

How to Future-Proof the Manufacture of Sterile Drug Products

ChargePoint Technology's Christian Dunne, Head of Sterile Solutions, explores the latest trends in containment and advises how pharma companies can adapt and thrive in a fast-evolving environment.

The aseptic pharmaceutical processing market is growing incredibly quickly – in fact it is projected to develop from \$62.2 billion in 2020 to \$73.6 billion by 2027.¹

This strong and sustained performance is being fuelled by greater demand for sterile drug products. To illustrate, the generic sterile injectable market is predicted to grow at a compound annual growth rate of 11.3% moving from 2020 to 2030 to reach a value of \$198.7bn.²

A factor that is driving this growth is the way in which modern therapies have changed their approach to helping patients. There has been a shift towards more targeted therapies, which has resulted in products being produced in smaller batch sizes. This is increasingly true in aseptic processing and that means pharma manufacturers have to consider how to produce these products efficiently and cost-effectively at a smaller scale. This has significant implications for manufacturers, who have to rethink how facilities are designed and re-assess capex spending.

As with any significant shift in process, any changes that are implemented need to be ones that are functional in the long-term, especially in today's rapidly changing environment. This can only be achieved by first assessing the principal challenges facing manufactures involved in aseptic processing.

The challenges faced

The pharma industry is operating in an increasingly complex environment. The shift towards personalised treatments often means that it is not cost-efficient option for drug developers to build out facilities specific to each treatment, with all of the associated capex spending. In turn, this has led to greater outsourcing of many stages of

the manufacturing process that has resulted in a more fragmented supply chain.

Reliability of the supply chain

The changing nature of the supply chain has also led to some problems, notably the reliability of supply. This is now driving by pharma companies to consider diversifying their supply chains through the on-shoring of certain relationships, and the search for new suppliers that are more robust and reliable than existing partners.

As a result, manufacturers in the area are exploring ways of differentiating themselves from the competition. They are looking to do this through the expansion of their operational capabilities and building new aseptic lines, including the exploration of new markets.

This latter factor is crucial to drug developers, as it makes them less reliant on individual countries or regions, minimising any risk of future disruption. This has become a significant concern, after the impact of the COVID-19 pandemic led to problems in the supply of supplies for sterile manufacturing, such as ingredients for products and materials for packaging.

Regulatory

Managing customer demand for aseptic processing cannot just be met by expanding existing sterile capacity and maintaining standard operations.

The Good Manufacturing Practices (GMP) Annex 1 (sterile products)³ is about to have revisions come into action, after a consultation draft released in 2020.⁴ The updated Annex 1 contains a number of revisions that will have wide-ranging implications for aseptic processing and containment, particularly in relation to Contamination Control Strategy (CCS) in cleanroom zones.

An entire section has been added regarding closed systems, which provides a number of additional factors that pharma manufacturers will need to adhere to in order to ensure their CCS complies with the new Annex 1. This means that pharma manufactures will need to minimise the

number of manual interventions to ensure sterility, as well as being designed for integrity. As a result, a priority will be placed on carrying out thorough risk assessment and the monitoring of integrity, which will require additional methods to be put in place to comply with regulation.

Transit between facilities and regions

One area that should not be overlooked is the transportation of drug substances which, due to the changing nature of the industry, is becoming more important. For instance, the greater level of outsourcing is greatly influencing increased travel. The contract manufacture of sterile drugs allows pharma companies to reduce the demands for in-house means of producing their products. This is a trend seen across the industry and is expected to continue to grow. This will result in ingredients travelling more, across different facilities and different locations. All the while, sterility will need to be managed.

Batch size

As mentioned, it is now more common for smaller batches sizes to be needed for new types of products. For instance, 'precision treatments' in an area such as oncology will be catered towards the genetic profile of a patient, reducing the number of treatments produced in that particular area. With this comes a change within the manufacturing facilities themselves, where it is more common for a greater number of products to be manufactured in the same facility, with more specific process requirements. This means that equipment, and the facility itself, need to be able handle multiple process lines. The past saw greater investment into large-scale equipment and facilities, while the future may favour greater flexibility.

Speed

Directly related to the batch size is the speed at which operations are carried out. This can be directly linked to the product itself, where speed to market is becoming ever more important. This is particularly difficult when a processing environment must be sterile at every stage in production.

Cost

The traditional manner of producing large

batches is no longer cost-effective for all types of products. It is therefore imperative to find ways of reducing costs or gain efficiencies in the process. This is especially true as more stringent regulation increases demands on manufacturers.

Innovation is key

The obvious question is then how to increase the output of the end product whilst complying with increasing regulation and mitigate the aforementioned challenges? The answer is that this is happening through the updated offerings of containment technology offered by specialist solution providers.

The development and adoption of hybrid Single use (SU) technology, such as SU powder transfer bags and SU passive valves are examples of the way that containment equipment is changing to meet drug developers' needs.

The key advantages of SU equipment in sterile pharmaceutical production are numerous:

- SU technology can ensure the aseptic integrity of products during logistics, and in the manufacturing facility itself
- SU equipment is generally easy to use, with only limited training or production line upgrades needed
- The technology streamlines cleaning and validation procedures, as they are designed to be only used once prior to disposal. This improves integrity and also reduces production downtime
- Adoption of SU technology can also reduce the cost basis of the process, through the added efficiency gained by avoiding cleaning and washdown
- Transit between facilities or regions can be simplified through the use of SU bags instead of reusable alternatives

These factors allow firms to ensure optimum product quality, while improving process efficiency and reducing production costs. This is achieved because there is no need for cleaning or washdown procedures between batches. The SU equipment, such as SU bags, can be discarded immediately after use, which significantly streamlines the hygiene procedures required to maintain a sterile environment. This reduces production downtime compared to reusable alternatives. Manufacturers can also use SU bags to reduce the reliance on alternative means of transport, such as plastic or fibre drums, making the entire process more cost- and time-effective.

Added to this improved efficiency means that manufacturers can optimise the output of their lines, which enables them to produce more product without compromising on quality. In this way, the greater efficiency also reduces the cost base for the product created.

Innovation within SU technologies

A standout example of a piece of SU technology that can support drug developers in ensuring compliance with the developing containment legislation is the split butterfly valve (SBV). This technology provides a solution for the sterile transfer of powders, including drug substance and drug product. SBVs enable the transfer of powders into and out of process equipment during the pharmaceutical manufacturing process.

The SBV is comprised of two components: an active half, which is attached to the production line equipment and a passive half that connects to a filling container. The two halves are connected together in order to create a single plate. This allows the product to transfer from the line into the container via the interior of each half. The end result is that the power does not come into contact with the surrounding environment, which ensures aseptic integrity through the process.

A new SBV that functions with a disposable version of the passive components have also now been created. The principal benefit of this is to manage the same quality of aseptic processing but also greatly improving the efficiency of the process.

The disposable passive half is attached to a SU flexible charge-bag, enabling it to be contained and sterile during the transfer of powders through the manufacturing process, as well as between facilities. Once the disposable passive half has been used, there's no need for cleaning because it can be disposed of between fillings, improving efficiency.

The disposable SBVs are sterilised prior to use and their manufacture takes place within an ISO6 cleanroom environment. The sterilisation commonly takes place through the use of gamma radiation, qualified according to ISO11137. However, X-rays are now increasingly being adopted to reduce the degradation which sometimes occurs during the irradiation process. This sterilisation process, whether by gamma radiation or by X-rays, allows for the SBVs to

be used in aseptic processing environments – ensuring sterile integrity conforming to existing and forthcoming regulation.

The future of productivity and sterility

SU technology is just one element of measures to improve productivity, efficiency and sterility across the industry. Change is also arriving from other areas, particularly in the realm of improved technology and the use of data. Similar to other manufacturing industries, the potential for the integration of smart monitoring technology is enormous.

A growing example of continued innovation in the space is "smart factory" technology, which has huge potential to advance aseptic integrity. The "smart factory" concept allows pharmaceutical production lines to have real-time usage data of their equipment. This can aid drug developers to establish an audit trail quickly and efficiently.

For the individuals, such as health and safety teams, and those responsible for compliance, to have access to rich real-time data on the status of equipment installed on the line is invaluable. Through this, everyone involved can manage the validation programmes for the aseptic lines proactively.

More than this, the real-time data can be made available remotely to those individuals from a mobile device or through an online dashboard. As a result, health and safety team are able to gauge the usage of valve components at any time. This even allows individuals to monitor processing lines and individual components that are housed in different facilities.

The data can also be synchronised via WiFi to a portal, where data are stored in the cloud for production and process managers to analyse remotely and export for further reporting.

"Smart factory" technology is therefore able to significantly improve on traditional strategies to assess the health status of valves on the line, by providing a reliable and fully automated means of monitoring the technology.

The real-time data generate can then help line operatives to determine where and when maintenance is needed, before a situation arises whereby aseptic integrity or productivity is affected. This allows for



preventative action to take place proactively, minimising any potential downtime and helping to ensure compliance with the new Annex 1 integrity requirements.

An evolving space

As the demand for aseptic pharmaceutical processing continues to grow, it is certain that the space will continue to evolve. The trends that are already clear are the continued movement towards fewer manual interventions, as well as the push towards greater integrity and thorough risk assessment.

Luckily, there are now a greater number of tools that are being developed specifically to aid manufacturers to develop their processes alongside these changes. One of the benefits of SU technology is that they are a flexible tool that can be seamlessly introduced into current processes.

Moreover, the newer “smart” technology is able to go beyond just making the processes more streamlined to also provide a tool to the individuals working directly on the processing lines to be more proactive in maintaining operations. Reacting to the

larger movements in the industry now, through the adoption of such technology, is one way that manufacturers can prepare themselves now for future challenges and to advance aseptic integrity.

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Christian Dunne

Christian Dunne is the global product manager at ChargePoint Technology for the sterile containment solutions. For the past 20 years Christian has been creating innovative solutions for the pharmaceutical, biotech, cell therapy and fine chemical industries to overcome high potency containment and aseptic processing challenges. His technical expertise spans high containment isolators, grade A (ISO5) sampling & dispensing facilities, together with R&D and production filling line restricted access barrier systems (RABS) and isolators. For the past six years, Christian has been working with ChargePoint Technology on the advancement of its split butterfly valve technology, designed to handle highly potent/sterile powders and small-scale components, where both product and operator protection are paramount. While working on many aseptic applications, Christian integrated a number of different bio-decontamination systems and consequently has an in-depth understanding of their performance and application. This knowledge was key to the development of the now established ChargePoint AseptiSafe Bio®, used for the transfer of sterile powders in the industry. Christian is an active member of the International Society for Pharmaceutical Engineering (ISPE) and The Pharmaceutical Healthcare Sciences Society (PHSS).