

CIP: Current Challenges and Future Developments



Cleaning in Place may have been around for over 50 years, but many of its original challenges still remain to be resolved

By Nick Jeffery and Elliott Sutton at Suncombe Ltd

Nick Jeffery is a Project Engineer at Suncombe Ltd. He has been working with CIP technology for nearly 15 years and has been involved in all aspects of the entire life-cycle of CIP projects, from initial concepts to hand-over. Originally an electrical and control engineer, he has worked with Suncombe for over ten years, successfully performing a number of roles throughout the organisation, gaining experience in all aspects of CIP such as projects, design elements, operations and current legislation. Nick has lectured widely and written numerous articles on the subject of CIP.



Elliott Sutton is a CIP engineer at Suncombe Ltd. A highly qualified engineer, he obtained a BSc in Product Development and an MSc in Design Engineering from the University of Middlesex (North London, UK). He has extensive knowledge of the technology of CIP, as well as of lean manufacture, concurrent engineering and other prevalent engineering management concepts.

Cleaning in Place, more commonly termed CIP, is a method of cleaning the interior surfaces of vessels, process equipment, pipes, associated fittings and equipment, with the minimum of disassembly and human intervention. Up until the 1950s, closed systems were disassembled and cleaned manually. The advent of CIP was a blessing to industries that needed frequent internal cleaning of their process equipment. CIP has developed over the years into a well-defined discipline with recognised design standards.

So let's take a look at the results of CIP. Cleaning in Place results in the equipment being chemically clean; this is defined as "the removal of all residues of soil and all CIP agents so that contact with the cleaned surface does not

result in physical contamination". If the equipment being cleaned needs to be micro-biologically clean, then an additional process – Sterilising in Place (SIP) – needs to be carried out. SIP is the generic term for sanitising, disinfecting or sterilising equipment, and results in the removal of any remaining microbiological contamination.

CIP started as simply a manual system involving a storage tank for the cleaning solution, centrifugal pumps and a connection to the system

being cleaned. Since the 1950s, CIP has evolved to include fully automated systems with programmable logic controllers, multiple tanks, sensors, valves, heat exchangers, data acquisition and specially-designed spray nozzle systems.

The technique relies on the basic principle of applying a suitable detergent solution or solvent at an appropriate flow, pressure, temperature and concentration for a given length of time. In order to ensure successful cleaning, the required amount of energy must be applied to the surface of the equipment being cleaned. The cleaning energy is primarily provided by the temperature of the solution (thermal energy), the detergent or solvent used (chemical energy) and the application of suitable pipeline velocities or pressures (kinetic energy). As well as the level of cleanliness achieved, CIP has brought a number of other benefits, including speed and turn-around times, labour reduction, health and safety, repeatability and the ability to validate.

After 60 years of CIP, most challenges would have been expected to be overcome, especially considering that the basic principles of CIP have not changed. The recommended cleaning velocities, times and methodologies are still valid and are still required. But even after nearly 60 years of use, many of the original challenges to CIP designers still remain.

CURRENT CHALLENGES

Design for Cleanability

Design for Cleanability was one of the main original design hurdles. Plant and equipment had not been

Figure 1: Suncombe PharmaCIP™ – Total Loss CIP





Figure 2: Suncombe PureCIP™ – CIP for Clean Areas

designed to allow it to be cleaned without first being disassembled. This lack of 'Design for Cleanability' manifested itself in many ways, including equipment that could not be effectively drained at the end of a CIP clean, dead legs in pipework that produced bug traps, valve designs that were not hygienic and so on. Although processing equipment is now normally designed with CIP in mind, it is worth noting that specifying cleanability is worthwhile for every piece of equipment.

In the past, CIP was often considered as an afterthought when designing an overall process scheme. Although things have improved, it still often happens that the CIP aspect of equipment is designed after the processing functions have been defined and detailed. Worse still, aspects of CIP are often affected by the budget cuts that normally occur within a project.

Cleaning is often one of the first operations done during a processing plant's commissioning activities, and consequently needs to be one of the main factors to be considered in the design. If not, then this can result in

One of the main challenges to CIP systems throughout their life-time has been the selection of chemicals – something which is often carried out late in the project life-cycle. At this stage, it can be difficult to incorporate any design requirements related to the selected chemical solution. The chemical requirements need to be considered early in the project brief, as the chosen chemical becomes part of the validated methodology

equipment that does not operate at its optimum design capabilities.

Early Chemical Selection

One of the main challenges to CIP systems throughout their life-time has been the selection of chemicals – something which is often carried out late in the project life-cycle. At this stage, it can be difficult to incorporate any design requirements related to the selected chemical solution. The

chemical requirements need to be considered early in the project brief, as the chosen chemical becomes part of the validated methodology. CIP design can also be influenced by the selection of chemical, and this necessitates selection at the earliest stages. Design factors that can be affected include materials of construction (for example, problems with chlorine-based chemicals and stainless steel), the number and type of chemical pumping stations required, chemical storage requirements, instrumentation design and selection, and the chemical safety systems.

Sometimes a basic chemical is selected through prior use, or simply its availability. The chemical needs to be considered in more depth to ensure the optimum solution for every specific requirement. There are a number of global chemical companies which offer the facilities to test and develop a chosen chemical solution, and provide a validated chemical with a guarantee of availability over many years. Early selection is beneficial because the later the changes happen in the design process, the higher the costs of initiating those changes.

Change of Operating Environment

Trends suggest that pharmaceutical manufacturing systems are moving away from dedicated single product facilities to highly flexible multi-purpose plants, with the ability to switch to shorter campaigns with more product diversity in a fully validated facility.

This smaller batch, multi-product environment means even more product change-overs, thereby increasing pressure to reduce turn-around times. In some campaigns, the cleaning time is in the range of 30 to 50 per cent of the processing time and, in some extreme cases, the equipment could spend more time cleaning than processing. This cleaning time has a significant impact on the efficiency of the overall production

operation. Designing for CIP, therefore, needs careful attention, as a good cleaning design will minimise the time (and cost) that the processing equipment needs to stay in clean mode.

Quality and Standards

CIP engineers have welcomed the acceptance of a number of biopharma standards and guidelines to try and standardise the quality requirements of CIP equipment. Incorporating aspects of ASME BPE, GAMP, HACCP and 21 CFR 11, CIP is now fairly well-defined, and the end-user is aware of the type of standards that CIP needs for successful design and manufacture. The issue remains, however, that these standards need to be rigidly applied.

CIP Education

Clean-in-Place is a vital component in most pharmaceutical manufacturing processes and consequently knowledge of CIP is required by engineers, project managers and operators. The increase in the number of training courses and qualifications in CIP is to be welcomed (for example SME, ISPE, NVQ and so on).

There is no doubt that the knowledge obtained is excellent and provides a tremendous amount of information on the basic principles and validation requirements of CIP. Understanding Cleaning in Place requires a deeper understanding than just the theoretical principles, with a real need for practical application knowledge. Some industry suppliers (for example, equipment and chemical suppliers) also run training courses; these encompass the theoretical aspects of CIP, but often also provide a more practical approach to CIP.

FUTURE DEVELOPMENTS

Lean Manufacturing

In the 21st century, 'Lean Thinking' is becoming a dominant trend in production and manufacturing management, with a focus on 'Lean' in most management courses and qualifications. Lean manufacturing is the production implementation of lean thinking, and is based on maximising value and minimising waste in the manufacturing process.

Lean manufacturing in production often means the adoption of shorter runs, quicker change-overs and lower inventories. In order to achieve this, the production line of today must be more flexible. One of the difficulties with the lean-manufacturing, short-run philosophy lies

in the down-time consumed to make the change-over for the next run. This normally requires cleaning the equipment for each change-over and creates an inefficient hold-up.

Taking the Lean Manufacturing model of seven forms of waste, CIP cleaning is a critical component (see Table 1).

Life-Time Costs

One critical insight is that most costs are incurred when a product is designed. CIP systems can have a high capital cost, and this tends to encourage a tendency to short-cut the budgets on CIP as this is not seen as a critical part of processing. This reasoning, whilst reducing initial capital financial risk, in reality increases life-time financial risk. An outcome of taking short cuts on CIP design and equipment is that any of a number of contaminants may be present in the next batch manufactured on the equipment, such as:

- ◆ Precursors
- ◆ By-products and/or degradation products
- ◆ The previous product
- ◆ Solvents and other materials employed during the manufacturing process
- ◆ Micro-organisms
- ◆ Cleaning agents themselves and lubricants

Increased Product Potency

The increase in potency, and hence value, of active pharmaceutical ingredients is steadily increasing – a trend which is necessitating more stringent system designs. This is prevalent in Powder-Handling equipment including isolators, powder transport and storage systems. As the potency levels increase, the

Table 1: Lean Manufacturing model of waste		
1	Overproduction	To minimise overproduction means shorter runs and hence more flexible equipment which requires more cleaning.
2	Waiting	Cleaning can take a major proportion of the available production time and Cleaning in Place minimises cleaning times.
3/4	Transportation/Motion	A CIP system has all of the cleaning equipment permanently fitted, thereby minimising the transportation of cleaning media and movement of people and goods which would otherwise result in wasted time, efforts, damage, deterioration and cost.
5	Defects	Automatic cleaning guarantees product quality and minimises defects.
6	Lower inventory	This means shorter runs and hence more flexible equipment that requires more cleaning.
7	Over-processing	Processing using clean equipment increases efficiency and minimises unnecessary processing.

Figure 3: Suncombe PureKleen™ – Validated Parts Washer



standards for operator protection must also increase. One aspect of this is the cleaning of equipment after production. Many powder-handling operations are currently carried out semi-manually, but these are gradually being phased out in favour of full CIP cleans – providing a guarantee of high potency product removal prior to operator intervention.

Reduced Use of Utilities

The worldwide trend towards a reduction in water usage will have a significant impact on the biopharma industry. CIP is one of the major users of water of all types in most facilities, and the trend will be to continue to reduce the volume of supply and thus reduce the resultant effluent. Spray device technology continues to advance and reduce the required flow rates to achieve the same cleaning results as with traditional spray devices. CIP systems will also include pressure and flow control automation as standard to optimise flow-rates and pressures. Minimising spray cleaning flow-rates obviously reduces water usage, but furthermore it reduces effluent loading (both in contained and non-

The worldwide trend towards a reduction in water usage will have a significant impact on the biopharma industry. CIP is one of the major users of water of all types in most facilities, and the trend will be to continue to reduce the volume of supply and thus reduce the resultant effluent. Spray device technology continues to advance and reduce the required flow rates to achieve the same cleaning results as with traditional spray devices.

contained effluent), electrical energy, heating energy and detergent usage.

Increased Demands for Operator Protection

While production issues will remain of key importance, the health and safety of personnel and protection of the environment will become a catalyst for design improvements, for example, in effluent handling and component maintenance.

As demands for lower and lower occupational exposure limits (OELs) grow, so too will the focus on other health and safety issues including lifting and workstation ergonomics. Manual cleaning – by its very nature of being manual – requires the movement, setting up and application of equipment. Less and less human intervention is deemed appropriate in industry, and consequently design and production protocols will focus on automatic and remote operation for many cleaning duties.

Cleaning Validation

Cleaning validation in the context of pharmaceutical manufacturing may be defined as:

“Establishing documented evidence which provides a high degree of assurance that the cleaning methods employed within a facility will consistently control carryover of product, detergents and extraneous material to a level which is below pre-determined level”.

Cleaning validation is an essential consideration in the pharmaceutical industry, as ineffective cleaning can result in cross-contamination of products, detergents and extraneous material. Such contaminants must be proven to be either completely removed or controlled to pre-determined levels, for quality systems, regulatory authorities and – not forgetting the ultimate necessity – the safety of the patient.

CONCLUSION

Cleaning validation in a way summates this entire article. The ultimate aim of conquering all of the challenges, and succeeding in all of the developments, in CIP is to ensure that there is always a fully validatable method of meeting cleaning, regulatory, and health and safety requirements. After its 60 years of operation, CIP still offers this solution and – with so much focus on the subject – can only improve over time.

*The authors can be contacted at
info@suncombe.com*