Upstream Intensification with High-Density Cell Cryopreservation

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A new single-use system workflow offers reliability at a range of scales

In all stages of bioprocessing, developers and manufacturers aim to intensify as many steps as possible. For upstream processes, the result is significant productivity gains via the evolution of bioreactor train design that takes advantage of the achievement of higher titers to compress the train and intensify the output. The upstream intensification of production-scale bioreactors has driven bioprocess productivity evolution for several years. Recently, interest is growing in what can be achieved in lab-scale cell expansion, which has remained a fairly static process involving serial scale-up from vials to multiple flask volumes before reaching the reactor for production or the next laboratory for continued process development and characterization.

From early stage development through manufacturing, bioprocessors often expand cells for downstream applications. This often requires a method of safely storing cells for prolonged periods. In some cases, especially in today's decentralized industry, developers need reliable ways to move cell samples from one site to another. Both needs can be met with a new approach to high-density cell cryopreservation based on Aramus™ single-use bag assemblies from Entegris.

With high-density cell banking, a bioprocessor can save weeks in starting an upstream process. With Aramus bag assemblies, that banking is faster and lower risk. Starting with cells cultured from 1-mL vials, a scientist delivers samples into single-use bioreactor bags. Highly concentrated cells are harvested and transferred to fluoropolymer, gamma stable Aramus bags, which go into cryoshells for protection. A –80°C freezer is used to control freezing before placing the bag-cryoshell assemblies into the vapor phase of a liquid-nitrogen tank for longer-term storage. Cryoprotectant is optimized for the concentrated cells, such that it is diluted in later scale-up into the bioreactor, eliminating the need for subsequent washing steps.

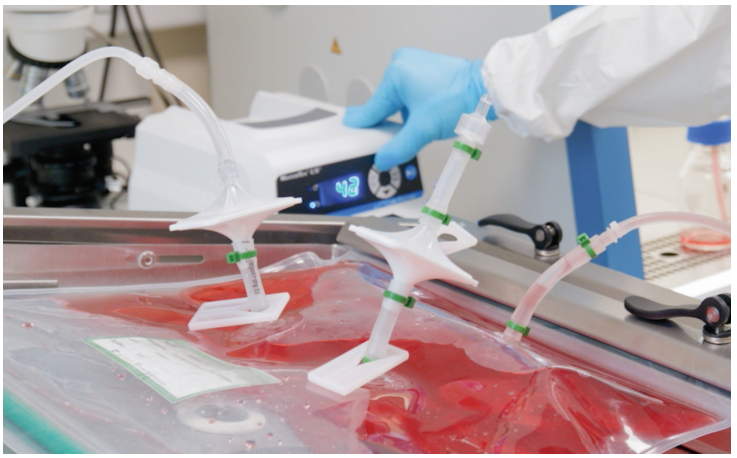
Those concentrated cells can be stored for later use or transported to another site. When needed, a scientist removes the assembly from the liquid-nitrogen tank, takes the bag out of the cryoshell, and initiates the thaw process. Then, the cells can be transferred to a large bioreactor.

Benefits of the bag

Instead of using small vials to seed a bioreactor, an Aramus bag assembly can add 50–500 mL of highly concentrated cells to a 20-L bioreactor, for example. That's some significant intensification!

More upstream intensity makes an entire process more productive and efficient. This productivity increase can also allow for more commercial expansion. For that, though, a manufacturer needs this kind of technology to freeze a culture with confidence—at the right volume and cell density for scale—and be able to get a culture where it needs to go or keep it safely stored as long as needed.

Process protection also increases when using Aramus bags. Instead



of relying on multiple small vials, developers can use this closed-system approach, which requires less handling— including omitting the need to wash out cryoprotectant—and that means less complexity and fewer opportunities for contamination.

Opportunities for exploration

Scientists can utilize this workflow for cell-freezing applications to explore the potential productivity and risk-reduction outcomes. So far, the studies used Chinese hamster cells (CHOs), which had not been optimized for bioprocessing. So, better results might be found with further optimized production cells.

Scientists can start with Aramus bag assemblies and incorporate this technology in existing workflows of standard fluid management and small-scale storage. In developing a new biotherapeutic, a variety of volumes could be explored to find the optimum for a particular workflow. In collaboration with scientists at École Supérieure de Chimie Physique Électronique de Lyon, bags up to 500 mL were used, but larger bags could also be tested.

Providing intensity to bioprocessing—from early stage development through manufacturing—depends on trying new approaches, testing new tools. To keep processes efficient and products as affordable as possible, high-density cell cryopreservation makes a good place to find your next gains in flexibility and productivity.

To learn more, please view our recorded webinar,
"How Fluoropolymer Single-use Bags Shorten Seed Train Processes,"
www.entegris.com/hdcbwebinar

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