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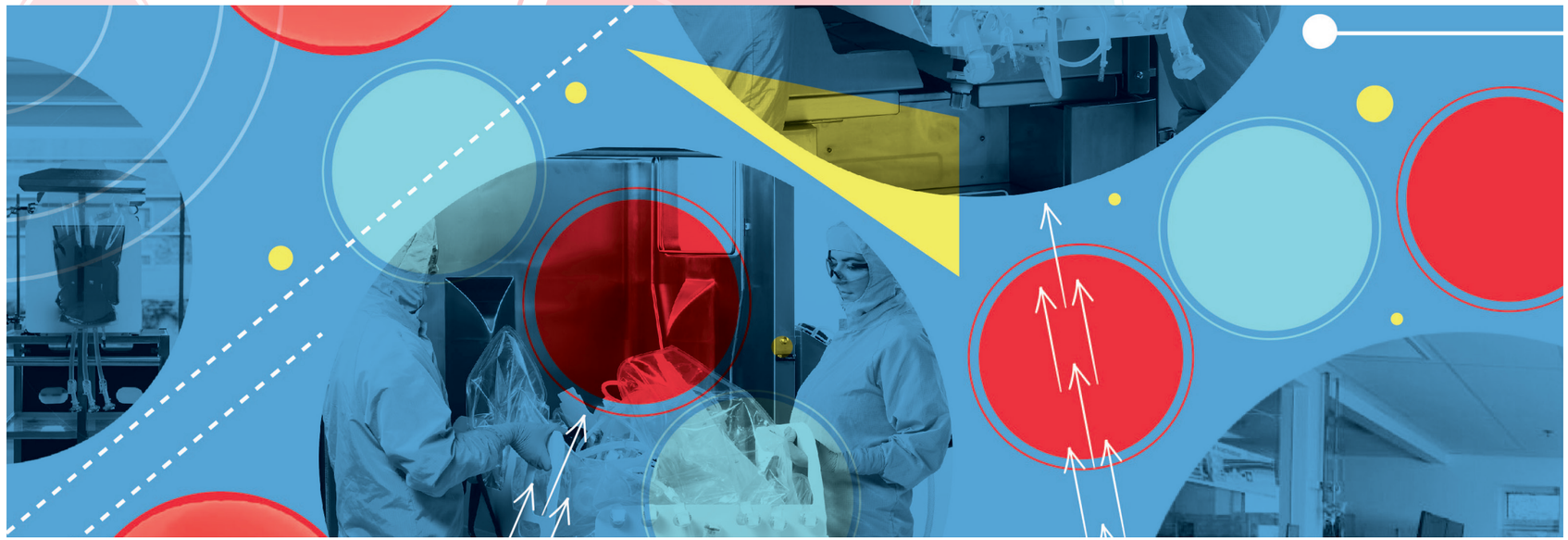
The Next Chapter in Single Use

Single-use systems have proven their worth in the industry, but where will advances in the future come from?



The Next Chapter in Single Use

Disposable technology has found its place in the biopharma industry, but where does the story go from here?

By Mario Philips

The evolution of single-use technologies so far – and their growing uptake in the biopharma industry – is a fascinating story. My first experience with single use started in a completely different industry: semi-conductors. This industry used very high purity chemicals supplied in stainless steel containers and glass bottles, but faced a great deal of cleaning and contamination challenges (sound familiar?). The company I worked for at the time – ATMI – developed a single-use technology made of polyethylene and Teflon materials that could cope with up to around 500 liters. It was designed for transporting and pressure dispensing chemicals in the semi-conductor industry.

In time, we looked at how we could bring the same technology to other industries – and we certainly saw potential in life sciences. But as a newcomer it was difficult! We had no real credibility in the field, so we had to be innovative. Instead of bringing yet another storage solution to life sciences (the "me too" approach is rarely an effective path), we decided to focus on single-use mixing and single-use bioreactors. And I think it's fair to say that it turned out rather well in the end; indeed, ATMI became a very successful company in the field. As a stranger to the industry, we did have one big advantage: the ability to see things from a fresh perspective.

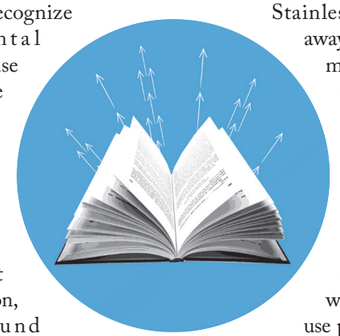
Nevertheless, it has taken a very long time for the biopharma industry to accept and routinely use single-use technologies. Contract manufacturing organizations were some of the first companies to embrace the technology. Not surprising as single use is very much associated with flexible manufacturing – and flexibility is incredibly valuable for companies that work with many different projects and processes. Today, many biopharma manufacturers themselves are also adopting single use, particularly for new facilities or new capacity expansion projects. As just one example, in late 2014, Amgen opened a biomanufacturing facility in Singapore that makes extensive use of single-use technologies (1).

Today's talking points

Given the fact that stainless steel equipment had been used for so long, it was natural there would be some questions with the move to single-use components. The number one concern initially was extractables and leachables (E&L), and this issue is still a significant talking point today. It is well accepted that foreign molecules from single-use materials can interfere with biologic drugs, and this has led to enormous collaboration between suppliers and manufacturers as they work to understand the potential for E&L risks and how to mitigate them. Suppliers have also worked to ensure full transparency over the supply chain of raw materials needed for single-use components, and to develop products with reduced potential for leachables, while industry groups, such as the BioPhorum Operations Group, have also released best practice guides (2). E&L can never be completely eliminated, but the widespread use of single use today shows that there is high confidence in the systems.

"Stainless steel is not going away, particularly for large manufacturing volumes."

Another important ongoing discussion point with single use is the environmental impact. Plastics are very often associated with a high impact on the environment (and for a number of good reasons). However, the industry is also becoming more aware of the environmental impact of cleaning stainless steel. If you have a vessel of 1000 liters, you are typically using around six to eight times that volume in cleaning, which includes different acid steps, water for injection, and steam. Just consider the volumes required for a much larger tank! Clearly, stainless steel usage also has a huge impact on the environment – some would argue more of an impact than plastic! Supply companies recognize the environmental challenges of single-use material and continue to look for innovative ways to make this waste stream more environmentally friendly.



A third significant conversation point today is standardization, particularly around extractables testing. Different companies use different methods and prefer different types of data and risk assessments. If we can all agree on standards, it would save everyone in the industry a great deal of time and reduce the duplication of work. Suppliers do try to supply data, but it may not be the data that some manufacturers want. We have not agreed on standards yet, but I think the industry is making good progress in this area, and it's fantastic to see industry groups, manufacturers and suppliers all coming together on the topic.

Simply the best?

The benefits of single use are numerous. Aside from the reduction of carbon footprint, the reduction in cleaning also leads to reduced costs and downtime. There is also more flexibility with single use because you don't have the same fixed stainless steel equipment (and costs); planning and building time for new facilities can be much faster, which ultimately means that decisions on whether to build or not build can be delayed until more data are available. We've all read about (or been involved in!) situations where large factories have been commissioned and built in anticipation of success, only to be left redundant when the market changed or the drug failed.

However, it's not a case of single use being "better" than stainless steel. Stainless steel is not going away, particularly for large manufacturing volumes. Once you reach around 3000 liters, I'd say that the cost benefits of single use become less appealing. Moreover, there is a current limit to the volumes that single-use can cope with. There are single use products on the market capable of handling 5000 liters, but handling such a large biocontainer in a cleanroom environment is tricky. How do you safely install them? How do you transport them? How do you store them? And if anything goes wrong? That's a lot of product to lose! It's certainly not impossible to use single use for such large volumes –

The FDA View on Continuous

At the 2018 International Symposium on Continuous Manufacturing (ISCMP) held in London in October, Janet Woodcock spoke extensively about the need to modernize pharma manufacturing (see page 8). Discussing FDA breakthrough designations, where the aim is to accelerate drugs through clinical development, Woodcock explained that commercial manufacturing can be a rate-limiting step.

For targeted therapies in oncology, the FDA can approve drugs for very small populations of cancer patients based on expanded phase I cohorts – where a drug is tested in various tumors, and then expanded if one tumor shows a good response. Drugs in these types of trials can be approved quickly… "But then the question is: are you ready? Do you have a commercial drug available? These are often expensive drugs, and your managers are probably jumping up and down and turning blue in the face…" said Woodcock, during the presentation. One of the big decisions is whether you need to open a new facility, but companies must also keep in mind that the drug may never be used in a very large population. On the other hand, the FDA has also approved drugs that have gone on to treat other susceptible tumors – and suddenly, the drug becomes a global hit, and production must be scaled up rapidly. "FDA does not infrequently encounter situations where manufacture at a commercial scale is a rate limiting step and it's a real heart-breaker to everybody – probably including your senior management, when you have a product approved and your manufacturing isn't ready," Woodcock added. "It's a different process completely from what we're used to back in the 1990s and early 2000s in drug development."

Woodcock discussed a number of advantages that continuous processes may offer, including the environmental impact (less solvents, waste and cleaning) and the fact that smaller manufacturing footprints may open up the possibility to have more facilities located around the world. Right now, finished dosage forms are "world travelers" and it can be very hard for regulators to know where they are made. Complex supply chains also put products at risk in the event of natural disasters. "We have a very slow response capability if a dominant manufacturer stops making a drug – for example, if there is an issue at a plant or there is a hurricane. We can't scale up quickly. So, the ability to respond faster will become more and more important," said Woodcock.

When it comes to continuous technologies and biologics, Woodcock explained that the specific advantages were:

- Decreased use/cost of media
- Reduced manufacturing footprint
- Reduction/elimination of costly, time-consuming cleaning operations between campaigns
- Integration of downstream steps to reduce time/costs
- Use of multi-attribute methods to replace conventional quality control and release tests
- Rapid screening of performance space over many conditions with automated experimentation
- Ability to conduct development studies at commercial scale.

and many people do successfully – but I think that stainless steel tends to be the preferred option in these cases. And there will always be special scenarios where the product is simply better suited to stainless steel rather than single use; for example, liquids with extremely high or low pH requirements. Ultimately, manufacturers need to examine their product, consider demand, and then decide which technology is most suitable.

Today, suppliers of single use systems are focusing on making single use more "industrial". What does that mean exactly? Essentially, it's all about making the components more robust and keeping the end user very much in mind during development. Products need to have fail safes and they need to be easy to use in a busy manufacturing environment. Single use adoption initially began in process development laboratories, where workers tend to have a little more flexibility. With single use now moving into cGMP manufacturing suites, the requirements are more stringent. Equipment needs to be installed quickly, and it must be hassle free, and risk free. Many single-use systems are operator friendly, but in some cases there is still room for improvement.

Once we've cracked the "industrialization" angle, there are other areas for improvement. Single use has already evolved from storage, through to sterile connections, to more complex bioreactors and mixers, but now the industry is looking to combine unit operations into real process solutions. I believe that single use could be a key enabler for continuous bioprocessing – an ongoing topic of discussion in the biopharma industry, partly thanks to regulators who are encouraging manufacturers to consider new technologies that could lower production cost. The industry has already seen much success with continuous chromatography, especially in conjunction with a perfusion bioreactor, which is commonly performed using single-use technology. Continuous chromatography can offer huge cost savings because it uses less resin. Now there is keen interest to transform other unit operations. Continuous bioprocessing will drastically shrink the footprint required for manufacturing and add flexibility – and single use compliments both of these very well.

"A fully continuous line won't be suitable for all biopharma companies, but it is another option that manufacturers can consider."

Again, it is not necessarily a case of continuous being better than batch – a fully continuous line won't be suitable for all biopharma companies, but it is another option that manufacturers can consider, and it should help drive increased efficiency and lower capital investment and operational costs. Many other manufacturing industries have already made the switch. Is biopharma really that different? There is a lot of momentum – or pressure – on both the supplier and the end user to make this work – and I think we'll see increasing experimentation with continuous in the coming years, but that's not a bad thing. Let's face it – continuous bioprocessing is a very exciting prospect! Imagine having a continuous line that can produce monoclonal antibodies for phase I, II and III trials – and for early commercialization too. You could produce the product easily in the lab and delay large investments until you have evidence that the drug will be commercially viable.

Those of us working for suppliers must always focus on innovation, but we must also be modest – we are only a very small part of the drug development puzzle, after all. Every day, tens of thousands of researchers in the biopharma industry are working hard on cutting-edge research designed to help patients – and right now there is some incredible research going on. I find the activity in cell and gene therapies, for example, very inspiring. Knowing that we suppliers can contribute to helping researchers realize their vision and aspiration – by helping them to more easily scale up their drug manufacturing processes – is what honestly gets me up in the morning to go to work.

Mario Philips is Vice President and General Manager at Pall Biotech.

References

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2. *BioPhorum Operations Group, "Best practices guide for evaluating leachables risk from polymeric single-use systems used in biopharmaceutical manufacturing." Available at https://bit.ly/2Qantxq.*