The key challenge currently faced by all segments of the pharma manufacturing industry is how to apply reproducible and consistent cleaning methods with sufficient process control, monitoring and batch documentation to meet validation requirements.

In the pharmaceutical industry, CIP was introduced in the 1980s and then became increasingly popular in the 1990s – especially in the biotech industry – as a direct consequence of the US FDA’s requirements for cleaning validation. Compared with the dairy industry, cleaning requirements and challenges in the pharmaceutical industry are significantly different and more complex: the process equipment is smaller and designed differently, and (typically) does not have the built-in CIP components found in a dairy plant.

**PHARMA MANUFACTURING SEGMENTS**

When it comes to CIP, the pharmaceutical industry cannot be viewed as one homogeneous whole. Instead, it is necessary to take a look at factors such as product characteristics, applied manufacturing processes – and hence cleaning (sterilisation) methods – GMP levels and regulatory requirements. These are all vastly different and so require that the industry be divided into segments: active pharmaceutical ingredients (APIs), solid (oral) dosage forms, sterile (liquid) manufacturing and biopharmaceuticals. Within all these segments, however, cleaning validation requirements call for a scientific approach to be taken.

There is a need to define analytical sampling methods and acceptance criteria for cleaning verification, as well as to evaluate cleaning parameters. The chemical engineer Dr Herbert Sinner defined four critical cleaning parameters in his TACT cleaning cycle: Time, Action flow, Chemical and Temperature. (Water quality is also a crucial factor when washing glass). These four parameters have been employed in recent years to define the requirements of automated CIP cleaning methods and systems.

In short, all segments of pharmaceutical manufacturing share common challenges that stem from cleaning validation – namely, how to apply reproducible and consistent manufacturing and cleaning methods with sufficient process control, monitoring and batch documentation to meet validation requirements.

**CLEANING CHALLENGES**

Traditional CIP approaches and designs do not address the specific issues and requirements within each pharmaceutical segment; these have often been manifest in the frequency of warning letters regarding ‘Equipment Cleaning & Maintenance’ cited by the US FDA and other regulatory bodies.

The distribution of applied cleaning methods for each pharmaceutical segment is illustrated in Figure 2.

**Active Pharmaceutical Ingredients (APIs)**

This segment covers the manufacture of chemically derived APIs that are used in the production of solid (oral) dosage forms. The traditional cleaning method for this segment is
based on a reversal of the manufacturing process – that is, it employs the solvents used for the primary manufacturing process as cleaning agents. The method – also known as ‘fill, boil and dump’ – relies solely on chemical cleaning with limited coverage of equipment surfaces and no physical (kinetic) cleaning effect.

Bearing in mind that product residuals are virtually insoluble in water, and that process equipment includes large reactors, condensers, scrubbers and 6-10” piping, traditional cleaning methods are rendered virtually useless from a cleaning validation perspective.

**SolidDosage Forms (SDFs)**

Solid (oral) dosage form (SDF) equipment is difficult to clean because of the complex equipment designs involved; these often require manual intervention to disassemble and clean. They also incorporate various parts that are impossible to clean *in situ* such as filter bags in fluid bed dryers and spray nozzles in coating pans. In addition, dry materials and semi-solid product residuals are partially or completely insoluble in water and cannot effectively be removed by traditional CIP methods.

Limitations in traditional CIP design have made it impossible to meet cleaning validation requirements and, as a direct consequence, SDF facilities have dedicated production lines that incorporate manual procedures. Despite the implementation of cleaning validation rationales and SOPs, cleaning still tends to be inconsistent and inefficient, and so the majority of cleaning operations are handled manually.

**Sterile Manufacturing**

When drawing a direct comparison with chemical APIs and SDFs, sterile (liquid) manufacturing has more stringent requirements for cleaning and sterilisation processes such as inline control of critical CIP/SIP parameters, batch reporting, QA documentation, cleaning validation and so on.

Following well-known guidelines from the International Society of Pharmaceutical Engineering (ISPE) and the American Society of Mechanical Engineers (ASME) 2009 Bioprocess Equipment (BPE) standard, sterile manufacturing facilities have accepted a standard approach to CIP/Sterilise in place (SIP) equipment design and processes; this is basically controlled by the same companies that drew up the guidelines – namely engineering firms and component vendors.

These accepted industry standards, however, do not always take account of up-to-date technologies and know-how. Instead, they tend to be copies of dairy CIP systems with certain additional design features such as a centralised CIP system comprising multiple (pressurised) vessels, flow-control as the main operating parameter, single-stage centrifugal pumps (high flow/low pressure) and static spray balls. There are a number of serious deficiencies with using this type of equipment design as its cleaning performance is somewhat lacking with regard to coverage and impingement. Furthermore, excessive amounts of water and chemicals are required to achieve a satisfactory level of cleaning.

If product residues are difficult to remove or the production equipment is complex – for example with built-in devices (formulation and mixing vessels) that cause shadowing and various pipe diameters (aseptic filling machines) with laminar flow concerns – then a traditional CIP system will fail as it will not have the performance and flexibility required to ensure efficient cleaning.

**Biopharmaceuticals**

Biopharmaceutical (and biotech) manufacturing facilities share many of the same requirements and deal with similar process-related issues as sterile (liquid) manufacturing facilities; however, when it comes to cleaning (sterilisation) there is an added layer of complexity with regard to microbial contamination.

Microbial and bio-film containment – and thus bio-burden reduction – represent some of the most important challenges in this segment, but there has been little progress or development in the US with regard to newer technologies for cleaning and sterilisation. Often, the ‘what if?’ risk scenarios promoted by engineering firms have prevented the implementation of robust, efficient cleaning methods and systems.
While, in the US, biopharmaceutical process equipment is cleaned either manually or using traditional, dairy-type CIP systems, in Europe the industry has moved on to newer CIP methods. These include the use of equipment that is designed to apply dynamic spray devices, thereby providing a resolution to the inherent problems with static spray balls in that:

- The rotation provides full coverage
- The higher operating pressures use kinetic energy to remove effectively even non-water soluble product residuals and eliminate blockage issues

**TRENDS & FUTURE DEVELOPMENTS**

When it comes to CIP as used by the pharmaceutical industry, some clear trends and developments are apparent. In order to comply with regulatory and validation requirements, current CIP designs and standards – as stipulated in for example the BPE 2009 – will need to be upgraded. Sanitary and hygienic considerations need to be linked to operational and performance requirements, and the implementation and use of all available cleaning parameters – as per the Sinner cycle – will be necessary for both clean-in-place and clean-out-of-place (COP) cleaning methods.

For this reason, decentralised modular hardware and software platforms for CIP (SIP) equipment will become increasingly popular, replacing traditional centralised CIP systems – currently custom-designed for each application by engineering companies – because they will meet process and validation requirements through the utilisation of all available cleaning parameters and tight process controls.

The FDA’s initiative regarding process optimisation and PAT will be implemented with greater force than ever, supported by systematic approaches – such as, for example, Six Sigma (1) – that can be successfully applied to optimise cleaning (sterilisation) processes, based on the collection, evaluation and use of valid process data. Again, the operation and performance limitations of current CIP methods and equipment make process optimisation impossible.

The FDA can also be expected increasingly to scrutinise manual cleaning methods in its efforts to move the industry to fully automated – and therefore repeatable and documented – cleaning methods.

Current cleaning validation master plans and approaches tend to be developed with little consideration given to actual CIP/COP cleaning methods and equipment designs. As such, the rationale for and justification of issues such as equipment hot spots, swabbing areas, limits of detection, carry-over, maximum allowable daily intake and so on will come under pressure, as they all represent ways in which equipment can fail to be cleaned properly.

Lean initiatives will become increasingly popular due to the high operating costs of US and European pharma manufacturers. As a result of manufacturing optimisation and pressure to reduce operating costs, dedicated production lines (originally implemented to reduce or eliminate cross-over contamination issues) will be replaced by multi-purpose lines: this trend will increase the need for efficient automated CIP cleaning methods. As an example, Pfizer is now closing several manufacturing facilities after its purchase of Wyeth, and plans to focus more on process optimisation (2).

With regard to the cleaning chemicals used, the industry will move towards formulated detergents manufactured in a GMP facility. This will limit the selection of available detergents as they are classified as APIs, and result in a greater focus on analytical methods for validation and online monitoring to prove the complete removal of detergents from process equipment.

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