Capacity for Success

There is hardly an area in pharma that has not been affected by tightening regulations and the need to keep costs low and productivity high. The bioproduction sector is now beginning to recognise these requirements, and has started to update their technology accordingly

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The global bioprocessing industry is growing rapidly, with more than 1,300 companies generating a staggering combined annual revenue of over $200 billion (1). Progress has been driven by the widely recognised benefits of biopharmaceutical products, including increased effectiveness, fewer side effects and the likelihood of them serving as disease cures rather than just treatment solutions to ease symptoms. Worldwide, the evolution of the bioprocessing industry has triggered the development of innovative technologies that facilitate the use of living cells and tissues for a range of pharmaceutical and clinical applications.

As such, bioprocessing – or bioproduction – has come to involve all current Good Manufacturing Practice (cGMP) employed in the development, scale-up and manufacture of biomolecular and cellular products, including monoclonal antibodies, vaccines, therapeutic proteins and cell-based therapies. In recent years, mammalian cells have been found to produce proteins with the correct conformations and post-translational modifications for the development of safe and effective treatments. In response, there has been a notable shift of the bioprocessing industry towards the use of mammalian cells for the manufacture of 55% of biopharmaceuticals (2).

The typical bioprocessing workflow is split into three stages – namely upstream processing, harvesting and downstream processing. During upstream processing, cells are grown in a controlled environment and scaled up to create maximum cell and protein concentrations with optimal target product profiles. Harvesting subsequently involves the removal of cells, cell debris and other such particulate matter from the product solution, before proceeding with downstream purification of the final product.

Challenges to Face

The bioprocessing industry is under constant pressure to enhance productivity and workflow efficiencies, as well as

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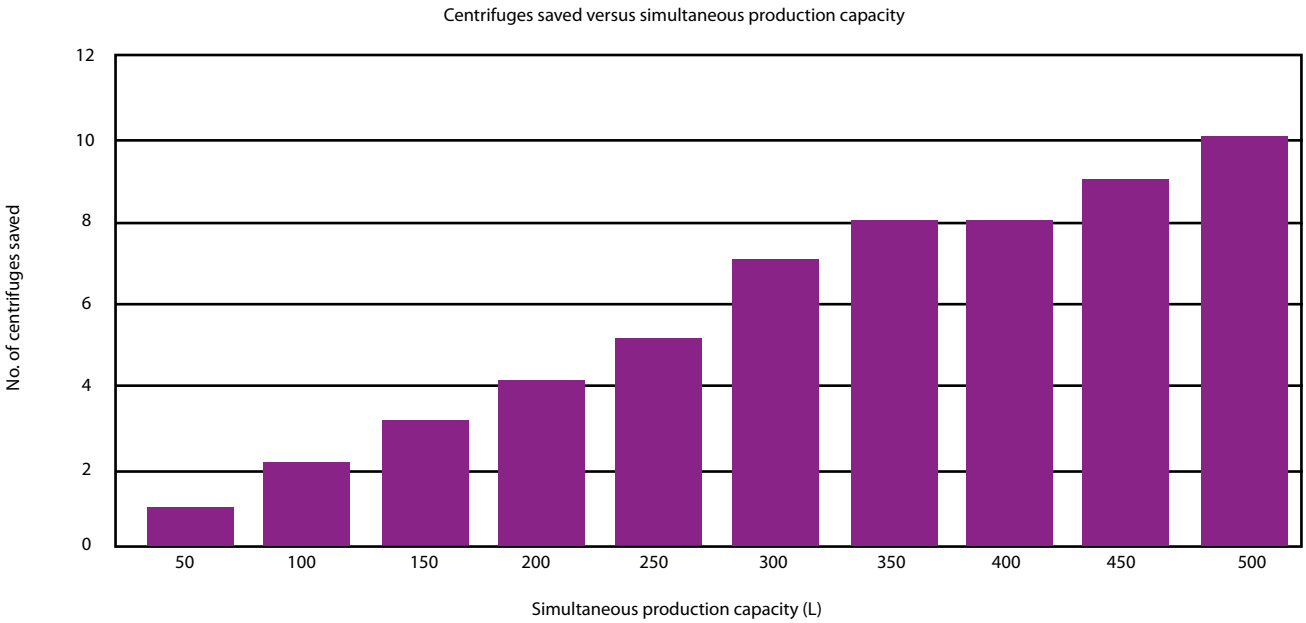

Figure 1: New large capacity centrifuges can separate more sample when compared to legacy units. Data based on comparison of maximum capacity of new and legacy centrifuges

deliver continuity of supply and reproducible quality while reducing the associated costs. There is also an increasing market need for the production of biosimilars, which are projected to serve as a key driving force for industry growth. Additionally, all of this must be accomplished under the safety regulatory compliance demands, with rising expectations to improve sustainable working practices, decrease energy consumption and minimise the environmental footprint of the laboratory.

The cGMP regulations specific to the production of drugs and active pharmaceutical ingredients stipulate the minimum requirements for the methods, facilities, controls and equipment used in the manufacture, processing and packing of drug products. Enforced by the FDA, the cGMP regulations aim to ensure that products actually have the ingredients, strength, quality and purity characteristics they claim to possess, thus being safe for use (3). Currently, these regulations are strictly enforced in more than 100 countries including all of North America and Europe, Japan, Korea and China.

In addition, legislation has been in force since February 2003 restricting the use of hazardous substances in electrical and electronic equipment (the Restriction of the Use of Certain Hazardous Substances (RoHS) Directive 2002/95/EC), as well as promoting the collection, treatment and recycling of such equipment (The Waste Electrical and Electronic Equipment (WEEE) Directive 2002/96/EC). The RoHS Directive requires heavy metals like lead, mercury, cadmium and hexavalent chromium, alongside flame retardants such as polybrominated biphenyls or polybrominated diphenyl ethers, be replaced with safer alternatives (4). The WEEE Directive enforces measures to protect the environment and human health by preventing or reducing adverse impacts of potentially hazardous substances (5).

In order to efficiently address all of these challenges, bioprocessing facilities must employ advanced technologies capable of maximising output and producing the best quality results possible, while decreasing both financial and environmental impact.

A Central Role

Centrifugation is a powerful tool, playing a critical part in the harvesting, separation and purification procedures of the bioprocessing workflow. Batch centrifuges that have been specifically designed for use in the bioprocessing industry are intended to undertake separation and purification methods, requiring high quality with run-to-run reproducibility and traceability. Applications range from R&D to large-scale production of biologics, vaccines, biofuels, cell therapies, veterinary medicines and recombinant proteins.

When it comes to large-scale manufacturing, microfiltration can be used during cell harvesting and clarification prior to downstream purification. However, centrifugation has proven to be a more cost-effective method, which enables high cell density clarification. The technique is also suitable for applications involving a broad range of cell types without having to make significant alterations to the instrument – like changing filters to provide different pore sizes, for example. Centrifugation also poses less physical stress on cells, reducing the probability of cell damage due to shearing.

Despite the benefits, some conventional centrifuge technologies have presented challenges for bioprocessing applications – such as not meeting the high production levels required. This, therefore, limits batch-to-batch consistency

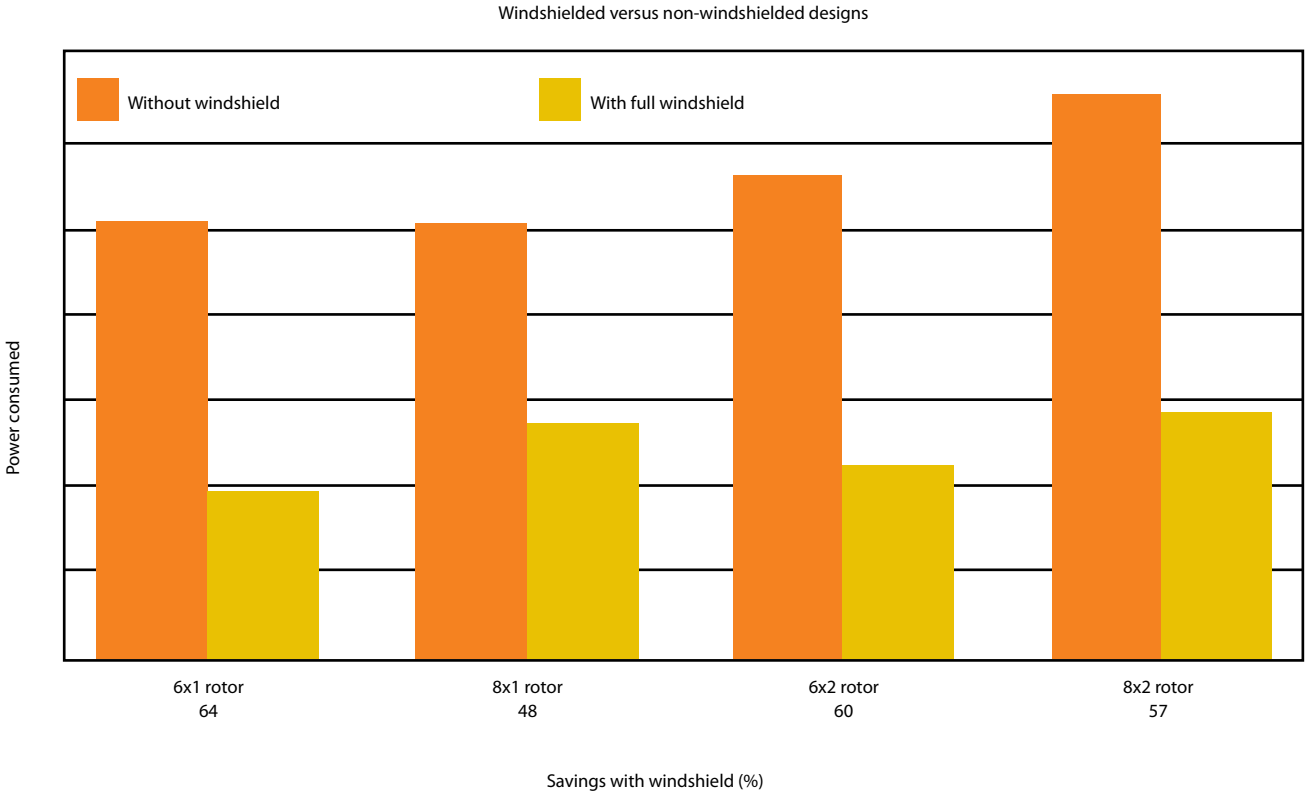

Figure 2: Facilities can save up to 64% of power consumption by using windshielded rotors compared to non-windshielded options. Data based on engineering evaluation of windshielded and non-windshielded designs of the same rotor body

during cell harvesting, while simultaneously increasing the environmental impact through the concurrent operation of multiple instruments.

In response to the key role of batch centrifugation in the bioprocessing workflow, system providers have long focused on the development of equipment capable of improving productivity in a cost-effective manner while maintaining batch-to-batch consistency. The latest technological advances have led to the introduction of novel systems designed to provide the specific application requirements of modern bioprocessing facilities, helping them to alleviate the increasing pressures facing the industry.

Technology Breakthroughs

Conventional centrifuges have been able to accommodate sample sizes of 750mL to 1L. However, with bioprocessing facilities having to deal with increasing sample volumes, scientists have come to recognise the unique advantages of using large capacity batch centrifuges for improved reliability and productivity in bioprocessing applications.

Innovative instruments have been developed to cater to the needs of high-throughput labs, capable of accommodating a range of tube sizes and even larger bottles, as well as offering enhanced processing capacities of up to 16L in a single run. This 33% increase, compared with the capacity of conventional centrifuges, makes it easier and more convenient to work with large sample volumes, thereby increasing lab productivity and maximising time efficiency. With the ability to separate the same amount of sample as several smaller capacity models, the need to invest in multiple centrifugation systems is reduced, valuable space is saved and the volume of simultaneous centrifugation increases (see Figure 1). Combined with the ability of modern systems to manually swap in a number of different rotor types, facilities can rely on a single centrifuge for multiple applications and throughputs.

Often used in production environments on a 24/7 schedule, large capacity centrifuges can significantly contribute to the overall energy consumption of the lab. To reduce energy consumption and the environmental impact of labs, modern systems have been developed that feature an energy-efficient windshielded rotor design, which facilitates energy savings of up to 64% when compared with instruments using non-windshielded rotors (see Figure 2). Energy consumption is then further diminished due to the increased volume capabilities, meaning that fewer centrifuges are running at any given time and the ability of the cooling function allows automatic shut-off when the instrument is not in use.

Automation is an inherent component of advanced models of large capacity batch centrifuges, featuring technologies

to enable the automatic opening and closing of the door and rotor lid with just a push of a button. As a result of this hands-free operation, time can be saved – especially in busy labs, where these tasks are sometimes repeated up to 30 times per day. The physical strain on staff is also reduced by eliminating the need to transport or store the large windshielded rotor lid, while maintaining accessibility for all operators, independent of height or strength.

In line with current legislative requirements, advanced large capacity centrifuges do not use chlorofluorocarbon refrigerants. Furthermore, new systems are RoHS and WEEE compliant, ensuring that hazardous substances are avoided, environmental pollution is lessened and electronic substances are optimally designed.

Producing Results

Separation is a critical step in the bioprocessing workflow. It is therefore important for bioprocessing lab managers to carefully consider the centrifugation requirements and technical specifications for each particular application need. Recently developed large capacity batch centrifuges are designed to deliver reliable and repeatable performance as well as ease-of-use, spin after spin. Reproducible separations for high-throughput applications are thereby enabled, at the same time as reducing environmental impact and ensuring compliance with the latest global industry standards.

References
1. Visit: www.top1000bio.com
2. BioPlan Associates, Report and Survey of Biopharmaceutical Manufacturing Capacity and Production, 2015
3. Visit: www.fda.gov/drugs/developmentapprovalprocess/manufacturing/ucm090016.htm
4. Visit: www.ec.europa.eu/environment/waste/rohs_eee/index_en.htm
5. Visit: www.eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32012L0019

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