Advancements in clean-in-place technology

Critical in automating process cleaning

Clean-In-Place (CIP) facilitates automated cleaning of production and processing equipment without having to disassemble them, as the machine condition influences product quality, thus saving a lot of time and efforts in the cleaning process. It is a reliable & repeatable process used in the pharma, biotechnology, food, dairy and such other industries, which demand stringent hygiene regulations.

Eductor-assisted CIP System

Compact-design portable CIP system

Samuel Lebowitz

In-place cleaning was first applied in the dairy industry in the late 1940s and by mid-1960s, automated in-place cleaning of dairy plants was widely used. The CIP procedures led to the development of all-welded product piping systems, application of air-operated CIP cleanable sanitary valves and appreciable increase in the size of processing tanks as compared with vessels that had to be manually cleaned.

Today, CIP is applied to various pharmaceutical processes both for liquid (biotechnology, fermentation, blood fractionation, IV solutions, parenteral solutions, respiratory care products, etc) and solid (crystallisation, filtration, drying, milling, blending, bulk container filling, etc) product manufacturing.

Further, process cleaning is a critical factor in the qualification of current Good Manufacturing Practice (cGMP) production facilities. Often, non-cleanable process design, inadequate process cleaning strategies and poor CIP implementation become painful obstacles blocking the way towards completion of validation for a new process.

CIP cleanable processes

CIP is a procedure by which chemical wash & rinse solutions are brought into immediate contact with all soiled surfaces and continuously replenished. The cleaning process is essentially chemical in nature, and generally uses recirculation to minimise water & chemical costs.

Solution contact is accomplished through recirculation with the help of spray devices for tanks or pumped recirculation through process lines, all under controlled conditions of time, temperature and chemical concentration in a reproducible manner.

Processing equipment and piping systems that are cleaned-in-place receive less wear and tear (damage) than comparable items, which are manually cleaned. With automated CIP, labour required for cleaning and maintenance is substantially reduced and the processing system productivity is increased through a reduction in down-time. At the same time, reproducibility increases as automation replaces manual cleaning procedures.

In the last decade, end-users and equipment fabricators have been making concerted efforts to establish a level of consistency in expectations for acceptable hygienic design practices for biopharmaceutical manufacturing. Organisations

like ASME BPE, EHEDG and P-3A have addressed various aspects of requirements applicable to subjects such as hygienic design, materials of construction, fabrication methods, vessels, piping, inspection, testing and certification.

While design consistency is important, substantial experience has shown that successful CIP/Sterilisation-In-Place (SIP) implementation involves far more than the selection and application of cleanable pumps, tanks, sprays, valves & controls. The design of a cleanable process requires the consideration of unit operation processing equipment design conducive to CIP cleaning, process equipment layout, application of specialised CIP systems and, finally, the interconnecting piping design for the process to provide for proper cleaning via configuration into CIP circuits.

Processing tanks and piping systems comprising pumps, interconnecting piping, valves & instrumentation are well understood to be CIP cleanable. CIP technology is equally applicable to any equipment in which solution contact can be achieved via recirculation through spray devices or pumped recirculation through process lines.

Directionally drilled CIP spray devices

Since the early days of CIP in dairies, universal coverage spray devices have been available. These off-the-shelf sprays incorporate standard patterns such as 180° upward, 180° downward or 360° all-round coverage. Universal coverage drilled sprays provide a fixed pattern, while rotating sprays provide a moving pattern. All types of spray devices rely on a falling film of solution to supplement the specific coverage. In the case of rotating sprays with gears & bearings, there is always the question of whether the device continues to provide the desired as-designed coverage over the life of the spray due to mechanical wear and damage. Thus, rotation and frequency verification are generally acknowledged as being required for cGMP facilities.

The development of directionally drilled spray devices with coverage based on 3D CAD modeling has opened the way to ensuring optimum coverage. *Figure 1* shows the plan and elevation views of a typical process vessel having multiple process nozzles, manway, annular agitator flange, multi-tiered agitator blades and a baffle. Vessel spray device locations are located on opposite sides of target areas to ensure a cross-chop trajectory is available for hard to reach areas. *Figure 2* shows the 3D CAD model of the same vessel, identifying the trajectory from individual holes of directionally drilled spray devices. In this manner, optimum CIP cleaning coverage can be achieved at the least possible flow rate. *Figure 3* shows a collection of common spray device types. Spray balls are used to provide coverage to targeted areas as well as broad areas. Spray bubble spheres can target specific areas, and are particularly useful for hard-to-reach process equipment zones.

CIP operating flow rates

The first-step of 'sizing up' a particular application is to assess the flow rates that will be required of the CIP system for proper cleaning.

The generally accepted criterion for cleaning of price lines is to achieve a velocity of 5 ft/sec (1.52 m/s). For a half-inch (12.7 mm) Outer Diameter (OD) tubing, this velocity calculates to 1.7 gpm (6.3 lpm); for 1 inch (25.4 mm), 9.3 gpm (35 lpm); and for 2 inch (50.8 mm), it is 43 gpm (162 lpm).

Dished-head vertical vessels are cleaned with the majority of flow directed with spray devices toward the upper head and sidewall area at the knuckle radius. Gravity then provides for a continuous solution sheeting over the sidewall and bottom head. Specific streams may be directed at appurtenances such as baffles and agitator impellers. To provide sufficient coverage in vertical vessels with dished heads, the following are examples of cleaning flow rate guideline that have been usually found to be adequate.

- For a 3 ft (900 mm) diameter vessel, spray device flow rate will be in the order of 28 gpm (106 lpm)
- For a 5 ft (1,500 mm) diameter vessel, spray device flow rate will be in the order of 47 gpm (178 lpm)
- For an 8 ft (2,500 mm) diameter vessel, spray device flow rate will be in the order of 75 gpm (285 lpm)

A logical use of flow rate data is to ensure a match with equipment design. For example, it is important that tank outlets be sized commensurate with the CIP flow rate, permitting unrestricted discharge of solution to CIP return.

Return flow motivation

Based on process design, facility layout, project budget and other considerations, the engineer decides on the optimum configuration for CIP return motivation. Practical field experience reveals that often it is easier to pump water into process tanks than to get it back to the CIP system through CIP return. For this reason, proper system hydraulic balance is greatly dependent on the concept of CIP return configuration.

Solution return may be accomplished by gravity, return pump, eductor (vacuum created by venturi flow effect) motivation or a combination of the previous methods.

Gravity return flow: Gravity return flow is applicable only when the tank being cleaned is at one or more levels above the CIP system. Flushing, washing and rinsing solutions must be continuously removed from the vessel being spray cleaned at a rate equal to the solution supply. The size of tank outlets and return piping systems must

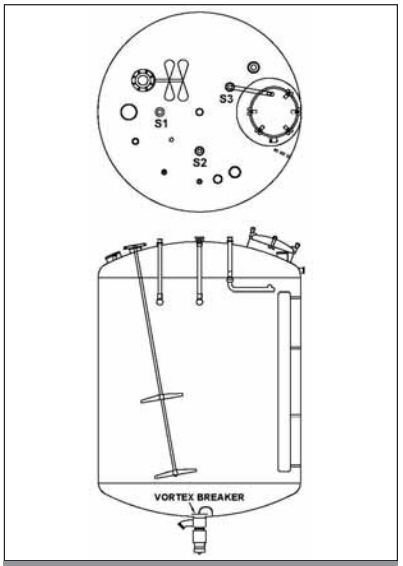

Figure 1: A typical process vessel

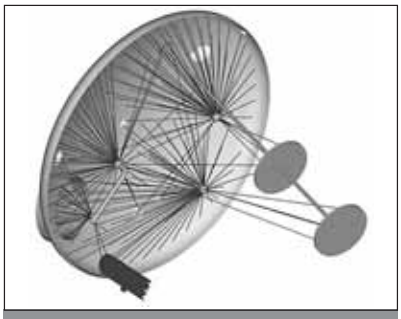

Figure 2: 3-D CAD model of directionally drilled CIP spray device coverage of vessel

Figure 3: Commonly used CIP spray device types

be large enough to permit return by gravity alone. When properly engineered, gravity drainage is more effective than any other method for removing final traces of liquid from a circuit.

Pumped return flow: Low-speed (1,500 rpm) return pumps either with the head rotated by 45° from vertical or of a 'self-priming' type provide effective and reliable return flow if the return header pitches continuously from the tank being cleaned to the pump inlet. CIP return pump performance is reduced by elevated water temperature.

Eductor-assisted return flow: A substantial advancement in CIP for biopharmaceutical production has come through the combination of a high-speed motive pump and eductor incorporated in eductor-assisted CIP return flow systems. An eductor-assisted CIP system will pump both air and water with 15-18 inch (381-457 mm) of mercury CIP return flow vacuum motivation. While eductor return flow can be used as a sole motivating force for short CIP return runs involving minimal static head, an eductor is most commonly used in conjunction with gravity return or a CIP return pump. The eductor continuously primes the return pump, which in turn is able to handle an air-water mixture. Thus, a standard low-speed hygienic centrifugal pump is always suitable, and the more expensive self-priming pumps are not necessary. Eductor performance, relative to the vacuum capacity being generated, decreases with an eductor assist at elevated water temperature, but there is always sufficient vacuum remaining to prime the return pump.

CIP systems

The CIP system is designed to provide automatically controlled spray cleaning operations of storage tanks & processing vessels and pumped recirculation washing of product transfer piping systems. The integrated system makes it possible to achieve complete & uniform control of time, temperature and chemical concentration, all of which are important for success with any mechanical spray or pumped recirculation cleaning process. Proper application and engineering with respect to return pump selection, spray device selection and piping installation makes it possible to conduct such cleaning operations with a high degree of uniformity and dependability in accord with cGMP.

Frequently, CIP system types are referred to as being of '3-tank', '2-tank', '1-tank', etc. Large multi-tank CIP systems are remnants of conventional dairy equipment companies. The multi-tank CIP system concept implies that a dedicated tank is provided to serve as a 'wash tank' for caustic and acid detergent cleaner makeup. Additional tanks beyond the first tank would be for DI, purified and/or WFI water storage. In reality, most CIP programmes can be served from a single multipurpose tank, with as little as 50 gallons (189 ltr) capacity, if the water supplies are adequate to keep up with the requisite delivery, especially during rinses. However, if DI, WFI or other purified water supply is substantially lower than the CIP delivery rate, then the CIP system may require one or more storage tanks of the required forms of purified water.

Also, for CIP systems that use an eductor, a minimum of two tanks is required. One tank serves to allow motive recirculation through the eductor simultaneous with rinse water supply from another tank. Thus, from the beginning of the cleaning cycle to the end, the eductor is able to continuously exert negative pressure on the CIP return flow path.

Full-featured portable CIP systems are now available, which pass through a standard door opening of 3 ft (1 m) width or less. Of course, for manoeuvrability, it is advantageous for a portable CIP system to have absolutely as compact a footprint as possible. In a portable CIP application, the CIP system is wheeled to within close proximity of the process area equipment to be CIP cleaned. At the use location, utility services are required with quick-disconnect hook ups.

Future considerations

With increasing regulatory attention to process cleanability and sterility, design engineers encounter greater need for automated CIP in a variety of process sectors, each with particular challenges. Examples are large-scale production chemically synthesised active pharmaceutical ingredients, dry product processes and personal hygiene products.

The scope of the design challenge is less daunting and burdensome when one understands that much of what is required has been achieved previously, perhaps in another context. By utilising the resources of industry experts early in the concept design, cleanable construction and automated CIP can most effectively & efficiently be integrated into processes. MPh

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