

NOVEMBER 2006

DRUG DELIVERY



- Exubera: sparking a revolution
- New drug, new delivery system?
- Paediatric drug delivery: challenges and rewards


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DRUG DELIVERY

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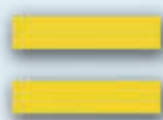
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An industry evolving

Elizabeth Cairns casts an eye over 2006's drug delivery landscape and discovers there's no such thing as the norm in this innovative industry

2006 finds the drug delivery industry at a very interesting point in its evolution. With extended-release drug formulations well established in the market, and the first products utilising nanotechnology beginning to make inroads and prove profitable, the risk always associated with novel delivery techniques has proved to be well worth taking. This year's approval of Pfizer's Exubera sent shockwaves through not only the drug delivery sector but the wider pharmaceutical arena, and demonstrated that concepts long considered unfeasible can indeed be realised.

Drug delivery is often thought to be focused on convenience – where drug development companies create new drugs to cure fatal diseases, drug delivery simply means allowing rich, developed-world patients to take one pill per day rather than three. This is manifestly false; innovative techniques allow solubilisation of erstwhile useless drugs, or successful delivery of a molecule to its target tissue where previously it had been eliminated by first-pass metabolism.

Patient benefits

Drug delivery also permits therapies to be tailored to specific types of patient. As Jane Lamprill points out in her article on page 9, taste-masking technology can be employed to cater to paediatric patients who must take their drugs orally but dislike its flavour (this also makes the job of administering the medicine, whether by a healthcare professional or a parent, much easier). Buccal delivery is particularly appropriate for patients who are unable to swallow, and encapsulation of biologics can eliminate the need for long intravenous infusions, freeing up hospital beds and saving money.

The success of the sector cannot be attributed to innovation in delivery alone. The majority of 2006's most noteworthy products are the result of partnerships. Exubera is a case in point; Nektar Therapeutics invented the

inhaler and powder formulation, but the product would not have reached market nearly so rapidly had it not been backed by the might – and the money – of Pfizer. However, the increasing tendency of pharma and biotech firms to merge, forming fewer, larger, companies, reduces the number of potential partners (see the article written by Peter Knight on page 6). The resulting giant companies are as likely to acquire a whole firm as they are to broker a licensing agreement for a single technology.

The mergers and acquisitions of recent years have changed the landscape considerably. Pfizer's buyout of private company PowderMed gave credence to the UK firm's technology – a needle-free DNA injection device involving microscopic particles of pure gold. This technique, though esoteric, has great potential, particularly for the delivery of DNA vaccines against pandemic influenza.

Vectura's forthcoming acquisition of Innovata in a deal worth nearly £130million (US\$246million) is another example of the benefits of consolidation. As both companies specialise in respiratory drugs, the merger not only creates a broader pipeline of products in clinical development, and the cash resources to progress their development, but also goes some way towards eliminating competition. It will also allow only the best drugs in the extended pipeline to reach market, further benefiting patients.

Naturally, this trend towards consolidation ought to mean that successive mergers reduce the number of firms involved in drug delivery until one vast conglomerate dominates the market. Clearly this has not happened, and it is highly unlikely that it ever will. This is because of the ceaseless activity at the other end of corporate development: the formation of new companies.

Start-ups tend to begin life as a means of developing a novel technology. Often spun out of larger companies or universities where the



technique was developed, usually by only one or two individuals, these firms must prove their products' efficacy before initiating funding rounds or partnerships. It's a risky business, but the sheer number of new drug delivery start-ups appearing every year is a testament to the relative ease of entering this market.

Maximising profits

Indeed, drug delivery is, of its nature, rather less risky than drug development. Developing a new pharmaceutical is hugely expensive and the risk of failure is high. A delivery or formulation technology, by comparison, is much cheaper to develop and enables the increased use of already established drugs. Drug delivery techniques have long been used for pharmaceutical lifecycle management, maximising profits from molecules developed at great expense. Now this innovation is being used to benefit patients as well as shareholders, widening the uses to which established drugs can be put. The industry is evolving before our eyes; the only constant is the extraordinary imagination and innovation demonstrated by drug delivery professionals.

Elizabeth Cairns is editor of Target World Drug Delivery News. She is based in London, UK.

Transforming potential for difficult drugs

As the hype gives way to the first wave of marketed nanomedicines, Dr Peter Knight reviews some of the hottest areas of innovation in drug delivery technology

Getting a drug delivery form right is almost as important as the active ingredient itself. Studies suggest that one in ten marketed drugs have solubility problems and almost a third fail to reach profitability due to poor bioavailability or pharmacokinetics. Accordingly, it is not surprising that drug delivery technologies have been widely adopted by the pharma industry as a powerful element of lifecycle management strategies, and by specialty pharmaceutical companies to reinvigorate off-patent compounds.

Many early drug delivery technologies, such as controlled release products and transdermal patches, are rapidly becoming commoditised. But the advent of hard-to-deliver biologics (peptides, proteins and DNA/RNA-based drugs), the discovery that many drugs show improved efficacy with controlled release compared with conventional burst release techniques, and recognition of the benefits of targeted delivery of certain drugs (for example, chemotherapeutics) is now driving the evolution of a new generation of drug delivery technologies. Advocates hope that by solving the delivery problems of new drug classes, these technologies will become an intrinsic part of drug discovery and development, rather than a retrospective refit to increase the lifespan of old drugs.

Nanoparticles

Hyped in healthcare for the past decade, nanomedicines are finally reaching the market in the form of nanotechnology-based drug delivery products. The earliest of these address the fundamental issue of solubility by formulating the drug as nanocrystals, whose large surface area enhances solubility.

The leader in this area is Elan, whose NanoCrystal technology employs a proprietary wet-milling technique in aqueous solution to produce drug nanocrystals; crucially, the presence

of a stabiliser inhibits particle aggregation. The resulting colloidal dispersion can be processed into multiple dosage forms, solid or liquid.

There are already four approved drug products in the US that use the NanoCrystal technology: Wyeth's Rapamune (sirolimus) tablets, Abbott's TriCor (fenofibrate) tablets, Merck's Emend (aprepitant) capsules and Par Pharmaceutical's Megace ES (megestrol) oral suspension. Furthermore, both Johnson & Johnson and Roche have licensed the technology; the former is in Phase III development of a long-acting NanoCrystal reformulation of its schizophrenia therapy, paliperidone palmitate.

Competing methods for producing pharmaceutical nanocrystals include homogenisation in aqueous solution (SkyePharma's Insoluble Drug Delivery (IDD), Baxter's NanoEdge platforms), and homogenisation in non-aqueous solution (PharmaSol's Nanopure platform); all of these require the presence of stabilisers to reduce particle aggregation.

SkyePharma has launched an IDD-based fenofibrate drug, Triglide, which competes directly with Abbott's TriCor. Using a similar technique, Abraxis BioScience's technology creates an albumin-stabilised nanoparticle formulation of the poorly soluble chemotherapy drug, paclitaxel, by homogenising crystals of the drug in a solution of human serum albumin. The product, branded Abraxane, is approved in the US as second-line therapy for breast cancer, and in Canada for metastatic breast cancer. Nanoparticle technology is particularly suitable for use as part of a lifecycle management strategy, since it can be retrospectively applied to already marketed drugs.

Lipid-based emulsions

Micellar nanoparticle technology takes the nanoparticle concept a step further, forming a

lipid-based colloidal emulsion in which the drug is distributed in various forms: as nanocrystals/nanoparticles, in solution form in the lipid phase, or associated with micelles. Micellar nanoparticles not only solubilise insoluble drugs, but the multi-phasic drug distribution means the active ingredient is present in a readily available solution form as well as a long-acting particulate depot form, useful for sustained drug release. In addition, the formulation is well suited for transdermal drug delivery.

Novavax has applied the technology to hormone replacement therapy, with an oestrogen-containing micellar nanoparticle product, Estrasorb (estradiol), approved by the US FDA. The company is also applying the technology to a range of other small molecule drugs. Other companies are not far behind: NanoBio Corporation is developing its similar NanoStat micellar nanoparticle technology as an anti-infectives platform, with treatments for herpes virus, shingles and onchomyiasis in the clinic, and plans to adapt the approach for the nasal delivery of vaccines.

Dendrimers

Other nano-scale drug delivery technologies are at an earlier stage of development, and include pioneering concepts such as quantum dots and nanospheres. Among these, dendrimer technology holds particular promise. Dendrimers are globular macromolecules, constructed in a step-wise fashion from monomers radiating from a central core, to form a three-dimensional framework of predictable size and surface chemistry. Large dendrimers can encapsulate poorly soluble drugs, forming a depot for sustained release. A variety of ligands can theoretically be attached to each chain of the dendrimer, which opens up the possibility of targeted drug delivery using these macromolecules.

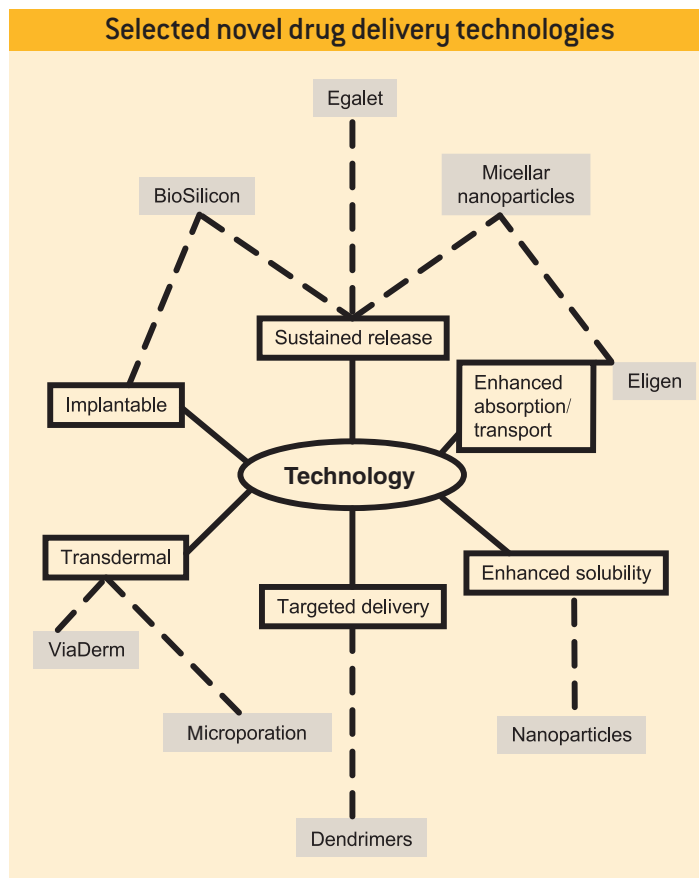
The Michigan Nanotechnology Institute for Medicine and Biological Sciences (M-NIMBS) is a leading force in dendrimer research, and has already created a catalogue of dendrimers. However, its ultimate goal is the development of multi-functional dendrimers that can recognise malignant cells (via cancer-specific cell surface markers), deliver a toxic drug, and monitor and report cell death via an attached imaging agent – a true ‘magic bullet’.

Other companies have dendrimers already in clinical trials. Starpharma and Dendritic NanoTechnologies are developing VivaGel, a water-based topical gel containing a dendrimer modified to bind to and block the receptor sites for a variety of viruses. The candidate has shown promise in clinical trials aimed at preventing the transmission of HIV and herpes viruses.

Dendrimers appear to have enviable functional flexibility and considerable promise for drug delivery, but remain some way from the market. Aside from the technical barriers, two significant hurdles that remain are the establishment of reproducible manufacturing processes, and the need for regulatory bodies such as the FDA and the European Medicines Agency (EMA) to develop approval procedures to deal with these novel nanodevices.

Biosilicon

An Australian company, pSivida, has developed BioSilicon as a platform for the controlled release of drugs for a wide range of clinical applications. The company nanoengineers elemental silicon to form a porous honeycomb structure that can be loaded with drugs, including proteins and nucleic acids. By varying properties such as particle and pore size, BioSilicon can be made biodegradable, and drug release rates can be tailored to a period varying from hours to months. This latter property makes BioSilicon valuable as a long-term drug depot. As its first commercial product, pSivida is developing BrachySil, an implantable brachytherapy device composed of BioSilicon loaded with radioactive elements that is injected directly into the tumour. BrachySil has successfully completed a Phase II trial in patients with inoperable liver cancer.



Timed release technologies

For orally-administered drugs, controlled release has several benefits over conventional batch release: reduction in drug blood level fluctuation, reduction in local or systemic side-effects and better patient compliance. However, there is growing recognition that constant drug release is imperfect in many circumstances. For example, the symptoms of rheumatoid arthritis are often at their worst upon waking, but common anti-inflammatory medications such as ibuprofen need 4–6 hours from administration to be maximally effective, and their effect tails off thereafter. This window of activity is sub-optimal from a dosing perspective – unless a time delay can be built into drug release.

To meet this need, the Danish company Egalet has developed an oral tablet that relies on erosion rather than diffusion to control delivery. Egalet tablets consist of an impermeable shell enclosing a matrix. The matrix contains the active drug, and is surface-erodible, hydrophobic and composed of polyethylene glycol (PEG)-stearate. By changing the properties of the matrix, Egalet has developed a constant release system, and a burst release system with a predetermined delay. Burst release is achieved by closing the

ends of the tablet with biodegradable plugs, whose composition and length then determine the time lag before the active ingredient is exposed and delivered. The formulation can be used for virtually any type of drug and, unlike water soluble diffusion technology, it is not affected by the pH of the body fluid it comes in contact with. Egalet is employing its eponymous tablets to advance products in various therapy areas: two are entering Phase III studies for hypertension and pain management.

Delivery of biomolecules

Peptide, protein and DNA therapeutics represent an increasingly important group of new drug entities. But biologics are far less robust than small molecule drugs when taken orally, being quickly digested in the stomach with most never reaching the bloodstream. Consequently, most are delivered by injection or infusion, neither of which is

popular with patients. New technologies are providing alternative delivery routes, such as pulmonary, intranasal and transdermal, as well as new approaches to oral delivery.

The challenges of delivering biomolecules orally extend beyond survival of the drug in the gastrointestinal (GI) tract, and encompass passage through the intestinal wall. Emisphere Technologies has developed its Eligen technology to address this issue. The platform relies on low molecular weight compounds, dubbed drug delivery agents or carriers, which form a complex with a target protein, increasing its lipophilicity and thereby its ability to cross the gastrointestinal epithelium using the body's natural passive transcellular transport process. The company has established a library of delivery agents with varying properties, applicable to a wide range of drugs. Emisphere is applying its technology to the oral delivery of peptides including heparin, insulin, salmon calcitonin and human growth hormone. Its lead candidate, heparin, has successfully completed Phase II trials.

Earlier patch-based transdermal delivery systems deliver hydrophobic small molecules across the epithelium by passive diffusion, but are generally less suited to large molecule biologics. Several companies are developing advanced, active transdermal delivery systems

which potentiate the delivery of larger molecules, including biologic drugs. Altea Therapeutics' skin microporation technology uses a short electrical pulse to heat metallic filaments that painlessly ablate the skin and facilitate delivery of drugs into the bloodstream. TransPharma Medical's ViaDerm platform uses radio-frequency current to open micropores in the skin. Both technologies require the use of small handheld devices to open the pores, after which a patch-like drug reservoir is placed on the skin allowing large hydrophilic molecules, including proteins such as insulin, to diffuse into the blood.

Changing business strategies

The traditional 'pure play' drug delivery business model follows a pattern common to most biotech platform technologies: that of selling improved productivity to big pharma, and signing non-exclusive licensing deals with multiple companies to generate revenue. But consolidation in the pharma industry has reduced the number of potential partners. Furthermore, increasing competition almost

inevitably results in the eventual commoditisation of any technology platform, a fact not lost on investors and shareholders. As a consequence, many drug delivery companies are now transitioning from technology licensing towards product development and marketing – they are becoming specialty pharmaceutical companies in their own right.

Attitudes to drug delivery vary widely within the pharma industry. While many companies have embraced the technology as a key aspect of their lifecycle management strategies, fewer have adopted it as an integral part of the entire drug development process, starting as early as molecule discovery. A notable exception to this is Johnson & Johnson with its landmark 2001 acquisition of Alza, a drug delivery expert. This has resulted in drug delivery technology permeating many aspects of Johnson & Johnson's R&D operations. But perhaps the biggest opportunity for novel drug delivery technologies lies with the biotech industry, the products of which are less amenable to traditional delivery routes meaning companies are inherently more

willing to experiment with non-validated approaches.

Drug delivery is a rapidly evolving and ever more competitive sector. Novel technologies under development or recently introduced to the market are increasingly sophisticated, and are addressing many of the problems that can decimate early-stage discovery (solubility, permeability), reduce drug efficacy (timed/continuous release) or place pressure on medical resources (injections/infusions). And technologies are increasingly multifaceted, combining solutions to different delivery problems – witness the promise of dendrimers. A common goal is the development of self-administered, targeted, sustained-or-variable release methods with increased bioavailability, a gold standard for future advances. Without the development of these new drug delivery technologies, new therapeutic advances may well fail to fulfil their potential.

Dr Peter Knight is principal analyst and biotechnology research manager at Wood Mackenzie. He is based in Edinburgh, UK.

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Paediatric regulation: reasons to be proactive

The Regulation on Medicinal Products for Paediatric Use will revolutionise the European drug development process and increase the number of medicines available for children.

Why will companies have to take a proactive approach?

Jane Lamprill reports

The European Medicines Agency has been given considerable legal powers by the European Commission to mandate and reward companies for paediatric data. By being proactive, the pharma industry can take advantage of this golden opportunity to be rewarded for developing paediatric medicines and contribute greatly to improved child health. However, companies that are not proactive and fail to comply with the regulation will be unable to submit their Marketing Authorisation Applications for the adult drug and thus lose out to competitors.

Reasons for the regulation

Publication of the proposed paediatric regulation in the EU's Official Journal is pending at the time of writing, but objectives are to:

- ◆ Increase the development of medicines for use in children.
- ◆ Ensure that medicines used to treat children are subject to high quality research.
- ◆ Ensure that medicines used to treat children are appropriately authorised for use in these patients.
- ◆ Improve the information available on the use of medicines in children.
- ◆ Achieve these objectives without subjecting children to unnecessary clinical trials and in full compliance with the European Community (EC) legislation on clinical

trials, namely Directive 2001/20/EC.

- ◆ Not to delay the authorisation of the adult drug.

Sick children are very vulnerable. Most of them don't like needles or bitter tastes, find tablets hard to swallow and young children may need to be restrained for medication delivery. They may not understand the cause and effect of unpleasant medicine bringing benefit. Hence babies and children need medicines that are easy to administer and with minimal stress if current and future dosing is to be effective.

There is an urgent need not only for medicines to be tested on children and licensed for paediatric age groups at the optimum dose for safety and efficacy, but for those drugs to be in suitable, stable formulations that are easy to give. Current efforts by hospital staff and parents to administer paediatric doses often involve the untested extemporaneous alteration of adult medicines, for example, crushing of tablets or cutting of suppositories in half in the hope of a 50% dose, although how much drug is in which 'half' is unknown.

Children and babies given medicines in this way could be under or overdosed, sometimes with catastrophic consequences. Drug delivery can also be problematic with decimal point calculation errors. A French boy died in 2004 from a ten-fold overdose of morphine after routine surgery because the formulation was difficult to calculate for smaller doses.



The challenges of being proactive

Easier paediatric drug delivery is a tall order and, interestingly, the challenges involved are similar to those faced by the veterinary sector – smaller market, high cost of developing innovative technologies and the potentially long period before product profitability. It is a high-wire balancing act for shareholders and the cost to member state healthcare providers must be competitive to attract sales.

Tastes and cultural acceptability of different formulations and routes of administration can vary around the world which makes designing a palatable global solution problematic. Most importantly, there are safety and ethical challenges involved in testing medicines on children. Recruitment usually takes longer and the costs are higher than for adult trials.

On the plus side, the new Paediatric Regulation will soon be law and will reward

companies for producing paediatric data. There will also be a substantial market of around 105 million children in January 2007, when Romania and Bulgaria join the EU. Spin-off products and further sales can be generated if new paediatric drug delivery mechanisms are adapted for the elderly and/or disabled patients. Novel technologies and better formulations for easier drug delivery will improve child health, increase sales and can lengthen drug lifecycles in the face of generic company competition.

Lessons from the veterinary sector

Reducing drug delivery distress in animals and children involves giving drugs less often and with less pain. For example, sustained release and needle-free technologies could work well in both settings, especially as some companies make medicines for both.

In the sustained release field, the US company PR Pharmaceuticals' TheraPhase technology delivers livestock growth promoter using one subcutaneous injection every five months. The delivered molecules of biodegradable polymer change into active drug over time. This raises the question – could this system be adapted, with different drugs, to reduce the frequency of injections in serious paediatric disease?

Bioject Medical Technologies, another US firm, has a needle-free injection system, Vitaject, which has been modified for the

animal health company Merial to deliver insulin to dogs and cats. A similar system could spare children the more intense pain of injections, reduce fear of needles and abolish the risk of needlestick injury.

Current therapeutic need

The European Medicines Agency (EMA) has established a paediatric expert group to draw up priority lists of medicines that need a suitable dosage, formulation or better method of drug delivery in the neonatal and paediatric populations. In addition the UK medicines regulator, the MHRA, initiated a voluntary request for information from companies about paediatric data already held. The agency has published a 'top 20' list of drugs that it thinks require a better paediatric formulation to avoid extemporaneous and untested usage.

There is also a lack of suitable medications for terminally-ill children. Paediatricians have to be creative in managing distressing symptoms such as severe pain and nausea. For example, buprenorphine is available in potentially child-friendly slow release dermal patches for severe pain. However it requires cutting into 1/36th-size portions for babies because a paediatric dose is not available. Drug distribution may vary throughout the patch and lead to breakthrough pain.

Paediatric pharmacists were recently asked to

draw up a palliative care 'wish list' (see Figure 1). As companies will now be compensated for the financial outlay of developing specialist paediatric medicines, the opportunity to address the pharmacological needs of the dying or very sick child has never been greater.

US regulatory experience

Over in the US, legislation covering children is already in place, particularly the US FDA Best Pharmaceuticals for Children Act (2002) and the Pediatric Research Equity Act (2003). These both mandate (by written request) and reward companies for the inclusion of paediatric data as part of new drug and biological licence applications. To date, the paediatric exclusivity reward, effectively a six-month patent extension, has been granted to 126 products representing a significant increase in return on investment and benefit to companies' shareholders. However, uncertain times are ahead as the incentive 'sunsets' in 2007. This will mean a revision of the legislation and the reward extension is not guaranteed.

However, results to date are impressive. The FDA's Dr Murray Lumpkin stated at the recent European Forum for Good Clinical Practice meeting in Brussels that there have been paediatric informational label changes on 114 products, 22 dosing recommendations, 24

Palliative care wish list

Symptom	Drug	Current dose; route of administration	Desired dose	Desired route	Reason
Severe pain	MST continus suspension	20mg, 30mg, 60mg, 100mg, 200mg granules; Oral	5 mg, 10mg	Oral	Smaller doses are needed. Accuracy is not possible below 20mg because it does not provide uniformity of suspension for fractionating to smaller doses.
Nausea	Cyclizine	50mg tablets, 50mg/ml injection	Liquid, e.g. 25mgs in 5mls	Oral	Currently, splitting tablets provides very inaccurate doses.
Nausea	Levomepromazine	25mg tablets, 25mg/ml injection	Liquid, e.g. 5mg/5ml	Oral suspension	Not available at present, so pharmacies have to make up their own despite minimal data on stability and no information on bioavailability. Short-dated preparation requires extra trips to hospitals for parents to pick up solution.
Excessive secretions	Hyoscine hydrobromide	1mg/72 hours; Transdermal patch	0.25mg, 0.5mg	Dermal patch	Accuracy of dosing for better symptom management. Currently, 1mg patches are cut into quarters.
Intestinal colic	Hyoscine butylbromide	10 mg tablets, 20mgs/ml injection	10mg/5ml	Oral solution	Currently, injection solution is given orally. Parents have to snap open glass ampoules then strain through a filter straw to ensure no glass particles are administered.

Source: Author request from Pharmacy Department, Royal Liverpool Children's NHS Trust, UK

Figure 1: The inaccuracy of current drug delivery for serious symptom relief is a strong justification for companies to develop paediatric formulations of drugs for use in very sick and terminally-ill children.

enhanced safety instructions, 63 age group expansions and ten new paediatric formulations. Interestingly safety and efficacy were not established in 21 products, which is of critical importance to paediatric prescribing. As a result of 323 written requests, 732 paediatric clinical trials will be/are being performed, requiring an estimated 43,427 child research participants.

The FDA and EMEA's confidentiality agreement means that information on written requests is shared, so presumably children will not be exposed to a study drug by the same company in repeat clinical trials just to receive the European reward. These are complex issues, which will be made clearer next year when the EMEA's new Paediatric Committee (PC) is in place.

Get proactive!

The EMEA's new Paediatric Committee will be given extensive powers. It will give free scientific advice and review the timing and content of flexible Paediatric Investigation Plans (PIPs) that outline planned paediatric research. They will also instigate and maintain an inventory of paediatric therapeutic need in consultation with the EC, member states and other interested parties, such as patient groups. Companies will find this list a useful business development tool.

The agreed PIP and results must be provided with every new drug in order to obtain the Marketing Authorisation Application (MAA). Current timing of the plan (not the research) is the end of Phase I to encourage early dialogue between industry and the PC and to prevent possible delay of the MAA. However, this may be problematic if, for example, Phase I and Phase II trials overlap or if companies have insufficient data at the end of Phase I so a deferral may be necessary. If a drug is only for adults, such as for prostatic hypertrophy, then a waiver of paediatric data is appropriate. However this is flexible too if a paediatric indication is found at a later date.

The PC will scrutinise the PIPs not only for scientific integrity but for paediatric clinical benefit. If the PIP is purely for financial gain, for example if there is already a similar marketed medicine, the committee will reject the PIP and the reward will not be given as it would be unethical to duplicate paediatric clinical trials. Companies will therefore be incentivised to produce easy routes of administration, new palatable paediatric formulations or more suitable dosing to reduce the risk of medication errors.

The rewards of taking action include:

- ◆ A six-month extension to the supplementary protection certificate (SPC) for new drugs when all the required criteria for paediatric data, authorisation and labelling have been met. There will be a transition phase and some drugs, such as those for HIV, may not have SPCs and this is currently under review.
- ◆ Companies will receive the reward for "significant" studies even if the outcome is negative for paediatric therapeutic benefit in certain age groups.
- ◆ A new optional Paediatric Use Marketing Authorisation (PUMA) for off-patent medicines will enjoy a reduced authorisation fee, ten years of data protection and permission to continue brand name recognition. This will be useful for line extensions for drugs nearing the end of their patent and for the generics industry.
- ◆ Orphan drugs, when tested for a paediatric indication, will receive 10+2 years' market exclusivity.

Pharmaceutical innovations

In the Autumn/Winter 2005 Drug Delivery Report from PharmaVentures, Dr Catherine Tuleu, a paediatric formulation expert at the School of Pharmacy, University of London, maintains that the ideal medicines for children should be efficacious, tailored, tolerable, convenient to give and dispense, good quality and safe, as should their routes of administration. They should be easy to give for increased compliance and excipients should be chosen with care, she says. Extemporaneous methodology should also be tested for bioavailability, stability, safety and efficacy.

Innovative drug delivery approaches in the paediatric sector include:

- ◆ "Sip" technology, developed by Grünenthal of Germany, uses the drinking straw principle enabling a liquid permeable 'controller', which draws up tiny dissolvable drug granules contained in the straw and indicates when all drug is taken. It comes predosed and is neutral tasting so the drug can be sucked up with the child's favourite drink.
- ◆ Captopril liquid, which can be used to reduce hypertension and therefore kidney damage in children awaiting renal transplant, has been formulated by the UK's Special Products Ltd with a long half-life to enable once-daily dosing and a raspberry flavour to increase compliance.
- ◆ Epistat, also made by Special Products, is special order unlicensed midazolam, administered buccally while a child is fitting. It is fast-acting, can be given when teeth are clenched, and avoids the complexity and



indignity of the rectal route of delivery.

- ◆ Chewing gum is proven to be acceptable to older children. It hides bitter tastes, can be taken anywhere without water and is convenient and discrete. Drugs impregnated into gum can be hydrophilic or lipophilic and have included fluoride against tooth decay and dymenhydrenate to prevent travel sickness. Interestingly, the MHRA announced in December 2005 an initiative to help prevent the morbidity and mortality associated with early addiction to cigarette smoking. Nicotine replacement therapy can now be given to children aged 12 years and above for up to 12 weeks, in a counselling context.
- ◆ The EMEA's reflection paper on paediatric formulations mentions some current non-invasive drug delivery techniques: paediatric anaesthesia uses S-ketamine and patient-controlled intranasal analgesia is being investigated. Intranasal diamorphine is used for pain relief following trauma and desmopressin and some vaccines can also be given via this route.
- ◆ Other products under development include melts, lyophilised wafers, oral strips, mini tablets, beads, granules and mini microspheres.

Europe's new paediatric regulation will revolutionise not only medicines for children but the whole European drug development process. Companies will need supportive shareholders as it will be an expensive and precarious challenge, fraught with ethical and practical difficulties. It remains to be seen how this will work in practice. Those companies that are proactive and seek to meet the clinical needs of children with innovative and easy to give drug delivery will surely be rewarded.

Jane Lamprill is a paediatric research consultant based near Oxford, UK. She advises companies on the practical, ethical and management aspects of paediatric clinical trials.

A revolution in waiting

The approval of an inhalable formulation of insulin has helped remove some of the convenience and compliance hurdles in the treatment regimen of insulin-dependent diabetics. So is the market about to be flooded by other drugs delivered via the pulmonary route?

Sylvia M Findlay reports

Venturing into an era of advanced pulmonary delivery, the healthcare community is awaiting a revolution in drug delivery technology. The trigger has been the approvals in early 2006, in both the US and Europe, of Pfizer's inhaled insulin Exubera. This represents an important milestone in the treatment of systemic diseases through pulmonary delivery and has opened up a whole world of possibilities for the delivery of drugs to the deep lung. As such, it is all set to revolutionise the drug delivery market.

Other key factors driving drug developers to move towards pulmonary delivery, and to maximise the potential for this market, include mounting pressure on the pharma industry to cut R&D costs, technological advancements, increasing unmet medical needs, dissatisfaction with current therapies and the need for pharma companies to stay ahead of their competitors. In the case of insulin in diabetes management, the end-users have also become part of the equation in the sense that more challenging customer requirements are shaping the trajectory of this market growth curve.

It is estimated that 15-20% of therapeutics are administered through the lungs and pulmonary drug delivery is one of the fastest growing markets. In fact, the market is likely to grow from US\$13billion today up to US\$20billion by 2012. In parallel, increased attention is being showered on systemic drugs.

Industry challenges in pulmonary drug delivery

- ◆ Long-term safety concerns
- ◆ Premium pricing
- ◆ Reimbursement issues
- ◆ Lack of regulatory guidelines/standardisation for device performance
- ◆ Consistent dosing performance is still an issue

The players

The economic benefits offered by the pulmonary mechanism of delivery include lower R&D costs and higher return on investment as the development of a pulmonary drug delivery product consumes only US\$50million compared with around US\$900million in the case of researching a new chemical entity. So going forward, this market is set to attract a large number of partnership deals. In addition, the constant influx of new protein and peptide drugs from the biotech industry is creating a demand for novel devices that can deliver these therapeutics through the pulmonary route. This is opening up avenues for major alliances and M&As between pharma and biotech companies and device manufacturers.

Pfizer and Nektar Therapeutics, the US company that developed the dry powder formulation in Exubera and the device used to deliver the drug, may be the first movers in the inhaled insulin segment, but interest in this field has been such that a host of other pharma and biotech companies have teamed up to explore this new arena.

Some of the companies in pursuit of insulin inhalation devices follow.

- ◆ Novo Nordisk collaborated with Aradigm in 1998 on the development and commercialisation of the AERx inhaled insulin system, currently in Phase III trials.
- ◆ Lilly and Alkermes are partnered in the development of AIR insulin, which entered Phase III trials in 2005.
- ◆ Mannkind is developing Technosphere, a dry powder formulation also in Phase III trials.
- ◆ Kos Pharmaceuticals (Abbott) is developing a line of inhalation devices for the delivery of large and small molecules. It is also working on inhaled insulin.
- ◆ BioSante Pharmaceuticals is developing BioAir.
- ◆ Epic Therapeutics, a subsidiary of Baxter Healthcare, is working on ProMaxx microspheres for the pulmonary delivery of proteins.

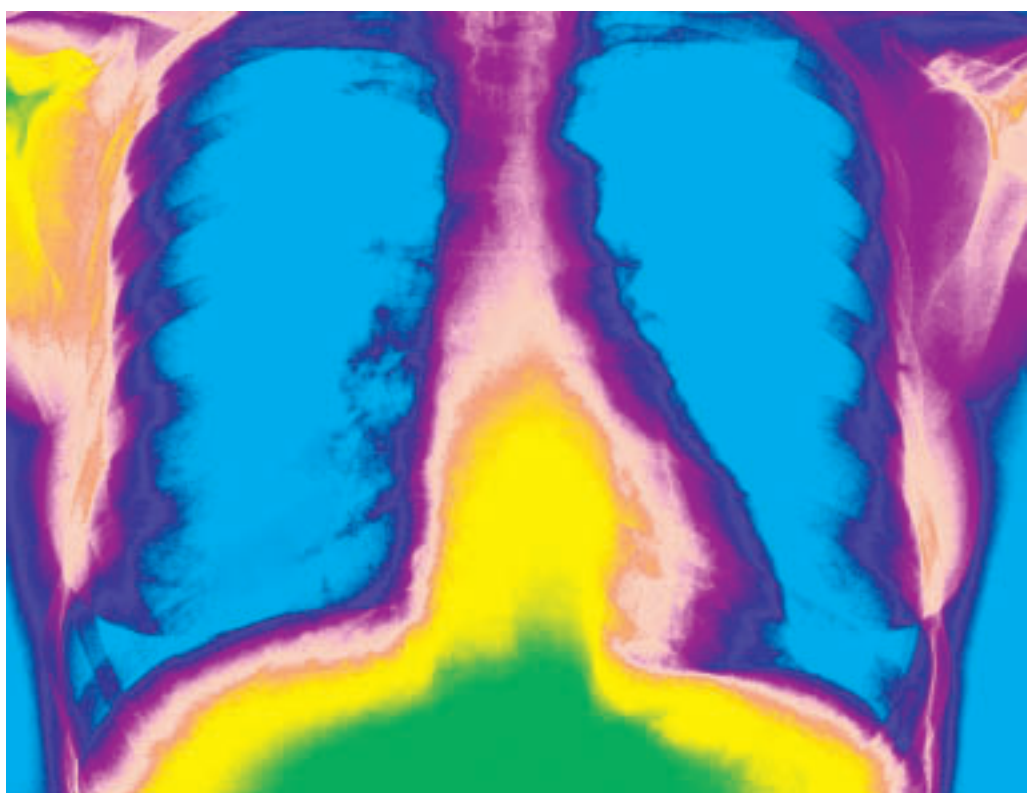
Although most pipelines at present feature drug candidates born out of licensing deals or strategic alliances, the future is more in favour of companies licensing novel drug delivery technologies. Going forward, the primary aim of such activity will be to create in-house capabilities in a range of technologies, not just pulmonary delivery. Elan, for instance, transformed from a drug delivery company into a specialty pharma firm mainly through various M&A activities. Such licensing and M&A between pharma and drug delivery companies offers them with key product differentiation and the competitive edge that they yearn for.

Safety concerns

Initial demand for pulmonary drug delivery was primarily driven by the respiratory diseases market. The environmental safety concerns that led to the withdrawal of CFC propellants from the market by 2000, in accordance with the Montreal Protocol, and the successful launch of dry powder hydrofluoroalkane (HFA) inhalers to replace CFC inhalers, have changed the market. Pressurised metered dose inhalers (pMDI) have played a part in drug reformulation and the market for such pulmonary drug delivery devices is likely to expand. However, only those devices that score high in terms of safety and efficacy, and that are easy on the purse, will be a sure-fire hit among patients.

The diagnosis, treatment and management of diabetes are still major concerns for the diabetic community, with convenience and compliance in treatment regimen proving to be major hurdles. Hence the introduction of a novel alternative in delivering insulin through systemic pulmonary delivery, such as Exubera, is likely to remove some of the hurdles in this therapeutic area. Even so, long-term safety and efficacy remain major challenges and Exubera is still viewed with scepticism. For example, occurrences of pulmonary fibrosis during clinical trials on the drug have caused concerns over its safety. The occurrence of side-effects such as coughing tends to deter the patients from using the inhaled insulin. In addition, there are a number of industry challenges that plague pulmonary drug delivery (see table opposite).

Beyond diabetes management, therapeutic areas where there remains unmet medical need, and that could benefit from systemic pulmonary drug delivery, include multiple sclerosis, anti-infectives, pain management, osteoporosis, migraine, male sexual dysfunction, immunosuppression, smoking



cessation, premature ejaculation, growth hormone deficiency, neurological problems and even certain cancers. The cost factor involved in treating chronic diseases is crucial here – some illnesses warrant higher expenditures, frequent dosing and constant visits to the physician. Lilly and Alkermes' venture to produce an inhaled formulation of the parathyroid hormone Forteo (teriparatide), for example, is intended to ensure better compliance and improve the lifestyle of patients suffering from osteoporosis.

The concept of pulmonary vaccines, meanwhile, has triggered immense interest from pharmaceutical developers. Such technology would facilitate administration and empower greater compliance to the community. Although there are very few such vaccines under development, one being Aktiv-Dry's inhalable vaccine for measles, the future holds great promise for this drug category. In addition to measles, diseases like pneumonia and influenza are promising indications for inhaled pulmonary vaccines. The global vaccines market was valued at US\$10 billion in 2005. However, the needle-free delivery of vaccines, especially pulmonary delivery, will likely double this market value by 2012.

Pulmonary delivery: the outlook

Pulmonary drug delivery has generated immense interest and the very concept of non-invasive drug delivery is welcomed by the

healthcare community. This has been a major driving force for this market, which is bound to experience explosive growth rates. Frost & Sullivan estimates the market to grow in the next 5–6 years thanks to the influx of many biotechnological products onto the market.

As the market expands, the focus will likely be on new indications and also the delivery of new macromolecules. In terms of pulmonary drug delivery, current pipelines house various molecules including interferons for the treatment of multiple sclerosis and hepatitis B and C, alpha 1 antitrypsin for emphysema and cystic fibrosis, heparin for blood clotting, interleukin-1 receptor for asthma, and calcitonin and other peptides for the treatment of osteoporosis.

Even so, drug developers are also trying to overcome the various disadvantages associated with pulmonary delivery by focusing on other innovative technologies. Nanotechnology and gene therapy are two research areas being studied for the efficient and painless delivery of various therapeutic macromolecules like insulin and other hormones. While they are still in their infant stages, these technologies are bound to garner significant attention and expand the drug delivery market in future.

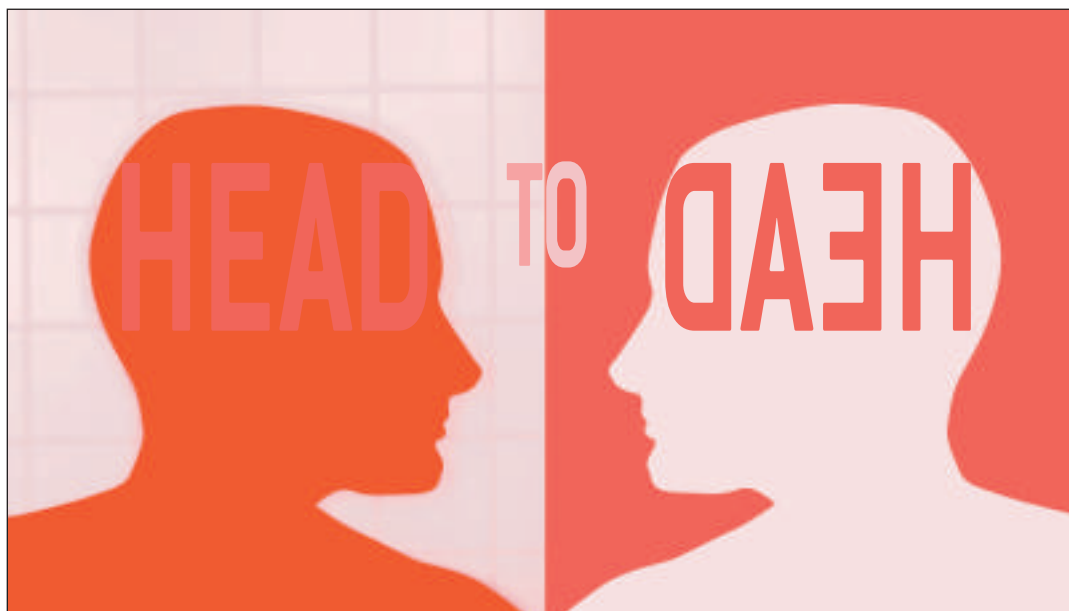
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Facing risk – head-on

Scrip's Pete Chan explains why we have partnered with 3M to ask: "Should a new drug be launched in a new delivery system?"

Global pharma giant Pfizer undisputedly stole the headlines in January 2006 when it received back-to-back approvals from the European Commission and the FDA allowing it to sell Exubera, its powdered, inhalable formulation of insulin, to the lucrative European and US markets. At the same time, the product registrations delivered a tide of good fortune to a smaller player, Nektar Therapeutics, the US company that partnered with Pfizer and that developed both the dry powder formulation and the inhaler used to deliver the drug.

Nektar revised its 2006 guidance from US\$60-80million to US\$70-90million, most of which it expected to come from manufacturing sales to Pfizer and

the company is also in line to receive additional royalties on sales. In mid-September, Pfizer and Nektar's product was thrust into the spotlight once again when it topped the biotech-medical category of *The Wall Street Journal's* 2006 Technology Innovation Awards before pocketing the third place prize for innovation overall.

The Exubera story is a good example of a successful drug delivery partnership. But this isn't to say that the drug enjoyed a straightforward route to market. Development work took over 15 years and involved input from diverse scientific disciplines spanning biology, chemistry, mechanics, manufacturing, fluid engineering and physics. Even aeronautical engineers had their part to play. Then came concerns over the safety of inhaling insulin into the lungs – Exubera is the first drug to be approved for this mode of delivery. Even now, Pfizer is being dragged into the courts by Novo Nordisk's lawyers

who claim that Exubera infringes patents the Danish company owns covering inhaled insulin.

All of which highlights the considerable risks involved at every stage of the drug development process, not only for pharma companies, but also innovator biotechs and firms focused on developing novel ways of administering drugs to patients. Over several years' worth of development work, partners could quite feasibly clear all the anticipated hurdles and pull out all the stops to almost get a product to market, only to come across some stumbling block they hadn't foreseen at the start of their relationship. In this increasingly tricky development environment, it pays to consider from the outset all the issues that are likely to crop up – that way companies can reduce the risk of an unexpected factor throwing a spanner into the works at the last minute.

Risk management could involve verifying the ownership of intellectual property in the

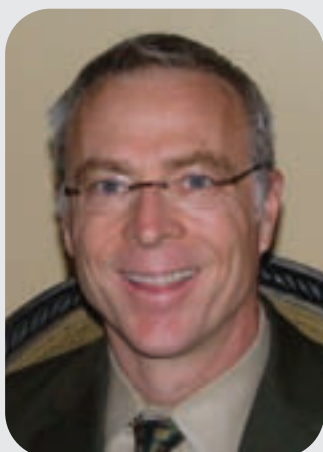
"It's well worth their while getting to grips with what partner firms think about risk in order to be able to offer them the best possible service"

THE HEADS

Dr Paul Colthorpe is head of Inhalation and Device Development at Novartis Pharma. He serves on the board of the International Pharmaceutical Aerosol Consortium on Regulation & Science (IPAC-RS) and was previously a board member of the Academy of Pharmaceutical Sciences (APS). He also co-founded the APS' Inhalation Focus Group.



Dr William K McVicar is a program director and vice-president of Development Operations – Respiratory at Sepracor. He oversees all development teams in the respiratory field and is responsible for a multidisciplinary team that helps manage the company's respiratory portfolio and assess candidates for in-licensing.



Dr James Stefely is a manager in the Early Pharmaceuticals and New Technology department in 3M's Drug Delivery Systems division where he has served since 2002. He has also worked for 3M's Life Sciences Materials Sector lab, the company's Biomaterials Technology Center and 3M Pharmaceuticals.



technologies being used to avoid becoming embroiled in lawsuits further down the line. But it also means dealing with relatively simple elements such as ensuring that suppliers have the right materials and a robust supply chain in place. As for companies trying to compete in their respective markets, it's well worth their while getting to grips with what partner firms think about risk in order to be able to offer them the best possible service.

The value of this type of information is the reason *Scrip* has teamed up with 3M Drug Delivery Systems, a global leader in the drug delivery field, to produce this opinion piece under the broad heading: 'Should a new drug be launched in a new delivery system?'

Unlike in typical business environments, where partner companies need to take a sensitive approach to dealing with their working relationships, this *Scrip*/3M 'Head to Head' has posed a number of key questions and created an open and frank forum for industry experts to honestly air their views and concerns. Seemingly basic questions such as what is considered to be a new drug

The importance of new drug delivery systems to the pharma and biotech sectors hardly needs stating – technological advances offer considerable advantages in terms of lifecycle management, market positioning and product differentiation, for instance, and businesses are well aware of this.

Companies detected by the *Scrip* drug delivery radar in 2006 range from the UK's Vectura, which has spun out its oral and dermal technology division, Pharmakodex, in order to focus on its pulmonary drug delivery technologies; through to Gilead Sciences, which in August acquired the drug delivery firm Corus Pharma for a sum of \$US365million. Aradigm has divested its Intraject needle-free drug delivery system to a new firm, Zogenix, allowing it to focus on its AERx pulmonary delivery platform. Merriion Pharmaceuticals, meanwhile, has both in-house and partnered programmes in which it is developing oral formulations of therapies that can only be delivered by injection at present.

As for 3M Drug Delivery Systems, 2006 is a milestone in the company's history for a completely different reason. This year marks the 50th anniversary of

"Seemingly basic questions such as what is considered to be a new drug delivery system are open to considerable differences in interpretation"

delivery system are open to considerable differences in interpretation. As are different companies' views on the risks involved in launching new drugs in novel delivery systems, what actions are needed to keep risk to a minimum, and how these risks should be prioritised. This discussion aims to get the views of the market's key players and identify the factors that underpin the launch of new drugs, new delivery systems or, in some cases, both.

the launch of the first pressurised metered dose inhaler (pMDI), which 3M subsidiary Riker Laboratories originally developed for asthma in response to patient dissatisfaction with existing aerosol delivery technologies. Fast forward 50 years and the patient of the 21st century is infinitely more clued up on the various formulations of medicines available to them. What better time for market leading companies to discuss the way ahead?

“ Should a new drug be launched in a new delivery system? ”

Novartis's Paul Colthorpe, Sepracor's William McVicar and 3M's James Stefely discuss the pros and cons of this approach. Scrip's Peter Charlish reports

There are many reasons for marketing a drug in a novel delivery system. They may be related to the clinical usefulness of the drug, to assist with product differentiation, or part of the lifecycle management process. By and large, novel delivery systems tend to be used with drugs that are already on the market, either in different formulations or in different presentations. But is it possible to make a case for launching a new chemical entity (NCE) using novel delivery technology?

The case for...

William McVicar certainly thinks so. A program director at Marlborough, Massachusetts-based Sepracor, with responsibility for all development projects in the respiratory field, McVicar identifies three good reasons to launch a new drug in a new delivery system. “The first is to improve the therapeutic index of the drug, either by reducing side-effects or increasing efficacy,” he says. “Because drugs can cause unwanted effects in non-target tissues, a better therapeutic index can sometimes be achieved by delivering the drug selectively to the target tissue. Examples of this include topical formulations to treat skin diseases or the injection

of chemotherapeutics directly into tumours. Such techniques allow for higher local concentrations of a drug in the target tissue and perhaps better efficacy while avoiding the side-effects that might accompany systemic exposure to the drug.”

The second good reason, in McVicar's view, is to improve patients' quality of life. Examples of this include developing a controlled-release formulation so that dosing can be less frequent and compliance perhaps improved, or delivering an antimigraine medication via inhalation, so the patient benefits from a faster onset of action than with oral or subcutaneous administration. “Finally”, McVicar says, “a certain measure of competitive protection can be obtained by developing a unique drug product with a superior delivery system that is patent-protected. This adds to the composition of matter protection an NCE is likely to have.”

James Stefely, a manager in the Early Pharmaceuticals and Technology Department in 3M's Delivery Systems Division in St Paul, Minnesota, is another believer in the new drug/new delivery system model. “It is a misconception that there are more inherent barriers to launching an

NCE in a new drug delivery system,” he says. After all, anyone launching a new drug product is faced with the same questions, regardless of the novelty of the drug, the delivery platform or of a component within the system. Is the product safe? Is it efficacious? Is the formulation sufficiently robust? Can it be manufactured reproducibly?

Recognising risk

Paul Colthorpe, head of the Inhalation and Device Development Department at Novartis Pharma in Basel, Switzerland agrees with the upsides but points out a number of risks associated with developing a new drug in a new delivery system. They include anything that could affect the safety of patients

the development, scale-up and manufacture of a new device, we can work to mitigate them as we develop the new technology.”

McVicar agrees there are risks. “All significantly complex delivery systems add cost, time and risk to the drug product's development,” he says. “If the active pharmaceutical ingredient is a therapeutic advance when given in an old-fashioned, tried and true delivery system, this is probably the best way to develop the original product. An improved delivery system can then be used to introduce a differentiated, improved line extension while enjoying revenues and brand awareness from the original product.” But, he says, if the delivery system is required for a truly differentiated product, the

“It is a misconception that there are more inherent barriers to launching an NCE in a new drug delivery system”

using the device as well as potential problems during development and registration. “Each of these areas can lead to lengthy delays to approval, and hence to the introduction of the new system to patients,” he says. “But if we can successfully identify risks as we go through

decision to develop must include consideration of the greater risk, cost and time that comes with a novel delivery system.

Defining design

According to Stefely, the belief that launching an NCE in a new delivery system is inevitably

associated with unexpected barriers and costs arises because, in the past, many delivery systems were developed alongside the drug, which meant that the delivery system did not have its own defined design space. Delays and unexpected costs are best avoided by accurately defining the critical factors at the outset and designing a research or development programme to address them early on. In that way, the delivery system does not become rate-limiting to the NCE development programme.

All three agree that a robust and reliable supply chain is vital. “Supply chain considerations become particularly important when the product cost is high or when the medical need is great,” says McVicar. Colthorpe adds that it is critical to work in partnership with the regulatory agencies to ensure delivery of devices that exceed the latest standards and hence have a high chance of approval. He predicts that cost will remain an important factor in this area, and that the burden on pharmaceutical companies to demonstrate a positive impact of new delivery systems on the overall cost of treatment will increase.

So when should a new drug be launched in a new delivery system? What criteria need to be taken into account? And what are the anticipated benefits?

Finding balance

A major consideration is the balance of risks between the technical development and the clinical development, McVicar says. “It would not make sense to develop a high-risk drug in a high-risk delivery system. There are too many ways to fail. A better balance is a high-risk drug in a simple delivery system unless the delivery system is critical to the drug’s ability to improve on current products. Likewise, a complex delivery system makes more sense with a less risky drug – or a series of drugs, so the cost



of the delivery system development can be amortised over more products.”

“Delivery systems are initially chosen in the belief that they provide the greatest probability of safely obtaining the desired clinical outcome in a patient-preferred manner,” says Stefely. The ideal delivery system should provide the desired dose, at the target location, with the optimal release profile and at the correct time, in a manner that improves patient freedom and compliance. Every new drug delivery platform introduced over the past half-century has improved at least one of these elements: “When 3M Riker introduced the metered dose inhaler (MDI) 50 years ago, it addressed several of those issues,” Stefely explains. “The MDI’s development was market-driven, by providing patients freedom from the bulky powered nebulisers of the 1950s. It improved the compliance of asthmatics, delivered the drugs more efficiently, and provided portability in a very cost-effective, stable system.”

In more recent times broader questions such as environmental impact and the effect of the delivery system on development timelines have also become important considerations when selecting a new delivery system. For example, the replacement of chlorofluorocarbons (CFCs) as propellants in MDIs with hydrofluoroalkanes (HFAs) was initially driven by concerns about the environmental impact of CFCs.

With numerous inhalation delivery-related patents and publications to his name, Stefely clearly speaks as someone with considerable experience of developing new vehicles for clients’ molecules. From the pharma perspective, Colthorpe says that the criteria for putting a new drug molecule in a new delivery system include whether the development schedule for the drug product has sufficient flexibility to allow for the introduction of a new delivery system as well, and the degree of technical and regulatory risk associated with the new system,

although he points out that the latter concern may be mitigated by co-developing a backup system using established technology.

Colthorpe also makes the point that a new delivery system may offer advantages in terms of increased compliance and/or user convenience, performance, cost and so on, which would be particularly important for ‘me too’ drugs to provide a further degree of differentiation and competitive advantage. There may also be technical reasons why a new delivery system is required for a new drug – for instance if the company’s current dry powder inhaler provides insufficient moisture protection for a moisture-sensitive NCE. At Novartis, the potential benefits are evaluated on a case-by-case basis, and technical considerations are weighed against marketing drivers. Colthorpe says that to make these decisions effectively it is critical to bring together cross-functional teams comprising representatives from the relevant functions – marketing, regulatory, clinical, operations, and technical R&D.

Stefely echoes the latter point. “Early involvement of multifunctional teams is vital to keeping a new platform development project on target,” he says. “A partner who has an established organisation to manage complex supply chains, or who is vertically integrated, significantly reduces the risk associated with launching a new delivery platform, especially if that partner has experience with developing and manufacturing multiple drug delivery platforms.”

Of course, all these different elements are interdependent. For example, says Stefely, if the delivery system is capable of local delivery, thereby reducing both the systemic dose required and the incidence of side-effects, it can impact both safety and compliance. Or if an extended-release profile enhances efficacy (technical benefit), it also reduces the dosing schedule (which confers a market/compliance benefit). Improved compliance typically improves patient outcomes, which in turn may enable the drug to obtain a premium price while still being considered a more cost-effective treatment than a cheaper alternative product.

New or different?

At this point it is perhaps germane to ask, when is ‘new’ really new? As Colthorpe says, there are plenty of ‘different’ delivery systems, but genuinely new, innovative systems are rare. Stefely agrees: “There is really a continuum in the definition and degree of risk associated with ‘new,’” he says. “At one extreme is a new delivery system targeting an entirely new delivery route, such as when nebulisers were first used to deliver drugs to the lung. Less risky is a new delivery system through a known route: for example when MDIs were first introduced, they were a radically new delivery system that filled a significant patient need, but inhalation was an established

delivery route. Since then there have been continual minor changes to the MDI, which typically present less risk because you are building on the existing delivery platform’s knowledge base.”

On the other hand, the transition from CFCs to HFAs was a substantial change because it affected every aspect of the delivery system, from the formulation approach and dose consistency to the container stability and valve function. Even so, the transition was not as risky as developing an entirely new delivery system and actually enabled a large number of minor improvements to the MDI. These improvements have resulted in a significantly better MDI delivery system, but cumulatively they are still not large enough for the modern MDI to be considered a ‘new’ system.

Colthorpe takes a regulatory viewpoint. “A ‘different’ system is anything that could potentially affect performance, functionality, user handling, safety and so on,” he says. So although it would commonly be a lifecycle management activity, Colthorpe considers the change from a standard press-and-breathe MDI to a breath-activated MDI to represent a different delivery system. “Changing from one DPI to another, for example from a Single Dose Dry Powder Inhaler (SDDPI) to a Multi Dose Dry Powder Inhaler (MDDPI), or one type of MDDPI to another, would also constitute a different system,” he says.

McVicar defines a delivery ‘system’ as anything in the drug product except the active pharmaceutical ingredient, for example tablet excipients for a controlled-release tablet, canisters and valves for MDIs, or materials in active or passive transdermal patches. A new system is one that provides the same (i.e., bioequivalent) delivery cheaper, with better shelf life, or with a lower manufacturing scrap rate

(i.e., offers economic advantages), or one that truly improves the therapeutic performance of a new or existing drug, such as a targeted mono-dispersed aerosol. So like Colthorpe, McVicar views the transition from pMDI to DPI, or from a press-and-breath pMDI to a breath-actuated pMDI, as changes to ‘new’ systems. In short, for a delivery system to be ‘new’ it must confer an advantage to the patient (therapeutic or quality of life) or the drug company (economic).

For a system to be considered genuinely ‘new’ Colthorpe says there would need to be an innovative change involved rather than a stepwise evolution of current technology. This could for instance be diagnostic/self-titrating systems, delivery via a new route of administration, or the use of active, electronically driven DPI systems to generate aerosol without the requirement for inspiratory effort by the patient. The need for new delivery systems could be driven by a desire to better meet the needs of patients or to keep pace with, or stay ahead of, the competition, changes in legislation, and the delivery demands associated with new therapies and formulations.

The case against...

Are there any occasions when it would definitely not be appropriate to put a new drug in a new delivery system? That depends on what type of ‘new’ system you mean, says Colthorpe. “Delivery systems that are already available and used by others, but which are ‘new’ for a particular company so that no internal experience is available yet, represent one category. This is a ‘reduced risk’ scenario for a combination with an NCE,” he says. But delivery systems new for the entire pharmaceutical arena represent a substantial risk. “Here you add the risk of developing a new technology to the intrinsic development risk of an NCE. Whilst this can often lead to a

breakthrough new therapy for patients, it does mean that pharmaceutical companies have to take on a very large amount of financial and technical risk to achieve their goal.”

Stefely takes a similar view. “If existing delivery technologies can provide a safe, efficacious product, which is likely to have a strong competitive position in the market through the majority of its life, there is less reason to utilise a new delivery system,” he says. “However, you have to look at the prospect of having a competitive drug product utilise the novel delivery system in deciding if you will have a strong competitive position throughout the product’s lifecycle. You should also consider the impact of the novel delivery system on the ability of generic competitors to copy your product. When you are making this decision it is important to be able to assess accurately the true costs and benefits of the new delivery system during the product’s lifecycle.”

McVicar identifies three situations when a novel delivery system is inappropriate for an NCE. The first is when introducing a new therapeutic approach in an area of great medical need, when the patients’ need for the new therapy in any form outweighs the benefit of the new delivery system. In this case, he says, the ‘simpler’ product can be introduced much earlier as possible, with a more sophisticated delivery system to follow. The second situation is when there is a high probability of ‘biological’ failure that does not justify the extra cost, time and risk of a new delivery system. The third is when the cost of the delivery system cannot be supported by the marketplace.

Clearly, using a new delivery system is not appropriate for every new drug. But provided the appropriate checks and balances are in place, there are times when it is a very attractive proposition.

Reactions

Scrip went back to the 'Heads', for their comments and conclusions



I think we are in agreement that a careful risk/benefit analysis must be conducted for each opportunity to combine a new drug and delivery system. Whilst concern for patient safety is a given, perhaps the weighting applied to some of the other variables in this analysis may differ based upon whether the commentator is working for a CRO drug delivery company or in pharma. Another factor which should be considered is that much of this discussion has focused on delivery systems for inhalation. However, these systems tend towards the more complex end of the spectrum and carry with them more technical risk in development. The tipping point in the risk/benefit analysis will be markedly different for other routes of delivery.

Another relevant question is whether companies should try to rationalise the number of new delivery systems they present to patients. For instance, in asthma and COPD many patients need multiple drugs, and hence multiple inhalers, to manage their condition effectively. It is therefore critical to balance the need for better inhalation devices against the need for simplicity and consistency for the patient. This implies that it may be more effective to develop technically robust and versatile platforms with a range of medicines rather than innovating for each new molecule or combination.

Dr Paul Colthorpe



Competition for new, innovative drug products is greater now than ever. The high burden of healthcare cost on businesses and governments will make it harder each year to justify the value of new products that don't offer a significant advantage to the patient and/or payor. The consolidation of multinationals has created a pool of 'mega-customers' looking for 'mega-products' they desperately need to feed their infrastructures and maintain growth despite the relative success for their internal discovery efforts. So while the development of a new drug in the simplest form is a dauntingly complex and risky task, the extra advantage that may be conferred via a more complex delivery system may just create the benefit for patients and the resulting marketing differentiation. The strategic decision to couple the biological uncertainty of an NCE and that of a novel, complex delivery system must be carefully considered as discussed, but can no longer be ignored as a viable option.

Dr William K McVicar



Our viewpoints on launching new drugs in novel delivery systems are substantially in agreement. Do it when it makes sense. We agree that a holistic, lifecycle view of the risks to the product have to be taken into consideration as well as the potential benefits to patients. True novelty clearly means we are in unexplored territory, which implies we have increased the range of possible risky and rewarding outcomes. It is important to remember that increasing the number of negative possibilities, in other words risk, is different from saying that the probability of having a negative event has increased. The negative possibilities are balanced by mitigation strategies and by the positive possibilities that encouraged us to choose a novel approach. We accept increased risk because we believe the probability of having a breakthrough new therapy has increased.

We agree a risk mitigation strategy can be to utilise experienced teams or companies that have demonstrated the ability to navigate new territories and who have greater capabilities to address the unexpected events in a timely manner. Experienced innovators have frequently been rewarded for their risk-taking.

We also agree that the increased risk associated with utilising a new delivery system has to be balanced by an increased probability of success in another aspect, for example patient compliance or competitive advantage. Additionally the risk to one programme may be further balanced by the increased probability of success on future programmes – in other words, developing new delivery capabilities pays future dividends. The more holistic your viewpoint, the greater the acceptability of the risk associated with a new delivery system.

Dr James Stefely



The final word...

Nola Bowles, 3M's product development manager, sums up what we have learned by answering the question: "Should a new drug be launched in a new delivery system?"

There is broad agreement that yes; launching a new drug in a new delivery system is a viable option in the right circumstances. The reasons why industry would follow this path are primarily patient-driven. As our industry experts point out, from the patient's perspective a new delivery system should be considered if it would improve the effectiveness or safety of their medicines.

A new delivery system would also be beneficial if using it was easy, or meant less restriction on patients' life styles, thereby leading to better compliance. So, really understanding the needs of patients is core to understanding the benefits that a new delivery system should convey and where industry should be focusing its innovation efforts.

The secondary driver for launching a new drug in a new delivery system is to gain additional competitive advantage. The costs and complexity of pharmaceutical R&D continue to rise and the remaining patent protection on a new chemical entity at the time of launch has decreased over the years, hence the ever-increasing importance of having other forms of protection against generic competition to maximise payback. The additional advantage that can be gained by using a new delivery system, which can confer that protection, is an important consideration in the overall life cycle management for a new product. Understanding the patent landscape and maximising patent coverage for new delivery systems are critical success factors.

Perhaps 'should' and 'why would' a new delivery system be used are not the real questions; it is really more a question of 'when' and 'how' should one be used. All three participants have raised the classic dilemma of risk versus benefit, risk management being at the heart of everyone's thinking. Early identification of the risks and consideration of possible mitigation strategies will increase the likelihood of success. For example, understanding and managing the complexity and security of the supply chain is fundamentally important to avoiding delays and unexpected costs.

One of the key mitigation strategies to the inherent risks is to leverage experience. So with more than 50 years' experience in bringing new delivery systems from concept successfully to market, including the first pressurised metered dose inhaler, the first breath-actuated inhaler and the first non-CFC inhaler, 3M is well placed as a drug delivery company with that depth of experience and understanding of the challenges involved, underpinned by financial security.

Other strategies that have been highlighted include involving the relevant multifunctional disciplines early in any development programme and working in partnership with the regulators. The need to evolve continuously to meet the changing needs of the regulators and the market place is undoubtedly important. Finally, in the case of a high risk/high potential gain programme, co-development of a back-up established system may also be warranted.

At the end of the runway, being able to demonstrate the positive value of a new delivery system in the overall costs of patient care is of increasing importance. Returning to the Exubera story, despite regulatory approval to market in the UK, Pfizer failed to gain approval earlier this year from the National Institute for Health and Clinical Excellence (NICE) as it could not convince the Institute of the product's cost-effectiveness. The visibility of likely costs of a new delivery system as well as the advantages it will confer are likely to be key decision factors for any company deciding to use it for its new drug.

In summary, the key take-away message is that there are times when the potential advantages to launching new drugs in new delivery systems outweigh the risks – good news for patients whose needs are not being met today.



"Perhaps 'should' and 'why would' a new delivery system be used are not the real questions; it is really more a question of 'when' and 'how' should one be used"

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Welcome to Drug Delivery Partnerships 2007!

DDP, the world's largest drug delivery and speciality pharma event takes place in January. Here, we give you a taste of this prestigious event

We are pleased to introduce you to the 11th annual Drug Delivery Partnerships (DDP) event, which will take place next January 22-24 at the Red Rock Casino, Resort and Spa, in Las Vegas, Nevada, US.

DDP is the world's largest international drug delivery and speciality pharmaceutical event. Its purpose is to drive and enhance pharmaceutical and drug delivery alliances. DDP's sessions tackle industry challenges, providing solutions towards more transparent competitive intelligence, strategic business transactions, innovative product development, and informative lifecycle management strategies – to ultimately improve business sustainability and growth.

DDP 2007 is the only event of its kind to combine a top-notch programme, a premium line-up of speakers, and optimal networking opportunities with more than 500 of the industry's key decision-makers.

Programme highlights

Senior Executive Keynote Panel: How Are We Creating Sustainable Business Models Out of Evolving Technology Companies?

Bioworld Columnist Cynthia Robbins-Roth, CEO of Norgine, Peter Stein, Senior Vice President, corporate development of Santarus, Michael Step, Executive Vice President of Medicis, Joseph P Cooper, and Managing Partner of Sanders Morris Harris, James Gale will examine the driving forces behind the move away from 'pure play' business models towards 'products, products, products'.

Growth Opportunities for Drug Delivery Systems: Development Trends for New Drugs in the Pipeline

Renowned director of economic analysis at the prestigious Tufts Center for the Study of Drug Development, Dr Joseph Dimasi will evaluate the economics of new drug development, and the implications for drug delivery systems. Dr Dimasi will review crucial factors like time, risks and costs, and will examine pipeline and in-licensing trends.

Wall Street Address: Stock Updates, Market Trends and Key Technologies to Watch

David M Steinberg, Managing Director, equity research, specialty pharmaceuticals and drug delivery for Deutsche Bank delivers his annual Wall Street perspective and offers both an assessment of the 2006 environment as well as the outlook for the remainder of the decade.

Drug Delivery Partnerships Trend Report 2007 – What's Fuelling Market Changes?

Roger Longman, Managing Partner of Windhover information, reports on the deals that have fuelled market changes, explores the strengths and the pitfalls of various deal structures, and examines the mergers and acquisitions that have had an impact on the drug delivery industry.

How the End-User Can Inspire New Opportunities: Bridging the Patient, Physician and Payer

Hamilton Jordan, White House Chief of Staff under President Carter, best-selling author of 'No Such Thing As a Bad Day', and four-time cancer survivor moderates this patient compliance panel. As a man who has always been in tune with the pulse of the nation and who has tackled not only political challenges but personal obstacles, Hamilton Jordan will share his extraordinary strength and vision to give the end-user's view on the importance of patient-friendly treatments.

The following pages – *Scrip's* official preview to DDP 2007 – will give you a taste of what you can expect from our expert speakers. This series of interviews provide indispensable opinion and advice on how to improve your drug delivery partnerships. To meet these industry experts face-to-face and hear their insights first-hand, be sure to join us in Vegas!

I look forward to seeing you there.

Miriam Glick
Programme Director – Drug Delivery Partnerships 2007

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“Tremendous diversity in types of devices”

Q Why do biotech and pharma companies choose to develop injection devices for biopharmaceuticals as opposed to non-invasive technologies such as inhalers or transdermal patches?

“Non-invasive technologies are presumably the most appealing drug delivery system to a patient, but the physicochemical properties of biologics make them difficult or impossible to administer by non-invasive routes. Extensive research and development would be required, costs would be significant, the timelines to commercialisation would be long, and there’s significant risk that the system will not be commercially viable. Device technologies are doable and pose less risk. Injection devices provide convenience, improve ease of use and may reduce the anxiety of an injection – these features make injections more tolerable than the conventional methods of administration. These benefits drive patient preference and can lead to increased market share. The downside I see is that although a company can use devices to improve the market share of their products, their competitors have access to similar technologies, so these systems may not provide a long-term competitive advantage.

Q Are injection devices valued differently in self-administration vs clinical settings?

“In self-administering markets, the value is patient convenience and ease of administration. Devices can ease and/or enable self-injection for patients who have dexterity limitations, needle phobia or that lack experience with injections. The increased convenience of a device can be particularly valuable in markets in which injections are frequent or chronic. In my opinion, convenience and ease of use factors aren’t as relevant in the clinical setting. Healthcare professionals are comfortable with needles. Safety, prevention against needle stick injuries, and enabling the clinic or hospital to comply with needle stick prevention laws or guidelines



Dr Donna French is executive director, drug delivery engineering at Amgen. She is responsible for the development and commercialisation of injection devices and aids with external partners. She has over 12 years’ experience in various aspects of injectable drug delivery and novel formulations for proteins.

is a key requirement and success factor in these settings. This is particularly true for the US, as federal legislation requires that healthcare professionals take appropriate actions to prevent accidental needle sticks.

Q How do you think the market for injection devices has evolved over the past decade?

“In the last decade, the tremendous growth of the biopharmaceutical market and increased competition in the industry has spurred the development and commercialisation of devices for injectables worldwide. I have several observations that I think demonstrate the growth of devices in the marketplace. Ten years ago, injection devices were primarily used for insulin, human growth hormone and some emergency antidote products. Within the last ten years, pre-filled syringes have entered the market and become a common dosage form for injectable products. In the last five years, numerous injection devices and user aids have been launched in at least ten new biopharmaceutical markets. Companies are launching second and third generation systems, and there is also a trend from reusable towards pre-filled disposable systems. Needle stick prevention devices are now marketed with clinically administered products – these devices were not on the market ten years ago. Another

observation is that a wider variety of device types are being developed and commercialised – ‘hybrids’ and variations of the conventional device types are being developed and have been commercialised. For the first time, there have been some new product launches in which the drug is available only in combination with a device and not in other more common conventional dosage forms such as vials. Lastly, there are more companies in the injection device and user aid business developing and marketing technologies to the biopharmaceutical industry than ever before.

Q How do you see the market for devices evolving over the next 5-10 years?

“I think that the insulin and human growth hormone markets today may be representative of the future for devices in biopharmaceutical markets. These markets have advanced drug delivery technologies and a long-standing history with devices in a highly competitive environment. Some companies offer as many as four devices for a single product and many companies do not provide the product in less convenient dosage forms such as vials. Eventually, I believe injection devices will become commonplace, and that there will be tremendous diversity in the types of devices on the market. ”

“Companies wait too long to seek a European partner”

Q How does the US differ from Europe when it comes to developing a novel delivery system applied to a well established active ingredient?

“All too often we are offered the European rights for products originally developed in the US and find that the development strategy was not optimised for the European market. This leads to delay and a loss of potential profits. Commercial and pricing strategies must be determined much earlier in Europe than in the US.

Europe is a single market with respect to the registration process and, consequently, a product will emerge with a single European label. However, that product will still need to compete in 25 national markets. Medical practice and competitors will be different and, for historic reasons, a single competitor may even have a different label across Europe. These national characteristics must be considered before beginning a development programme.

Europe has also always been a heavily price regulated market for pharmaceuticals. While the details of the systems are in constant flux and vary from country to country, the movement is all towards further decreasing prices. European companies need to build a robust pricing and reimbursement strategy and conduct clinical studies to generate the outcomes data necessary to implement that strategy. This is particularly true for products that combine novel delivery systems with well established pharmaceutical actives.

We frequently see companies develop products for the US marketplace on the assumption that the data will be adequate for European registration. In fact, these studies are rarely sufficient for the commercially successful launch of the product due to differences in the nature of Phase III trials, differences in the target label and the added hurdle of the reimbursement systems.

Q How has the European environment changed in the past few years?

“Perhaps the most significant change is that, despite the remaining national differences, there is an inexorable drive towards

Peter M Stein is the CEO and principal shareholder of Norgine, an independent specialty pharmaceutical company with operations throughout Europe. Stein previously co-founded and was vice-president of Invitron, a spin-off from the Monsanto Company.



a single European market. One registration and one label inevitably also leads to the need to execute one strategy across Europe. This is particularly true in the specialty pharmaceutical sector where so many of the scientific forums are now multinational. This means that a US drug delivery company must, more than ever, seek a single European partner for its product.

Q What should a US-based drug delivery company look for in a European partner?

“Developing a product for Europe will be complex and will take time and therefore, first and foremost, you must find a partner that you can work with for the long haul. Is their corporate culture compatible with your own? Does the company have the long-term strategic interest in your product? Does the top management of the company have the necessary, long-term, commitment to the project?

Once the cultural fit is there, look for companies with a proven track record across Europe in your specialty area. All too often, we see companies ask the wrong questions about their European partners. For example, many European companies have affiliates across multiple countries, which sell different products to different medical specialities. They will lack the integrated and consistent structure that you will need to develop and launch your product. Don't just ask about where they have an office or a company. Go one step further to look at the real structure of the business. Are the sales force targets consistent across Europe? Do they have experience in launching and

selling a product across Europe? Do they have the strong central management team to drive implementation across Europe and maximise the sales of your product?

Finally, look at the specialist knowledge. Is your partner able to manage the clinical studies that will be necessary across multiple markets? Are you confident that these trials will be done to the quality necessary for European registration? Will they support your regulatory submissions elsewhere? Will they be able to manage pharmacovigilance reporting across 25 countries and a similar number of languages in order to allow you to comply with both European and US reporting requirements? Choosing the best European partner should involve detailed due diligence about the company's operations and not just a simple comparison of the draft term sheets.

Q When should you look for a European partner for your product?

“As a rule, companies wait too long to seek a European partner. It is tempting to wait until the next Phase II or Phase III data are available and, of course, positive data will help to attract a partner. However, waiting for the 'best time' often involves delaying the European launch of the product and losing downstream value. This is particularly true when additional clinical or pharmacoeconomic studies will be required to support the European launch. If in doubt, find a partner now so that you can be sure that the project will advance in Europe in parallel with the US.

“Push pricing research earlier in development”

Q What are major challenges to opportunity valuation and dealmaking in new drug delivery technologies?

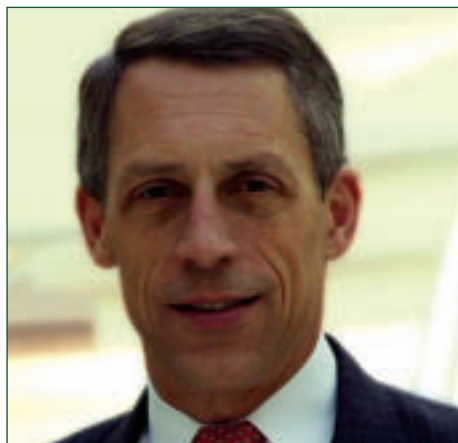
“There’s often a cultural divide between technology-driven and market-driven companies. The former may choose a convenient proof-of-principle demonstration of their drug delivery technology, using a well worn path to show their technology’s potential, unaware that other companies are doing the same thing. This puts the end-product in a competitive space with similarly-fashioned formulations of the same molecule. On the other hand, products may be much more competitive if companies considered a different molecule, so that their product is not compared with other formulations of the same molecule.

This technology-driven culture can be at odds with that of a market-driven company, which will view opportunities from competitive and market needs perspectives. The two perspectives need to come together in a successful opportunity. From a technology-driven perspective, companies need to educate market-driven firms on the value of their technology and how it can be applied. Market-driven companies need to understand the vision of the technology and then translate it into where the best market opportunity is. It may mean adjusting expectations on both sides. Drug delivery technology companies will do well to meet early with prospective partners to obtain market insights for future potential products.

Q What challenges and opportunities does the current market present to globally-focused organisations?

“The market preference for compounds may vary by global region, a result of the history of those compounds and how they were developed. If a compound was discovered in Europe and initially introduced there, it may not have made its way to the US or Japan, meaning there might be no history of that compound in these other markets.

A challenge with global deals is then not only establishing the right drug delivery platform from a technology point of view, but



Allen Downs is senior executive director of licensing and business development at Purdue Pharma. He has led teams that completed a biotech acquisition, a product co-development alliance, and several in-bound and out-bound licences.

also identifying the right compound, one that will be broadly accepted across all the major markets.

One approach is to select a compound that is well known in one country, but less familiar in other regions. That way, when it’s introduced into these other markets, it’s a new chemical entity that can be positioned in its own right. But that also creates a challenge because different regulatory hurdles have to be overcome. Additionally, introducing a product de novo means setting up the whole market education process so that the compound and technology are both appreciated. This is a conundrum to sort out for each market to identify the optimal choice.

There are many products in Japan that have not been introduced in the US or Europe because the companies that own them haven’t licensed them to western firms and have chosen not to introduce the drugs themselves outside Japan or the Asia region. There’s a class of companies, in the US at least, that scour the world for these regional compounds and identify opportunities to market them in other regions.

Q Are drug developers pushing ahead with innovation without considering how well their technologies would be reimbursed?

“Drug delivery-based improvements to well established therapies are not always well appreciated by payers such that there may not be a sufficient price premium available to provide an adequate return on the investment required to bring the innovation to market.

For example, Japan has historically been one of the most attractive markets in the world. However, Japan’s reference pricing system now caps the price the government will pay for drugs by a comparison with other country prices, irrespective of what might be a comparative price within the Japanese market. So even though there may be a precedent within Japan of higher prices, new products can be introduced at a much lower price level given the competitive nature of other markets.

We can’t assume that we can price new products at a premium to their predecessors. Pricing will in fact be more what certain key payers will bear. Those payers have a growing influence over what will become successful innovations and what kind of price premiums they’ll be able to support.

Drug developers should push pricing research earlier in the development cycle of an opportunity and evaluate what prices payers will accept before they invest significant sums into a technology. It also means looking at market segments where there is less competitive pricing, where there are fewer products and where there remain significant unmet medical needs that novel formulations could address.

Drug Delivery Partnerships in Europe

Now you know what you can expect from the US-based Drug Delivery Partnerships 2007, read on to find out about its European counterpart

Dear colleagues,

I would like to introduce you to the 6th annual European Drug Delivery Partnerships 2007, which will take place on May 15-16 in Germany.

This practical and strategic networking and partnering event for pharma, biotech and innovative drug delivery companies will, next year, bring together the leaders of the most innovative drug delivery companies from all over Europe in order to help you decide which strategic business transactions will profit you the most.

The event will enable you to:

- ◆ Examine the opportunities and challenges faced by the European drug delivery industry
- ◆ Better understand the business aspects of partnering with big pharma, in order to stay ahead of your competitors
- ◆ Understand what factors make partnerships successful, and build robust relationships that work
- ◆ Find out how pharma companies choose their technology partners and be the first on their list
- ◆ Be aware of the legal and regulatory aspects of drug delivery partnering in Europe and comply with industry standards

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This year's highlights

- ◆ NEW dedicated networking space for one-on-one business meetings. Forge new business alliances on site!
- ◆ Our NEW Evening Working Dinner on May 14, which will showcase the latest advances in protein and peptide delivery
- ◆ Speed networking breaks and extensive roundtable sessions to promote in-depth discussion on technologies and partnering

More networking opportunities

As a registered delegate of European Drug Delivery Partnerships, you will have the opportunity to meet and do business with delegates from the Scrip's co-located events: Developing and Managing Strategic Alliances and Licensing and Alliances in the Generics Industry.

I look forward to meeting you in May.

Tahira Rashid, PhD
Programme Director – European Drug Delivery Partnerships 2007



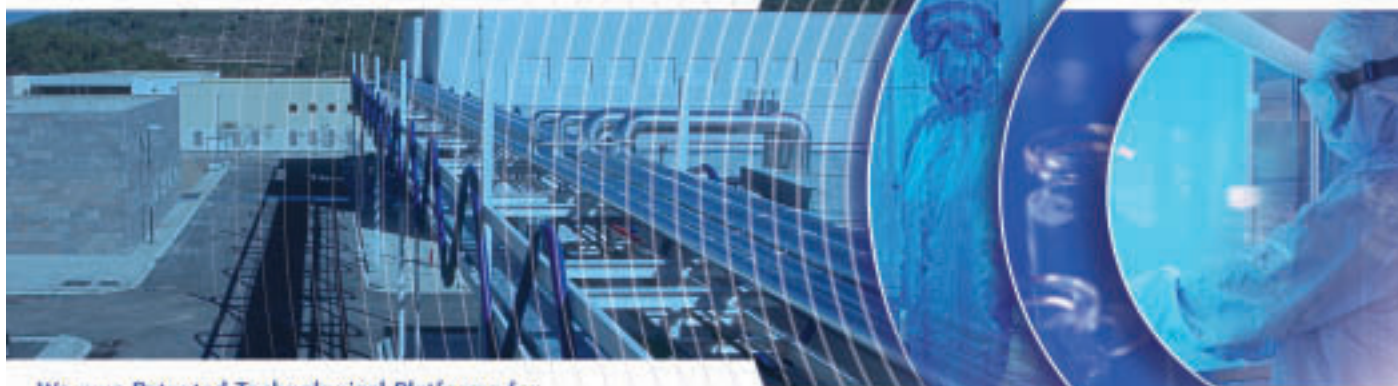
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Elan's Paul V Breen
 explains why we should be
 excited by the potential for
 nanotechnology in the
 lifecycle management arena

Small-tech – big potential

The US National Nanotechnology Initiative (NNI) defines nanotechnology as “research and technology development at the atomic, molecular or macromolecular scale leading to the controlled creation and use of structures, devices and systems with a length scale of approximately 1 to 100nm”.

Nanotechnology has gained recognition in many disciplines, including the pharmaceutical and drug delivery sectors. This recognition is illustrated by the fact that, in February 2006, US President George W Bush dedicated, through the NNI, US\$1.28billion of funding for nanotechnology for Fiscal 2007 – bringing the cumulative total invested since the NNI's inception in 2001 to over US\$6.5billion.¹

Optimising drug delivery

In the pharmaceutical industry, nanotechnology is being embraced particularly as a means of improving or enhancing the delivery of drugs. At present, approximately US\$65billion in annual drug revenues are accounted for by pharmaceuticals with poor bioavailability, which far too often results in inefficient treatment but also, more importantly, in increased risk of toxicity. Reducing drugs to nanoscale has the immediate impact of making otherwise poorly soluble drugs much more bioavailable, soluble and safer. Unsurprisingly, industry analysts predict that the drug market for nanotechnology products could be worth as much as US\$200billion by 2015.²

The poor bioavailability of pharmaceuticals is often caused by poor water solubility. Combinatorial screening programmes suggest that more than 40% of all active substances are affected.³ The result is that these compounds are not effectively formulated, which leads to a variety of problems. As well as having poor and highly-variable bioavailability, drugs with poor water solubility are more easily influenced by the patient fed/fasted state, can have a slower onset of action, and can cause the undesirable side-effects associated with co-solvents in

Figure 1: FDA approvals 2003-2005

	NCE's	New forms/combinations
2003	21	48
2004	31	70
2005	19	30

(Source: FDA approval lists, www.fda.gov)

parenterals. Any or all of these issues can lead to sub-optimal dosing and poor clinical performance. Nanotechnology has the potential to address these deficiencies and therefore provide significant value to pharmaceutical portfolios. Indeed, in accepting that 40% of any company's product portfolio may be poorly water-soluble, and that nanoparticulate technology can reduce or eliminate the problem, we find significant reason to become excited by the potential for nanotechnology in the lifecycle management (LCM) arena.

An industry under pressure

In 2005, despite pharmaceutical research spend being at an all-time high, the number of new chemical entity (NCE) approvals was down from previous years.⁴ For the period 2003 to 2005, NCEs accounted for only one in four products approved by the US Food and Drug

Administration (FDA) (see Figure 1). Indeed, in 2005, several major pharmaceutical companies failed to win approval for an in-house NCE.

These figures illustrate why LCM strategies have become key to maximising a branded drug's profitability. Employed properly and providing real patient benefits, they can enable a company to sustain revenue streams and fill gaps in its pipeline. So, for those products in a portfolio that have poor water solubility, application of a nanoparticulate technology to optimise the drug can be a worthwhile strategy to pursue.

The value of reformulations

As well as sustaining revenue streams and boosting pipelines, LCM strategies can be seen to save money. The cost of a reformulation is minimal compared to the cost of developing a 'next generation' product. The typical cost of a next generation product is, on average, US\$330million. A new formulation costs approximately US\$40million – and takes only 4-5 years to develop. This lesser cost can be seen as a saving if we consider that, according to a recent study, the overall perceived effectiveness of a next-generation is equal to that of a

Figure 2: Reformulations deliver excellent return in terms of investment and perceived effectiveness

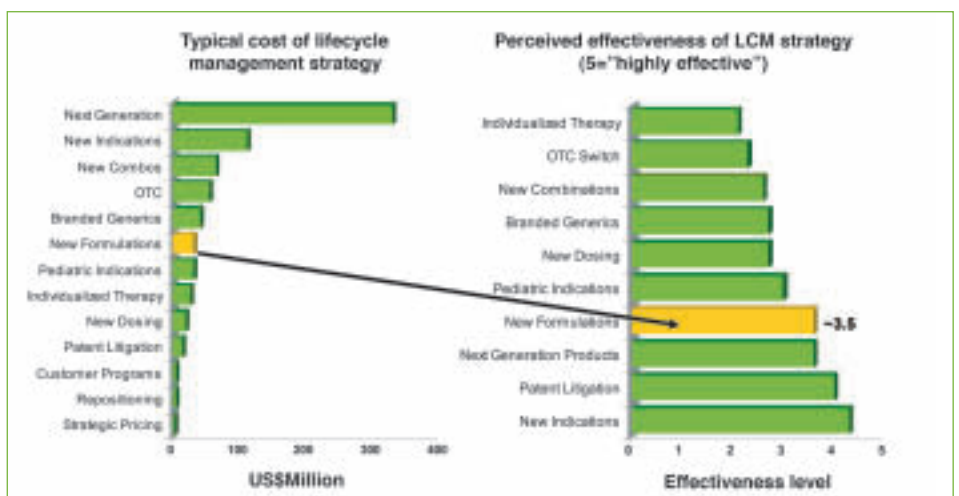
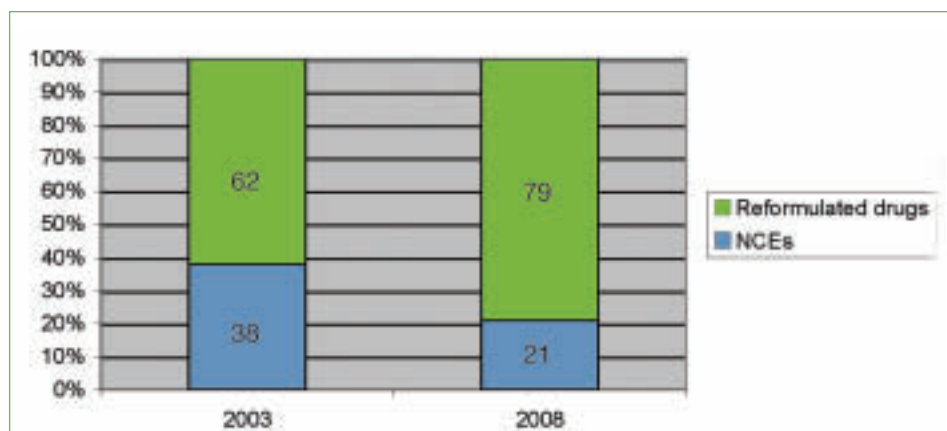


Figure 3: % share by type of total US drug revenue – 2003 and 2008 (expected)



reformulation (see Figure 2). The study, which surveyed many of the world's biggest pharma companies, compares the average costs and perceived effectiveness of each LCM approach.⁵

Unsurprisingly, this NCE/reformulation 'imbalance' is expected to continue. By 2008, sales of reformulated products (soluble and insoluble) are expected to account for 80% of total pharmaceutical sales in the US market (see Figure 3).⁶

Where are we now?

While the future seems bright for nanotechnology in the pharmaceutical industry, what of the present? Although many pharmaceutical products utilising nanotechnology remain in development, significant achievements have been made since the first nanoparticulate product, Rapamune, which was launched in the US in July 2001. This product, marketed by Wyeth, was developed using Elan's NanoCrystal Technology. The tablet formulation of this immunosuppressant (sirolimus) was previously available only as an oral solution, available in bottles or sachets. It required refrigeration and reconstitution in water or orange juice. The new tablet, developed with

Elan Drug Technologies' (EDT's) key business is focused around product development and optimisation. Their lead technology, NanoCrystal Technology, which has been incorporated into common dosage forms, has the potential for substantial improvements to the drug performance of poorly water-soluble compounds. Now successfully used to launch four products in the US, the NanoCrystal Technology has contributed to more than US\$1.3billion in annual in-market sales of these drugs. For more information on EDT's range of technology solutions go to www.elan.com/EDT.

NanoCrystal Technology, provides patients with more convenient administration and storage.

Since the launch of Rapamune, a number of nanoparticulate products have been launched, many of which are LCM plays. These include:

- ◆ Three additional products, all of which are delivered orally, using Elan's NanoCrystal technology: Emend by Merck in 2003, TriCor by Abbott in 2004 and Megace ES by Par in 2005.
- ◆ The first topical product, Estrasorb developed by Novavax, in 2004.
- ◆ Abraxane, an injectable formulation of paclitaxel, in 2005, by Abraxis Biosciences.
- ◆ Triglide, incorporating Skyepharma's IDD solubilisation technology.

These products are enjoying considerable success. Their annual combined sales are estimated to be in excess of US\$1.4billion.⁷ For nanotechnology to have a significant impact on poorly water-soluble molecules the technology must be:

- ◆ Capable of being rapidly utilised in discovery at the milligram scale, using a standardised cost-effective approach;
- ◆ Up-scalable to commercial production, and use excipients generally regarded as safe (GRAS);
- ◆ Capable of being formulated into conventionally acceptable dosage forms, such as tablets, using conventional secondary processing equipment;
- ◆ Capable of being combined with other drug delivery technologies including oral controlled release, delayed release and pulsatile release; and
- ◆ Provide proprietary protection.

In the past, companies may have been able to succeed without capitalising on rigorous portfolio management. But in today's market and regulatory climate, portfolio optimisation strategies will become essential if a product is to achieve its true potential. Over the next

decade the benefits of enhancing the dissolution rate of poorly water-soluble compounds through nanoparticulate technologies will be more greatly appreciated as a prudent LCM strategy.

Trademarks

NanoCrystal Technology is a registered trademark of Elan Pharma International Limited, Ireland.

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Paul V Breen is executive vice-president and head of Elan Drug Technologies.

Coatings for protection

Micro-encapsulation technology is becoming increasingly popular in the pharma industry worldwide owing to its many applications and the advantages it offers over traditional techniques, says Nabiqasim's Dr Abdul Majid

Micro-encapsulation is a process by which small particles or droplets are coated in order to produce capsules that shield the active ingredient from the surrounding environment. Such products are common in the pharmaceutical industry, especially since they allow the slow release of medicines. They can also perform a number of other functions, including controlled and targeted drug delivery of active pharmaceutical ingredients (APIs), with the coating material varying according to where in the gastrointestinal tract the drug is designed to be released.

Coatings are also used to mask the bitter or unpleasant tastes and/or odours of many APIs (the hot-melt coating process may be applied to taste-mask granules for the development of tablet formulations) and to protect APIs from moisture. APIs sensitive to the gastric environment, such as omeprazole, esomeprazole and pentaprazole, can be formulated as coated pellets, ready to fill into capsules. The technology likewise enables toxic materials to be handled safely.

The preparation of a micro-encapsulated product requires, first of all, the recognition of a need for micro-encapsulation, whether in order to improve an existing product, or to develop a new one. Next, a shell material that provides the desired release characteristics must be identified. Finally, a process to prepare the microcapsules must be selected.

The substance that is encapsulated may be called the core material, active ingredient, agent, fill, payload, nucleus or internal phase. The material encapsulating the core is referred to as the coating, membrane, shell or wall material. Microcapsules may have one wall, or multiple shells arranged in varying thicknesses around the core. Many hydrophilic and lipophilic shell materials are available and meet food and drug regulatory requirements, such as proteins, hydrocolloids, gums, waxes, fats, organic polymers and resins.

The micro-encapsulation technique chosen will depend on purpose. Substances may be micro-encapsulated with the intention that

the core material be confined within capsule walls for a specific period of time. Alternatively, core materials may be encapsulated so that they will be released gradually through the capsule walls – with the wall dissolving or melting, or with the material being diffused through the wall – or more abruptly, when the wall is ruptured. Less common release mechanisms include ablation (slow erosion of the shell) and biodegradation.

Micro-encapsulation processes are usually categorised under one of two headings: chemical and mechanical/physical. These labels can be misleading, as some processes classified as mechanical may involve or even rely upon a chemical reaction, while some chemical techniques depend entirely on physical events. It may be useful to consider whether the capsules are produced via chemical processes in a tank or reactor containing liquid, or by mechanical or physical processes, which employ a gas phase as part of the encapsulation and rely chiefly on commercially available devices and equipment to generate microcapsules. Some commonly employed processes are briefly discussed below.

Spray drying

Spray drying is a mechanical micro-encapsulation method developed in the 1930s. An emulsion is prepared by dispersing the core material (usually an oil or material immiscible with water), into a concentrated solution of wall material until droplets of a desired size are attained. The resultant emulsion is pumped through a rotating disc into the heated compartment of a spray drier. There, the water portion of the emulsion is evaporated, yielding dried capsules of variable shape that contain scattered drops of core material. The capsules are collected through continuous discharge from the spray-drying chamber. This method can also be used to dry small micro-encapsulated materials from aqueous slurry, which are produced by chemical methods.



Coatings can also be used to mask unpleasant tastes

Fluid bed coating

Fluid bed coating technology, another mechanical encapsulation method, is restricted to encapsulation of solid core materials, including liquids absorbed into porous solids. This technique is used extensively to encapsulate pharmaceuticals. Solid particles to be encapsulated are suspended on a jet of air and sprayed from below with a liquid coating material. The capsules are then moved to an area where their shells are solidified by cooling or solvent vaporisation. The process of suspending, spraying, and cooling is repeated until the capsule walls are of the desired thickness.

Pan coating

In pan coating, solid particles are mixed with a dry coating material. The temperature is raised so that the coating material melts and encloses the core particles; it is then cooled so the

material solidifies. The coating material can be gradually applied to core particles tumbling in a vessel, rather than being mixed with the core particles from the beginning of the process. The temperature of the inlet air can be adjusted within a range of 25°C to 80°C, depending on the requirement and temperature sensitivity of the material to be coated. Temperature-sensitive materials are coated at between 25°C and 35°C. A three-component nozzle emits a very fine spray of

Surge Laboratories, based in Pakistan and a member of the Nabiqasim Group, performs micro-encapsulation of various molecules, employing the latest technologies and equipment. The company also has its own development facilities and offers contract/toll manufacturing/development services to its customers worldwide.

solution, applying a thin coating to each granule, so they are of homogeneous size and both evenly and thoroughly coated. A microclimate feature within the nozzle helps produce a good spray cone while keeping the front part of the nozzle clean and ensuring a continuous flow. Dynamic filters enable recirculation of the coating product.

Micro-encapsulation is now coming into play in nearly all pharmacological groups. These techniques have become common in Europe and US, and are also gaining popularity and market share in Asia.

Dr Abdul Majid is chairman of Pakistan's Nabiqasim Group. His knowledge and experience of the API and formulations market, as well as of the pharma industry as a whole, have helped establish Nabiqasim as a leader in the manufacture and marketing of pharmaceutical and healthcare products for Asia, the Middle East and Africa.

Placebo Pellet ←→
Drug Layer ←→
Protective Layer ←→
Enteric Layer ←→



MICROENCAPSULATION

Nabiqasim is leading Pakistani Pharmaceutical Group, having 40 years experience in Pharmaceutical manufacturing, formulations & marketing. More than 165 products covering psychiatry, Cardiology, Neurology, Orthopedics, Pediatrics, Dermatology, Gynecology, Medicine, Surgery, ENT, Laxatives and ophthalmology in all required dosage forms are manufactured at groups cGMP compliant production facility having segregated sections for cephalosporin, prostaglandins & hormones. Nabiqasim's R&D department is working successfully to develop new formulations, drug delivery systems and microencapsulation of various molecules. Group also offers consultancy services regarding drug formulation, technology transfers and Stability studies. Nabiqasim is exporting products to Far-East, Central Asian, African countries & also offers contract/custom manufacturing services.

Surge Laboratories (Nabiqasim Group) is focused to develop various microencapsulated products and have their own development lab with latest technology equipment system which can perform series of functions like drying, mixing, granulation and coating etc.

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Market trends: self-injection devices

Ypsomed's Ian Thompson reviews the development of self-injection technology and examines the key features incorporated into modern-day devices, as well as future developments

The market for self-injection devices – pens and auto-injectors – continues to show above-average growth as a result of several factors. For one thing, the surge in biotech-based research means that many more protein therapeutics are reaching the market, driving demand for injectable products as a whole. Also, the increased incidence of diseases such as diabetes and the availability of therapies for previously untreatable conditions are expanding the injectables market. The advanced features of modern self-injection devices are making them much more acceptable to patients. If patients can self-administer their own medications, then not only is it more convenient for them, it also saves on healthcare resources and costs – making self-injection much more cost-effective.

Pens and auto-injectors

Pen injectors are essentially sophisticated 'cartridge-based' syringes. The first pens were introduced for insulin in 1984 and were developed for the reliable and accurate self-administration of the first wave of biotech molecules, mainly insulin and human growth hormone (hGH). Today, insulin still dominates the market for self-injection devices, followed by hGH and newer therapies such as fertility treatment (FSH) and osteoporosis (PTH). During the 1990s, the insulin pen market became segmented with the introduction of disposable pens and reusable pens incorporating improved handling functions and electronics.

These therapies require frequent, often daily, manual injection with weight-based dosing or dose titration, and injections are repeated until the cartridge is empty – usually after one to two weeks. The drugs in the multiple-dose cartridges require the use of preservatives, while individual dose volumes are typically 0.5 ml or lower. Pen injector patients are



Pens to cover a range of dosing needs and cartridge types

accustomed to injecting themselves manually with 29-31G pen needles and their desire for discreet and easy-to-use devices has traditionally overshadowed the need for automated needle insertion or injection.

Auto-injectors have been on the market as long as pen injectors but, until the 1990s, their use was restricted to emergency situations such as epinephrine for treating anaphylactic shock and sumatriptan for treating migraine. Reusable auto-injectors have been used since the 1990s for syringe-based hormone replacement therapies, and are increasingly being used for newer waves of biotech molecules as prefilled formulations became available for example, interferon for treating multiple sclerosis (MS). The first disposable auto-injector for a therapeutic protein was launched in 2005 by Amgen for its EPO product, Aranesp.

Auto-injectors, as their name implies, automatically insert the needle and perform the injection – typically spring driven – and are usually designed for use with fillable or prefilled syringes. A key requirement for auto-injection is the need for liquid-stable formulations in a prefilled syringe or cartridge-based drug reservoir. Some of these drugs are injected daily, but many long-acting therapeutics are now injected weekly or even less frequently,

particularly those for treating autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. Most of these newer drugs do not contain preservative (mono-dose formulations) and have comparatively large injection volumes of 0.5 to 1.0ml.

Factors influencing development

There are a range of patient and technological factors influencing the further development of pens and auto-injectors which are blurring the lines between the two types of devices.

Firstly, the fear of injections (needle-phobia) has spawned the development of needle hiders and automated needle insertion systems for pens, and auto-injectors for prefilled syringes. Studies performed with needle-naïve patients confirm that up to half of patients are unwilling or reluctant to inject themselves. As patients gain experience giving injections the proportion with needle phobia falls to 10-15%. Among insulin-dependent diabetics who inject themselves very frequently the proportion of needle phobic patients is less than 10%.

Secondly, whether a prefilled syringe or cartridge-based injection is being performed the need for needle safety is essential for injections performed in the clinic or at home. This has led to the development of safety pen needles for pen injectors, safety syringes for use

with prefilled syringes and disposable auto-injectors.

Thirdly, finer needles for pen cartridges and prefilled syringes are reducing the pain of injection. The introduction of 31G pen needles has however increased the force required to push the drug through the fine cannula – this means that for larger volume pen injections some form of energy assisted injection mechanism can help the patient to perform the injection more easily. Prefilled syringes are being equipped with finer thin-wall 29G needles, which have the same flow-characteristics as traditional 27G needles.

Fourthly, many new biotech drugs are in a freeze-dried state and not available as a liquid in a prefilled syringe. The dual-chamber cartridge provides a convenient means of self-injecting these drugs. In the case of multidose formulations such as hGH, pens have been available for many years. But many of these new lyophilised drugs are mono-dose formulations, injected immediately after reconstitution. If the dose needs to be varied, a pen-like dosing device used with a safety pen needle is ideal.

Cartridge-based systems

Patient needs for a broad range of pen therapies require pens with a range of functionality. The pen systems can be broken down into the following categories.

Reusable and disposable insulin pens incorporating all the functionality expected by diabetics, such as easy dose-setting and clear last-dose indication when the cartridge is nearly empty. For reusable devices simple cartridge exchange is essential. Above all the dose display must be large and easy to read, while the device itself needs to suit the target patient group. Insulin pens are today very much a consumer product where design, look and feel are very important. Accessories and options offered to diabetics, such as needle-hiders, auto-inserters and electronic displays, are also available for pens in other therapeutic areas. Safety pen needles developed for insulin injections performed in care-giving situations can also be used for other pen therapies.

Pens are also available to deal with dosing requirements for non-insulin therapies. Many therapies require weight-based dosing, but once this dose is defined, the patient does not have to change the dose. Dose-memory pens simplify handling so that the patient only needs to set the required dose once. For all subsequent injections the patient only needs to pull and push the dosing knob until the cartridge is empty. Other therapies require very small doses and the pen must incorporate

mechanisms to clearly communicate that the dose has been set and injected.

The use of dual-chamber cartridges puts special demands on the pen system in terms of intuitive reconstitution, priming and dose-setting steps. It is very important for the patient that these steps are therefore easy to learn and always performed in the correct order.

Which pen device is ultimately selected depends on the dosing demands and patient preferences.

Scale of convenience

In conjunction with efforts to move mono-dose formulations from the vial into the prefilled syringe, pharma partners are looking for easier ways of giving injections. A simple prefilled syringe alone can bring much convenience to a self-injection therapy. When used with a passive safety syringe the clinician or patient is provided with needle safety, and an injection aid, making it easier to perform the injection. The passive safety syringe devices – with their low activation forces – can also be used in conjunction with new generation reusable auto-injectors. This has the advantage that the same safety syringe (single SKU – stock-keeping unit) can be used in both the clinic and home environment with the simple addition of an auto-injector for home care without the cost and risk of packaging every syringe in a disposable auto-injector.

In terms of convenience, the fully disposable auto-injector device is the obvious gold standard for self-injection. Here, the prefilled syringe is already packaged in the auto-injector, providing both ease of use and convenience for the patient. All the patient needs to do is remove the device cap, press the device against the skin and start the injection process. The device automatically performs the insertion of the needle and the injection. After injection, the needle is automatically covered and made safe, as the device is removed from the injection site. With disposable auto-injectors a clear indication of the device status before, during and after injection is important; the handling should be intuitive and the device should give visual and audible notification that the injection has been successful.

Ultimately, which device is selected from the prefilled ‘scale of convenience’ (see Figure 1) depends on the competitive environment, the proportion of patients self-injecting, and their specific needs.

Patient-driven development

It is the patient who drives the continued development of new self-injection devices and

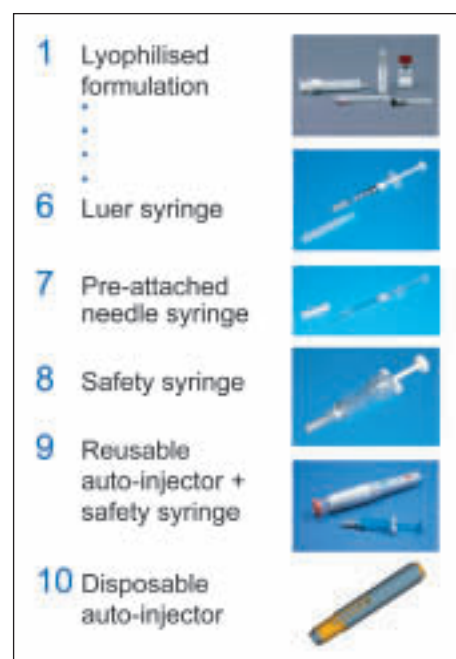


Figure 1: ‘Scale of convenience’

this is why device companies are developing standardised device platforms that have been tried and tested with patients to cover their basic needs of ease of use, safety and reliability. The diverse range of therapies and needs of pharma partners mean that the device manufacturers must be in a position to provide tested and standardised devices at short notice which can then be customised to the needs of each drug, therapeutic area and patient segment as needed.

Beyond the patients’ basic needs there are a range of special needs depending on their age and clinical condition. For example patients with visual impairment (such as diabetics or the elderly) have special requirements, as do those with age-related or motor disabilities (multiple sclerosis, rheumatoid arthritis, cancer). Care about needles is an issue with AIDS and HCV (hepatitis C virus), while 10–15% of the population can be expected to have needle phobia.

In summary, the market for self-injection devices – pens and auto-injectors – continues to grow at above-average rates, based on patent-protected technical designs customised to patient and pharma companies’ specific needs. Novel technical features to provide safe and reliable use have by no means been exhausted, and the choice of the correct device requires careful selection and close collaboration between the patient, the device company and the drug manufacturer.

Ian Thompson is manager business development at Ypsomed AG.

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E-patch technology, an innovative
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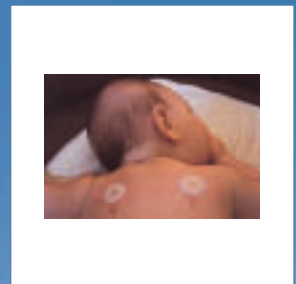
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Product focus: The E-patch

Bertrand Dupont, directeur industriel of DBV

Technologies, describes the properties and benefits of DBV's unique cutaneous drug delivery patches, which combine powder and electrostatic technologies for epicutaneous or transcutaneous delivery

Quite simply, the E-patch is a 'dry patch' electrostatic technology that stores, on the cutaneous device, active ingredients in powder form. The ingredients are delivered when the patch is stuck to the skin. The E-patch consists of a non-adhesive polymeric support (backing) stuck on the skin by a peripheral adhesive crown. The backing is a biocompatible polymer film with cutaneous tolerance. Although the technology is simple to describe it is a significant advancement to existing cutaneous systems!

Creating an E-patch

First, the active ingredient must be in a powder form, with a controlled particle-size distribution. It is 'powdered' (sprayed) onto the support using a proprietary process. During this powdering step, the powder particles become, and remain, electrically charged. The active ingredient is therefore absorbed and held in place on the backing by electrostatic attraction forces.

The amount of powder required will vary from one compound to another. Typically, from 600 µg to 1000 µg of powder can be adsorbed on a 1cm² backing. Indeed, the powder must be perfectly matched to the backing. This matching process may require the application of special treatments to the backing – for example, employing an electret (see Figure 1). Application of electrets and other special

treatments (such as grinding) have no impact on the active ingredient.

Delivering the drug

Once the patch has been applied, its backing forms an airtight chamber with the skin, which collects natural water loss. Occlusion results in rapid hydration of the powder which consequently loses all adhesion to the plastic support. When the substance has dissolved, the active ingredient comes into contact with the skin. Diffusion is usually very quick. This original kinetic is nevertheless dependent on the size of the molecules and the way in which they travel through the cells of the skin.

It is also possible (and often necessary) to purposely alter the characteristics of an E-patch – its occlusive volume, the size of the gap between the backing and skin, the powder grading, its permeability etc. Altering these elements will affect the solubilisation time of the powder, the amount of powder adsorbed on the backing and the acceptance of the patch by the skin.

For instance, Diallertest Milk, a diagnosis patch-test for milk allergy (and the first E-patch application, now sold in French drugstores as well in Mexico the Middle East and Australia) is designed to stay in contact with children or babies' skin for 48 hours. The occlusive room, therefore, is not too tight – to prevent the backing being in direct contact

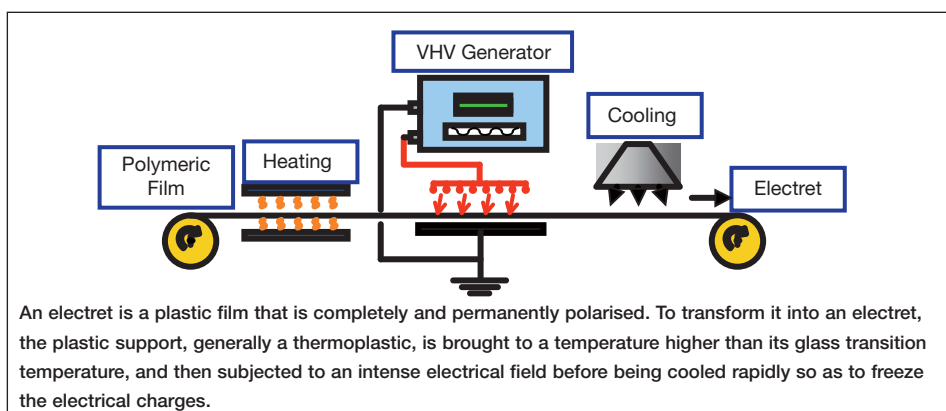


Figure 1: The electret

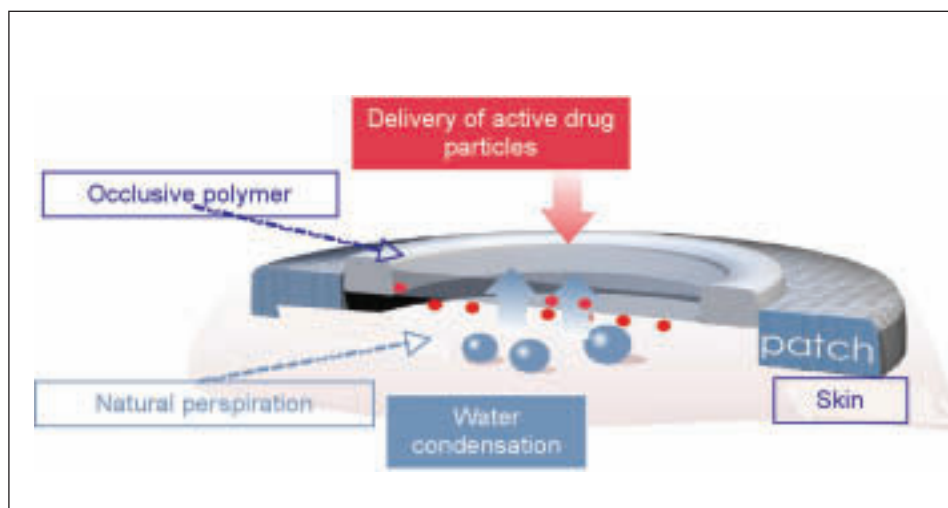


Figure 2: The E-patch – delivering the active ingredient

with the skin for too long, and causing irritation. In addition, the backing is water-permeable enough to prevent soaking as moisture builds over the application period.

On the other hand, for applications which do not require a long application period, the backing of the patch is almost in direct contact with the skin – provoking very quick dissolution and absorption of the active ingredient by the skin (see Figure 3).

Why use the E-patch?

As well as the flexibility of its design, the E-patch has many characteristics that mean it has a variety of applications.

- ◆ **Long-lasting and stable:** the active ingredient is a dry powder without adhesive or solvent; therefore it is perfectly suitable to fragile molecules such as proteins and peptides. It is deposited in a dry atmosphere and packaged in a dry and waterproof bag. It is easy to preserve, whatever the storage conditions – even if of organic nature or particularly fragile. It can be kept at room temperature and does not require a cold chain. Typically, the shelf life of an E-patch is two years.
- ◆ **Economical:** unlike reservoir or matrix patches which require a large amount of the active ingredient, E-patches retain only a very small amount of the active ingredient after use. The quantity of active ingredient deposited on a dry patch is the dose required, no more no less.
- ◆ **Safe:** the patch cannot be re-used and does not cause pollution.
- ◆ **Efficient:** unlike most of the patches on the market which deliver a more-or-less constant flow of active ingredient, the E-Patch can be used as a one-dose-release patch.

When to use the E-patch

Allergy diagnosis: E-Patch is a perfect technology for the Atopy Patch Test (APT) – indeed, this was its first diagnostic application. Every food-allergen or pneumo-allergen powder can be properly spread on an E-patch. Specificity and sensitivity of ‘E-patch-tests’ are at least as high as other patch-tests.

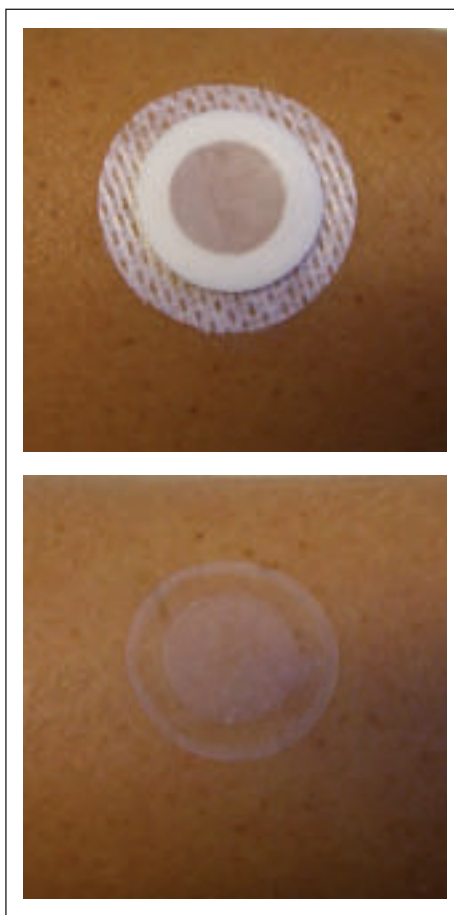


Figure 3: Altering the characteristics of an E-patch changes its effects

Epicutaneous immunisation: E-patch technology provides ideal access to the skin immune system (SIS). Dominated by densely distributed and potent antigen presenting cells, it can be stimulated to cause immune system responses. Practical advantages of epicutaneous immunisation using a patch include:

- ◆ Needle-free systems improve patient compliance,
- ◆ Avoidance of transmission of disease,
- ◆ Stabilisation of antigens, avoiding the cold chain.

Transcutaneous delivery

The traditional patch technique has some drawbacks:

- ◆ The use of adhesive as a solvent may denature some active ingredients which, consequently, cannot be administered transdermally,
- ◆ The absorbed dose depends on the length of the application period,
- ◆ A significant quantity of active ingredient remains after use.

As discussed above, E-patch technology, can overcome these problems. With an E-patch:

- ◆ There is very little of the active ingredient left on the patch after use,
- ◆ There is no risk of overdose,
- ◆ ‘Peak’ action kinetics are possible with ‘fast transdermal passage’ molecules, using a low quantity of active ingredient,
- ◆ Fragile active ingredients can be used in their native state, without risk of modification by any interaction with a solvent or an adhesive (peptides),
- ◆ There is little waste and environmental damage,
- ◆ Large scale production is economical.

For more information on DBV Technologies and the E-patch see our company profile opposite.

DBV Technologies

Specialising in epicutaneous vaccination: desensitisation, biodefence, mass vaccination



Established in 2002, DBV Technologies is a private limited company. In January 2006, DBV raised €12.3m, with Sofinnova (leading investor) and Apax.

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 Bertrand Dupont, CTO, Ingeneer (founder)
 Dr Jorge Ronco, CSO (former Corporate Responsible at Pasteur Mérieux Connaught)
 Dr Pierre-Henri Benhamou, Paediatrician – gastroenterology, nutrition (founder)

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Prof. Christophe Dupont, Chairman, Professor of Paediatrics, Head of Neonatology and Nutrition Department, Hospital Saint Vincent de Paul, Paris (founder)

PRODUCTS/SERVICES

DBV is working towards painless delivery of many other drugs and vaccines via the skin. In particular, DBV aims to successfully cross the protective outer layer of skin and to deliver fragile molecules (peptides and proteins) in their native form, without excipients.

The E-patch

- E-patch technology devices are innovative, cost-effective and easy to use
- E-patches deliver larger and fragile molecules on (epicutaneous) or into (transcutaneous) the skin, for controlled, pain-free delivery of drugs or vaccines.
- Patch technique is particularly adapted to epicutaneous treatment, taking advantage of the huge immunological potential of the skin.

MAIN AREAS OF ACTIVITY

- Diagnostics: (non-invasive kits for testing for milk, dust-mite and wheat allergies):
 Diallertest milk is DBV's first product – launched in France in June 2004
- Epicutaneous vaccination: biodefence, oncology
- Cosmetic: skin treatment patches
- Desensitisation treatment for food allergy (under development)
- Biochemical research in allergy, immunology and drug delivery
- Industrial development (manufacturing process, machines and production)

Competitive advantages of E-patch technology:

In allergy diagnosis and desensitisation:

- Allergen applied without excipients
- Easy to use, apply and read
- Standardised and reliable
- Safe, no risk of systemic shock

In epicutaneous administration of active ingredients:

- Administration of fragile molecules
- Storage at ambient temperature
- Very low amount of active ingredient remaining on the patch after use

CONTACT INFORMATION

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Baxter Healthcare Corporation



Baxter Healthcare Corporation's award-winning BioPharma Solutions business is dedicated to pharma and biopharma customers, offering contract services and proprietary technologies focused on parenteral (injectable or pulmonary) delivery. Contract services include: development, form/fill/finish into syringes, vials, and cartridges, lyophilisation and cytotoxics manufacturing. Proprietary technologies include NANOEDGE dispersion and PROMAXX microsphere formulation technologies and enhanced packaging.

CONTRACT SERVICES

Recipient of the 2006 pharmaceutical Facility of the Year Award, Baxter's Bloomington facility has expanded capacities for syringe and vial filling/finishing, making Baxter the global SCF leader in prefilled syringes. We have added new capability in cartridge filling/finishing, as well as a fully automated kitting line. Our newest lyophilisation and vial-filling lines are specifically designed for biologics; lyophilisation capacity has increased along with the advancement of the Lyophilisation Center of Excellence. Baxter can also provide analytical and microbiological services as well as validation and regulatory assistance.

In our German facilities, we can take you from scale-up to commercial production for dedicated cytotoxic contract services. Our state-of-the-art facility features advanced aseptic processing using barrier isolator technology. Our technologies include lyophilisation, aseptic liquid vial filling, dry powder vial filling and sterile crystallization. Other services include stability storage, validation and documentation, and analytical services.

Baxter is a proven CMO provider offering best-in-class parenteral outsourcing solutions including:

- Reliable supply – complete contract manufacturing resources.
- Expertise – highly skilled solutions for a streamlined path to market.
- Bottom-line results – lower expenses and increased revenue.

PROPRIETARY FORMULATION TECHNOLOGIES

NANOEDGE dispersion technology offers innovative formulations for your solubility challenges and is applicable for multiple routes of administration. It reduces the particle size of most drugs to nanometer size, which can enhance a drug's saturation solubility and dissolution rate and eliminates the need for undesirable cosolvents.

The PROMAXX microsphere technology is a unique, elegant and cost effective formulation platform, tailored to fit your specific requirements. It is applicable to a broad range of molecules – from small molecules and nucleic acids to peptides and proteins. PROMAXX technology can offer high drug loading and precise particle size control and enable dosing flexibility across various administration routes.

CONTACT INFORMATION

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The Baxter logo, featuring the word "Baxter" in a bold, blue, italicized sans-serif font.

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The power of pulmonary delivery with PROMAXX microsphere technology.

By giving you precise control over microsphere size and uniformity, PROMAXX facilitates development of pulmonary formulations. This versatile platform works with a wide range of compounds, from proteins and peptides to small molecules.

Plus, you can trust the experienced Baxter team to work with you to solve your unique formulation challenge.

Add powerful new potential to your drug pipeline with PROMAXX. To learn more, visit www.baxterbiopharmasolutions.com. For specific requests, send an e-mail to PROMAXX@baxter.com, or call 1-800-422-9837.

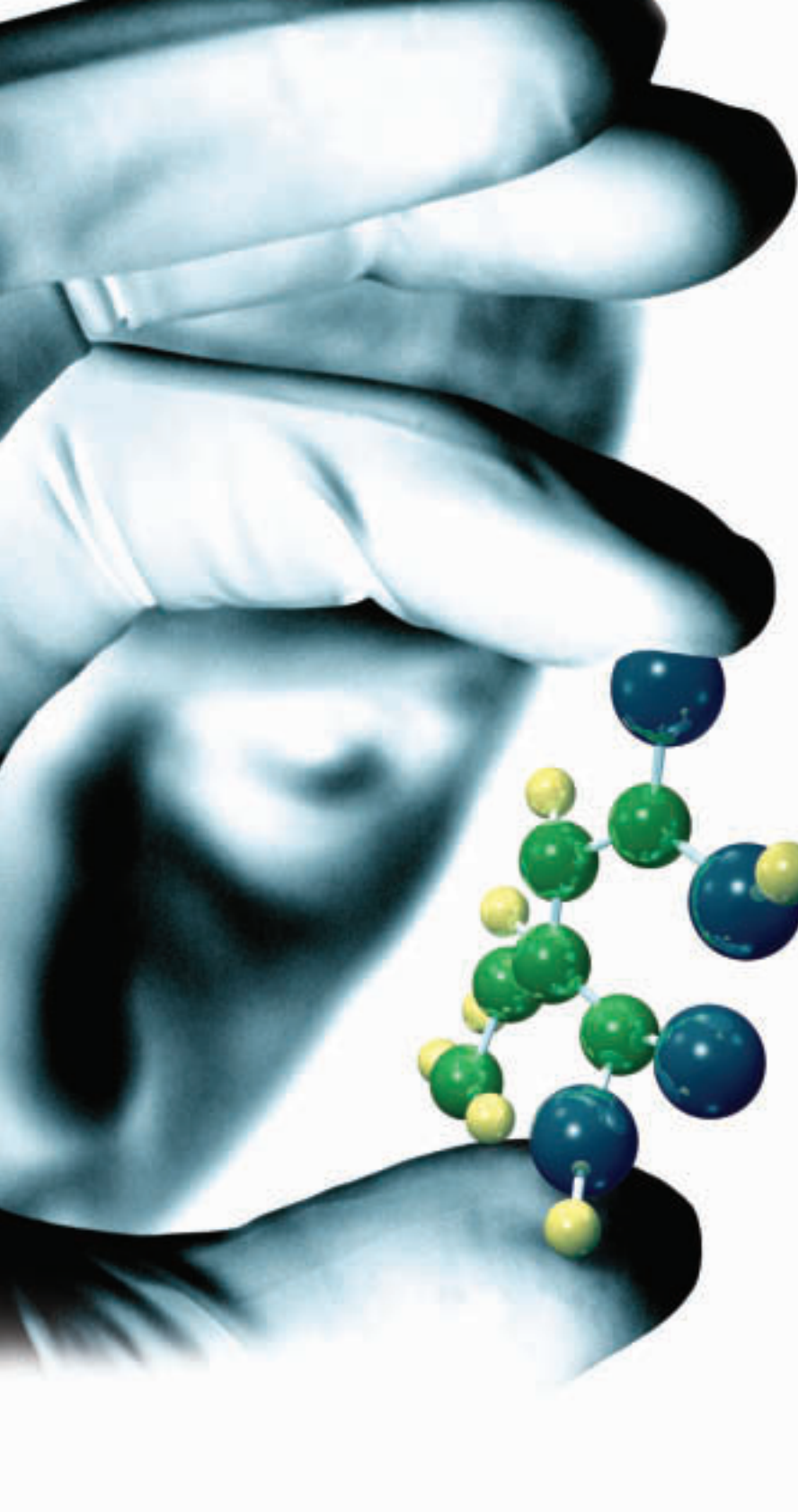


PROMAXX microsphere technology delivers unique particle size control ideal for inhalation therapies.

BioPharma Solutions

Baxter

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