Pharma Logistics IQ

SINGLE-USE SYSTEMS:
Overcoming challenges and mitigating risk in bioprocessing

This Pharma Logistics IQ report, produced in association with Parker Hannifin, explores the emergence of single-use systems in bioprocessing and their benefits compared to reusable equipment

Inside:

- Find out what the key current challenges are for bioprocessing and how single-use systems addresses these
- How single-use equipment can reduce complexity and decrease time to market

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Single-use items and their applications in bioprocessing

The pharmaceutical sector is becoming increasingly specialized. At the same time, pharma businesses are finding that they must diversify their portfolios to meet new and rising demands.

It is no longer the case that organizations have long-running campaigns focused on one individual drug before switching to their next product. Today's pharma manufacturers have fast-paced production schedules to respond to the needs of the market, such as the need for large quantities of the Covid-19 vaccine, which necessitated large-scale production facilities to be set up at record speed.

To enable this, manufacturers are shifting from utilizing reusable equipment, often made from stainless steel or glass, toward facilities kitted with single-use items made from plastics.

A typical single-use system consists of fluid path components – in other words, a container and mechanism intended to store or transfer fluids that is fully enclosed with a protective cover or packaging to protect from contamination. This is crucial in bioprocessing, where a sterile environment is required for processes such as vaccine development, monoclonal antibodies (mAB) purification, and cell and gene therapy manufacture.

In this report, produced in association with Parker Hannifin, Pharma Logistics IQ explores how single-use items can help solve biopharma's process challenges, including avoiding contamination, increasing speed-to-market and scaling up production.

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Current challenges for bioprocessing

A proportionally small number of drugs make it to market after undergoing clinical trials, estimated at around **12 percent in the US**. As a result, drug companies need to test as many concepts as possible with minimal spend to be viable.

This has led to a growing trend over the last two decades for producing biologic drugs that are targeted to individuals or very specific conditions and/or parts of the body, as the industry has realized that there is no single cure that can treat all patients. In 2020, biologics accounted for a quarter of the drugs market.

Biologics differ from other therapeutic classes because they are developed from living cells rather than chemical active ingredients through bioprocessing. These personalized medicines are produced in smaller volumes than "blockbuster" drugs, which have historically been manufactured in batches, allowing companies to respond according to the demands of the market.

As a result, more and more pharmaceutical organizations are switching to continuous processing, where manufacturing units are constantly utilized, increasing speed of production and preventing fluctuations. Fixed, reusable equipment requires thorough sterilization between production batches, meaning it is not well-suited to continuous processing. Instead, single-use items that can be discarded after a production run removes the requirement for re-sterilization between batches, reducing production lead times.

Research carried out by Pharma IQ among its members, found that by 2017 over 60 percent of survey respondents believed that biomanufacturing sites would one day become 100 percent disposable. Additionally, 59 percent said they were aiming to deploy a fully disposable system themselves.

In the intervening years, the Covid-19 pandemic has further accelerated this, impacting the manufacturing sector due to the need to rapidly scale up to produce vaccines at speed. The global crisis caused manufacturers around the world to deploy single-use bioreactors to enable the production of millions of doses of the vaccine at affordable costs.

The vaccine produced by AstraZeneca for example, required the growth of "producer cells" derived from humans in single-use bioreactors to avoid cross-contamination. Within these containers, conditions such as the temperature and pH are monitored very closely to ensure efficient growth.

Ken Wong, Head of Procurement, Asia at Sanofi Pasteur, says that having faster implementation times provides more flexibility to production plants. "Speed is everything," he says. "If you have competitors developing the same drug, the company with the greater speed-to-market will corner the market share. Single-use systems allow you to do that."

He adds, "Covid-19 demonstrated this, because the speed of developing a drug had to be so fast, that there was no way you could meet those manufacturing times without single-use equipment. As a result, many manufacturers have had to adapt."

The next section of this report delves into the emergence and rise of single-use technologies.

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The emergence of single-use technologies

Single-use equipment for pharmaceutical manufacturing first emerged in the 1980s with the appearance of disposable filter capsules made of plastic to replace stainless steel. Biocontainers made from plastic that were more typically used for food storage were adapted, as an effective way to transfer and keep fluids in a sterile manner.

By the mid-1990s processing plants had begun requesting that suppliers preconnected disposable bags and tubing to their assembly systems. The shift to single use was encouraged as it meant the time-consuming cleaning of equipment to meet regulatory requirements could be avoided. Instead, companies could use pre-assembled, pre-sterilized items, which decreased the risk of contamination and reduced the long hours that highly qualified staff had been spending on sterilization.

As suppliers improved the design of disposable items, adoption increased. Today single-use products encompass equipment for formulation, cell culture, harvesting, separation and purification, storage, transportation and final fill. These include plastic bag chambers for storing and transferring fluids, connectors, tubing and filling needle manifolds, which can be utilized individually or as part of complete systems designed for the purpose of operating with disposable equipment.

Furthermore, with advances in technologies such as robotics, these can be integrated into systems that leverage automation to remove human intervention, reducing the possibility of mistakes and further decreasing contamination risks. This is made possible by using pre-calibrated sensors that detect pressure, conductivity and temperature and can provide accurate data for measuring, a key regulatory requirement.

As an example, automated filter and dispense units deploy single-use systems that automate the filling process, from large scale volumes of 100 liters, to more manageable quantities processed in a 10-liter container. This enables more precise measuring and removes the possibility of human error.

According to the **American Pharmaceutical Review**, single-use systems are now widely adopted in clinical or process development scale. In its 2020 survey, it found that nearly 85 percent of processing in these areas made significant use of disposables.

The research outlines that single-use equipment has taken the lead over reusables, especially for upstream processes such as cell culture, cell separation and harvest. Dr Heinz-Christian Rost, Life Science Market Manager at Parker Hannifin, Engineered Materials Group Europe, comments, "The previously very well-known types of stainless-steel bioreactors, tubing and other equipment that had been used for ages in the biopharmaceutical industry have gradually been replaced by more flexible and smaller systems."

The next section explores some of the reasons why single-use equipment has become so popular in these fields.

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The benefits of single use vs. permanent equipment

"Single-use systems are very easy to set up and implement," states Parker Hannifin's Rost. "They are a type of plug-and-play system for drug manufacturers. This means that the process and product development timeline can be dramatically reduced, because it is much easier to set up a new process." Here we look in more detail at what this means.

Space and handling

Single-use systems have a smaller capacity compared to reusable items. A traditional manufacturing plant may have 1,000-litre stainless steel bioreactors on site, but this capacity may not be necessary for smaller batch production.

Rost cites Covid-19 vaccine as an example of the benefits of using smaller, single-use systems to scale up production. "The vaccine production industry went from using large-scale bioreactors to smaller-scale 3D bag systems that are much easier to handle," he says. "The production of billions of vaccine doses in record time would not have been possible without single-use container systems downstream – be it advanced sampling systems, closed cold chain transportation and storage containers or customized, overmolded manifolds for final fill."

This also worked in reverse for manufacturers who needed to grow from being a small R&D lab operating with 50-liter bioreactors, to suddenly needing to increase volume of production to millions of vaccine doses.

Additionally, single-use systems require lessequire less space and weigh less, making them easier to handle and set up. "In terms of space requirement, the whole production setup can be much leaner," Rost says.

While disposable items in general are typically associated with harming the environment because they create waste, according to the Bioprocess Systems Alliance, single-use items actually cause less harm because they have less of an environmental footprint than systems that use chemicals and have energy-intensive sterilization processes.

Wong explains, "Modelling has shown that water and energy savings from using disposables offset the waste issue. But it also depends who you talk to. Some people care more about the fact that waste can become an eyesore."

A facility engineered for disposables also uses less space, so the total energy consumption is reduced.

Customizable systems

The ability to customize systems was not possible with fixed assemblies. As Rost says, "You were stuck with the configuration you had".

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"It is important to be able to adjust single-use systems so if you have a certain volume that you want to pump through a system you can make the tubing diameter larger to have more throughput over time," he notes.

Solutions that have an open architecture enable the operator to reconfigure them to their requirements. During the harvesting process, a complex, vital step in monoclonal antibody production – different diameters of plastic tubing, for example – can be combined to acquire the correct size to ensure it is a fully closed system to any potential contaminants.

Reduced contamination risk

Bioprocessing can be impacted by cross contamination, microbial contamination and biologic contamination within the facility.

Cross contamination occurs when equipment is used to produce more than one drug, which can be potentially very dangerous for the patient it is administered to. Clean in Place (CIP) and Sterilization in Place (SIP) are procedures that manufacturers are required to perform to prevent this. These sterilization methods need large quantities of heat and costly purified water as well as hazardous chemicals such as caustics. CIP and SIP are also labor-intensive and regular testing of equipment must be carried out which may necessitate partial or complete CIP revalidation, increasing time and labor costs.

Disposable items remove the need for sterilization between batches, reducing the risk of contamination due to batch-per-batch changeover. It also prevents the likelihood of cross- contamination through repeated use. "With stainless-steel systems you always have to clean in place or sterilize them, which is a concern when you need to quickly switch products," Rost explains.

With single-use systems the process is simplified. Rost adds, "You are basically plugging in a fully validated sterile product into your production environment."

Turnaround times

By eliminating the need for CIP and SIP, lead times are reduced. In terms of product readiness, switching from one production run to another by simply discarding items that have been used already greatly reduces downtime.

Mia Filali, CEO of Pharma 5, a leading manufacturer and exporter of generic drugs in Morocco, says: "This system has a lot of advantages. The first is flexibility of course. You can work on multiproduct lines and you have no cleaning validation, which takes up a lot of time, because cross-contamination is avoided by disposing of single-use items." Filali adds that while single-use systems are currently too costly for Pharma 5 to implement, the company plans to do so in the future. "Once the prices of single-use equipment become more affordable, we will be very interested in using this because it would give us even more flexibility," she says.

Meanwhile Wong explains why single-use equipment remains more efficient. "You may not adopt it internally, but you might select a contract development and manufacturing company (CDMO) who can use disposable systems to manufacture products quickly without the need for you to build fixed equipment that require a lot of capital and more time to be validated," he says.

Wong adds, "Covid-19 demonstrated this, because the speed of developing a drug had to be so fast that there was no way you could meet those manufacturing times without single-use equipment. As a result, many manufacturers have had to adapt."

CONCLUSION

The future of single-use: wider adoption

Single-use systems are now widely used by manufacturers, taking the lead over reusable items in almost all phases of R&D to manufacture to final fill.

The benefits of using disposable systems have become evident as pressure has increased on manufacturers. While there has been a general shift with many organizations adopting single-use in their production lines and others committing to fully implement this one day, this is still a challenge to some that will require a change in mindset.

Wong says, "Most regulatory people are still used to the old change control approach. Single-use systems give you a different degree of freedom and it is a learning curve for everybody. There is a push right now at the global industrial level where we are collaborating to establish guidance so that it becomes more broadly adopted."

The establishment of formal guidelines, along with continued rising demand will lead to an increase in the number of companies offering single-use assemblies with ever more advanced designs. This will lead to increased availability, which will spur a broader usage of these systems in biopharma, along with more sophisticated designs as they become more accessible to manufacturers around the world.

About Parker

We combine product innovation with quick-turn customization to deliver critical solutions for your upstream and downstream needs. Our comprehensive set of bag solutions, bioreactors, mixing systems, and microcarrier separation systems meet the emerging requirements of fast-growing, single-use bioprocessing applications. Our transformative solutions for the life sciences industry include also: fluid management, single-use assemblies and corrosion-resistant applications, particle characterization, liquid packaging, filtration and purification, specialty and fine chemicals, organophosphorous and organosilanes.

Our over 50+ years of proven materials science experience in the most complex manufacturing environments positions us to serve as a trusted strategic partner to companies in the life sciences industry. Our solutions, which are among the cleanest, most scalable, and most reliable currently available, reduce your validation time, development costs, and time to market.

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