BIOPROCESSING

A Critical Look at Bioproduction Approaches

Continuous Improvement Remains Key

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Much has been written about biomanufacturing's failure to keep up, technologically, with the complexities of and demand for biotech products. According to a survey by Ajaz Hussain, Ph.D., a deputy director at the FDA, biotech's manufacturing efficiency is around 25%—far lower than in other process industries.

While innovation has traditionally lagged due to regulatory uncertainty, comfortable profit margins shielded biotech from its production inefficiencies. Now, with the FDA encouraging innovation through risk-based manufacturing and process analytics, and with biogenerics looming, biotechnology can no longer be satisfied with business as usual.

Express Yourself

Novel expression systems are a potential avenue for achieving orders-of-magnitude improvements in cost of goods. For example, switching from Chinese hamster ovary (CHO) cultured cells to microbial fermentation would offer huge cost and productivity savings.

What if yeast were somehow coaxed into expressing human-friendly glycans in the right patterns? **GlycoFi** (www.glycofi.com) is doing just that. Its engineered yeast variants could eventually offer an alternative to expensive, variability-plagued CHO, while providing the familiarity of yeast fermentations.

Marketed yeast-derived products include insulin, interferon beta, and vaccines, none of which are glycosylated. GlycoFi's yeast secrete proteins bearing human glycans which, according to CEO Sylvie Gregoire, Pharm.D., provide

Improvements On the Way

Biotech's productivity gains will be evolutionary, not revolutionary. The diversity of bioproducts and processes effectively bars a one-size-fits-all approach. Following are trends and technologies identified by some of the experts interviewed for this article:

• Harry Lam, Ph.D., director of manufacturing quality engineering at **Genentech** (www.genentech.com), believes that protein titers of up to 10 grams per liter will be commonplace in tomorrow's biomanufacturing plants. This fivefold improvement will arise through improvements in cell culture productivity, process optimization, cell line screening, and gene vector design. At the operational level Dr. Lam likes disposable technology, PAT, and process control both up- and downstream.

• According to Fiona Godsman, marketing director at **Bioreliance** (www.bioreliance.com), companies are planning for large-scale manufacturing earlier, long before such manufacturing is actually needed.

"They're thinking of the endgame when still in the opening phase of the game. Companies are thinking about their manufacturing cell lines and optimizing lines early for yield and scalability, to mitigate any regulatory risk of switching production technologies."

• Capacity issues will continue to affect scientific and business decisions for biotech, says Shawn R. Smith, business segment director at **Invitrogen GIBCO** (www.invitrogen.com). Companies will continue to assess their capacity needs, he says, by scrutinizing their pipelines, while relying on contract manufacturers for stop-gap capacity. Glitches will occur, not all of them bad.

better compatibility and lower immunogenicity.

Moreover, GlycoFi can express and attach specific single glycans to study which sugars and glycosylation patters are responsible for activity, circulating half-life, toxicity, etc. "By understanding glycosylation better we, and regulators, can better understand the product," says Dr. Gregoire.

Advantages of yeast compared with CHO include lower capacity and equipment costs, culture conditions that are easier to duplicate, and cycle times of three days vs. two to three weeks.

"At roughly equal protein titers, yeast cost one-half to one-third as much as CHO cells at Phase I or II quantities," notes Dr. Gregoire. More importantly, gene-to-protein development time can be as little as six months, compared to six to eighteen months for CHO.

Glycofi claims that through controlled glycosylation it can produce more-potent proteins that require lower dosing.

Transgenics—Promise Amidst Uncertainty

Transgenic animals and plants face years of regulatory uncertainty but companies continue to innovate and investors remain bullish. Transgenics firms fail for a variety of reasons: long lead times for developing founder herds and crops, downstream purification hurdles (desired products are often expressed along with structurally related animal proteins), safety concerns, and, for plants, the potential of pollen-producing strains to crossbreed with and contaminate food crops.

Still, the promise of transgenics keeps this avenue alive. The key will be overcoming scientific and regulatory objections while providing a genuine advantage over cell culture.

For example **Biolex** (www.biolex.com) offers a transgenic expression system based on Lemna (duckweed), a plant the company claims offers the best characteristics of mammalian cell and plant cell systems.

Lemna which resembles three- to four-millimeter lily pads, reproduces "like crazy," according to senior vp of R&D David Spencer, Ph.D.

The plant doubles its biomass every 36 hours and reproduces clonally, which means offspring are identical to parent. Dr. Spencer likens Lemna to "green CHO" that grow like plants and glycosylate like mammalian cells.

Unlike animal cells, however, green plants do not carry receptors

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GlycoFi says its engineered yeast variants offer rapid cycle times from gene to protein.

For example **Centocor's** Remicade was originally developed for Crohn's disease, but recent approval for rheumatoid arthritis significantly expanded its manufacturing capacity requirements.

• Combining technologies and unit operations—for example, continuous perfusion cell culture with disposable containers—will create efficiency synergies. Wave Biotech's Vijay Singh relates that one of his customers uses a 500-liter disposable container bag to make 15,000 liters of cell-conditioned media over 30 days through perfusion culture.

• Vaccine manufacturing methods dating back to the 1950s will be replaced as the public health system emphasizes disease prevention. Vaccines against emerging infectious diseases as well as chronic, noncommunicable illnesses will spearhead manufacturing innovation.

• Disposable technology will establish itself downstream, particularly into large-scale chromatography, as less-expensive alternatives to protein A capture resins emerge.

• Cell culture media and cell line development will continue to advance. Super cell lines such as **Lonza's** (www.lonza.com) Glutamine Synthetase system, which bioengineers NSO (a hybridoma) and CHO lines directly, and **Crucell's** (www.crucell.com) PER.C6 line for both adenoviruses and Mabs, will provide high titers and reduce capacity needs.

Simultaneously, relationships between media developers and manufacturers will tighten as industry recognizes this "free" source of added productivity. Invitrogen, for example, works with customers to optimize serum-free, protein-free, and animal-origin-free culture media and complementary reagents/supplements for specific engineered cell lines.

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for human proteins, which may cause down-regulation of expression. As nonmammalian systems, plants have no need to fold proteins inappropriately, which simplifies isolation and purification. According to Dr. Spencer, Lemna expression could reduce the cost of unglycosylated alpha interferon by a factor of 1,000.

Biolex has a shot to be the first plant technology company to succeed in commercializing a transgenic product (**GTC Biotherapeutics**, with its Atryn goat-derived protein currently in European review, should be the first overall). The company expects to have applied for an IND on its lead protein product, interferon alpha 2b, by the end of the year. Biolex has several other proteins in preclinical development and has signed collaborations with **Bayer** and **Centocor**.

Son of Hatch-Waxman?

The arrival of Biogenerics in three to five years will affect biotechnology in the same way small-molecule generics changed pharmaceuticals.

"Biotech is now at a crossroads defined by the intersection of patent and regulatory law," says Stephen Bent, an attorney and co-chair of the life sciences industry team at Foley & Lardner (Washington, DC).

Twenty years ago, the Hatch-Waxman act helped propel small-molecule generics to a $10 billion business by streamlining regulations and allowing manufacturers to test generics before branded drug patents expired. Unfortun-ately, Hatch-Waxman specifically excluded biologicals, so industry and government must start from scratch.

Without the proper legal-regulatory framework, biogenerics will not happen. "If it took an act of Congress to provide a framework for generic small molecule drugs, we'll need 'son of Hatch-Waxman' to cover biologicals," notes Bent. "FDA will probably not act without such a law."

But with so much at stake it must. By 2015, biopharmaceuticals with annual sales of between $10 billion and $30 billion will come off patent. And when the Medicare drug benefit comes online in 2006 that agency will become a significant payor for biologics as well as small-molecule drugs.

Innovator biotech companies and potential biogenerics manufacturers are currently hammering out how to define biosimilarity in a way that satisfies science, regulators, and the understandable desire of innovator firms for market exclusivity.

Biogenerics developers will probably be offered some form of regulatory relief, similar to today's generics companies, provided standards for chemical similarity and biological activity are met.

Much of the action in biogenerics will occur overseas, according to Vijay Singh, Ph.D., president of **Wave Biotech** (www.wavebiotech.com).

"Four Indian generic pharmaceutical companies already each have annual sales of more than $1 billion. They have nowhere to go but up," notes Dr. Singh.

Because of their need to compete on price, biogenerics manufacturers will need to invest in process improvements, process analytics, and even new expression systems. The immediate benefit will be lower cost for generic biopharmaceuticals, but it is expected that these process innovations will trickle up into innovator companies.

Reducing Variability

Process variability has been so much a fact of life in biotech that some companies jump through hoops simply to avoid variability issues, explains Lou Bellafiore, president and CSO at **TechniKrom** (www.technikrom).

For example, variability avoidance leads some processors to chromatograph an entire batch of product on one large column without monitoring fractions.

"They don't even use a detector," notes Bellafiore. "Everything is fractionated and in-process QC segregates good cuts from bad."

Such practices can turn out disastrously since they place the entire batch at risk.

Enlargement of the aquatic plant *Lemna* used in Biolex' LEX SystemT for the production of recombinant therapeutic proteins.

Automation workarounds can sometimes be worse than the original problem.

"The possibility of automating chromatography actually took a step backwards when LC equipment vendors began adding PLC's (programmable logic controllers) and PCs to their equipment—calling them 'automated' without addressing buffer variabilty from both the feedstocks and their non-adaptive equipment designs," continues Bellafiore.

"This practice, which required highly trained operators to perform critical buffer-related operations manually, became en-trenched as the approach of choice."

Many biomanufacturing and vendor firms are responding to the FDA's Process Analytical Technology (PAT) Initiative, which has the stated goal of better understanding and controlling the pharmaceutical manufacturing process. TechniKrom, for instance, has championed the use of "adaptive PAT," an approach based on real-time analysis and corrective process control.

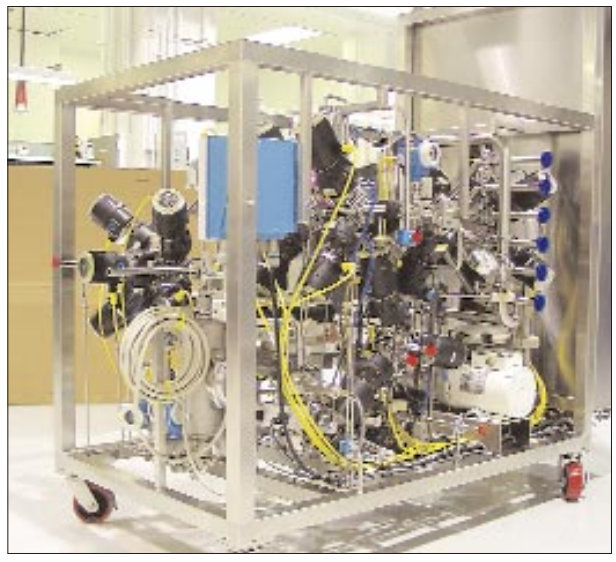
TechniKrom's buffer dilution and blending systems and Bioprocess LC systems incorporate adaptive PAT through the use of on-board intelligence that automatically adapts, on a millisecond basis, to in-line analytical data sent to a feedback control system.

"PAT's impact on biomanufacturing is more than just 'super-QC'", notes Bellafiore. "It enables innate product quality by controlling processes as well as significantly increasing the recovery of high-value products, thereby reducing costs and product loss due to error. For example adaptive PAT detects connection of an incorrect feed to a system."

In biotech, PAT will be helped along by the arrival of biogenerics, where cost pressures will finally hit biomanufacturing. There is always the danger, observes Bellafiore, that generics firms could become motivated to cut corners to remain competitive, rather than using manufacturing science to reduce costs.

FDA is working to make them aware that the proper application of PAT will give them the economic advantage they need as well as providing regulatory compliance through well-characterized, non-variable processes.

The TechniKrom Sanitary Bioprocess LC System with Adaptive PAT™



Uncertainty is your Friend

To meet demands for tomorrow's markets, companies will need to adopt risk management as a big-picture philosophy—not just for manufacturing but for all types of business risk.

More than one biotech company has been done in by huge facility construction costs. The culprit, says Uriel Kusiatin, a principal at consulting firm 2Value (New York City), is the view that plant construction is an all-or-nothing proposition. By hedging bets on a pipeline product's success and taking a piecemeal approach to construction, biomanufacturers may be able to have their cake and eat it too.

Kusiatin and colleagues have developed a strategic capacity planning model, Real Options, which, Kusiatin claims, allows biotech firms to exploit drug approval uncertainty.

"Real Options allows you to mitigate downside risk while taking advantage of opportunities from the upside perspective," he explains.

Real Options breaks drug development and capacity needs into manageable, parallel time points. Each stage (e.g., corresponding to clinical trial stages), depending on the chance of success, prompts drug sponsors to take an additional step toward renting or acquiring manufacturing capacity.

Developers might acquire land and engage architects early in Phase I, construct a building shell as the product enters Phase II, etc. At every point the investment is commensurate with development progress. If and when their drug succeeds companies applying the Real Options model are prepared. If it fails companies may take solace in the fact that they have invested the "right amount" in the venture.

"Executives typically make decisions based on net present value, which assumes 100 percent certainty," says Kusiatin. "With biopharmaceuticals the risks of losing out are simply too great not to begin until you're 100 percent certain. Real Options allows you to invest just enough until you determine if there's any value in further investment." GEN

New U.K. Center for Biomanufacturing

Construction is moving along on a center to develop and manufacture new biopharmaceutical medicines for clinical trials in Speke, Liverpool, U.K.

Operated by **Eden Biodesign** (www.edenbiodesign.com), the lab-based manufacturing service provider of the Eden Biopharma Group, the National Biomanufacturing Centre is a government-funded initiative led by the Northwest Regional Development Agency that is designed to help establish England's Northwest as a major center for biomanufacturing in Europe.

A Range of Services

The center will provide the expertise and facilities to support new and existing biotech companies, offering product development services designed to fill skill and resource gaps that exist within these organizations. The 4,100 m^2 biomanufacturing and development center is expected to open in 2006.

Government investment includes an access fund of approximately £3 million which will allow U.K. biotech SME companies, particularly from Merseyside, to purchase services from the National Biomanufacturing Centre.

Officials at Eden Biopharma Group, which recently raised £5 million in investment to provide the working capital to launch and operate the biomanufacturing center, say that Eden Biodesign won the competitive tender for the contract due to its expertise in biopharmaceutical manufacturing, especially in early-stage development.