

Advances in fermentation and cell culture technology

We review recent technical developments in the science, technology and applications of fermentation and cell culture processes for pharmaceutical production.

Fermentation and cell culture are important technologies for the production of biopharmaceuticals and a number of technology and business acquisitions have occurred in the sector over the past few years. In this article, we review some of the most recent developments.

Last September, the former JRH Biosciences business transferred into the SAFC Biosciences brand, which became a legal entity in January 2006. The company is now a leader in cell culture reagents and services for therapeutic proteins. The business supports 63 per cent of approved cell culture based drugs and is the primary vendor to more than 50 per cent of approved drugs.

SAFC Biosciences provides an integrated services package in mammalian cell culture media development to support customer programmes from preclinical and clinical development through to commercialisation. Analytical and regulatory support is also part of the package. Headquartered in Lenexa, Kansas, SAFC Biosciences has five production facilities in the USA, Europe and Australia and employs 650 people.



Following SAFC's acquisition of the JRH Biosciences business, SAFC Biosciences has become strongly established in the cell culture sector.

Last October, the company announced a non-exclusive agreement with ProBioGen under which SAFC Biosciences will market ProBioGen's cell line engineering services for the development of high-titre cells for production of biotherapeutics. The agreement expands SAFC Biosciences' process development offering for biopharmaceutical markets and ProBioGen's global sales marketing coverage.

ProBioGen is an internationally recognised specialist for cell line development, viral vectors and the manufacture of glycoproteins. Combined with the use of novel, inactivation-resistant promoters, ProBioGen's vector design and sequential double selection strategy, allows the development of clone pools with high average cell-specific productivity.

"The agreement with ProBioGen will provide our customers with access to state-of-the-art technology, offering clear, competitive advantage through the development of cell lines and cell culture media which achieve significantly greater amounts of protein than current technology," says Bruce Lehr of SAFC Biosciences.

Cell line engineering system

Last September, SAFC Biosciences and Chromos Molecular Systems Inc entered into a non-exclusive co-marketing arrangement whereby the companies jointly market and offer Chromos' proprietary ACE System for cell line engineering for protein production applications. The agreement adds to SAFC's process development service offerings for biopharmaceutical markets and expands Chromos' access to the global biopharmaceutical market with its ACE System.

"Chromos' ACE System is a unique and powerful vehicle for transferring genes into cells for the subsequent expression of proteins. The ACE System demonstrates a significant improvement in cell engineering technology and gene expression," says Lehr.

Recently, Chromos signed a contract with AppTec Laboratory Services, Inc for scale-up and manufacture of its monoclonal antibody drug product candidate CHR-1103. Chromos has used its proprietary ACE System to engineer cell lines for CHR-1103; AppTec will scale up and manufacture CHR-1103 for use in preclinical toxicology studies and Phase I clinical trials.

CHR-1103 is one of two drug product candidates gained through Chromos' acquisition of Targeted Molecules Corporation in February 2006. A humanised monoclonal antibody for the treatment of the inflammatory disease, CHR-1103 is being developed initially to treat acute flares associated with relapsing forms of MS.

Earlier this year Chromos expanded the scope of its collaboration agreement with Pfizer to use its ACE System to develop a cell line for a Pfizer therapeutic protein product candidate. The companies will also initiate a collaborative programme to genetically engineer production cell lines.

"Our relationship with Pfizer has been exceptionally productive as evidenced by their expanded commitment to the



New Brunswick Scientific's BioFlo® Pro fermentors and bioreactors are modularly designed for quick delivery and ready customisation, even in the field. Illustrated is a 150 litre reactor.

ACE System”, says Alistair Duncan, president and CEO of Chromos. “We look forward to continuing to work on multiple programmes with Pfizer to take advantage of the unique features and significant benefits of the ACE System for cell line engineering.”

Expanded bioreactor range

New Brunswick Scientific Co, Inc is a global

provider of a range of research equipment and scientific instrumentation for use in the life science industry. The company's products are used in the creation, maintenance and control of physical and biochemical environments required for the growth, detection and storage of microorganisms for medical, biological and chemical applications, as well as environmental research and commercial product development.

In March of this year the company announced the expansion of its range of cell culture systems to include new pilot- and production-scale bioreactors in 75- to 300-litre capacities. The new BioFlo® Pro Cell Culture Bioreactors feature a modular design, enabling ready customisation, rapid delivery and on-the-spot field upgrades as processing or manufacturing needs change.

These cell culture systems are typically used to grow suspension cell cultures in order to obtain antibodies or proteins, which can be used in turn for treating a large range of medical conditions including asthma, hemophilia, cancer and AIDS. The large-scale units complement NBS' existing, full line of cell culture systems, which now includes a 500-ml disposable system as well as a series of autoclavable and sterilisable-in-place bioreactors for research through production.

New Brunswick Scientific president and chief operating officer James Orcutt comments: “We find that scientists and engineers are choosing our BioFlo Pro cell culture systems because of the success they have had using our smaller-scale systems, as well as the systems' built-in versatility and quick delivery - often in as little as 12 weeks. In fact, our new field-upgradeable bioreactors combine the best features of our BioFlo Pro fermentation line, including ease of operation, maintenance and systems integration, with a modular design that not only enhances reactivity and adaptability to fluctuating demands, but does so at a very competitive price.”

Bioprocessing products and services

Celliance™ offers an expanding array of bioprocessing products and services including diagnostic products, contract research and manufacturing services, and cell culture media supplements. The company's cell culture supplements products

include EX-CYTE®, the largest selling cell growth supplement, Probumin(tm), a proprietary line of bovine serum albumin and Incelligent(tm), the Company's recombinant human insulin. It is also the world's leading provider of monoclonal antibodies for the blood typing industry. Celliance™ is part of the Serologicals Corporation family of companies.

Last October, Celliance acquired the UCOE (ubiquitous chromatin opening element) gene expression technology from Innovata plc. UCOEs improve the yield, consistency and stability of protein production in cultured mammalian cells, allowing simpler and quicker generation of proteins at small scale for drug discovery and research, as well as quicker and easier isolation of stable, highly productive cell lines suitable for larger-scale manufacture of protein therapeutics. Further applications of the technology include gene therapy, transgenics and generation of cell lines for drug screening. This technology is under licence to a number of pharmaceutical and biotechnology companies in North America, Europe and Japan.

Pioneering applications in research and production

HyClone is a global supplier of cell culture and bioprocessing systems for application in research and production. The company is widely known as the premier supplier of quality fetal bovine serum and other sera for cell culture. HyClone also manufactures classical media and new serum-free and protein-free media formulated for commonly used cell lines. It works with clients to develop custom media formulations.

HyClone began in 1967 when founder Dr Rex Spendlove, then a professor at Utah State University, was studying a viral disease fatal to children, especially in developing countries. At that time, the quality of commercially available fetal bovine serum (FBS) was so poor that Dr. Spendlove was forced to develop his own methods to produce a high quality serum to meet his research needs. Recognising a real need in the scientific community for high quality FBS, he founded a company that would meet that need.

HyClone pioneered serum collection, filtration, and processing techniques used to produce consistently high quality, reliable serum products. To produce FBS, HyClone collects fetal bovine blood using a patented closed-system collection method that results in serum with exceptionally low levels of endotoxin and hemoglobin. HyClone pioneered the use of high retentive filtration techniques including triple 100 nm and 40 nm pore size rated filters to ensure sterility. Vertical integration of all serum collection and manufacturing processes provides complete traceability and high quality.

In addition to its primary facilities in Logan, Utah, USA, HyClone operates a cGMP manufacturing facility in Cramlington, UK. This facility produces liquid media and process liquids for the biotechnology industry. Products manufactured in Cramlington include basal cell culture media, serum-containing media, serum-free media, process buffers and reagents, and WFI quality water.

The expansions to the Cramlington manufacturing facility have both increased production capacity and provided segregated manufacturing areas that are free from animal derived components. Included in the next phase of the facility upgrade will be the addition of a HyNetics™ single-use product contact manufacturing module.

Phase II expansions will also include a dry powdered media facility featuring the same high-speed micronisation system used in Logan. These expansions enable HyClone to better serve the European community and provide manufacturing backup to HyClone's operations in the USA.

