NDF RESEARCH

Providing independent research coverage of ASX-listed Life Science companies

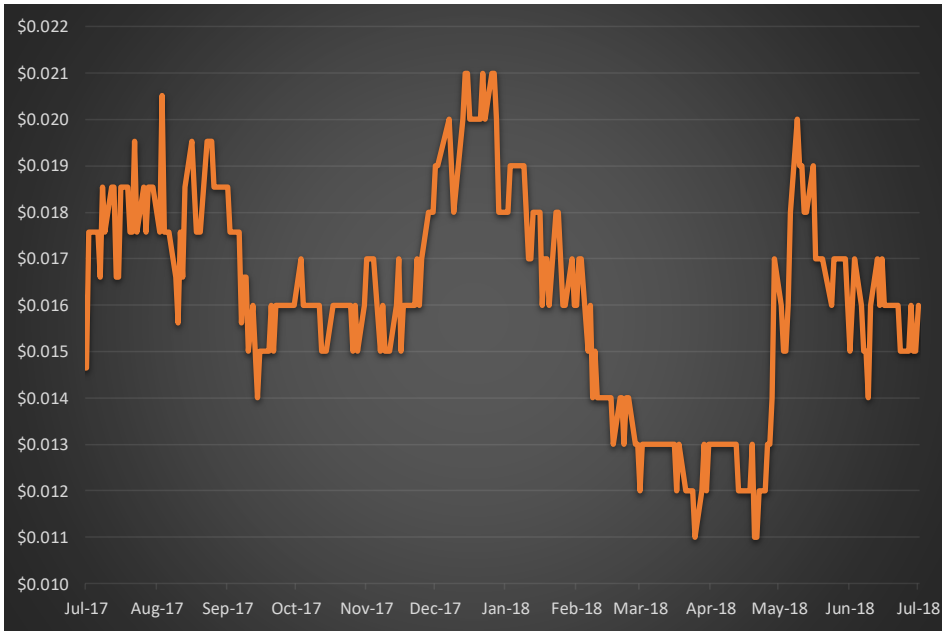
Phosphagenics (ASX: POH)

Initiation of Coverage – Monday 23 July 2018

Returns coming from a >$100m investment

Since the early 2000s Phosphagenics has spent more than A$100m on its drug reformulation technology called TPM®, built from Vitamin E. The company has ample pre-clinical and clinical data showing that TPM® is not only an effective transdermal drug delivery system, but it can also improve oral bioavailability as well as improve the solubility, stability and safety of injected drug formulations. The company has finished topical products sold by the pharmaceutical giant, Novartis, in India. The company has developed and completed early clinical work on what could become the first patches for transdermal delivery of the opioid analgesics oxycodone and oxymorphone. It is in a global partnership with the Japanese medical device major Terumo, working on a new formulation of the anaesthetic drug propofol. In addition, it has significant potential for upside from an international arbitration with Mylan, expected to be decided soon. We value Phosphagenics at 5.6 cents per share base case and 11.7 cents optimistic case. Our target price of 9 cents sits at the midpoint of our valuation range. The current A$25.2m market capitalisation, in addition to markedly undervaluing the replacement value of TPM®, discounts the reasonable chance of commercial success for this company under its current leadership team.

Rating	Risk	Current price	Target price
Buy	Speculative	$0.016	$0.09



Stock details

Daily Turnover: ~A$30,000
Market Cap: A$25.2m
Shares Issued: 1,577.5m
52-Week High: $0.021
52-Week Low: $0.011

Analyst: Stuart Roberts
stuart@ndfresearch.com
+61 447 247 909

Please note: This report has been commissioned by Phosphagenics and NDF Research will receive payment for its preparation. Please refer below for risks related to Phosphagenics as well our General Advice Warning, disclaimer and full disclosures. Also, please be aware that the investment opinion in this report is current as at the date of publication but that the circumstances of the company may change over time, which may in turn affect our investment opinion.

About NDF Research

NDF is an independent equity research firm based in Sydney, Australia. It focuses on Life Science companies that are publicly traded on the Australian Securities Exchange (ASX), most of which are headquartered in Australia and New Zealand. ASX hosts one of the world's premier equity markets for biotech and medical device companies and is home to world-beating companies such as CSL and ResMed and emerging pioneers such as Mesoblast and Impedimed.

NDF's Founder and Senior Analyst, Stuart Roberts, has been involved in Life Sciences since 2002 as a sell-side analyst as well as an executive of two ASX-listed immuno-oncology drug developers.

NDF believes that ASX-listed companies have been largely overlooked in the global Life Sciences boom that began in late 2008, partly because of insufficient quality research. NDF's goal is to provide such research and introduce investors around the world to potential future billion-dollar companies from 'Down Under'.

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Ferry at the end of a rainbow on Sydney Harbour, August 2014

In this report

Introducing Phosphagenics, ASX: POH

Phosphagenics is a Melbourne-based drug reformulation company whose TPM® technology, based on phosphorylated Vitamin E, has shown promise as a transdermal drug delivery tool and as an agent for improving the stability and solubility of drugs. Historically Phosphagenics is best known for having used TPM® to create, and taken into the clinic, what could become the world's first patches for the opioid analgesics oxycodone and oxymorphone. Today the company is primarily focused on using TPM® to make injectable drugs more stable and soluble. A collaboration with the major Japanese healthcare conglomerate Terumo is working on an improved formulation of the injectable anaesthetic drug propofol. A number of field studies have also established the utility of TPM® in improving the feed efficiency or performance of livestock animals. We see the potential for sizeable commercial upside from these projects as well as the chance of a favourable and potentially 'company-making' outcome from an ongoing arbitration matter with Mylan, expected to be decided shortly.

Why do drugs need to be reformulated, and how does Phosphagenics have competitive advantage in this space? The pharmaceutical industry is always on the lookout for alternative delivery systems for a drug[1], or other technologies that can improve the utility and profile of drugs being delivered[2]. TPM® can do both. It can create easy-to-administer and long-acting gels or patches as an alternative where pills are problematic. It can also increase the amount of an oral drug absorbed by recipient. Furthermore, it can increase the solubility and/or stability of an injectable drug, allowing the removal of existing excipients known to be toxic. In each case the projects that Phosphagenics has chosen are ones where it believes TPM® can beat competing approaches and where there is an attractive commercial opportunity. When drugs are reformulated, new patent-protected products with significantly higher market reach are often the result. A classic case of this was in testosterone replacement therapy with the introduction of the first testosterone gels in the early 2000s[3]. Testosterone had been routinely delivered in injectable form since the 1950s, and there had been oral pills since the 1970s[4] but it was the topical gels, with their reliability and patient convenience, that made testosterone replacement a blockbuster category.

TPM® IS A VERSATILE TECHNOLOGY

What is TPM® and what is the evidence that it can form the basis of new products. TPM®, short for 'Tocopheryl Phosphate Mixture', is a mixture of two phosphorylated forms of Vitamin E. Phosphorylation is simply the addition of phosphate groups to a molecule. Phosphagenics has shown, in well over a dozen clinical studies and in published *in vitro* and *in vivo* work, that formulating drugs with TPM® can quickly deliver the drug through the skin and into the bloodstream in therapeutic quantities. More recently, Phosphagenics has shown that TPM® can be used to formulate drugs that would otherwise be difficult to solubilise or would only be stable for short periods of time. This reformulation technology has become the basis for an important collaboration with Terumo and Phosphagenics is working on a pipeline of new injectable products.

[1] Such as a pill to provide an alternative to injections: It is believed that more than one fifth of adults may be afraid of needles (see Aust Fam Physician. 2009 Mar;38(3):172-6), so any injectable drug that can be made available in pill form would represent a new market opportunity for a drug developer.
[2] Such as extended release versions to replace the old immediate release products.
[3] By Solvay, which gained FDA approval for AndroGel in 2000, and Auxilium Pharmaceuticals, whose Testim gel was approved in 2002.
[4] They weren't very good. Akzo Nobel had launched Andriol (testosterone undecanoate) in 1978, but typically this product caused poor and variable levels of testosterone, even though the patient had to take 4-6 capsules daily.

What is the potential upside from the Mylan arbitration matter? One drug reformulation project in which Phosphagenics has been involved is the development of an alternative version of the injectable antibiotic daptomycin. This collaboration had begun with an Indian injectable drug maker called Agila, which was acquired by the major multinational generic drug company Mylan[5] in 2013[6]. Phosphagenics, disappointed with the collaboration, referred the matter, as per the license agreements, to arbitration in January 2016. This matter has a sizeable potential payoff. Phosphagenics's legal team, headed by the London-based advocate and arbitrator John Rowland QC and assisted by independent experts, estimate that the potential damages could range up to US$300m. In the event of a payout Phosphagenics has publicly committed to a portion being returned directly to shareholders (subject to shareholder approval).

If Phosphagenics is such a good investment how come it is only capitalised at A$25.1m/US$18.6m? We believe three sentiment issues explain the currently low market capitalisation of Phosphagenics. Firstly, there has been disappointments over the last five years in terms of some product or clinical developments not working out as planned. Secondly, some people still remember the mid-2013 scandal in which Phosphagenics's then CEO was found to have defrauded the company out of ~A$6m over around nine years. Thirdly, the company historically has billed itself as developer of new transdermal products for opioid analgesics, but this effort has yet to result in late stage clinical success or commercial success for Phosphagenics despite more than a decade of work[7].

An impressive quality of Phosphagenics over the years has been its ability to pivot and go after new opportunities as old opportunities fade. Consider the company's collaboration with Terumo. Phosphagenics optioned Terumo the Japanese rights to its oxymorphone patch technology in April 2016, adding the oxycodone patch the following month as well as a collaboration over other products including the anaesthetic drug propofol. Terumo signed a term sheet for the oxymorphone patch in January 2017 and a development agreement for the patch in August 2017. However, in March 2018 Terumo decided not to develop an oxymorphone patch. The market has, we think, reacted negatively to Terumo's decision on oxymorphone, but forgets that this collaboration enhanced the investment in the development of the patch for all markets outside of Japan, and that a Terumo global collaboration working on reformulating propofol with TPM® to improve its solubility and stability is not only continuing, but has now reached the IND-enabling toxicology stage. Moreover, Terumo are exploring further TPM®-based injectable candidates.

POH KNOWS HOW TO PIVOT AFTER NEW OPPORTUNITIES

We see Phosphagenics overcoming the negative sentiment issues in the near term. For a start, there have been notable successes in addition to the TPM®/Propofol Project, such as various successful animal health field trials. Secondly, new and seasoned leadership is in charge with a track record of success in the Life Sciences. And thirdly, the company has, since 2015, diversified its suite of TPM® projects, most notably into injectables and animal health, so that it is not reliant on the legacy opioid projects.

[5] Mylan (Pittsburgh, Pa., Nasdaq:MYL, www.mylan.com) is the world's 23rd largest pharma company with US$10.8bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[6] For up to US$1.75bn, which included US$250m in contingent consideration.
[7] Also, as we'll see below, opioids as a drug class have become politically charged because of the high level of opioid abuse in Western societies.

Ten reasons to look at Phosphagenics

1) **Phosphagenics's TPM® drug reformulation technology is versatile**. Over many years of development Phosphagenics has shown that TPM® can efficiently deliver drugs across the skin barrier. In more recent years the company has shown that TPM® can increase oral bioavailability, as well as the solubility and stability of reconstituted injectable drugs, which has led to significant commercial collaborations.
2) **The Terumo collaboration holds promise**, with that company using TPM® to develop a clearer formulation of the anaesthetic propofol that doesn't have the allergenic excipients extracted from egg or soy products currently used with the drug. This product is currently in the preclinical toxicology testing phase and on track for clinical testing.
3) **Phosphagenics has multiple products available for partners to work with**, its R&D effort having identified numerous injectable drugs that could benefit from TPM®, as well as other products in transdermal drug delivery, animal health, nutrition and cosmetics.
4) **Phosphagenics has a number of marketed products in its portfolio**, with revenue being earned from bulk sales of proprietary Vitamin E variants (TPM® & Vital ET™), and from a TPM®-delivered diclofenac gel marketed by Novartis in India and now being introduced to a number of other emerging markets.
5) **TPM® has shown promise in animal nutrition**, with various field studies showing that TPM® delivered in the feed of various livestock (i.e. pigs and poultry) results in significant improvements in the performance or feed efficiency of these animals.
6) **There is still potential for Phosphagenics in opioid patches**, with a commercial oxymorphone patch developed in conjunction with Terumo, and an oxycodone patch completed. The oxymorphone patch concept worked well in Phase 1. Although the challenges of side effects and abuse are negatively impacting the pain market, this is providing a large market opportunity for transdermal patches that have the capability of overcoming the compliance, safety, efficacy and significant abuse problems associated with the oral dosage forms. Phosphagenics aims to engage with the FDA soon on these products to ensure that the products capture the most desirable attributes.
7) **The time to market is potentially short,** with Phosphagenics, as a reformulator of other approved injectable products, not constrained with the usual multi-phase clinical development process of innovator molecules. For reformulations of approved injectable drug products in the US, for example, a single bioequivalence study in humans using the 505(b)(2) pathway is generally sufficient.
8) **There is potential for upside from the current Mylan/Agila arbitration**, with the arbitrator set to hand down his decision shortly. Phosphagenics and Phosphagenics's shareholders will both benefit in the event of success, with the company committed to returning part of any award to the shareholders and using the remainder to accelerate the rich pipeline of potential TPM® based injectables now being assembled.
9) **Phosphagenics has a seasoned management team**. CEO Dr Ross Murdoch, who has worked in both large and small pharma companies, founded and grew both the Emerging Products Business and the Haematology Business at Shire before joining Phosphagenics. Chairman Dr Greg Collier took

THE MYLAN ARBITRATION COULD LEAD TO A RETURN OF CAPITAL

ChemGenex Pharmaceuticals from a genomics play in 2002 to a late stage cancer drug developer in 2009, facilitating its acquisition by Cephalon for over US$230m in 2011.

10) **Phosphagenics is undervalued on our numbers**. We value Phosphagenics at 5.6 cents per share base case and 11.7 cents per share optimistic case, using a probability-weighted DCF approach. Our target price of 9 cents represents a midpoint of this range. We see Phosphagenics being re-rated by the market as its various commercial collaborations make progress and, potentially, should the Mylan arbitration come down in Phosphagenics's favour.

Phosphagenics's versatile TPM® technology

TPM® is a modified version of Vitamin E. Specifically it is alpha-tocopherol, one of the eight molecules that make up the Vitamin E family[8], with a phosphate group attached. In the late 1990s researchers working with what became Phosphagenics discovered that the addition of the phosphate could not only improve alpha-tocopherol's bioavailability but also its ability to pass through the skin. From the early 2000s the latter body of knowledge was optimised into a transdermal drug delivery system which the company called TPM®, short for 'Tocopheryl Phosphate Mixture'. TPM® is simply a mixture of mono- and di-alpha-tocopheryl phosphates, in an approximate 2:1 ratio by weight. More recently the company has focused on the ability of TPM® to improve the solubility and stability of injectable drugs.

TPM® can carry drugs through the skin barrier. As we note in Appendix I, Phosphagenics spent the years 2002 to 2015 primarily working on transdermal drug delivery, with TPM® consistently showing, in study after study, that it had this capability. The reason that it could do so – and we know this from basic research conducted by Phosphagenics – is that TPM® forms highly elastic particles that are able to entrap drug with high efficiency. These particles are readily absorbed into the skin where they release their payload[9]. It is also a natural anti-inflammatory[10] and does not cause skin irritation[11], which is very important for patient acceptance of any transdermal drug delivery system.

TPM® can also help improve drug solubility and stability – this is a current priority of Phosphagenics. In the very early days of what became Phosphagenics, founder and inventor Simon West, who had discovered the basic phosphorylation process behind TPM®, experimented with using that process to convert drugs from being fat-soluble to being water-soluble. Later work on TPM® itself showed that this product could increase the solubility and stability of injectable dosage forms of various drugs. Since around 2011 Phosphagenics has been collaborating with partners on the use of this technology, and since 2016 this effort has been a priority. We look at how TPM® works as a drug solubility and stability platform in the next section of this report.

TPM® CAN IMPROVE DRUG SOLUBILUTY AND STABILITY

[8] Vitamin E is not a single molecule, but rather a family of eight molecules, of which four are called 'tocopherols' and four 'tocotrienols'. In each case the molecule has a Greek letter, either alpha, beta, gamma or delta.
[9] See Drug Deliv Transl Res. 2017 Feb;7(1):53-65.
[10] Clin Exp Pharmacol Physiol. 2010 May;37(5-6):587-92. Epub 2010 Jan 17.
[11] See the WO/2003/011303 patent application.

TPM® as a drug solubility and stability platform

A drug's water solubility is very important. For a drug to be absorbed by the patient, it must be present in the form of a solution at the site of absorption. When a drug is water-soluble this task is easy, since water is non-toxic and present everywhere in the body. Frequently, however, drugs with the right treatment properties are lipophilic, with a chemical structure that makes them difficult to solubilise in water[12]. The list of approved water-insoluble drugs is a long one and includes such mainstays of modern medicine as the seizure drug carbamazepine[13], the anti-inflammatory ibuprofen[14] and the immunosuppressant drug cyclosporine[15]. Often such drugs can still be orally available so long as the solvent used is relatively non-toxic. In the case of carbamazepine, for example, the drug is soluble in alcohol and acetone. Sometimes, however, the solubility issues are such than they are only available via injection with surfactants and organic co-solvents that can cause toxicity at the administered doses. The classic case of this problem is the cancer drug Taxol® (paclitaxel), which is delivered in Cremophor® EL, a castor oil-derived solvent that, while it can solubilise the Taxol®, has also been associated with kidney damage and anaphylactic shock[16].

The pharmaceutical industry needs new solubility tools. As recently as 2010 it was estimated that 40% of drugs then on the market were poorly soluble, but that 90% of drugs in development could be characterised as such[17]. It's reasonable to expect the list will increase in the future - with the 'low hanging fruit' of validated targets having already been drugged, more and more water-insoluble drugs will enter pharma company pipelines. With global pharma sales now >US$900bn[18], that represents a large market opportunity.

PERHAPS 40% OF MARKETED AREN'T WATER SOLUBLE

TPM® formulation can make a drug more water-soluble. Vitamin E, that is, alpha-tocopherol, has poor water solubility. However, when a phosphate group is added to create the phosphorylated tocopherol mixture, TPM®, the molecules are 'amphiphilic or amphipathic', meaning that they contain a hydrophilic part that is soluble in water (the phosphate group) and a hydrophobic part soluble in fats (the tail of Vitamin E). Ordinarily in an aqueous solution such amphiphilic molecules form sphere-shaped aggregates called 'micelles' where the hydrophilic heads form an outer shell in contact with water, while the hydrophobic tails are sequestered in the interior. Hydrophobic molecules are entrapped within the micelles amongst the hydrophobic tails, which has the effect of dispersing them within the aqueous solution.

Phosphagenics has worked on two major solubility projects for injectable drugs to date. The first was with an Indian company called Agila, later acquired by Mylan, on the antibiotic daptomycin. This project is now subject to a major arbitration proceeding, with potential upside for Phosphagenics. The second project was with the

[12] Technically, the drugs are 'non-polar'. A polar molecule is one that has a positive electrical charge at one end and a negative charge at the other end. Polar molecules are water-soluble because in chemistry the general principle is 'like dissolves like', and water is also polar (ie it has a partial negative charge near the oxygen atom due to an unshared pairs of electrons, and partial positive charges near the hydrogen atoms).
[13] PDA J Pharm Sci Technol. 2010 May-Jun;64(3):264-77.
[14] Drug Dev Ind Pharm. 2018 Feb;44(2):173-183. Epub 2017 Oct 30.
[15] AAPS PharmSciTech. 2001 Jan 18;2(1):E2.
[16] Pharmazie. 2007 Feb;62(2):126-32.
[17] J Pharm Pharmacol. 2010 Nov;62(11):1607-21.
[18] ACS Chem Neurosci. 2017 Aug 16;8(8):1635-1636.

Japanese medical device and hospital supplies company Terumo, related to the anaesthetic drug propofol. We look at both of these projects in more detail below.

Phosphagenics's stability and solubility platform will allow more reformulation candidates to be identified. Since around 2016 Phosphagenics's scientists have been working with a high-throughput screening engine to examine which drugs with known solubility problems are able to be dissolved using TPM®. Formulations with promise are rapidly moved into short term stability studies to identify candidate formulation compositions with the desired attributes. This engine has allowed Phosphagenics to quickly assemble a long list of potential drug reformulation projects, some of which are advancing to the feasibility stage. We believe that, if the Terumo collaboration works out as planned, Phosphagenics can create significant shareholder value out of TPM® as a formulation solution through further collaborations, including with companies who have failed to advance otherwise highly effective drugs in the clinic, due to solubility issues.

POH IS CURENTLY EVALUATING NUMEROUS CANDIDATES FOR IMPROVED SOLUBILITY AND STABILITY

Phosphagenics's Terumo collaboration

There is a strong clinical need for a new propofol formulation. Propofol is a lipophilic anaesthetic. When the AstraZeneca precursor ICI Pharmaceuticals first developed the drug in the 1970s it used Cremophor® EL as the main excipient, but then withdrew that formulation because of the anaphylaxis issues and replaced it with a somewhat safer emulsion that includes egg lecithin and soybean oil[19]. The product relaunched in 1986 and gained FDA approval in 1989 under the brand name Diprivan®. The current propofol emulsion still has drawbacks. It is difficult and expensive to manufacture. It can produce pain on injection[20] and has been associated with sepsis[21] and hyperlipidaemia[22]. And that's before the obvious issue of its use in patients with egg and soy allergies[23]. A TPM® formulation, able to solubilise propofol without the requirement for additional adverse excipients would help overcome all these issues.

There is strong demand for propofol, due to its effectiveness as an intravenous drug. Propofol, while infamously associated with the 2010 death of the American musician Michael Jackson, is a well-regarded, and indeed the world's most widely-used anaesthetic due to its rapid onset and offset[24], and its ability to do away with all inhalational agents such as nitrous oxide. The drug enjoyed peak US sales of ~US$500m in 2005 for AstraZeneca[25]. This large market opportunity, combined with the difficulty of formulation and product shortages from 2009 due to manufacturing issues, prompted Phosphagenics to begin work on a TPM®-enabled propofol

[19] Anesthesiology. 2005 Oct;103(4):860-76.
[20] Anaesthesia. 1998 May;53(5):468-76.
[21] Since the emulsion supports bacterial growth - see Anesth Analg. 1999 Jan;88(1):209-12. To prevent this, the drug is often co-administered with antimicrobial agents.
[22] That is, too much fat in the bloodstream, caused by propofol's inhibition of lipid metabolism. For more on 'propofol infusion syndrome' see Acta Anaesthesiol Belg. 2008;59(2):79-86.
[23] Where the evidence suggests that, for adults at least, the product is safe – see N. J. N. Harper; *Propofol and food allergy*, BJA: British Journal of Anaesthesia, Volume 116, Issue 1, 1 January 2016, Pages 11–13.
[24] It works mainly through $GABA_A$ receptors, where it harnesses the inhibitory function of the neurotransmitter gama-aminobutyric acid (GABA) – see Curr Med Chem. 2000 Feb;7(2):249-71.
[25] AstraZeneca sold its US anaesthetics and analgesic products, which included Diprivan, to Abraxis BioScience in 2006. This business then went to APP Pharmaceuticals when Abraxis spun out its hospital injectables business in 2007. Germany's Fresenius bought APP Pharmaceuticals in 2008. Fresenius therefore owns the innovator brand in the US. The authorized generic went to Teva.

formulation from around 2013. Proof-of-concept work on this formulation had been completed by mid-2016[26] when the product attracted Terumo as a collaborator[27].

Terumo is a great partner for Phosphagenics to have. Terumo[28], with US$4bn in annual revenue and a current market capitalisation in Tokyo of US$20bn, is a Top 2000 company globally[29]. While the company is mainly known for its cardiac and vascular products, it also has a sizeable general hospital business, and the need to be competitive in this space has driven the collaboration over propofol. We believe that having Terumo as a major partner adds considerable credibility to Phosphagenics given the discipline with which large pharma and medical device companies typically conduct their due diligence on new technologies.

TERUMO IS A TOP 2000 COMPANY GLOBALLY

What is the next step in the Propofol Project? In late 2017 Phosphagenics announced that TPM®/propofol had performed well in stability testing and seemed to have potential for a two-year shelf life. The product has now reached the animal testing stage. We expect a single clinical study in 2019 designed to establish bioequivalence before submission for 505(b)(2) approval in the US and the comparable filings for other markets.

Phosphagenics has more injectable projects that it can partner with, as we have seen, the TPM® platform broadly applicable across a range of drugs. We see the success of the TPM®/Propofol Project as potentially unlocking more of these deals.

The opportunity in daptomycin – the Mylan arbitration and beyond

Daptomycin represented Phosphagenics's first injectable drug reformulation project. In October 2012 Phosphagenics announced that it had licensed its TPM® platform to an Indian company called Agila Specialties, then a subsidiary of the major Indian drug maker Strides Arcolab. Agila was a specialist manufacturer of sterile injectable drug with plants around the globe that made it one of the world's largest suppliers of lyophilised drugs. Agila was interested in whether TPM® could increase the solubility or stability of a particular injectable antibiotic. Mylan inherited this project when it acquired Agila in 2013 and Phosphagenics were suggesting by mid-2014 that the product[30] could be ready for launch in the US by Mylan in 2015 or 2016. Agila and Mylan never permitted disclosure of which antibiotic was the subject of the license and it was not until January 2016, when Phosphagenics commenced an arbitration action in Singapore against Mylan, that the market learned that the drug in question was daptomycin.

[26] See Pharmaceutical formulation, WO/2017/096427, priority date 9 December 2015
[27] See the Phosphagenics market release dated 29 April 2016 and headlined *'Phosphagenics signs Japanese license option agreement and R&D alliance'.*
[28] Tokyo, Japan, TYO: 4543, www.terumo.com.
[29] Currently No. 1,559 on the Forbes Global 2000.
[30] See the company's April 2014 corporate presentation, slide 20.

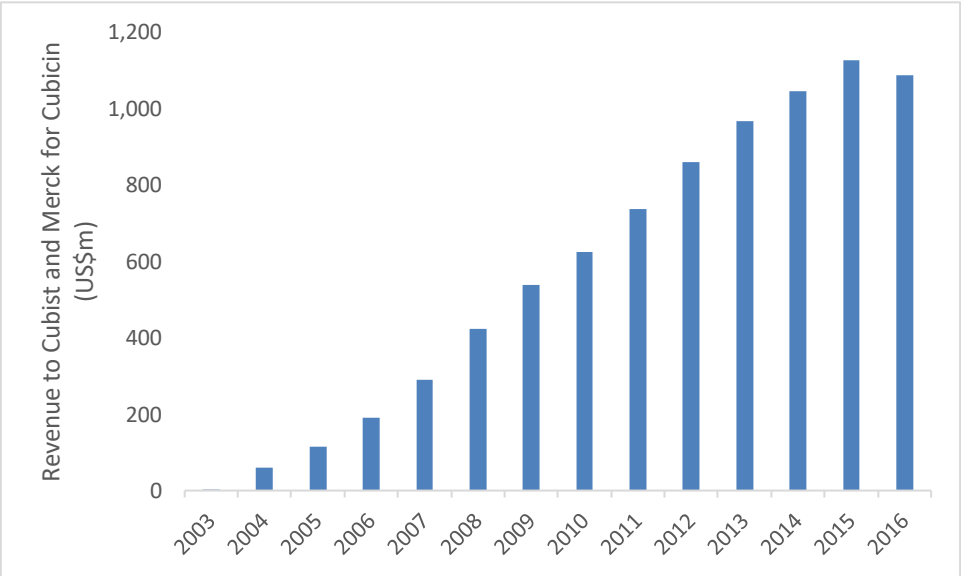
Between 2012 and 2016 Phosphagenics and Agila developed a daptomycin formulation that worked as intended. A key shortcoming of the original branded formulation of daptomycin, a Merck drug called Cubicin®[31], was the slow speed of reconstitution, which at 15-45 minutes[32], is a long time when a potentially fatal *Staphylococcus aureus* bloodstream infection needs to be treated right away. Also, the drug tended to degrade at room temperature after about 12 hours[33], so unused vials of the drug had to be thrown away[34]. TPM® was seen as a way to overcome these difficulties. Subsequent development work bore this hypothesis out[35]. The first patent application over this TPM®-enabled daptomycin formulation published in March 2014, but with a priority date several months before the signing of the Phosphagenics/Agila collaboration agreement[36]. It was reported in late 2015 that a TPM®-enabled antibiotic had cut the reconstitution time in half and doubled the shelf life of the product at room temperature.

POH'S DAPTOMYCIN PRODUCT WORKS AS PLANNED

Phosphagenics commenced its arbitration action against Mylan in early 2016, with the filing of the relevant notices at the Singapore International Arbitration Centre[37]. In that filing Phosphagenics alleged '*breaches of several provisions under the two relevant agreements, fraudulent or negligent misrepresentations, breaches of confidence and/or unjust enrichment in relation to intellectual property and commercial licensing terms, amongst others*'. Details were not disclosed to the market, but this description suggests that Phosphagenics had multiple claims to make in its filing. The timing of the filing was interesting, coming as it did shortly after a November 2015 ruling by the U.S. Court of Appeals for the Federal Circuit that invalidated all but one Cubicin patent, which was expiring in June 2016. This meant that once Teva's generic had its 180-exclusivity period[38], presumably late in 2016, the market would be open for full generic competition.

The substantive hearing for the Mylan arbitration took place in October and November 2017, over a ten-day period, with an expectation that the arbitrator would hand down his decision in the first half of calendar 2018. In May 2017 Phosphagenics had filed an expert opinion with the arbitrator that assessed the damages at up to US$300m. Phosphagenics's leadership has planned ahead in the event that some or all of that US$300m comes its way – in September 2017, the company announced that it intended to recommend a pay out of part of any arbitration award to shareholders in the form of a return of capital, tiering the payout from 30% of net proceeds between zero and A$50m, to 50% between A$50m and A$100m, hitting a ceiling of 70% for all proceeds above A$100m (subject to shareholder approval).

[31] Originally developed by Cubist Pharmaceuticals, which Merck & Co. acquired for US$8.4 billion in late 2014. Cubicin had gained FDA approval in September 2003.
[32] See US Patent 9,662,397, issued to Cubist Pharmaceutcals.
[33] Source: Prescribing Information for Cubicin
[34] It's also worth noting that the Prescribing Information for Cubicin warns that '*anaphylaxis/hypersensitivity reactions have been reported with the use of antibacterial agents, including Cubicin*'.
[35] See Phosphagenics'ss November 2015 corporate presentation, slide 18.
[36] *Improved Daptomycin injectable formulation*, WO/2014/045296, priority date 23 August 2012. This patent application was made by Agila and had four of its Bangalore-based chemists as the inventors.
[37] See www.siac.org.sg. Singapore is widely regarded as a global centre for arbitration of commercial disputes.
[38] 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 drug is still on patent this ANDA is called a 'Paragraph IV filing'. 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 under Paragraph IV, which in the case of Cubicin was Teva, gets a 180-day exclusivity period once a branded drug goes off-patent or a court rules in favour of the generic drug maker. When Cubist and Teva settled their patent litigation in 2011 Cubist named Teva's product as its 'authorised generic', and this launched in September 2016.



What happens after the arbitration concludes? With the Mylan license still in place and not abrogated by the outcome of any arbitration, there is potential to negotiate continued development of the product with Mylan. The commercial opportunity of the daptomycin product is strong. Cubicin® was a >US$1bn best seller for Merck just prior to the loss of US market exclusivity, and a new formulation called Cubicin® RF, which is stable at room temperature and only requires sterile water to reconstitute, has helped maintain the franchise at US$382m in 2017 sales. More broadly, the daptomycin reformulation will have shown the power of TPM® to reformulate large-market injectable drugs and with antibiotic drug development now coming back into favour globally thanks to concerns about drug-resistant microbes, there will be other injectables to work on in this space. The global market for injectable antibiotics has been estimated at ~US$9bn[39].

INECTABLE ANTIBIOTICS IS A MULTI-BILLION DOLLAR MARKET

The opportunity in animal health

In recent years Phosphagenics has stepped up its work in animal health and nutrition, with several successful studies showing the effectiveness of TPM® in improving nutrient uptake:

- **Dairy cattle, December 2013**. Phosphagenics announced a field trial, demonstrating that the product was able to cut the use of antibiotics in clinical mastitis cases by up to 50% after three months of use.
- **Weaner pigs, January 2016**. In the pork industry a 'weaner' is any pig between weaning (at three to five weeks of age) and either eight weeks of age or 20 kg liveweight[40]. In 2015 Phosphagenics conducted a field study in over 1,500 weaners to evaluate whether TPM® could improve feed efficiency. For this study

[39] Source: Forest Laboratories press release dated 14/12/2006 and headlined '*Forest Laboratories Announces Acquisition of Cerexa*'. Forest, which Allergan bought in 2014, paid US$480m to get into this market when it bought Cerexa, which was developing two injectable antibiotics, the most advanced of which was in Phase 3.
[40] Source: Queensland Department of Agriculture and Fisheries web site, Pig industry terms and definitions.

days zero to 14 post-weaning were called 'phase 1', and days 15 to 34 'phase 2'. The weaners were randomly assigned to feeding groups with varying doses of TPM®, or standard vitamin E[41], to observe if TPM® could improve the 'feed conversion ratio' of the weaners – the quantity of feed consumed compared to the meat yield. What the investigators found was a statistically significant improvement in feed conversion in Phase 1, albeit not in Phase 2, with a dose of 40mg TPM®/kg of feed (the highest dose tested) improving feed conversion by 3% over the best dose conventional Vitamin E (which was ~3 times the optimally tested TPM® dose). Phosphagenics regarded this data as encouraging given the metabolic stress to which weaner pigs are subjected. The subsequent study looked at the feed conversion efficiency of mature pigs (i.e. 'grower/finisher' stage pigs, which is any pig after weaning to 100 kg liveweight). Phosphagenics's reported in June 2016 that that study had not yielded a statistically significant improvement in feed conversion after TPM® administration was commenced in these older pigs.

- **Broiler poultry, December 2016**. In broiler chickens, that is, those destined for eating, the addition of TPM® to their feed resulted in significant improvements on several metrics, but it needs to be noted that these were measured against base feed, a different control to the aforementioned pig trial which achieved significance compared to high-dose Vitamin E. The independently-run study was conducted in an Australian research facility and included over 500 broilers. Investigators tracked various measures of broiler quality when their feed was supplemented with various doses of TPM® – not just feed conversion but also weight gain. There were encouraging results, with TPM®-enhanced feed working at far lower doses than those observed in newly weaned pigs (i.e. 10 ppm instead of 40 ppm) and improving the live and average daily weight gains by 5.6% and 5.7% respectively, compared to base feed. The weight gain outcomes were statistically significant.
- **Broiler poultry, December 2017.** This study, which evaluated ~500 chickens under heat-stress conditions, generated similarly significant results as the previous broiler study, and confirmed the 10ppm TPM® dose was optimal.
- **Dairy cattle, December 2017.** Cows, disappointingly, gained little from TPM®. Despite showing reduced cases of mastitis, there were no statistically significant improvements in milk quality and fertility in TPM® treated cows. Despite dairy oral drench studies reported in 2013, which showed significant improvements in milk quality, the supplementation of TPM® in a ruminant feed preparation in this study did not. In hindsight, a potential reason for the null result seems fairly clear – cows have a complex digestive system that involves four 'stomachs', and drenching by-passes the ruminant which may reduce the effective TPM® level available to aid with nutrient absorption.

TPM® CAN IMPROVE FEED CONVERSION IN PRODUCTION ANIMALS

Where Phosphagenics can go in animal health. We argue that the record of the 2016 and 2017 studies, while mixed, has allowed Phosphagenics to learn a good deal about the power of TPM® in improving the production efficiency when administered in an animal feed – which works in chickens and piglets. We expect another round of field studies can better identify other markets on which Phosphagenics should focus. We argue there is a billion-dollar opportunity for any technology that can improve the efficiency of meat production while reducing antibiotic

[41] Di-alpha tocopherol acetate.

use, particularly where the regulatory environment for antibiotics is negative and where the major fast food chains are phasing out meat produced using antibiotics.

Phosphagenics already has some revenue

Phosphagenics enjoys revenue from Vitamin E raw materials. Phosphagenics's original commercial product is Vital ET™, a derivative of their tocopheryl phosphate mixture. This is manufactured in their plant in Melbourne and sold to Ashland to distribute to end-users in the cosmetic industry around the world. Apart from 2017, where Ashland dealt with an overstocking issue, the company earns around A$1m p.a. from these sales.

Sales of a TPM® formulation of diclofenac earn a small revenue stream for Phosphagenics. Diclofenac is a non-steroidal anti-inflammatory drug (NSAID) that has been marketed since the 1970s. Many consumers will know by the brand name Voltaren® Gel[42]. In 2009 Phosphagenics reported the results of two clinical studies in which it showed TPM® could transdermally deliver diclofenac faster and deeper than Voltaren® Gel[43]. This work attracted the attention of a Mumbai-based company called Themis Medicare[44], which licensed the Indian rights to the product in November 2011. Themis in turn sub-licensed the product to Novartis in April 2013, which launched it on the Indian market in January 2014 under the Voveran® brand as a competitor to Themis's own brand, which is called Instanac®. In May 2016 Phosphagenics granted Themis the rights to TPM®/diclofenac in another 16 jurisdictions beyond the Indian market. Rights to the product in China, Hong Kong, Macao and Taiwan were included as part of a term sheet with a Chinese company called Sichuan Credit Pharmaceutical in September 2017, however this deal did not transition to a full agreement.

TPM® / DICLOFENAC IS NOW MARKETED

There is still potential for Phosphagenics's opioid patches

Over the years since 2007, Phosphagenics has worked on opioid patches. The opportunity has been tremendous because of the large amount of chronic pain in the community and the lack of strong non-opioid alternatives. We outline this history of this development in Appendix I of this note.

After some false starts, Phosphagenics now has two promising patches. After years of often frustrating development work, Phosphagenics now has:

[42] This product has been a huge commercial success historically for Novartis. The Novartis precursor company Geigy first launched diclofenac in 1973. Novartis switched over to OTC distribution of the product in 1999 but was still enjoying US$800m revenue from the franchise 11 years later.

[43] In February 2009 Phosphagenics showed, in a 12-subject study, that TPM® would be detectable in plasma within half an hour while the same concentration could not be achieved by Voltaren Gel until the four-hour mark. A second 12-subject study in September 2009 also compared TPM®/diclofenac to Voltaren and registered a similar outcome, showing in addition that penetration for the TPM® product was significantly higher for all levels of skin measured.

[44] Mumbai, India, privately held, www.themismedicare.com.

- **A completed oxycodone patch with pharmacokinetics that were well characterised in a Phase 1 human trial**[45]. This product is being developed for a new mechanism of action - the specific analgesic action of oxycodone on local tissue after topical application - which has been validated in animal models[46]. This new mechanism of action could avoid the adverse opioid effects that result from oral or injectable dosage forms. The company tested the patch in postherpetic neuralgia (PHN) patients in small Phase 2a study that showed analgesia for a subset of the patient population but did not demonstrate pain relief for the broad PHN population[47]. The company is now assessing what human indications would be most appropriate to progress its development.
- **An oxymorphone patch that also works in terms of its pharmacokinetics, having been optimised by German patch developed tesa Labtec**. Commercial complexities specific to the Japanese market (oxymorphone is not currently approved in Japan) prompted Terumo to return the Japanese license to Phosphagenics[48], however the US has always been the main game for this product, and the current political climate surrounding opioid abuse may see the FDA desperate for new opioid dosage forms that are harder to abuse. Phosphagenics aims to engage the FDA shortly to present the advantages of the product and submit an IND. In these uncertain times, favourable feedback from the FDA is seen as a valuable addition to a BD/licensing pack on the patch product.

Has the opportunity for an opioid patch been missed? The key regulatory issue for the opioid space for some years now has been the potential for abuse. In 2016 it was estimated that 11.5 million Americans over the age of 12 had misused opioid analgesics in the last twelve months[49]. This high level of misuse has led to the rise of various abuse-deterrence technologies designed to make the product more difficult for 'street chemists' to tamper with for abuse purposes. Purdue Pharma, creator of Oxycontin®, itself led the way in this regard, gaining FDA approval for an abuse-deterrent Oxycontin® in April 2010. However, the FDA has often declined to approve other abuse-deterrent formulations[50] and under a 2015 guidance note required further studies to support any abuse-deterrent claims[51]. That said, abuse-deterrent formulations have been approved under the 2015 guidance, most notably Xtampza®, from Collegium Pharmaceuticals[52], in April 2016 and Roxybond® from Daiichi Sankyo and Inspirion Delivery Sciences[53], in April 2017. A more recent FDA guidance note from November 2017 encourages would-be generic makers of opioids to replicate the abuse-deterrent features already used in the approved opioids[54]. Meanwhile there is strong demand for an abuse-deterrent oxymorphone product in the wake of the FDA's June 2017 request to Endo Pharmaceuticals to take Opana® ER, its extended release oxymorphone tablet, off the

OPIOID ANALGESICS ARE STILL BEING APPROVED

[45] Pain Manag. 2017 Jul;7(4):243-253. Epub 2017 Apr 19.
[46] J Pharm Sci. 2015 Jul;104(7):2388-96. Epub 2015 May 20.
[47] Pain Manag. 2017 Jul;7(4):255-267. Epub 2017 Apr 18
[48] In Japan fentanyl is the preferred opioid analgesic, and the potency of that drug is such that Phosphagenics could never have developed an oxymorphone patch as small as the standard fentanyl patch.
[49] Source: SAMHSA, National Survey on Drug Use and Health for 2016.
[50] For five examples, consider Acura Pharmaceuticals (Acurox, July 2009), Elite Pharmaceuticals (SequestOx, July 2016), Pain Therapeutics (Remoxy, September 2016), Egalet (Oxyado, June 2017) and Intellipharmaceutics (Rexista, September 2017).
[51] See the Agency's April 2015 Guidance for Industry note headlined '*Abuse-deterrent opioids - evaluation and labeling*'.
[52] Canton, Ma., Nasdaq: COLL, www.collegiumpharma.com.
[53] Morristown, NJ, privately held, www.inspiriondt.com.
[54] See the Agency's November 2017 Guidance for Industry note headlined '*General principles for evaluating the abuse deterrence of generic solid oral opioid drug products*'.

market. The FDA took this step because the post-marketing data had suggested that this supposedly abuse-deterrent formulation was, in fact, helping shift the pattern of abuse[55].

The way forward for Phosphagenics's patches. We believe that, so long as Phosphagenics can demonstrate clear marketable advantages such as potential claims around abuse/misuse/side-effect advantages, the way is still open for the product to move forward. We believe the success of Collegium will encourage other players to consider licensing the products. Phosphagenics intends to have a meeting with the FDA in 2018 in order to further understand what the Agency is seeking in its patches. The last opioid patch to come before the FDA was Purdue Pharma's Butrans®[56], a buprenorphine patch FDA approved in 2010.

Valuing Phosphagenics – A probability-weighted approach

Not all drug development projects succeed. Drug development is risky, and many drug candidates fail either at pre-clinical, in the various clinical stages of development (Phase 1, 2 and 3), or at the regulatory stage when agencies have to make the decision to approve or not approve a drug. For clinical stage drug candidates, there are databases available[57] stretching back to the 1960s that have allowed researchers to estimate the probability of success at various stages of development. One recent estimate is shown in Figure 1:

Figure 1: Historical probabilities of success in drug developments[58]

	SMALL MOLECULES	LARGE MOLECULES
Phase 1	63%	84%
Phase 2	38%	53%
Phase 3	61%	74%
Filing for approval	91%	96%
Phase 1 to approval	13%	32%

Looking at Figure 1, we see most drug candidates make it through Phase 1 (the safety stage of development) – 63% in the case of small molecules and 84% in the case of large molecules. For those that survive Phase 1 and

[55] For some published background here see Pain. 2016 Jun;157(6):1232-8. The new, reformulated Opana® ER never actually received an abuse deterrent label claim. It was formulated with the same abuse deterrent technology that went into oral oxycontin, but the required tests to get the formal abuse-deterrent claims were never completed. The FDA approved the product but refused the deterrent claims. The abuse deterrent technology in the new branded Opana® ER did make abuse harder than the generic oxymorphone tablets. What went wrong for the new formulation wasn't a function of the formulation itself not working, but the implications that resulted from how the pattern of abuse shifted in response to the reformulation. People could no longer easily crush the tablets for snorting, which had been one of the traditional routes of abuse for Opana®. Instead, they shifted their focus to injection, resulting in a serious increase in communicable diseases resulting from needle sharing. The increase in these diseases was so serious that the FDA no longer saw the benefits of this formulation of Opana® ER as outweighing the risks. The therefore requested its withdrawal. It is important to note that the original, 'non-abuse deterrent' Opana® ER formulation is still on the market as a generic. It hasn't been withdrawn, despite being easier to abuse than the reformulated Opana® ER.

[56] See www.butrans.com.

[57] Most notably from the Center for the Study of Drug Development at Tufts University in Medford, Ma. (see csdd.tufts.edu).

[58] Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.

enter Phase 2, only 38% of small molecules and 53% of large molecules are successful. And so on. Some drugs are successful in the clinical stage but then rejected by regulators - 8% (ie 100% minus 91%) for which approval is sought in the case of small molecules, and 4% in the case of large molecules. Multiplying the probabilities in each case suggests that the probability that a drug entering Phase 1 will ultimately gained regulatory approval is around 13% for small molecules and 32% for large molecules.

The kind of projects Phosphagenics is working on have higher probabilities of success than new drug candidates, once the products make it into the clinic, since the safety and effectiveness of the drug is not in question, only the delivery and formulation of the drug. However, for conservatism's sake, and to reflect the historic 'stop-start' nature of Phosphagenics's work in transdermal drug delivery, in this valuation we have used probabilities based on the probabilities of clinical success for new drug candidates.

Valuation – Opioid patches and propofol

We develop Discounted Cash Flow (DCF) models for four major programmes. For our valuation approach, we assumed payoffs from the oxycodone and oxymorphone patches, from the Propofol Project (whether or not licensed by Terumo) and from the injectable platform that Phosphagenics's injectable drug reformulation platform. We assumed no value from the company's bulk sales of TPM® & Vital ET™, nor from the TPM®-delivered diclofenac gel marketed in India, regarding these cash flows, as far as valuation goes, as relatively non-core. We assumed no value for the animal health projects but see upside here once further field trials show the right path forward for Phosphagenics. And we assumed no value from the Mylan arbitration, and see an award here as upside beyond this valuation. We calculated DCFs of the programmes being valued and weighted them by the historic probability of success of mid-stage clinical programmes. We conservatively chose 29% as our probability number, this being the average probability of success for both large and small molecules at Phase 2. For Propofol, where we understand Phosphagenics and Terumo will share the global opportunity outside Australia/New Zealand, and Japan, we assumed that Phosphagenics enjoyed 40% of the probability-weighted payoff.

Cost of capital. A key question in developing a DCF model is the cost of capital. At NDF Research we use the following approach:

- **Risk-Free Rate**. We use the Australian Ten-Year Bond Rate, which is currently 2.6%;

  Market Risk Premia. We regard Life Science companies with existing businesses, or who have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products, or have optioned their products to larger partners, but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'. The market risk premium in our models are higher depending on which category the company belongs to. We regard Phosphagenics as 'High Risk'

  Ungeared beta. We use an ungeared beta of 1.1.

This approach suggests a discount rate for Phosphagenics of 13.1% at the present time.

Elements of the commercial payoff for the opioid patches and propofol – pre-launch. We estimated, for the oxycodone and oxymorphone patches, from the Terumo Propofol Project, a base case and an optimistic case for the following elements:

- Level of expenditure required prior to a licensing deal;
- Timing of a prospective licensing deal;
- Level of upfronts in the deal (in US$);
- Level of milestones in the deal (in US$) – we assume that the probability of receiving those milestones declined evenly over time. We weighted the dollar value of milestones towards completion of Phase 2 and 3 as well as including some sales milestones.

Commercial life of future products. We assume that as 'enhanced generics' Phosphagenics's products could enjoy a commercial life of 15 years, after which they would be superseded by the next generation of generics. 15years is in line with the commercial window for the typical blockbuster drug prior to patent expiry[59].

Elements of the commercial payoff for each programme, post-launch. We estimated, for each product that ultimately could be launched from the programmes, a base case and an optimistic case for the following elements:

- Date of product launch in the US;
- Date of product launch for the Rest of the World (RoW);
- Level of royalties, as a percentage of net sales;
- The level of sales (in US$) to be achieved in the US at year five post launch;
- The level of sales (in US$) to be achieved in the RoW at year five post launch;
- The growth rate of sales in both the US and the RoW between years 6 and 14;
- The percentage of the US and RoW markets still held by the product when it goes generic;
- The terminal growth rate of the product franchise.

Currency: We converted the US dollar cash flow streams into Australian dollars at the forecast exchange rates listed in Figure 2:

[59] Consider the Roche/Genentech cancer drug Herceptin. It gained FDA approval in September 1998 and enjoyed peak sales in 2014, for a 16-year window. Going further back in time, Amgen gained FDA approval for Epogen in June 1989. Its peak sales year was 2004, another 16-year window.

Figure 2: Our AUDUSD exchange rate forecasts

Half	AUDUSD
30/06/2018	0.772
31/12/2018	0.760
30/06/2019	0.748
31/12/2019	0.735
30/06/2020	0.723
31/12/2020	0.712
30/06/2021	0.700
Later periods	0.700

Tax: We used the Australian corporate tax rate of 30%.

Further capital. We assume that with the current cash resources of the company no further capital needs to be raised.

Project parameters. We assumed the following parameters for the three projects:

Figure 3: Oxycodone project parameters

	Base case	Optimistic case
POH investment required (AUDm)	3	1
License date	2022	2021
License upfront (USDm)	10	20
License milestones (USDm)	20	30
Royalty rate	7.0%	11.0%
Earliest approval	2025	2023
Peak sales (USDm)	200	300

Figure 4: Oxymorphone project parameters

	Base case	Optimistic case
POH investment required (AUDm)	10	5
License date	2021	2020
License upfront (USDm)	10	20
License milestones (USDm)	10	20
Royalty rate	7.0%	11.0%
Earliest approval	2024	2023
Peak sales (USDm)	500	700

Figure 5: Propofol Project parameters

	Base case	Optimistic case
POH investment required (AUDm)	3	1
License date	2019	2018
License upfront (USDm)	5	10
License milestones (USDm)	20	30
Royalty rate	5.0%	7.0%
Earliest approval	2022	2021
Peak sales (USDm)	400	600

Valuation – Injectable drugs

We value the injectable drugs platform as a generic drug engine. Our general approach here was to assume that Phosphagenics can regularly bring to market new generic drugs where there was originally a sizeable market for branded drugs and where Phosphagenics captures a certain percentage of the market with its enhanced generic. We assume that the success of the Propofol Project can lead to other generics which Phosphagenics can develop itself and bring to market a range of these products between 2023 and 2027, with Phosphagenics going after a Local Market Value (LMV) of US$300m p.a. over these years with no further launches thereafter. We also assumed a 15-year time horizon and an ongoing tax rate of 30%. Our other assumptions were as follows:

- **Base case**. We assumed that Phosphagenics gained 7% of the LMV for its products. We assumed generic revenue decay rate of 3%, a generics gross profit of 40%, an initial cost base for a generics drug business of US$6m, general cost growth of 5%, R&D at 10% of revenue, working capital investment of 2% of sales p.a. and a terminal growth rate of minus 5%.

- **Optimistic case.** We assumed 10% LMV conversion, revenue decay of 5%, a generics gross profit of 50%, an initial cost base for a generics drug business of US$4m, general cost growth of 3%, R&D at 8% of revenue, working capital investment of 1% of sales p.a. and a terminal growth rate of minus 5%.

We probability-weighted our platform valuation, on the assumption that not every injectable project Phosphagenics works on will succeed in the formulation stages or in the clinic. We conservatively chose 29% as our probability of success, as per the other value projects of Phosphagenics.

Valuation – Putting it all together

We completed our valuation of Phosphagenics by adding.

1) The individual programme DCFs;
2) The notional value of the tax losses (ie the A$255m in retained losses as at December 2017 multiplied by the 30% Australian corporate tax rate);
3) The current cash on hand (A$4.3m as at December 2017);
4) The notional value of A$4.2m p.a. in corporate overhead, discounted in perpetuity at the discount rate calculated above, and adjusted for tax.

Valuation range $0.056 / $0.117. As per Figure 6 we value Phosphagenics at 5.6 cents per share base case and 11.7 cents per share optimistic case. We regard 9 cents per share as a reasonable mid-range value of the company.

Figure 6: Our valuation of Phosphagenics.

	Base	Optim.
Oxycodone (A$m)	9.1	27.2
Oxymorphone (A$m)	11.2	46.7
Propofol (A$m)	5.6	16.4
Injectable platform	5.5	39.8
Total programme value	31.3	130.1
Value of tax losses	76.6	76.6
Corporate overhead	-22.4	-22.4
Cash now (A$m)	4.3	4.3
Cash to be raised (A$m)	0.0	0.0
Option exercises (A$m)	0.0	0.0
Total value (A$m)	89.7	188.5
Total diluted shares (million)	1,612.5	1,612.5
Value per share	$0.056	$0.117
Valuation midpoint	$0.087	
Share price now (A$ per share)	$0.016	
Upside to midpoint	440.6%	

Re-rating Phosphagenics

We see the following factors as helping to re-rate Phosphagenics to our target price.

- A potentially favourable arbitration outcome in the Mylan matter, allowing more resources to progress Phosphagenics's existing technologies and other technologies and products it may in-license;
- Progress with the Propofol Project at Terumo;
- New licensing arrangements for the oxymorphone patch;
- Further clinical work on the oxymorphone patch;

- Development and clinical work on new animal health products.
- Potential in-licensing of new technologies.

Phosphagenics's seasoned leadership

Phosphagenics has a leadership team that knows how to create value in the Life Science space. CEO **Dr Ross Murdoch**, who joined Phosphagenics in 2015, brings strong Big Pharma credentials from his time at Shire[60], where he founded and grew both the Emerging Products business and the Haematology business over the period 2007 to 2012. Murdoch is, however no stranger to smaller companies, as attested by his time as President and Chief Operating Officer at Prana Biotechnology from 2002 to 2007.

ROSS MURDOCH WAS FORMERLY A SENIOR EXEC AT SHIRE

Dr Paul Gavin, Chief Scientific Officer and **Dr Roksan Libinaki,** GM of Animal Health and Nutrition, bring substantial corporate memory, having both been involved in the development of TPM® from its early days. Gavin's first exposure to TPM® was in 2002 when he was completing his PhD, while Libinaki has been working on TPM® since 2001. **Dr Alex Stojanovic**, VP Business Development and Commercial Operations since 2014, previously worked in marketing for the German pharma company Grünenthal[61], a specialty pharma company with a strong pain franchise, and he therefore knows the issue in analgesics very well. CFO **Anna Legg** brings financial skills that were valuable in identifying, in only a few months after she joined the company, the misappropriations that were publicly reported in June 2013.

GREG COLLIER BUILT THE SUCCESSFUL DRUG DEVELOPER CHEMGENEX

The Phosphagenics board is now a three-man team of Ross Murdoch, Chairman **Dr Greg Collier**, and Non-Executive Director **David Segal**. No member of this board was on the board at the time of the 2013 crisis. Greg Collier, who joined Phosphagenics's board in 2015 and became Chairman in April 2017, previously built the cancer drug developer ChemGenex Pharmaceuticals prior to its 2011 acquisition by Cephalon and is currently turning another ASX-listed company called Invion[62] into a developer of next-generation photodynamic therapy for the treatment of cancer. David Segal, a director since 2016, brings financial skills from his previous career in stockbroking.

Appendix I – The story so far for Phosphagenics

Phosphagenics's origins lie in late 1990s science experiments involving Vitamin E. Phosphagenics has its ultimate origins in a Melbourne-based company called Betatene[63], which became the world's largest producer of

[60] Shire (Dublin, Ireland, Nasdaq:SHPG, www.shire.com) is the world's 22nd largest pharma company with US$10.9bn in 2016 revenue (source: Pharmaceutical Executive magazine).
[61] Aachen, Germany, privately held, www.grunenthal.com. Grünenthal is owned by the Wirtz family.
[62] Brisbane, Australia, ASX: IVX, www.invion.com.au.
[63] While Betatene struggled in its early days – it had been capped at A$10m at the time of its 1985 ASX float but was valued at only A$9m in 1989 when it was folded into Denehurst, a lead-zinc miner – the business ultimately overcame all its scientific and commercial setbacks. Denehurst was able to sell 40% of Betatene to Henkel in 1993 for US$15m, and the other 60% to Henkel for $36m in 1995.

natural beta carotene before it was sold in 1995 to the German chemical company Henkel. The scientific brains behind Betatene was an inventor named Simon West while Betatene's CEO for much of its life was Harry Rosen. In 1999 Simon West was looking for better ways to fractionate tocotrienols, the more antioxidant of the Vitamin E molecules, out of palm oil. The intention was to provide a better Vitamin E than the usual alpha-tocopherol Vitamin E products obtained from soybeans. West discovered that by adding a phosphate group to the Vitamin E molecules, he could increase their hydrophilicity and therefore make them easier to extract from palm oil fatty acid distillate. He filed for patent protection over this process – which involved mixing it with phosphorus pentoxide (P_4O_{10}) at under 40 degrees Celsius[64] – and obtained funding for development of the process from a listed company called Vital Capital, of which Harry Rosen was a co-founder. West and colleagues were never able to obtain new Vitamin E that was cost-competitive with commercially-marketed Vitamin E. For a while they investigated using their phosphorylation technology to improve the bioavailability of lipophilic drugs. They then came up with what they considered an ideal use for the technology in transdermal drug delivery.

Phosphagenics discovers how to deliver drugs transdermally, 2001-2007. Vitamin E, first identified in 1922[65], is well known for its role in skin health[66], and around 2001 West was experimenting with the alpha-tocopheryl phosphates created using his phosphorylation technology in search of a new Vitamin E product with skin care applications. What he discovered was that when alpha-tocopheryl phosphate was mixed with di-alpha-tocopheryl phosphate (two tocopherol molecules joined to the phosphate group), the resulting formulation, was able to disrupt the outer layers of skin and allow deep penetration[67]. This led to the realisation that these 'tocopheryl phosphate mixtures' or TPM®s that could facilitate transdermal delivery of small molecule drugs that until that time had only been available in pill form or via injection. From mid-2002 Vital Capital was reporting that various drugs such as estradiol, atropine and morphine could be delivered transdermally using TPM®, and by 2004 transdermal drug delivery was the sole focus of the technology. Vital Capital changed its name to Phosphagenics in February 2004 to reflect this focus[68]. The company spent the next three years refining the TPM® technology in gel form before starting work on a patch that would transdermally deliver oxycodone, the opioid analgesic.

Phosphagenics works mainly on patches for the delivery of opioids, 2007-2013. In the mid-2000s the search was on at various companies for new delivery solutions for opioid analgesics. Oxycontin, an extended-release oxycodone tablet, had become a blockbuster for a privately held company called Purdue Pharma in part because of the high level of chronic pain in the US. There was, however, a range of unwanted side effects that accompanied oral ingestion of opioids. These included 'breakthrough' pain, nausea and vomiting, respiratory depression, and euphoria, which is the incentive for abuse. Phosphagenics reasoned that the transdermal delivery of oxycodone from a patch would provide a drug absorption profile able to minimise the side effects occurring after oral therapy. Phosphagenics set out to create such a patch around 2007 and announced its first prototype, developed in-house, in May 2009. In November 2010, after a number of clinical studies of its self-developed patches, Phosphagenics attracted 3M, a long-time player in patch technology, as a collaborator, and that company subsequently

[64] See WO/2000/069865.
[65] By two researchers at the University of California Berkeley, Herbert Evans (1882-1971) and his assistant Katherine Bishop. See Science. 1922 Dec 8;56(1458):650-1.
[66] See J Mol Med (Berl). 1995 Jan;73(1):7-17.
[67] See WO/2002/040033 and WO/2002/040034.
[68] Vital Capital was a Pooled Development Fund, however after the name change and the decision to focus solely on drug delivery technology the Pooled Development License was relinquished in late 2004.

developed a TPM® oxycodone patch that could deliver 4.5 times more oxycodone over three days than Phosphagenics's original patch[69]. However, as Phosphagenics reported in June 2012, the 3M patch design had a drug crystallisation issue. That issue was solved in 2013 by a patch redesign undertaken by a Germany firm called Labtec[70]. Development of an oxymorphone patch, benefiting from Phosphagenics's years of experience in patch development, was completed in early 2013[71].

Phosphagenics cleans house, 2013. Regrettably, the development of TPM®-based products took a back seat to other matters in July 2013 when Phosphagenics disclosed that its then CEO, Dr Esra Ogru, had been involved in a conspiracy with one other employee[72], and an external person, to defraud the company. The scale of this fraud turned out to be ~A$6m over a nine-year period from 2004. Much of the money that had been taken was quickly returned through subsequent legal settlements[73], and under the leadership of interim CEO Harry Rosen, who stepped up for this crisis, Phosphagenics was quickly refocused on technology development. The current CEO, Ross Murdoch, joined in January 2015.

Snakes and ladders with opioid patches, drug reformulations and animal health, 2013-2018. The last five years have seen Phosphagenics continue to work towards the goal of having TPM® technology used in a variety of products, but there have been various challenges along the way.

- The oxycodone patch was shown in late July 2013 to be able to deliver its active over a 72-hour period, however in a Phase 2 study in postherpetic neuralgia completed in January 2016 the patch was unable to register a statistically significant reduction in pain.
- For oxymorphone, Phosphagenics reported in October 2013 and August 2014 that its patch had performed well in terms of delivering therapeutic doses over three days as well, at plasma concentrations comparable to Opana® ER, however when the company proceeded to manufacture quantities of the patches for further clinical work it found that the quality was sub-optimal. The resulting reformulation programme, announced in May 2015 and mostly undertaken by Labtec[74], was not completed until December 2016.
- In October 2014 the company was able to show, in a randomised controlled study, that TPM-delivered tretinoin was better at treating acne than Valeant's Retin-A® product[75], however this study had not been powered to show statistical significance.
- Phosphagenics optioned its oxymorphone patch technology for the Japanese market to an unnamed Japanese group in April 2016, adding the oxycodone patch the following month as well as a collaboration over other products including the anaesthetic drug propofol. In its July 2016 newsletter Phosphagenics indicated that the Japanese company was Terumo. That company signed a term sheet for the oxymorphone patch in January 2017 and a development agreement for the patch in August 2017.

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[69] See Phosphagenics'ss market release dated 15 February 2012 and headlined *'Phosphagenics delivers further positive oxycodone patch trial results'*.
[70] Langenfeld, Germany, www.labtec-pharma.com. Labtec is a subsidiary of tesa, an adhesives maker (www.tesa.com), which in turn is owned by Beiersdorf (Hamburg, Germany, FWB: BEI, www.beiersdorf.com), the German maker of personal care products best known for the cosmetics brand Nivea.
[71] See Phosphagenics'ss market release dated 16 January 2013 and headlined *'Phosphagenics initiates clinical programme with oxymorphone TPM patch'*.
[72] Dr Robert Gianello, a co-inventor on Phosphagenics'ss WO/2005/084678 and WO/2006/133506 patent applications. He was sentenced to four years imprisonment for his role in the theft.
[73] Esra Ogru was subsequently sentenced to six years imprisonment in November 2014. She was released in 2016.
[74] Labtec had previously helped formulate Phosphagenics'ss oxycodone patch. Labtec were brought into the oxymorphone project in October 2015.
[75] This product had originally been part of J&J's Janssen Pharmaceuticals unit, which was sold to Valeant in 2011.

However, in March 2018 Terumo decided not to develop an oxymorphone patch, and instead focus on TPM®-enabled delivery of propofol.

- From 2015 the company had stepped up its work in animal health and nutrition, and over the next few years were able to announce successful studies demonstrating improvements in feed efficiency in weaner pigs (January 2016), and in poultry under normal conditions and when the birds were subjected to heat stress (December 2016 and December 2017 respectively). Despite previous positive supportive data in cattle, a dairy study announced in December 2017 proved less definitive, showing reduced cases of mastitis but without statistically significant improvements in milk quality and fertility.

The journey has consumed about A$100m so far, in multiple capital raisings since 2004:

Date	Shares (million)	% of current shares on issue	Price (AUD)	Raised (AUDm)	Type of raising
Jul-04	6.4	0.4%	0.143	0.9	UK placement
Nov-04	7.5	0.5%	0.283	2.1	SPP
Dec-04	16.1	1.0%	0.246	4.0	UK placement
Nov-05	46.9	3.0%	0.240	11.3	Placement
Dec-06	33.3	2.1%	0.300	10.0	Placement
Jan-07	23.3	1.5%	0.300	7.0	Placement and SPP
May-08	60.1	3.8%	0.150	9.0	Placement
Sep-09	76.1	4.8%	0.092	7.0	SPP
Mar-11	83.9	5.3%	0.090	7.6	Placement
Oct-11	194.0	12.3%	0.140	27.2	Placement and SPP
Jul-14	241.5	15.3%	0.080	19.3	Placement and SPP
Sep-17	224.0	14.2%	0.015	3.4	1 for 4 rights issue
Jan-18	91.4	5.8%	0.015	1.4	Placement
Total	1,105	70.0%	0.100	110.0	

Appendix II – A Phosphagenics glossary

Alkaloid – A class of nitrogen-based compounds generally derived from the opium poppy. A common example is morphine. Also includes synthetic opioids such as oxycodone.

Amphiphilic – A molecule that has both hydrophilic and hydrophobic properties. It can thus dissolve in water and oil. Soap is a common example. TPM® is amphiphilic.

Anaphylaxis – A sudden, severe allergic reaction to an allergen. Anaphylaxis can be life-threatening.

Arbitration – A form of alternative dispute resolution where two parties present arguments to a third party and agree to be bound to the third party's decision. Arbitration is a common method for companies to settle contractual disputes outside of the courts.

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

Broiler – Any chicken raised for meat rather than for egg production.

Diclofenac – A non-steroidal anti-inflammatory drug (NSAID). Phosphagenics has adapted diclofenac for delivery with its TPM® platform. The leading brand of diclofenac globally is Voltaren® Gel, from Novartis.

Emulsion – A mixture of two or more liquids in which one liquid is present as small droplets.

Enteral – A route of administration of a drug that involves the gastrointestinal tract. A common example is oral tablets.

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

FDA – The US Food and Drug Administration. To sell a therapeutic product in the US requires approval from the FDA.

Hydrophilic – A molecule is hydrophilic if it is attracted to water molecules, thus dissolving in water.

Hydrophobic – A molecule is hydrophobic if it is not attracted to water. Oil is a common example.

Injectable – A broad term used to describe drugs that are used for injection. An injectable may come in powder form vials and need added liquid before they are injected (such as daptomycin), or come in in ampoules or syringes that have been prefilled.

Lecithin – A yellow-brown fat substance often found in eggs.

Lyophilised – Freeze-dried.

Omega-3 – A polyunsaturated fatty acid found in a variety of foods. Omega-3 has known health benefits.

Phase – A stage of the clinical trialling process for a drug candidate. Phase 1 tests for safety. Phase 2 tests for efficacy in a small sample. Phase 3 tests for efficacy in a large sample.

PHN – Short for postherpetic neuralgia, PHN is nerve pain associated with shingles, which is the reactivation of the chickenpox virus. PHN typically occurs on one side of the abdomen and is very painful.

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

Propofol – An anaesthetic drug which Phosphagenics has been able to solubilise with TPM®.

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.

Soluble – Able to dissolve in water. Solubility is an important parameter to achieve desired concentration of drug in systemic circulation for desired pharmacological response.

Surfactant – Short for 'surface active agent', a substance that can reduce the surface tension of a liquid, making is easier for the liquid to penetrate solids.

Tocopherol – A form of Vitamin E. The common form is tocopherol acetate.

Tocopheryl Phosphate – A phosphorylated form of Vitamin E that is more water soluble than standard vitamin E.

Topical – A route of administration of a drug that involves application on the skin.

TPM® – Short for Tocopheryl Phosphate Mixture. A complex of mono- and di-tocopherol phosphates. This is the base technology that Phosphagenics uses to improve the delivery or solubility of drugs.

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

Vital ET™ – A raw form of Vitamin E produced in bulk by Phosphagenics.

Weaner – A piglet that has been weaned. Historically piglets become weaners between three and five weeks of age.

Appendix III –Phosphagenics's core Intellectual Property

The main intellectual property behind Phosphagenics is covered by 15 published patent families:

Improved process for phosphorylation and compounds produced by this process, WO/2000/069865, priority date 14 May 1999, invented by Simon West[76]

- This patent application describes the process originally developed by Simon West for the phosphorylation of compounds.

Formulation containing phosphate derivatives of electron transfer agents, WO/2002/040033, priority date 14 November 2000, invented by Simon West[77]

- This patent application covers the mix of mono- and di- alpha tocopheryl phosphates that comprises the core of Phosphagenics's TPM® technology.

Complexes of phosphate derivatives, WO/2002/040034, priority date 14 November 2000, invented by Simon West, Robert Verdicchio and David Kannar[78]

- This patent application covers the combination of alpha-tocopheryl phosphate with a surfactant as a dermal penetration agent.

[76] This patent application was granted in the US as Patent No. 6,579,995 in June 2003 and in Europe in October 2007 as EP 1 178 994.
[77] This patent application was granted in the US as Patent No. 7,648,710 in January 2010 and as Patent No. 8,173,145 in May 2012. It was granted in Europe as EP 1 339 412 in November 2011
[78] This patent application was granted in Europe as EP 1 339 413 in October 2009.

Dermal therapy using phosphate derivatives of electron transfer agents, WO/2003/011303, priority date 27 July 2001, invented by Simon West, David Kannar, Robert Verdicchio and Otto Mills, Jr.[79]

- This patent application covers the use of TPM® in treating skin conditions such as acne and sunburn.

Carrier, WO/2004/014432, priority date 9 August 2002, invented by Simon West and David Kannar[80].

- This is the basic patent application for TPM®, supported by Phosphagenics's early experiments on transdermal delivery of estradiol, atropine and morphine.

Alkaloid formulations, WO/2005/084678, priority date 3 March 2004, invented by Simon West, Esra Ogru and Robert Gianello[81]

- This patent application covers the use of TPM® in delivering alkaloid drugs generally, with examples in the delivery of atropine and morphine.

Carrier for enteral administration, WO/2006/012692, priority date 3 August 2004, invented by Simon West and Esra Ogru[82]

- This patent application covers the use of TPM® for oral delivery of drugs. A prominent example includes the delivery with TPM® of co-enzyme Q10, a dietary supplement often taken to promote cardiovascular health.

A carrier comprising one or more di and/or mono-(electron transfer agent) phosphate derivatives or complexes thereof, WO/2006/133506, priority date 17 June 2005, invented by Paul Gavin, Robert Gianello and Esra Ogru[83]

- This is the basic patent application for an improved version of TPM® called TPM®-02.

Carrier composition, WO/2011/075775, priority date 23 December 2009, invented by Paul Gavin, Mahmoud El-Tamimy, Jeremy Cottrell, Giacinto Gaetano and Nicholas Kennedy[84]

- This patent application covers the use of 'polar protic' solvents such as ethanol or isopropanol in improving TPM®-based drug delivery.

Carrier composition, WO/2011/094822, priority date 5 February 2010. Invented by Paul Gavin. Mahmoud El-Tamimy, Roksan Libinaki and Mohammad Mozafari

- This patent application covers other 'polar protic' solvents in TPM® formulations, most notably ethyl lactate.

[79] This patent application was granted in the US as Patent No. 8,008,345 in August 2011.
[80] This patent application was granted in the US as Patent No. 8,841,342 in September 2014. It was granted in Europe as EP 1 545 621 in November 2010.
[81] This patent application was granted in the US as Patent No. 8,529,947 in September 2013 and in Europe as EP 1 720 551 in January 2011.
[82] This patent application was granted in Europe as EP 1 778 289 in January 2011.
[83] This patent application was granted in the US as Patent No. 9,168,216 in October 2015.
[84] This patent application was granted in Europe as EP 2 516 011 in July 2017.

Carrier comprising non-neutralised tocopheryl phosphate, WO/2011/094814, priority date 5 February 2010, invented by Roksan Libinaki

- This patent application covers the use of TPM® to deliver omega 3.

Transdermal delivery patch, WO/2011/120070, priority date 30 March 2010, invented byJeremy Cottrell, Giacinto Gaetano, Mahmoud El-Tamimy, Nicholas Kennedy and Paul Gavin

- This patent application covers the use of TPM®-based transdermal drug delivery patches in the delivery of opioids.

Transdermal delivery patch, WO/2011/120084, priority date 30 March 2010, invented by Jeremy Cottrell, Giacinto Gaetano, Mahmoud El-Tamimy, Nicholas Kennedy and Paul Gavin[85]

- This patent application covers TPM®-based transdermal drug delivery patches for drug delivery generally.

New composition, WO/2012/122586, priority date 15 March 2011, invented by Roksan Libinaki and Robert Neely[86]

- This patent application covers the use of TPM® to delivery Vitamin A for the treatment of mastitis in cows.

Pharmaceutical formulation, WO/2017/096427, priority date 9 December 2015. Invented by Mahmoud El-Tamimy

- This patent application covers the use of TPM® in improving the solubility and stability of Propofol.

[85] This patent application was granted in the US as Patent No. 8,652,511 in February 2014 and as Patent No. 9,314,527 in April 2016.
[86] This patent application was granted in the US as Patent No. 9,561,243 in February 2017.

Appendix IV – Phosphagenics's capital structure

		% of fully diluted	Note
Ordinary shares, ASX Code POH (million)	1,577.5	99.8%	
Unlisted options (million)	3.0	0.2%	Average exercise price 17.2 cents, average expiry date 22-May-2019
Other options	35.1	2.2%	Employee options, yet to vest
Fully diluted shares	1,580.5		

Current market cap:	A$25.2 million (US$18.6 million)
Current share price	$0.016
Twelve month range	$0.011 - $0.021
Average turnover per day (last three months)	3.57 million

Appendix V – Major shareholders

Phosphagenics currently has only one substantial shareholder:

- **Mark Kerr** (6.9%), a Melbourne business who founded Vital Capital in the 1990s.

Appendix VI – Papers relevant to Phosphagenics

Munteanu et. al. (2004), *Modulation of cell proliferation and gene expression by alpha-tocopheryl phosphates: relevance to atherosclerosis and inflammation.* Biochem Biophys Res Commun. 2004 May 21;318(1):311-6.

- This paper demonstrated that Phosphagenics's TPM® could reduce, *in vitro*, cell proliferation related to atherosclerosis, suppressing proliferation of both smooth muscle cells and scavenger receptors, thereby reducing the oxidised LDL uptake.

Negis et. al. (2005), *On the existence of cellular tocopheryl phosphate, its synthesis, degradation and cellular roles: a hypothesis*. IUBMB Life. 2005 Jan;57(1):23-5 (full text available for free online).

- This paper hypothesises that alpha-tocopheryl phosphate is a signalling molecule.

Gianello et. al. (2005*), Alpha-tocopheryl phosphate: a novel, natural form of vitamin E*. Free Radic Biol Med. 2005 Oct 1;39(7):970-6.

- This paper reports the discovery of endogenous alpha-tocopheryl phosphate in various body tissue.

Libinaki et. al. (2006), *Evaluation of the safety of mixed tocopheryl phosphates (MTP) -- a formulation of alpha-tocopheryl phosphate plus alpha-di-tocopheryl phosphate*. Food Chem Toxicol. 2006 Jul;44(7):916-32. Epub 2005 Dec 6.

- This paper reports early toxicology work on TPM®.

Gianello et. al. (2007), *Subchronic oral toxicity study of mixed tocopheryl phosphates in rats*. Int J Toxicol. 2007 Sep-Oct;26(5):475-90.

- This paper provides further evidence of the favourable toxicology profile of TPM®.

Libinaki et. al. (2010), *Effect of tocopheryl phosphate on key biomarkers of inflammation: Implication in the reduction of atherosclerosis progression in a hypercholesterolaemic rabbit model.* Clin Exp Pharmacol Physiol. 2010 May;37(5-6):587-92. Epub 2010 Jan 17.

- This paper reports rabbit data on the effectiveness of TPM® in reducing atherosclerosis.

Smith et. al. (2015), *Topical application of a novel oxycodone gel formulation (tocopheryl phosphate mixture) in a rat model of peripheral inflammatory pain produces localized pain relief without significant systemic exposure*. J Pharm Sci. 2015 Jul;104(7):2388-96. Epub 2015 May 20.

- This paper showed that oxycodone could be delivered using TPM® in gel form and effect pain relief without allowing the drug to get into the bloodstream.

Gavin et. al. (2017a), *Tocopheryl phosphate mixture (TPM®) as a novel lipid-based transdermal drug delivery carrier: formulation and evaluation*. Drug Deliv Transl Res. 2017 Feb;7(1):53-65.

- This paper provides a review of the TPM® delivery system.

Gavin et. al. (2017b), *Transdermal oxycodone patch for the treatment of Post Herpetic Neuralgia: a randomized, double-blind, controlled trial*. Pain Manag. 2017 Jul;7(4):255-267. Epub 2017 Apr 18.

- This paper describes a Phase 2a study of Phosphagenics's oxycodone patch which showed a 'trend toward improved pain reduction'.

Gavin et. al. (2017c), *Pharmacokinetics, safety and tolerability of a novel Tocopheryl Phosphate Mixture/oxycodone transdermal patch system: a Phase I study*. Pain Manag. 2017 Jul;7(4):243-253. Epub 2017 Apr 19.

- This paper reported a Phase 1 study of a 3-day oxycodone patch.

Libinaki et. al. (2017), *The effect of tocopheryl phosphates (TPM®) on the development of atherosclerosis in apolipoprotein-e deficient mice*. Clin Exp Pharmacol Physiol. 2017 Jul 26. [Epub ahead of print].

- This paper reports favourable *in vivo* work on the use of TPM® in preventing atherosclerosis.

Gavin et. al. (2017d), *A Phase I study of the pharmacokinetics, safety and tolerability of a novel Tocopheryl Phosphate Mixture/oxymorphone transdermal patch system.* Pain Manag. 2017 Aug 17. [Epub ahead of print].

- This paper shows that TPM® patches could be used to deliver therapeutic amounts of oxymorphone in a sustained manner over a 72-hour period.

Libinaki and Gavin (2017), *Changes in bioavailability of omega-3 (DHA) through alpha-Tocopheryl Phosphate Mixture (TPM®) after oral administration in rats*. Nutrients. 2017 Sep 20;9(9) (full text available for free online).

- This paper demonstrates that TPM® could be used to improve the bioavailability of omega-3 supplements.

Appendix VII – Companies to watch

biOasis Technologies. This company's xB³ platform, based on a brain-penetrating peptide, allows drugs to be formulated so that they can cross the blood-brain barrier. The company is developing applications of this in brain cancer as well as neurodegenerative disorders.

Ceapro. This company uses proprietary technology to produce extracts and various active ingredients from oats and other renewable plant resources, turning them into nutraceuticals.

Emisphere Technologies. This company's Eligen technology centres on a library of absorption-enhancing compounds that harness natural passive transcellular transport processes for oral drug delivery. Eligen has been used for the delivery of various products including calcitonin, PTH, Vitamin B12, and oral GLP-1 analogues.

Pivot Pharmaceuticals. This company is commercialising a technology similar to TPM® called BiPhasix in which lipid vesicles enable transdermal delivery of drugs. Another technology called Solic allows drugs to become water-soluble. Pivot is applying these technologies to the delivery of cannabinoid products.

PixarBio. This company's NeuroRelease product is carbamazepine, best known as an anti-seizure drug, complexed with poly(lactic-co-glycolic acid) for extended release. The company has been seeking to indicate the products for post-surgical pain.

Pulmatrix. This company is a developer of pulmonary therapeutics based on a platform called ISPERSE for engineering inhaled small particles. PUR1800, for COPD, is an iSPERSE formulation of a kinase inhibitor in-licensed from J&J's Janssen unit. This product has been studied at Phase 2 and is now being reformulated into a formulation that can be used as a treatment for acute COPD exacerbations.

Tetra Bio-Pharma. This company formulates cannabinoid-based products using different delivery systems such as smokable pellets, oral tablets, eye drops and topical ointments.

Titan Pharmaceuticals. This company's ProNeura drug delivery system is a subcutaneous implant made out of ethylene-vinyl acetate that allows controlled release of the drug in which it is formulated. The first approved product is Probuphine, for the delivery of buprenorphine in the treatment of opioid addiction.

Company	Location	Code	Market cap (USDm)	Web
Emisphere Technologies	Roseland, NJ	OTCBB: EMIS	145	www.emisphere.com
Tetra Bio-Pharma	Orleans, On.	TSX-V: TBP	73	www.tetrabiopharma.com
Ceapro	Edmonton, Ab.	TSX-V: CZO	30	www.ceapro.com
Pivot Pharmaceuticals	Vancouver, BC	OTCQB: PVOTF	30	www.pivotpharma.com
biOasis Technologies	Vancouver, BC	TSX-V: BTI	21	www.bioasis.ca
Pulmatrix	Lexington, Ma.	Nasdaq: PULM	20	www.pulmatrix.com
Titan Pharmaceuticals	South San Francisco, Ca.	OTCBB: TTNP	20	www.titanpharm.com
PixarBio	Fort Lee, NJ	OTCQX: PXRB	5	www.pixarbio.com
Phosphagenics			18.6	

Risks related to Phosphagenics

Risks specific to Phosphagenics. We see six major risks for Phosphagenics as a company and as a listed stock:

- **Clinical risk**. There is the risk that Phosphagenics's compounds may fail to meet their primary of secondary endpoints in the clinical trials into which they are taken
- **Funding risk**. More capital will likely be needed to continue clinical development of Phosphagenics's compounds.
- **Arbitration outcome risk**. There is the risk that the Mylan arbitration may not go Phosphagenics's way.
- **Partnering risk**. There is the risk that Phosphagenics's various parting risks may not yield favourable commercial outcome for the company.
- **Timing risk.** There is the risk that the clinical studies we discuss in this note may take longer than we expect to complete.
- **Regulatory risk**. There is the risk that regulatory decisions may slow or stop the progress of Phosphagenics's various products.

Risks related to pre-revenue Life Science companies in general:

- The stocks of biotechnology and medical device companies without revenue streams from product sales or ongoing service revenue should always be regarded as speculative in character.
- Since most biotechnology and medical device companies listed on the Australian Securities Exchange fit this description, the term 'speculative' can reasonably be applied to the entire sector.
- The fact that the intellectual property base of most biotechnology and medical device lies in science not generally regarded as accessible to the layman adds further to the riskiness with which the sector ought to be regarded.
- Caveat emptor. Investors are advised to be cognisant of the abovementioned specific and general risks before buying any the stock of any biotechnology and medical device stock mentioned on this report, including Phosphagenics.

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