



NDF RESEARCH

Providing independent research coverage of ASX-listed Life Science companies

Admedus (ASX: AHZ)

Initiation of Coverage – Wednesday 20 March 2019

ADAPTing to market opportunities

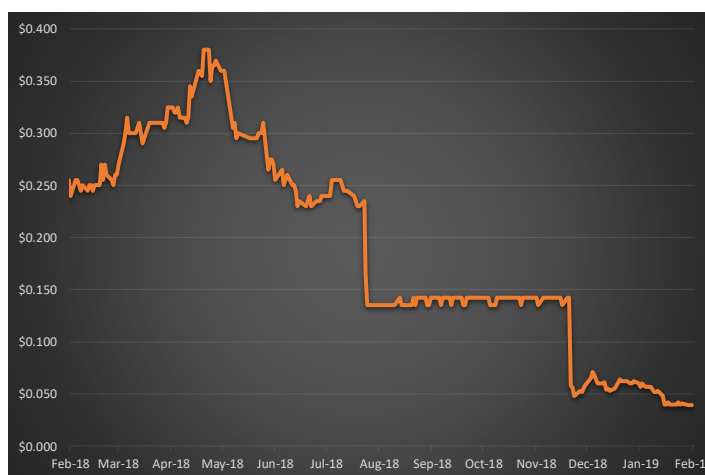
Admedus is a tissue engineering company whose ADAPT® range of approved cardiovascular tissue repair patches has enjoyed a steady increase in sales since its 2013 launch. We see a market opportunity for ADAPT® in the hundreds of millions of dollars. In the year to December 2018, Admedus booked A\$11.1m in revenue from its ADAPT® products, up from A\$7.2m in the previous corresponding period. A new leadership team focused on the market potential of ADAPT® took charge in 2017 and we foresee significant growth in the CardioCel® and VascuCel® products over the next few years. Admedus is currently developing what it considers to be a significant commercial opportunity from the ADAPT® technology that allows it to be used in Transcatheter Aortic Valve Replacement (TAVR). The market here is at least US\$3.5bn, growing to US\$12bn by 2025. Due to its novel single-piece aortic valve and anti-calcification properties, the Admedus 3D aortic valve has the potential to capture significant global market share. We value Admedus at \$0.08 per share base case and \$0.21 optimistic case, using a DCF-based approach. Our target price for Admedus is \$0.15. We see the market re-rating Admedus as ADAPT® sales increase and the company makes progress with its TAVR product.

Rating
Buy

Risk
High

Current price
\$0.038

Target price
\$0.15



Stock details

Daily Turnover: ~A\$82,000
Market Cap: A\$22.4m
Shares Issued: 589.9m
52-Week High: \$0.380
52-Week Low: \$0.030

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Please note: Admedus commissioned this report, and NDF Research will receive payment for its preparation. Please refer below for risks related to Admedus, and to 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 trading publicly on the Australian Securities Exchange (ASX). This Exchange 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 Science since 2002 as a sell-side analyst and 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 Science 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'.

To learn more about the Life Science sector on the ASX and our firm, please visit ndfresearch.com.



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



In this report

Introducing Admedus (ASX: AHZ).....	4
Twelve reasons to look at Admedus.....	6
ADAPT® – A breakthrough in soft tissue repair.....	8
ADAPT® – Building the commercial opportunity.....	11
Admedus ‘moonshot’ for ADAPT® in TAVR.....	13
Admedus’ infusion system business.....	15
Admedus has a seasoned management team.....	16
Valuing Admedus.....	17
Re-rating Admedus.....	19
Appendix I – Admedus’s non-core DNA vaccines.....	19
Appendix II – An Admedus glossary.....	20
Appendix III – Admedus’s core intellectual property.....	22
Appendix IVa – Capital structure summary.....	23
Appendix IVb - Previous capital raises, 2007-2018.....	24
Appendix V – Major shareholders.....	24
Appendix VI – Papers relevant to Admedus.....	24
Appendix VII – Companies to watch.....	27
Risks related to Admedus.....	28
General Advice Warning, Disclaimer & Disclosures.....	29



Introducing Admedus (ASX: AHZ)

Admedus is a tissue engineering company whose ADAPT® range of approved cardiovascular collagen bioscaffolds has been steadily growing sales since its 2013 launch. In the year to December 2018, Admedus booked A\$11m in revenue from the ADAPT® products CardioCel®, CardioCel 3D® and VascuCel®. This represented growth of 55% over the prior year. The ADAPT® products have been created using technology proprietary to Admedus that enables animal tissue to be prepared for use in a broad range of surgical repairs in humans. To date, the product is used mostly in the important (but niche) paediatric setting. Admedus also operates an infusion system distribution business, which generated A\$14m revenue in the year to December 2018. Admedus, which regards the ADAPT® technology as its core opportunity, believes that the market opportunity for the ADAPT® products including its 3D aortic valve is in the billions of dollars. It is currently developing what it considers to be a clinically superior product from the technology that enables the product to be used in Transcatheter Aortic Valve Replacement (TAVR), where the market opportunity is at least US\$3bn, growing to US\$12bn by 2025.

What is tissue engineering, and what is Admedus's technological strength in this space through ADAPT®? In medicine, 'tissue' is simply a group of specialised cells with a common structure and function, such as 'muscle tissue'. Tissue engineering is the growing of new tissue that allows damaged tissue to be repaired or reconstructed. Admedus's ADAPT® technology offers something unique in the repair of soft tissue, that is, tissue other than bone. Historically, animal tissue such as bovine tissue used for soft tissue repair in humans has quickly undergone calcium deposition, thereby limiting the usefulness of the tissue as it hardens and loses its flexibility. Clinicians have highlighted that this is the primary unmet medical need¹. For the first time ever, Admedus's ADAPT® technology enables animal tissue to be prepared without this major drawback. Consequently, the treated tissue can be used for long-term repair in humans with holes in the heart or damaged blood vessels, or in a multitude of other tissue repair indications.

What are CardioCel® and VascuCel®, and what are the benefits of the products? Admedus's first product from this technology, CardioCel® for the repair and treatment of a range of cardiac and vascular defects, gained CE Mark approval in August 2013 and 510(k) approval from the FDA in February 2014². Approvals in other jurisdictions have followed, based on favourable long-term (i.e. multi-year) clinical data on the acceptability, functionality and durability of ADAPT® bioscaffolds. Admedus initially launched CardioCel® in the paediatric congenital heart disease market. VascuCel®, for the repair of damaged blood vessels, gained 510(k) approval in late 2016. CardioCel 3D®, which gained FDA approval in May 2017, is a patch with a curved conduit for more complex tissue repair procedures that require more than one patch shape. The CardioCel® and VascuCel® products bring many benefits for patients. Along with no calcification, CardioCel® does not generate the cytotoxic issues seen with other products on the market and therefore facilitates an autologous regeneration around the implant. CardioCel® is also free from residual DNA, which makes it unique in the class. All this means fewer repeat or re-do surgeries for patients. The lack of calcification, no residual DNA and no cytotoxicity gives the Admedus products a significant

**ADMEDUS HAS
HAD
APPROVED
PRODUCT
SINCE 2013**

¹ J Appl Biomater Biomech. 2005 May-Aug;3(2):67-82.

² The initial US label was broad, whereas it took until November 2015 for the European label to be expanded merely from congenital heart defects to include repair and reconstruction of heart valves.



competitive advantage. Also, CardioCel® and VascuCel® are 'surgery ready' and off-the-shelf, which has short-term benefit in relation to time in surgery and consequent economic impact.

What is Transcatheter Aortic Valve Replacement, and why is it a significant opportunity for Admedus?

Transcatheter Aortic Valve Replacement (TAVR) is a relatively new treatment paradigm for aortic stenosis. After the onset of symptoms, patients with severe aortic stenosis have a survival rate as low as 50% at two years and 20% at five years without aortic valve replacement³. Approximately 12% of the population over the age of 75 years have aortic stenosis⁴. Historically, the only way to fix this problem was through surgical aortic valve replacement (SAVR), which is invasive, requires longer recovery times and is unsuitable for older 'high risk' patients. In TAVR, a catheter delivers a new valve to the site of the damaged valve, in a minimally invasive alternative not unlike the way stents are delivered for narrowed coronary arteries. Since 2017, Admedus has been designing a TAVR device in which ADAPT®-prepared tissue is used for the replacement valve. Admedus assembled an advisory board of TAVR physicians representing some of the biggest TAVR centres in the world and has been working with them to develop a TAVR that is clinically relevant to users. Admedus also has assembled a team of medical device engineers who are developing innovative delivery mechanisms. Admedus believes that this device can lead to a significant payday for shareholders, given the strong growth in the TAVR market – US\$3.5bn growing potentially to US\$12bn by 2025 – and the potential superiority of this device to existing devices. The market has only two notable players (Edwards and Medtronic), and it is a 'winner takes most' space. The Admedus TAVR device is designed in conjunction with medical engineers and physicians who practise TAVR. The device addresses three critical areas not yet dealt with by the current players:

**ADAPT® TAVR
WOULD MOVE
ADAPT®
USAGE INTO A
MUCH BIGGER
MARKET
SPACE**

- 1) **Valve durability.** It is acknowledged that current valves will calcify and require retreatment. This is a critical issue in the current marketplace. ADAPT®-treated tissue has shown to be calcium free over a 10-year period. This means the ADAPT® valve may demonstrate superior durability over current players in a 'blockbuster' market. With a recent study showing that TAVR can work better than surgery for low-risk patients⁵, the onus is now on suppliers of TAVR devices to show that their valve will be durable over the long term, since significantly younger patients will now potentially be undergoing TAVR procedures.
- 2) **Valve structure.** The current TAVR valves are constructed from three individual pieces of tissue and sewn into a frame. Admedus's unique single-piece design has been shown, *in vivo*, to be more durable because there is less stress at the joining points, and of better quality in terms of blood flow through the valve.
- 3) **Haemodynamics.** An interim analysis in February 2019 of the feasibility study in sheep for the 3D aortic valve showed positive results. The highlight of the results so far is a superior EOA of 2.5cm², EOA being 'Effective Orifice Area', the cross section of the blood flow into the aorta. Current valves on the market have EOAs of 1.6-2.0 cm². Should the results of the sheep study translate to humans, it would indicate that the Admedus 3D aortic valve offers significant clinical benefits over existing products.

If Admedus is so good, why is it capitalised at only A\$22.5m/US\$15.9m? We think the sales trajectory of the ADAPT® products compared to the market potential has held Admedus stock back over the last few years. Despite

³ Eur J Cardiothorac Surg. 2006 Nov;30(5):722-7. Epub 2006 Sep 6.

⁴ J Am Coll Cardiol. 2013 Sep 10;62(11):1002-12. Epub 2013 May 30.

⁵ See Popma et. al., *Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients*. New England Journal of Medicine, 2019; DOI: 10.1056/NEJMoa1816885.



60% year-on-year growth against much larger competitors, Admedus missed guidance in 2018. Also, we believe Admedus's long-running investment in an immunotherapy technology platform, which we profile in Appendix I of this report, has confused the story. In mid- to late 2018, the capital needs of the company, featuring a placement at 10 cents per share and a rights issue at eight cents, heavily diluted the stock. However, the resultant funding gives Admedus the chance to grow sales of ADAPT®, move towards profitability and prepare for the potential TAVR upside.

Twelve reasons to look at Admedus

- 1) **Admedus has commercialised important technology in the soft tissue repair space.** Its ADAPT® platform is consistently able to engineer animal tissue so that, in humans, the tissue will not calcify. Also, no potentially immunogenic animal DNA shows up on the patches. Follow-up from a clinical study in which ADAPT® tissue patches were used in reconstructive surgery to correct various congenital heart deformities between 2007 and 2009 has now yielded 10 years of data to prove the point on calcification. This data is unique in the space and supports the claims of significant clinical benefits.
- 2) **Admedus is innovating around its manufacturing process for ADAPT®.** For example, the company has developed a manufacturing process that allows it to 'thin out' the ADAPT® tissue at scale, thereby creating a whole new level of practicality and competitive advantage by allowing much thinner tissue patches to be deployed than are currently available. There is demand for thinner tissue amongst surgeons, which gives Admedus a competitive advantage.
- 3) **Admedus is growing sales of its ADAPT® products.** Since its first product, a cardiac tissue repair patch called CardioCel®, was launched in 2013, Admedus has consistently grown sales of this and subsequent products. Whilst growth has been significant in percentage terms, the market remains dominated by much bigger players.
- 4) **Admedus is continuing to develop new products from ADAPT®.** After CardioCel®, Admedus developed Vascel® for vascular repair, and most recently has launched CardioCel 3D®, an arched patch product for more complex tissue repair procedures. Admedus is the only company able to develop 3D-moulded surgical collagen solutions. Multiple projects related to 3D products are currently in the development portfolio. The company plans to launch new products in 2020.
- 5) **Admedus has made significant progress on development of its TAVR product.** Transcatheter Aortic Valve Replacement (TAVR) is a significant new market opportunity in the cardiovascular device space, currently worth US\$3bn and growing rapidly. Admedus believes that the ADAPT® catheter-based 3D valve is the basis for a new device in the field. Admedus's TAVR programme is now in the *in vivo* testing stage. Importantly, the device has other differentiated features alongside its use of ADAPT®. ADAPT® TAVR, if successful in reaching the market, will be a major player in a multi-billion-dollar space because of its unique ability to address the number one unmet medical need of calcification resistance.

ADMEDUS HAS THE FIRST AND ONLY BIOSCAFFOLD WITH PROVEN CALCIFICATION RESISTANCE



- 6) **Admedus has potential to partner with a major company on TAVR.** With TAVR dominated by Edwards with its Sapien device, other major companies are likely looking to enter this space. There is potential for Admedus to strike a co-development deal with a partner in 2019 or 2020 once its animal testing is complete. The prestige of such a deal has potential to unlock the value in terms of Admedus's market standing. Such a deal will likely come with both upfront payments and royalty payments factored into the future. Given the current market dynamic, it is not unreasonable to assume market share penetration of 20-50% in the future.
- 7) **Admedus has an established business distributing infusion systems in Australia.** This business generated A\$14m revenue in the year to December 2018. There is potential to spin off this business in the future as the company continues to focus on ADAPT®.
- 8) **Admedus is moving towards overall profitability.** With CardioCel® yet to fulfil its long-run potential over the last four years, Admedus is not in cash flow positive territory. That said, it is currently closing the gap thanks to market improvements and efficiencies in manufacturing. At the time of the 'Code Red' restructure⁶, costs as a function of revenue were 250%. This number declined significantly to 122% in the full-year 2018 financials.
- 9) **There is potential to realise value from Admedus's DNA vaccine technologies.** The Phase IIa study which Admedus completed with its DNA vaccine targeting HSV-2 suggested the possibility of a new therapy in genital herpes once larger studies establish the appropriate dose and clinical studies are powered for statistical significance. While Admedus is no longer funding this work, in April 2018 it optioned the programme to a Chinese group called Star Bright, with the understanding that A\$18m would be invested by that group for a 60% interest. This transaction, if completed, will leave Admedus with a minority interest in the upside.
- 10) **Admedus has a quality leadership team.** CEO Wayne Paterson and Chief Operating Officer David St Denis are both former senior executives of major pharma companies including Merck KGaA and Roche. Backing Paterson and St Denis is a quality board chaired by the Guidant veteran John Seaberg.
- 11) **Admedus has multiple physicians in the company,** including the inventor of ADAPT®, Prof Leon Neethling. Both substantial shareholders - SIO Capital and Star Bright - also have medical doctors on their boards.
- 12) **Admedus is undervalued, on our numbers.** We value Admedus at \$0.08 per share base case and \$0.21 per share optimistic case, using a DCF-based valuation. Our target price of \$0.15 sits around the middle of our DCF range. We see Admedus being re-rated by the market as ADAPT® sales increase and the company makes progress with its TAVR product.

**ADMEDUS IS
MOVING
TOWARDS
PROFITABILITY**

⁶ Code Red was a cost-lowering exercise undertaken by the company in 2016.



ADAPT® – A breakthrough in soft tissue repair

ADAPT® overcomes a key issue in soft tissue repair. At present there are three main materials used in soft tissue repair: human tissue, animal tissue (mainly bovine and porcine) and synthetic tissue. In all cases, surgeons want a biological 'matrix' to act as a scaffold which, placed at the site of disease or injury, allows new vascularised human tissue to grow at the site, thereby effecting repair⁷. Human tissue is the closest to the real thing but can be difficult to source and process. It also suffers from the potential for an immune reaction in the recipient. Synthetics are easy to make, but the developer must still worry about durability and biocompatibility⁸. Animal tissue is easy to source and can come close to the natural product in terms of structure and function, making it potentially the best kind of tissue repair product. However, it has the potential for calcification⁹. When calcium builds up in body tissue, that tissue becomes less flexible, which impairs function and can ultimately cause tissue failure. Animal tissue used in tissue repair calcifies because it is routinely fixed using glutaraldehyde. That chemical improves tissue durability through cross-linkages that prevent the rapid degeneration of the tissue's collagen structures. It also cuts the risk of an immune reaction by disinfecting the tissue. Glutaraldehyde, however, exposes phosphorus in cell membranes to calcium in the extracellular fluid, resulting in calcium phosphate mineral deposits¹⁰. ADAPT®, which was invented by Professor Leon Neethling at the University of Western Australia in the early 2000s, overcomes the calcification issue by first treating animal tissue with an alcohol-based solution, markedly cutting the glutaraldehyde subsequently needed. There are other advantages for ADAPT® beyond lower calcification. The product is easy to use¹¹, retains the natural tensile strength, flexibility and elasticity of the animal tissue – indeed, improves on the animal tissue – and is biocompatible¹². In fact, the Admedus products bring together the ideal solution: a scaffold that has the biological profile of a synthetic (zero DNA from the original animal tissue¹³) and the physical characteristics of collagen.

**ADAPT®
TISSUE
DOESN'T
CALCIFY
INSIDE
PATIENTS**

Background to ADAPT® – 1999 to 2005. The initial ADAPT® technology was invented around 1999 by Professor Leon Neethling¹⁴, a cardiovascular medical scientist originally from South Africa who did research in the field at Fremantle Hospital in Western Australia. When Neethling set out to create a better fixing solution than glutaraldehyde for animal tissue, he initially worked with kangaroo tissue before switching to bovine tissue¹⁵. Neethling developed a procedure that markedly reduced the use of glutaraldehyde and called his process ADAPT®, short for Advanced Processing of Tissue. He filed for patent protection over the various steps in the ADAPT® process before forming a company called Celxcel Pty Ltd to commercialise it. From late 2005, Celxcel's work was funded by a public company called bioMD, which became Allied Health Care Group in 2011 after it

⁷ When human tissue is used, the implant is either an 'autograft' ('self' tissue) or allograft (donated tissue). When animal tissue is used, the implant is called a 'xenograft'.

⁸ Many synthetic products are biocompatible in the sense that the body does not reject them. That said, synthetics present potential problems that are not issues when natural products are used.

⁹ An additional problem with animal tissue is that certain people groups are not enamoured of the idea of pig parts going into their bodies.

¹⁰ See *Ann Thorac Surg.* 2005 Mar;79(3):1072-80.

¹¹ Since there is no rinsing required prior to implantation, and the ADAPT® procedure naturally sterilises the tissue.

¹² As certified by NAMSA, the US verification agency (see www.namsa.com).

¹³ This has been verified in a recent NATA report received by Admedus. NATA is Australia's National Association of Testing Authorities.

¹⁴ Pronounced 'Neet-ling'.

¹⁵ Pericardial tissue and carotid artery tissue are the preferred tissues used by Neethling and his team. We understand he chose kangaroo tissue because of the ethical and disease-management issues associated with porcine tissue and the vCJD issues that have emerged in recent years regarding bovine tissue.



merged with a company of that name whose main focus had been a DNA vaccine technology platform. The merged group changed its name to Admedus in late 2013.

Pre-clinical evidence that ADAPT® works – 2005 to 2010. For Neethling and his colleagues, their animal tissue needed to achieve three things. It needed to be 'acceptable', in that the tissue would not provoke an immune response in the patient. It needed to be 'functional', in that it would promote revascularisation in the treated area and allow new cells to form within the structure of the implanted tissue. And it needed to be durable, that is, avoiding fibrosis and staying flexible over a long period of time. Early *in vivo* work showed ADAPT® achieving all three objectives.

- **Rat implant study, 2006.** This study, conducted over a 120-day period, showed that ADAPT® patches worked well over a long period¹⁶.
- **Sheep implant study, 2006 to 2008.** This study, in which ADAPT®-treated tissues were used as patches to repair damaged jugular veins of sheep over a 150-day period¹⁷ and a 200-day period¹⁸, showed the basic therapeutic power of the technology. The results were published in the *Journal of Heart Valve Disease* in July 2008¹⁹.
- **Comparison study in rats, 2007.** Leon Neethling had already done comparison studies of ADAPT® in 2004, with favourable results²⁰. However, in 2007 he performed another rat study that compared ADAPT® with two other commercially available patch materials, again with favourable results. At the 200-day mark, ADAPT® was performing much better over that period in terms of lower fibrosis and calcification issues²¹. The same outperformance was noted at the 12-month point²².
- **Published comparison study in rats, 2010.** In November 2010, Neethling et al. published 12-month comparison data in the *Journal of Heart Valve Disease* showing that the level of calcium in ADAPT® rats (n=10) was 98% lower than in rats that received comparator patches (n=10) after 12 months. The p-value on this comparison was less than 0.001²³.

ALL THE
COMPARISON
DATA ON
ADAPT® IS
FAVOURABLE

Clinical evidence that ADAPT® works – the Bloemfontein Study, 2007 to 2010. ADAPT®'s first clinical outing was the Bloemfontein Study, in which the patches were used in reconstructive surgery to correct various congenital heart deformities such as atrial and ventricular septal defects²⁴, aortic root enlargements²⁵ and outflow tract reconstructions²⁶. The Bloemfontein Study, so-called because it was conducted in the South African city of

¹⁶ See the bioMD market release dated 4 September 2006 and headlined 'bioMD achieves breakthrough with animal tissue implants'. The life expectancy of a domestic rat is around 2-3.5 years. 120 days of functionality in a rat is therefore worth something like 7-8 human years.

¹⁷ See the bioMD market release dated 21 February 2006 and headlined 'Celxcel's pre-clinical animal trial accelerates move to Phase 1 clinical studies'.

¹⁸ See the bioMD market release dated 7 January 2007 and headlined 'ADAPT®-treated patch and carotid bypass graft trial produces promising pre-clinical results'.

¹⁹ See *J Heart Valve Dis.* 2008 Jul;17(4):456-63; discussion 464.

²⁰ See *J Heart Valve Dis.* 2004 Jul;13(4):689-96; discussion 696.

²¹ See the bioMD market release dated 14 March 2007 and headlined 'Positive results from a 200-day comparative patch study'.

²² See the bioMD market release dated 10 September 2007 and headlined 'Positive results from a 12-month comparative patch study'.

²³ See *J Heart Valve Dis.* 2010 Nov;19(6):778-85.

²⁴ A septal defect is a defect in the walls that divide the chambers of the heart. A ventricular septal defect is a hole in the wall dividing the left and right ventricles (the lower chambers of the heart) while an atrial septal defect is a hole in the wall dividing the left and right atria (the upper chambers).

²⁵ An aortic root enlargement is an aneurysm (i.e. balloon-like deformity) in the wall of the aorta, which is the large artery that carries blood from the left ventricle of the heart to branch arteries.

²⁶ An outflow tract reconstruction involves the ventricular outflow tract through which blood from the ventricles of the heart pass before entering the large arteries. Right ventricular outflow tract reconstruction is most commonly done to prevent tachycardia, which is abnormally rapid heartbeat.



Bloemfontein at the Universitas Hospital there, was announced in May 2007²⁷. It ultimately recruited, between May 2008 and July 2009, some 30 patients whose average age was three years, with initial follow-up at six and 12 months. Favourable six-month data from the first 10 treated patients was reported in July 2009. In March 2010, the investigators were able to report that ADAPT® patches, after six and in many cases 12 months, had '*demonstrated reliable tissue strength and constant stitching characteristics with no reported leakages*' and '*no reported patch-related mortalities/morbidities*', indicating that in this trial the clinical experience matched the pre-clinical. MRI data on five patients at 12 months confirmed this outcome, as did 12-month follow-up on the remaining patients completed in April 2010²⁸. Admedus now has 10-year follow-up data from some patients, where there is still no sign of calcium build-up at the site of repair²⁹. The study results, which encompassed follow-up out to 36 months, were published in *Interactive Cardiovascular and Thoracic Surgery* in July 2013³⁰. The Bloemfontein Study allowed Admedus to gain CE Mark approval for CardioCel® in August 2013 and then 510(k) approval from the FDA in February 2014, in each case for use in both children and adults. The product registered its first sales in Europe in November 2013³¹.

There are now three ADAPT® products – CardioCel®, VascuCel® and CardioCel 3D®.

- CardioCel®, as we noted above, was launched in 2013.
- VascuCel®, which gained FDA approval in October 2016 and CE Mark in March 2019, was CardioCel® but in sizes such as 0.8cm x 8cm, which are suitable for vascular repairs like carotid endarterectomies³². Admedus has been selling VascuCel® commercially since 2015.
- CardioCel 3D®, which gained FDA approval in May 2017 and CE Mark in March 2019, is a patch with a curved conduit for more complex tissue repair procedures where more than one patch shape is required, such as in the aortic arch. CardioCel 3D® was launched commercially in early 2018.

There are many more ADAPT® products to come, thanks to a renewed product development effort. Admedus continually talks to its surgeon end-users and distributor customers, seeking to find out what the market needs. When Admedus's current CEO, Wayne Paterson, took over the company in 2016, he realised that the ADAPT® platform would allow three-dimensional tissue patches to be engineered for more complex surgeries. CardioCel 3D® is the first fruit of the consequent development effort. The 3D insight put Admedus in a great competitive position because Admedus believed that no other company in the world was able to make 3D-moulded surgical collagen solutions. Admedus has multiple projects currently in the development portfolio related to 3D products. More recently, Admedus has discovered how to make ultra-thin patches, useful for repair of very small organs, and we expect new products to emerge from that insight as well. The search for new ADAPT® products has also

**THERE ARE
MANY MORE
ADAPT®
PRODUCTS TO
COME**

²⁷ See the bioMD market release dated 30 May 2007 and headlined '*Human clinical trial of ADAPT®-treated cardiovascular patches*'.

²⁸ There was initially expected to be 50 patients in all, but the power of the ADAPT® technology was such that the investigators decided that at the 30-patient mark that this number would generate enough data to demonstrate effectiveness.

²⁹ For the passing of the seven-year mark see the Admedus market release dated 8 July 2015 and headlined '*CardioCel shows no evidence of calcification after 7 years in long-term follow up to Phase II trial*'. Previous announcements had been made at the four-year mark (March 2013), at five years (September 2013) and at six years (April 2014).

³⁰ *Interact Cardiovasc Thorac Surg.* 2013 Oct;17(4):698-702. Epub 2013 Jul 6.

³¹ The launch was helped by a A\$1.9m Commercialisation Australia grant announced in June 2013.

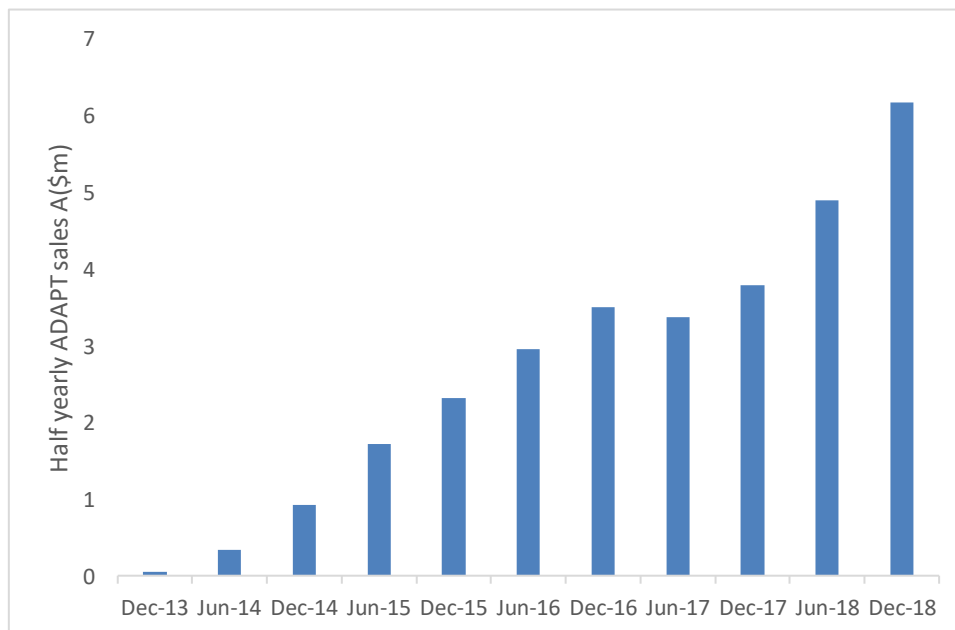
³² See the Admedus market release dated 18 May 2015 and headlined '*Admedus to launch CardioCel product for vascular repair*'.



led to what Admedus considers a significant project to develop a new device for Transcatheter Aortic Valve Replacement (TAVR), which we discuss below.

ADAPT® – Building the commercial opportunity

Currently ADAPT® sells in multiple markets around the world. The product is manufactured at an ISO13485-certified facility at Malaga in northern Perth³³ and ships from there to the US, Canada³⁴, Europe and other established and emerging (and high-growth) markets into which Admedus currently sells, including Singapore (since 2014)³⁵, Malaysia (November 2015), the UAE (November 2016), Saudi Arabia (February 2017), India (November 2017), and Spain and Portugal (May 2018). CardioCel® is currently available in more than 200 centres across the world.



Currently sales are ~A\$11m p.a. but on a growth trajectory of 60% YoY. Admedus has gradually built usage of the ADAPT® products since CardioCel® was launched in 2013. While A\$11m is not a profitable sales level, and way below the potential of the product, this business is now getting significant management focus to help it realise its potential. Costs continue to decline as a percentage of revenue.

³³ Admedus moved to bring production of CardioCel® in-house in late 2013 when it acquired this 2,000m² manufacturing site from Genzyme. In its original configuration, the Malaga facility had potential peak annual production of over 100,000 CardioCel® units annually. Admedus started producing CardioCel® here in August 2014. The Admedus facility had gained its ISO13485 certification for CardioCel® in February 2013.

³⁴ Health Canada approved the product in October 2014.

³⁵ Special access for CardioCel® was granted in Singapore in November 2014 while regular marketing authorisation was granted in June 2015.



What is the market potential of ADAPT®? A lot more than A\$11m. Admedus believes that cardiovascular repair is a US\$2bn market globally³⁶, which makes sense given that, in the US alone, 11% of women and 22% of men aged 60-79 years will have coronary heart disease, rising to 22% and 31% respectively for people aged over 80 years³⁷.

Admedus has competition, but it also has competitive advantage. Part of the problem for Admedus in breaking into the markets that it is seeking to serve is that other companies are already there, such as the privately held Aziyo Biologics³⁸ and Baxter International³⁹ through its BioSurgery business. A significant competitor is Edwards Lifesciences, which sells a bovine pericardial patch and has developed an anti-calcification combination of surfactants and solvents to go with it called XenoLogiX⁴⁰. Admedus argues that its ADAPT® product is superior and involves much less pre-operative preparation than XenoLogiX. Admedus's sales people have gradually won that argument with key accounts, but it is taking time. Ideally, Admedus could run a head-to-head study, which would likely attract a lot of attention in cardiovascular surgery circles.

Congenital Heart Disease was a dependable first indication for Admedus, but the company is now going after larger market opportunities. We estimate that around 0.3% of the population is living today after having survived a congenital heart disorder⁴¹. Annual incidence today may be around 0.6% of live births⁴² in the US, or 20,000-25,000 cases annually. However, others have suggested higher incidence⁴³. Vascular repairs are now a more significant market opportunity. Out of ~1.2 million inpatient vascular procedures in the US each year⁴⁴, perhaps 300,000 could benefit from VascuCel® patches, of which 180,000 are carotid endarterectomies⁴⁵. Current sales are still mainly in the niche paediatric segment, but Admedus aims to expand into bigger patient segments. Therefore, product development is a priority, and the company continues to expand its portfolio.

There are numerous other opportunities for ADAPT®, such as in vaginal wall prolapse, ventral hernia⁴⁶, dura mater damage⁴⁷, arteriovenous fistula, and cardiac artery graft bypass, to name a few. The only drawback to addressing these opportunities is that shareholder funds are required to conduct the necessary trials.

The US distribution network is building. In the US and Europe, Admedus is growing a field force for the ADAPT® product, and the efforts of this force seem to be paying off. Consider that in March 2018 Admedus was able to announce that a US Group Purchasing Organisation would be promoting CardioCel® and VascuCel® to its 1,500-member hospitals. That was a first for Admedus after having had sales people on the ground there for four years. In the US, a number of additional industry-experienced sales reps became active late in early 2018. CardioCel® is currently available in around 37 US states.

**THE MARKET
OPPORTUNITY
FOR ADAPT IN
HEART REPAIR
IS >US\$2BN**

**ADMEDUS HAS
SECURED NEW
US SALES
REPS**

³⁶ See the company's 2017 Annual General Meeting presentation.

³⁷ Source: American Heart Association, Heart Disease and Stroke Statistics—2018 Update, Chart 18:1.

³⁸ Silver Spring, Md, www.aziyo.com.

³⁹ Deerfield, Il., NYSE: BAX, www.baxter.com. Baxter, a Fortune 500 company, is a major supplier of essential renal and hospital products with US\$11.1bn in 2018 sales.

⁴⁰ For some early Edwards work on anti-calcification see Ann Thorac Surg. 2005 Mar;79(3):897-904.

⁴¹ Estimated using data from Am Heart J. 2004 Mar;147(3):425-39.

⁴² See J Am Coll Cardiol, 2002; 39:1890-1900.

⁴³ See Circulation. 2016 Jun 21;133(25):2716-33.

⁴⁴ See J Vasc Surg. 2012 May;55(5):1394-9; discussion 1399-400. Epub 2012 Jan 16.

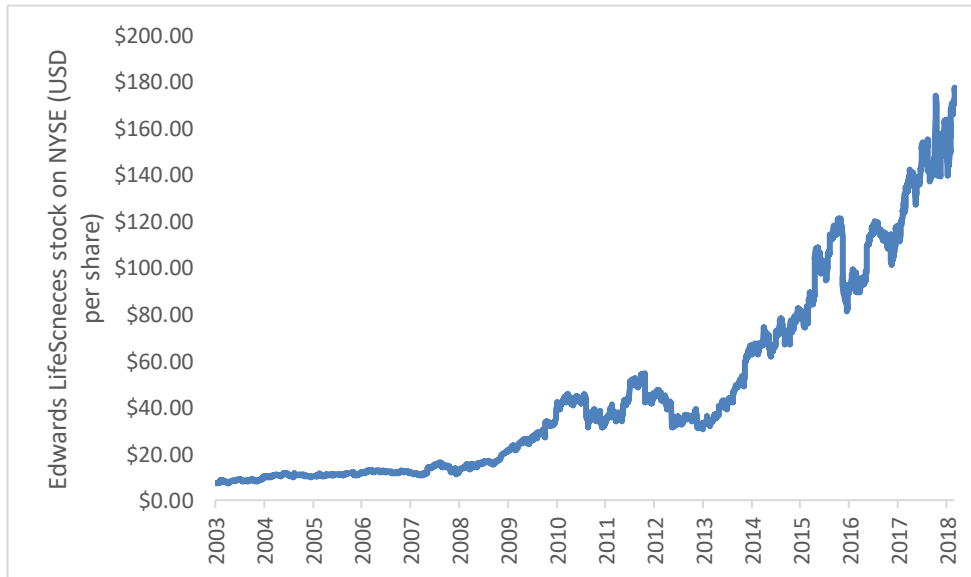
⁴⁵ See Tex Heart Inst J 2005; 32(3): 369-371.

⁴⁶ In March 2010, Admedus announced that its product had worked well in a rat study in ventral hernia defects.

⁴⁷ In April 2015, Admedus announced that it had done pre-clinical work showing that ADAPT® would be used to repair dura mater, the outer membrane enveloping the brain and spinal cord.



Usage is growing in the Rest of the World via distributors. Outside of the US and Europe, Admedus markets through distributors. In the Middle East and North Africa, for example, its distributor since April 2015 has been Genpharm, a Dubai-based pharmaceutical marketing company⁴⁸ which has been dependably growing accounts since the relationship was established. Distributors are being sought for other new and potentially sizeable markets, most notably China.



Admedus 'moonshot' for ADAPT[®] in TAVR

TAVR is an important new treatment paradigm for aortic stenosis. TAVR is short for Transcatheter Aortic Valve Replacement. It currently represents a hot growth area of the cardiovascular device market believed to be worth US\$3.5bn⁴⁹, growing to perhaps US\$12bn by the mid-2020s⁵⁰. TAVR is a relatively new treatment paradigm for aortic stenosis. The aorta is the large artery that carries blood from the left ventricle of the heart to various branch arteries. In aortic stenosis, the aortic valve⁵¹ narrows, depriving the body of oxygen-rich blood, leading to symptoms such as tiredness with minor activity, shortness of breath and chest pain. Aortic valve stenosis is understood to be present in 2% to 9% of the population over the age of 65 years⁵². Historically, the only way to fix aortic stenosis was through surgical aortic valve replacement (SAVR), which was expensive and not suitable for patients with co-morbidities. In the 1990s, an American company called Percutaneous Valve Technologies (PVT) pioneered Transcatheter Aortic Valve Replacement as an alternative, where a new valve would be delivered to the

**TAVR WAS A
COMPANY
MAKER FOR
EDWARDS**

⁴⁸ See www.genpharmservices.com.

⁴⁹ In the fourth quarter of 2018, Edwards reported that its Transcatheter Heart Valve Therapy business generated US\$592.4m in sales, up 14.1% year-on-year.

⁵⁰ See the Research and Markets press release dated 16 May 2017 and headlined 'Structural Heart Devices Market to Reach \$9 Billion by 2025'.

⁵¹ In the heart there are four main valves, that is, tissue flaps that control the flow of blood through the heart in the correct direction. The mitral and tricuspid valves let blood flow from the atria (the heart's two upper chambers) into the ventricles (the two lower chambers) while the pulmonary and aortic valves let blood flow from the ventricles out to the rest of the body. When the flaps of these valves, called 'leaflets', thicken, stiffen or fuse together, the result is a partial closure of the valve. When this happens, heart valves made from bovine tissue are used to reconstruct or replace the valve.

⁵² Cardiovasc Ultrasound. 2006 Jul 14;27.



site of the damaged valve in a minimally invasive manner using a catheter, in a not-dissimilar way to the way stents are delivered to occluded arteries (i.e. via the femoral artery). In late 2003, PVT was acquired by Edwards Lifesciences, the US medical device major⁵³, which gained FDA approval for the first TAVR device, called Sapien, in November 2011. It is fair to say that TAVR has proved a 'company-maker' for Edwards in the years since 2003, with the stock up 23% p.a. in the following 15 years.

Currently Edwards leads the TAVR market. Since 2011 the TAVR market has grown rapidly. It is now estimated to be a US\$3.5bn global market segment, expected to be a US\$12bn opportunity by the mid-2020s, driven in part by an expansion into younger, lower-risk patients⁵⁴. Edwards, a company which specialises in heart valves and hemodynamic monitoring, continues to lead the TAVR market it created, with an estimated 70% share, helped by various new generations of Sapien. Following way behind is the medical device giant Medtronic⁵⁵, whose CoreValve system gained FDA approval in January 2014 but is regarded as slightly inferior device⁵⁶. Boston Scientific⁵⁷ has a TAVR device called Lotus Edge that it wants to become the third option, but that company decided to delay commercialisation in February 2018 due to design issues⁵⁸. Boston Scientific is preparing to reintroduce the Lotus valve in Europe in 2019, with US approval to follow, but use of the device is expected to be restricted to high-risk patients. Boston Scientific's delay in becoming the third player may be Admedus's opportunity.

Admedus has a device that it believes can be superior to the currently marketed TAVR devices and attract challengers to Edwards and Medtronic. To get into the TAVR market a company has to be innovative given that the first two devices are markedly different from each other⁵⁹. In 2016, on the reasonable assumption that ADAPT® could provide the basis for superior heart valve tissue⁶⁰, Admedus assembled a regular advisory board of seven established interventional cardiologists and started taking their feedback on what an ideal new TAVR device would look like. Admedus's team proceeded to design such a device. What they came up with was a 3D single-piece moulded valve, which would allow differentiation from the Medtronic and Edwards valves, which are three-piece. Admedus's device, which obviously includes ADAPT® as the tissue valve being delivered, only requires 10-15 sutures to hold it in place whereas the competitor valves require 150-160. One of the largest unmet needs in the space is durability, and Admedus' ADAPT® TAVR would be the only product with the differentiated benefit of proven resistance to calcification.

**ADMEDUS
MAY HAVE A
BETTER TAVR
PRODUCT
THAN
EDWARDS**

⁵³ Irvine, Ca., NYSE: EW, www.edwards.com.

⁵⁴ JACC Cardiovasc Interv. 2016 Nov 14;9(21):2183-2185. Epub 2016 Oct 12.

⁵⁵ Minneapolis, Mn., NYSE: MDT, www.medtronic.com. Medtronic, a Fortune 500 member, is one of the world's largest medical device companies.

⁵⁶ For a head-to-head comparison see J Am Coll Cardiol. 2015 Aug 18;66(7):791-800.

⁵⁷ Natick, Ma., NYSE: BSX, www.bostonscientific.com. Boston Scientific, a Fortune 500 member, is a major supplier of cardiovascular, rhythm management and medical/surgical products. It enjoyed US\$9.8bn in 2018 sales.

⁵⁸ See *Wait continues for Boston Scientific's Lotus Edge* by Omar Ford, Medical Device and Diagnostic Industry, 2 February 2018.

⁵⁹ The Edwards Sapien device uses a balloon to expand the compressed valve once it is in position, while the Medtronic CoreValve has a special self-expanding valve that takes it signal to expand from an allow sensitive to body heat.

⁶⁰ As early as 2011 Admedus was thinking about opportunities in heart valve reconstruction. In December of that year the company announced that a comparison study with product from a 'global tissue heart valve manufacturer' had shown that ADAPT®-treated tissue heart valve leaflets had significantly less calcification over 24 weeks. In September 2015 Admedus even went so far as to commence a clinical study, never completed, that had been intended to show that ADAPT could be used as a better valve for surgical aortic valve reconstruction. This study followed from feasibility work in sheep conducted at Katholieke Universiteit Leuven in Belgium by Professor Bart Meuris, widely regarded as an authority on heart valves. For three aortic valve cusp replacement procedures that used CardioCel, performed by a team at Technische Universität München, see Ann Thorac Surg. 2015 Nov;100(5):1923-5. In 2016 Admedus realised that catheter-based valve replacement and not surgery was the wave of the future in terms of dealing with faulty valves.



Admedus has a device that will be highly differentiated from other TAVR devices on the market. Firstly, it has the anti-calcification properties shown consistently in the years since 2010. Secondly, the device itself has virtually no sutures. This in itself might attract a lot of attention because an ongoing issue in the TAVR field is 'paravalvular leak', where the new valve doesn't close firmly over the aorta⁶¹. In addition to the anti-calcification and non-suture advantages, Admedus's product will be hydro-packed in a way that makes it easy for the surgeon to prepare for use because it does not need to be sterilised upon unpacking. We understand that more properties are under development, and various patent applications related to Admedus's ideal prototype TAVR device are in the works.

The Admedus TAVR device is now at the *in vivo* testing stage. Admedus announced in May 2018 that its device had transitioned to testing in sheep. By February 2019, five sheep were implanted, and data from the first four sheep showed the single-piece design aortic valve to have the following characteristics:

- Up to 80% less stress on the commissures, that is, the points where the valve into attached to the aorta;
- ~ 150% more coaptation area, meaning that the valve can join aortic tissue from further apart; and
- As we noted above, a wider 'Effective Orifice Area' (EOA) than the currently marketed valves.

These are all very encouraging results and, if translated in human studies, could bring about significant benefits that the currently marketed products lack. We believe that the various animal testing can be completed in the first half of the current year, allowing human trials to commence earlier than expected.

A major co-development deal this year? Admedus could either develop this device or partner it. The size of the market suggests either strategy could succeed. However, Admedus has flagged that the pivotal trials of a new TAVR device could cost several hundred million dollars to complete. After a pilot trial in patients, possibly in 2019, there is potential for a co-development deal with an established medical device player.

New TAVR device candidates can prove valuable to the right bidder. When Edwards Lifesciences decided to bet on TAVR as a future treatment paradigm for aortic stenosis in 2003, it paid US\$125m in cash plus US\$30 million in milestones for Percutaneous Valve Technologies (PVT). By 2009, when it was apparent that TAVR would become a reality, Medtronic paid US\$900m to acquire CoreValve, which had obtained its CE Mark but was still years away from FDA approval. We think the CoreValve deal suggests that companies wanting a stake in this space will be prepared to pay up to get the right candidate device.

**ADMEDUS MAY
HAVE A TAVR
PARTNERSHIP
THIS YEAR**

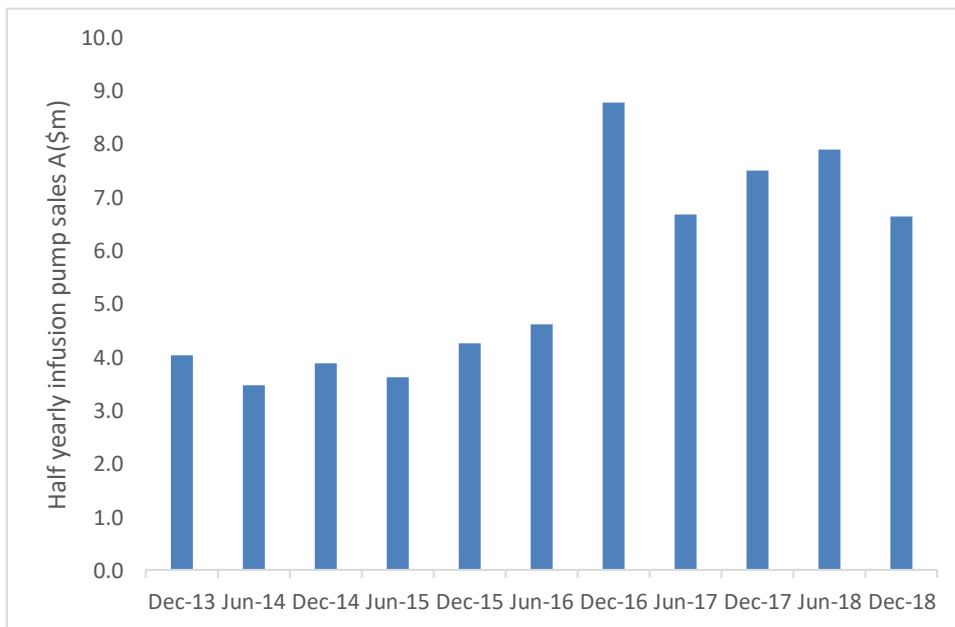
Admedus' infusion system business

The infusion system business has been a generally profitable sideline for Admedus in the years since the company became involved in the early 1990s. The business generated A\$14.5m in revenue in the year to December 2018, servicing a range of hospitals and clinics in Australia and New Zealand. At that level, it was marginally profitable despite revenue growth only being 2.5% due to the termination of one supply arrangement announcement in June 2018.

⁶¹ JACC Cardiovasc Imaging. 2015 Mar;8(3):340-60.



Admedus has a broad range of infusion products, thanks to multiple local licensing arrangements with all the important infusion system suppliers. Admedus attributes this range, plus rising demand in the Australian healthcare system, for a step-change in revenue in the December 2016 half-year. The infusion business was well suited to Admedus early in its business lifecycle. As Admedus develops its IP and builds its global footprint around the ADAPT business, the infusion division may be losing relevance. If Admedus is to focus on its core business, it may well divest the infusion business in the future.



Admedus has a seasoned management team

CEO **Wayne Paterson**, who was interim CEO from May 2016 to March 2017 and has been full CEO since then, brings to Admedus many years of experience at a senior level in the major pharma companies Merck KGaA⁶² and Roche. At Roche, he was Head of China, Head of Asia, and President of Korea. At Merck, he was President of Japan, President of Emerging Markets, President of Europe, and Global Head of Cardiovascular Medicine. With this background, Paterson was able to quickly focus Admedus on the upside from CardioCel®, which is now being realised. Under Paterson, the board and management team of the company have been markedly reconstructed. Paterson’s direct presence in the world’s medical device capital of Minneapolis-St Paul – Admedus’s headquarters is in Eagan, Mn., 30 minutes’ drive from Medtronic’s global headquarters – bodes well for future co-development deals on the TAVR device.

Chief Operating Officer **David St Denis** joined the company in July 2017 and is based alongside Paterson in Minneapolis. He joined Admedus from Germany, where he had been Head of Commercial Operations for Europe with Merck KGaA. Prior to Merck KGaA, David was head of Strategy & Operations for the Emerging Markets at

**WAYNE
PATERSON
FOCUSED
ADMUEDUS
BACK ON
ADAPT®**

⁶² Merck KGaA (Darmstadt, Germany, ETR: MRK, www.merckgroup.com) is the world's 27th largest pharma company, with US\$6.9bn in 2017 revenue (source: Pharmaceutical Executive magazine).



Merck Serono. He worked closely during his tenure at Merck KGaA with Wayne Paterson: Firstly in Japan, where they launched innovative cancer therapies; then in Emerging Markets to restructure China, Brazil, Mexico, Russia and India; and finally in Europe, where they drove a major efficiency program. Prior to Serono, St Denis worked at leading biotech company Millennium Pharmaceuticals⁶³ under the leadership of industry veterans in personalised medicines.

The Admedus board, which includes Paterson, has the skills required to grow an emerging business in the medical device space. Chairman **John Seaberg**, an Admedus director since 2014, was senior member for many years of the executive team at Guidant Corp, a major player in pacemakers and defibrillators, before Guidant's US\$27bn sale to Boston Scientific in early 2006⁶⁴. **Stephen Denaro** brings corporate and accounting skills. Dr **Wenyi Gu** of the Australian Institute for Bioengineering and Nanotechnology at the University of Queensland contributes a scientific research background. **Lishan Zhang** and Dr **Yanheng Wu**, of Star Bright, bring knowledge of the biotech and medical device sector in China.

Valuing Admedus

	Base case	Optimistic case
ADAPT business (A\$m)	19.7	76.8
Infusion business (A\$m)	5.6	19.1
TAVR (A\$m)	78.1	204.8
Total business value	103.4	300.7
Value of tax losses	34.1	34.1
Corporate overhead	-78.9	-78.9
Cash now (A\$m)	12.0	12.0
Cash to be raised (A\$m)	25.0	25.0
Option exercises (A\$m)	32.7	32.7
Total value (A\$m)	128.3	325.7
Total diluted shares (million)	1,564.0	1,564.0
Value per share	\$0.082	\$0.208
Valuation midpoint	\$0.145	
Share price now (A\$ per share)	\$0.038	
Upside to midpoint	281.6%	

We value Admedus at \$0.08 per share base case and \$0.21 optimistic case, using a DCF-based valuation. Our target price for Admedus is \$0.15, which sits around the midpoint of this DCF range. Our basic approach was as follows:

- We separately valued the ADAPT[®] business, the Infusion business and the TAVR venture;

⁶³ Acquired in 2008 by Japanese pharma company Takeda for US\$8.8bn.

⁶⁴ When one hears about the Guidant / Boston merger one often hears it described as a 'disaster' because, after it closed, Boston Scientific had to deal with a host of Guidant product recalls. See, for example, *Thousands of devices for hearts are recalled* by Barnaby Feder, New York Times, 27 June 2006.



- We used a WACC of ~12.4%, appropriate in our view for a 'High' risk rating⁶⁵;
- We assumed for purposes of this valuation that the company raises \$25m at \$0.035 per share to fund its corporate development;
- For the ADAPT® and Infusion businesses, we used a conventional DCF approach;
- For the TAVR venture, we used a probability-weighted DCF approach that valued the upside from a potential licensing deal of the device;
- We assumed A\$14m p.a. for corporate overhead and R&D expense; and
- We assumed no value for any upside in Admedus Immunotherapies going forward.

Valuing ADAPT® and Infusion. We took constructed DCFs with a 15-year time horizon in which the following assumptions applied. The terminal growth rate for the ADAPT® business assumes that the business does not go generic at year 15, with ongoing innovation allowing continues intellectual property protection over the products.

ADAPT	BASE OPTIMISTIC		INFUSION	BASE OPTIMISTIC	
	BASE	OPTIMISTIC		BASE	OPTIMISTIC
Peak sales (A\$m)	96	130	Peak sales (A\$m)	22	23
Gross margin year 14	70%	80%	Gross margin year 14	35%	45%
SG&A / revenue % year 14	45%	35%	SG&A / revenue % year 14	19%	15%
Capex (% of sales)	5%	3%	Capex (% of sales)	5%	2%
Ongoing tax rate	30%	30%	Ongoing tax rate	30%	30%
Amount set aside to working capital	5%	3%	Amount set aside to working capital	5%	3%
Terminal growth rate	3%	5%	Terminal growth rate	3%	5%
Terminal margins	20%	20%	Terminal margins	20%	25%

Valuing TAVR. We valued TAVR using a probability-weighted DCF approach. Here we assumed a 15-year pay-off after which the product loses market exclusivity but has been superseded. We assume 15 years since this is the typical level of exclusivity for most patent-protected medical therapies. For TAVR we assume:

- US\$5-10m more expenditure by Admedus on the project prior to partnering;
- A 21% probability of the device ultimately gaining regulatory approval, as per the historic success rates for drug molecules in Phase 1⁶⁶;
- A licensing in 2019/2020 or 2021, for US\$40-60m upfront, US\$150-300m in milestones and a 10-15% royalty rate, putting it in between the PVT and CoreValve deals in terms of upfront and milestone size;
- First regulatory approval in FY24-FY25;
- Peak sales of US\$07-1.2bn as key competitor in the TAVR device market which is now US\$3.5bn and potentially growing to US\$12bn;

⁶⁵ For a relevant discount rate, we use WACCs of between ~11% and ~15% depending on the risk for Life Science companies. This is derived from a RFR of 2.0%; a MRP of 7.5%-11.5% (7.5% for 'medium risk' companies, 9.5% for 'high risk' companies and 11.5% for 'speculative' companies); and an ungeared beta of 1.1. We regard Life Science companies with existing businesses, or which have enough capital to reach the market with their products, as 'Medium' risk. Companies that have small revenue streams from marketed products but that are still potentially in need of capital are 'High' risk. Everything else is 'Speculative'.

⁶⁶ Clin Pharmacol Ther. 2010 Mar;87(3):272-7. Epub 2010 Feb 3.



- 10% market share post-exclusivity, with a 3-5% negative terminal growth rate;
- A 30% tax rate.

Re-rating Admedus

We look for the following potential events over the next 12 months helping to drive a re-rating of Admedus stock:

- Further clinical data related to CardioCel®;
- Completion of animal studies of the TAVR device;
- Continued sales and margin growth both for the ADAPT® products and the infusion solutions business;
- Completion of the Star Bright collaboration and funding arrangements for Admedus Immunotherapies;
- New sales channels for the existing ADAPT® products; and
- New ADAPT® products.

**WE SEE TAVR
HELPING TO
RE-RATE
ADMEDUS**

Appendix I – Admedus’s non-core DNA vaccines

Admedus owns the majority of a potentially valuable DNA vaccine platform in Admedus Immunotherapies.

When bioMD merged with Allied Health Care Group in 2011, one of the key assets in Allied was a platform to create more effective DNA vaccines. This platform was developed at the University of Queensland in the laboratory of Professor Ian Frazer, famous as one of the co-inventors of the Merck & Co. cervical cancer vaccine Gardasil. The Frazer laboratory had taken two basic technologies, codon optimisation⁶⁷ and ubiquitination⁶⁸, and shown *in vivo* that DNA vaccines created using these approaches could generate a strong immune response from both arms of the immune system⁶⁹. Over the years 2011 to 2017, DNA vaccines created with the platform have been studied clinically, with interesting results. Admedus is now seeking partners to take this technology forward, with the company currently owning 72.8% of Admedus Immunotherapies.

Admedus Immunotherapies enjoyed some clinical success with a DNA vaccine against HSV-2. The initial target Admedus Immunotherapies went after with its platform was genital herpes. This condition, characterised by painful recurrent lesions in the genital area, is caused by the Herpes Simplex Virus 2 (HSV-2), a virus against which existing anti-virals have limited efficacy and where there is no prophylactic vaccine. Admedus Immunotherapies used its platform to develop a DNA vaccine based on glycoprotein D, a HSV-2 envelope protein which facilitates the virus’s entry into cells. In February 2014, Admedus announced that an initial 20-subject Phase I study of this vaccine in healthy volunteers had shown the product to be safe at all doses, and capable of

**THE HSV-2 DNA
VACCINE DATA
WAS
ENCOURAGING**

⁶⁷ Codon optimisation involves changing codons in an antigen from one preferred by viruses/bacteria (where the vaccine is originally developed) to one preferred by mammals. Frazer et. al. believed that vaccines designed with codon optimisation would have an enhanced humoral response.

⁶⁸ Ubiquitination involves the use of ubiquitin-encoding sequences in vaccine antigens. Ubiquitin’s regular job in the immune system is to take antigens to the proteasome for processing into peptide fragments, leading to a strong cellular immune response. The Frazer lab believes that ubiquitination helps enhance a DNA vaccine’s cell-mediated response.

⁶⁹ Recent patent grants include US Patents 9,993,542 (June 2018), 9,795,658 (October 2017) and 9,593,340 (March 2017).



generating a T-Cell response to HSV-2⁷⁰. In a subsequent Phase IIa study that initiated in 2015, Admedus administered its vaccine to people with genital herpes. The company read out data from this study in May 2017. Out of 44 evaluable subjects (34 treated, 10 on placebo) the vaccine was found to be safe and generated much less viral shedding in the treatment group (52% versus 31%). Also, the time to first outbreak post-vaccination for the treatment group was 6.6 months versus 1.2 months for the placebo group. These differences were, however, not statistically significant as the study was primarily evaluating safety.

Why Admedus Immunotherapies is now non-core to Admedus. The trouble with DNA vaccines is that they have shown promise over the years, but none have been approved for human use, and large-scale studies of such vaccines are likely to be expensive. Admedus's post-2016 leadership team believes better returns can be gained from investing shareholder funds in growing the commercial potential of ADAPT®.

Admedus Immunotherapies is looking into the synergies with checkpoint inhibitors. In 2018, Admedus Immunotherapies changed direction and moved to study its vaccines in head and neck cancer, to see if the vaccine could be synergistic with the checkpoint inhibitors. It now has pre-clinical data showing that such a vaccine could work with an anti PD-L1 inhibitor monoclonal antibody and is moving to study this clinically at Phase I using AstraZeneca's Imfimiz drug, whose target is PD-L1⁷¹.

Admedus may have a partner for Admedus Immunotherapies. Admedus announced in April 2018 that it had attracted a potential partner for Admedus Immunotherapies in the form of Star Bright, a Chinese group associated with businesswoman Madam Lishan Zhang. Under this agreement Star Bright paid a A\$0.5m option fee and is currently conducting due diligence on a potential A\$18m investment that would see Star Bright earn 60%⁷². This would leave Admedus and the other investors in Admedus Immunotherapies with a continuing equity upside.

Appendix II – An Admedus glossary

α-GAL epitope – A shape or marker on the surface of animal cells that triggers an immune response in people.

510(k) – Regulatory approval for a medical device in the US where the device has been found to be functionally equivalent to a device that was on the market before 1976. ADAPT® will be able to apply for FDA approval through a 510(k) application.

Aorta – The large artery that carries blood from the left ventricle of the heart to various branch arteries.

Aortic stenosis – A narrowing of the aortic valve.

ADAPT – Admedus's tissue-fixing and sterilisation technology.

Biocompatibility – The ability of a material to not be injurious or toxic to living tissue, and to avoid generating an immunologic reaction.

⁷⁰ As Admedus reported in October 2014, 19 out of 20 subjects registered such a response.

⁷¹ Generic name durvalumab, see www.imfinzi.com.

⁷² The initial option agreement was for six months but has been extended to 12 months.



Bovine – From cows. Bovine tissue is often used in soft tissue repair.

Calcification – The build-up of calcium in tissues, which reduces their flexibility and durability.

CardioCel – Admedus's trademark for ADAPT® when used for cardiovascular conditions.

Carotid artery – One of two major blood vessels in the neck that supply blood to the brain, neck and face.

Carotid endarterectomy – A surgical procedure to open the carotid artery, with the goal of stroke prevention.

Catheter – A tube inserted into a body cavity, duct or vessel to allow drainage, injection of fluids or implantation of devices.

Collagen – The fibrous protein that makes up connective tissue.

CE marking – The process of gaining European approval for a medical device. CE stands for Conformité Européenne.

Coaptation – The drawing together of separated tissue around a gap.

Cross-links – Bonds that link one polymer chain to another.

Commissure – A location at which two anatomical objects are joined.

EOA – Short for Effective Orifice Area, the size of a cross section of the flow from a heart valve, as measured in square centimetres.

Explant – Removal of a medical device from the patient's body.

FDA – America's drug and medical device regulatory body.

Fibrosis – The abnormal formation of scar tissue, which generally limits the flexibility of the surrounding tissue.

Glutaraldehyde – A chemical used to stabilise the collagen structures in animal tissue when fixing them for surgical implantation in people.

Hernia – A rupture of the wall or cavity containing an organ, so that the organ protrudes through it.

ISO 13485 – The international standard for the design and manufacture of medical devices.

Leaflet – The thin, triangle-shaped flap of a heart valve.

Matrix – The body substance in which tissue cells are embedded. Also called the 'extracellular matrix'.

Mitral valve – The valve that lets blood flow from the left atrium to the left ventricle.

Pericardial – From the pericardium, that is, the membrane surrounding the heart. ADAPT is frequently used on bovine and kangaroo pericardial tissue.

Phase – A stage of the clinical trialling process for a drug candidate. Phase I tests for safety. Phase II tests for efficacy in a small sample. Phase III tests for efficacy in a large sample.

Phospholipids – Compounds composed of fatty acids and phosphoric acid with a nitrogenous base. Phospholipids are found in cell membranes, among other places.



Polymer - A large molecule composed of repeating structural units connected by chemical bonds.

Pre-clinical – Work such as animal testing that prepares a drug or medical device for clinical trials in humans.

Porcine – From pigs. Porcine tissue is often used in soft tissue repair.

Remodeling – Reorganisation or renovation of existing tissues.

Revascularisation – The formation of new blood vessels.

Soft tissue – Tissues of the body that are not bone. ADAPT® is useful in soft tissue repair.

Statistical significance - The probability, measured by the 'p-value', that an observed outcome of an experiment or trial is due to chance alone. Generally, p-values below 0.05 are taken as markers of statistical significance.

Subcutaneous – Refers to matters 'below the skin'. A subcutaneous injection is one that is given below the skin rather than directly into the bloodstream.

Tissue – A group of specialised cells with a common structure and function, such as 'muscle tissue'.

Tissue engineering – The process of creating tissue for use in repairing tissue defects in patients.

Transcatheter Aortic Valve Replacement (TAVR) – The delivery via catheter of a replacement aortic valve.

Vaginal prolapse – A female health condition in which the organs inside the pelvis protrude into the vaginal wall. Vaginal prolapse is treated via a pelvic floor reconstruction.

Appendix III – Admedus's core intellectual property

Admedus's intellectual property over ADAPT® is covered by four disclosed patent families⁷³.

A method using potassium dihydrogen phosphate to reduce calcification of tissue, WO/2000/074692, priority date 3 June 1999, invented by Leon Neethling and Andrew Hodge.

- This patent application covers the use of potassium dihydrogen phosphate as a blocking agent to replace those that would ordinarily be needed with glutaraldehyde fixing.

An implantable biomaterial and a method of producing same, WO/2006/066327, priority date 24 December 2004, invented by Leon Neethling and Andrew Hodge⁷⁴.

- This patent application covers the ADAPT® process⁷⁵.

Sterilization process, WO/2013/067598, priority date 10 November 2011, invented by Leon Neethling.

⁷³ The company made its initial patent filings, which have yet to be published, over its TAVR product in October 2017.

⁷⁴ This patent application was granted as US Patent 9,205,172 in December 2015. It was granted in Europe as EP 1835 948 in February 2016.

⁷⁵ ADAPT® reduces the use of glutaraldehyde from 0.2% down to 0.05% by first treating the tissue with an alcohol solution whose main ingredient is ethanol (70%). This alcohol removes various unneeded material such as phospholipids, DNA and RNA, and the α -GAL epitope. After this decellularisation process, only a small amount of glutaraldehyde is needed to cross-link the remaining collagen.



- This patent application covers terminal sterilisation process for ADAPT®, based on propylene oxide, which allows the tissue to be sterilised within its final packaging.

Sterilized packaging system for catheter, WO/2019/018290, priority date 17 July 2017, invented by Leon Neethling, Christopher Olig, Scott Bliss, Wayne Paterson, Philip Haarstad, Tuan Doan, Alex Peterson and David Blaeser.

- This patent application covers the packaging for a catheter that would deploy ADAPT® tissue.

Appendix IVa – Capital structure summary

		% of fully diluted	Note
Ordinary shares, ASX Code AHZ (million)	589.9	69.4%	
Unlisted options (million)	259.7	30.6%	Average exercise price 12.6 cents, average expiry date 13-Feb-2022
Fully diluted shares	849.7		

Current market cap: A\$22.4 million (US\$15.9 million)

Current share price \$0.038

Twelve month range \$0.03 - \$0.38

Average turnover per day (last three months) 1.04 million



Appendix IVb - Previous capital raises, 2007-2018

Date	Shares (million)	% of current shares on issue	Price (AUD)	Raised (AUDm)	Type of raising
May-07	1.1	0.2%	1.000	1.1	Share Purchase Plan
Dec-07	0.2	0.0%	2.000	0.3	1 for 10 issue to optionholders
May-09	4.3	0.7%	0.200	0.9	1 for 2 rights issue of shares
Oct-11	7.9	1.3%	0.280	2.2	Placement
Mar-12	14.0	2.4%	0.300	4.2	Placement and 1:5 rights issue
Dec-12	23.0	3.9%	0.200	4.6	Placement and SPP
Sep-13	20.9	3.5%	0.500	10.4	1:5 rights issue
May-14	18.3	3.1%	1.000	18.3	Placement and SPP
Mar-15	17.0	2.9%	0.700	11.9	Placement
Mar-15	23.1	3.9%	0.700	16.1	1:7 rights issue
Dec-15	11.3	1.9%	0.660	7.4	Placement
Jul-16	30.3	5.1%	0.330	10.0	Placement
Jul-16	25.2	4.3%	0.330	8.3	1:9 rights issue
May-18	29.2	5.0%	0.300	8.8	Placement and SPP
Aug-18	42.6	7.2%	0.100	4.3	Placement to Star Bright
Sep-18	26.3	4.5%	0.130	3.4	Placement to Star Bright
Dec-18	237.1	40.2%	0.080	19.0	5 for 7 rights issue
Total	531.4	90.1%	0.247	131.1	

Appendix V – Major shareholders

Admedus currently has one substantial shareholder:

- Star Bright, a Chinese investment group associated with Madam Zhang Lishan (30%).
- SIO Capital, a US based healthcare hedge fund (22%)

Appendix VI – Papers relevant to Admedus

Neethling et al. (2004). *ADAPT-treated porcine valve tissue (cusp and wall) versus Medtronic Freestyle and Prima Plus: crosslink stability and calcification behavior in the subcutaneous rat model.* J Heart Valve Dis. 2004 Jul;13(4):689-96; discussion 696.

- This paper compared ADAPT® to other tissue patches in terms of reduced calcification in porcine valve tissue.



Neethling et al. (2006), A multi-step approach in anti-calcification of glutaraldehyde-preserved bovine pericardium. *J Cardiovasc Surg (Torino)*. 2006 Dec;47(6):711-8.

- This paper demonstrates that the ADAPT® process could improve the material stability and reduced the calcification potential of bovine pericardial tissue.

Neethling et al. (2008), *Enhanced biostability and biocompatibility of decellularized bovine pericardium, crosslinked with an ultra-low concentration monomeric aldehyde and treated with ADAPT®*. *J Heart Valve Dis*. 2008 Jul;17(4):456-63; discussion 464.

- This paper reported the results of the sheep study of ADAPT®.

Neethling et al. (2013), *Evaluation of a tissue-engineered bovine pericardial patch in paediatric patients with congenital cardiac anomalies: initial experience with the ADAPT®-treated CardioCel patch*. *Interact Cardiovasc Thorac Surg*. 2013 Oct;17(4):698-702. Epub 2013 Jul 6.

- This paper reported the data from Admedus's Bloemfontein Study.

Brizard et al. (2014), *New engineering treatment of bovine pericardium confers outstanding resistance to calcification in mitral and pulmonary implantations in a juvenile sheep model*. *J Thorac Cardiovasc Surg*. 2014 Dec;148(6):3194-201. Epub 2014 Aug 7.

- This paper demonstrates the effectiveness of CardioCel® in a sheep model of pulmonary valve and mitral valve reconstruction.

Neethling et al. (2014), *Biostability, durability and calcification of cryopreserved human pericardium after rapid glutaraldehyde-stabilization versus multistep ADAPT® treatment in a subcutaneous rat model*. *Eur J Cardiothorac Surg*. 2014 Apr;45(4):e110-7. Epub 2014 Jan 14.

- This paper compared bovine pericardium to cryopreserved human pericardium in a subcutaneous rat model and showed that ADAPT® could bring about improved biostability and durability with reduced calcification.

Strange et al. (2014), *An evaluation of Admedus's tissue engineering process-treated (ADAPT®) bovine pericardium patch (CardioCel®) for the repair of cardiac and vascular defects*. *Expert Rev Med Devices*. 2015 Mar;12(2):135-41. Epub 2014 Nov 28.

- This paper provides a review of CardioCel®.

Prabhu et al. (2017), *Histologic evaluation of explanted tissue-engineered bovine pericardium (CardioCel®)*, *Semin Thorac Cardiovasc Surg*. 2017 Autumn;29(3):356-363. Epub 2017 Jun 1.

- This paper reports on a histological evaluation of explanted CardioCel®, finding that there was remodeling in most explants without inflammatory cells or calcification.

Salameh et al. (2017), *Calcification or Not. This Is the Question. A 1-Year Study of Bovine Pericardial Vascular Patches (CardioCel) in Minipigs*. *Semin Thorac Cardiovasc Surg*. 2017 Oct 9. pii: S1043-0679(17)30284-8. [Epub ahead of print]



- This paper, from a group at the University of Leipzig, suggests a contrary view on the anti-calcification potential of CardioCel®. The group implanted CardioCel® in the aortic and pulmonary arteries of miniature pigs and found 'calcification and neo-formation of hyaline cartilage in both vessel types one year after implantation'. The study did not have any p-value, and the histology was not shown. We understand Professors Christian Brizard (University of Melbourne – see the Brizard et al. paper from 2014 above) and Bart Meuris (KU Leuven), both of whom have worked on CardioCel® with Admedus, have personally communicated with the authors and voiced their concerns over the data.

Neethling et al. (2018), *Comparison of physical and biological properties of CardioCel® with commonly used bioscaffolds*. *Interact Cardiovasc Thorac Surg*. 2018 Jan 18. [Epub ahead of print].

- This paper compared CardioCel® with XenoLogiX from Edwards Lifesciences, Peri-Guard from Baxter BioSurgery, PhotoFix from CryoLife⁷⁶ and CorMatrix from Aziyo Biologics and showed Admedus's product in a favourable light.

Pavy et al. (2018), *Initial 2-year results of CardioCel® patch implantation in children*. *Interact Cardiovasc Thorac Surg*. 2018 Mar 1;26(3):448-453.

- This paper, from a group at Royal Brompton Hospital in London, reported generally favourable two-year results on children with congenital heart diseases.

Tomšič et al. (2018), *Initial experience and early results of mitral valve repair with CardioCel® pericardial patch*. *Ann Thorac Surg*. 2018 Oct;106(4):1241-1244.

- This paper reported good outcomes using CardioCel® in mitral valve repair on patients at Leiden University Medical Center in the Netherlands.

⁷⁶ A major processor and distributor of implantable living human tissues for use in cardiac and vascular surgeries (Atlanta, Ga, NYSE: CRY, www.cryolife.com).



Appendix VII – Companies to watch

We think the listed companies most easily comparable to Admedus are six companies, mostly with a focus on tissue engineering at the early stages of developing their technologies⁷⁷:

Company	Location	Code	Market cap	Web
PolarityTE	Salt Lake City, Ut.	Nasdaq: PTE	325	www.polarityte.com
Organovo	San Diego, Ca.	Nasdaq: ONVO	125	www.organovo.com
Bonus Biogroup	Haifa, Israel	TASE: BONS	115	www.bonusbiogroup.com
Tissue Regenix	Leeds, UK	LSE: TRX	103	www.tissueregenix.com
Covalon Technologies	Mississauga, On.	TSX-V: COV	83	www.covalon.com
Sanuwave Health	Alpharetta, Ga	OTCQB: SNWV	27	www.sanuwave.com
Admedus	Brisbane, Australia	ASX: AHZ	16	www.admedus.com

Bonus Biogroup. This company's technology allows the production of bone grafts from autologous adipose tissue-derived cells. The initial intended application for the technology is in maxillofacial bone gap reconstruction.

Covalon Technologies. This company develops polymer-based solutions, mainly in the wound-care and infection control spaces, and it also develops coatings for improving intravascular medical devices. A key technology of Covalon's is the BioMatrix Platform, which is a matrix of collagen that is partly triple helix (i.e. native state) and partly random coil (i.e. denatured) that has been found to provide a robust scaffold for tissue ingrowth in wound-healing applications.

Organovo. This company, based on scaffold-free 'bioprinting' technology originally developed at the University of Missouri–Columbia, is working on functional, three-dimensional tissues that can potentially be implanted or delivered into the human body. At present the target market is researchers needing functional human tissue to experiment with. Kidney and liver tissue were the first Organovo products.

PolarityTE. This company's platform allows for tissue to be engineered that is 'functionally polarised', meaning that the cells in the tissue have the asymmetric organisation that the cell is meant to exhibit⁷⁸. The lead product is SkinTE, for skin regeneration, to be followed by OsteoTE for bone applications.

Sanuwave Health. This company's devices allow delivery of high-energy, acoustic shock waves to tissue in order to initiate tissue repair and regeneration, and revascularisation. The company's dermaPACE System gained FDA approval in late 2017 for the treatment of diabetic foot ulcers.

Tissue Regenix. This company's dCELL decellularisation technology allows DNA and other cellular material from tissue to be removed from scaffolding material. The company develops decellularised scaffolds for use in wound care, orthopaedics, and cardiovascular tissue repair.

⁷⁷ Note: Market capitalisations as at 15 March 2019.

⁷⁸ It can do this in part through the use of stromal vascular fractions – see *Plast Reconstr Surg.* 2016 Feb;137(2):495-507.



Risks related to Admedus

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

- **Market acceptance.** There is the risk that CardioCel® will fail to attract a strong following from cardiovascular specialists despite the product's good qualities.
- **Funding risk.** More capital will likely be needed to continue clinical and commercial development of the ADAPT® technologies.
- **Product risk.** There is the risk that Admedus's TAVR product may either fail in pre-clinical or clinical development or that the regulators may require more data on clinical effectiveness before Admedus and its co-developers can seek to realise its commercial potential.
- **Distribution risk.** There is the risk that Admedus will fail to find dedicated commercial partners to grow the various ADAPT® technologies.
- **Technology risk.** There is the risk that newer technologies emerge in tissue repair with a superior cost profile to ADAPT® while also avoiding the calcification issue.

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 or medical device stock mentioned on this report, including Admedus.



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