The Race to Billions: How Amplifying Adherent Cultures Can Get You There

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Adherent cell culture is a versatile bioproduction platform that has diverse applications from viral vaccine to gene therapies, but each with a common goal: to expand billions of cells. That means plenty rides on which cell expansion platform labs choose, especially for commercial-scale production. Here, Austin Mogen, Ph.D., senior field application scientist, and Cat Siler, Ph.D., field application scientist, both from Corning Life Sciences, discuss platforms for adherent cell culture scale-up, how to trim time and costs, and how to deliver high-efficiency output across adherent applications.

BIOPHARM: Adherent cell culture is well established, and researchers are familiar with plates and flasks, but they don't scale to production. Which platforms can be used to expand cells for a bioprocess workflow?
SILER: You can imagine why people wouldn't want to work with hundreds or thousands of flasks, and lots of better options are available. For example, if people want something 2D, they can try a stacked option such as Corning® CellSTACK® culture chambers or the more compact Corning HYPERStack® cell culture vessels. For higher scales, we recommend Corning CellCube® systems or the new Corning Ascent™ fixed bed reactor (FBR). And if a 3D system is needed, Corning microcarriers are a good option.

All vary in complexity and how much time they take to implement. The CellSTACK or HYPERStack vessels have a familiar footprint and can be compatible with automation platforms, which may reduce the time needed for process development. By contrast, microcarriers will save space and offer process control, but they may take more time to implement if you're new to them. Meanwhile, the Ascent FBR system offers a compact footprint, and is designed to provide process control and support efficient cell recovery.

The choice depends on your goal: How many cells do you need, how quickly do you need them, and what's important to you along the way?

BIOPHARM: How might users go from a vial to production scale?
MOGEN: A bioproduction process often starts with a frozen vial of cells, which is either a working cell bank or a master cell bank. The cells are then thawed and seeded, usually into a small vessel like a T-flask. Those cells would then expand and be harvested and passaged to larger vessels.

The process of going from a small T-flask into larger vessels is called a seed train. It's done multiple times. The choice of seed-train vessels and what that process looks like depends on the application. The final scale of the process dictates the number of vessels needed and how long it takes to go from one vessel to another to get to production scale.

The harvest and reseed process has its own challenges. They can be cell-type-specific. For example, some cell types are more readily harvested and reseeded than others, and that can impact the selection of the platform to use in the process.

Finally, when scaling up cells and the seed train, it's often helpful to work in reverse: Determine the final scale based on the expected yield and number of cells, or on the products being produced by those cells, and then work backward from there.

BIOPHARM: Can you discuss some automation and process controls for adherent platforms?
MOGEN: Different process controls and automation options depend on the platform used to scale up the cell culture. With stacked vessels such as CellSTACK and HYPERStack, there haven't historically been many options for process control. However, Corning offers an automated manipulator platform that automates the handling steps associated with movement of the CellSTACK and HYPERStack vessels. This is a critical component to maintaining consistency within production and from lot to lot.

Regarding next generation of adherent cell culture platforms such as the Corning Ascent FBR system or microcarriers paired with a bioreactor, there is additional built-in process control. For example, you typically have control over the gassing strategy—dissolved oxygen and CO_2. There's pH control, as well as tight control of temperature.

Taking that one step further, there's a move in the bioproduction field to automate many of the liquid-handling and process steps in these bioreactor systems. Corning's Ascent FBR uses touchscreen controls, as well as tubing management to automate many manual process steps involved in moving liquid into and out of the bioreactor, thereby removing some operator-introduced variability.

BIOPHARM: What technological solutions can improve adherent cell harvest?

SILER: First is automation. With vessels such as CellSTACK or HYPERStack, the Corning automated manipulator can be programmed at sharp angles or to make very quick motions to facilitate moving the liquid over the surface quickly to help the cells lift off. That automation component gives you batch to batch consistency. Cell removal is also automated on the Ascent FBR platform. We've designed the system to enable uniform flow rates at which the reagents reach the fixed bed and the volumes of those reagents, which can make the process more straightforward.

Another option is for the substrate to go away entirely. With Corning dissolvable microcarriers, you dissolve the substrate from the cells, so you don't have to worry about separation. You separate the cells from one another; but any connections they've made with the substrate disappear entirely.

BIOPHARM: What makes the Ascent fixed-bed bioreactor unique?
SILER: The Ascent FBR system has several exciting features. The substrate is a woven PET mesh, which has a very regular pattern. Within the fixed bed, there is even fluid distribution and even distribution of cells. That homogenous substrate gives the cells the same access to nutrients during the growth process and to harvest reagents during harvest.

Regarding harvest, fixed bed reactors are often associated with secreted products. This platform can be used for that purpose, but it also gives you the ability to collect cells at the end of your growth period as a final product or even in a seed train to larger Ascent FBR systems, which are forthcoming. It's intended to be very scalable. Since it's a fixed bed, there's a favorable media-to-surface-area ratio, too.

One of the best features may be the automated process steps. The touchscreen interface is designed to prompt you for next steps in the process and then the system will do a lot of the work for you—opening and closing valves and pumping the liquid.

MOGEN: With the Ascent FBR system, we see increased productivity per cell for applications like AAV production because of the uniform exposure of cells to nutrients and gases. The Ascent FBR system decreases the bioproduction footprint and optimizes the cell culture conditions to ensure cells are as healthy and happy as possible. Healthy, happy cells produce more, which is better for therapy workflows.