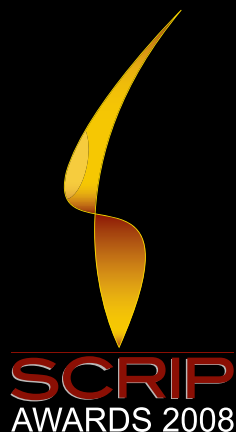




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 SYNEXUS



**BENEFITS ALL ROUND:** Robust delivery platforms offer numerous advantages such as improving the stability of medicines, thereby increasing the time they circulate in the body

# New life from controlled-release

*With days to go before the 35th Annual Meeting of the Controlled Release Society, Tom Moberly looks at the latest developments in one of the most vibrant sectors in pharmaceutical research*

**A**dvances in controlled-release therapy continually offer new opportunities to provide improved treatments to patients and new potential sources of income to pharmaceutical companies.

In the past year a range of innovative treatments have reached the market, not least Janssen-Cilag's (Johnson & Johnson) novel needle-free transdermal fentanyl treatment (Ionsys), which was launched in the UK, Germany and Ireland at the beginning of this year. Ionsys is a pre-programmed, battery-operated system for the treatment of postoperative pain. It transports doses of fentanyl into the bloodstream using an electric current, which is activated when patients touch a button, allowing them to manage their own pain relief. Ionsys is also more convenient for healthcare providers as it is less cumbersome than the pumps conventionally used to administer pain relief.

Another transdermal delivery device, TransPharma Medical's ViaDerm, has shown promise in early trials. ViaDerm comprises a pocket-sized electronic controller and a patch that together deliver human parathyroid hormone, for the treatment of osteoporosis, across the skin. It uses a modified radiofrequency to create microchannels in the skin's surface allowing delivery of products that cannot be transferred across the skin using current technologies.

In addition to the development of modified-release devices,

patients with a range of conditions have benefited from the continued development of controlled-release formulations. Such innovations allow dosing frequency to be lowered, reducing the burden of treatment on patients. The US FDA's approval of Critical Therapeutics' extended-release tablet formulation of zileuton (Zyflo CR), for example, means that patients with chronic asthma can take tablets two, rather than four, times a day.

Extended-release formulations can also help to reduce the impact of unwanted effects of drugs by reducing peak levels of metabolites in the body. Addrenex Pharmaceuticals has filed for US approval of a 12-hour formulation of the antihypertensive clonidine hydrochloride (CloniBID). The company designed the new formulation to reduce the side-effects of clonidine, including a peak of sedation when the drug is absorbed and a subsequent rebound of hypertension once the drug's effects wear off.

## new strategies in CNS

The therapeutic area which has some of the largest efforts devoted to new controlled-release formulations has been treatments for central nervous system (CNS) disorders, with the aim of increasing convenience, and hopefully adherence and symptom control.

Janssen-Cilag has used its OROS extended-release technology to create a once-daily formulation of the atypical antipsychotic

paliperidone, a metabolite of J&J's antipsychotic Risperdal (risperidone), which went off patent in December 2007. The product, Invega, has been approved in the US and EU for the treatment of schizophrenia.

AstraZeneca has also used extended-release formulations to increase treatment options for patients taking antipsychotic medicines, developing a once-daily, extended-release formulation of its atypical antipsychotic Seroquel (quetiapine fumarate). Seroquel was launched in 1997 and is indicated in the US for bipolar depression, bipolar mania, bipolar maintenance, and schizophrenia. It is AstraZeneca's second best-selling product, but its patents are due to expire in 2011 in the US and 2012 in the EU. Seroquel XR, the extended-release formulation, is patent protected until 2017. AstraZeneca says its new formulation is simpler and more convenient than immediate-release Seroquel.

The US FDA approved Seroquel XR for the treatment of schizophrenia in 2007. AstraZeneca has since filed in the EU and US for approval in bipolar disorder and generalised anxiety disorder (GAD). This is the first time that approval has been sought for an atypical antipsychotic medicine in GAD, indicating that the indications of controlled-release formulations can go beyond those of the standard-release medicines from which they have been developed.

It is important to remember that patients can derive benefit not only from formulations designed to lengthen, but also from those designed to shorten the release profiles of drugs acting on the CNS. And sometimes both types of modification will be sought for the same drug. For instance, Johnson & Johnson and Grünenthal are developing an extended-release version of the investigational oral analgesic tapentadol, for chronic pain conditions such as osteoarthritis, peripheral diabetic neuropathy, back pain and cancer pain. Johnson & Johnson has also filed, however, an immediate-release formulation of tapentadol, for the relief of moderate-to-severe acute pain, where a faster onset of action would bring benefits to patients.

A further way in which the release profiles of drugs acting on the CNS are being modified is to reduce their abuse potential. The Swedish drug delivery firm Orexo, for instance, is developing opioid formulations using bioceramics, which the company hopes will have much lower abuse potential than conventional formulations.

## continued success in pegylation

One of the most successful strategies used for extending the release of medicines remains pegylation, in which polyethylene glycol (PEG) is conjugated to peptides, proteins, antibodies or antibody fragments.

Pegylation makes protein-based medicines less susceptible to breakdown by enzymes in the body, increasing their stability and therefore the time they circulate in the body, allowing a reduction in the frequency at which patients need to be dosed. It has been used in a range of marketed products, including Amgen's/Roche's Neulasta (pegfilgrastim), Gilead's Macugen (pegaptanib octasodium) and Roche's Pegasys (PEG-interferon alpha-2a), and it is thought that pegylation could improve the safety and efficacy of drugs in most major classes.

Nektar Therapeutics and Baxter International's subsidiaries are developing new pegylated therapeutics for haemophilia, as are Bayer and Novo Nordisk. Bayer has shown that its pegylated recombinant Factor VIII offered prolonged bleeding protection in preclinical tests, and Novo Nordisk has begun trials of its long-acting Factor VII product. Novo Nordisk's product was formulated using Neose Technologies' Glycopegylation technology, which was also used to develop with a long-acting investigational erythropoietin-polyethylene glycol product, NE-180, which is in Phase II clinical trials, and an investigational glycol-

## Box 1: The Controlled Release Society

The Controlled Release Society (CRS) was conceived in 1973, and incorporated as a not-for-profit organisation five years later. An international organisation which serves 3,000 members from more than 50 countries, it is devoted to the advancement of the science and technology of controlled release.

Two-thirds of CRS members represent industry, with the remaining members drawn from academia and government. It is a multi-disciplinary group that works to improve patients' quality of life by advancing science and education in the field of delivery of bioactive substances.

In the 35 years since the founding of the society, research into controlled-release therapeutics has become a research discipline whose future depends on a thorough understanding of the interactions between the delivery system and the biological or environmental barriers to delivery of active substances. As it is one of the most vibrant sectors in pharmaceutical research, the future of drug delivery is hard to predict. The CRS, the foremost organisation in the area, will oversee many exciting developments in the years to come.

The 35th Annual Meeting and Exposition of the Controlled Release Society will take place on July 12th–16th, 2008 in New York, NY, US.

PEG granulocyte-CSF product being developed by Neose and Biogenex, which is in Phase I.

Haemophilia is just one of a number of therapeutic areas likely to benefit from the introduction of new pegylated products in the coming years. For instance, Zydus Cadila of India and the US drug delivery R&D company Prolong Pharmaceuticals entered into a collaboration to develop a pegylated version of erythropoietin for the treatment of severe anaemia. Schering-Plough's Caelyx (pegylated liposomal doxorubicin HCl) chemotherapy was recommended last year for a new EU additional indication in multiple myeloma. And, in April this year, UCB's pegylated anti-TNF antibody Cimzia (certolizumab pegol) was approved by the US FDA for the treatment of Crohn's disease.

## great expectations

Expectations for the continued success of modified-release formulations are likely to remain high for some time, given the number of development agreements being announced in this area. For instance, Zogenix has entered a licence agreement with Elan to develop a controlled-release opioid pain treatment using Elan's SODAS (spheroidal oral drug absorption system) technology. Merck Serono and Flamel have agreed to investigate extended release formulations of an undisclosed Merck Serono therapeutic protein using the latter company's Medusa technology.

Penwest Pharmaceuticals has struck deals with both Otsuka Pharmaceuticals and Cobalt Laboratories to develop sustained release formulations using the TIMERx technology. Penwest used this technology, in collaboration with Endo Pharmaceuticals, to develop Opana ER, an oral extended-release formulation of oxycodone hydrochloride. In addition, Yissum, the technology transfer arm of the Hebrew University of Jerusalem, has spun off a new company, Nanolymp, which it says will focus on developing a nanotechnology-based controlled-release drug delivery platform to increase the bioavailability of orally administered lipophilic drugs, so that they can be administered orally, rather than by injection.

The number of such deals and their range suggests that the industry continues to have faith in the ability of controlled-release therapies to offer benefits to patients and, in turn, produce profits for pharmaceutical companies.

Tom Moberly is a science reporter for Scrip. He can be contacted at [tom.moberly@informa.com](mailto:tom.moberly@informa.com).



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DR GURVINDER SINGH REKHI

## Four decades on the front line

*Dr Gurvinder Singh Rekhi explains how a long list of companies has launched products and optimised lifecycle management for their products through innovative delivery platforms*

### Q To what extent has Elan evolved over its 40-year history in the drug delivery sector?

Since it was established almost 40 years ago, Elan has developed and reformulated more than 30 drugs for clients. We have expanded our technology platforms to offer clients controlled release, delayed release and pulsatile release delivery systems as well as technology solutions for poorly water soluble compounds. Since 2001, our technologies have been used in the launch of nine products, contributing to sales of close to \$2 billion in 2007. We believe our range of technologies puts us in a strong position to offer well differentiated products to pharmaceutical companies and more importantly provide significant patient benefits. Today, more than 2.5 million patients worldwide use drug products based on or enhanced by our technologies.

### Q What have been the company's greatest successes to date in the field of oral controlled release technologies?

Our OCR platform has been integral to the launch of dozens of products worldwide, including many lifecycle management candidates. One of our first successes was the development of Cardizem SR and CD (diltiazem) for Marion, now part of Sanofi-Aventis, which became one of the largest product franchises in the US at the time, with annual sales in excess of \$900 million at peak.

The development of once-daily and subsequently night-time release verapamil products under the Verelan franchise was also a great success for Elan in the 1990s. The most recent launches in the US using this technology platform include Avinza (King Pharmaceuticals' extended-release morphine sulphate), Afeditab (Watson Pharmaceuticals' nifedipine), Ritalin LA (Novartis's methylphenidate), Focalin XR (Novartis's dexamethylphenidate) and most recently Luvox CR (Jazz Pharmaceuticals' fluvoxamine). Our SODAS technology has been one of the industry's most successful drug delivery technology platforms.

Our success has also expanded beyond OCR, with the successful commercialisation of our NanoCrystal technology, a technology for poorly water soluble compounds. Since 2001, four products have been launched worldwide using the technology with over \$1.5 billion annual in-market sales.

### Q What makes Elan's technology platforms unique? What advantages do they offer?

First and foremost we have a unique platform of validated technologies, from OCR to Nanoparticulate technologies, and a strong history of developing products for our clients. With a 40-year track record, our people have successfully dealt with the challenges encountered in formulation development for all types of molecules. We have a complete range of capabilities from formulation development through to commercial-scale manufacture in modern facilities.

Our technologies are supported by a robust patent estate of over 1,500 patents and pending patents. These proprietary technologies enable the development of new products and the enhancement of existing products.

### Q What company highlights can you pick out from the past year?

The past year has been a very busy and successful one for Elan. Last October our client Johnson & Johnson submitted its NDA to the US FDA for paliperidone palmitate, which incorporated our NanoCrystal technology into the once-monthly IM injection. In November we executed a deal with Zogenix which granted our partner exclusive rights to a late-stage opioid product for the treatment of pain. And this April, Jazz Pharmaceuticals launched the SODAS technology-based Luvox CR for the treatment of depressive illnesses. Earlier this month, Acorda Therapeutics announced very positive results for its Fampridine-SR product for the treatment of symptoms associated with multiple sclerosis; filing with the FDA is expected in Q1 2009.

### Q What factors underpin companies' search for lifecycle management through novel delivery systems?

Market dynamics continue to move towards risk-averse development that includes new formulations rather than relying solely on NCEs. Simply reformulating a product without considering the clinical benefits offered is not a sufficiently robust business strategy, however. Successful reformulations differ significantly from the original product, they are marketable and ideally they are also patentable. By getting its lifecycle management strategy right, a company can expect to generate sustained revenue streams from its portfolio of branded drugs, and these revenues can in turn be used to fund the discovery, development and commercialisation of innovative new medicines.

### Q What can we expect of Elan Drug Technologies in the near future?

We are focused on using our extensive experience, our drug delivery technologies and our commercial capabilities to develop innovative products for our clients that deliver clinically meaningful benefits to patients. We anticipate a number of product approvals for clients in the near to medium term. We plan to continue to grow our business, expand our technology offerings to clients and help bring more products through to market.

Combining our OCR with our NanoCrystal technology has the potential to expand significantly the drug delivery market. With 15 pipeline products in the clinic and multiple preclinical programmes also underway, and a strong client base of over 20 large pharma companies, Elan Drug Technologies will be a key player in the substantial growth of the drug delivery sector.

Dr Gurvinder Singh Rekhi is Director, Research & Development at Elan Drug Delivery.

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