Perfusion and single-use bioreactors: A partnership for scale up

Perfusion has emerged as a viable technology for the commercial production of biopharmaceuticals. Perfusion solutions can offer very cost-efficient scale up solutions, driving down operating costs due to the smaller equipment and facilities needed as compared to batch or fed-batch systems. Alternating Tangential Flow Filtration devices from Refine Technology, PBS Biotech’s partner in perfusion have produced a record-high titer of 1.5g/L/day in a concentrated perfusion process and 24 g/L for an antibody grown in concentrated fed-batch culture. The ability to continuously harvest product is a unique advantage of perfusion systems that can be of utmost importance for labile products.

PBS bioreactors feature very efficient, low shear mixing and high mass transfer rates due to the patented AirWheel™ mixing mechanism. For perfusion processes, the bioreactors are easily and conveniently coupled to Refine Technology ATF™ System perfusion devices with the aid of aseptic connectors and very short tubing lengths.

Experiment
In this trial, we coupled a PBS15 single-use bioreactor (15L maximum working volume) with a Refine Technology ATF-4 System.

Figure 1: Perfusion matched with PBS Biotech bioreactors. Perfusion is seen to help sustain cell viability and boost cell density, while keeping lactate waste levels low.

Product Information
- PBS 3 - Volume range of 1.5L-3L
- PBS 15 - Volume range of 7.5L-15L
- PBS 80 - Volume range of 40L-80L
- PBS 500 - Volume range of 250L-500L
- Future Release - PBS 2500
  Single-use bioreactor system, (1200-2500L working volume, respectively).

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A Refine Technology ATF-4 System was fitted with a 0.22 μm membrane device and a GE ready-mate connector on the main line, then sterilized by autoclaving according to manufacturer’s directions. After autoclaving, a connection was made to the PBS 15 bag using a bottom entry port. The bioreactor was batched to 10L, equilibrated and inoculated, and the cells were grown to a density of nearly 7 M c/mL before the perfusion was started on day 3. The glucose concentration at the beginning of perfusion was approximately 1 g/L.

The cell density, viability, glucose and lactate levels were monitored continuously during the run.

The perfusion rate was increased frequently to keep up with the glucose demand, and the cells grew continuously while the viability remained above 90%. A maximum cell density of 29 M cells/mL was achieved on day 7. Interruption of the feed medium supplied to the culture (several occurrences on day 7) led to an interruption of the perfusion and thus to the premature end of the run on day 8.

Although this experiment was cut short, the data show that PBS bioreactors can be run successfully with predictable outcomes in perfusion mode. It is easy to interface the PBS systems with the Refine Technology ATF™ Systems. Very high Mass Transfer Rates in the PBS systems (KlA up to 20/hour) combined with very efficient mixing suggest that the PBS systems will be able to support the very high cell densities that can be achieved in perfusion processes.

**PBS Biotech and Refine Technology Applications**

Together, these innovative technology applications include concentrated perfusion, concentrated fed-batch, continuous culture, and primary recovery/clarification. Benefits of this partnership include increased cell density, simpler cell separation, high performance, low profile and ease of use. They also reduce costs of equipment, vaccine and protein development and production, by boosting process efficiency.