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Disposables Reach Out to New Markets

Development and Application of Single-use Products Is Expanding Throughout Industry

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There is no denying the growing usage of disposables—only three percent of biopharmaceutical manufacturers claim to use none, according to a report by BioPlan Associates.

Frost & Sullivan opines that biologics manufacturing is expected to reach 3.6 million liters in 2011. Although disposables are not entirely replacing stainless steel systems, they are being utilized for process development and in pilot plants to speed commercialization. In addition, companies are developing and/or optimizing disposables for new markets and applications. Many of these companies will be presenting their latest technology at IBC's "BioProcess International Conference," to be held in October.

Making the Right Choice

"I've seen companies embrace disposables much more over the past five years, and a lot of the excitement has to do with the available disposable sensor technology, which eliminates many previous limitations," says Craig Sandstrom, Ph.D., director of process engineering for **Fluor** (www.fluor.com). Dr. Sandstrom has completed several case studies of facilities designed around trying to implement disposables.

"You have to adopt the technology early on because it affects the facility layout. Disposable bags increase material handling and material flow issues and should be in a facility on one level versus a traditional biomanufacturing facility, which is multilevel."

Dr. Sandstrom is surprised that many people expect disposables to reduce facility costs by up to 80%. "Everybody is in shock when they discover that this isn't the case. There are a lot of facility costs involved with disposables that you can't reduce—you're only saving about 10 to 20 percent." In addition, he says, the overall facility footprint is larger with portable equipment.

Deciding whether to use disposables or stainless steel often depends on the automation requirements of the facility. Overall, disposables are more labor-intensive and less automated than stainless steel systems. Every case has to be examined individually, Dr. Sandstrom says, but often disposables provide more flexibility for faster construction renovation.

Virxsys (www.virxsys.com) is currently conducting Phase II trials in HIV patients using lentiviral vectors for gene therapy. After the Phase I trial was completed, the company realized it would need to manufacture enough cells to administer multiple infusions, requiring a change to its manufacturing process.

"We have to grow large concentrations of cells, but this needs to be done from individual patients. We needed something efficient and manageable that could be scaled up," explains Gerard McGarrity, Ph.D., vp, scientific and clinical affairs.

The company decided to use the Wave Bioreactor® and Cellbags® from GE Healthcare (www.wavebiotech.com), which, Dr. McGarrity reports, eliminate cleaning and validation and can be installed rapidly.

"The basic challenge was optimization. We were familiar with the products, but everything had to be optimized. It was an innovative process in that this was the first time the lentiviral vector was administered to human

patients," adds Dr. McGarrity.

The company decided to use disposables since it is treating individual patients with ex vivo gene therapy. "We didn't want hardware we had to clean and recertify for each patient. Also, the disposables allow for processing several patients' cells simultaneously." However, Dr. McGarrity explains, disposables require more vigorous training since they involve more handling. Yet, for small- and medium-sized biotech companies, he agrees that disposables are an attractive option for cell expansion.

Chromatography Gaining Momentum

There is a major trend toward the use of disposables in all phases of manufacturing including downstream processing. However, notes Uwe Gottschalk, Ph.D., vp, purification technology at **Sartorius** (www.sartorius.com), this is creating a bottleneck because "we are getting so much out of mammalian cell cultures (i.e., higher biomass and expression rates) that we can't keep the pace with the current technology."

The limitations are mostly technical, Dr. Gottschalk admits. The early steps of downstream processing, dominated by protein A and affinity chromatography, have no disposable solution. "This material is so expensive and powerful, you can't throw it away after one cycle."

However, he says that for downstream processing steps including recovery, capture, microfiltration, and virus filtration, there are disposable solutions such as the ones that Sartorius offers for flow-through chromatography. These include a membrane device called Sartobind®, which ranges in size from one milliliter (the newest product in this line is Sartobind Nano) up to the jumbo size of five liters. "These have the full capacity of a chromatography column in a single-use filter design that can be run in parallel," he reports.

"I've been working in this area for the past 20 years, and this trend toward disposable chromatography in bioreactor contaminant clearance is the most remarkable trend that I've ever seen in chromatography, if not downstream processing. The trend is going back to simpler and more robust methods. That's why it's so remarkable because it challenges the common thinking," Dr. Gottschalk concludes.

Higher antibody production has shifted the bottleneck from upstream to downstream processes, especially to the protein A chromatography capture step. The concept of continuous chromatography has been adapted by **Tarpon Biosystems** (www.tarponbiosystems.com) to include a disposable format based on simulated moving bed (SMB) technology, which was originally used in the petroleum distillation process.

"We have developed and improved the SMB technology for biotech applications," says Marc Bisschops, scientific director, bioprocessing. "This simulates movement of the resin without actually moving it. Instead, we connect multiple columns and switch the inlets that contain fresh cell supernate."

Previously, use of continuous multicolumn chromatography or SMB has been hampered in biomanufacturing by system complexity and validation issues. The company's BioSMB™ system uses an entirely disposable fluid path. It also utilizes disposable format modules for the valving system as well as for the columns.

"Our system is more flexible because chromatography columns have one size. If you have a cell culture with a certain expression level, you have to go through multiple cycles. Our technology differs in that it runs continuously and allows users to fine-tune the process like the resin transport rate," explains Bisschops.

Scaling up Bioreactors

The increasing acceptance of disposable bioreactors is driving an expansion of their use from start-up bioreactors to production. "More people look at these as their workhorse production bioreactor, with scales increasing to the 1,000 to 2,000 liter size, which is a reasonable production size for smaller processes or perfusion," says Geoffrey Hodge, vp, process development and technology, **Xcellerex** (www.xcellerex.com).

Disposable bioreactors are not feasible for traditional batch manufacturing like for antibodies with high demands of 10,000–20,000 L, Hodge reports. However, he says that "with better genetic screening, clinical diagnostics, delivery systems, and higher productivity per liter, the average size of the production bioreactor will be around 2,000 liters for more commercial products in the future."

In order to overcome the challenges inherent with large-scale disposable bioreactors, the company performed a case study of a 1,000 L perfusion culture using its XDR™-1000 stirred tank bioreactor.

One of the challenges was controlling CO2 while providing high enough oxygen transfer as well as CO2 removal while harvesting a steady stream of medium. Another difficulty was working out the conditions for centrifugation with a completely disposable flow path. “A lot of it was logistics—how to make all the connections and stage the work,” explains Hodge.

New Brunswick Scientific (NBS; www.nbsc.com) offers a disposable cell culture system that produces milligram quantities of protein, virus, or biomass from a wide variety of cells. The FibraStage™ system comes with FibraStage disposable bottles, each with a solid-support matrix (FibraCel disks) for producing high-density cultures.

This saves labor and time by keeping the cell growth to one bottle instead of dozens of T-flasks, the company reports. In addition, the cells remain entrapped in the FibraCel disk during the entire run, keeping the medium cell-free. The system eliminates autoclaving, costly start-up expenses, and cross-contamination between batches.

FibraStage fits most CO2 incubators, and the magnetized controller is stored outside on the incubator wall. “The controller allows the user to regulate the up and down movement of the platform that drives media into the FibraCel disk. These cycles can be regulated in seconds or minutes to regulate top-hold positions where the cells are kept in media and bottom-hold positions where there is CO2 exchange,” explains Mike Sattan, marketing director. “This method is a simple way to create an elaborate bioreactor.”

NBS also offers an automated cell counter for mammalian or yeast cultures. The NucleoCounter® uses the same principles to determine cell concentrations as those used in conventional methods involving hemacytometers and microscopes.