# Biologics make their mark as therapeutic agents

***Biopharmaceuticals are accounting for a constantly increasing share of the drugs market due to improvements in identifying biologic drug candidates and in manufacturing technologies, with several of the leading companies in the sector making major investments in new facilities.***

There have been a number of significant investments in the biopharmaceuticals sector over the past couple of years, as well as a number of new products reaching the marketplace. For example, Lonza's Board of Directors has approved a significant expansion plan for the Lonza Biologics facility in Portsmouth, New Hampshire, USA in line with its commitment to delivering new mid-scale capacity. The company says demand for mid-sized bioreactors is continuing to gain momentum as a result of its robust project pipeline. The groundbreaking for the 5,000-litre reactors is planned for April of this year.

The expansion complements the existing large-scale 20,000-litre reactors in Portsmouth. The increased capacity in the mid-scale range will also accommodate preclinical production needs. In addition, the technology transfer from laboratory through to large scale will ensure customer scale-up consistency, the company says.

The planned expansion follows an investment in large-scale bioreactor capacity. The fourth 20,000-litre bioreactor in Portsmouth will become operational in the middle of the year.

## Developing monoclonal antibody business

Dutch biotechnology company Crucell NV and DSM Biologics, a business unit of DSM Pharmaceutical Products, are expanding the development of the PER.C6® protein and monoclonal antibody licensing business. The two companies will create an integrated solution for the production of recombinant proteins and monoclonal antibodies on PER.C6 in order to increase licensing and royalty income and accelerate the development and roll-out of the technology platform.

**Lonza has been investing extensively in biologics manufacturing capacity. Pictured is one of the company's 20,000-litre bioreactors located at its Portsmouth, New Hampshire, USA facility.**

Crucell and DSM will develop and offer a fully integrated protein and monoclonal antibody production package for licensees for protein and monoclonal antibody production. The system will include optimised clone generation technology, tailored media, batch, fed-batch and perfusion fermentation processes, fermentation equipment design, scale-up and scale-down solutions and regulatory support. The partnership's research and development to create this new platform will be based around a new joint R&D centre, located in the Netherlands and the US East Coast.

"The protein market is growing rapidly and may reach $200 billion in 15 to 20 years, and we believe that PER.C6 has the potential to become the production platform of choice for an attractive part of that market," says Leendert Staal, president of DSM Pharmaceutical Products. "We want to pursue the significant income potential of the PER.C6 licensing business model."

To date, Crucell and DSM have signed 20 PER.C6 licences for production of various proteins, including licences to companies with marketed proteins, including Roche, Ely Lilly and Centocor.

## Partnering in microbial expression technology

In December, Cambrex became the first biopharmaceutical manufacturing partner for Dowpharma's Pfenex expression technology. Cambrex Bio Science Baltimore, Inc and Dowpharma have agreed to use the *Pseudomonas*-based technology in an initial technology transfer production run and establish a standardised technology transfer package for customer projects. The collaboration will allow Cambrex to manufacture biologic drug substances for third-party product companies using the Pfenex Expression Technology.

"Cambrex is impressed by the superior growth performance and expression characteristics of the Pfenex technology compared to conventional *Escherichia coli*-based systems," says Christopher Dale, PhD, vice president technology of the Cambrex Biopharma business. "The complementary services offered by Dowpharma and Cambrex scientists, combined with standardised technology transfer protocols, will streamline the transition of customer projects from Dowpharma to Cambrex."

"We are pleased to work with Cambrex to help them leverage Pfenex Expression Technology to cost-effectively deliver higher yields of their customers' therapeutic proteins," says Patrick Lucy, business leader of Microbial Biopharmaceuticals, Dowpharma. "As a leading cGMP service provider, Cambrex will be an important part of the manufacturing network supporting the Pfenex Expression Technology."

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Dowpharma is well-established in developing high-productivity strains for the manufacture of numerous protein products, for both clinical and industrial applications. The Pfenex Expression Technology is built around specially modified strains of *Pseudomonas fluorescens* bacteria that increase cellular expression of recombinant proteins and peptides while maintaining critical solubility and activity characteristics. Dowpharma says the technology often gives yields of five to ten times the next-best expression alternative.

Since the mid-1990s, Cambrex has been active in helping customers develop their active pharmaceutical ingredients (APIs) and drug substances more efficiently and cost-effectively, and has been especially active in the biopharmaceutical area in recent years.

## Acquisition of biopharma business

Last October Novartis announced its intention to acquire the remaining 58 per cent stake that it does not currently own in US pharmaceutical company Chiron Corporation for about $5.1 billion. In December the company received approval from the US Federal Trade Commission for the acquisition, which it expects to complete in the first half of 2006.

"Planning for the integration of Chiron into Novartis is on track, and this rapid review and approval by the FTC brings us closer to completing this transaction," says Dr Daniel Vasella, chairman and CEO of Novartis. "Novartis brings the necessary expertise, scale and resources needed to address the vaccine production issues at Chiron and to strengthen R&D efforts aimed at bringing novel vaccines to patients."

Novartis says the acquisition will provide it with an attractive growth platform in the dynamic vaccines market and in a rapidly growing molecular diagnostic business. Chiron's biopharmaceutical activities will be integrated into the Novartis Pharma drugs business.

Chiron had overall sales of $1.7 billion in 2004 and net income of $152 million. Its product portfolio includes an antibiotic for infections associated with cystic fibrosis; a treatment for metastatic kidney cancer and metastatic melanoma; and interferon beta-1b, a multiple sclerosis drug. The company's development pipeline includes several oncology products with research activities targeting the most promising approaches in cancer therapy, including monoclonal antibodies and molecular oncology.

## Clinical trial for antibody Alzheimer's treatment

MorphoSys recently announced that its partner Roche has filed all necessary applications to commence a European Phase I clinical trial with one of MorphSys's HuCAL®-derived antibodies to treat Alzheimer's disease. The antibody targets abnormal build-ups of amyloid beta protein in cerebral tissue, which are typical of Alzheimer's patients, and is intended to help remove them. The applications filing to commence clinical trials triggers a clinical milestone payment from Roche to MorphoSys.

"We are very proud to take a fully human antibody identified with MorphoSys's HuCAL technology into the clinic. This is an important and innovative step towards the treatment of Alzheimer's disease with a new class of medicines," says Andrew Sleight, head of Central Nervous System Research at Roche.

## Expression and fermentation at large scale

Wacker Biotech GmbH has been operating since early 2005 as the direct successor of ProThera GmbH and is a wholly-owned WACKER Group subsidiary. The company has been positioning itself as a full-service contract manufacturer of active pharmaceutical proteins, offering a range of services from molecular biology, process development and GMP-compliant production of clinical test samples and active materials for commercial market supply up to comprehensive analytical services. Examples are the *E. coli* secretion system and the company's high-cell-density fermentation technology.

**Wacker Biotech GmbH has established itself as a major provider of large-scale expression and fermentation biological manufacturing since its foundation in 2005.**

The company offers rapid development of robust, efficient and high-quality processes, as well as GMP-compliant production in its multi-purpose facility in Jena, Germany. These services are coupled with comprehensive in-house analytical facilities, comprising the development of analytical methods for in-process control as well as final product characterisation and process validation.

The *E.coli* K12-based secretion system allows the highly efficient extra cellular production of proteins and antibody fragments. The system comprises a series of high-expression plasmids and a host strain that can transfer proteins in a native conformation across the outer membrane into the culture broth. Exhibiting highly stable performance during fermentation, the strain is routinely used in commercial-scale fermenters up to a volume of 4.5 cubic metres. This way, product yields of over 7 g/l are attained.

Another proprietary technology offered by Wacker Biotech is a special high-cell-density fermentation process for *E. coli*. Under strictly monitored and robust conditions, this process enables high cell dry weights of over 50 g/l and an optical density of well over 100. Due to its extremely high volumetric productivity, the process has already been able to generate product yields exceeding 10 g/l. Using high-cell-density fermentation and efficient purification processes, Wacker Biotech can manufacture several hundred grams of purified protein per production run in a 300-litre fermenter. This means higher product yields with reduced reactor volumes and downstream costs.

Wacker Biotech says it will continue to expand its production capacity in coming years in order to meet the demands of the pharmaceutical and biotech industries. sp²

## FURTHER INFORMATION

**For further information on the biotech and biopharmaceutical companies featured in this article visit the following websites:**

**www.lonza.com**
**www.crucell.com**
**www.cambrex.com**
**www.novartis.com**
**www.morphosys.com**
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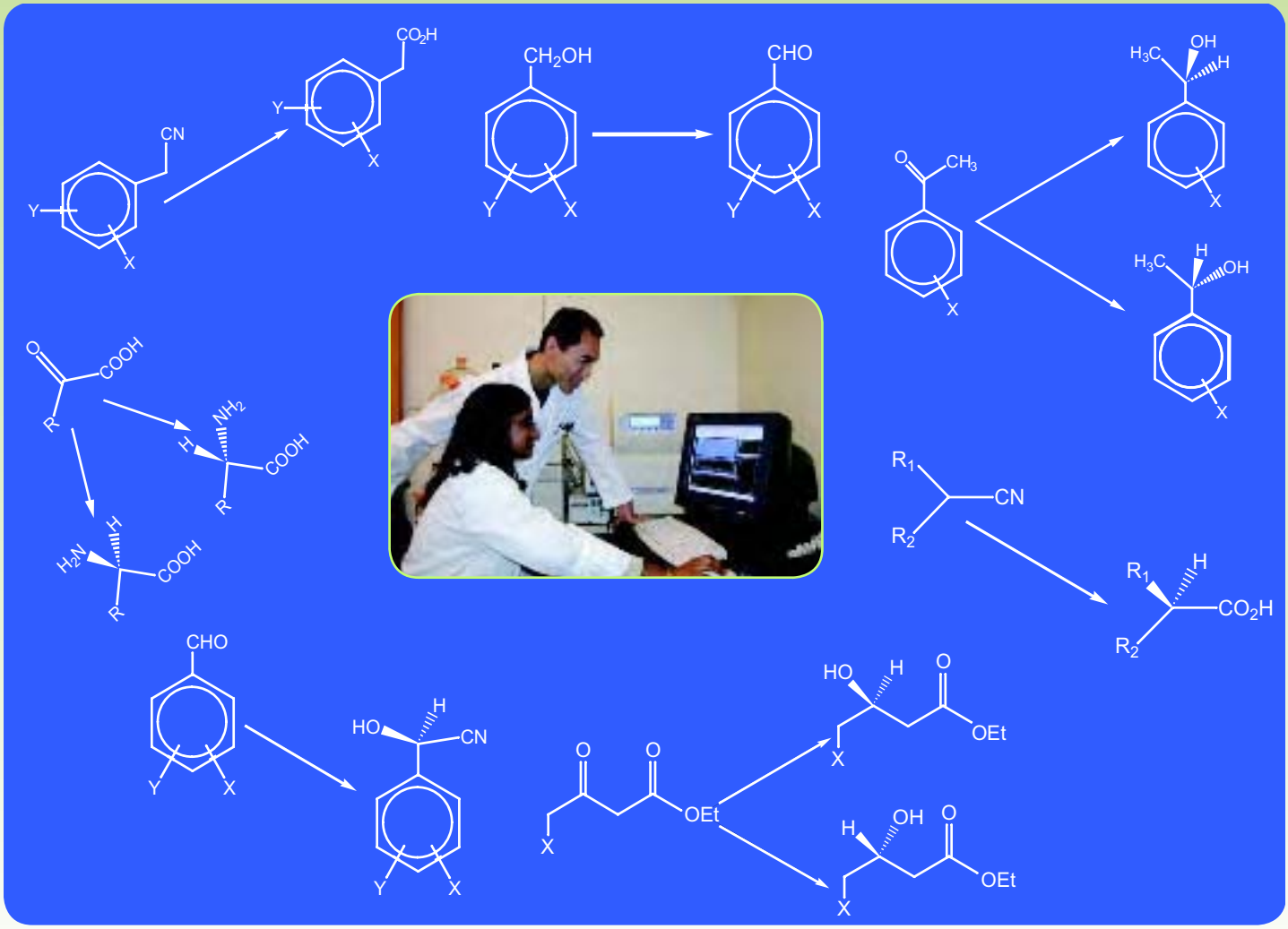


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