

WHITEPAPER

WHY A CIP SYSTEM IS ONLY AS GOOD AS ITS CIP LANCE



CIP/SIP in pharmaceutical production – no chance for cross-contamination

Cleaning is an important process step in pharmaceutical manufacturing and part of GMP-compliant production. The aim is to prevent contamination and cross-contamination so that pharmaceutical manufacturers can provide patients with safe, high-quality medicines. In accordance with GMP regulations, the cleaning of product-critical surfaces must be carried out and documented in accordance with defined procedures that have been tested for suitability. Cleaning in place (CIP) followed by sterilization in place (SIP) has become the standard procedure for cleaning equipment and containers in the manufacture of pharmaceuticals, biopharmaceuticals and active pharmaceutical ingredients (APIs). While manual processes, in which the equipment was dismantled and cleaned by hand, still dominated in the 1950s, automated CIP systems are now state of the art. Since some systems have to be cleaned and sterilized several times a day, depending on the process, product variety and batch size, an automatic cleaning system saves time and labor and ensures process reliability. The cleaning systems permanently installed in the systems ensure that hygiene standards and regulatory requirements (e.g., GMP, FDA, EU-GMP Annex 1) are met.

"Our innovative orbital welding technology enables us to manufacture CIP lances with minimal dead space and tight angles. This allows us to clean even systems with complex geometries."

Dr. Lydia Fehlberg

Setup of a CIP system

A typical fully automatic CIP system consists of peripheral equipment with controls, tanks, sensors, valves, and heat exchangers. The actual cleaning process is carried out by individually and specially developed spray nozzle systems, known as CIP lances.

The fixed or rotating spray devices are designed and positioned in the system in such a way that even hard-to-reach areas are thoroughly cleaned and dead spaces and spray shadows are avoided. This ensures that all areas are reached by the spray film. CIP lances are therefore not only one of the most important components of a CIP system, but are also subject to the same GMP-compliant design requirements as the system itself. Their construction and design must therefore be in the hands of specialists with extensive project, material, and manufacturing expertise.

"Dockweiler stands for high quality in the manufacture of interior and exterior surfaces and guarantees GMP-compliant CIP lances."

Dr. Lydia Fehlberg

Cleaning process sequence

The automated CIP cleaning process consists of six steps:

1. **A pre-rinse with acid or lye removes coarse contaminants.**
2. **The post-rinse removes cleaning agent residues.**
3. **Acidic cleaning solutions tackle mineral and protein deposits.**
4. **A disinfectant kills microbes.**
5. **The final rinse is carried out with ultrapure water.**
6. **Finally, the SIP process uses hot ultrapure steam (>120°C) to eliminate bacteria, viruses, and other microorganisms and sterilize the system.**

Acids, alkalis, and water for injection (WFI) or purified water (PW) are used as cleaning fluids. Due to the aggressiveness of the cleaning agents and the high temperatures, all components must be made of corrosion-resistant materials. This applies in particular to the spray system, including the CIP lances.

Every CIP system is a prototype

The variety of equipment used in pharmaceutical production is high, ranging from biopharmaceutical plants to solid manufacturing. Each CIP system therefore has its own special features and requires detailed planning, as tubing, valves, and tanks must be optimized for complete cleaning. During construction and design, the manufacturer must avoid dead spaces, observe the angle of inclination of tubes, and much more, which makes every CIP system a prototype and complicates standardization. A concept for the disposal, treatment, and/or recycling of cleaning fluids is also part of the planning. More and more pharmaceutical companies are demanding a sustainable approach in this area.

Reproducible cleaning results

Reproducibility and documentation are crucial for the validation of the CIP process. For each CIP process, there are critical parameters such as temperature, flow rate, chemical concentration, cleaning agent, cleaning time, and conductivity of the final rinse, which are subject to defined specifications. All parameters must remain within these specifications throughout the entire CIP cycle and are continuously monitored. If the results are outside the specifications, the cleaning must be repeated and the start of the next batch is delayed.

A common method for identifying weak points in a CIP system is the riboflavin test. To do this, the inside of the system is sprayed with a riboflavin solution and then cleaned according to SOP. Riboflavin residues then become visible under UV light, indicating dead spaces and incomplete cleaning.

The conductivity of the final rinse is also used to check the cleaning. If the conductivity exceeds a defined value, this indicates that there are still residues in the water that require further rinsing of the system.

The CIP lance in the lyophilizer's CIP/SIP system – always unique

The design of lyophilization plants is typical special-purpose machine engineering. No two plants are alike: the size of the drying chamber, the footprint, the ice condenser chamber – many factors depend on the individual process of the pharmaceutical company. To prevent contamination by germs and cross-contamination during batch changes, automated CIP cleaning processes are state of the art. These are adapted to the freeze drying plant and equipped with flexibly configurable CIP lances. The cleaning agent is fed through the CIP lance system and enters the interior of the plant via the spray nozzles.

Dockweiler specializes in tailor-made CIP lances for freeze drying plants that are more than just an installation component. The provider of process solutions for the transport of liquid and gaseous media is a leading manufacturer of stainless steel tube systems and custom-made products for the pharmaceutical industry as well as semiconductor manufacturing. Dockweiler has designed over 1,200 customer-specific CIP lances since 2009, with another 150 added each year.

Lyophilization systems – indispensable in biopharmaceutical production

Lyophilization is an important process step in biopharmaceutical production. It preserves drugs with sensitive active ingredients in a gentle manner and protects them against external influences such as light or temperature fluctuations. The liquid formulation is first frozen and then the water is removed through a series of sublimation and desorption steps. This involves three steps: freezing, primary lyophilization and secondary lyophilization.

What is a CIP lance and what installation options are available?

In simple terms, a CIP lance is a straight pipe with various welded nipples and branch tubes, which are also equipped with welded nipples. These nipples have threads onto which spray nozzles are screwed later. Each welded nipple is mounted at a defined angle to avoid spray shadows and to clean the interior of the lyophilizer completely. In the basic configuration, there is a lance in each corner of the system, which can branch out into a complex spray system to clean hard-to-reach areas inside the freeze dryer.

CIP lances are usually permanently installed. However, there are also retractable lances that are retracted after cleaning so as not to interfere with the process.

Every Dockweiler CIP lance is a prototype. It is manufactured in batch size 1 at the request of the freeze-drying manufacturer and individually adapted to the specific geometry of the plant. The inner and outer surfaces of the tubes and welded nipples are made of high-quality stainless steel. The internal orbital welding technology enables the welding of dead space-free and particularly tight-fitting branches. The spray nozzles can thus reach even the most remote corners of the freeze-drying system and completely eliminate spray shadows. This benefits the CIP process and ensures that the riboflavin test, which is mandatory for the validation of every system, is passed without any problems. For optimum corrosion resistance, purity and quality, Dockweiler offers the option of final wet cleaning, which also removes tarnish in the area of the weld seams.

"Together with our welding engineers, we check every design drawing provided by our customers for practicability and manufacturability."

Dr. Lydia Fehlberg

Focus on the customer

Image: Dockweiler



A typical project begins for the Dockweiler experts with drawing the desired CIP lance and configuring it. The drawing is then checked in-house for technical feasibility and manufacturing options. The experts are often able to optimize the adaptation of the weld-on nipples in order to reduce manual weld seams and optimize orbital weld seams. This brings many advantages for the customer. Above all, the documentation effort is reduced, as each manual weld has to be laboriously checked for leaks. Orbital welding, on the other hand, is a semi-automated process step that saves time and money. Once all optimization steps have been completed, the costs are calculated and a quote is prepared.

Design and manufacture: Expertise makes a difference



Image: Dockweiler

Modern welding technology

The GMP-compliant design of pharmaceutical plants and components involves several aspects. Dead spaces, i.e. areas of the plant that cannot be reached by the cleaning medium, are particularly feared. That is why Dockweiler uses orbital welding technology for the manufacture of CIP lances, which is always used when precision and high quality are required. This particularly innovative welding process makes it possible to weld dead space-free and close-fitting branches. "Dirt corners" where preliminary products or even germs can accumulate are thus largely eliminated, preventing cross-contamination and contamination. Another advantage of orbital welding is the high reproducibility of the weld seams. Once a welding sequence has been successfully completed and stored, it can be repeated virtually indefinitely, with consistent results and virtually no weld seam defects. In terms of CIP lances, the result is a high-quality product in which every weld seam is virtually identical. Pharmaceutical customers also benefit from the experience Dockweiler has gained in semiconductor manufacturing. The acceptance criteria here are particularly strict: seams with a narrow root (to minimize the weld seam surface inside the tube), complete penetration of the inner diameter, and no permanent discoloration are requirements that the industry demands.

GMP-compliant surface treatment

Another important requirement in GMP-compliant plant engineering is surface quality. A smooth surface that is easy to rinse off is a top priority. Grooves or cracks are not permitted

Standards and specifications for CIP/SIP systems

CIP/SIP systems and components, such as CIP lances, must comply with international standards to ensure safety and quality:

- **GMP (Good Manufacturing Practice):** Requirements for the manufacture of medicinal products and life sciences.
- **FDA (Food and Drug Administration):** Hygiene standards for the food and pharmaceutical industries.
- **EU GMP Annex 1: Guideline on the "Manufacture of Sterile Medicinal Products"**
- **EHEDG (European Hygienic Engineering and Design Group):** Guidelines for hygienic design and cleaning.
- **HACCP (Hazard Analysis and Critical Control Points):** Food safety standards.



here, as bacteria or pre-product can accumulate in them. Dockweiler subjects its CIP lances to various surface treatments to achieve roughness values that guarantee the required cleanability:

- **Pickled:** Pickling in an acid or alkali bath removes, for example, discoloration in the weld seam area or other contaminants.
- **Electropolished:** The electrochemical process reduces micro-roughness and creates a smooth, corrosion-resistant surface without imperfections.

In addition to needle marking, Dockweiler also offers electrolytic marking, which enables smooth surfaces. To prevent aggressive cleaning agents from damaging the surfaces of the CIP lances, the components of the CIP lances are made of corrosion-resistant stainless steels (usually 1.4404, 1.4435, or 316L).

Image: Dockweiler



Tarnish in the area of the weld seam of CIP lances not only detracts from the appearance, but also poses a hygiene risk. The surfaces roughened by the tarnish are a gateway for rust and a place where bacteria can settle. Dockweiler therefore offers several methods for removing tarnish, e.g. wet cleaning and pickling.

At Dockweiler, the final step is internal quality control, without which no CIP lance leaves the production facility. For hand welds, this includes dye penetration testing and video endoscopy of the welds inside the CIP lance.

Qualification - fully documentation and digitally available

Many manufacturers of lyophilization systems carry out system qualification prior to hand-over if requested by the pharmaceutical operator. Dockweiler supports GMP-compliant implementation by providing complete documentation of all CIP lance manufacturing steps and ensures that the path from raw material to delivered product can be traced. Depending on customer specifications, this includes technical documentation such as video endoscopy of weld seams, dye penetration testing of hand welds, and electropolishing certificates. It goes without saying that the CIP lances meet all necessary specifications. These include, for example:

- **VT inspector qualification according to DIN EN ISO 9712**
- **Welding products according to DIN EN ISO 9606-1**
- **Evaluation of welds by visual inspection according to DIN EN ISO 5817**
- **ASME BPE**

Modern orbital welding machines, such as those used by Dockweiler to manufacture CIP lances, feature real-time measurement and display of process-relevant parameter values. Each weld is fully logged and stored as a data record.

Using the online WebCert tool, customers can access all the necessary certificates, documents and other paperwork for an order via the Internet – worldwide, as soon as the CIP lance leaves the warehouse. A simple search by order number, project number, batch number, etc. is possible at any time and also allows users to search for past orders.

Brief profile of Dockweiler

Dockweiler AG is one of the world's **leading suppliers of stainless steel tube systems for technical gases and sensitive liquids**. Our products, such as tubes, fittings, connections, and customized solutions, are used for media supply in the future-oriented industries of micro-

electronics (semiconductor industry), life sciences (pharmaceuticals and biotechnology), and new energy (photovoltaics and plasma fusion). For many decades, we have been supporting our customers with our **expertise as a supplier to high-tech industries**.

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