What's making progress in the pharma pipeline?

Big Pharma companies may not have as many drugs in their development pipelines as in earlier times but nevertheless there are some interesting products gaining marketing approvals from the FDA and EMEA. We present just a few examples of Big Pharma products that have progressed well this year.

In June of this year, Pfizer completed the acquisition of worldwide rights to new drug candidate fesoterodine from Schwarz Pharma AG. Pfizer and Schwarz Pharma entered into a global licence agreement in April for Pfizer to acquire exclusive worldwide rights to fesoterodine, a new drug candidate for treatment for overactive bladder. Earlier this year, Schwarz Pharma submitted new drug applications for the drug with both the FDA and the EMEA. Overactive bladder is a debilitating condition that affects up to 100 million people around the world. Fesoterodine is expected to provide additional choice for managing the symptoms of overactive bladder. Pfizer will make an initial payment of $100 million to Schwarz Pharma.

Pfizer has also announced that its product CHANTIX™ (varenicline) has been shown to be effective with a favourable safety profile as an aid to smoking cessation treatment. Chantix is the first new prescription smoking cessation medication approved in nearly a decade, and received FDA approval in May of this year. In trials, Chantix was generally well tolerated with overall discontinuation rates similar to placebo. In November 2005, Pfizer submitted a European Marketing Authorisation Application for varenicline for smoking cessation.

GSK leukemia and cervical cancer treatments

Also in June, GlaxoSmithKline submitted a Marketing Authorisation Application to the EMEA seeking marketing approval for ATRIANCE® (nelarabine) injection to treat adults and children with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to chemotherapy or has relapsed following at least two previous chemotherapy regimes.

GSK's corporate headquarters in Brentford, UK: the company has reported good results for its cancer treatments.

"The submission of nelarabine is an extremely important milestone for patients and physicians across Europe. Rare cancers such as T-ALL and T-LBL are often overlooked in terms of clinical research and development, and GSK's work towards bringing this important therapy to market underscores our commitment to all cancer patients around the world, no matter how rare and difficult to treat their disease may be," comments Paolo Paoletti, MD, senior vice president of the Oncology Medicine Development Centre at GSK. "Patients with these forms of cancer have limited treatment options and nelarabine may offer new hope for T-ALL and T-LBL patients who have not had successes with previous chemotherapy."

Both T-ALL and T-LBL are rare conditions, which both predominantly occur in children. The safety and efficacy of nelarabine has been evaluated in trials performed by the US National Cancer Institute. The EMEA granted Orphan Drug status to nelarabine in June 2005. The FDA granted marketing approval for nelarabine in October 2005 under the trade name of Arranon®, which was then launched in the USA in January, 2006.

GSK has also announced that the FDA has approved Hycamtin (topotecan HCl) in combination with cisplatin, for the treatment of stage IV-B, recurrent, or persistent carcinoma of the cervix. Following a six-month priority review by the FDA, the expanded indication is based on Phase III results that demonstrated a survival advantage by using Hycamtin in combination with cisplatin compared to cisplatin alone.

"The expanded use of Hycamtin in treating these patients with cervical cancer demonstrates GSK's ongoing commitment to bringing therapies to physicians for the treatment of women with cancer," says Kevin Lokay, vice president of oncology and acute care at GSK. "In addition to developing treatments, GSK is also developing therapies for the prevention of this disease. We are currently developing a vaccine for Human Papilloma Virus (HPV), the leading cause of cervical cancer."

Merck investigates sleep disorders

Merck & Co, Inc has released results from Phase II studies demonstrating the effects of gaboxadol, an investigational agent under clinical development, on sleep architecture in both primary and transient insomnia. Gaboxadol is a first-in-class selective extrasynaptic GABAA receptor agonist (SEGA). Treatment with gaboxadol was generally well tolerated in the study with the majority of adverse events mild to moderate in nature. Gaboxadol is a novel compound currently in Phase III development for the treatment of insomnia. Merck and H. Lundbeck A/S are collaborators in the clinical development and commercialisation of the drug.

Pharmaceutical research at the Novartis Institute for BioMedical Research in Basel, Switzerland. The company's Tasigna product was discovered at the Institute.

Janssen and Vertex in hepatitis C collaboration

Johnson & Johnson has announced that Janssen Pharmaceutica has established a collaboration with Vertex Pharmaceuticals to develop and commercialise Vertex's protease inhibitor VX-950 for the treatment of hepatitis C. Janssen has obtained exclusive rights to the product in Europe and other regions. Vertex retains exclusive commercial rights to VX-950 in North America. Tibotec Pharmaceuticals, Ltd, another Johnson & Johnson company, will lead the development and commercialisation of VX-950 for Janssen.

VX-950 is an investigational oral inhibitor of hepatitis C virus protease, an enzyme essential for viral replication, and is one of the most advanced investigational agents that specifically targets HCV. In clinical studies to date, researchers have observed rapid and dramatic antiviral activity with VX-950 and no patients have discontinued treatment and no serious adverse events have been reported.

Novartis presents chronic myeloid leukemia trial results

Novartis has announced that patients with treatment-resistant leukemia achieve high responses to Tasigna (nilotinib) in the product's first-ever published clinical trial results. The data showed the compound helped more than 90 per cent of patients diagnosed with an unresponsive form of leukemia. Patients in the most advanced phases of chronic myeloid leukemia responded to Tasigna therapy. The study investigators concluded that Tasigna was generally well tolerated. Discovered in the biomedical research facilities of Novartis, Tasigna (investigational name AMN107) entered Phase I clinical studies just 21 months after it was first synthesised. It is a next-generation tyrosine kinase inhibitor. The FDA has granted both Fast Track designation and Orphan Drug status to Tasigna, which has also received Orphan Drug status from the EMEA. Novartis is now planning to submit Tasigna for US and EU regulatory approval in late 2006 compared to earlier estimates for submissions in 2007.

sanofi-aventis and Taiho in anticancer agreement

sanofi-aventis and Taiho Pharmaceutical Co, Ltd have established an agreement giving sanofi-aventis the rights to develop and market an oral anticancer agent, S-1, a proprietary product from Taiho.

S-1 is a new oral pyrimidine fluoride-derived anticancer agent in which a prodrug of 5-fluorouracil (5-FU), Tegafur, is combined with two inhibitors of enzymes to increase the amount of circulating 5-FU with less gastrointestinal toxicity.

S-1 has been marketed in Japan since 1999. Today the drug is prescribed in the following indications: gastric cancer, colorectal cancer, head and neck cancer, non-small cell lung cancer, and inoperable or recurrent breast cancer. The product is currently in Phase III trials in Europe, the USA and other regions.

sanofi-aventis will lead and fund the development of the product worldwide, except in Japan and certain Asian countries, and the company will be responsible for the commercialisation of the product worldwide except for those countries.

Taiho will participate in the development of the product and will have the option to participate in the promotion of the product in any country in which sanofi-aventis will commercialise the product. Taiho will manufacture the product and supply it to sanofi-aventis.

sanofi-aventis will make an upfront payment to Taiho, milestone payments at certain stages in the commercialisation of the product, and will pay royalties on sales. Taiho will retain the rights to develop and commercialise the product in Japan and certain other Asian countries. sanofi-aventis says the addition of S-1 to its existing R&D portfolio should reinforce its strong position in oncology and provide significant advantages for patients.

Bayer moves antithrombosis drug forward

Bayer HealthCare says that data from recent Phase II clinical studies support the company's decision to proceed with Phase III programmes for its antithrombosis drug BAY 59-7939 in two chronic indications. The compound with the active ingredient rivaroxaban will be tested in stroke prevention in atrial fibrillation (SPAF) and treatment of venous thromboembolism (VTE) in a once-daily dose regimen.

The company has also announced that four pipeline projects (one in cancer; three in cardiovascular), one more than originally planned, have already reached Phase II, and that seven new development candidates are scheduled to undergo clinical testing in humans later this year.

Bayer HealthCare and Ortho-McNeil Pharmaceutical Inc, a Johnson&Johnson company, which are jointly developing and marketing the antithrombosis drug, have conducted the largest ever Phase II dose-finding programme with more than 1,100 patients for VTE therapy and stroke prevention in atrial fibrillation.

"The phase II data are impressive and underline our confidence in rivaroxaban," says Arthur J. Higgins, chairman of BHC's Executive Committee. "There is currently a pressing

Peptides & Proteins Supplement

2006

From the publishers of sp² Magazine

Peptides & Proteins

Peptides and proteins: the fastest-growing sector for new therapeutics

The publishers of *sp*² are pleased to bring you the 2006 edition of our regular publication, the annual Peptides & Proteins Supplement. Biopharmaceuticals based on peptides and proteins represent a higher proportion of drugs in R&D and in commercial development than at any time in the past, currently accounting for about 25 per cent of developmental drugs. These products are receiving even greater attention than ever before, as new large-molecule drugs form the fastest-growing sector of the pharmaceutical marketplace, with a number of Biologics Licensing Applications (BLAs) having been recently filed and several new biologic drug approvals being expected in the near future.

Of course simple peptides have been established as therapeutic entities for considerably longer than protein-based drugs, representing as they do a 'bridge' between the small-molecule and biologic therapeutic sectors. The Peptides & Proteins Supplement reflects this significance, as just a glance at the companies' technologies chart in the publication reveals the very wide range of peptides technologies now on offer from the major suppliers in the sector for the development of new peptide-based drugs.

Peptides and proteins continue to generate interest as potential drug candidates because of their very broad range of application across many therapeutic areas and their significant potential to meet unmet medical needs. This Peptides & Proteins Supplement is intended to give you an overview of the types of companies active in supplying peptides, proteins, related chemicals and supporting technologies to the pharmaceutical and biotechnology industries, and I am sure you will find it a useful guide in your business.

Tom Mulligan, MSc
Editor - *sp*²

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Activotec

Activotec was formed in December 2002 as a spin-out from the University of Southampton, with the support of the University's Enterprise Office, the CEI, and benefiting from its partnership with the IP Group. Activotec owns extensive intellectual property based on the chemical synthesis and modification of peptides and proteins.

Activotec provides a range of products and services for peptide and protein synthesis including custom peptide synthesis, peptide R&D, automated peptide synthesizers and chemicals. Customers are worldwide including Europe, the USA and Asia.

Activotec's custom peptide facility has been providing the highest-quality peptides at competitive prices for many years offering mg to multiple grams at all required purity levels and with any modifications required. Particular expertise focuses on difficult-to-synthesise sequences, non-natural modifications, and the design and synthesis of highly-effective peptide therapeutics.

Activotec has an extensive R&D programme based on the modification and production of peptides and proteins for therapeutic use. Activotec develops and pioneers novel methods for the synthesis and modification of peptides and proteins. Using these synthetic methods as an advanced technological platform, the company is able to produce a wide range of peptides and proteins that are difficult to make via other techniques.

The company aims to establish Activotec as the partner of choice for peptide-based drug discovery.

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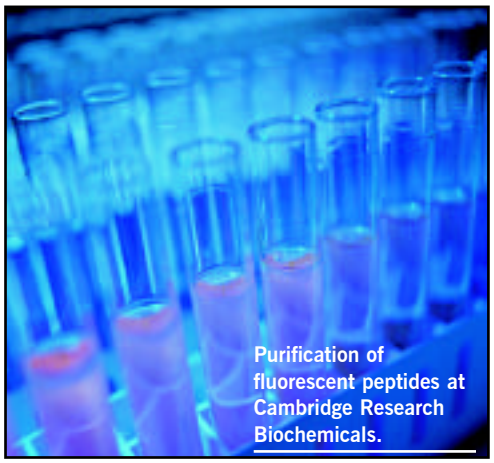
CRB

Founded in 1980, CRB is now based in the north-east of England. Once part of the ICI, Zeneca and Avecia groups, it is now privately owned and run by three directors through a management buy-out that took place in 2000. Since the spin-out, CRB has gone from strength to strength, seeing a relocation to new expanded facilities in 2001, accreditation to ISO9001:2000 and a partnership deal with Amersham Biosciences for fluorescent peptides.

The company is focused on the custom manufacture of peptides and antibodies. It has long-standing annual agreements in place for providing these custom services with large pharmaceutical clients. The secret to CRB's success and longevity of its relations with key accounts is the company's dedication to building strong relationships with clients and encouraging clear dialogue to ensure all their needs are met. CRB's key account customers in early drug discovery research have been using its services for more than fifteen years and its aim is to exceed their expectations in product quality, speed of delivery and ease of working with the company. CRB provides technical expertise and a high degree of flexibility, tailoring its services to individual researcher's needs.

Now in its 26th year and having achieved a strong position and reputation in the supply of custom peptides and antibodies, CRB is actively seeking growth from new collaborations and complimentary service offerings.



Purification of fluorescent peptides at Cambridge Research Biochemicals.

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NeoMPS

Specialists in peptide synthesis and organic chemistry for 20 years, NeoMPS is a unique organisation formed by the alliance of NeoMPS SA, Strasbourg, France (formerly Neosystem) and NeoMPS, Inc, San Diego, USA (formerly Multiple Peptide Systems).

Both companies were created in 1986. The European plant started cGMP production in 1998, has been inspected by the French Health Products Safety Agency (AFSSAPS) and audited successfully by many pharmaceutical and biotech companies. The American plant started cGMP operations in 1990 and has successfully undergone seven FDA inspections.

As a leading peptide manufacturer, NeoMPS is ready to assist customers in all product development phases, from research-grade peptide synthesis up to cGMP manufacturing for clinical trials or for commercial application.

NeoMPS offers the following products and services:
- Custom & catalogue research-grade products (peptides, peptidomimetics, small molecules, special amino acids and building blocks);
- Lead optimisation and innovative solutions in support of peptide development;
- cGMP manufacturing of peptides and non-peptidic organic molecules up to tens of kilograms (nearly 400 peptides manufactured for clinical trials to date);
- Process research and development;
- Flexibility of solid and liquid phase chemistry;
- Full support with regulatory filings: IND, DMF, NDA...(CMC in CTD format);
- Partnership approach focused on customer satisfaction.

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Peptisyntha

Peptisyntha's activities are focused on the production of bulk peptides for the pharmaceutical industry. Both liquid-phase and solid-phase technologies are available. Peptisyntha is able to scale up the production of peptides to large-volume production of up to hundreds of kilograms, under fully cGMP-compliant conditions. As far as liquid-phase production is concerned, Peptisyntha applies a specific technology that allows a significant reduction of the number of steps and hence leads to cost-effective production of large quantities of peptides. Preparative HPLC is available in commercial production units, pilot and micropilot units, as well as in the laboratory. Similarly, a full range of lyophilisation equipment is available.

Peptisyntha is an expert in scaling up the production of cGMP peptides.

Peptisyntha is a member of Solvay Organics, a new technology-driven business unit established recently within the Solvay Group to develop applications of complex, multi-stage organic chemistry, following the acquisition of a majority stake in Girindus.

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PolyPeptide Laboratories is a world leader in the industrial-scale manufacture of proprietary and generic GMP peptides used as APIs by pharmaceutical, biotech and research organisations. Non-GMP peptides are also offered for R&D and preclinical applications. With corporate roots going back to the 1950s, PolyPeptide Laboratories was formally created in 1996; the privately held corporation now comprises a group of five companies located in the USA, Sweden, Denmark, the Czech Republic and India. PolyPeptide Laboratories employs more than 300 specialists and support personnel worldwide, and ranks among the top three independent pharmaceutical peptide manufacturers in business today (Frost & Sullivan, 2005).

PolyPeptide Laboratories focuses exclusively on the manufacture of peptides, biologically active compounds used to treat an expanding scope of medical conditions. The company's exclusive focus on peptide synthesis gives it an advantage in meeting the needs of customers with challenging proprietary peptide projects, from the earliest phases of preclinical development through regulatory approval and beyond. All sizes of projects can be accommodated, from small-scale custom synthesis of milligram and multi-10-gram quantities for basic research up to full-scale commercial manufacture (>100 kilograms) of pharma-grade peptides under cGMP.

Synthesis is accomplished using Solid Phase Peptide Synthesis (both Fmoc and Boc) and Liquid Phase Peptide Synthesis technologies, as well as strategies utilising fragments produced by solid phase synthesis which are then coupled in solution to produce the final peptide. Process decisions are based on specific peptide sequences and customer requirements. Purification is achieved primarily with large-scale HPLC; products are isolated via lyophilisation or precipitation. Exceptional product quality is a company hallmark. PolyPeptide Laboratories chemists are experts in maximising product purity and creating robust processes that translate effectively during scale-up.

PolyPeptide Laboratories prefers to take a partnership approach with its customers. Experience shows that freely sharing processes and information benefits both parties in the long term. Unlike companies that only provide manufacturing and consulting services 'a la carte', PolyPeptide Laboratories includes in its GMP packages the full complement of quality assurance and regulatory support services needed to fully support peptide product development. The company firmly believes that free access to these services is a major advantage in bringing new peptide drugs to approval.

Ultimately, all aspects of manufacture will be scrutinised by regulatory agencies during the pre-approval inspection (PAI), including batch-specific data as well as the supporting documentation system. Careful preparation and coordination of product and quality data are the keys to speeding the approval process, avoiding additional costs, and otherwise increasing the project's chances of success.

Solution phase reactors at PolyPeptide Laboratories AB (Malmo, Sweden).

A 270-litre solid phase reactor at PolyPeptide Laboratories A/S (Hillerod, Denmark).

The PolyPeptide Laboratories Group has an impressive record of getting peptide-based APIs to approval, with seven APIs approved in the USA and more than a dozen others worldwide. The company is supporting the growing demand for peptides with plans to increase manufacturing facilities in the USA, Scandinavia and India in the coming months.

In addition to custom synthesis, the company also manufactures many generic peptides, including calcitonin, octreotide, leuprolide, gonadorelin, goserelin, deslorelin, desmopressin, ACTH and somatostatin. DMFs and other regulatory documents are available for most generics.

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