

# Integrating technologies for complete chemical synthesis

*CSS has expanded its offerings in chemical process development through the addition of new technologies, the formation of alliances, and through acquisition. David Moody, vice president of commercial operations, explains how the company's strategy is proving successful.*

Pharmaceutical services group Almac Sciences and its affiliated companies (CSS, CTS, ICTI, PDMS, and ArraDx) provide pharmaceutical services across drug discovery, API manufacture, clinical trials and drug product manufacture. The group has operations based in the USA (Pennsylvania, North Carolina and California), as well as in London and Craigavon in the UK. One of the group's companies, Northern Ireland based CSS, is an established provider of seamless services from contract research and development at laboratory scale to kilo-lab scale-up and transfer to pilot plant. These services range from literature and patent analysis to route design, optimisation and scale-up, and to cGMP manufacture up to 100-kilo scale. The company has specialist expertise in the synthesis of potent compounds, including in cytotoxics, contained micronisation, synthesis of parenteral APIs, low-temperature synthesis, chemo- and biocatalysis and isotopic labelling.

In addition to its manufacturing services, CSS offers comprehensive analytical solutions through the application of a wide range of advanced analytical instrumentation. Analytical services supporting drug discovery and development to commercialisation include stability testing for drug substances and drug products in accordance with ICH guidelines; batch release - both IMPs and commercial; QP release of drug products into the EU; bioanalysis of serum, urine and tissue; method development and validation; structural elucidation; and the identification of impurities and metabolites.

CSS has been steadily increasing its chemistry, analytical and custom manufacturing technology portfolio in recent years, the latest addition being the introduction of carbon-14 labelling services. "Customers now need a range of services and technology skills," says David Moody, vice president of commercial operations, "including cytotoxic compounds, peptides, micronisation services, and drug substance stability studies. Customers are now asking for more than GMP manufacturing. We can now provide services that are often individually unusual and rare in combination. Production of cytotoxic conjugates is one example."

## New radiolabelling service

Moody says the newly-introduced radiolabelling service illustrates this approach, as the technology can be used with all the company's other technologies, making it possible to produce, for example, radiolabelled compounds under GMP, radiolabelled peptides or radiolabelled cytotoxics. The new service is designed for the development of compounds from drug discovery to the launch of APIs, and includes the synthesis of metabolites, intermediates and APIs. Moody says the GMP synthesis of carbon-14 labelled APIs for clinical studies is an unusual departure from the radiolabelling service provided by others:

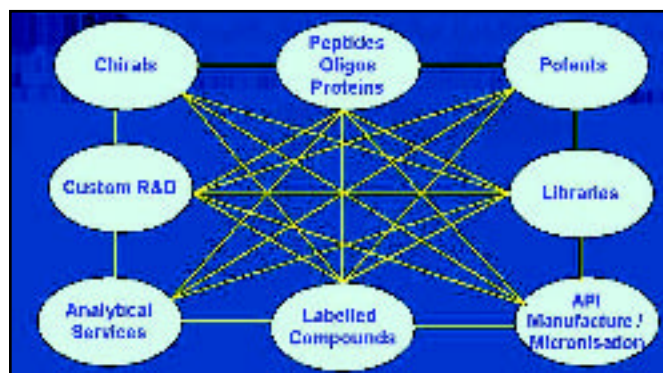
"Our customers benefit from the significant synergies that exist between the supply of NCEs, their metabolites and the radio-labelled analogues of both, and we offer synthesis to GMP and non-GMP," says Moody. "Cold and hot labelling are available, including 13C and 2H labelling of a diverse range of products from food contaminants to immuno-suppressant drugs, plus 14C and 3H labelling in newly-constructed dedicated laboratory facilities.

"This investment provides our customers with both a highly competitive stand-alone service and the opportunity to meet their most complex needs," he says. "In this regard, early indications are that many of our customers are interested in the supply of radiolabelled peptides, chirals and cytotoxics. This is another key step towards fulfilling our ambition of delivering diverse, different and highly 'connected' services."

## Offerings in chiral chemistry

The new service complements the company's chiral chemistry services established through the formation of the Chiral Consortium a year ago. The Consortium allows the company to deliver a range of chiral custom synthesis services that provide new routes based on biocatalysis and chemocatalysis for the production of new and established molecules. A range of chiral building blocks is also available.

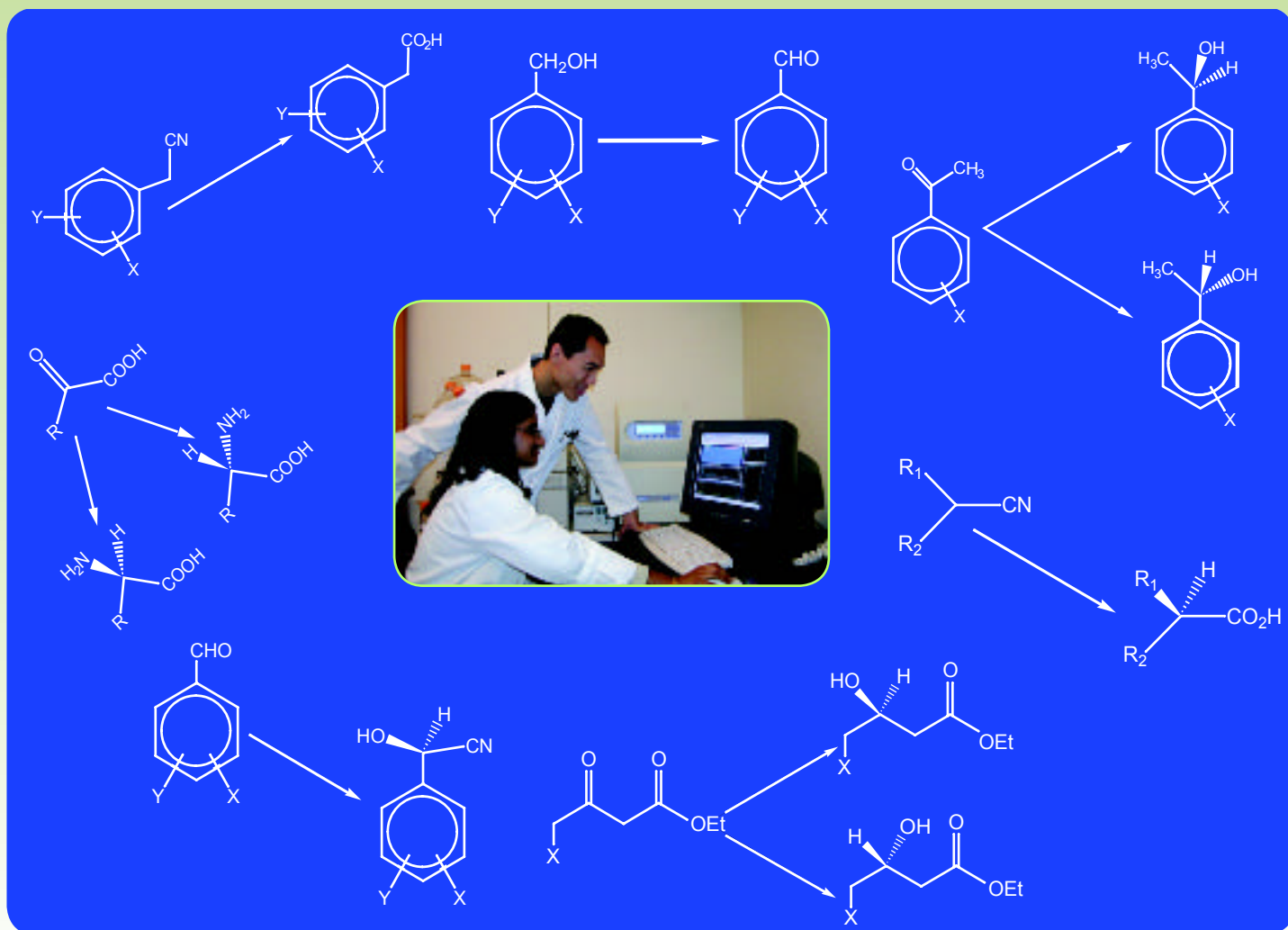
The Chiral Consortium was formed with ChiralQuest and IEP to serve the needs of the pharmaceutical marketplace for complex chiral products. In the Consortium, CSS provides route invention, scale-up and manufacture, and the company's in-house bio-resolution expertise is augmented by the chemocatalysis expertise of ChiralQuest and IEP's bio-reduction capabilities. The Consortium serves three main areas of chiral chemical synthesis: 'right first time' custom synthesis, in which new technology is developed for the synthesis of new molecules; synthesis of versatile chiral building blocks; and low-cost manufacture of existing pharmaceuticals, in which new



**CSS: Making and offering connections between a wide range of technologies and services for the pharmaceutical sector.**

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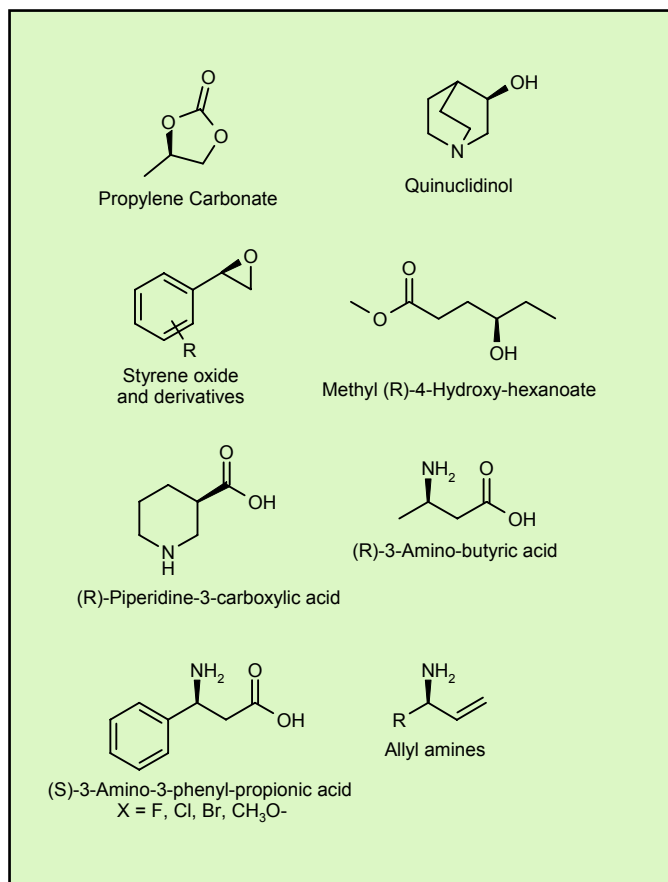


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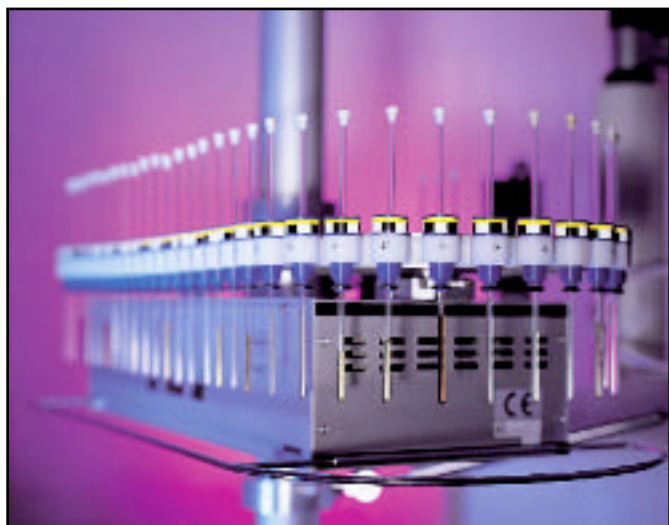
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Examples of chiral building blocks available from CSS through its membership of the Chiral Consortium.

technology is developed for the more cost-effective synthesis of molecules currently available.

"The cost-efficient synthesis of complex chiral products remains one of the greatest challenges in the manufacture of pharmaceuticals," says Moody. "In a climate of globalisation of product sourcing and remorseless cost-cutting by major pharma, Western suppliers have used chiral technology as a 'business attractor'. The result has been a bewildering array of technology solutions - each touted as better than the rest with fine chemical companies vying for the title of leader in chiral technology.



CSS offers a full analytical service using state-of-the-art equipment including NMR spectroscopic analysis.

"CSS has now entered this arena. The goal is to provide our customers with access to optimum manufacturing solutions while providing maximum flexibility in how those solutions are used. We will site winning solutions wherever our customers wish," he says.

"Wonderful technology already exists in the hands of dynamic, entrepreneurial technology companies. We provide the route invention, scale-up, pilot manufacture and technology transfer - true partnership is the best answer," he adds.

There is also the possibility that the Consortium will expand:

"We would be happy to welcome technology partners with complementary skills to our current membership. Of course, the trick is to have a compelling proposition for customers, and I think we have one," says Moody.

## Complex peptides and proteins

In complex peptide and protein manufacture, the company is able to offer the speed, purity and biological activity that were only previously possible with small peptides. The chemical synthesis of proteins up to 170 residues in length and in high purity has now been achieved. Services include the synthesis of therapeutic peptides, peptides for raising antibodies, and peptide libraries. CSS also performs cGMP manufacture in a Class 100,000 cleanroom of oligonucleotides and derivatives for research, diagnostic, and therapeutic applications in addition to APIs for use in clinical trials. Product groups include DNA and DNA modified with fluorescent labels, linkers, and by phosphorylation, amongst others; RNA, siRNA, and ribozymes; and aptamers and longmers. The company operates an optimised purification strategy based on combination reverse phase and ion exchange HPLC in Class 10,000 cleanroom facilities, with full analytical support including MALDI-TOF, ESI-MS, NMR, and CE.

Peptide synthesis is an increasingly important part of CSS' business. The company's facilities are based in Elvingston in Scotland, where it employs 16 people, including five chemists who joined in the past six months, and is focused on non-GMP peptide synthesis for early-stage R&D. CSS' Craigavon facility in Northern Ireland allows the larger-scale GMP synthesis of peptides, which can be combined with the company's other services to produce cytotoxic or radiolabelled peptide synthesis at various scales, if required. The company currently manufactures peptides from milligram to 100-gram scale, and is investing in a multi-kilo-scale facility to broaden its offering.

An area that is becoming increasingly significant within the peptides field at present is that of chemokine synthesis. These are messenger proteins ranging from 60-80 amino acids in length that play important roles in switching biological mechanisms on and off. CSS' core expertise is in the synthesis of long peptides, avoiding some of the difficulties associated with recombinant peptides such as purification problems and batch-to-batch reproducibility. The chemical synthesis routes employed by CSS avoid the production of endotoxins and therefore allow easier purification and the elimination of any impairment of the biological activity of the protein. CSS has registered IP for the coupling reagent used in the chemical synthesis of chemokines, which performs with very high efficiency, allowing the achievement of very high overall yields even after several coupling reactions. The company has also invested in a range of equipment that allows it to perform the fully automated synthesis of peptides in the 20+ amino acid range.

## Development of cell-based screening assays

In March of this year, CSS-Albachem secured part of a

£3.7 million R&D programme from ITI Life Sciences focused on the development of cell-based, pharmaceutical screening technologies to address a significant bottleneck in the drug discovery and development process. This was the first programme launched by ITI Life Sciences, a Scottish organisation looking to identify, develop and commercialise valuable technology-based intellectual assets in the life sciences sector. The group's aim is to bridge the increasing funding gap between publicly-funded early-stage research and privately-backed commercial development.

The three-year programme is taking place in Scotland as a three-way collaboration between CSS-Albchem Ltd, Edinburgh Instruments Ltd and Hannah InterActions Ltd. Initially the programme is focused on developing instrumentation and 3D cell-based screens for breast cancer, with plans to expand to other disease areas as the technology develops.

CSS-Albchem was founded on the science of Professor Robert Ramage, a world expert in the chemical synthesis and purification of peptides and proteins. The company is a leading player in the provision of complex and challenging peptides and proteins to the pharmaceutical and biotechnology industries for application in basic research, drug discovery, diagnostics and therapeutics development. CSS-Albchem became part of the Almac Sciences group in 2004, when CSS acquired a controlling interest in Albchem.

Cell-based screening is a key step in the drug discovery and development process, where it is used to rapidly evaluate cellular mechanisms of disease as well as the effects of new drug candidates, such as distribution, metabolism or toxicity, in relevant cells. The information is vital to pharmaceutical companies as it allows the selection of the most appropriate compounds to develop further. 3D cell screens are expected to provide the best *in vitro* models, but will require complementary advances in cell culture techniques, fluorescence-linked assay technologies and state-of-the-art optics and detection instruments.

In the ITI Life Sciences programme, the three participating companies involved will provide complementary expertise in order to develop and commercialise 'Fluorescence Lifetime' 3D cell-based assay products, including 'off the freezer shelf' cells ready for screening, unique fluorescence-linked reagents and the required optics and detection instruments.

## Drug discovery alliance

In April of last year CSS established an alliance with BioFocus for the development of new products for the identification of drug candidates. The alliance combines CSS' novel chemistry and BioFocus' design capabilities for the production of novel focused screening libraries in target areas such as nucleosides and proteases. This was followed a year later by the launch of a C-nucleoside library.

"We are delighted with the success of our collaboration with BioFocus," says Moody. "Our first C-nucleoside library sold out in a record six weeks! Two further libraries will be launched early in 2006."

## Investment in cytotoxics

In the cytotoxics area, CSS supports preclinical, clinical and commercial needs through process research and development; cGMP manufacture up to 600 litres; contained micronisation; analysis and stability studies; and the synthesis of reference standards.



**CSS, part of the Almac Sciences group, operates full cGMP chemical manufacturing facilities at its Craigavon, Northern Ireland site.**

"The themes for us have been selective internal investment, for example cytotoxics and radiolabelling; acquisition, for example peptides; and partnership, that is in the Chiral Consortium and with BioFocus. All of these are helping to drive growth through provision of cost-effective solutions to meet customers' needs," says Moody.

"We are committed to solving challenging problems for our customers from drug discovery to API supply and partnerships such as this are important in achieving that end and will remain a feature of our strategy," says Moody, who expresses a highly positive attitude about the future:

"This year has been a very good one for us and we are very optimistic about 2006. We have been successful through making internal investments, in completing acquisitions and in establishing partnerships. Our clients are making technology 'connections' through accessing the services available within CSS and throughout the Almac group in general, especially in formulation development. The company is serving customers on a global basis, from across the USA, right throughout Europe and in the Far East. We are meeting diverse needs across projects and diverse needs within projects." 

## FURTHER INFORMATION

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