# CIP OF A LIQUID MIXING AND BFS PROCESS

## CIP Cleanable Processes

In-place cleaning was first applied in the dairy industry in the late-1940's. The first dairy plants to apply automated in-place cleaning to an extensive degree were placed into operation in 1960, with considerable equipment in even those early operations still being manually cleaned. Beginning in 1965, CIP was recognized as the key factor for many other changes in dairy and food processing technology. CIP procedures led to the development of all-welded product piping systems, application of air-operated CIP cleanable sanitary valves, and appreciable increases in the sizes of processing tanks as compared with vessels that had to be manually cleaned. During this period Clean-In-Place procedures were applied extensively in many non-dairy, food and beverage industries, including brewing, wine processing, meat processing (smokehouses), as well as numerous processes which handled dry products in stainless steel equipment.

By the late 1970's, full CIP systems were implemented on liquid feeding solutions, albumin solutions, and blood fractionation processes. Today, CIP has been applied to various pharmaceutical processes both for liquid (fermentation, blood fractionation, IV solutions, parenteral solutions, respiratory care products, etc.) and solid (crystallization, filtration, drying, milling, blending, bulk container filling, etc.) product manufacturing.

By the late 1980's, CIP had been applied to the product formulation equipment supplying blow-fill-seal (BFS) packaging systems. Product blending, storage, and high-temperature sterilization were all accomplished under automated programmable logic control. Complete cleaning of the BFS system was accomplished manually or as a combination of manual and automated procedures.

## CIP Technology

As practiced today, CIP (Cleaning-In-Place) is the procedure by which flush, wash, rinse, and (generally) sanitizing solutions are brought into immediate contact with all soiled surfaces and continuously replenished. The cleaning process is essentially chemical in nature, and generally utilizes recirculation to minimize water and chemical costs.

CIP cleaning is usually accomplished via flush, chemical wash, and rinse solution contact utilizing spray devices for tanks or pressure recirculation for lines, all under controlled conditions of time, temperature and chemical concentration in a reproducible manner.

Processing equipment and piping systems which are cleaned-in-place receive less wear and tear (and damage) than comparable items which are manually cleaned. With automated CIP, labor required for cleaning and maintenance is substantially reduced and the processing system productivity is increased through a reduction of down-time.

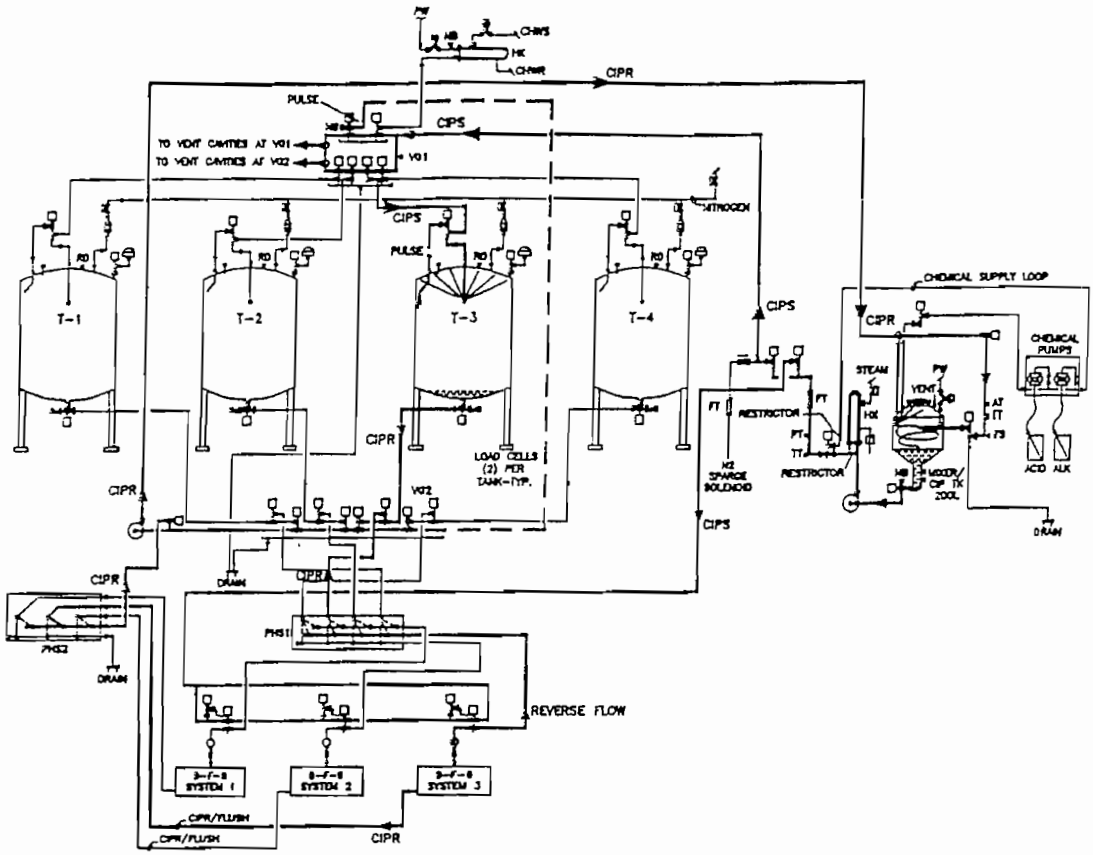
## Integrated BFS Process and CIP

The 1996 process suite expansion at Dey Laboratories (Napa, CA) included liquid mixing, storage, and transfer to blow-fill-seal (BFS) systems. The entire multi-product process train, from liquid mixing through all product-contact areas of the BFS system, is cleaned utilizing an automated CIP system. This process includes the equipment and interconnecting piping shown on Figure 1, which is heavy lined to define a BFS CIP circuit to be described in a subsequent paragraph.

## Solution Preparation

Small quantities of readily water soluble ingredient powder are added to a pre-weighed quantity of water via recirculation. The mixing process occurs as ingredient is charged through the manway of an Electrol Specialties Company Model SUTR recirculating system, modified to serve both as the CIP recirculating unit and product mixing vessel.

Figure 1: Schematic flow diagram of process for product mixing, storage, and transfer to the BFS system, with heavy line indicating the combined CIP circuit of these areas.




Features of the Mixer/CIP System are as follows:

a) Two PW drops, one used to supply the process tanks with PW for formulation operations and the other for supplying the Mixer/CIP tank with PW for CIP operations.

b) Four jacketed process tanks equipped with spray balls for CIP operations, and a no foam inlet for PW addition and recirculation/mixing during formulation.

c) A Mixer/CIP tank equipped with a spray ball for PW addition, a second spray ball for tank self-cleaning during CIP, and a tangential inlet for product recirculation during formulation operations along with CIP return during the cleaning cycle.

d) Two centrifugal pumps, one used for recirculation from the Mixer/CIP System to formulation tanks, and the other used for recirculation from the formulation tanks through the filling machine or to return solution to the Mixer/CIP System.

e) Sanitary mix proof valves to prevent cross-contamination while running multiple operations.

Other features of the system include flow control valves for control of the flow rate of solution, a flow meter used to control the quantities of solution used for recirculation and rinsing, a heat exchanger for temperature control, and a PLC-based control system with datalogging for recording process parameters during CIP and formulation operations.

The mixing process begins as PW from the facility loop is weighed into any of four 2000 L product holding tanks, designated T-1 through T-4.

Recirculation is then established between the selected holding tank and Mixer/CIP System for addition of the dry ingredients (actives and excipients). At the end of drug addition, and some additional recirculation to assure complete mixing in the holding tank, a sterile nitrogen blowdown system transfers all solution to the selected holding tank by first clearing the line from the tank to the mixer, and then clearing the discharge line to the holding tank.

### Tank/Filler Utilization

A U-bend transfer panel (PHS1) provides a physical make/break connection between any of the four holding tanks and any of three BFS filling systems. Solution is transferred from the holding tank to the designated BFS system by application of over pressure on the source vessel. After the filling transfer is complete, transfer panel PHS2 allows rinsing the hold tank through the BFS system and to drain, this procedure normally being used between batch change overs. Transfer panel PHS2 permits return flow from the BFS systems to be directed to drain (for rinsing), or to the CIP return system.

Following mixing of each batch, the transfer piping and mixer are isolated from the product holding tanks by mixproof valves, to permit CIP cleaning of the mixing flow path, without risk of contaminating product-containing tanks with cleaning chemicals.

After product transfer to the BFS system is complete, the hold tank may be cleaned in combination with the mixing lines only, or with the BFS system included in the circuit per the heavy-lined path shown on Figure 1.

### CIP of BFS Systems

The three Rommelag Model 360 BFS filling systems are capable of being interfaced with the CIP system to achieve automated cleaning of all product contact areas. CIP solution from the CIP supply line follows the product flow path through the filler surge tank and nozzle feed lines, including cleaning the two sterile filter housings, from which the cartridge has been removed prior to CIP. A "slide valve" closes off the bottom of the left and right air shower boxes, creating a liquid-tight enclosure. In addition to the nozzles, the air shower boxes are included in the CIP process to remove potential aerosolized product residue. The BFS system is cleaned in a three-step sequence that is repeated during the pre-rinse, wash, and final rinse steps of the CIP cycle.

Step 1 - CIP Solution is supplied through the filler surge tank, feed lines, and to both the left and right nozzle sets and then exits to CIP return via air shower box and slide valve connections. A side stream of CIP supply also flows through the respective air bleed lines and to CIP return. Figure 2 is a simplified representation of the Rommelag 360 process lines pertinent to CIP.

Step 2 - The CIP solutions are next diverted through the high-volume air supply line permitting greater flow to flood the left air shower, with exit to CIP return via a dedicated connection at the top of the chamber Figure 3.

Step 3 - The right air shower box is cleaned in an analogous manner to the left side.

### Cleaning Validation

Cleaning validation for the blending and storage tanks was conducted via established swab and rinse methods.

Separate protocols were developed for cleaning validation of the BFS system. Swab residue samples for product and cleaning chemical residue were taken at the bottom of the filler surge tank, the top of the second sterile filter housing, a set of nozzle tips, the air shower box wall, and the CIP return line (Figure 4). The maximum acceptable limit for the active in swab samples was established as one-thousandth of the active concentration in the finished product. The highest level found in swab samples was 0.09 ppm, with a limit of detection of 0.01 ppm.

Figure 2: Schematic flow diagram of selected BFS system lines, with heavy line showing CIP sequence step for solution supplied through the filler surge tank, feed lines, and to both the left and right nozzle sets.

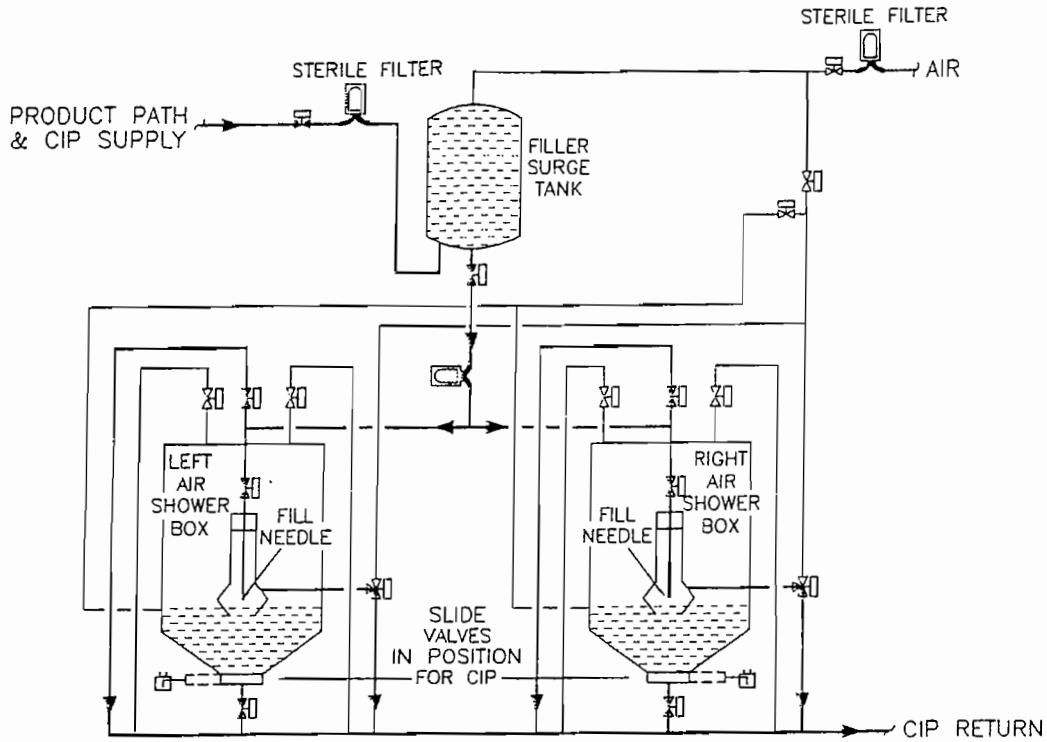



Figure 3: Schematic flow diagram of selected BFS system lines, with heavy line showing CIP sequence step for solution supplied through the left air shower box.

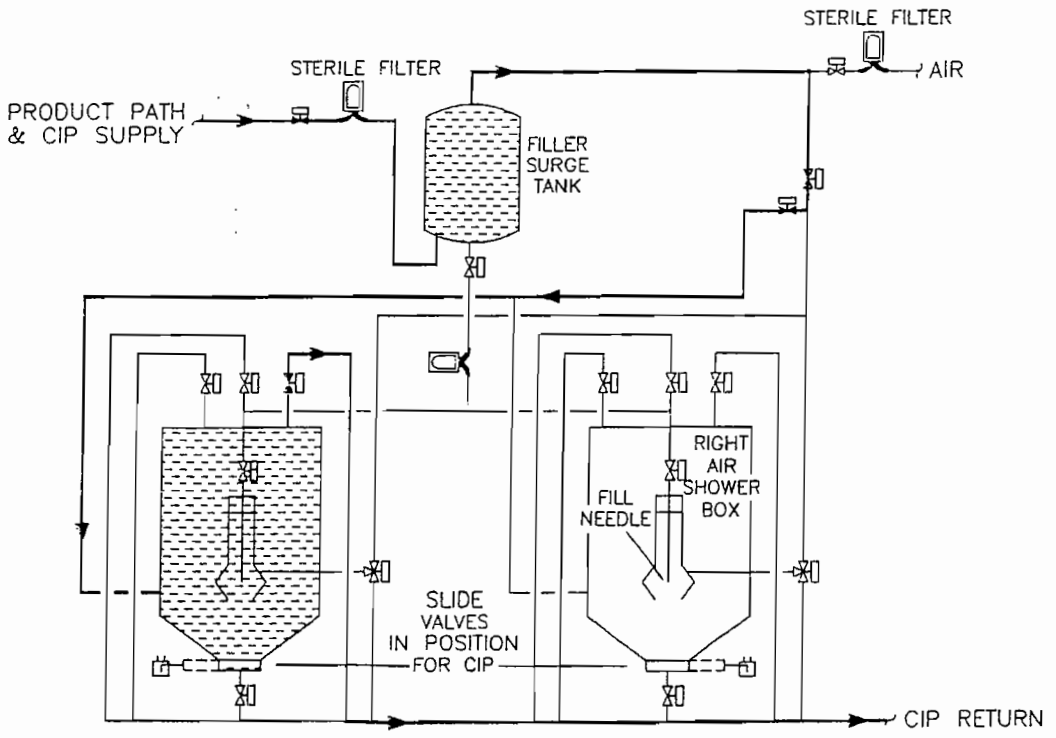
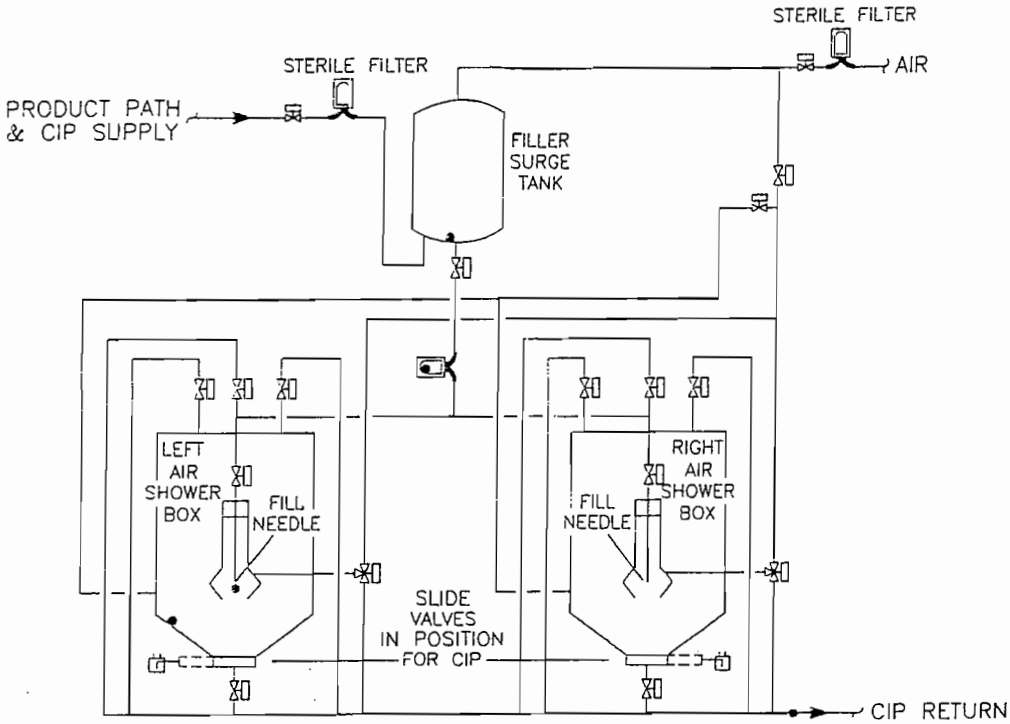


Figure 4: Cleaning validation swab sample locations for BFS system.




Microbiological swabs were taken of 25 sq. cm (2 in. by 2 in.) areas. The maximum acceptable working limit was established as 1 colony forming unit (CFU) per sq. cm (25 CFU per sample). The highest level found in swab samples was 5 CFU.

In addition, endotoxin rinse sampling was performed on CIP return effluent.

## Conclusion

The CIP/SIP process implementation at Dey Laboratories involved far more than the selection and application of cleanable pumps, tanks, sprays, valves and controls. The integrated cleanable design of the product mixing, storage, and BFS filling process incorporated processing equipment design conducive to CIP application, equipment layout, and finally the design of the process to provide for proper cleaning via configuration into CIP circuits. Accountability for these critical aspects from process conceptualization through final installation was central to achieving the fully cleanable process.

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