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# Phosphagenics (POH)

Unique drug delivery technology

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**Authorisation**

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**Recommendation**

**Spec Buy**

**Price**

**\$0.125**

**Target (12 months)**

**\$0.40**

Phosphagenics (POH) is commercialising a transdermal drug delivery technology called TPM. Using patches and gels, the technology has generated strong clinical data for both large and small molecule drugs, and there is the potential to license the product from 2011 for the delivery of the analgesic drug oxycodone. Other potential applications include insulin, diclofenac, lidocaine and tretinoin.

**Expected Return**

Capital growth **220%**

Dividend yield **0%**

Total expected return **220%**

**Company Data & Ratios**

Enterprise value **\$82m**

Market cap **\$93m**

Issued capital **739.7m**

Free float **100%**

12 month price range  
**\$0.05-\$0.175**

GICS sector

**Healthcare Equipment and Services**

**Transdermal drug delivery technology that works**

Over the last six years POH has demonstrated clinically that its TPM technology, based on phosphorylated Vitamin E, can transdermally deliver therapeutic doses of drugs that until now have had no transdermal option. With TPM patches working efficiently and without skin irritation or inflammation, there is the potential for POH to develop the world's first patches for the analgesic drug oxycodone (which represents a US\$3bn market in the US alone), and for insulin (a US\$13bn market globally). POH is also targeting a number of other drugs that are presently without transdermal options and where there are significant revenue opportunities.

**A near-term payoff**

POH is currently preparing to conduct a pivotal trial of TPM for oxycodone delivery which we think can yield late stage data and a licensable product by 2011.

**Commercial management**

POH's management team, including joint CEOs Harry Rosen and Dr Esra Ogru, have done a good job over the last six years in positioning TPM for clinical and commercial success. We believe they have the smarts to bring about a suite of solid, value-accretive licensing deals for TPM beginning with oxycodone.

**Target price 40 cents attainable with clinical data**

With this note we are initiating coverage of POH with a 40 cent price target and a Speculative Buy recommendation. We value POH at 41 cents base case and 81 cents optimistic case using a probability-weighted DCF valuation, diluted for a further \$15m capital injection. As the near-term nature of TPM becomes apparent, helped by the emergence of further clinical and pre-clinical data, we expect POH to be re-rated by the market.

**Absolute Price**



SOURCE: IRESS

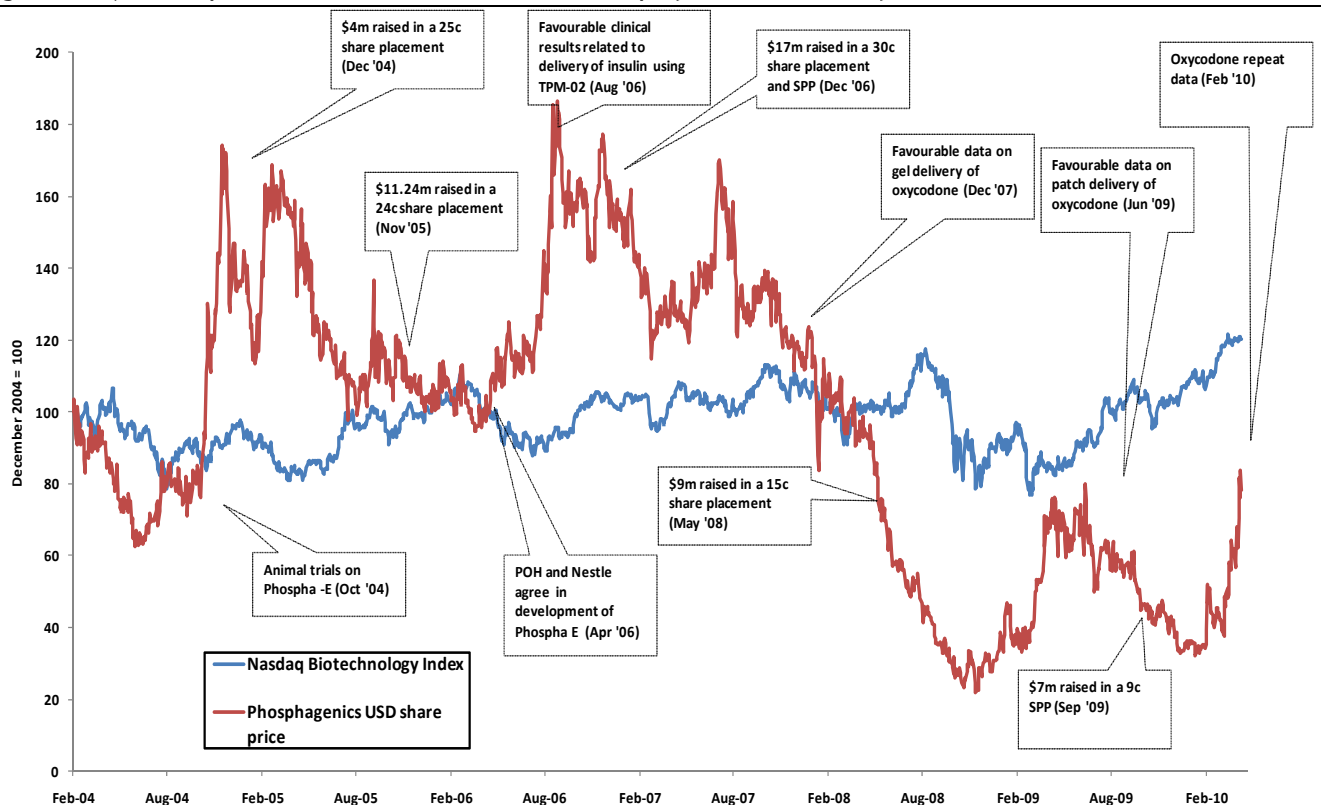
**NOTE:** In April 2010 Southern Cross Equities was appointed a corporate advisor of POH, with a grant of options associated with this arrangement. For more details see the last page of this note.

# Phosphagenics (POH)

## Phosphagenics (POH) – Unique drug delivery technology

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Figure 1 – Major developments for POH since TPM became the company’s main focus in early 2004



SOURCE: POH, SOUTHERN CROSS EQUITIES

# The state of play for Phosphagenics

## Introducing Phosphagenics

**Who is Phosphagenics?** A Melbourne-based biotech company, Phosphagenics (ASX: POH) is commercialising a drug delivery technology called TPM, which is based on phosphorylated Vitamin E. TPM allows conventional pharmaceuticals usually delivered by injection or orally, to instead be delivered 'transdermally', that is, through the skin using gels or patches. With TPM patches working efficiently and without skin irritation or inflammation, we believe that POH has developed the first workable patch for the delivery of the narcotic analgesic oxycodone, opening up the potential to address a multi-billion dollar market. The technology has also been successfully applied to a number of other drugs including insulin, the painkiller lidocaine, the acne drug tretinoin and the anti-inflammatory diclofenac.

**Strong value is emerging in drug delivery.** Drug delivery, particularly transdermal drug delivery, is a booming area of the pharmaceutical market as Big Pharma looks to boost the therapeutic power of its drugs as well as extend their commercial life and better address patient populations. We see the short time to market and low cost of clinical development as benefiting players in the space like POH. For more on this see the section headed 'Drug delivery is a valuable market space'.

**There is solid science behind POH's core drug delivery technology.** POH has been developing and patenting TPM since 2002 so that it can deliver both small and large molecules in patch or gel form. We see these eight years of technology optimisation as having considerably strengthened the commercial value of TPM. We outline the technology in Appendix II of this note and the intellectual property position in Appendix III.

**There have been four years of favourable clinical data on TPM.** POH has been gathering human data on the effectiveness of drug delivery via the full range of TPM technologies since early 2006, with 12 trials since that time having been conducted, all of them successful. We think this bodes well for future clinical trials, particularly given the experience and knowledge the company has gained on the way through. We detail TPM's recent experience in the clinic in the section headed 'TPM – A powerful transdermal drug delivery product'.

**POH has clearly defined its market positioning.** The field of drug delivery technology is a busy one, with between forty and fifty listed companies that we have identified competing in the space. However we see POH as positioned to succeed because of the unique attributes of TPM as well as the company's positioning in drug markets where there are fewer competitors. For more on this see Appendix V.

**A well-managed company.** We have a high regard for POH's leadership team of joint CEOs Harry Rosen and Dr Esra Ogru. For our analysis of the quality of the leadership at POH see the section headed 'Commercial Leadership'.

**Large potential upside.** We are initiating coverage with a target price of 40 cents and a valuation of 41 cents base case and 81 cents optimistic case. For our valuation assumptions see the section headed 'Valuing POH – target price 40 cents'.

**POH has a number of valuable assets besides TPM.** In addition to TPM, POH has also worked on a number of other applications of its 'technology competency' around phosphorylated Vitamin E. We see strong potential for value to emerge

**POH has conducted 12 successful clinical trials of its TPM technology since 2006**

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in these 'non-core' areas. For more on this, see the section headed 'Cosmetic, nutraceutical, OTC and other opportunities'.

**In 2009 POH had its worse year in the share market even after its best year with the TPM technology**

## The POH story is mature

Between 2002 and early 2008 POH developed TPM as a gel. Then it found that in order to go after the big market for oxycodone and other narcotic analgesics the FDA, patients and clinicians were going to want a patch instead<sup>1</sup>. The delay caused by the patch development programme, which was not completed until mid-2009, resulted in the market losing interest in POH stock, even though the patch programme was successful. In 2009 POH was a classic case of a company that had its best technical year at the time of its worst investor reception.

## There is potential to re-rate POH in 2010 based on strong news flow

We see the potential for POH stock to be re-rated in 2010 and 2011 as the company moves towards commercialising and licensing of its technology, particularly given the demand for new delivery options for many existing drugs. We see a number of news events in 2010 that have the potential to assist in this re-rating:

- An IND filing in the US for oxycodone;
- Initiation of a Phase II or Phase III clinical trial for oxycodone under the IND, the choice of phase depending on whether company wants to do a dose-finding or product optimisation study first;
- Potential licensing for oxycodone and/or other products;
- Collaborations with other companies exploring the potential of TPM for large molecule (or difficult molecule<sup>2</sup>) delivery<sup>3</sup>;
- Formulation development and dose optimisation work for insulin;
- A phase II/III study for insulin;
- A phase II study for tretinoin;
- A phase II/III study for diclofenac; and
- Sales success for cosmeceuticals.

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<sup>1</sup> So as to be able to 1) bypass potential abuse issues, and 2) provide a more convenient delivery format.

<sup>2</sup> That is, difficult to formulate.

<sup>3</sup> In June 2009 POH announced that the Australian plasma products major CSL (Melbourne, ASX:CSL, www.csl.com.au) had optioned the TPM technology to evaluate its potential for delivering large molecules. Terms were not disclosed. We think CSL has begun to explore the potential for transdermal delivery of some of its biotech products in the R&D stage (it is unlikely to be looking at transdermal IVIG delivery because the molecular weight of a typical IgG molecule are in the order of 150,000 daltons, way over the 30,000 dalton level which POH regards as TPM's upper limit). We think POH will attract further collaborations like this one given that biological products in medicine are on the rise but are generally only available by injection or infusion.

## Ten reasons to look at POH

**POH may have created the world's first oxycodone patch**

**Time to market for POH's products is less than 3 years**

**POH also has a potential insulin patch**

- 1 **POH has a strong technology offering.** POH's TPM technology, which is based on the ability of phosphorylated Vitamin E to cross the skin, has been successfully adapted to the delivery of a range of drugs, which have worked well in Phase I clinical trials. The company's gels and patches are notable for the speed and safety of drug delivery and the lack of skin irritation.
- 2 **Large markets are being addressed.** The US markets for the products to which TPM has been adapted are large. For example, lidocaine enjoys US\$1.2bn in US sales, tretinoin \$300m and diclofenac \$700m. Meanwhile with Big Pharma seeking to grow its existing drug franchises in the face of lower new drug approval rates and strong generic competition, the licensing demand for new drug delivery solutions, particularly transdermal systems like POH's, is strong.
- 3 **Oxycodone and other painkillers provide the potential for a big near-term payday.** Clinical data to date has shown that POH now has the first patch in the world to deliver oxycodone, which is a US\$3bn market in the US alone. The record of another painkiller called fentanyl is that the ability to deliver it via a patch boosted sales eighty-fold over a 15 year period. While POH's oxycodone breakthrough positions the company for a good licensing deal, it also opens up development of other patches for narcotic analgesics that have yet to be patch-delivered.
- 4 **Lead time to market is short.** The regulatory process for getting a drug delivery technology approved is substantially faster than for new drugs (ie < 3 years), with clinical trials in many instances being performed in months rather than years. Consequently, we see the ability for POH to license TPM within the next couple of years.
- 5 **Low cost of clinical development.** POH estimates that it has spent only around \$400,000-\$500,000 on its most recent 20-subject Phase I trial of its oxycodone patch. A Phase II/III efficacy study might cost A\$5-8m depending on the size of the study. We see these low costs as heightening POH's chances of commercial success.
- 6 **Insulin provides the blue sky.** POH has managed to get its insulin patch to work. This opens up a US\$13bn global market not as yet being addressed.
- 7 **Potential for cosmeceutical sales revenue.** The company has created some Vitamin E-based cosmeceuticals which are now beginning to retail at high-end department stores in the US.
- 8 **News flow is good.** 2010 will be a strong year for news from POH.
- 9 **Strong leadership.** We have a high regard for the POH management team led by joint CEOs Harry Rosen and Dr Esra Ogru. Harry Rosen helped foster Betatene, which became the world's largest producer of natural beta carotene, in the 1980s and 1990s before it was sold in 1995 to the German company Henkel, resulting in a large gain for long-term shareholders. Esra Ogru, a biochemist by background, has overseen much of the technology and clinical development of TPM to the point where it is now ready for later stage clinical trials.
- 10 **POH is undervalued on our numbers.** We value POH at 41 cents base case and 81 cents optimistic case using a probability-weighted DCF valuation, diluted for a further \$15m capital injection. As the near-term nature of TPM becomes apparent, helped by the emergence of further clinical and pre-clinical data, we expect POH to be re-rated by the market.

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## Valuing POH – target price 40 cents

We value POH at 41 cents base case and 81 cents optimistic case using a probability-weighted DCF approach, diluted for another potential \$15m capital raising.

Figure 2 – Key parameters for valuing TPM

Product	Sales at maximum growth rate - base (USDm)	Sales at maximum growth rate - optimistic (USDm)	POH remaining expenditure - base (USDm)	POH remaining expenditure - optimistic (USDm)	Royalty - base	Royalty - optimistic	Upfronts and milestones - base (USDm)	Upfronts and milestones - optimistic (USDm)
Insulin	500	800	0	0	10%	13%	100	200
Oxycodone	300	400	20	10	10%	13%	100	200
Diclofenac	100	200	10	5	8%	10%	50	100
Lidocaine	200	300	20	10	8%	10%	50	100
Tretinoin	75	150	20	10	8%	10%	25	50

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

Figure 3 - Our valuation of POH

	Base case	Optimistic case
Insulin and Oxycodone (\$m)	256.2	495.1
Other opportunities (\$m)	81.5	205.0
Estimated cash now plus cash to be raised (\$m)	25.9	25.9
Cash from options (\$m)	4.3	4.3
Total value (\$m)	367.9	730.3
Total diluted shares on issue (assumes another \$15m raised at 11 cents per share) (million)	903.4	903.4
Value per share	\$0.41	\$0.81
Valuation midpoint	\$0.61	
Share price now	\$0.125	
Upside to midpoint	386.2%	

SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

**We value POH at 41 cents base case and 81 cents optimistic case, using a probability-weighted DCF approach**

We value POH on the basis of potential licensing deals for TPM. To attempt a valuation of POH we took the five drug delivery programmes which the company has worked on since mid-2006, and valued each using a probability-weighted DCF methodology where we assumed dates in which products enter the clinic and gain regulatory approval. We also:

- modelled each product using certain notional sales levels reached at the point of maximum sales growth in year 3, after which sales only rise 5% pa (see chart below for an example). We feel we have been conservative here, assuming, for example, only 10% penetration of the oxycodone market and 5% of the insulin market;
- estimated in each case the milestone and royalty payments that could be realised;
- applied various probability assumptions, which give the products a roughly 1-in-3 chance of clinical success;

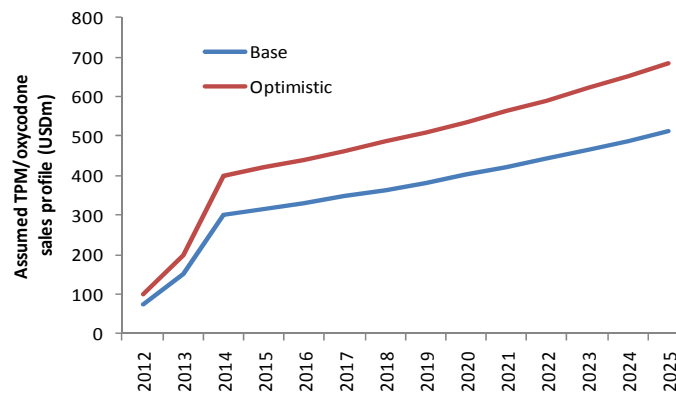
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- calculated the NPV of the resulting cash flow at a 25% discount rate and adjusted for a 30% tax rate; and
- converted the resulting valuations back to AUD at an AUDUSD exchange rate of 0.93, the level around which the currency has encountered resistance since late 2009.

The various valuation parameters used are laid out above.

**We assume a further \$15m capital raising.** POH, as an early stage company, has raised \$51m in equity capital over the last six years and burned around \$650,000-\$700,000 a month. There was \$10.9m cash at December 2009. With the forthcoming oxycodone trial plus other preclinical and clinical work needed to be funded we assume a further \$15m capital injection via an equity issue at 11 cents per share that increases the fully diluted shares on issue to 903.4 million. We also assume that a partnering deal for oxycodone after 2011 can provide funding beyond this point.

**Figure 4 - Assumed sales profile for TPM/oxycodone**



SOURCE: SOUTHERN CROSS EQUITIES ESTIMATES

**Target price 40 cents.** Our valuation of the TPM technology plus increased dilution from the capital raising resulted in our valuing POH at base case 41 cents per share and optimistic case 81 cents per share. Our 12-month target price sits at the base case valuation.

**A licensing deal for POH's products could yield upfronts and milestones in the order of US\$100-200m**

**A licensing deal has the potential to be lucrative.** We see strong potential for TPM to be licensed to Big Pharma or specialty pharma companies given the clinical data discussed above, the large markets being targeted, and the patient-friendly nature of TPM patches. Recent history suggests that such a deal, usually combining a mixture of upfront payments, milestone payments and royalties, can be lucrative, with upfronts and milestones in the order of US\$100-200m for products with large market appeal, as well as royalties. Consider 18 drug delivery licensing deals from the last five years (note, all figures below in US dollars):

- **Vectura / Arakis / Novartis, April 2005.** This deal saw Arakis, a British drug developer<sup>4</sup>, license NVA237, a COPD<sup>5</sup> drug that had been designed using aerosol formulation technology provided by Vectura, to Novartis. Arakis and Vectura shared a US\$30m upfront with \$375m in milestone payments and royalties to come.

<sup>4</sup> Now owned by the Japanese drug company Sosei.

<sup>5</sup> COPD is chronic obstructive pulmonary disease, a progressive lung disorder characterised by breathing difficulties, wheezing, and chronic coughing.

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**A good licensing deal in drug delivery can bring upfronts above US\$100m**

- **Alkermes / Cephalon, June 2005.** This deal saw Alkermes license Vivitrol, a long acting version of the detox drug naltrexone, to Cephalon, the specialty pharma company<sup>6</sup>, for \$160m upfront and \$110m on FDA approval of the drug<sup>7</sup>.
- **Durect / Pain Therapeutics / King Pharmaceuticals, November 2005.** This deal saw Pain Therapeutics license Remoxy, an anti-abuse oxycodone formulation, to King Pharmaceuticals, for \$150m upfront and another \$150m in milestones followed by a 15-20% royalty. Under an early 2002 licensing deal Durect, developer of the formulation technology, receives a 6.5%-11% royalty on sales.
- **Emisphere / Novartis, March 2006.** This deal saw Novartis exercise an option over Emisphere's Eligen drug delivery technology for use in oral delivery of parathyroid hormone, used in the treatment of osteoporosis. The deal generated a \$30m milestone payment for Emisphere plus a royalty arrangement.
- **Cell Therapeutics / Novartis, September 2006.** This deal saw Cell Therapeutics license its OPAXIO drug, which is polyglutamate-delivered paclitaxel, to Novartis for \$270m in milestone payments.
- **Halozyme / Roche, December 2006.** This deal saw Halozyme license to Roche its Enhanze drug delivery technology for use in developing drugs for Roche-identified targets. Roche paid \$20m upfront, agreed to \$111m in milestone payments for the first three targets, and invested \$11m in Halozyme stock.
- **Nektar / Bayer, August 2007.** This deal saw Nektar license NKTR-061, which was an inhaled version of the antibiotic drug amikacin, to Bayer for \$50m upfront, \$125m in milestones and tiered royalties rising to 30%.
- **Acura / King Pharmaceuticals, October 2007.** This deal saw Acura license Acurox, another abuse-resistant oxycodone formation, and the technology behind the formulation, to King for \$30m upfront and \$28m in milestones as well as \$50m in sales milestones and a royalty ranging from 5% to 25%<sup>8</sup>.
- **Alexza / Endo, December 2007.** This deal saw Alexza license AZ-003, a reformulated fentanyl product, to Endo for \$10m upfront, \$40m in milestone payments and royalties.
- **Transpharma / Eli Lilly, June 2008.** This deal saw Transpharma, a privately held Israeli transdermal drug delivery company<sup>9</sup>, license to Eli Lilly a transdermal PTH delivery product for \$35m upfront and unstated milestones and royalties.
- **Durect / Alpharma, September 2008.** This deal saw Alpharma, a specialty pharma company subsequently acquired by King Pharmaceuticals, license from Durect a product called ELADUR, which is patch-delivered bupivacaine for the treatment of postherpetic neuralgia. There were \$20m in upfronts, \$93m in regulatory milestones and \$150m in sales milestones.

**Many drug delivery companies have done deals with large pharma companies over the last five years**

<sup>6</sup> Cephalon (Frazer, Pa, Nasdaq: CEPH, www.cephalon.com) is also, through its CIMA business, a provider of drug delivery technology specialising in orally disintegrating tablets, oral transmucosal and oral powder drug delivery, taste-masking and customised release profiles.

<sup>7</sup> This happened in April 2006. Cephalon handed the drug back to Alkermes in late 2008 following reports of adverse events in patients and a move by Cephalon to focus on a new lymphoma drug called Treanda.

<sup>8</sup> An FDA advisory committee recommended against approval of this drug in April 2010. The drug purportedly works to inhibit oxycodone abuse because it is formulated with niacin, the B vitamin. The niacin is supposed to promote dysphoria and therefore lower abuse. The FDA committee didn't feel there was enough evidence that there would be a deterrence effect.

<sup>9</sup> See [www.transpharma-medical.com](http://www.transpharma-medical.com).

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- **Depomed / Solvay, November 2008.** In this deal Solvay Pharmaceuticals, the drug arm of the Belgian chemical company<sup>10</sup>, licensing from Depomed a compound called DM-1976, which was a reformulated version of the epilepsy and pain drug gabapentin. The deal involved \$25m upfront, \$70m in regulatory milestones, \$300 million in sales milestones and a 14-20% royalty.
- **Merrion / Novo Nordisk, November 2008, January 2009.** This deal saw Novo Nordisk license Merrion's reformulation technology in order to create an orally available insulin product. \$58m in milestones were agreed for the product. Two months later Novo Nordisk also licensed the technology to use in a GLP-1 receptor agonist drug, for another \$58m in milestones.
- **Nektar / AstraZeneca, September 2009.** This deal saw AstraZeneca in-license two drugs concerned with opioid-induced constipation that had been developed using Nektar's polymer conjugate technology. The deal involved \$125m upfront, and \$235m in regulatory milestones and \$375m in sales milestones.
- **SurModics / Roche-Genentech, October 2009.** This deal saw Roche-Genentech license SurModics' biodegradable microparticle drug delivery technology for use in delivering the eye drug Lucentis. The price was \$3.5m upfront and \$200m in milestone payments.
- **Alexza / Biovail, February 2010.** This deal saw Biovail license AZ-004, a reformulated version of the schizophrenia drug loxapine, for \$40m upfront, \$90m in milestones and tiered royalties.
- **Acrux / Eli Lilly, March 2010.** This deal saw Eli Lilly license Acrux's AXIRON product, which is transdermally delivered testosterone, for \$50m upfront, \$87m on FDA approval and \$195m in sales milestones.
- **Mersana Therapeutics / Teva, April 2010.** This deal saw the privately-held Mersana<sup>11</sup>, whose technology centres on biodegradable polymers for improved drug delivery, license to Teva, the Israeli drug company, a polymer-conjugated version of the cancer drug camptothecin for \$334m in milestones.

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<sup>10</sup> Solvay sold this business to Abbott Laboratories in early 2010.

<sup>11</sup> Cambridge, Ma, [www.mersana.com](http://www.mersana.com).

## Drug delivery is a valuable market space

**Drug delivery has created a number of billion dollar companies**

**What is drug delivery?** Drug delivery is the mechanism by which a drug's active ingredient gets into the body of the patient. Most drugs are available either by injection or orally, that is, in pill form. However for many patients these two forms of delivery are not acceptable, leading to low levels of compliance with therapy. For other drugs, the time in which the active ingredient is working is too short for many patients. To solve these problems drug delivery companies such as POH seek to develop alternative forms of delivery such as transdermal (through the skin) or pulmonary (inhaled into the lungs), or ways to extend the effectiveness of drugs inside the body.

**Why the drug delivery industry is booming.** Over the last 30 years the drug delivery industry has boomed, creating large, established companies such as Endo (2009 revenue US\$1.46bn) Biovail (US\$789m), Enzon (US\$625m) and Alkermes (\$327m). In addition to the demand by patients and pharma companies for new delivery mechanisms, we see the rise of this industry being driven by:

- 1) efforts by Big Pharma to get more commercial life out of their existing drugs, many of which are nearing the end of patent life in a time when Big Pharma R&D productivity has been declining;
- 2) the ease with which a new delivery technology for an already approved drug can gain US regulatory approval, thanks to the so-called '505(b)(2)' route. With 505(b)(2), the applicant only needs to demonstrate that the drug to be delivered shows up in the blood in similar quantities as the existing drug; and
- 3) the speed and lower trial cost of getting a drug ready for regulatory approval under the 505(b)2 regime. Typically a new drug will cost US\$800m<sup>12</sup> and 10-13 years to bring to market. By contrast, reformulation of that same drug, once developed and marketed, can take a mere three to five years at a cost of US\$5-10m.

We see POH as benefiting from the abovementioned cost and timing issues – the company has conducted 12 clinical trials in just the last four years – as well as strong demand for the end-product.

**Why transdermal drug delivery is best.** Transdermal drug delivery is difficult because the skin is set up to keep stuff on the outside from easily getting inside the body. Think of the outermost layer of skin - the stratum corneum - as being like a brick wall where the bricks are made out of a protein called keratin and the mortar is a complicated mixture of water and lipids, that is, fat cells. Any compound that can bypass the bricks and somehow slip an accompanying drug through the mortar is therefore a candidate to become a transdermal drug delivery vehicle. POH has achieved this with TPM. For many observers of the drug delivery space transdermal delivery, while technically difficult, represents the most attractive option since:

- it can bypass the issue of 'first pass metabolism', that is, the amount of drug that doesn't make it to the bloodstream when taken orally because of elimination in the gastrointestinal tract;
- it can guarantee a more steady rate of drug delivery;
- it is more convenient for many patients than having to take a pill;
- for potentially addictive drugs such as narcotic analgesics, it's harder for patches to be abused; and

<sup>12</sup> See Journal of Health Economics 22 (2003) 151-185.

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- the transdermal field has become well established, with ALZA having introduced its first patch in 1981. Since patches are now available for a wide variety of drugs<sup>13</sup> as well as for smoking cessation, patient acceptance of such delivery is quite high.

We see POH as benefiting from having transdermal solutions to a number of drugs that until now have only been available by injection or orally.

**POH is well placed for commercial success in transdermal drug delivery.** We see the TPM technology, as well placed for success because:

- TPM works via natural cellular transport mechanisms and has known anti-inflammatory properties. This guarantees that its patches will not cause skin irritation; and
- TPM has been shown to be a transdermal drug delivery option for drugs that have proven hard for competitors to put into patch form.

## **Acrux as an example of commercial success in drug delivery**

We regard the Melbourne-based drug delivery company Acrux (ACR), currently capped at around A\$305m (as at 11 May 2010) versus POH's \$93m, as a good example of the potential for POH over the medium term:

**ACR is another transdermal drug delivery developer.** Like POH, ACR is a transdermal player, with its MDTs technology involving sprays in which the active ingredient is formulated with two penetration enhancers called 'padimate O' and 'octyl salicylate', both non-toxic chemicals commonly used in sunscreens.

**ACR has had late stage clinical success and licensing success with testosterone.** In September 2009 ACR reported that a Phase III trial of AXIRON, which is MDTs for delivery of testosterone, had achieved testosterone in the normal bloodstream concentration range in 84% of subjects after four months of treatment. This was better than the FDA's 75% requirement. The trial data allowed Acrux to license the product to Eli Lilly in March 2010 in a deal involving a US\$50m upfront payment, plus US\$87m on FDA approval (still pending) and US\$195m in sales milestones.

**ACR's rerating bodes well for POH.** We expect that POH will be similarly rerated by the market as its technology attracts licensing interest coming out of Phase III. ACR's commercial success doesn't preclude similar success for POH, since the two companies have notable differences:

- *ACR develops sprays while POH develops patches.* While there is likely to be strong demand for drug delivery sprays in the future, with AXIRON helping to foster the market, the patch market is more established;
- *ACR and POH are working on different drugs.* POH is focused primarily on oxycodone and insulin, whereas for its pipeline ACR has sex hormones, nicotine and NSAIDs. While ACR had been looking at the narcotic analgesic fentanyl, it decided not to proceed with this product in early 2009;
- *POH's product has certain technical advantages,* including the natural transport mechanism and anti-inflammatory properties noted above, the ability to deliver a wider range of drugs, the ability to deliver drugs in gel, foam, or patch form, and a higher level of dermal penetration. All of this suggests TPM will be even better received than MDTs has been to date.

**POH can do what  
ACR has done**

<sup>13</sup> Most notably, Lidoderm for lidocaine and Duragesic for fentanyl, two patches that we touch on later in this note.

# TPM - A powerful transdermal drug delivery product

## What is TPM?

TPM is a clinically-validated technology that allows conventional pharmaceuticals to be delivered transdermally, that is, across the skin barrier, via patches placed on the skin.

**The TPM technology** is based on phosphorylated Vitamin E, that is, Vitamin E altered by the addition of a phosphate group to make it more water-soluble. Vitamin E phosphates are known to be deft at penetrating the skin, and POH can formulate TPM in such a way as to trap the drug to be delivered inside self-assembling vesicles, that is, small bubbles of Vitamin E phosphates. The vesicular nature of some TPM formulations is important because the vesicles allow large molecules (that is, drugs not-so-easy to be delivered transdermally) to get through the skin<sup>14</sup>. For more on the TPM technology see Appendix II of this note. For the relevant patents pending and granted see Appendix III.

**TPM has been evolving since 2002**, when it was first invented by POH scientists. Initially the technology was based solely on Vitamin E phosphates, but this would only allow delivery of certain small molecule drugs. Consequently in 2005/06 POH scientists came up with 'TPM-02', in which the Vitamin E phosphates contained self-forming and malleable vesicles capable of handling and entrapping large molecule drug delivery. Then in 2008 the company found that for some applications it needed to deliver via patch rather than via the gels it had used until then, and this required further development work. We see this multi-stage evolution of TPM as having considerably strengthened the value of the technology.

**TPM today is potentially very valuable**, for five main reasons:

- 1) The technology in its present iteration has been used successfully in 12 different clinical trials to deliver therapeutic quantities of a wide variety of drugs. The evidence for the efficacy of the TPM technology has been building since 2005/06, when the company first took the technology into the clinic. It now has solid clinical data on the delivery of insulin, the analgesic drug oxycodone, the local anesthetic drug lidocaine, the anti-inflammatory diclofenac, and the skin drug tretinoin;
- 2) The technology can be used either for dermal delivery of drug (drug delivered into the skin for subsequent extended release into the bloodstream), or for systemic delivery (that is, directly through the skin and into the bloodstream), by adjusting the TPM formulation used.
- 3) The technology has been shown to be able to deliver drugs transdermally where presently there are no transdermal options. The particular case in point here is the painkiller oxycodone, which has a multi-billion dollar global market;
- 4) Unlike other commercial drug delivery patches, TPM patches do not appear to cause skin irritation, which we attribute to the known anti-inflammatory properties of Vitamin E phosphates; and

**Eight years of development work has helped optimise the TPM technology**

<sup>14</sup> POH does not always use vesicular entrapment with TPM. Sometimes the company simply formulates actives with TPM to allow their passage into the skin or blood. For more on this see Appendix II.

# Phosphagenics (POH)

- 5) The technology is now available for delivery in patch form, which enables it to be targeted towards the narcotic analgesic market in particular, while increasing the licensing appeal of the technology for other options where patches may be attractive.

**Figure 5 – POH's 12 clinical trials of TPM since development of TPM-02**

Trial	Results reported	POH share price (cents)
Morphine Phase Ib	Jan-06	26.0
Insulin Phase Ia	Aug-06	37.0
Insulin Phase Ib	Aug-07	31.5
Oxycodone gel Phase Ia	Dec-07	23.0
Lidocaine Phase I	Dec-08	7.9
Insulin Phase IIa (Type 1 diabetics)	Jan-09	9.0
Diclofenac Phase Ia	Feb-09	10.5
Tretinoin Phase I	Apr-09	17.0
Oxycodone patch RIPT	Jun-09	14.5
Diclofenac Phase Ib	Sep-09	11.5
Oxycodone patch Phase Ia	Sep-09	11.0
Oxycodone patch Phase Ib	Feb-10	6.7

SOURCE: POH

## TPM may become the world's first insulin patch

**Insulin is a US\$13bn a year market**

POH can address a huge and growing market for insulin delivery. Since 2006 POH has had solid clinical evidence that TPM can transdermally deliver insulin. This is exciting because:

- there are currently around 280 million adult diabetics worldwide (4% of the planet's population), with their numbers currently rising 6-7% pa and strong growth expected for the next 20 years<sup>15</sup>;
- around 27% of diabetics currently use insulin as part of their therapy<sup>16</sup>, while around half of all diabetics get to insulin within six years of diagnosis<sup>17</sup>. Since diabetes is a chronic disease, this means many years of insulin usage by patients<sup>18</sup>;
- the global market for insulin, now worth around US\$13bn pa, is increasing at a 10% pa rate as more diabetics go to insulin therapy<sup>19</sup>;
- almost all insulin is currently delivered by injection since large molecule size has hitherto precluded other delivery routes; and
- the insulin market is completely dominated by three giant players – America's Eli Lilly, the French company Sanofi-Aventis and Denmark's Novo-Nordisk<sup>20</sup>. Alternative delivery systems potentially allow other companies to break in, now that recombinant human insulin is off-patent.

<sup>15</sup> Source: International Diabetes Federation.

<sup>16</sup> Source: CDC. Most newly diagnosed diabetics start on various drugs such as metformin or glipizide which help boost the body's production of insulin, before moving to insulin therapy later on.

<sup>17</sup> This was a finding of the United Kingdom Prospective Diabetes Study.

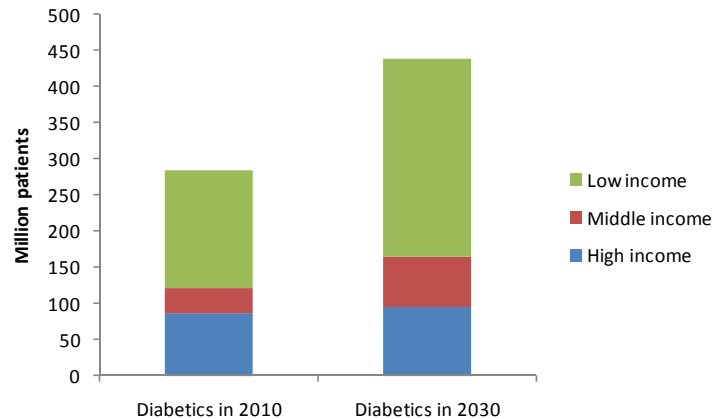
<sup>18</sup> Generally Type 2 diabetics have the same life expectancy as the general population - see PLoS One. 2009 Aug 28;4(8):e6817. In the US average age at diagnosis is around 46 - see Ann Fam Med. 2005 Jan-Feb;3(1):60-3 - and US life expectancy is around 78. This potentially means up to three decades of insulin usage.

<sup>19</sup> Source: Novo Nordisk. As well as the 'natural' switch from diabetes drugs to insulin as the drugs fail, the growth in the insulin market also partly reflects the rise of long-acting and ultra-short acting insulin analogues, which improve the effectiveness of insulin therapy - see Arch Intern Med. 2008;168(19):2088-2094. There has also been a trend towards earlier initiation of insulin treatment - see Cleve Clin J Med. 2004 May;71(5):385-6, 391-2, 394 passim.

<sup>20</sup> Bagsværd, Denmark, OMX: NOVO B, www.novonordisk.com

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**Figure 6 – The number of diabetics in high and middle income countries is set to rise at two to three times population growth for the next 20 years**



SOURCE: IDF, CIA WORLD FACTBOOK, SOUTHERN CROSS EQUITIES

**Favourable Phase I clinical evidence for TPM.** POH conducted two Phase I trials in 2006 and 2007 which not only confirmed that TPM for insulin delivery was safe and well tolerated but also provided indications of efficacy. In each case healthy male volunteers were given a single dose of either TPM/insulin (with TPM then in gel form) or placebo. The insulin response over the following nine hours, assessed using two oral glucose tolerance tests, was favourable.

**TPM has a good clinical record with insulin delivery**

- Phase Ia, July-August 2006** – This trial, with 20 subjects, delivered insulin lispro, the ‘short acting’ insulin analogue that starts working faster than regular insulin but also has a shorter duration<sup>21</sup>. TPM proved effective in terms of delivering ‘*insulin into the blood stream at levels high enough to produce significant effects*’, with the treated patients showing lower blood glucose concentrations, lower ‘endogenous’ blood insulin levels<sup>22</sup> and lower C-peptide levels, with statistical significance in each case<sup>23</sup>. Also, doses appeared to be therapeutic for longer than would be the case with injected insulin lispro. This indicated that TPM was experiencing the ‘depot effect’ – the forming within the skin of a depot of drug that was then slowly released into the bloodstream. This was favourable because it indicated that TPM could be used for extended release of drug.
- Phase Ib, May-August 2007.** This trial, with 45 subjects, assessed the ability of TPM to deliver regular human insulin<sup>24</sup>. Results from this trial were similar to those of the first trial in terms of blood glucose, endogenous blood insulin and C-peptide levels. However, this time the results for endogenous insulin and C-peptide were highly statistically significant ( $p < 0.001$ ) while there was also a very statistically significant result in blood glucose concentrations ( $p = 0.016$ ). Moreover the therapeutic effect lasted for up to eight hours, which is around the duration of regular insulin.

This data suggests that POH with TPM may have solved the mystery, which has defeated all research efforts to date, of how to deliver insulin transdermally. If so,

<sup>21</sup> Probably the best known insulin lispro is Eli Lilly’s Humalog product, which gained FDA approval in 1996. It takes up to 15 minutes to start working, reaches peak effect at between 30 to 90 minutes and has an overall duration of less than 5 hours. Regular insulin takes effect between 30 to 45 minutes, reaches peak effect at 2 to 4 hours, and lasts from 6 to 8 hours.

<sup>22</sup> That is, insulin generated by the trial subject rather than delivered via TPM. Treated patients needed less endogenous insulin because the delivered insulin was taking care of outstanding glucose. For this first trial in people POH used insulin lispro because by measuring lispro concentrations in the blood of test subjects it could demonstrate transdermal delivery of ‘exogenous’ insulin. Detailed analysis that confirmed exogenous insulin was reported to the ASX in October 2006.

<sup>23</sup> POH stock closed at an all-time high of 42 cents on 25/8/2006, immediately after the announcement of this result.

<sup>24</sup> That is, recombinant human insulin, such as Eli Lilly’s Humulin product. We understand that regular human insulin initially proved difficult to formulate but POH was able to overcome this problem.

# Phosphagenics (POH)

the product will likely enjoy a huge market opportunity for the simple reason that most patients don't like injections.

**A TPM insulin patch would have strong market appeal.** Clearly injection technology is getting better, thanks to the rise of the 'insulin pen', a pen-like device that markedly boosts the convenience and discreteness of injections while lowering the pain<sup>25</sup>. However it's worth considering the results of a 2008 survey of 500 insulin-dependent diabetics in the US<sup>26</sup>, in which 2% of respondents acknowledged 'often' skipping an insulin injection that they should have taken. Moreover:

- 47% of patients said they would be more compliant with their therapy if they could ease the pain and discomfort of insulin injections;
- 33% of patients had 'some level of dread' associated with injections;
- 29% felt that injections were the hardest aspect of their diabetes care; and
- 14% felt that insulin injections had 'a negative impact on their life'.

It's also worth noting three other common problems with injections

- sterility and disposal issues raised by needles;
- 'site reactions', that is, inflammation at the site of injection, which can affect at least 10% of people on insulin therapy<sup>27</sup>; and
- lipohypertrophy, that is, the formation of fatty lumps at sites in which insulin is constantly injected. These lumps subsequently reduce insulin clearance from the area. Lipohypertrophy is understood to affect about 4% of Type 2 diabetes patients<sup>28</sup>.

A TPM patch would avoid all these issues.

**The Phase Ib data suggests TPM will work for basal insulin.** The key to insulin therapy today is to have the right mix of 'basal' and 'bolus' insulin, with basal insulin being the base levels required to keep blood glucose stable between meals and overnight, and bolus insulin being the extra insulin needed to cope with sudden glucose intake at mealtimes. In the last fifteen years the insulin market has segmented, with the short-acting insulins like the abovementioned insulin lispro emerging to provide the bolus solution, and two long-acting insulins - insulin detemir and insulin glargine - leading the basal insulin space. Of these two segments, basal is growing the fastest (ie 20-25%), in no small measure because the long-acting insulins provide up to 24 hours of basal insulin from just one shot. The TPM/insulin Phase Ib data suggests that a TPM patch could address the basal insulin market:

- the steady flow of insulin through the skin typified by the Phase Ib data is ideal for maintaining basal insulin; and
- the ability to use regular off-patent recombinant human insulin for basal insulin rather than more expensive (and patent-protected) long-acting insulins would provide a prospective TPM licensee with market access and cost-of-goods advantages<sup>29</sup>.

**TPM represents a good, low cost basal insulin solution**

<sup>25</sup> Pain is reduced by use of higher gauge needles (ie 31 or 32 gauge).

<sup>26</sup> See the American Association of Diabetes Educators' Injection Impact Report.

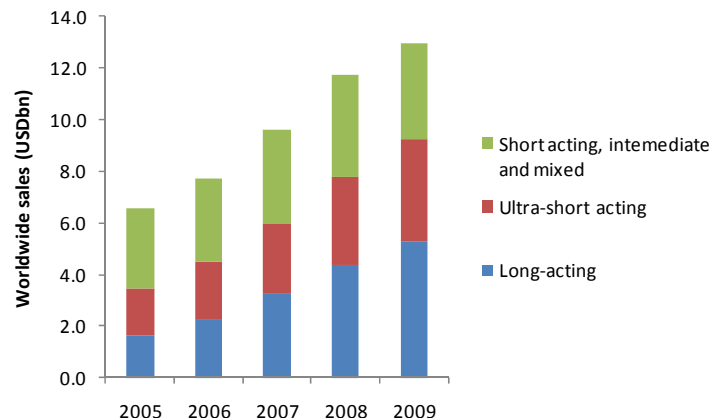
<sup>27</sup> A Sanofi-Aventis trial which compared Apidra, its ultra short acting insulin product (insulin glulisine) with a competitor, Novo Nordisk's Novolog (insulin aspart), incurred site reactions in 10% and 13% of cases respectively. Source: www.apidra.com.

<sup>28</sup> See Exp Clin Endocrinol Diabetes. 1996;104(2):106-10.

<sup>29</sup> Levemir, which is Novo Nordisk's insulin detemir product, goes off-patent in the US in 2019 while Lantus, Sanofi's insulin glargine product, is generic from 2015. For a sense of the cost advantage of TPM-delivered regular insulin (more correctly, 'insulin neutral'), consider that on Australia's Pharmaceutical Benefits Scheme Eli Lilly's Humulin product is currently priced at 13.4 Australian cents per insulin unit whereas Levemir and Lantus are 28.8 cents per insulin unit (source, PBS, Schedule of Pharmaceutical Benefits, April 2010).

# Phosphagenics (POH)

**Figure 7 - The basal insulin market has been the fastest growing, thanks to the long-acting insulin analogues**



SOURCE: NOVO NORDISK, ELI LILLY, SANOFI-AVENTIS, SOUTHERN CROSS EQUITIES

**Some clinical work in Type 1 diabetics has indicated that TPM delivery can work in patients.** In January 2009 POH reported that it had successfully tested TPM/insulin in some Type 1 diabetics. For this trial<sup>30</sup> POH only reported that a primary endpoint of ‘glucose lowering efficacy’ and a secondary endpoint of safety were met, with a majority of treated patients experiencing ‘reduced glucose levels’. No data was made available. We understand that POH’s reticence regarding the trial was twofold:

- patient numbers were low due to high dropout rates, and there was no placebo arm, so results weren’t statistically significant<sup>31</sup>; and.
- the use by investigators of a technique called ‘euglycemic clamping’ to avoid hypoglycaemia in the patients made the clinical efficacy measurements difficult to explain to investors<sup>32</sup>.

While we would have preferred to see more data disclosed from this trial, we nonetheless think the trial improves the case for TPM/insulin, since it showed the product actually working in patients that are more difficult to treat than the Type 2 diabetics who will be the main patient base for TPM/insulin. Moreover by 2009 POH was working with a better TPM/insulin than was used in this trial.

## Insulin is being prepared to go back to the clinic

**TPM/insulin is getting ready to go back to the clinic.** Since 2007 POH has done a good deal of work to improve TPM/insulin:

- the formulation has been optimised to allow vesicular entrapment of more insulin molecules inside TPM, which means that dose sizes can ultimately be reduced<sup>33</sup>;
- TPM itself has been converted to patch delivery, meaning that the next clinical trial can be with patches, which POH has become convinced from clinician feedback is a preferred delivery mechanism<sup>34</sup>; and

<sup>30</sup> POH unveiled a 60-patient Phase II trial to test TPM in both Type 1 and Type 2 diabetics in September 2007. In the end only the Type 1 arm of the study was undertaken, completing in 2008.

<sup>31</sup> The study was not designed to reach significance. It was designed to demonstrate safety and proof of concept.

<sup>32</sup> Hypoglycaemia is where a diabetic gets too much insulin and therefore has an excessively low blood sugar level, resulting in dizziness, sweating, shaking and palpitations. This unpleasant experience is what is commonly called a ‘hypo’. To avoid hypos in the Type 1 trial, POH’s investigators used euglycemic clamping, where levels of blood sugar were kept steady by infusing glucose into the patient in line with insulin levels. Euglycemic clamping is normally used to measure insulin sensitivity, that is, the ability of the body to respond to insulin. With POH’s Type 1 trial it was used to measure notional blood glucose concentrations, where an increased glucose infusion rate corresponded to lower notional glucose concentrations. POH’s investigators were able to detect such a lowering trend over a 4-8 hour period.

<sup>33</sup> We understand the patch would, as a result, be only 20x10 cm in size.

<sup>34</sup> For more on this see Appendix II.

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- the company has been testing the patches and new formulations in diabetic rat models in order to better determine dosing.

We expect that this work will allow POH to take TPM/insulin patches into the clinic in 2010 for another study in healthy volunteers, in which the trial will measure dose response and the effect of repeat application of patches, as part of a continued product optimisation programme. We believe this could significantly improve the commercial attractiveness of TPM/insulin by lowering the risks involved for a licensee.

**At the moment TPM has no patch competitors for insulin near the market**

**TPM/insulin has few competitors.** A number of companies around the world are also working on alternate insulin delivery systems to needles, however we don't see many of these as competing for TPM/insulin's market space.

- AFREZZA.* Regulatory approval for this inhaled insulin product is now being sought by its developer, the California biotech company Mannkind<sup>35</sup>. AFREZZA is being positioned as a short-action bolus insulin, which as we noted above isn't where TPM/insulin is going. AFREZZA may face the kind of market difficulties faced by Pfizer and Sanofi-Aventis when they introduced Exubera, the world's first inhalable insulin, in 2006. That product was pulled off the market in late 2007 because of low patient acceptance. The size of the inhaler, difficulties adjusting the dose, and concern over the risk of lung problems were all factors weighing against the product<sup>36</sup>. AFREZZA has a less bulky inhaler than Exubera, but we argue that patches are still more discrete than an inhaler as far as the user is concerned.
- Oral-lyn.* This product is an insulin mouth spray from the Canadian biotech company Generex<sup>37</sup> that is currently in Phase III under a US IND. Generex has targeted Oral-lyn as a bolus insulin, with data showing it to have faster onset and a shorter duration of action when compared with regular insulin given subcutaneously<sup>38</sup>.
- Insulin pills.* A number of companies around the world are pursuing the development of insulin pills, most notably Novo Nordisk, which commenced Phase I in 2009<sup>39</sup>. Also playing are the Indian biotech major Biocon<sup>40</sup>, Israel's Oramed<sup>41</sup> and America's Access Pharmaceuticals<sup>42</sup>. We expect that ultimately the puzzle of delivery via the gastrointestinal tract will be solved, however the presence on the market of pills doesn't negate the opportunity for patches, since there will be patients that prefer one mode of delivery over another. Moreover Novo's product, which everyone is watching given this company's status in the global insulin market, probably won't be FDA approved until around 2016, in time to help it offset loss of US patent protection on insulin detemir.

**Big Pharma is already interested in TPM/insulin.** The fact that Novartis Animal Health is working on a TPM-enabled insulin delivery solution for companion animals<sup>43</sup> suggests that Big Pharma already has its sights on what POH has been

<sup>35</sup> Valencia, Ca, Nasdaq: MNKD, [www.mannkindcorp.com](http://www.mannkindcorp.com).

<sup>36</sup> In March 2010 the FDA asked for further information on the safety and efficacy data of AFREZZA, and this caused Mannkind stock to sell off strongly.

<sup>37</sup> Toronto, On, Nasdaq: GNBT, [www.generex.com](http://www.generex.com).

<sup>38</sup> See Diabetes Obes Metab. 2010 Feb;12(2):91-6. Epub 2009 Nov 2.

<sup>39</sup> Using delivery technology sourced from Ireland's Merrion Pharmaceuticals (Dublin, IEX: MERR, [www.merrionpharma.com](http://www.merrionpharma.com)).

<sup>40</sup> Bangalore, BOM: 532523, [www.biocon.com](http://www.biocon.com). Biocon enjoyed ~US\$330m in revenue in 2008/09. The company's IN 905 pill is in Phase III in India and an IND has filed with the FDA.

<sup>41</sup> Jerusalem, OTCBB: ORMD, [www.oramed.com](http://www.oramed.com). Oramed's ORMD-0801 has completed Phase IIb.

<sup>42</sup> Dallas, Tx, OTCBB: ACP, [www.accesspharma.com](http://www.accesspharma.com). This company, which uses Vitamin B12 as a delivery vehicle, has demonstrated high insulin oral bioavailability using its technology in animal models. It intends to take this product into the clinic.

<sup>43</sup> See POH's 31/3/2010 announcement.

# Phosphagenics (POH)

doing in the insulin space. This bodes well for a future licensing in human applications for POH.

**PassPort is worth keeping an eye on.** One competitor transdermal system which POH will be watching is PassPort, from the privately held Altea Therapeutics<sup>44</sup>. PassPort uses thermal energy to create channels in the surface of the skin through which drugs can flow. Altea reported favourable Phase I results for a PassPort insulin patch in October 2007 showing effective insulin concentrations from around two to 12 hours post delivery<sup>45</sup>. Altea is targeting PassPort at the basal insulin market, and we think its licensing prospects are good in the light of the 2007 data. Given the size of the insulin market there's likely to be room for more than one insulin patch, and TPM has in its favour the fact that it doesn't disrupt the skin (leaving its protective barrier in place and not opening the door to irritation) and has known anti-inflammatory properties.

## TPM may help take delivery of oxycodone and other narcotic analgesics to the next level

**POH can address the vast underserved market for pain management.** Since 2005 POH has been building clinical evidence that TPM can transdermally deliver therapeutic quantities of narcotic analgesic drugs in a way which limits their potential for abuse<sup>46</sup>. In particular the company has enjoyed solid clinical success with oxycodone. This opens up strong commercial opportunities for POH:

- prescription of narcotic analgesics has been rising since the mid-1990s even though the incidence of non-cancer pain appears to be falling, suggesting changed expectations regarding pain on the part of patients<sup>47</sup>;
- around 45% of early stage and 75% of late stage cancer patients undergoing treatment are estimated to experience cancer-related pain<sup>48</sup>, and much of this is managed using narcotic analgesics. This represents perhaps 2-3 million people in the US alone with their numbers rising due to increased cancer incidence;
- the global market for narcotic analgesics, now worth around US\$12bn pa, has been growing 8-12% pa in recent years;
- narcotic analgesics, being opioids (that is, based on opium) have the potential to be highly addictive, so there is strong demand for alternate delivery vehicles that can limit the potential for abuse;
- oxycodone is a US\$3bn pa drug in the US, being considerably more potent than morphine with fewer adverse effects; and
- at present there's no transdermal delivery option for oxycodone, and a transdermal option could grow the market significantly without increasing the potential for abuse.

**Narcotic analgesics are a US\$12bn market globally**

<sup>44</sup> Atlanta, Ga, [www.alteatherapeutics.com](http://www.alteatherapeutics.com).

<sup>45</sup> At this stage Altea's lead products for PassPort are insulin and the opioid analgesic drug fentanyl.

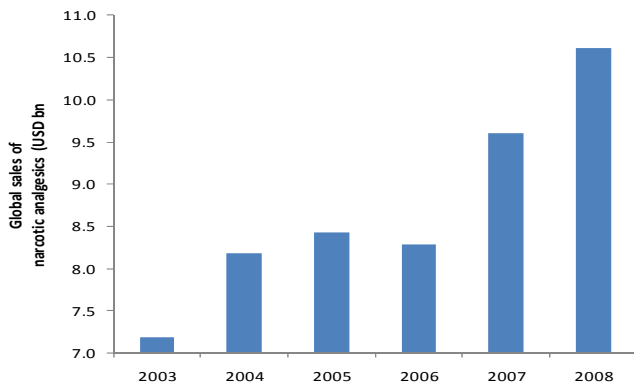
<sup>46</sup> As we detail in Appendix II of this note, POH demonstrated clinically in 2005 and 2006 that TPM could be used to deliver morphine, probably the best known narcotic analgesic. The attraction of morphine as a drug was that it represented a US\$450m US market where delivery was primarily via injections, with no other morphine patches approved for use, and morphine tablets such as MS Contin having low bioavailability (estimated at around 30%, that is, only 30% of the active ingredient actually provides analgesia while the rest fails to make it through the gut wall). Further, success in delivering morphine would open up the potential for POH to address the (then) US\$8-9bn market for narcotic analgesics generally. In May 2006 POH announced that it would conduct a Phase IIa morphine trial in healthy volunteers, however this trial never happened. About the time of this announcement the company talked to clinicians in the pain management field and found there was a greater demand for transdermal delivery of other, higher value narcotic analgesics, particularly oxycodone. Accordingly, in March 2007, the company announced that it would develop a patch form of TPM and go after oxycodone.

<sup>47</sup> Between 1997 and 2007 estimated incidence of severe migraine/ headache, lower back pain and neck pain as a percentage of the US adult population fell 23%, 9% and 11% respectively, while prescriptions of narcotic analgesics as a percentage of the population rose 76% over the same period (source: CDC: Health, United States, 2009).

<sup>48</sup> See J Pain Symptom Manage. 1999 Nov;18(5):358-68.

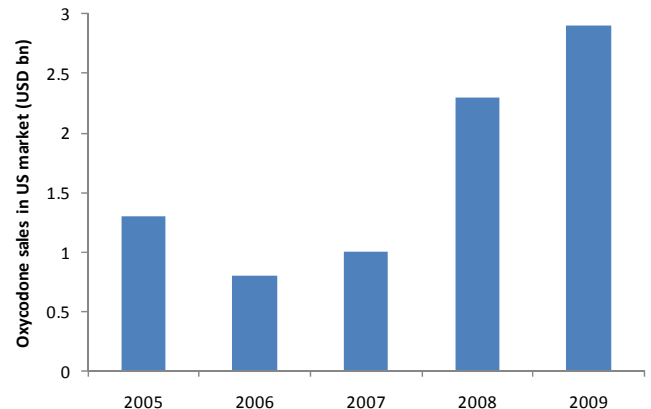
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**Figure 8 - The global market for narcotic analgesics is growing strongly**



SOURCE: IMS HEALTH

**Figure 9 - Oxycontin is a strong performer in the US pharmaceutical market**



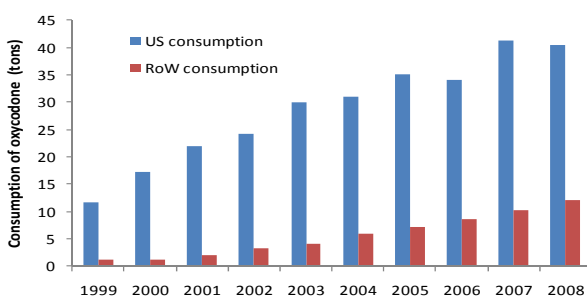
SOURCE: IMS HEALTH

## Oxycodone is a US\$3bn market in America

**Oxycodone is a large market.** Oxycodone represents a significant market opportunity for TPM both in the United States and globally:

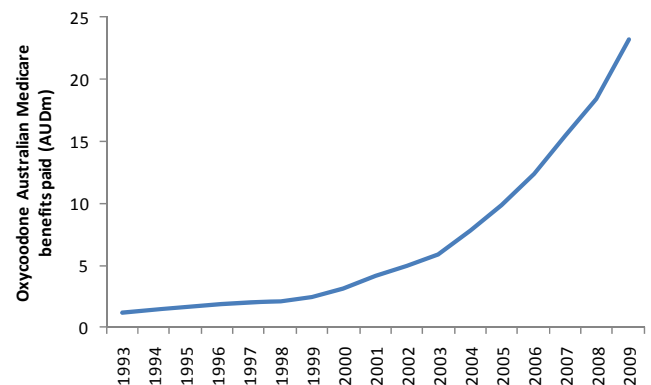
- the current multi-billion size of American market has largely been the work of the privately-held Purdue Pharmaceuticals<sup>49</sup>, which gained FDA approval for its Oxycontin product in 1996<sup>50</sup> and grew it to blockbuster status by 2001. Today Oxycontin's US\$3bn pa in US sales comes from 8 and 12 hour tablets formulations of various sizes<sup>51</sup>; and
- globally consumption of oxycodone has risen 17% pa since the late 1990s, with countries other than the US having grown consumption 28% pa. The drug is particularly popular in Canada and Scandinavia, while in Australia prescriptions rose 18% pa between 1999 and 2009.

**Figure 10 - Global consumption of oxycodone is rising sharply**



SOURCE: INTERNATIONAL NARCOTICS CONTROL BOARD

**Figure 11 - Australian doctors have been big oxycodone prescribers**



SOURCE: MEDICARE

The reason for the success of the drug is that it is 1.5 times more potent than morphine<sup>52</sup> with fewer adverse effects<sup>53</sup>. Regrettably its potency has also led to

<sup>49</sup> Stamford, Ct, www.purduepharma.com.

<sup>50</sup> Oxycodone has been around since 1916. Purdue's Oxycontin product was a timed-released version of the active ingredient, which was a breakthrough because it allowed people in pain to sleep through the night or work during the day, something the company's shorter acting MS Contin oral morphine product did not.

<sup>51</sup> Oxycontin was the 15<sup>th</sup> biggest selling drug in the US in 2009. Source: IMS Health.

<sup>52</sup> See J Pharmacol Exp Ther. 2000 Oct;295(1):91-9.

<sup>53</sup> There is less respiratory depression, sedation, itching sensation, nausea, and euphoria.

# Phosphagenics (POH)

## There have been four successful trials of TPM/oxycodone

an illegal market for oxycodone addicts<sup>54</sup>, which means that legitimate makers of the drug are now looking seriously at developing abuse-resistant formulations<sup>55</sup>.

**The clinical data on TPM/oxycodone has been favourable.** After considerable work on formulation<sup>56</sup> to create TPM/oxycodone, POH went on to generate strong clinical data over the product's first four trials:

- **Oxycodone gel Phase Ia trial, September-December 2007** – Following favourable animal data<sup>57</sup> POH tested TPM/oxycodone in 16 healthy subjects in which a single transdermal application was administered via a gel. Oxycodone showed up in therapeutic quantities in the blood plasma of test subjects<sup>58</sup> at around the 4-5 hour mark, and remained high for at least 44 hours thereafter, peaking at around the 24 hour mark. All this suggested efficient bioavailability<sup>59</sup> and a sustained release profile longer than Oxycontin's with no peaks and valleys;
- **Oxycodone Repeat Insult Patch Test, June 2009.** –After POH completed its patch development work (see Appendix II), TPM/oxycodone came back to the clinic in mid-2009 with a Repeat Insult Patch Test (RIPT) in 50 healthy adults. This test showed no significant erythema or sensitisation<sup>60</sup> being generated by the patches, which was important because opioids tend to cause skin irritation;
- **Oxycodone patch single-dose Phase Ia trial, September 2009** –This trial showed that TPM/oxycodone could be delivered via a matrix patch. The test subjects were given a single dose of oxycodone from the patch, which was left on the skin for three days. At this time point, the oxycodone plasma concentrations were still increasing, while plasma oxycodone continued to be detected at day seven, indicating steady delivery of drug and a 'depot effect' similar to what POH found with its insulin lispro trial in mid-2006; and
- **Phase Ib repeat dose trial, December 2009 – February 2010** – This 20-subject trial saw oxycodone administered via both TPM reservoir and matrix patches on a daily basis. The trial showed the matrix patch to be the superior product, allowing oxycodone plasma concentrations to increase throughout the entire ten day dosing period, but be eliminated quickly after patch removal at day ten.

## TPM/oxycodone can deal efficiently with breakthrough pain

**TPM/oxycodone can deal more efficiently with breakthrough pain.** What these trials demonstrate is that TPM/oxycodone patches have the potential to reduce breakthrough pain, that is, acute periods of pain that start rapidly despite the use of analgesics. The key to reducing breakthrough pain is keeping drug levels steady. Oxycodone tablets can reach therapeutic plasma levels within an hour, providing rapid analgesia, but this early effect wears off after 6-12 hours as the drug is cleared from the body. This leads to what patients experience as 'peaks and valleys' of pain relief between pills. What POH's TPM/oxycodone work

<sup>54</sup> In the US oxycodone is a Schedule II drug under the Controlled Substances Act, meaning that it has 'high potential for abuse' which the Feds are watching out for. An estimated 478,000 Americans abused oxycodone for the first time in 2008. Source: Substance Abuse and Mental Health Services Administration, 2008 National Survey on Drug Use and Health.

<sup>55</sup> In April 2010 Purdue gained FDA approval for a new, abuse-resistant formulation of Oxycontin that is harder to crush, cut, ground, chew or dissolve in liquid.

<sup>56</sup> We understand oxycodone is a difficult drug to formulate due to poor solubility of the hydrochloride form in alcohol. This is one reason why no one has managed to develop a transdermal option before. In effect POH's chemists succeeded where others failed.

<sup>57</sup> See Slide 20 of POH's November 2006 Investor Presentation.

<sup>58</sup> A therapeutic concentration being >8 ng/ml.

<sup>59</sup> Since TPM had already performed well with morphine, oxycodone delivery presented no serious issues. Oxycodone has a molecular weight of 315 daltons, only 10% larger than morphine.

<sup>60</sup> The RIPT involved an 'induction phase' in which the patch was applied to the same skin area and then assessed for erythema on alternate days, and a 'challenge phase' in which the patch was placed on a new area to assess whether there would be an immune response. Over the three week induction phase, no patients exhibited erythema scores above 1 (on a scale of 0 - 4) with most scores registered as zero, demonstrating that TPM/Oxycodone does not cause irritation. Importantly, all patients during the challenge phase had scores of zero, establishing that TPM/Oxycodone is not a sensitiser.

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has shown is that the technology can maintain stable therapeutic plasma concentrations once an initial orally available dose has gotten plasma concentrations quickly up to therapeutic levels.

**TPM/oxycodone can hinder abuse of the drug.** By eliminating ‘dose spiking’ oxycodone patches, even if many are used at once, effectively reduce the ‘rush’ that produces euphoria in patients. This is a potential abuse-deterrent. In addition, a would-be abuser who wants to extract oxycodone from a TPM patch will find it next to impossible to do so. Firstly, it will be difficult to remove the TPM/oxycodone from the patch material. Moreover if he or she did so, they would then need to remove the drug from the TPM formulation, and that would require more than one solvent. Consequently POH thinks that it has developed an abuse-resistant product, which is what the FDA is looking for in new opioid analgesic products<sup>61</sup>.

**Duragesic shows what patchifying a narcotic analgesic can do.** We think J&J’s Duragesic product<sup>62</sup>, which is a reservoir patch that delivers the analgesic fentanyl<sup>63</sup> and is indicated for chronic pain, provides a hint of the commercial possibilities for TPM/oxycodone. Fentanyl had been around since J&J launched it in 1963, but the drug was only doing \$10-12m pa in sales by the late 1980s before Duragesic gained FDA approval in 1990<sup>64</sup>. Duragesic’s first year of sales, 1991, saw \$25m in revenue, and by 2001 the product was worth US\$875m pa. At peak sales in 2005 prior to patent expiry the product sold just over US\$2bn and, five years after generics came in, branded Duragesic sales in 2009 were still close to \$900m. What drove this extraordinary growth was the combination of an abuse-deterrent delivery system combined with ease of administration for the patient, both qualities which TPM/oxycodone apparently has<sup>65</sup>. Duragesic’s success has since spawned development of other analgesic patches, most notably Transtec (marketed in Australia as Norspan), the world’s first opioid analgesic matrix patch, which delivers buprenorphine<sup>66</sup> and was launched by the German pharma company Grünenthal<sup>67</sup> in 2001. We see Duragesic and Transtec as having heightened Big Pharma demand for new patch products such as what POH has developed with TPM/oxycodone.

## TPM/oxycodone’s competitors are all oral solutions

**A TPM/oxycodone patch will have few competitors.** Purdue has been successfully fighting off-patent challengers for Oxycontin since 2000. As a consequence that drug is unlikely to go generic until 2013, and companies looking to enter the oxycodone market before then have to do so using alternative formulations. At the moment POH is mainly competing with two emerging oxycodone products, both to be delivered orally:

- **Remoxy**, from King Pharmaceuticals, a specialty pharma company focused on pain management products<sup>68</sup>, is oxycodone reformulated into an anti-abuse gel cap<sup>69</sup>.

<sup>61</sup> In order to deal with the narcotic abuse issue the FDA indicated in early 2009 that developers of opioid analgesics will likely have to have a ‘Risk Evaluation and Mitigation Strategy’ or REMS for their product in the future. While the REMS requirements are still being worked out by the FDA, it’s reasonable to expect abuse resistance to be one of them.

<sup>62</sup> See [www.duragesic.com](http://www.duragesic.com).

<sup>63</sup> Considered to have around 50-100 times the potency of morphine.

<sup>64</sup> The product was patchified with the help of ALZA, which pioneered patch delivery of drugs in the 1960s and 1970s. J&J bought the company for US\$10.5bn in 2001, but by 2007 had effectively shut down the unit as a creator of new products.

<sup>65</sup> It ought to be noted that potential TPM/oxycodone licensees are going to require strong safety data in the light of Duragesic’s recent experience – a number of product liability lawsuits in the US related to fentanyl overdoses and deaths have resulted from excess drug leaking through the patch membrane. See, for example, [www.findtherightduragesicfentanylpatchlawyer.com](http://www.findtherightduragesicfentanylpatchlawyer.com).

<sup>66</sup> A drug used both as an analgesic and as a detox agent.

<sup>67</sup> Aachen, Germany, privately held, [www.grunenthal.com](http://www.grunenthal.com).

<sup>68</sup> Bristol, Tn, NYSE:KG, [www.kingpharm.com](http://www.kingpharm.com).

<sup>69</sup> That is, a capsule made out of gelatin.

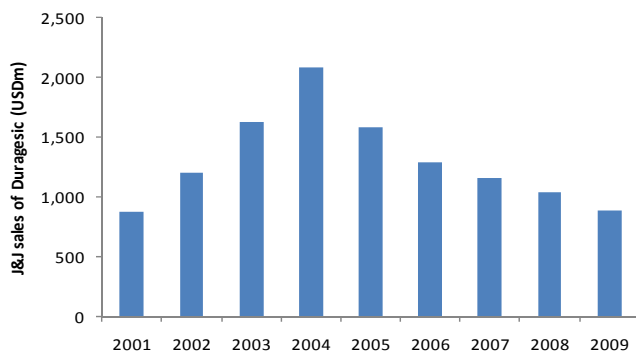
# Phosphagenics (POH)

- **MoxDuo**, from QRX Pharma<sup>70</sup>, which is oxycodone combined with morphine in such a way as the dosage for both is reduced, allowing fewer side effects for the same level of analgesia.

King expects to refile for regulatory approval of Remoxy this year<sup>71</sup> while QRX expects that 2010 will see it file for approval of the first MoxDuo application.

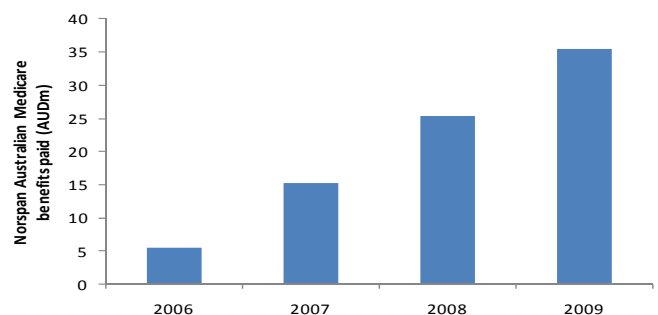
We think, given the size of the existing oral oxycodone market, that there will be other challengers besides these two<sup>72</sup>. TPM's principal competitive advantage in the field is that TPM/oxycodone patches have anti-abuse properties and are non-irritating. As a consequence they are likely to be well-received by the physician community after the success of Duragesic.

**Figure 12 - Duragesic was a blockbuster narcotic analgesic patch**



SOURCE: J&J

**Figure 13 - Demand for Transtec/Norspan has been strong in Australia**



SOURCE: AUSTRALIAN MEDICARE

**We expect TPM/oxycodone to return to the clinic in 2010, headed for potential regulatory approval in 2011/12**

POH could be in pivotal trials for TPM/oxycodone from this year. POH is currently evaluating its clinical options for TPM/oxycodone. The likelihood is that the next trial will take place under an IND and will be part of a series of pharmacokinetic studies currently in planning that will evaluate up to 150 patients in total in a Phase II/III format, at a cost of approximately A\$8m. We expect the product to return to the clinic later in 2010 with a clear path towards regulatory approval, potentially in 2011/12.

## TPM may help create effective competition to Voltaren Gel

TPM can deliver the active ingredient in Voltaren Gel faster than the original. In 2009 POH completed two Phase I clinical trials in which TPM transdermally delivered diclofenac, the non-steroidal anti-inflammatory drug (NSAID), in therapeutic qualities. This work was significant because:

- the control for each trial was Voltaren Gel, the popular Novartis product commonly in treating inflamed tendons and joints from sports injuries. Voltaren Gel's 1% active ingredient is diclofenac sodium<sup>73</sup>;

<sup>70</sup> An ASX-listed company but substantially run out of the US (Bedminster, NJ: ASX: QRX, www.qrxpharma.com).

<sup>71</sup> King licensed Remoxy from Pain Therapeutics, a company focused on developing pain drugs (San Mateo, Ca, Nasdaq: PTIE, www.paintrials.com) in 2005. The Remoxy formulation is achieved using ORADUR, a sustained release oral gel cap technology from Durect (Cupertino, Ca, Nasdaq: DRRX, www.durect.com). King first filed for regulatory approval for Remoxy in June 2008 but six months later the FDA asked for further non-clinical data.

<sup>72</sup> For example, there is also EL-216, from Elite Pharmaceuticals (Northvale, NJ, OTC:BB: ELTP, www.elitepharma.com), which is oxycodone formulated with naltrexone, a well-known opioid antagonist that is often used in treating drug and alcohol abuse. Elite designed a pivotal trial for EL-216 in 2007 but funding issues appear to have prevented this from proceeding. Meanwhile IntelliPharmaCeutics (Toronto, On, Nasdaq: IPCI, www.intellipharmaceutics.com) completed a pilot trial (that is, proof-of-concept prior to the formal Phase I trial) in 2008 of its Rexista product, which is oral oxycodone formulated to be abuse-resistant. Labopharm (Laval, Qc, Nasdaq: DDSS, www.labopharm.com) has done an early stage study on an abuse-resistant oxycodone/acetaminophen combination.

<sup>73</sup> See www.voltarengel.com.

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## Diclofenac is at least a US\$800m opportunity for TPM

- in both cases TPM was able to get considerably more diclofenac through the skin than Voltaren Gel, the result being therapeutically active levels of the drug in plasma at a much faster rate than Voltaren Gel.

**Voltaren represents a significant market opportunity.** Diclofenac, a small molecule<sup>74</sup>, has been off-patent in most jurisdictions for many years<sup>75</sup>, but through effective brand management and line extensions the Voltaren brand is still worth around US\$800m pa in revenue for Novartis. While Voltaren is available in tablet form and via injection, most of that US\$800m is represented by Voltaren Gel. Consequently TPM's clinical success against Voltaren Gel opens up important commercial possibilities for a would-be Voltaren competitor:

- since much of Voltaren's revenue represents over-the-counter sales in Europe, the transdermal diclofenac market notionally has low barriers to entry in that there's no patent protection to surmount;
- in the United States Voltaren Gel is relatively new, having gained FDA approval in late 2007 as a prescription-only product indicated for osteoarthritis, that is, degeneration of joint bones and cartilage resulting from chronic inflammation<sup>76</sup>. So while it only made US\$79m in revenue for Novartis' licensee Endo Pharmaceuticals<sup>77</sup> in 2009, the product's usage is growing due to the high and rising incidence of osteoarthritis in the US<sup>78</sup>.

**TPM/diclofenac Phase Ia, November 2008 – February 2009.** This clinical trial<sup>79</sup> compared diclofenac delivery via TPM/diclofenac to diclofenac delivery via Voltaren Gel in 12 healthy subjects<sup>80</sup>. For the TPM-treated subjects diclofenac showed up in the bloodstream within 30 minutes, as against 2 hours for test subjects who got Voltaren Gel. By that time diclofenac concentrations in the TPM-treated group were seven times the level of Voltaren group. Moreover Voltaren did not catch up to TPM/diclofenac in terms of diclofenac blood concentrations until the 4 hour mark.

**TPM/diclofenac Phase Ib, September 2009.** This trial, also using 12 healthy subjects, sought to compare the efficiency of diclofenac penetration using both TPM/diclofenac and Voltaren Gel. Once again TPM/diclofenac was the superior product. Using tape stripping<sup>81</sup> the investigators determined that at the 30 minute mark TPM/diclofenac had delivered around four times more diclofenac than Voltaren into both the stratum corneum and the deepest levels measured, with a p value less than 0.001 in each case. Moreover the superior delivery continued for at least six hours, which was the extent of measurement.

**A potential pivotal trial for TPM/diclofenac in 2010.** We expect that POH's clinical work to date will allow the company to take TPM/diclofenac into the clinic in 2010 for a Phase II/III study. We think success in this trial will attract licensees eager to break into Voltaren's attractive market space. Both Phase I trials of TPM/diclofenac have seen the drug delivered in gel form, but the company envisages no difficulty converting the product to a patch should a prospective

<sup>74</sup> Molecular weight 296 daltons.

<sup>75</sup> The original US patent protection expired in 1993. The drug itself was launched in Europe by the Novartis precursor company Geigy in 1973.

<sup>76</sup> It has market exclusivity for this indication until October 2010.

<sup>77</sup> Chadds Ford, Pa, Nasdaq: ENDP, www.endo.com.

<sup>78</sup> As estimated 27 million people in the US had osteoarthritis in 2005, representing 9% of the population - source: Arthritis Rheum 2008;58(1):26-35 - with patient numbers rising 2.5% pa.

<sup>79</sup> Earlier pre-clinical work had been favourable - see Slides 16-18 of POH's October 2008 presentation to the Pain Therapeutics Summit at New Brunswick, New Jersey, which was released to the ASX.

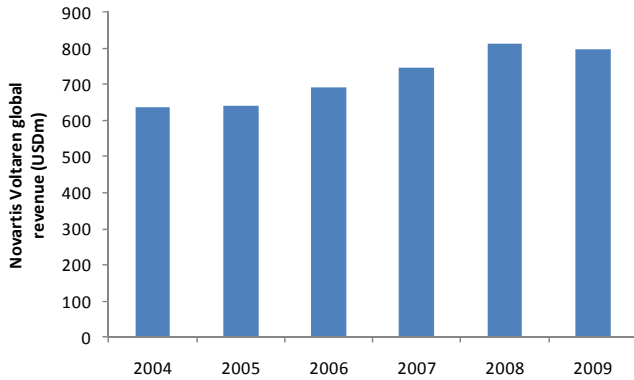
<sup>80</sup> Both 1% and 2% TPM/diclofenac formulated were used.

<sup>81</sup> Tape stripping is a method of determining the penetration of topically-applied drugs into the skin where, after the drug is applied to the skin, adhesive films are repeatedly put onto the treated areas and taken off again. The presence of drug in a film indicate that the drug has penetrated to the level represented by that film.

# Phosphagenics (POH)

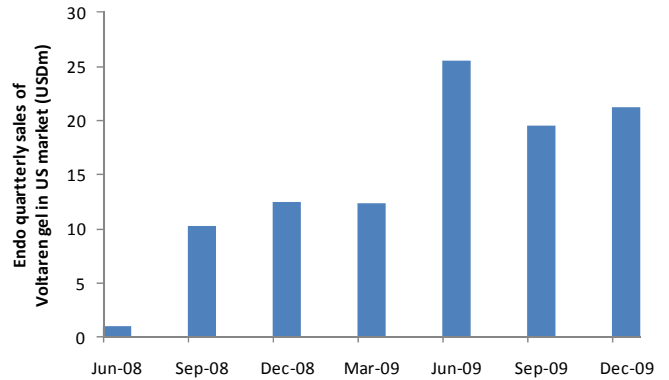
licensee require that, this exercise having already been successfully undertaken for oxycodone.

Figure 14 - Voltaren has been a strong product for Novartis



SOURCE: NOVARTIS

Figure 15 - Endo has been growing US sales of Voltaren Gel

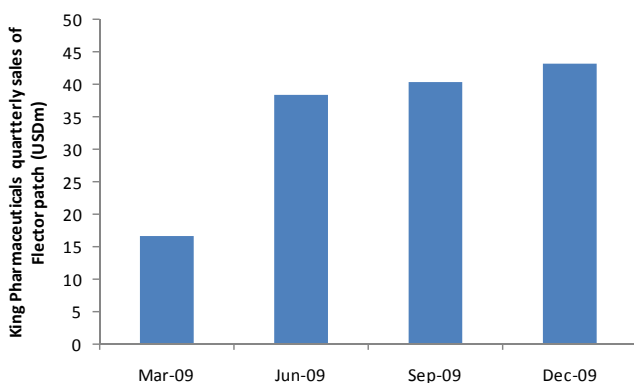


SOURCE: ENDO PHARMACEUTICALS

**There have been significant commercial enquiries regarding TPM/diclofenac**

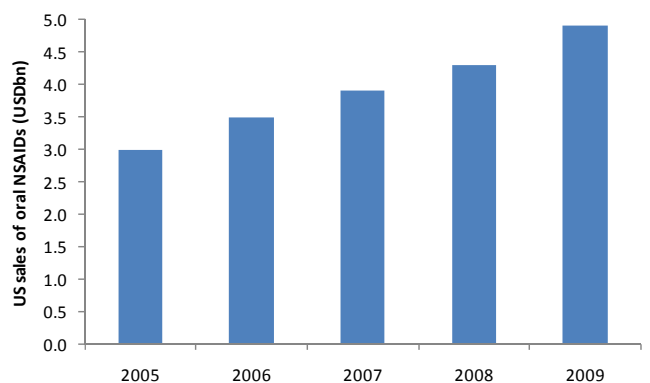
With diclofenac, TPM will have competitors, but the potential market is huge. As well as Voltaren Gel and a new topical diclofenac product called Pennsaid<sup>82</sup>, there is already a diclofenac patch on the US market, the Flector Patch<sup>83</sup>, from King Pharmaceuticals. However we argue that there is likely to be room for other transdermal patches including POH's. In the US in particular there is rising demand for topical NSAIDs due to the well-known gastrointestinal side effects of oral NSAIDs, most notably gastrointestinal bleeding<sup>84</sup>, that can be avoided by topical administration. In spite of these side effects, the current US market for oral NSAIDs is worth around US\$5bn pa, rising at 10-15% pa. This explains why, after the second of its two Phase I diclofenac trials, POH was able to report that it was receiving 'significant commercial enquires' related to TPM/diclofenac<sup>85</sup>.

Figure 16 - The Flector Patch has been growing the market for diclofenac patches



SOURCE: KING PHARMACEUTICALS

Figure 17 - US oral NSAID use has been rising fast



SOURCE: IMD

<sup>82</sup> Pennsaid, from the Canadian pharma company Nuvo Research (Mississauga, On, TSE: NRI, www.nuvoresearch.com) gained FDA approval in late 2009. It is diclofenac delivered in dimethyl sulfoxide (DMSO), a solvent that easily penetrates the skin.

<sup>83</sup> See www.flectorpatch.com. The Flector Patch is diclofenac epolamine 1.3%. The product, which was launched in the US market in early 2008, was inherited by King through its acquisition of Alpharma in late 2008. The patch generated US\$139m in revenue for King in 2009.

<sup>84</sup> It is estimated that such side effects cause around 2% of all hospital admissions. See BMJ. 2004 Jul 3;329(7456):15-9.

<sup>85</sup> See POH's 9/9/09 release to the ASX.

There is the potential to target TPM/diclofenac to actinic keratosis. Another well known topical diclofenac product on the market is Solaraze<sup>86</sup>, whose main indication is treatment of a skin condition called actinic keratosis (AK)<sup>87</sup>. In the event that the topical diclofenac market to treat regular inflammation becomes overcrowded, we see the potential for TPM/diclofenac to be licensed in the AK space. Typically Solaraze and competitor products like Aldara<sup>88</sup> or Efudex<sup>89</sup> are slow working and result in the skin getting red and raw, leading to poor compliance rates. We think TPM's anti-inflammatory properties would allow it to be positioned as a superior product in the AK space in terms of lower dosages required. Around 5-6 million physician office visits a year in the US are generated by AK<sup>90</sup>.

## TPM may help a licensee go after Endo's Lidoderm patch

**TPM/lidocaine is likely to be a better product than Lidoderm**

TPM can deliver the local anaesthetic drug lidocaine. In 2008 POH generated Phase I data showing that TPM can transdermally deliver the local anaesthetic drug lidocaine. This drug is understood to represent a billion dollar market opportunity globally<sup>91</sup>, but more specifically, it represents an opportunity for a POH licensee to elbow in on an American patch market pioneered by the drug delivery major Endo Pharmaceuticals.

**Lidoderm has created the market, but it may go generic soon.** Endo Pharmaceuticals was effectively built on Lidoderm<sup>92</sup>, an 8% lidocaine patch indicated for the treatment of postherpetic neuralgia<sup>93</sup> which gained FDA approval in 1999 and is now a US\$700-800m pa product. The first Lidoderm patents expired in 2009, and the first FDA filing for a potential future generic was made by Watson Pharmaceuticals in January 2010. So while Endo thinks the product has patent protection until 2015, generic versions of LidoDerm could arrive as early as 2012/13<sup>94</sup>.

**TPM/lidocaine Phase I, September-December 2008.** This trial of 12 healthy volunteers, which followed favourable pre-clinical work on lidocaine<sup>95</sup>, saw TPM/lidocaine compared with Xylocaine, a 5% lidocaine topical formulation<sup>96</sup>. The result was 500% more lidocaine in the stratum corneum for TPM ( $p < 0.001$ ) and 450% more penetration of the drug to the deepest layer of skin. However the plasma levels of lidocaine were the same at the six hour mark, an indication that the drug did not move into systemic circulation, something local anaesthetics are not supposed to do.

<sup>86</sup> A product developed by the UK drug delivery company Skyepharma and subsequently licensed to the Switzerland's Nycomed and Spain's Almirall. See [www.solaraze.com](http://www.solaraze.com). Michael Ashton, CEO of Skyepharma from 1996 to 2006, is a non-executive director of POH.

<sup>87</sup> In which scaly, crusty bumps appear on the skin, generally as a result of exposure to the sun.

<sup>88</sup> From the privately held Graceway Pharmaceuticals (Bristol, Tn, [www.gracewaypharma.com](http://www.gracewaypharma.com)), which bought 3M's pharmaceutical business in 2006 - see [www.aldara.com](http://www.aldara.com).

<sup>89</sup> From Valeant Pharmaceuticals (Aliso Viejo, Ca, NYSE: VRX, [www.valeant.com](http://www.valeant.com)) - see [www.efudex.com](http://www.efudex.com).

<sup>90</sup> Source: [www.peplin.com/keratosis.php](http://www.peplin.com/keratosis.php).

<sup>91</sup> Lidocaine is long off-patent, having been first introduced as Xylocaine by Sweden's Astra in the early 1950s.

<sup>92</sup> See [www.lidoderm.com](http://www.lidoderm.com).

<sup>93</sup> That is, pain associated with shingles even after the rash is healed. Postherpetic neuralgia allowed Lidoderm to gain an Orphan Drug designation. In the US an Orphan Drug is one treating a disease affecting less than 200,000 patients, which would ordinarily limit the attractiveness of the market for drug developers. Designation as an Orphan Drug brings with it, among other advantages 1) seven years of marketing exclusivity after approval and 2) 50% tax credits for clinical trial expenses.

<sup>94</sup> Under the rules governing generic drug approvals in the US, a would-be marketer of a generic files an Abbreviated New Drug Application (ANDA) with the FDA showing that its drug is equivalent to the branded product. If the patent holder for the branded drug files suit against the generic drug maker in a Federal court for patent infringement, the FDA cannot approve the new generic for the lesser of 30 months, or until the court rules that patents have not been infringed. The first to file for a generic gets a 180 day exclusivity period once a branded drug goes off-patent.

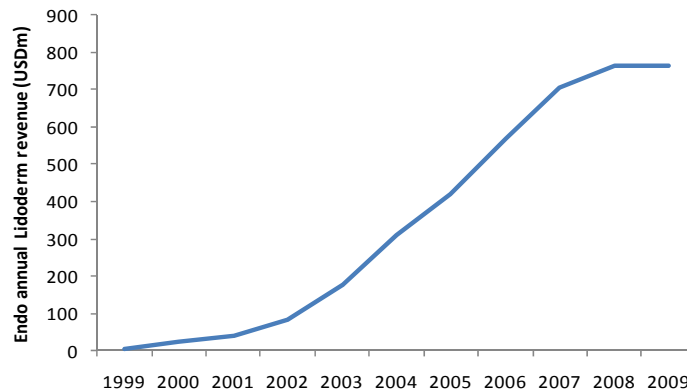
<sup>95</sup> See the company's 30/4/2008 announcement.

<sup>96</sup> For proper comparison, lidocaine was 5% of the total TPM/lidocaine product.

# Phosphagenics (POH)

TPM provides potential for a licensee to access this space. We think TPM could allow a potential Lidoderm competitor to enter the market before pure generics are permitted. Lidoderm is basically a skin-adhesive hydrogel in which lidocaine is formulated without any 'penetration enhancement' material<sup>97</sup>. Since TPM represents a substantially different delivery system, there is the potential for it to not be subject to Lidoderm patent coverage.

**Figure 18 – Endo's Lidoderm lidocaine patch has been a huge commercial success**



SOURCE: ENDO PHARMACEUTICALS

## TPM may markedly improve acne treatment

**TPM can improve penetration of tretinoin.** In 2009 POH gained clinical evidence that TPM can increase the skin penetration of tretinoin, a compound commonly used in skincare as an anti-wrinkle agent and an acne treatment. Tretinoin is one of a number of compounds in the retinoid class of Vitamin A derivatives that include retinoic acid (RA) and have in common the ability to promote skin health<sup>98</sup>. POH's success in tretinoin delivery is important because:

- acne generates around 4 million physician visits a year in the US<sup>99</sup>, with around 30% of these resulting in a prescription for topical retinoids such as J&J's Retin-A or Allergan's Tazorac<sup>100</sup>; and
- the US market for prescription anti-acne topical retinoids is understood to be worth around US\$300m pa even with all major products off-patent<sup>101</sup> and even though the big downside to retinoids is that they cause significant irritation with even small doses<sup>102</sup>.

**Phase I studies showed both reduced skin irritation and deeper penetration.** Following on from successful pre-clinical work in 2007<sup>103</sup>, POH conducted two studies as part of Phase I trial of TPM/RA in healthy subjects that were reported in April 2009:

<sup>97</sup> Basically, it delivers drug by hydrating the surface of the skin, allowing water-soluble drug to pass through. The actual penetration rate for the drug is only 3%, but this is still therapeutically effective.

<sup>98</sup> Retinoids work by 1) building collagen, the connective tissue protein, in the skin; 2) regenerating the elastin that lets skin stretch, and 3) reversing abnormal pigmentation in the skin.

<sup>99</sup> Source: CDC, National Ambulatory Medical Care Survey data.

<sup>100</sup> See J Drugs Dermatol. 2005 Mar-Apr;4(2):172-9.

<sup>101</sup> The original Retin-A product gained FDA approval in 1971. Its successor product, Retin-A Micro, went generic in 2005. Roche's Accutane product went generic in 2001.

<sup>102</sup> J&J notes on the web site for its Retin-A Micro product that 6% of patients involved in testing its 0.1% product 'discontinued due to irritation'. See [www.retinamicro.com](http://www.retinamicro.com).

<sup>103</sup> See POH's announcement of 21/6/2007.

# Phosphagenics (POH)

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- The first study looked at 27 healthy subjects and measured the erythema caused by TPM/RA and Retin-A, the latter being used as a general proxy for retinoid-generated skin discomfort<sup>104</sup>. There was significantly less erythema with TPM/RA after about two weeks of daily treatment than was the case with Retin-A; and
- A second study, in 10 patients, looked at skin penetration of TPM/RA versus Retin-A. After only 1 hour 375% more tretinoin had penetrated the skin than the control patients who were treated with Retin-A. Penetration to the deepest level of the skin measured was 20 times greater with TPM/RA.

**TPM/RA was not irritating to the skin**

**The low irritation scores suggest strong licensing opportunity in acne and in cosmetics.** Because of the irritation issue, topical retinoid products today have concentrations of the active no higher than 0.4%. What the data in the first of POH's two TPM/RA studies shows is that TPM can be used to create a retinoid-based acne product that works at higher concentrations, with more speedy results. This could give a POH licensee seeking to enter the acne space a significant marketing advantage. The trials also strengthen the case that TPM can find a strong market in cosmetic-style applications, where penetration of the active is important for the product to work

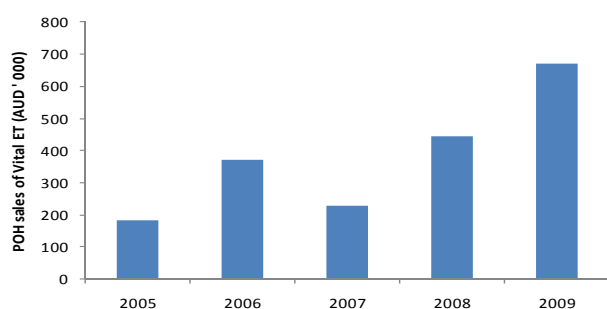
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<sup>104</sup> As well as irritation and erythema, retinoids are noted for generating a burning sensation as well as causing itching.

## Cosmetic, nutraceutical, OTC and other opportunities

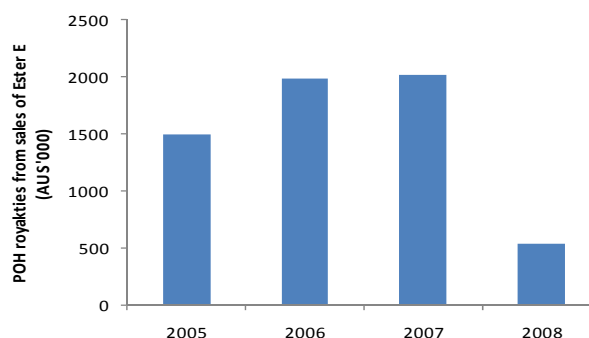
TPM originated from work that POH did in the late 1990s and early 2000s on phosphorylation of Vitamin E, which improved the bioavailability of the original vitamin as well as opened up transdermal delivery options. As a consequence of this history – which we cover in detail in Appendix II of this note – POH has spent time and money over the years developing opportunities in Vitamin E-based nutraceuticals (that is, foods with pharmaceutical properties) and cosmeceuticals (that is, cosmetics with pharmaceutical properties) in addition to its core business in drug delivery. While these non-core ventures have yet to bear substantial commercial fruit, and we have allowed no value for them in our overall valuation of POH, we think there remains the potential to realise upside from them.

Figure 19 - POH enjoys a revenue stream from making and selling phosphorylated Vitamin E



SOURCE: POH

Figure 20 - Ester E provided POH with a \$2m pa royalty stream for a period.



SOURCE: POH

**POH makes  
~A\$700,000 pa from  
sales of Vital ET**

### POH's early Vitamin E products still have promise

The company enjoys some commercial revenue from Vital ET. An early POH product was Vital ET, which is POH's original tocopheryl phosphate mixture, sold to end-users in the food and cosmetics industries via International Specialty Products (ISP), a US chemical company<sup>105</sup>. POH makes Vital ET in a small plant in Melbourne<sup>106</sup> and ships it to ISP in the US<sup>107</sup>. This arrangement only brought in around A\$670,000 pa in revenue to POH in 2009, but over the years it has yielded manufacturing expertise to POH relevant to TPM, as well as free access to a large amount of safety and toxicity data that ISP has generated on TPM.

**Ester E demonstrates that phosphorylated Vitamin E as a dietary supplement can find a market.** In late 2003 POH announced an arrangement with Zila, an Arizona-based developer of 'preventative healthcare technologies and products', where that company would sell POH's phosphorylated Vitamin E as an antioxidant dietary supplement in return for a 10-17% royalty<sup>108</sup>. The deal included a five-year minimum royalty guarantee. POH's product was given the

<sup>105</sup> Privately held, Fort Wayne, NJ, www.ispcorp.com.

<sup>106</sup> This plant was upgraded in 2006 to a production capacity of 100 tonnes of high purity tocopheryl phosphates.

<sup>107</sup> We understand that Vital ET wholesales for around A\$80,000 per tonne. POH sold around 8 tonnes worth of product in calendar 2009.

<sup>108</sup> The deal was for the US, Canadian and Indonesian markets.

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brand name Ester E<sup>109</sup> and was launched in mid-2004. By 2006 the product was yielding POH around A\$2m pa in royalty revenue. However in mid-2006 Zila sold its nutraceuticals business to NBTY, a major nutritional supplement maker<sup>110</sup>, and that company terminated the distribution arrangement in April 2008, considering the minimum royalty guarantee to be uneconomic. POH then turned its attention to other opportunities and did not seek another licensee to replace NBTY. However we think POH's success with the product indicates the potential to re-enter this market under the right conditions<sup>111</sup>.

**POH may have an atherosclerosis drug in its deep pipeline**

## APA-01/Phospha E still has potential in the cardiovascular space

A major area of research interest for POH between 2003 and 2009 was the potential of phosphorylated Vitamin E to treat cardiovascular disease, with two products emerging from this work:

- *APA-01*, potentially a drug for the treatment of atherosclerosis, which is the clogging or hardening of blood vessels caused by plaques of fatty deposits, usually cholesterol; and
- *Phospha E*, a functional food for the prevention and treatment of both atherosclerosis and high cholesterol/triglycerides.

**The animal evidence was good.** Between 2003 and 2008 POH established that its phosphorylated Vitamin E product<sup>112</sup> could:

- reduce, *in vitro*, cell proliferation related to atherosclerosis<sup>113</sup>;
- reduce LDL (ie 'bad cholesterol') and lower triglycerides blood concentrations in animal models<sup>114</sup>;
- prevent the development of atherosclerosis in animal models<sup>115</sup>;
- reduce and treat existing atherosclerotic plaques in animal models<sup>116</sup>; and
- enhance the activity of statins such as Pfizer's Lipitor drug in treating atherosclerosis<sup>117</sup>.

**Phospha A attracted a major industry partner.** On the basis of the animal data POH was able, in April 2006, to option Phospha E to Nestlé Nutrition, the functional foods arm of the Swiss packaged food company<sup>118</sup>. Nestlé Nutrition was interested in trialling the product as a potential functional food to treat

<sup>109</sup> This was TPM-01, POH's original phosphorylated Vitamin E for drug delivery, minus that product's surfactant but packaged in an oil suspension.

<sup>110</sup> NYSE: NTY, Ronkonoma, NY, www.nbty.com.

<sup>111</sup> In 2008 American consumers spent around US\$360m in Vitamin E supplements. Source: See *Will Ginkgo Sales Continue to Slip Following Recent JAMA Study?*, Nutrition Business Journal, 5/1/2010.

<sup>112</sup> In all the following studies the product was the same – TPM-01, POH's original phosphorylated Vitamin E for drug delivery, minus that product's surfactant, in capsulated powder form.

<sup>113</sup> This *in vitro* work was reported to the ASX in June 2003 and January 2004 and in more detail in POH's WO/2004/064831 patent application. Atherosclerosis is believed to start when the innermost layer of an artery becomes injured, leading to proliferation of smooth muscle cells to rebuild the artery and inflammation designed to repair the damage. This actually makes the problem worse. The smooth muscle cells help narrow the artery, while some of the cells generated by the inflammation – the monocytes and macrophages - express CD36 'scavenger molecules' to help clean up the mess, but these molecules take up oxidised LDL which is then laid down within the arteries as cholesterol plaques with the potential to cause a blockage. POH's investigators found that their drug suppressed the proliferation of smooth muscle cells (examples 1 and 2 in the patent application) as well as inhibited the proliferation of the scavenger receptors, reducing the oxidised LDL uptake (example 3). This work was published in the journal *Biochemical and Biophysical Research Communications* in May 2004 - see BBRC 318 (2004) 311-316.

<sup>114</sup> This work was announced to the ASX in March 2005 and was detailed in the 1<sup>st</sup> example of POH's WO 2006/092025 patent application.

<sup>115</sup> This work, in rabbits, was announced to the ASX in April 2005. Rabbits receiving phosphorylated Vitamin E had about 60% fewer cholesterol plaque lesions in their arteries than the controls and around 30% less expression of CD 36 receptors. This work was published in the journal *Archives of Biochemistry and Biophysics* - see Arch Biochem Biophys. 2006 Jun 1;450(1):63-6. Epub 2006 Mar 15.

<sup>116</sup> This work, performed in mouse models, was announced to the ASX in October 2005 and was detailed in the 2<sup>nd</sup> example of POH's WO 2006/092025 patent application.

<sup>117</sup> This work, performed in mouse models and using Lipitor (generic name atorvastatin) as the statin, was announced to the ASX in January 2008.

<sup>118</sup> See www.nestlenutrition.com.

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Metabolic Syndrome, which is the cluster of medical conditions - including obesity, high blood pressure, high cholesterol and diabetes - that increase the risk of heart disease, strokes, and vascular disease. With Metabolic Syndrome hitting a quarter of the US population<sup>119</sup>, the market potential of such a product was enormous. Nestlé-funded animal studies announced in December 2006 confirmed earlier work, and the product entered a 160-patient Phase II clinical trial for which recruitment was completed by November 2008<sup>120</sup>.

**The Phospha E results warrant further follow up.** Results from the Nestlé trial, announced in December 2009, were a disappointment in that the trial did not reach its endpoint, which was a reduction in high-sensitivity C-reactive protein<sup>121</sup>. Nonetheless POH noted 'a statistically significant improvement in some heart disease and diabetes risk factors - particularly in smokers'. We argue that this suggests the potential for POH to revisit Vitamin E-based therapies for Metabolic Syndrome later, with a different dosage and trial structure.

**There also remains potential to follow up the APA-01 lab work.** We think the pre-clinical data on atherosclerosis bodes well for a potential clinical trial of APA-01 in conjunction with a statin. Atherosclerosis is a significant market, with around 16 million Americans affected<sup>122</sup>, and an atherosclerosis indication has been one reason why AstraZeneca's Crestor drug<sup>123</sup>, a statin, grew global sales 25%, to US\$4.5bn, in 2009. Crestor, however, doesn't go generic in the US until 2016. APA-01 potentially allows a licensee looking to develop an atherosclerosis treatment to do so with POH's product plus Lipitor, which goes off-patent in June 2011.

## There is a potential cancer drug deep in POH's pipeline

In January 2006 POH made a remarkable announcement to the ASX, reporting that, in experimenting with  $\gamma$ -tocopherols, phosphorylated using the West Process, the company had discovered a potential cancer drug. POH's  $\gamma$ -tocopherol phosphate mixture, codenamed GTP-0805, was found *in vitro* to be powerful in killing prostate cancer cells (in combination with lycopene, a carotenoid<sup>124</sup> found in tomatoes) and breast cancer cells. A later *in vitro* study which was reported in September 2006 found a 78% reduction in tumour growth when the compound was combined with the well-regarded cancer drug tamoxifen, compared to 21% for tamoxifen alone. POH has not revisited this work since 2006, but has patent applications over GTP-805, giving it an option to pursue yet another potentially high-value Vitamin-E-based drug<sup>125</sup>.

## Recent investments in cosmeceuticals show promise

In 2008 POH made a strategic decision to enter the personal care space with various cosmetic products. The company saw the potential in this space to quickly develop and launch products at little cost, since the relevant work already having been done over the previous nine years - while addressing a market worth

**Cosmetics are an easy way for POH to enjoy near-term revenue**

<sup>119</sup> Source: NHLBI.

<sup>120</sup> Among other activities associated with this trial Nestlé convened an expert's panel which in March 2008 unanimously concluded that Phospha E was Generally Recognized As Safe (GRAS), meaning that it could be used in the food industry.

<sup>121</sup> C-reactive protein, a protein in the blood which rises in response to inflammation, has come to be regarded in recent years as diagnostic of Metabolic Syndrome. See *Circulation*. 2003;107:391-397.

<sup>122</sup> Source: Merck Manual.

<sup>123</sup> See [www.crestor.com](http://www.crestor.com).

<sup>124</sup> Carotenoids are red, yellow, and orange fat-soluble pigments found in many plants. They have antioxidant and potentially anti-cancer properties.

<sup>125</sup> There were around 194,000 new breast cancer cases in the US in 2009 and around 40,000 deaths. Source: American Cancer Society, *Cancer Facts and Figures*, 2009.

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US\$200bn pa worldwide. This has resulted in two product lines, one for the US market and one for the Australian market.

## The Métier Tribeca relationship gets POH into the US premium cosmetics market.

In July 2009 POH announced an arrangement with Métier Tribeca, a New York cosmetics firm<sup>126</sup>, whereby POH would develop a range of premium, Vitamin E-based products to be sold by Métier Tribeca in the US under its Le Métier de Beauté brand. Profits from this deal will be shared equally between POH and Métier Tribeca. We see the deal as having limited downside and potentially considerable upside for POH, since

- Métier Tribeca, who will pay for all product sourcing and costs, already has distribution arrangements in place through the high-end department store chains Neiman Marcus and Bergdorf Goodman;
- the products can get to market quickly. Métier Tribeca launched the Peau de Vierge Anti-Aging Collection<sup>127</sup> only four months after the deal with POH was signed; and
- the products retail at prices in the order of US\$100 each, meaning that volume isn't a great issue either for POH or Métier Tribeca.

**Elixia allows POH to sell into the Australian cosmetics market.** This range of skincare products<sup>128</sup> was developed for the Australian market in 2009 and launched in April 2010. Elixia retails through the 75-store Pulse Pharmacy chain.

We think these cosmetic products have strong potential. We understand the La Métier products only cost \$20,000 to develop, and the Elixia products another \$80,000. This capital can be earned back fairly easily from early sales, leaving plenty of upside for POH in the event of strong commercial success.

## AOD9604 allows POH to realise some of the promise of Metabolic Pharmaceuticals

In August 2009 POH announced that it was collaborating with another Melbourne biotech company, Metabolic Pharmaceuticals, on Metabolic's AOD9604 drug, to explore the drug's potential as a cosmeceutical that can reduce cellulite and subcutaneous fat. This work arose in part because Esra Ogru, POH's joint CEO, used to work at Metabolic prior to joining POH.

**POH wants to reprofile a failed obesity drug.** AOD9604, which is a peptide fragment of human growth hormone, had formerly been trialled by Metabolic as an obesity therapeutic, but had failed in this indication at Phase IIb in early 2007. Metabolic has since started to explore other biotech areas, changing its name late last year to Calzada<sup>129</sup>, but retains the intellectual property over AOD9604. To facilitate the current collaboration POH has an option over the drug for the cosmeceutical indication that, upon exercise, can turn into a licence.

**Why POH thinks it can succeed where Metabolic failed.** POH's basic thinking on AOD9604 is that the drug failed as an obesity therapy because it was made orally available, which likely reduced bioavailability and also potentially resulted in protein denaturation in the gastrointestinal tract which would have reduced the drug's activity. POH now wants to try transdermal delivery via a cosmetic cream, which would allow the drug to be delivered directly into subcutaneous fat tissue

**POH may have an effective anti-fat cream in AOD9604**

<sup>126</sup> A company founded around 2007. See [www.lemetierdebeaute.com](http://www.lemetierdebeaute.com).

<sup>127</sup> Peau de Vierge is French for 'skin of the maiden'. The products in the Peau de Vierge collection use TPM to deliver retinol, that is Vitamin A, which is known to be useful in maintaining skin health.

<sup>128</sup> See [www.elixia.com.au](http://www.elixia.com.au).

<sup>129</sup> ASX: CXD, [www.calzada.com.au](http://www.calzada.com.au).

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without alteration<sup>130</sup>. A cellulite and subcutaneous fat indication would likely require less in the way of trial data to get on the market, since no therapeutic claims would be made and data would be mainly to substantiate label claims. AOD9604 was safe and well tolerated in Metabolic's Phase IIb trial.

**The time to market is fairly short.** POH believes that, should the research be successful, a commercial cosmetic cream can be launched by the first half of calendar 2011. The development costs of this product will likely be mild – only \$100,000 for pre-clinicals and a short clinical trial before product release.

## Quigley may leverage TPM's entry into OTC pharmaceuticals

In March 2010 POH announced a joint venture with Quigley Corp, an American maker of OTC products<sup>131</sup>, that allows TPM to access the OTC pharmaceutical space. Under this deal the two companies will work together on creating TPM-deliverable OTC remedies for the US market through a joint venture called Phusion Laboratories.

**Quigley may help  
TPM grow in the OTC  
space**

**A small company that is hungry to grow.** Quigley is famous in the US for its 'Cold-EEZE' brand of lozenges, designed to reduce the severity and duration of the common cold. However the company is small (calendar 2009 net revenue US\$19.8m) and it is keen to expand through new product development. Quigley paid US\$1m cash and US\$3m in its shares to access the TPM technology, and has committed US\$2.5m to develop the first TPM-enabled products

**There is strong potential upside.** Quigley thinks TPM can give it the edge in creating better transdermal OTC products, since TPM has no irritation issues whereas many other transdermal products do.

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<sup>130</sup> At a molecular weight of 1,815 daltons, AOD9604 is around one-third the size of insulin, meaning that be can be delivered transdermally by TPM fairly easily.

<sup>131</sup> Doylestown, Pa, Nasdaq: QGLY, [www.quigleyco.com](http://www.quigleyco.com).

## Commercial leadership

### Harry Rosen knows how to commercialise science

We have a high regard for POH's leadership, which has demonstrated commercial and scientific wisdom as it has built the company since the late 1990s.

**Harry Rosen**, a POH founder who is a lawyer by background and who owns 8.7% of the company, is an entrepreneur with a talent for commercialising science. He has already enjoyed significant commercial success through his leadership of Betatene Ltd, which in the 1980s pioneered the production of natural beta carotene for use in nutritional supplements and aquaculture feedstock<sup>132</sup>. While Betatene struggled in its early days, and was valued at only A\$9m in 1989<sup>133</sup> when it was folded into Denehurst, a lead-zinc miner<sup>134</sup>, the business ultimately overcame all its scientific and commercial setbacks in the 1990s. Denehurst was able to sell 40% of it to the German chemical company Henkel in 1993 for US\$15m, and the other 60% to Henkel for \$36m in 1995<sup>135</sup>. Rosen stayed on with Henkel after this for a number of years as VP, Corporate Development. The Betatene experience has made Rosen highly knowledgeable about the nutrition and health care industries, and has allowed him to bring valuable relationships to bear in building up POH, in that Simon West, the key scientific talent at Betatene, provided the basic invention impetus towards development of the TPM technology between 1999 and 2002. We have found Rosen to be judicious in terms of deploying POH's capital towards projects with the greatest potential commercial return.

**Dr Esra Ogru**, a joint CEO of POH alongside Harry Rosen from April 2010, and a research biochemist by background, has brought valuable scientific and operational insight to the company since she joined in 2001. She was instrumental in development of TPM-02, allowing POH to go after both large and small molecule drug delivery. She streamlined systems for manufacturing of the product. She has brought in-house expertise into POH to help move the TPM technology into the clinic, and she has cost-effectively structured POH's clinical programme which is now set to add considerable value to the company.

**Fred Banti**, who does business development for POH out of the company's New York office, brings valuable Big Pharma experience to the company. He has held business development and licensing roles at Sanofi-Aventis, Pfizer and Novartis and has also helped build two emerging companies - the drug delivery company Penwest and the cancer drug developer Gemin X Pharmaceuticals. We think this varied set of experiences will heighten POH's prospects in licensing TPM applications over the next few years.

**The Phosphagenics board**, to be chaired by Jonathan Addison (currently Investment Manager of the Meat Industry Employee Superannuation Fund) from late May 2010 represents, in our opinion, a good mix of the skills required to build an early-stage biotech company, with, in addition to Harry Rosen and Esra Ogru, a scientist (Professor John Mills, a clinician who specialises in infectious diseases), a pharmaceutical company executive (Michael Ashton, best known as CEO of the UK drug delivery company Skyepharm between 1998 and 2006) and a finance person (Addison).

<sup>132</sup> Beta carotene is an anti-oxidant and provitamin A derived from algae. Australia produces over 80% of the world's natural beta carotene thanks to Betatene, which extracts the raw material from open brine pond cultures of an alga called *Dunaliella salina* in South Australia and Western Australia.

<sup>133</sup> Betatene had been capped at \$10m at the time of its 1985 ASX float.

<sup>134</sup> Denehurst's major assets were the Woodlawn mine near Canberra and the Benambra base metals mine in Victoria. It was placed in administration in 1998, a victim of the low metal prices of the late 1990s.

<sup>135</sup> The business is now owned by Cognis, a privately-held German company (Monheim, Bavaria, [www.cognis.com](http://www.cognis.com)).

## The risks

### Biotechnology is high risk, high return

The stocks of biotechnology companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character. Since most biotechnology companies in Australia fit this description, the speculative moniker also applies to the entire sector. The fact that biotechnology's intellectual property base lies in science not generally regarded as accessible to the layman adds further to the riskiness with which biotechnology ought to be regarded. Investors are advised to be cognisant of this risk before buying any Australian biotech stock, including POH.

### POH is not without risk

We see six major risks specifically related to POH as a company and a stock:

- 1 **Clinical risk** – There is the risk that POH's planned clinical trials in oxycodone delivery and other applications could fail to reach their endpoints;
- 2 **Sentiment risk** – Biotech-oriented investors tend to prefer drug development stocks where the lead candidate is a new chemical entity or new protein-based drug in Phase III, rather than a drug delivery stock such as POH where the regulatory pathway and commercial payoff may be less well understood, and perceived to be somewhat crowded;
- 3 **Timing risk** – There is the risk that POH could take much longer to complete its trials than the timing we have postulated in this note, possibly because of slow recruitment;
- 4 **Partnering risk** – There is the risk that POH's prospective partners may strike too hard a bargain for POH shareholders to enjoy a strong return;
- 5 **IP risk** – There is the risk that POH could find itself locked in dispute over patent infringement should its science be found to lean too heavily on unrelated or unlicensed predecessor science; and
- 6 **Burn rate** – The company has raised \$51m in equity capital over the last six years and burned around \$700,000 a month in 2009. There was \$10.9m cash at December 2009. There remains the risk that POH may have to make further capital raisings to fund its burn rate in the future, and some of these raisings may take place when pharmaceutical and biotech stocks are out of favour.

**POH's burn rate is around \$700,000 per month**

## Appendix I – POH’s capital structure

Figure 21 - POH’s capital structure

Shares (ASX Code POH)	739,696,509	Share price	12.5
Shares that may result from the conversion of options	27,600,000	Undiluted cap (\$m)	92.5
Total diluted shares	752,296,509	F.D. Cap (\$m)	95.9

Options schedule

Code	Number	Exercise price	Expiry date	Cash
POHAI	1,000,000	\$0.21	18/08/2010	\$214,800
POHAK	500,000	\$0.24	28/03/2011	\$120,000
POHAM	1,600,000	\$0.23	22/05/2011	\$375,360
POHAO	100,000	\$0.36	28/08/2011	\$35,620
POHAQ	1,300,000	\$0.24	6/06/2012	\$307,710
POHAS	2,000,000	\$0.13	30/06/2018	\$267,400
POHAS	2,600,000	\$0.15	17/08/2013	\$390,000
POHAS	650,000	\$0.14	30/06/2018	\$89,050
POHAS	2,850,000	\$0.15	17/06/2014	\$427,500
New options (13/4/2010 announcement <sup>136</sup> )	15,000,000	\$0.14	31/03/2013	\$2,130,000
Total POH options on issue	27,600,000	\$0.1579	17/08/2013	\$4,357,440

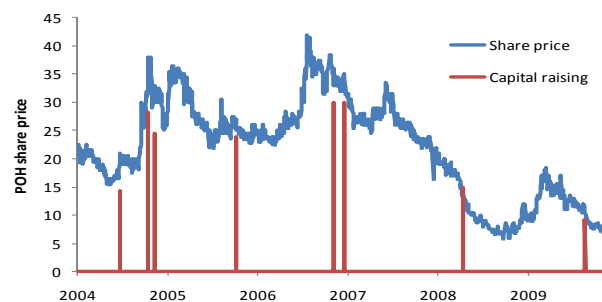
SOURCE: POH, SOUTHERN CROSS EQUITIES.

Figure 22 - POH’s equity capital raising history

Date	Shares (million)	% of current shares on issue	Price	Amount raised (\$m)	Discount to market	Note
Jul-04	6.4	0.9%	\$0.14	0.9	28.5%	UK placement
Nov-04	7.5	1.0%	\$0.28	2.1	18.0%	UK placement
Dec-04	16.1	2.2%	\$0.25	4.0	25.6%	Placement
Nov-05	46.9	6.3%	\$0.24	11.3	11.1%	Placement
Dec-06	33.3	4.5%	\$0.30	10.0	9.1%	Placement
Jan-07	4.9	0.7%	\$0.30	1.5	11.8%	Placement
Jan-07	18.4	2.5%	\$0.30	5.5	11.8%	SPP
May-08	60.1	8.1%	\$0.15	9.0	9.1%	Placement
Sep-09	76.1	10.3%	\$0.09	7.0	12.4%	SPP
Total	269.7	36.5%	\$0.19	51.3		

SOURCE: POH

Figure 23 – POH has raised \$51m in equity capital since early 2004



SOURCE: POH, IRESS

<sup>136</sup> To be issued to Southern Cross Equities in its role as a corporate adviser. See the last page of this note for details.

## Appendix II – The TPM technology

### The origins of TPM

TPM has its origins in a number of research projects conducted from around 1999 by Simon West, a Melbourne-based chemist with a long track record as an inventor who currently owns 6.8% of POH and remains a scientific advisor to the company<sup>137</sup>. The West projects and other work which originated from them were partly funded by POH until 2004<sup>138</sup> and wholly funded by it thereafter.

**1999 - It all started with Vitamin E.** West's initial researches for POH and its co-investors were concerned with Vitamin E, which is valued by nutritionists primarily for its antioxidant properties. Vitamin E is actually a family of eight molecules, of which four are called 'tocopherols' and four 'tocotrienols'. Most Vitamin E supplements on the market are of the  $\alpha$ -tocopherol variety, obtained from soybeans. In 1999 West was exploring ways to get tocotrienols, which have much greater antioxidant properties than tocopherols, from palm oil. Traditionally it had been difficult to fractionate tocotrienols out of palm oil fatty acid distillate because they were 'lipophilic', that is, soluble in fat. West dealt with this issue by altering the tocotrienols through addition of a phosphate group, using a new process which we have called the West Process and for which patent protection was sought<sup>139</sup>. The phosphorylated tocotrienols and tocopherols created by the West Process were 'hydrophilic', that is, water-soluble. This meant they precipitated out of the free fatty acid solution as froth on the surface of the flotation vessels. The partial success of this technique for Vitamin E recovery<sup>140</sup>, while it never proceeded to commercialisation<sup>141</sup>, pointed West towards a potentially larger payoff in drug delivery.

### Phosphorylating a drug improves its bioavailability

**2000 and 2001 - Improving drug bioavailability through phosphorylation.** The ease with which tocopherols could be converted from fat-soluble to water-soluble using the West Process suggested to West the possibility of using his process on pharmaceutical drugs to improve their bioavailability, that is, their ability to be available where they are needed in the body. Many drugs taken orally have poor bioavailability because they are lipophilic. Being lipophilic often allows such a drug good specificity for what it is targeting, which is more often than not a lipid on the surface of a particular kind of cell. However the rate of absorption by the body of the drug is often low because, being insoluble in water, it's harder for the drug to get through the water-rich environment of the gastrointestinal tract. Having demonstrated that many kinds of compounds were amenable to phosphorylation via the West Process<sup>142</sup>, West and his colleagues started to investigate:

<sup>137</sup> West's specialty is processes involving physical sciences. At Kraft he worked on innovations such as 'magnetic carbon' for separating trace elements out of food and on new methods to remove impurities from brewer's yeast. For Betatene he worked on the beta carotene process that enabled that company's commercial success. For Denehurst he came up with a new zinc tailings recovery process. And more recently for a privately held company called Petrecycle (formerly an investee company of Vital Capital before it became Phosphagenics) he invented a technology for recycling PET bottles. We counted 10 US patents issued since 1976 that list West as an inventor.

<sup>138</sup> When the company was called Vital Capital and was a Pooled Development Fund. Vital Capital's name was changed to Phosphagenics in early 2004 after the decision was taken to focus solely on drug delivery technology. The Pooled Development License was relinquished late in 2004.

<sup>139</sup> See *Improved process for phosphorylation and compounds produced by this process*, WO/2000/069865 (priority date 14/05/1999, invented by Simon West). Basically the process involves cooking the chemical to be phosphorylated with phosphorus pentoxide ( $P_4O_{10}$ ) at under 40 degrees Celsius.

<sup>140</sup> See *Recovery of chroman derivatives*, WO/2000/043380 (priority date 25/01/1999, invented by Simon West). A chroman is the core ring at the centre of a Vitamin E molecule.

<sup>141</sup> The process was, unfortunately, too costly relative to the cost of obtaining commercial available  $\alpha$ -tocopherol from companies like Archer Daniels Midland, the American soybean producer. Purity of product was also an issue.

<sup>142</sup> In WO/2000/069865 West demonstrates, among other potential applications, that the female sex hormone estradiol, various phytosterols (plant-derived compounds similar to cholesterol and believed to be useful as anti-inflammatory and cholesterol-lowering agents), and vitamin K1 (considered useful in maintaining bone health, among other potential applications) can be successfully phosphorylated using the West Process.

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- the potential of phosphorylated of pharmaceuticals to improve drug bioavailability<sup>143</sup>; and
- the potential use of phosphorylated compounds as delivery systems for better bioavailability of unaltered drugs.

The former approach would allow the creation of New Chemical Entities that would take the usual lengthy clinical testing process before gaining regulatory approval. The latter approach, by contrast, presented the possibility of a faster approval process since all that would be necessary to prove is that the delivery process put therapeutic quantities of an already approved drug into the bloodstream of the patient.

## TPM was initially focused on skin care

**2001 – Phosphorylated Vitamin E results in a better skin care product.** While West and his colleagues were working on the drug bioavailability and delivery potential of the West Process, they also applied it to Vitamin E so as to create a commercial product. Due to its antioxidant properties Vitamin E is frequently used in skin care products and cosmetics<sup>144</sup>. Usually tocopheryl acetate is used for these applications<sup>145</sup>. West et. al. were able to demonstrate that tocopheryl phosphate, prepared using the West Process, was a better skin care product than tocopheryl acetate, mainly because more of it could slip through the epidermis, the outer layer of skin, and into the next layer of skin, the dermis. This came about because:

- 1) the West Process generated an  $\alpha$ -tocopheryl phosphate product which was a 2:1 mixture of 'TP' and 'T<sub>2</sub>P'. TP was mono- $\alpha$ -tocopheryl phosphate, that is, a single unit tocopheryl phosphate molecule. T<sub>2</sub>P was di- $\alpha$ -tocopheryl phosphate, or two TP units linked together. T<sub>2</sub>P was lipophilic, making it ideal to disrupt the hydrophobic outer layer of skin, called the stratum corneum. This in turn made it easy for TP to slip through into the epidermis and dermis; and
- 2) West et. al. added a surfactant to the  $\alpha$ -tocopheryl phosphate mixture. Surfactants are substances that can reduce the surface tension of a liquid, making it easier for the liquid to penetrate solids.

These two factors ensured that when West's tocopheryl phosphate mixture was compared with tocopheryl acetate in a skin penetration study using human cadaver skin, 19-times more tocopheryl phosphate than tocopheryl acetate made it through to the dermis<sup>146</sup>. This transdermal penetration ability allowed reasonably early commercial take-up of POH's new product. It was launched by POH in 2001, and by 2003 the company had signed up the US chemical company International Specialty Products as a distributor. ISP continues to sell the product today under the Vital ET brand.

## Pre-clinical and early clinical success with TPM-01

**2002/03 – Phosphorylated Vitamin E becomes TPM-01, a workable drug delivery system.** The ability of the West et. al.'s tocopheryl phosphate mixture - or 'TPM' as it came to be called - to cross the skin barrier led directly to POH's first work in drug delivery. The POH team started formulating TPM with various

<sup>143</sup> POH first presented data on increased bioavailability of phosphorylated drugs in its October-November 2002 shareholder newsletter, which showed a chart demonstrating 50% greater tocopheryl phosphate concentrations in the livers of rats fed oral tocopheryl phosphate than those fed tocopheryl acetate. This work was reproduced in POH's WO 03/013550 patent application.

<sup>144</sup> Turning up in products as widespread as Stay On Cover Stick (a Nivea concealer product), Nivea for Men Shaving Gel, and Revlon Creme Gloss (a lipgloss).

<sup>145</sup> Since free tocopherol is inherently unstable. Tocopherol acetate is tocopherol combined with acetic acid as a stabiliser. Acetic acid is the compound that gives vinegar its sour taste and pungent smell.

<sup>146</sup> The data for this study was reported in POH's WO 02/040033 and WO 02/040034 patent applications. WO 02/040034 also shows various personal care applications of the tocopheryl phosphate mixture.

# Phosphagenics (POH)

small molecule drugs, and enjoyed transdermal delivery success in rat models with three drugs in particular over the course of 2002 and 2003<sup>147</sup>.

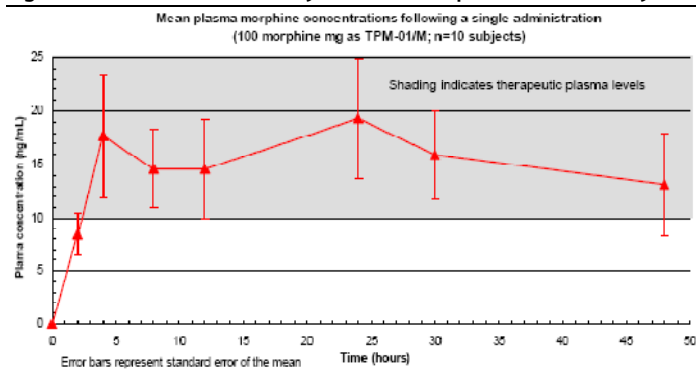
- **Delivery of estradiol, May 2002.** In this maiden drug delivery experiment, West et. al. phosphorylated the female sex hormone estradiol and delivered it, as well as the regular unphosphorylated hormone, through the skin and into the blood using TPM. In each case significant quantities of hormone made it across the skin barrier and therapeutically useful quantities of estrogens showed up in blood plasma<sup>148</sup>.
- **Delivery of atropine, March 2003.** The West team's next drug delivery success was with atropine, a drug used to increase heart rate. When TPM was used to deliver atropine sulphate, the usual delivery form of the drug, the heart rate of the treated rats sped up for six hours post delivery.
- **Delivery of morphine, August 2003.** Next West et al. used TPM to deliver the analgesic drug morphine. The treated rats in this experiment scored well on 'paw withdrawal latency' – they moved their paws away from a heat source more slowly than untreated controls, indicating that therapeutic amounts of morphine were being delivered and producing analgesia<sup>149</sup>.

These three experiments became the basis of POH's WO/2004/014432 patent application over TPM-01, which is what POH started calling its new drug delivery vehicle from 2004.

**Morphine was the first trialed product for TPM**

**2005 - Early clinical success with morphine delivery.** The early animal work on TPM-01 was followed up with a Phase I proof-of-concept trial of morphine delivery in humans. The results, reported in April 2005, provided a clear indication of the clinical potential of TPM. The challenge in morphine analgesia is keeping plasma concentrations of the drug from falling below 8 ng/ml, which is where the patient starts to feel pain again. Currently the 'gold standard' morphine therapeutic, which is extended-release tablets like MS Contin from Purdue Pharma, can achieve this for around 24 hours. In POH's trial, which saw 10 healthy volunteers receiving a single dose of 100 mg of morphine using TPM-01, the result was adequate plasma concentrations for up to 48 hours, around twice the gold standard.

**Figure 24 - TPM-01 successfully delivered morphine transdermally**



<sup>147</sup> As could be expected from a product based on Vitamin E and its cosmetic properties, in each experiment drug delivery took place without any signs of erythema. This has continued to be the case through subsequent iterations of the TPM technology.

<sup>148</sup> In 2002 POH also tested the ability of TPM-01 to deliver testosterone. This work was never announced to the ASX, probably because the results were not as strong as for estradiol.

<sup>149</sup> POH subsequently did further pre-clinical work on TPM-based morphine delivery in pigs, with what we understand to be favourable results. This work was announced to the ASX in May 2004. Transdermal delivery in pigs was significant because pigs are physiologically like humans but they have thicker skin.

# Phosphagenics (POH)

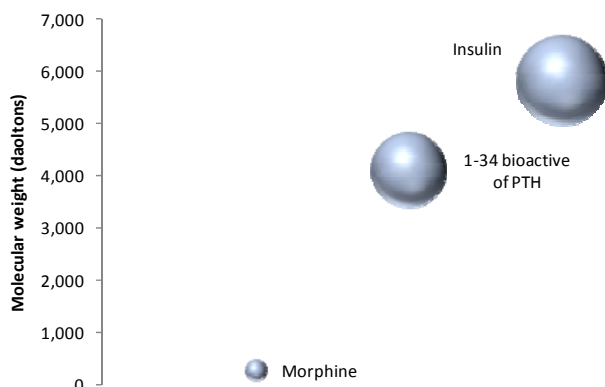
**TPM-01 was only good for small molecule delivery**

## TPM-02 takes the technology to the next level

2005 – TPM-01 is tried out for large molecule drug delivery. The TPM-01 morphine trial indicated that the technology worked well in a clinical setting when the delivery payload was a small molecule drug. However in mid-2005 POH also began to explore TPM-01’s potential with biological drugs, where large molecular weight would make it more of a challenge for the drug to get through the skin. Two animal experiments hinted at the possibilities:

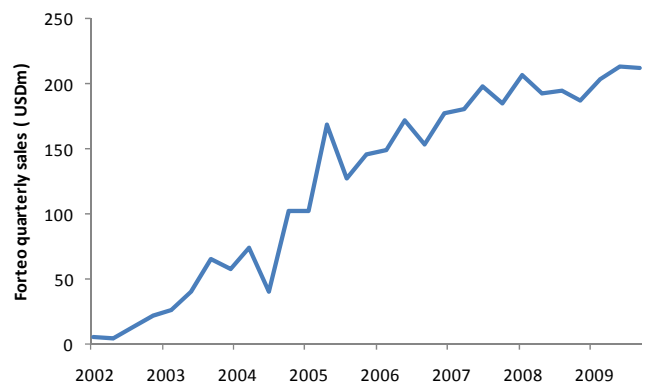
- **Delivery of PTH, June 2005** – The first experiment involved using TPM-01 to deliver Forteo, an Eli Lilly osteoporosis drug (generic name teriparatide), which had gained FDA approval in 2002. Forteo is the bio-active fragment of human parathyroid hormone (PTH)<sup>150</sup> and is around 13 times larger than morphine in terms of molecular weight. Commercially the drug had been performing well for Lilly, with around US\$275m in worldwide annual sales by mid-2005<sup>151</sup>, so success in PTH delivery would show how a fast-growing biological drug, which hitherto was only available by injection, could notionally have its market size and useful life extended by a POH transdermal delivery option. POH reported no data at the time of this experiment but indicated to the market that PTH had been ‘successfully delivered’.
- **Delivery of insulin, September 2005** – The second experiment involved TPM-01 delivery of insulin, which represented an even bigger technical challenge than PTH, insulin being 19 times larger than morphine. This time POH gave some colour as to the success of the experiment, indicating that average glucose concentrations in the treated animals were 25% lower than the controls. This was particularly interesting given the potential market size – in mid-2005 the global market for insulin was worth around US\$6-7bn, was growing around 20% pa<sup>152</sup>, and had no transdermal delivery options in sight.

Figure 25 - PTH and insulin were much bigger drug molecules to deliver than morphine



SOURCE: SOUTHERN CROSS EQUITIES

Figure 26 - Forteo has grown strongly for Eli Lilly over the last 10 years



SOURCE: ELI LILLY

So TPM showed promise for large molecules as a transdermal drug delivery vehicle. POH’s scientists, however, were dissatisfied with the low level of drug penetration, which hindered the potential therapeutic effects. The company therefore set out to reinvent TPM so that it could accommodate large molecules,

<sup>150</sup> That is, the first 34 amino acids of the protein. The entire protein has 84 amino acids.

<sup>151</sup> The drug is now doing over US\$800m pa in revenue.

<sup>152</sup> Today the global insulin market is worth around US\$13bn pa.

# Phosphagenics (POH)

## TPM-02 enabled large molecule delivery as well as small molecule

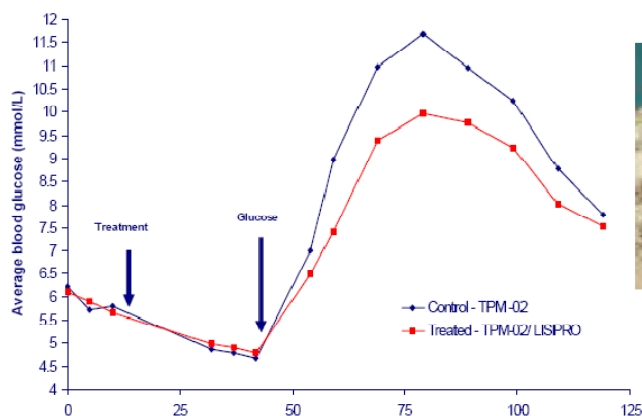
and by 2006 its scientists<sup>153</sup> had come up with a workable solution which they called TPM-02.

**2005/06 – TPM-02 provides the ability to deliver large molecules.** TPM-02 was similar to TPM-01 in that it retained the basic approach of mixing TP and T<sub>2</sub>P that had characterised TPM-01. However this time around, instead of formulating TPM with a surfactant, the scientists added ethanol as an excipient<sup>154</sup>. The result was the formation of vesicles, that is, small bubbles, of tocopheryl phosphate within the mixture. This proved to be a significant breakthrough because:

- when the drug intended for transdermal delivery was formulated with the new TPM mixture, the result was entrapment of the drug within the vesicles;
- the vesicles proved large enough to house large molecules as well as small;
- the scientists found that they could vary the size of the vesicles by altering the percentage of TP in the TP/T<sub>2</sub>P mix. This allowed flexibility in terms of the drug packaging; and
- the vesicles proved highly flexible in terms of their ability to squeeze between skin cells to penetrate beyond the stratum corneum.

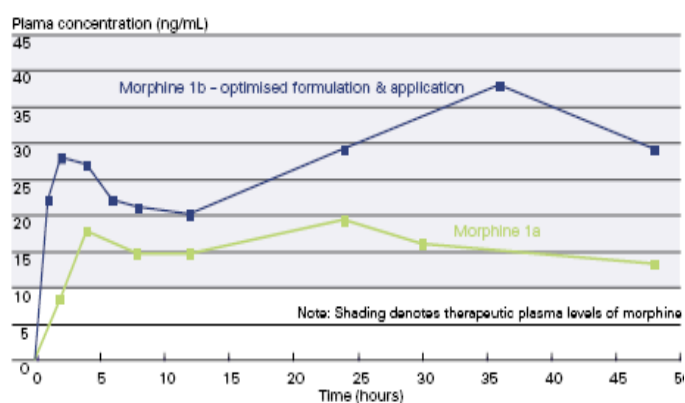
These factors enabled TPM-02 to enjoy greater success in large molecule transdermal delivery than was the case with TPM-01. For PTH, TPM-02 was able to boost level of the hormone in rat plasma by 70% compared to TPM-01. For insulin, rat and pig studies<sup>155</sup> demonstrated significant and immediate lowering of blood glucose in the treated groups as against the controls when oral glucose tolerance tests were run. These experiments became the basis of POH's WO/2006/133506 patent application over TPM-02.

**Figure 27 - TPM-02 showed early promise in animal models as a transdermal delivery agent for insulin**



SOURCE: POH - NOTE, THE HORIZONTAL AXIS REFERS TO HOURS

**Figure 28 - TPM-02 markedly boosted delivery levels of morphine in treated patients**



SOURCE: POH

**TPM-02 demonstrates clinical success in small molecule drug delivery using morphine, January 2006.** POH demonstrated that TPM-02 was useful for small molecules as well as large by using it in a Phase Ib clinical trial in morphine delivery in late 2005. This study, which recruited 18 patients, was open label and randomised. It saw results similar to the earlier proof of concept trial using with TPM-01, in that therapeutic plasma morphine concentrations were maintained

<sup>153</sup> By this stage West was not involved in the TPM project.

<sup>154</sup> The scientists later found that other alcohols related to ethanol would be more effective.

<sup>155</sup> The pig studies, which were announced to the ASX in May 2006, saw short-acting insulin lispro being delivered using TPM. The work generated a p-value of 0.005 on blood glucose levels for the treated pigs versus the controls. The study was reported as Example 4 in POH's WO 2006/133506 patent application.

# Phosphagenics (POH)

above 8 ng/ml for over 48 hours. However with TPM-02 markedly higher drug levels were registered than were reached in the Phase Ia trial, and the therapeutic threshold was crossed in around two hours rather than the four hours in the Phase Ia trial. However, full clearance of the drug had occurred by 72 hours. This indicated that even with higher plasma concentrations there could be little concern about morphine toxicity resulting from extended use.

## Since 2006, POH has sometimes used TPM-01, sometimes TPM-02

The last four years has seen the company enjoy a great deal of pre-clinical and clinical success with TPM, which we cover in the body of this note. This has seen POH use both TPM-01 and TPM-02:

- insulin, because of its molecule size, has been delivered using TPM-02, taking advantage of the fact that large molecules assemble into vesicles when in the presence of TPM; and
- small molecules have been formulated using TPM-01 at varying TP/T<sub>2</sub>P ratios depending on whether systemic or simply dermal delivery of drug is required. This builds on the discovery that altering the TP/T<sub>2</sub>P ratio can change how deeply the drug being delivered penetrates. Four small molecules have been focused on since 2006 - the analgesic drug oxycodone, the local anesthetic drug lidocaine, the anti-inflammatory diclofenac, and the skin drug tretinoin.

## Patch delivery provides the final technology step for TPM

In terms of technology development, there remained in 2006 the issue of the appropriate delivery format. That is, should TPM be a patch or a gel?

**2007 – POH’s move towards narcotic analgesic drug delivery necessitates development of a patch.** Until 2007 POH was happy to deliver TPM via gels that were rubbed into the skin, since gel formulation work was relatively easy and the company had the in-house skills to do so. The clinicians to whom POH talked then posed a significant problem. By 2007, following on from its earlier work on morphine, the company had come to see the narcotic analgesic oxycodone as candidate with the greatest commercial potential, since the drug had yet been delivered transdermally but was a blockbuster in terms of the existing market. Opioid analgesics are, however, drugs of abuse, and making them available in gel form has the potential to facilitate such abuse. The clinicians therefore wanted to see a patch form of the drug where extraction of the active by addicts would be difficult. The company therefore announced in March 2007 that it would create a TPM patch for oxycodone.

**2009 – POH unveils its patch prototypes.** POH’s patch development proved more difficult than expected. An initial effort to outsource the project didn’t go as planned, and in the end POH found it necessary to do the work in-house. Consequently the prototype patches weren’t unveiled to the market until May 2009. By that stage, however, POH had created both reservoir and matrix patches<sup>156</sup>, allowing extra licensing flexibility in terms of being able to offer what the prospective licensee wants.

**POH did all its patch development work in-house**

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<sup>156</sup> A reservoir patch is one in which the drug is stored in a gel-type reservoir within the body of the patch, rather than spread through the material of the patch, as in a matrix patch.

## Why TPM works so well as a transdermal delivery vehicle

In the process of developing TPM, POH's scientists and their collaborators discovered two interesting things about phosphorylated Vitamin E:

- 1) **It utilises natural dermal transport mechanisms to get across the skin without disrupting or damaging its surface.** Following on from work showing that  $\alpha$ -tocopheryl phosphate was naturally present inside cells, the scientists postulated that the phosphate form of  $\alpha$ -tocopheryl was a signalling molecule<sup>157</sup>, and by 2007 they had elucidated the mechanism by which this molecule gets across cell membranes<sup>158</sup>. This work was not only new to science, it showed how TPM could go straight through the cells of the stratum corneum without disrupting that barrier.
- 2) **It is a natural anti-inflammatory.** POH was first able to study TPM's anti-inflammatory capability in work which went into the WO/2003/011303 patent application in 2001 and 2002<sup>159</sup>. These anti-inflammatory properties became better understood with the company's work on phosphorylated Vitamin E as a potential treatment for atherosclerosis, which became the basis for the WO/2004/064831 patent application in 2003 and 2004.

These two aspects of phosphorylated Vitamin E suggested in theory that TPM gels or patches would not irritate or inflame the skin, and this has been the company's experience over 12 clinical trials since 2006.

**TPM is a natural anti-inflammatory**

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<sup>157</sup> See IUBMB Life. 2005 Jan;57(1):23-5.

<sup>158</sup> Biochem Biophys Res Commun. 2007 Jul 27;359(2):348-53. Epub 2007 May 24.

<sup>159</sup> Which showed how TPM-01 could treat acne and erythema.

## Appendix III - POH's intellectual property

### The TPM intellectual property has patent protection out to 2025

#### The TPM platform patent applications

The intellectual property behind the TPM technology is covered by five published patent applications where the earliest priority date is late 2000 and the most relevant patent application, for TPM-02, has a priority date of 2005. This means that while most US and European patents are still pending, POH's core technology has basic patent protection out to 2025.

- 1 Complexes of phosphate derivatives, WO/2002/040034<sup>160</sup>** (Priority date 14/11/2000; Invented by Simon West, Robert Verdicchio<sup>161</sup> and David Kannar<sup>162</sup>).  
This patent application covers the combination of  $\alpha$ -tocopheryl phosphate with a surfactant which was the basis of TPM-01. This patent application is mostly exemplified by the personal care applications which the company had in mind when it developed Vital ET around 2001.
- 2 Transdermal transport of compounds, WO/2003/049774** (Priority date 13/12/2001; Invented by Simon West and David Kannar).  
This patent application covers the transdermal delivery of phosphate derivatives of drugs using TPM-01 as the carrier.
- 3 Carrier, WO/2004/014432** (Priority date 9/08/2002; Invented by Simon West and David Kannar).  
This is the basic patent application for TPM-01, supported by POH's 2003 experiments on transdermal delivery of unphosphorylated estradiol, atropine and morphine. In the morphine and atropine examples the inventors also demonstrate that the carrier/drug combination can be delivered via a patch<sup>163</sup>.
- 4 Carrier for enteral administration, WO/2006/012692** (Priority date 3/8/2004. Invented by Simon West and Esra Ogru).  
This patent application covers the use of TPM-01 for oral delivery of drugs. Here the inventors used rat models to demonstrate higher levels of bioavailability of morphine and co-enzyme Q10, a dietary supplement often taken to promote cardiovascular health, when delivered using TPM-01.
- 5 A carrier comprising one or more di and/or mono-(electron transfer agent) phosphate derivatives or complexes thereof, WO/2006/133506** (Priority date 17/06/2005. Invented by Paul Gavin<sup>164</sup>, Robert Gianello<sup>165</sup> and Esra Ogru).  
This is the basic patent application for TPM-02.

#### Other patent applications

POH also has widespread intellectual property related primarily to phosphorylation and Vitamin E. At this stage there are 14 published patent applications:

<sup>160</sup> This patent has been granted in Europe as EP 1 339 413.

<sup>161</sup> Dr Robert Verdicchio is an organic chemist formerly of J&J and now an independent consultant based in Succasunna, NJ. Verdicchio consulted to POH on the TPM project in its early stages.

<sup>162</sup> Dr David Kannar, an organic chemist whose research field is plant-based functional foods, worked for POH at the time of this invention. We understand he is now on the staff of Southern Cross University at Lismore in northern NSW.

<sup>163</sup> Which is to say, the scientists, while they rubbed the carrier cream on with an applicator, covered the delivery space on the skin with a patch made out of the 3M wound dressing product Tegaderm.

<sup>164</sup> Dr Paul Gavin is currently VP, Research and Development at POH.

<sup>165</sup> Dr Rob Gianello is a biochemist at Monash University in Melbourne whose research focus is insulin and diabetes drugs. He worked on the AOD9604 molecule with Esra Ogru.

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**POH has started to receive US and European patents for its technology**

- 1 **Recovery of chroman derivatives**, WO/2000/043380<sup>166</sup> (Priority date 25/01/1999; Invented by Simon West)  
This patent application covers the use of the West Process in extracting tocotrienols and tocopherols from out of free fatty acid distillate.
- 2 **Improved process for phosphorylation and compounds produced by this process**, WO/2000/069865<sup>167</sup> (Priority date 14/05/1999; Invented by Simon West)  
This patent application describes the West Process for phosphorylation of compounds.
- 3 **Formulation containing phosphate derivatives of electron transfer agents**, WO/2002/040033<sup>168</sup> (Priority date 14/11/2000; Invented by Simon West )  
This patent application, which is similar to WO/2002/040034, covers the 'TP+T<sub>2</sub>P' part of TPM-01.
- 4 **Dermal therapy using phosphate derivatives of electron transfer agents**, WO/2003/011303 (Priority date 27/07/2001; Invented by Simon West, Robert Verdicchio, David Kannar and Otto Mills<sup>169</sup>)  
This patent application covers the use of TPM in treating various skin conditions including acne, sunburn, photodamaged skin etc.
- 5 **Micronutrient phosphates as dietary and health supplements**, WO/2003/013550<sup>170</sup> (Priority date 6/08/2001; Invented by Simon West and David Kannar)  
This patent application covers the use as dietary supplements of compounds phosphorylated using the West Process. The examples used are for delivery of coenzyme Q10 and Vitamin E.
- 6 **Modulation of vitamin storage**, WO/2003/026673 (Priority date 26/09/2001; Invented by Simon West and David Kannar)  
This patent application covers the use of phosphorylated compounds as storage forms of the compound. It follows on from the theory that Vitamin E is stored in the body as a phosphate and is 'de-phosphorylated' should the body need to use it as an anti-oxidant<sup>171</sup>.
- 7 **Compounds having anti-proliferative properties**, WO/2004/064831 (Priority date 17/01/2003; Invented by Simon West and Esra Ogru)  
This patent application covers the use of TPM-01 in treating atherosclerosis. The examples used demonstrate that, *in vitro*, the product can inhibit various aspects of the disease centred on inflammation.
- 8 **Phosphates of secondary alcohols**, WO/2004/092186 (Priority date 15/04/2003; Invented by Simon West and David Kannar)  
This patent application covers methods to phosphorylate, using the West Process, the statin drugs atorvastatin and pravastatin as well as the antidepressant venlafaxine, in order to improve their bioavailability.

<sup>166</sup> Granted in the US as Patent No. 6,403,811 and in Europe as EP 1 147 100.

<sup>167</sup> Granted in the US as Patent No. 6,579,995 and in Europe as EP 1 178 994.

<sup>168</sup> Granted in the US as patent No. 7,648,710.

<sup>169</sup> Dr Otto Mills does dermatology research at the Robert Wood Johnson Medical School in New Brunswick, NJ.

<sup>170</sup> Granted in Europe as EP 1 414 470.

<sup>171</sup> For more on this theory, see the 2003 paper entitled *Vitamin E phosphate: an endogenous form of vitamin E* in the Scientific Publications section of POH's web site, [www.phosphagenics.com](http://www.phosphagenics.com).

# Phosphagenics (POH)

**POH has a potential cancer drug deep in its pipeline**

- 9 **Phosphate derivatives, WO/2004/092187** (Priority date 15/04/2003; Invented by Simon West and David Kannar)

This patent application covers methods to phosphorylate the anaesthetic drug propofol using the West Process, to improve its bioavailability.

- 10 **Phosphate derivatives of pharmaceutical products, WO/2004/091636** (Priority date 15/04/2003; Invented by Simon West and David Kannar)

This patent application covers methods to phosphorylate, using the West Process, the opioid analgesic morphine, the cancer drug paclitaxel and the anaesthetic drug alfaxone, once again to improve their bioavailability.

- 11 **Alkaloid formulations, WO/2005/084678** (Priority date 3/03/2004; Invented by Simon West, Esra Ogru, and Robert Gianello)

This patent application covers the use of TPM-01 in transdermal delivery of alkaloid drugs generally, with studies of delivery of the alkaloid drugs atropine and morphine in pigs and morphine delivery in rats being used as examples.

- 12 **Compounds having anti-cancer properties, WO/2006/092024** (Priority date 3/03/2005; Invented by Simon West, Esra Ogru and Robert Gianello)

This patent application covers the company's phosphorylated  $\gamma$ -tocopherol cancer drug, GTP-805.

- 13 **Compounds having lipid lowering properties, WO/2006/092025** (Priority date 3/03/2005; Invented by Simon West, Esra Ogru and Roksan Libinaki<sup>172</sup>)

This patent application covers the use of TPM-01 in lowering LDL cholesterol (ie 'bad cholesterol') as well as triglycerides. The company demonstrates this, as well as reduction of atherosclerosis, using a kind of mouse model called the 'APOE knockout mouse', which naturally has high cholesterol.

- 14 **Compounds having cytokine modulating properties, WO/2007/070981** (Priority date 23/12/2005; Invented by Esra Ogru, Roksan Libinaki and Robert Gianello)

This patent application covers the use of TPM-01 in lowering levels of inflammation. The patent uses *in vitro* data on inhibition of inflammatory cell proliferation as well as rabbit data indicating on the effectiveness of TPM-01 in reducing atherosclerosis.

<sup>172</sup> Dr Roksan Libinaki is another Monash biochemist who worked on AOD9604 with Esra Ogru and Rob Gianello.

## Appendix IV – A POH glossary

**AOD9604** – A peptide fragment of human growth hormone which POH is investigating as the basis of a potential cosmetic cream to reduce subcutaneous fat.

**505(B)2** – An FDA regulatory approval process that applies for new drug delivery technologies where the drug being delivered is already FDA approved. With 505(B)2 applications only the safety and efficacy of the delivery technology needs to be demonstrated to the agency. POH will likely apply for FDA approval of TPM via the 505(B)2 route. 505(B)2 refers to the relevant section of America's Food, Drug & Cosmetic Act.

**$\alpha$ -tocopherol** – See tocopherol.

**Active ingredient** – The part of a drug with pharmaceutical activity. Also called 'the active'.

**Amino acids** – The building blocks of proteins. There are around twenty amino acids.

**Analgesics** – Pain management drugs.

**Analogue** – A protein drug similar to the natural protein but with some amino acids changed so as to improve the drug's performance.

**Antioxidants** – Substances that neutralise oxygen in free radicals, which can damage cells in the body. Various vitamins including Vitamin E have antioxidant properties.

**Atherosclerosis** – The clogging or hardening of blood vessels caused by plaques of fatty deposits, usually cholesterol.

**Atropine** – A small molecule drug used to accelerate heart rate in patients. POH has used TPM to deliver atropine in rat models.

**Basal Insulin** – Insulin that keeps blood sugar stable between meals and overnight.

**Big Pharma** – A collective term referring to the world's largest pharmaceutical companies, including J&J, Abbott Laboratories and Pfizer.

**Bioavailability** – The amount of a drug that is available where it is needed in the body.

**Biologicals** – Drugs based on proteins that occur naturally in living organisms. Most biologicals are large molecule drugs. Insulin and PTH are biologicals.

**Blockbuster** – A pharmaceutical drug with more than US\$1bn in sales.

**Bolus Insulin** – Extra insulin needed to cope with a sudden glucose influx at mealtimes.

**Buccal delivery** – Delivery of drugs through the buccal mucosa in the inner cheek of the mouth.

**Cadaver** – A dead human body.

**Carrier** – Material used to carry a drug for delivery into the body. TPM is a carrier technology.

**CMC** – Short for Chemistry, Manufacturing, and Control, the description of a how a drug is manufactured. CMC data is included in a Drug Master File.

**CNS** – Short for Central Nervous System.

# Phosphagenics (POH)

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**Compliance** – The following by a patient of a prescribed course of treatment.

**Cosmeceutical** – A cosmetic that also has pharmaceutical properties.

**C-Peptide** – A peptide produced during the synthesis of insulin. Rising C-peptide insulin levels indicate that a person is making more of their own insulin.

**C-reactive protein** – A protein in the blood, the levels of which rise in response to inflammation.

**Depot effect** – The forming within the skin of a ‘depot’ of drug that then slowly released into the bloodstream, allowing extended release of the drug.

**Dermis** – The deep vascular inner layer of the skin underneath the epidermis.

**di- $\alpha$ -tocopheryl phosphates** – Two units of  $\alpha$ -tocopherol phosphates joined together. Also called ‘T<sub>2</sub>P’.

**Diclofenac** – An NSAID. POH has adapted diclofenac for delivery with its TPM platform. The leading brand of diclofenac is Voltaren, from Novartis.

**Dose finding** – A small clinical trial for a drug designed to find the optimal dose at which to conduct a larger trial. Often Phase I trials are used for dose finding.

**Drug Master File** – The file of information submitted to a regulator when seeking approval of a new drug. The Drug Master File includes the CMC data.

**Elixia** – POH’s range of cosmeceuticals.

**Endpoint** – The outcome that a clinical trial is designed to evaluate, such as disease progression or death.

**Enteral administration** – A situation where a drug is delivered orally and therefore enters the body via the gastrointestinal tract.

**Epidermis** – The outer layer of the skin, with the stratum corneum at its outermost point.

**Erythema** – An abnormal redness of the skin resulting from inflammation.

**Estradiol** – A female sex hormone, being one of the estrogens. POH has used TPM to transdermally deliver estradiol in rat models.

**Excipient** – An inert substance used to prepare a drug for administration rather than being an active part of the drug itself.

**Extended release** – An orally available drug that has been formulated so that it dissolves slowly and releases the active over time.

**FDA** – The US drug regulator.

**Forteo** – Eli Lilly’s osteoporosis drug, which is the bioactive portion of PTH.

**Free radicals** – Molecules with unpaired electrons that therefore have to combine with complementary molecules before they become stable. If a free radical bonds with a positive charge molecule, its charge is neutralised. Oxygen in the free radical form can damage cells in the body in a process called oxidative stress.

**Functional food** – Food that provides health benefits beyond energy and essential nutrients.

**$\gamma$ -tocopherol** – See tocopherol.

**Good Manufacturing Practice (GMP)** – The set of standards that have been laid down by regulators such as the FDA for the production of clinical-grade pharmaceuticals.

**GRAS** – Short for ‘Generally Regarded as Safe’.

**Hydrophilic** – Able to dissolve in water. Tocopheryl phosphate is hydrophilic.

# Phosphagenics (POH)

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**IND** – Short for Investigational New Drug, an FDA designation of a drug that has been approved for clinical trials in the US.

**Insulin** – The hormone that regulates blood sugar levels which diabetics lack and which they have to take regularly, generally by injection. POH has adapted insulin for transdermal delivery with its TPM platform. Insulin is a large molecule.

**Insulin lispro** – A short-acting insulin analogue. Insulin lispro is insulin with some amino acid differences to improve the product's speed of action. The best known insulin lispro brand is Eli Lilly's Humalog product ([www.humalog.com](http://www.humalog.com)).

***In vitro*** – Latin for 'in glass', referring to data obtained in a test tube.

**Keratin** – The basic protein of skin cells.

**Lamellar** – Fine, alternating layers of different materials POH's TPM vesicular entrapment system results in a multi-lamellar and malleable carrier.

**Large molecule** – A drug with a molecular weight of >500 daltons. Biological drugs tend to be large molecules.

**LDL** – Short for 'low-density lipoprotein', LDL is 'bad' cholesterol because it can be deposited in the arteries, increasing the risk of heart attack or stroke.

**Lidocaine** – A topical anaesthetic drug. POH has adapted lidocaine for delivery with its TPM platform. Lidocaine is often branded as Xylocaine.

**Lipids** – Fat molecules.

**Lipophilic** – Able to dissolve in fats.

**Lispro** – See insulin lispro.

**Matrix patch** – A drug delivery patch in which the drug to be delivered is embedded throughout the patch material (called a 'matrix'). Matrix patches are more suitable than reservoir patches for delivery of opioid drugs, since the patch structure makes extraction of the drug difficult, thereby hindering drug abuse.

**Metabolic syndrome** – The cluster of medical conditions, including obesity, high blood pressure, high cholesterol and diabetes that increase the risk of heart disease, strokes, and vascular disease.

**Microemulsion** – A liquid mixture of oil, water and surfactant. Microemulsions are part of the TPM formulation process.

**Micron** – One millionth of a metre.

**Molecular weight** – The size of a drug molecule, the standard unit of measurement of which is the dalton.

**Mono- $\alpha$ -tocopheryl phosphate** – A single unit of  $\alpha$ -tocopherol phosphates, also called 'TP'.

**Morphine** – An opioid analgesic. POH has used TPM to deliver morphine transdermally.

**Nanometer** – One billionth of a metre.

**Narcotic analgesic** – See opioid analgesic.

**Ng** – Short for nanogram, ie one billions of a gram.

**New Chemical Entity** – A drug that has yet to gain FDA approval.

**NSAID** – Short for non-steroidal anti-inflammatory drug, that is, a drug such as aspirin designed to relieve pain and reduce inflammation and fever, but which is not a steroid or a narcotic.

**Nutraceutical** – A food product that also has pharmaceutical properties.

**Occlusion** – The covering of a transdermal drug delivery site with a patch.

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Occlusion tends to help in transdermal drug delivery by hydrating the skin in the area, which allows drugs to pass through.

**OGTT** – See oral glucose tolerance test.

**Open label** – A clinical trial in which both patients and doctors know which treatments are being given.

**Opioid analgesics** – Pain killing drugs that work by interacting the nervous system's opioid receptors. The best-known opioid analgesic is morphine, which is a derivative of opium. Oxycodone is an opioid analgesic.

**Oral glucose tolerance test** – A diagnostic for diabetes that involves administration of a high-glucose drink, after which blood samples are checked.

**Oxidative stress** – Cell damage that results from oxygen-linked free radicals.

**Oxycodone** – A small molecule opioid analgesic drug. POH has adapted oxycodone for delivery with its TPM platform. The leading brand of oxycodone is Oxyntin from the American company Purdue Pharmaceuticals.

**Parathyroid hormone (PTH)** – A hormone which acts to increase the concentration of calcium in the blood, making it essential for maintenance of bone health. PTH is a large molecule. POH has used TPM-01 and TPM-02 to transdermally deliver Forteo. That drug is the 1-34 bioactive fragment of PTH, that is, the first 34 out of a total of 84 amino acids.

**Paw withdrawal latency** – A measure of the effectiveness of an analgesic when tested in animal models. Paw withdrawal latency looks at the speed with which the test rat withdraws its paw from a heat source. The longer time period before withdrawal, the more the presumed analgesic effect of the drug being tested.

**Pegylation** – The combining of a drug to polyethylene glycol in order to extend the drug's half life.

**Penetration enhancer** – A compound that helps other compounds to penetrate through the skin. Tocopheryl phosphate is a penetration enhancer.

**Peptide** – Two or more amino acids linked by chemical bonds. Insulin is a large peptide.

**Pharmacodynamics** – The study of the physiological effects of drugs on the body.

**Pharmacokinetics** – A drug's profile of absorption, distribution and metabolism within the body and excretion from the body.

**Phase I** – A clinical trial in humans to test safety in a small sample. Phase I allows 'proof of concept' to be gathered regarding the viability of a particular medical technology.

**Phase II** – A clinical trial in humans to test efficacy in a small sample.

**Phase III** – A clinical trial in humans to test efficacy in a large sample. Phase III trials are also called 'pivotal trials'.

**Phospha E** – POH's Vitamin E dietary supplement, which Nestlé trialled as a functional food for the prevention of Metabolic syndrome.

**Phosphate group** – A compound based on phosphorus. Addition of a phosphate group to a biochemical compound can significantly change its function.

**Phosphorylation** – The addition of a phosphate group to a chemical. POH's technology centres on phosphorylation of Vitamin E.

**Pivotal trial** – See Phase III.

**Plasma** – The clear fraction of the blood that contains the white blood cells. The

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presence of drug in plasma indicates successful delivery of the drug.

**Preclinical** – Work such as animal testing that prepares a drug for clinical trials in humans.

**Priority date** – The date on which an invention is considered to have ‘occurred’ for patent protection purposes. In recent years basic patent protection has been granted to inventions for 20 years from priority date.

**Proof of concept** – See Phase I.

**PTH** – See parathyroid hormone.

**p-value** – A measure of statistical significance. Generally a p-value below 0.05 is considered statistically significant.

**RA** – Short for retinoic acid.

**Randomised** – A clinical trial in which a participant has an equal chance of being assigned to any of the various trial groups.

**Recombinant** – Proteins produced using the tools of genetic engineering.

**Reservoir patch** – A drug delivery patch in which the drug is stored in a gel-type reservoir within the body of the patch, rather than spread through the material of the patch, as in a matrix patch.

**Retinoic acid** – One of various derivatives of vitamin A that are often used in the treatment of acne and other skin problems. Tretinoin is a retinoic acid.

**Repeat Insult Patch Test** – A test used to determine if a material has the potential to cause contact sensitisation or skin allergies. In the RIPT a small patch of the test material is applied to the skin of a human volunteer on two occasions to see if a contact allergy results on the second application.

**RIPT** – See Repeat Insult Patch Test.

**Sensitisation** – Provoking an immune response.

**Small molecule** – A drug with a molecular weight of <500 daltons.

**Specialty pharma** – A drug company with approved products that specialises in a particular kind of drug. For example, King Pharmaceuticals is a specialty pharma company focused on pain management drugs.

**Statins** – A class of drugs that lower cholesterol.

**Statistical significance** – The probability that an observed outcome of an experiment or trial is due to chance alone. Generally p-values below 0.05 are taken as markers of statistical significance.

**Stratum corneum** – The outermost layer of skin, at the edge of the epidermis.

**Subcutaneous** – Pertaining to the fatty layer under the skin.

**Surfactant** – Short for ‘surface active agent’, surfactants are substances that can reduce the surface tension of a liquid, making it easier for the liquid to penetrate solids. Surfactants are often found in cleaning fluids, since reducing the fluid’s surface tension makes it easier for it to penetrate solids (in this case what is being cleaned). TPM-01 is  $\alpha$ -tocopheryl phosphate complexed with a surfactant to improve skin penetration.

**Systemic** – Delivered to the bloodstream rather than to a particular tissue.

**T<sub>2</sub>P** – See di- $\alpha$ -tocopheryl phosphates.

**Tape stripping** – A method of determining the penetration of topically-applied drugs into the skin where, after the drug is applied to the skin, adhesive films are repeatedly put on the treated areas and taken off again. The presence of drug in

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the film indicates that the drug has penetrated that far.

**Tocopherol** – A form of vitamin E. Tocopherol comes in a variety of forms, the most common of which is  $\alpha$ -tocopherol, which is what POH uses to make TPM. The company has also used  $\gamma$ -tocopherol to create a potential cancer drug.

**Tocopheryl phosphate** – POH's drug delivery platform, obtained by phosphorylation of Vitamin E.

**Tocotrienol** – A form of vitamin E.

**Topical** – A drug applied to the skin.

**TP** – See mono- $\alpha$ -tocopheryl phosphates.

**TPM** – Short for 'Tocopheryl Phosphate Mixture', or 'Targeted Penetration Matrix'. TPM is POH's drug delivery platform. TPM is a phosphorylated version of Vitamin E.

**TPM-01** – POH's first generation carrier, which was  $\alpha$ -tocopheryl phosphate plus a surfactant. See POH's WO/2003/049774 patent application.

**TPM-02** – POH's second generation carrier, which is a 2:1 mixture of mono- and di- $\alpha$ -tocopheryl phosphates plus an alcohol such as ethanol as an excipient. See POH's WO/2006/133506 patent application.

**Transdermal** – Delivered across the skin.

**Tretinoin** – The form of retinoic acid used to treat acne and other scaly skin disorders. POH has adapted tretinoin for delivery with its TPM platform. The leading brand of tretinoin is Retin-A, from J&J's Ortho Dermatologics unit.

**Triglycerides** – The major form of fat consisting of three molecules of fatty acid combined with the alcohol glycerol. High levels of triglycerides are linked to heart disease and atherosclerosis.

**Type 1 diabetes** – 'Insulin-dependent' diabetes, where the body can't produce any insulin at all. This affliction generally shows up before the age of 35 but only 5% of diabetics are type 1.

**Type 2 diabetes** – A disease condition where the body can't generate enough insulin, or alternately can't respond to what is produced. 95% of diabetics have type 2. Most are over the age of 40.

**Vesicle** – A pharmaceutical formulation that is hollow on the inside, enabling drugs to be carried. See vesicular entrapment.

**Vesicular entrapment** – The method by which TPM-02 works, with the molecule to be delivered entrapped inside vesicles of  $\alpha$ -tocopheryl phosphate.

**Vital ET** – The brand name of POH's Vitamin E excipient product which is sold via a distribution agreement with the US chemical company International Speciality Products.

**Vitamin E** – A vitamin best known for its antioxidant properties. POH has adapted Vitamin E as a drug delivery agent with its TPM platform. Tocopherols and tocotrienols are two kinds of Vitamin E.

**West Process** – Southern Cross Equities' term for the process whereby POH phosphorylates molecules to improve their bioavailability. The West process was invented by Dr Simon West, who did much of the early work on what became POH's TPM technology. Basically the West Process involves cooking the chemical to be phosphorylated with phosphorus pentoxide ( $P_4O_{10}$ ) at under 40 degrees Celsius.

## Appendix V – Companies working on drug delivery

The drug delivery has many players. We identified over 40 listed companies, mainly in the US and Canada, that were participating in the drug delivery space at various stages of development. We profile each of these companies individually below.

Figure 29 - Listed companies working on drug delivery (market caps as at 11 May 2010)

Established		Emerging		Early stage	
Company	Market cap (USDm)	Company	Market cap (USDm)	Company	Market cap (USDm)
Biovail	2,675	MannKind	778	Cell Therapeutics	320
Endo Pharmaceuticals	2,556	Halozyme	701	Durect	225
Abraxis BioScience	1,932	Eurand	433	BioSante Pharmaceuticals	149
Impax Laboratories	1,241	QLT	349	Antares Pharma	135
Nektar Therapeutics	1,232	Acrux	284	Emisphere Technologies	114
Alkermes	1,136	Depomed	199	Genexer Biotechnology	96
Enzon	625	Flamel Technologies	191	Columbia Laboratories	76
		Alexza	190	CPEX Pharmaceuticals	65
		Vectura	189	NexMed	54
		Acura	156	Scolr Pharma	51
		Penwest Pharmaceuticals	113	Soligenix	50
		Labopharm	68	Echo Therapeutics	41
		BioDelivery Sciences International	67	InSite Vision	35
		Octopus	54	Cipher Pharmaceuticals	35
				Access Pharmaceuticals	33
				AP Pharma	31
				Oramed	29
				Intellipharma	25
				IntelGenx	16
				Transdel Pharmaceuticals	16
				SkyePharma	14
				Aradigm	13
				Bone Medical	11
				NeoPharm	11
				Skinvisible	8
				AlphaRx	7

SOURCE: SOUTHERN CROSS EQUITIES

**Why POH has competitive advantage in the drug delivery space.** We see three reasons why POH has competitive advantage as a drug delivery company:

- 1) *The company is a transdermal delivery player.* Most companies working on drug delivery are focused on reformulation of drugs to allow extended release of orally available drugs, or to convert injectable drugs to oral delivery. This leaves relatively few players focused on the high-value transdermal space,

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where the principal emerging competitor is Acrux;

- 2) *The company can patch-deliver its products*, allowing it to take advantage of this highly patient-friendly and generally accepted format; and
- 3) *The company's success with oxycodone suggests that it can be a player in the highly lucrative market for alternative delivery of narcotic analgesics*, allowing it to compete against companies like Acura, Depomed and Biodelivery Sciences.

## The companies

**Abraxis BioScience** (Los Angeles, Ca, Nasdaq: ABII, [www.abraxisbio.com](http://www.abraxisbio.com)). This company's drug delivery technology involves binding the drug to the blood protein albumin, which allows better delivery of chemotherapy drugs to tumour cells. Its first marketed product is Abraxane, which is albumin bound to the breast cancer drug paclitaxel. Abraxis's 2009 revenue was US\$359m.

**Access Pharmaceuticals** (Dallas, Tx, OTCBB: ACP, [www.accesspharma.com](http://www.accesspharma.com)). This company, which is based on nanopolymer technologies for improved drug delivery, is FDA approved for MuGard, a mucositis treatment. A number of the company's cancer drugs have made it to Phase II. Access' Cobalamin Oral Drug Delivery Technology uses Vitamin B12 for as a delivery vehicle. This technology is being adapted for an oral insulin candidate.

**Acrux** (Melbourne, Victoria, Australia, ASX: ACR, [www.acrux.com.au](http://www.acrux.com.au)). This company uses topical sprays based on penetration enhancers to transdermally deliver various sex hormones as well as nicotine and NSAIDs. A testosterone replacement product was recently licensed to Eli Lilly.

**Acura** (Palatine, Il, Nasdaq: ACUR, [www.acurapharm.com](http://www.acurapharm.com)) This company, which is focused on developing abuse-resistant narcotic analgesic formulations, has been built on its 'Aversion' technology, in which aversive ingredients are added to the formulation to induce dysphoria in the world-be abuser. This company's lead product is Acurox, which is oxycodone with niacin as the aversive. Licensee King Pharmaceuticals has filed for FDA approval of this product, but this was rejected in April 2010.

**Alexza** (Mountain View, Ca, Nasdaq: ALXA, [www.alexza.com](http://www.alexza.com)). This company has been built on a technology called Staccato, which vaporizes excipient-free drugs to form an aerosol that can rapidly deliver systemic drug. The company is filing for FDA approval of a Staccato formulation of the schizophrenia drug loxapine, which has been licensed to Biovail.

**Alkermes** (Cambridge, Ma, Nasdaq: ALKS, [www.alkermes.com](http://www.alkermes.com)). This company has been built on a technology called Medisorb that allows extended release of drugs through encapsulation in a polymer called polylactide co-glycolide. The technology has allowed the creation of two marketed products with more to come<sup>173</sup>. Alkermes AIR technology allows pulmonary delivery via the use of dry powders suitable for the lungs<sup>174</sup>. 2009 revenue<sup>175</sup> was US\$327m.

**AlphaRx** (Hong Kong, OTCBB: ALRX, [www.alpharx.com](http://www.alpharx.com)). This company is working on a number of drug delivery technologies, including colloidal lipid dispersion (CLD) for topical and transdermal delivery, self emulsifying controlled release technology for oral delivery, and nanoparticles technology for site specific

<sup>173</sup> The marketed products are Risperdal Consta (an extended release version of the J&J schizophrenia drug Risperdal), and Vivitrol (an extended release version of naltrexone, a drug used to treat alcohol abuse). The diabetes drug Bydureon (a long-acting version of Eli Lilly's BYETTA drug) is currently under regulatory review.

<sup>174</sup> ALKS27, for the treatment of COPD, is tiotropium (drug often used to treat urinary incontinence) reformulated for pulmonary delivery using AIR. It's in Phase II clinical trials.

<sup>175</sup> Year to 31 March.

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delivery. The company's lead product, an inhaled formulation of the antibiotic drug tobramycin, is preclinical.

**Antares Pharma** (Ewing, NJ, Amex: AIS, [www.antaresharma.com](http://www.antaresharma.com)). This company, which has developed various needle-free injection devices and a number of gel products for dermal delivery of hormones which are on or near the market. The company has also developed fast-melt oral disintegrating tablets for patients with difficulty swallowing. The injector products have been partnered with Teva, although deal terms have not been disclosed.

**AP Pharma** (Redwood City, Ca, Nasdaq: APPA, [www.appharma.com](http://www.appharma.com)). This company has been built on a polymer-based drug delivery technology called Biochronomer, which involves poly ortho esters with bonds that, when they undergo hydrolysis, increase the acidity of the microenvironment and gradually erode the polymer, allowing controlled release of drug. AP Pharma's lead product from the technology is APF530, which is granisetron for the treatment of chemotherapy-induced vomiting. The FDA rejected APF530 in March 2010.

**Aradigm** (Haywood, Ca, OTCBB: ARDM, [www.aradigm.com](http://www.aradigm.com)). This company is commercialising a pulmonary drug delivery system called AERx, which allows drugs to be aerosolised<sup>176</sup>. The first drug to be delivered using the technology will be the antibiotic ciprofloxacin for the treatment of cystic fibrosis and bronchiectasis. There are currently two Phase IIb studies in bronchiectasis.

**BioDelivery Sciences International** (Raleigh, NC, Nasdaq: BDSI, [www.bdsinternational.com](http://www.bdsinternational.com)). This company's BEMA technology allows buccal delivery of drugs via a polymer film, while Bioral allows oral delivery of hitherto injection-only drugs by wrapping them in lipids. The company's fentanyl buccal film is now on the market and the company is in Phase II with a buccal film for the delivery of the pain drug buprenorphine. 2009 revenue was US\$63m.

**BioSante Pharmaceuticals** (Lincolnshire, Il, Nasdaq: BPAX, [www.biosantepharma.com](http://www.biosantepharma.com)). This company is focused on gels to treat various sexual health conditions. The company has also worked on the drug delivery potential of calcium phosphate nanoparticles. In addition a cancer vaccine called GVAX has shown promise against leukaemia and prostate cancer.

**Biovail** (Toronto, On, TSE: BVF, [www.biovail.com](http://www.biovail.com)). This company was built on a number of drug-delivery technologies such as controlled release, enhanced absorption, taste masking and oral disintegration. From 2008 the company has moved away from drug delivery and towards the development of proprietary CNS drugs. Biovail's 2009 revenue was US\$789m.

**Bone Medical** (Perth, Western Australia, ASX: BNE, [www.bone-ltd.com](http://www.bone-ltd.com)) This company has been built around Axxess, a UK-developed technology for the oral delivery of peptides and proteins. Calcitonin and PTH are the principal product focuses.

**Cell Therapeutics** (Seattle, Wa, Nasdaq: CTIC, [www.celltherapeutics.com](http://www.celltherapeutics.com)). This cancer drug development company is best known as the developer of Pixantrone, a non-Hodgkin's lymphoma drug for which regulatory approval has been sought but which was rejected by the FDA in April 2010. However the company also has a cancer delivery technology that involves conjugating drugs to polyglutamate, allowing the drug to be captured in tumour tissue. OPAXIO, which is polyglutamate-delivered paclitaxel, is in Phase III. The product is a monthly maintenance for ovarian cancer patients who have achieved a complete response following standard first-line chemotherapy.

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<sup>176</sup> Aradigm's CEO since 2006, Dr Igor Gonda, was formerly CEO of Acrux.

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**Cipher Pharmaceuticals** (Mississauga, On, TSE: DND, [www.cipherpharma.com](http://www.cipherpharma.com)). This company has developed an oral semi-liquid capsule technology called Lidose which allows improved bioavailability of water-insoluble compounds. It has been applied to delivery of the cholesterol-lowering drug fenofibrate and the acne drug isotretinoin<sup>177</sup>. Another technology, this one for controlled-release, was used on the narcotic analgesic tramadol, with that product gaining FDA approval in May 2010.

**Columbia Laboratories** (Livingston, NJ, Nasdaq: CBRX, [www.cbrxir.com](http://www.cbrxir.com)). This company supplies various women's reproductive health products that are delivered using bioadhesive materials for controlled and sustained release.

**CPEX Pharmaceuticals** (Exeter, NH, Nasdaq: CPEX, [www.cpexpharm.com](http://www.cpexpharm.com)). This company is developing a penetration enhancer called CPE-215, which has been used in a testosterone gel and an intranasal bolus insulin product. In March 2010 CPEX reported that the insulin product had turned in a non-statistically significant result in 94-patient Phase IIa trial in Type 2 diabetes.

**Depomed** (Menlo Park, Ca, Nasdaq: DEPO, [www.depomedinc.com](http://www.depomedinc.com)). This company's AcuForm technology allows drugs to be contained within gels and released slowly within the gastrointestinal tract. The company has used the technology to reformulate the diabetes drug metformin and the antibiotic ciprofloxacin, with both products now marketed, while a reformulated version of the epilepsy and pain drug gabapentin is in Phase III. 2009 revenue was US\$58m.

**Durect** (Cupertino, Ca, Nasdaq: DRRX, [www.durect.com](http://www.durect.com)). This company has a number of drug delivery technologies including SABER (a depot injection system), ORADUR (sustained release oral gel-cap technology) and TRANSDUR (transdermal patch technology). Remoxy, which is ORADUR-enabled oxycodone, has reached the regulatory approval stage, while POSIDUR, which is SABER-enabled bupivacaine for the treatment of post-operative pain, is in Phase III. TRANSDUR patches are also in Phase II for the pain drugs sufentanil and bupivacaine.

**Echo Therapeutics** (Franklin, Ma, OTCBB: ECTE, [www.echotx.com](http://www.echotx.com)). This company's AzoneTS penetration enhancer technology for use in transdermal drug delivery has been applied to the corticosteroid triamcinolone as well as other drugs such as the anti-inflammatory drug ibuprofen and the anti-fungal drug terbinafine.

**Emisphere Technologies** (Cedar Knolls, NJ, OTCBB: EMIS, [www.emisphere.com](http://www.emisphere.com)). This company's Eligen technology, which uses the body's natural passive transcellular transport processes to allow oral drug delivery, is being used for the delivery of various products including calcitonin for osteoarthritis and osteoporosis (in Phase III development with Novartis), PTH (also partnered to Novartis), Vitamin B12, and oral GLP-1 and GLP-1 analogues for Type 2 diabetes.

**Endo Pharmaceuticals** (Chadds Ford, Pa, Nasdaq: ENDP, [www.endo.com](http://www.endo.com)). This specialty pharmaceutical company has been involved for many years in developing new drug delivery technologies. Through the acquisition of Indevus in 2009, Endo gained control of HYDRON, a hydrogel reservoir drug delivery system<sup>178</sup> that has been adapted to a number of different drugs. Endo's 2009 revenue was US\$1.46bn.

**Enzon** (Bridgewater, NJ, Nasdaq: ENZN, [www.enzon.com](http://www.enzon.com)). This company is a key player in pegylation technology, with two pegylated products on the market<sup>179</sup>.

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<sup>177</sup> Another retinoic acid similar but slightly different to tretinoin. Isotretinoin was Roche's Accutane acne drug, which went generic in 2002 and has since been implicated in causing inflammatory bowel disease in patients.

<sup>178</sup> That is, the drug is contained within an extremely hydrated polymer gel.

<sup>179</sup> ONCASPAR (pegylated L-asparaginase for the treatment of acute lymphoblastic leukemia) and ADAGEN (pegylated adenosine deaminase for the treatment of Severe Combined Immunodeficiency Disease).

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The company is also working on RNA antagonist technology for the treatment of various cancers. Enzon's 2009 revenue was US\$185m.

**Eurand** (Amsterdam, The Netherlands, Nasdaq: EURX, [www.eurand.com](http://www.eurand.com)). This company has a number of proprietary technologies for bioavailability enhancement, customised drug release, taste masking, and drug conjugation. The company currently has two marketed products – Zenpep for gastrointestinal disorders and SourceCF for cystic fibrosis – as well as number of partnered products such as Axcan's ULTRASE and Cephalon's AMRIX. Eurand's 2009 revenue was US\$173m.

**Flamel Technologies** (Lyon, France, Nasdaq: FLML, [www.flamel.com](http://www.flamel.com)). This company's Medusa technology uses poly-aminoacid nanoparticles as protein carriers to extend the half life of drugs, while its Micropump technology allows controlled oral delivery of small molecule drugs via microparticles. A Medusa-delivered interferon product for the treatment of Hepatitis C infection is going to Phase IIa in 2010. Flamel enjoyed US\$42m in revenue in 2009, mainly from licensing and research income.

**Generex Biotechnology** (Toronto, On, Nasdaq: GNBT, [www.generex.com](http://www.generex.com)). This company has developed technology for buccal delivery of aerosolized liquid drugs. The company is currently adapting the technology to insulin (now in Phase III under an IND), fentanyl, morphine and the blood thinning drug heparin.

**Halozyme** (San Diego, Ca, Nasdaq: HALO, [www.halozyme.com](http://www.halozyme.com)). This company's Enhance drug delivery technology is based on hyaluronidase, the enzyme which degrades hyaluronic acid, a major component of connective tissue. Halozyme has adapted this enzyme to subcutaneously deliver a wide variety of biological drugs including some Roche/Genetech monoclonal antibodies as well as IVIG and insulin.

**Impax Laboratories** (Haywood, Ca, Nasdaq: IPXL, [www.impaxlabs.com](http://www.impaxlabs.com)). This company's main focus is the generic drug market, although it is starting to focus on proprietary CNS drugs. It has been built on a number of drug delivery technologies mainly involving timed release. Impax's 2009 revenue was US\$358m.

**InSite Vision** (Alameda, Ca, OTCBB: INSV, [www.insitevision.com](http://www.insitevision.com)). This company is seeking to commercialise slow release ophthalmic drugs using its DuraSite technology, which is a synthetic polymer of cross-linked polyacrylic acid. Its first product, AzaSite, delivers the antibiotic azithromycin.

**IntelGenx** (Ville St-Laurent, Qc, OTCBB: IGXT, [www.intelgenx.com](http://www.intelgenx.com)). This company owns a suite of oral controlled-release delivery technologies. The first drug it is intending to deliver using the technology in the antidepressant bupropion.

**IntelliPharmaCeutics** (Toronto, On, Nasdaq: IPCI, [www.intellipharmaceutics.com](http://www.intellipharmaceutics.com)). This company's Hypermatrix platform encompasses a range of drug formulation technologies used to design controlled-release versions of difficult-to-formulate drugs. The company has developed generic versions of the ADHD drug Focalin, the anti-depressant Effexor and the hypertension drug Coreg. Its Rexista product, which is oral oxycodone formulated to be abuse-resistant, has completed an encouraging pilot trial prior to formal Phase I.

**Labopharm** (Laval, Qc, Nasdaq: DDSS, [www.labopharm.com](http://www.labopharm.com)). This company's Contramid technology allows controlled release of drugs, the first application of which has been a once-daily version of tramadol, which is now marketed. The company is also working on Contramid-delivered versions of the anti-depressant trazodone and the pain and fever drug acetaminophen. 2009 revenue was US\$24m.

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**Mannkind** (Valencia, Ca, Nasdaq: MNKD, [www.mannkindcorp.com](http://www.mannkindcorp.com)). This company has been built on Technosphere, a technology allowing pulmonary delivery of drugs currently delivered by injection. The first product from the technology is AFREZZA for the delivery of insulin, for which FDA approval is being sought after successful Phase III trials.

**Nektar Therapeutics** (San Carlos, Ca, Nasdaq: NKTR, [www.nektar.com](http://www.nektar.com)). This company, which is perhaps most famous as the developer of Pfizer's failed Exubera inhaled insulin product<sup>180</sup>, is a player in both inhalation and pegylation technologies<sup>181</sup>. The latter focus has been used to on a number of market products, which generated US\$72m in 2009 revenue, as well as deep pipeline of products in development.

**NeoPharm** (Lake Bluff, IL, OTCBB: NEOL, [www.neopharm.com](http://www.neopharm.com)). This company, whose main product is an anti-cancer drug called Cintredekin Besudotox, also has a drug delivery technology called Neolipid, which centres around drug delivery using liposomes<sup>182</sup>. The lead Neolipid product is LEP-ETU, which delivers the breast cancer drug paclitaxel.

**NexMed** (San Diego, Ca, Nasdaq: NEXM, [www.nexmed.com](http://www.nexmed.com)). This company is primarily a contract research organisation but it also owns NexACT, a transdermal drug delivery technology that works by enhancing drug penetration. The technology has also been adapted for oral administration, and a pipeline of products has been built around it beginning with the antifungal drug terbinafine and the erectile dysfunction drug alprostadil.

**Octopus** (Leiden, The Netherlands, Euronext Amsterdam: OCTO, [www.octoplus.nl](http://www.octoplus.nl)). This company has developed a number of drug delivery technologies such as OctoDEX (dextran-based microsphere delivery technology) and two polymer technologies for controlled release of drugs called PolyActive and SynBiosys. The company also does contract formulation and manufacturing work which helped earn US\$26m in revenue in 2009.

**Oramed** (Jerusalem, Israel, OTCBB: ORMP, [www.oramed.com](http://www.oramed.com)). This company is based on various compounds designed to protect peptide or protein drugs in the gastrointestinal tract and promote uptake through the intestinal wall. The company has adapted the technology to insulin and has completed Phase IIb for this indication.

**Penwest Pharmaceuticals** (Danbury, Ct, Nasdaq: PPCO, [www.penw.com](http://www.penw.com)). This company is best known for developing the TIMERx 'agglomerated hydrophilic matrix system' that allows for controlled release of drugs. TIMERx is used in a number of marketed products which helped generate US\$24m in revenue for Penwest in 2009. Penwest also has a few other drug delivery technologies in its intellectual property portfolio. However at present the company is focused on becoming a developer of CNS pharmaceuticals.

**QLT** (Vancouver, BC, TSE: QLT, [www.qltinc.com](http://www.qltinc.com)). This company is best known for Visudyne, a drug used in photodynamic therapy for wet AMD, which enjoyed US\$42m in revenue in 2009. The company has also historically been a significant drug delivery player. Atrigel, an injectable polymer product that allows drugs to be delivered in a controlled release fashion, was exclusively licensed to Reckitt Benckiser in mid-2008. The company's 'punctal plug drug delivery system' uses the tear ducts to house a drug-eluting device with which to treat eye diseases. A

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<sup>180</sup> Pfizer handed the rights to the product back to Nektar in 2007 after it decided to cease marketing the product due to poor market acceptance.

<sup>181</sup> Pegylation involves combining the drug to polyethylene glycol, which extends its half life. Nektar calls its pegylation know-how 'advanced polymer conjugate chemistry technology'.

<sup>182</sup> This is, sphere-shaped vesicles made out of lipids.

# Phosphagenics (POH)

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Phase II trial for the eye drug latanoprost yielded encouraging results in mid-2009.

**Scolr Pharma** (Bothell, Wa, Amex: DDD, [www.scolr.com](http://www.scolr.com)). This company is developing its Controlled Delivery Technology, which is a suite of various oral drug delivery technologies. The company has applied the technology firstly to ibuprofen, and FDA approval will be sought for this product in 2010.

**Skinvisible** (Las Vegas, Nv, OTCBB: SKVI, [www.skinvisible.com](http://www.skinvisible.com)). This company has developed a polymer-based dermal delivery system called Inviscare which, by bonding to the skin, allows transdermal drug delivery. The company is applying the technology to a number of dermatological drugs.

**SkyePharma** (London, UK, LSE: SKP, [www.skyepharma.com](http://www.skyepharma.com)) This company has a wide range of drug delivery technologies including Geomatrix and Geoclock - technologies for the controlled or timed-release of drugs - as well as various inhalation technologies. 2009 revenue was US\$94m, mainly from royalty and manufacturing revenues on approved products. Skyepharma stock has been under considerable pressure lately because of delays in US regulatory approval for Flutiform, which is a combination of the asthma drugs fluticasone and formoterol.

**Soligenix** (Princeton, NJ, OTCBB: SNGX, [www.soligenix.com](http://www.soligenix.com)). This company's main focus is orBEC, a drug for the treatment of GvHD. However it continues to develop its LPM drug delivery technology, which is based on a lipid structure called the 'reverse micelle' that allows intestinal absorption of peptides not otherwise orally bioavailable. Soligenix' lead candidate for LPM drug delivery is the prostate cancer drug leuprolide.

**Transdel Pharmaceuticals** (La Jolla, Ca, OTCBB: TDLP, [www.transdelpharma.com](http://www.transdelpharma.com)). This company has developed a penetration enhancement technology called Trenadel. Transdel's lead product, Ketotransdel, for the delivery of the anti-inflammatory drug ketoprofen, is in Phase III.

**Vectura** (Chippenham, Wiltshire, UK, LSE: VEC, [www.vectura.com](http://www.vectura.com)). This company has been built on a number of formulation technologies allowing effective pulmonary delivery of drugs. An example is PowderHale, an excipient which allows aerosolised drug particles to achieve high lung penetration with low dose variability. The company has also developed a number of inhaler devices. Vectura markets a number of its own products and earns revenue from partnership arrangements on drugs in clinical trials. 2009 revenue<sup>183</sup> was US\$53m. The company has been collaborating with Novartis on a generic version of GSK's Advair drug, for the treatment of asthma and COPD, but early in 2010 Novartis handed back the US rights and in April 2010 Novartis bought Oriel Therapeutics, a company that also makes asthma inhalers. This has been a negative for Vectura's share price.

# Phosphagenics (POH)

## Phosphagenics

### COMPANY DESCRIPTION

The Melbourne-based Phosphagenics (POH) is an early stage biotechnology company commercialising a drug delivery technology known as TPM, which allows drugs that previously could only be injected to be delivered transdermally in gel or patch form. We see potential for TPM to be licensed for use in delivering the analgesic drug oxycodone while a number of other drugs, including insulin, the acne drug tretinoin and the anti-inflammatory diclofenac, have also shown promise using TPM.

### INVESTMENT STRATEGY

We see a payoff to shareholders arising from favourable clinical outcomes, followed by a licensing of the technology to pharmaceutical and biotechnology companies looking to expand their product range. We also see POH benefiting from improved sentiment towards Australian biotech stocks. The end of the Global Financial Crisis came at a time when many Australian biotech companies had reached late stage maturity. Consequently a year later the Southern Cross Equities Australian Biotechnology Index was up three-fold on the level of a year earlier.

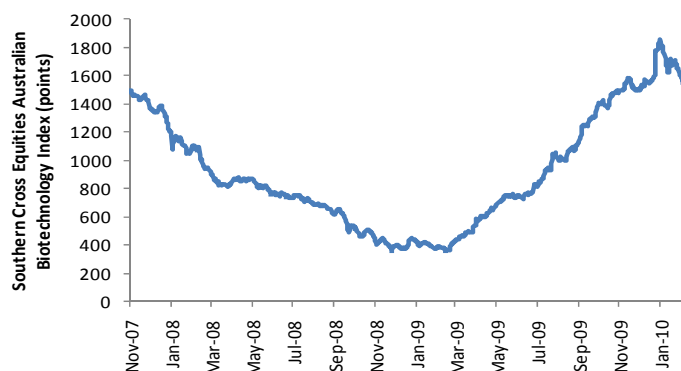
### VALUATION

We value POH at 41 cents base case and 81 cents optimistic case using a probability-weighted DCF approach, diluted for another potential \$15m capital raising. Our target price of 40 cents sits at our base case valuation. We assume that POH can be re-rated by the market as the near-term nature of TPM becomes apparent, helped by the further emergence of clinical and pre-clinical data.

### RISKS

We see the main risk in POH as being clinical risk – ie that products fail to perform in human trials. Another major risk facing the company is that prospective licensing partners may drive too hard a bargain for POH shareholders to enjoy a strong return. A third significant risk is burn rate. At 31 December 2009 POH had \$10.9m cash but has burned around \$700,000 per month since early 2004 when it began to focus solely on development of TPM. The company has raised \$51m in equity capital over the last six years. It may have to make further capital raisings to fund its burn rate until the clinical programmes yield licensable products.

Figure 30 – Sentiment toward Australian biotech stocks improved in 2009



SOURCE: IRESS, SOUTHERN CROSS EQUITIES

# Phosphagenics (POH)

## Recommendation structure

Spec Buy: Expect >30% total return on a 12 month view but carries significantly higher risk than its sector

Buy: Expect >15% total return on a 12 month view

Accumulate: Expect total return between 0% and +15% on a 12 month view

Reduce: Expect -15% and 0% total return on a 12 month view

Sell: Expect <-15% total return on a 12 month view

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Southern Cross Equities Ltd and its associates hold 260,000 shares in POH as at the date of this report. This position is subject to change without notice. In April 2010 Southern Cross Equities was appointed a corporate advisor to POH. As part of this arrangement Southern Cross has been granted 5 million options exercisable at 14.2 cents expiring 31/3/2013. These options vest immediately. In the event that the corporate advisory role continues, being terminable by POH at any time, Southern Cross Equities may potentially be granted another 5 million options in April 2011 and 5 million in April 2012 with the same exercise price and expiry date. In the event that POH stock trades at or above 50 cents for 20 consecutive business days all options shall vest immediately.



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