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# Single-use bioreactors: challenges and perspectives

The application of single-use bioreactors is an ever-expanding area in pharmaceutical bioprocessing. Alice O'Hare, Commissioning Editor, spoke to three experts in the field and discussed the current status and future direction of single-use bioreactors in the bioprocesing community.

**Christel Fenge,** Sartorius Stedim Biotech, August-Spindler-Str. 11, 37079 Göttingen, Germany; christel.fenge@sartorius-stedim.com

**» The rising demand for biosimilars and bulk quantities of antibodies has pushed pharmaceutical plants to become more creative and flexible in enhancing their productivity. How do you predict single-use bioreactors will aid this development? What are the merits, as well as flaws, of using this type of bioreactor, as opposed to reusable stainless steel bioreactors?**

Single-use bioreactors provide an excellent option to adapt the production capacity to the market demand. This is especially attractive to the biosimilar industry as it allows managing the capital investment into production capacity and reducing the financial risk associated with this. Compared with stainless steel, the upfront investment is significantly lower and capacity can quickly and easily be increased as market demand grows due to considerably shortened lead times. Here, not only the volume range from 500 to 2000 l is attractive, but also the reduced need for water for injection and steam, which adds to the investment demand and facility footprint. When it comes to innovative antibody drugs, we mainly see a trend to control development costs and increase flexibility in the clinical phase. Single-use bioreactors eliminate the need for cleaning validation and avoid cross-contamination in a multiproduct facility.

**» A recent press release suggested that there is a divide between the USA and Europe in terms of uptake of single-use bioreactors. In your experience, would you agree with this? What do you think might be contributing to this?**

Based on our market insight, we cannot really support this finding. We see that the uptake of single-use bioreactors is mainly driven by the activity of the different regions regarding development of new disease treatments and biosimilars. In addition, existing production capacity comes into play and company strategies regarding manufacture of clinical material. As the USA is indeed leading in the field of developing innovative treatments, we see a strong uptake of single-use bioreactors, but Europe and Asia are not far behind, especially as we have a very strong market presence in all regions.

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**» In your opinion, what has been the biggest technological advance in single-use bioreactors in the last 5 years?**

From our point of view, a significant step forward has been the ability to build reliable single-use bioreactors that are based on the same design and operation principles as proven stainless steel stirred-tank bioreactors, as it enables a smoother process transfer and scale-up. Furthermore, as control of materials and traceability has taken a significant step forward recently, security of supply and reliability has significantly improved.

**» What do you believe the future holds for single-use bioreactors, in terms of technological advances?**

For us, the main advance is the introduction of post-installation, point-of-use bag testing. This new technology really brings risk mitigation to the same level as historically experienced with stainless steel bioreactors. Furthermore, we also work on increasing our scope of single-use sensor technology towards biomass and viability. Additionally, we see the need to reduce development costs further by introducing single-use vessels in process development, again equipped with single-use sensor technology and ready-to use chemometrics tools to streamline process development and validation.

**» Single-use bioreactors can be pre-sterilized – do you believe this is an indication of the future direction of the industry, in terms of a reduction in validation steps on-site?**

We see that our customers focus on their core competencies, which are typically disease knowledge, drug development and marketing. Furthermore, they are under tremendous pressure to increase development effectiveness, reduce cost and develop new markets. Wherever our industry and especially single-use technology (SUT) can support this, this is the way to go.

**» In terms of minimizing the risks associated with extractables and leachables – what would you say are the biggest challenges facing the single-use bioreactor community?**

The biggest challenges are associated with traceability and security of supply of raw materials and components. Those vendors that have the strongest supply chain and relationship to their sub-suppliers, in combination with polymer expertise and biological competence to assess material quality, will be in control of what they provide to their customers and a dependable partner for the biopharmaceutical industry.

**Mark Bamforth**, Gallus BioPharmaceuticals, St Louis, MO 63134-3117, USA; mark.bamforth@gallusbiopharma.com

**» The rising demand for biosimilars and bulk quantities of antibodies has pushed pharmaceutical plants to become more creative and flexible in enhancing their productivity. How do you predict single-use bioreactors will aid this development? What are the merits, as well as flaws, of using this type of bioreactor, as opposed to reusable stainless steel bioreactors?**

Flexibility, speed, predictability and cost to change the total installed capacity. There is the perception that stainless steel must be lower in cost: not true if a facility is designed with all of the advantages of disposables rather than a retrofit: smaller footprint, less utilities, lower capital and operating cost with increased disposable cost.

**» In your opinion, what has been the biggest technological advance in single-use bioreactors in the last 5 years?**

Achieving consistent scale-up from process development to commercial scale at 2000 l. Large single-use bioreactors are standardized – this is the first time that bioreactor design

has been standardized rather than every bioreactor being individually designed. Consistent scale-up performance allows better performance predictability and the ability to clone facilities for deployment in different countries/regions with confidence in the performance and reproducibility of the product.

**» Looking at the future, what are the key challenges facing SUT with respect to pharmaceutical bioprocessing? Where do you predict the growth will lie in the next 5–10 years?**

Improving the downstream technologies to make them single use and single pass, that is, having capacity to support a whole batch versus having to divide the lot to match the unit operation step, to match a high-yielding 2000 l scale bioreactor process. Single-use bioreactors are unlikely to increase in scale beyond 2000 l, with multiple 2000 l bioreactors being used where needed. Development in prepacked chromatography and chromatography alternatives, single-use centrifuges and other downstream steps to process high-yielding cell lines is needed.

**» What design specifications need to be considered in future biotech facilities using SUT?**

Smaller footprint, more flexible space with the ability to change the number and scale of bioreactors and to reconfigure the downstream for different products. If companies build a facility specifically for single use then the facility footprint will be smaller due to lower utility requirements and cleaning in-place/sterilization in-place infrastructure. If companies adopt ballroom style downstream processing instead of multiple room suites then the footprint will be reduced further and flexibility increased with the ability to add or remove equipment easily. A retrofitted traditional stainless steel facility will not achieve these capital and operating cost savings.

**Stephen Brown,** Valneva, 6 rue Alain-Bombard, 44800 Saint-Herblain, France; stephen.brown@valneva.com

**» The rising demand for biosimilars and bulk quantities of antibodies has pushed pharmaceutical plants to become more creative and flexible in enhancing their productivity. How do you predict single-use bioreactors will aid this development? What are the merits, as well as flaws, of using this type of bioreactor, as opposed to reusable stainless steel bioreactors?**

There are a number of advantages to using SUT and I think that these can be summarized in the following manner:

- There can be a gain in process operational efficiency and throughput;
- They help avoid cross-contamination;
- There is no need for sterilization in-place and cleaning in-place processes and their validation;
- The capital investment can be reduced or is more favorable than for stainless steel systems;
- The facility set-up time is faster.

All of the above can help render a new plant or a refitted facility more efficient and aid the development process. However, as with any technology, there are some pitfalls. The exploitation of single-use systems (SUS) can bring forward complex issues such as:

- Biocompatibility, and extractables and leachables;

- Sterilization/irradiation of the SUS;
- Disposal of the SUT requires careful following and verification;
- Potential lack of structure in implementing and exploiting SUS at a user level can lead to poor or inappropriate choices;
- There is potential for inconsistency of the resins used for films, components and tubing;
- Absence of change management can sometimes occur leading to compliance problems;
- Standardization.

Failure to address the points listed above can lead to longer and more complex development timelines or implementation failure. In this context, it is essential to have a transparent relationship with, or control of, the supplier.

Careful attention to compatibility and suitability for purpose of the SUS must be paid via technical diligence. This is based on established principles – i.e., verification of technical capabilities and applied as the first step in a quality audit program; it is a recurring theme over the implementation process and subsequent routine procurement. Technical diligence implies documented visits to the supplier(s)/vendor(s). The outcome is an appropriate and measured understanding of all of the technical issues concerned with the SUS, its manufacture and end-user fit.

**» A recent press release suggested that there is there a divide between the USA and Europe in terms of uptake of single-use bioreactors. In your experience; would you agree with this? What do you think might be contributing to this?**

In some ways yes. As I recall, the quote came from a product manager for a major SUS supplier based both in the USA and EU. I think that there has been considerable uptake of SUT in both the USA and the EU; for example, my experience of meeting different companies and participating in SUS meetings would suggest that. On the other hand, if you look at where a lot of new products originate it is possible to argue that this innovation has been more Eurocentric (European-based) than from the USA.

**» Looking at the future, what are the key challenges facing SUT with respect to pharmaceutical bioprocessing? Where do you predict the growth will lie in the next 5–10 years?**

SUT will take an important part of the R&D and product development market for bioreactors and other applications such as downstream processing and fill and finish. Utilization at a larger scale is limited by technology constraints related to materials compatibility; resistance to pressure, and so forth, and this will be a key challenge. In other words production scales will likely be limited to a maximum of approximately 3000 l. Larger capacities with SUS will likely need to be filled with multiple single-use bioreactors of approximately 1000–3000 l. A key growth area will be in the so called, 'ready-to-use' services area, which can reduce on-site work during SUS deployment.

**» Single-use bioreactors can be pre-sterilized – do you believe this is an indication of the future direction of the industry, in terms of a reduction in validation steps on-site?**

First of all, this is not an indication of the future direction of the industry as it is already standard. I would not try to organize the single-use bioreactor irradiation process myself because that should be handled carefully and by an experienced supplier. There is some sense in this remark though because the recommended implementation approach is adopting the Quality by Design approach for SUS; this concerns being smarter about on-site validation/qualification, while maintaining product quality. It does not remove the need for qualification, but

it is a better, more efficient way to do that, employing a Quality Risk Management (risk-based) approach. In doing so you effectively outsource your quality management system to the supplier. However, you must retain an appropriate level of control over this via technical diligence, audits and control strategies.

### » What design specifications need to be considered in future biotech facilities using SUT?

Such facilities can be made more compact with a simpler layout; but, bear in mind that most bioprocesses will likely require more than one supplier's equipment so key areas of facilities often overlooked for SUT are storage space – warehousing and intermediate storage can be more important for SUS-based facilities. Equally, the solid waste processing end of the process – autoclaving and disposal – although that also depends on your geographical region; in some areas it is possible to use landfill, but in others waste must be incinerated after decontamination.

### » In terms of minimizing the risks associated with extractables and leachables – what would you say are the biggest challenges facing the single-use bioreactor community?

The challenge is to reduce the risk, so appropriate technical diligence must be performed as part of the implementation process so that you have these parameters under control from the outset; this ensures that the information collected is all appropriate and subject to a risk-mitigation process.

### » Do you believe single-use bioreactors can support continuous processing?

Up to a point I would say yes, but there are limitations. We must not forget that these systems are after all designed to be single-use; there will be limitations to the ability of these systems to be used over a longer term process unless specifically designed with that intent. Even so, the materials used (films and components) may not necessarily be adapted to this type of bioprocessing operation and in this case a conventional stainless steel solution might be the best route.

### Disclaimer

*The opinions expressed in this interview are those of the interviewees and do not necessarily reflect the views of Future Science Ltd.*

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