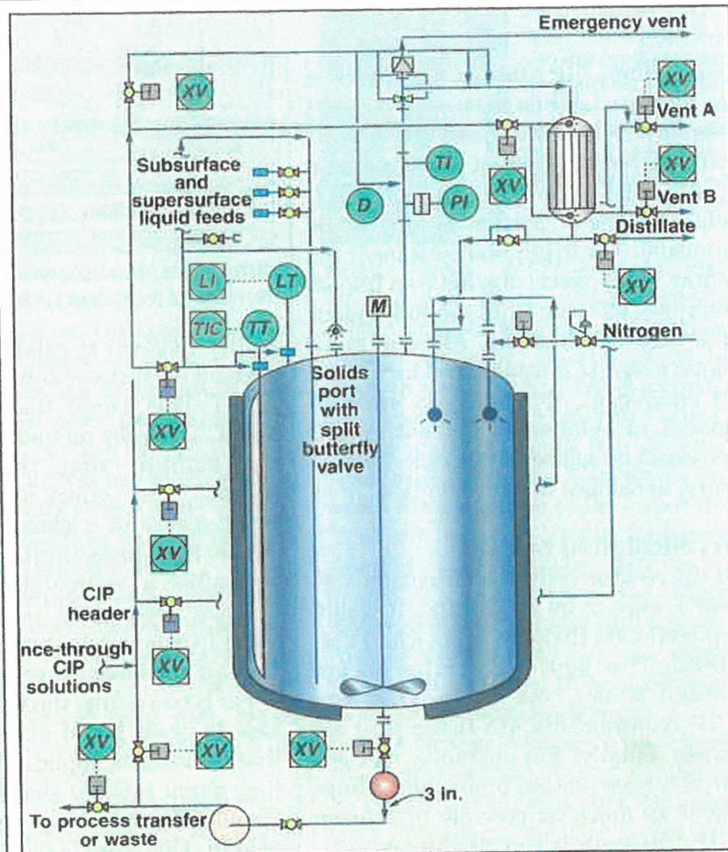


FIGURE 2. In a CIP reactor, cleaning is achieved by recirculating CIP solutions that solubilize and remove soil. A process transfer pump both removes process waste and circulates the CIP solution

process surface. This ability can be confirmed by a riboflavin test, discussed later, similar to those performed by the biotechnology sector.

Improving reactor cleanability

Glass-lined reactor systems are essential equipment for most multipurpose bulk-pharmaceutical facilities. They are favored for their resistance to corrosion and contaminant buildup, as well as for their comparatively low cost. While the examples shown are of glass-lined systems, the lessons learned are also applicable for alloy reactor systems.

Compare the traditional design of glass-lined reactor system to one that incorporates CIP enhancements. The traditional glass-lined vessel system, shown in Figure 1, has provisions for liquid and solids charges, nitrogen inerting, reflux-distillation, emergency relief and process transfer. Although the traditional glass-lined reactor system was neither designed for nor intended to be cleaned in place, the system can be modified for easier cleaning.

For example, condensers mounted horizontally or with a slight pitch are difficult to clean efficiently. Condensing boil-up vapors do not uniformly clean the tubes, and little cleaning action is directed at soil located on the bonnets and tube sheet. Flushing with solvent is an effective but inefficient way to clean, as it requires hundreds of gallons of solvent per minute. An alternative to changing the condenser orientation, a liquid fill-and-soak, uses less solvent, but the lack of solution movement renders inconsistent results.

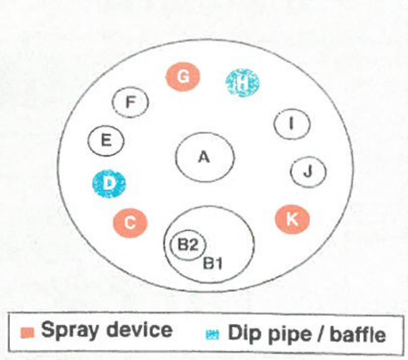
Another area of concern is the vapor riser and emergency vent piping. In operation, these lines can become soiled by reactor foam-over and the carryover of dust from solids-charging operations. As boil-ups produce only small amounts of condensing liquids, it is improbable that vapor will rise into the emergency vent line, effectively displace the inert atmosphere, and efficiently wet the surface uniformly at a rate sufficient to remove all soil consistently.

Nozzles designed for liquid charges can be cleaned easily. However, those that are not externally flushed, such as the baffle, level transmitter and solids-charge port, may be difficult to clean effectively and consistently with a solvent boil-up method.

To obtain an effective, repeatable method of cleaning reactors, it is necessary to wet all surfaces with sufficient quantities of fluid aimed directly at the areas where soil is likely to accumulate. Spray devices, including spray balls, bubble caps and bubble arms, are used to distribute cleaning solutions on large surfaces such as vessels and chutes, and pipes larger than 3 in. dia. Small lines of 3 in. or less can be successfully flushed at velocities of approximately 5 ft/s. [*1*, *5*].

The spray flowrate required to clean simple vessels is based on the diameter. Good results have been obtained by using 2–2.5 gal/min for each foot of vessel periphery [*1*]. Therefore a 5-ft-dia.-vessel can be cleaned effectively with 40 gal/min of cleaning solution, most of which is directed upward to wet the top head and then cascade down the sidewall in a uniform sheeting action.

As vessels are made more complex by the addition of agitators, dip pipes



Connections			
Item	Qty.	Size, in.	Service
A	1		Agitator
B1	1	18	Manway
B2	1	6	Lighted sight glass
C	1	4	CIP
D	1	4	Liquid charge
E	1	4	Sample
F	1	8	Vapor riser
G	1	4	CIP/Reflux
H	1	6	Baffle
I	1	4	Level
J	1	6	Solids charge
K	1	4	CIP/Nitrogen

FIGURE 3. For nozzles to function properly in a glass-lined vessel, the position and number of overhead spray devices should be optimized

and baffles, CIP solution rates have to be increased. While the precise amount required to clean the reactor depends on the specific layout of the top head, a value of 50 gal/min or more for a 5-ft-dia. (1,000-gal) reactor would not be unusual. The depth and position of the spray in the vessel also have an impact on spray efficiency and the subsequent flowrate requirement. After a minimum flowrate is established for a piece of equipment, that flowrate must be looked at relative to the entire CIP process and adjusted upward, if necessary, to balance circuit flowrates.

A redesigned reactor

If the reactor system portrayed in Figure 1 were to be redesigned, it would approximate the reactor shown in Figure 2. This figure illustrates an approach where both the process and CIP requirements are taken into account equally. For instance, the approach uses process piping and equipment as much as possible to achieve CIP. The process transfer pump is utilized for both removing process waste and circulating CIP solutions.

A CIP header has been added to supply solution to all circuits. Spray devices, both conventional spray balls and bubble caps, have been added to wet surfaces where line flushing is not practical. On-off valves have been included so that the sequence in which each circuit is brought into service can be controlled. This use of automated valves also serves to limit the total volumetric amount of wash solution required to a rate that can be handled by the reactor transfer pump.

It is important to note that this system allows for both once-through and recirculating modes of operation. Most of the cleaning will be achieved by recirculating CIP solutions. An appropriate volume of CIP solution, or aliquot, can be prepared, warmed and circulated through each leg of the CIP header and the sequence repeated as required. The solution acts over time to solubilize and remove soil. The aliquot can then be directed to waste.

Once-through flush solutions can be supplied by an external CIP system, which delivers liquid at the required temperature, pressure and concentration. These flushes are important for initial removal of solids that may be present on surfaces but not tightly adhered. This avoids the "bathtub-ring effect," whereby oil and soil remain in the bathtub after the liquid has drained. This effect is analogous to what occurs in a glass-lined reactor. The bottom head is often coated with soil after a recirculating aliquot is drained, requiring a once-through flush to completely remove the last of the soil and cleaning solution.

For good results, the vessel has to be able to drain liquid at the same rate that it intakes liquid. Outlet piping (i.e., pump suction) should be sized to account for vortexing and minimum holdup. This often leads to bottom outlet lines larger than would otherwise be required for the process. Vacuum-assisted returns have been used successfully to minimize the return flow issues in many applications. Frequently overlooked, this critical return-flow issue can be a CIP show-stopper if not properly addressed.

Another noteworthy feature is the way in which the overhead system is reconfigured. This arrangement allows for the piping to be completely wetted by CIP solutions.

Covering all bases

Several steps can be taken to improve the cleanability of glass-lined reactors. The best results can be achieved by focusing on the reactor vessel's configuration, as well and its manways, baffles and dip pipes, and all unflushed nozzles. Attention should also be paid to the facility's condenser, overhead vapor lines, special fittings, and solids-charge nozzles and chutes.

Vessel configuration. Conventional reactors are designed with a top head with a large agitator-removal cover. Such designs are hindered by an additional large-diameter gasket and an agitator cover that does not allow for CIP liquid sprayed into the top head to sheet uniformly down the vessel head and sidewalls. Anything that disrupts the sheeting flow of CIP solution needs to be addressed by designing out the disruption, or by providing a method to re-establish the sheeting flow.

Easier to clean is the modern one-piece top reactor. This design offers better CIP solution flow and allows for more nozzles. In larger-sized vessels (greater than 48 in. dia. and 500 gal), welded-top vessels are preferred. These reactors do not have a body flange and rely instead on a removable agitator-type. This eliminates the need for a very large gasket and the problems associated with it.

If there is no way to avoid the use of a split flange, then one of the high-purity gasket types should be used. Gaskets that are cut back, and do not have any ledges to hold up liquid or soil should be selected.

Manways. The manways of glass-lined reactors are farther from the head surface than those of an alloy vessel. This has to do with the methods required to fabricate glass-lined equipment. Because the interior surfaces are far from the head plane, special attention is required to get sufficient CIP solution into this area to effect cleaning.

Baffles and dip pipes. The addition of baffles and dip pipes further complicate cleaning within reactors. These vertical structures create shadows, which block cleaning fluid from striking the far side of the element and the vessel wall beyond. Generally, an additional spray is required for each shadowing device in a reactor.

Nozzles. The number of nozzles that can be fitted onto a glass-lined reactor is limited by several constraints related to vessel fabrication. While there are some novel techniques for introducing nozzles onto an alloy vessel, these methods cannot be used with glass. Thus, it is critical that the designer and the owner work together to

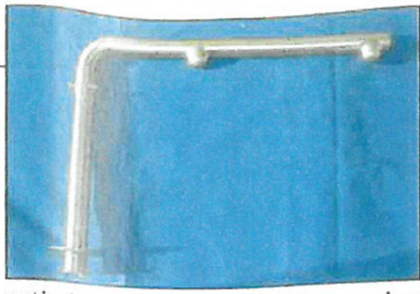


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FIGURE 4. A bubble arm, a single nozzle with multiple spray bubbles, is an option in installations that require additional nozzles

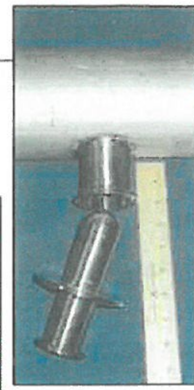

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FIGURE 5. This low-profile device, a bubble-cap spray, can be used to clean overhead vapor lines that can not be flushed. It sprays upward and across to form a falling film that wets the sides of the riser and sweeps away soil

optimize the position and the number of spray devices without compromising the nozzles required for processing.

Figure 3 is an overhead view of a 1,000-gal (60-in. dia.) vessel employing three spray balls. The manway has a spray device on either side. This arrangement provides good "sight" angles up into the manway. Additionally, the dip pipe and baffle each have an adjacent spray device and another spray device at a 90-deg angle.

Note that nozzles G and K serve a dual purpose — as an entry for two CIP spray devices as well as a source of additional clean fluid. The fluid enters from the side of the nozzle through full-size instrument tees.

In some cases, it is impossible to lay out a top-head arrangement in such an ideal way. This could be due to a lack of a nozzle, as in a revamp. In such situations, more-complex devices, such as bubble arms (Figure 4) or tee tubes that use a single nozzle to provide multiple spray bubbles can be used. However, these devices generally require a pinned, self-cleaning slip joint, and may require a tank entry for installation or maintenance. This pinned joint must be designed to prevent the loss of the pin and subsequent glass damage.

Properly designed spray devices can spray enough liquid into each nozzle so that the nozzle neck is covered. Alternatively, nozzles can be externally flushed as part of the line cleaning. Examples of externally flushed nozzles include all liquid feeds, refluxes, and the vapor riser. Shorter-neck nozzles are easier to spray and should be favored in the design stage if they can be fabricated by the vessel vendor.

Historically, the baffle nozzle has been a problem. Typically, this nozzle must be cleaned by spray directed from below. This problem has been addressed by extending the baffle and inserting a glass-lined instrument tee. Allowing for CIP fluid to be injected into the annulus, this approach can be used for any unflushed nozzle with a vertical member, such as a dip pipe, inserted in the vessel.

Condensers. As discussed previously, it is impractical to flush enough liquid through the condenser to achieve full wetting and required velocity. The multiple tubes of the condenser being flushed at 5 ft /s would result in an unacceptably high flowrate of hundreds of gallons per minute. The method that is preferable for cleaning condensers is not dissimilar to the method for cleaning vessels.

If a single-pass (process fluid on tube side) condenser is mounted vertically, it is possible to introduce CIP liquid at such a rate that a falling film is established in each tube. This film will consistently wet the tube surfaces and continuously sweep away soil . A second, smaller spray ball can be used to wet the bottom tube sheet.

Overhead vapor lines. Overhead vapor risers and reactor emergency vent piping are often the largest-bore process piping in a bulk pharmaceutical facility. Typical sizes may range from 4–6 in. for a 300-gal vessel to 8 in. for a 1,000-gal reactor.

The only effective way to clean these lines is to create a situation where the vapor riser and the overhead piping are cleaned by direct application of CIP solution from a spray device. A pair of spray devices can be positioned, as shown in Figure 2, at the high point of the vapor riser vertical section. These bubble-cap sprays are positioned at 180 deg relative to each other, so that they spray upward and across to form a falling film, which will wet the sides of the riser and sweep away soil. With this configuration, it is important to install a vertical riser without bends, and to aggressively minimize horizontal runs, which cannot take advantage of a falling film to decrease the number of sprays required.

The spray devices used for these applications are very low-profile versions. Depending on how far up they need to propel the solution, they may only extend 0.5–0.75 in. into the pipe or chute. Figure 5 illustrates a bubble-cap spray and its insertion into a pipe.

Special fittings. The insertion of these bubble-cap sprays into small-diameter lines can sometimes be handled using polytetrafluoroethylene (PTFE) fittings, but as line sizes increase, specialized pieces are required for the best cleaning geometry.

Typically, these pieces are fabricated from PTFE-coated steel, Hastelloy or glass-lined carbon-steel pipe. Consider, for example, a special fitting made of glass-lined carbon steel to serve as the tee depicted at the top of the vapor riser in Figure 2. The piece would hold two spray devices and a rupture disc, and would make the transition of the vapor riser from the vertical to the horizontal. Another special piece may be required to hold vapor-riser instruments, such as pressure and temperature transmitters, in a special orientation relative to a spray device to achieve adequate cleaning.

Solids-charge nozzles and chutes. Solids-charge nozzles and chutes can be a challenge to clean. By their nature they are always heavily soiled after use. They can, however, be cleaned like vertical chutes by applying falling films of CIP solution, initiated from properly positioned bubble-cap sprays.

The use of a split butterfly valve for contained-solids transfers has become quite popular in bulk pharmaceutical processing. Vendors of these devices offer special adaptors fitted with spray devices that allow for CIP of solids-handling valves.

Testing cleaning effectiveness

Ultimately, cleaning effectiveness can only be verified by accepted recovery techniques and analytical methods of quantifying surface residuals. The ultimate end result is a function of five key factors:

- Reactor design
- Spray design
- Effectiveness of cleaning solution
- CIP skid and software
- CIP supply and return piping

Riboflavin testing is frequently used to measure the effectiveness of spray coverage. More commonly known as vitamin B_2, riboflavin is an orange-yellow needle-like solid that, when dissolved in water, produces a yellow liquid. This liquid, usually applied at a concentration of 100–200 parts per million (ppm), fluoresces with a greenish-yellow glow when exposed to ultraviolet or black light.

Because riboflavin testing has no universally accepted standard, there are many of variations of the test. Generally, riboflavin is applied to the surfaces to be spray-cleaned, and either a complete CIP cycle is run and the equipment is then inspected, using a black light to verify that all riboflavin has been removed. Alternatively, a series of water-rinse cycles are run and then success is based upon evidence that riboflavin dilution has occurred.

Safety issues

In addition to the normal and generally obvious safety practices that must be applied to any automatic handling of potentially hazardous solutions, an additional issue is raised if solvents are sprayed through spray devices, which can result in static buildup. All spray devices and associated equipment and piping must be properly grounded, and the sprayed atmosphere made inert.

Automation is the solution

With proper consideration of the five key parameters for CIP design, an automated approach to cleaning will provide an improved repeatable method, as well as a long-term, cost-effective solution for cleaning equipment. To maximize the benefit and minimize the implementation cost of CIP, the design philosophy must be incorporated during initial concept development of the manufacturing facility. ■

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