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HEALTHCARE MARKET REVIEW AND OUTLOOK

In the end, the stars were perfectly aligned for the financial markets in 2017. Strong and synchronous growth around the globe, no signs of inflation, still accommodative monetary policies, few geopolitical events impacting the economy, and strong corporate earnings all made for a solid year. The MSCI AC World Index climbed another 5.7% during the last quarter, finishing up 24.0% for the year. This strong finish was driven by the successful passage of tax reform in the US, which added to the optimism about continued solid growth and corporate earnings in 2018. Naturally, economically sensitive sectors turned in the best performances.

As in Q3, healthcare lagged the global markets, but by an even greater margin. The MSCI World Healthcare Index ended the quarter up 0.9% and the year up 19.8%. The relative underperformance of healthcare, for a third year in a row, puts a muted perspective on what in absolute terms was a strong year. The perfect economic backdrop mainly benefited medtechs (+4.5%) and services (+9.0%), both of which rose substantially during the quarter: medtech because of the bigger cyclical component and both sectors thanks to the US tax overhaul. As a result, medtech and services ended up as the best performing healthcare industries for the year (see table below). Biotech, which had been the star performer until the end of Q3, suffered a reversal, as uninspiring Q3 results at most of the large-caps, including Gilead, Biogen, Amgen and, in particular, Celgene, which also suffered a clinical setback in Crohn's disease, prompted investors to take profits across the board. As a result, the sector ended the

INDEX	CLOSE 12/31/2017	RETURN					ANNUALIZED VOLATILITY	
		1 MONTH	3 MONTH	6 MONTH	9 MONTH	12 MONTH	30 DAY	90 DAY
MSCI World Index (all country)	246.2	1.6%	5.7%	11.2%	16.0%	24.0%	5%	5%
MSC World Index	5928.6	1.4%	5.5%	10.6%	15.1%	22.4%	5%	5%
MSCI World Healthcare Index	301.7	-0.1%	0.9%	3.3%	10.5%	19.8%	7%	7%
MSCI World Pharma	212.5	0.5%	-0.4%	0.5%	5.7%	13.3%	7%	8%
MSCI World Biotech	1417.0	0.4%	-6.3%	2.6%	8.5%	18.2%	10%	13%
MSCI World Equip and Supplies	459.2	-1.7%	4.5%	4.9%	15.1%	29.9%	9%	9%
MSCI World Healthcare Prov & Serv	586.8	0.5%	9.0%	8.7%	18.9%	26.0%	12%	12%
MSCI Emerging Market Healthcare	645.6	7.6%	16.6%	20.5%	25.8%	32.7%	17%	14%
MSCI Emerging Markets	521.5	3.6%	7.4%	15.9%	23.2%	37.3%	11%	10%

quarter down 6.3% and finished the year up 18.2%. Finally, pharma finished the quarter flat (-0.4%) and showed a relatively modest 13.3% advance for the year, clearly lagging the broader healthcare sector and markets. The subdued performance is primarily attributable to the defensive nature of these companies, clearly not a desirable attribute in this environment. Behind all of this activity, the real healthcare stars of 2017 were small- and mid-caps, as investors were once again willing to systematically take on more risk. As a result, small- and mid-caps rose strongly with the Russell 2000 Healthcare Index up 35.9%, and the S&P Biotech Select Index up 43.8%. Beyond a greater willingness to assume risk from the investor side, a continued constructive regulatory environment (especially in the US), a significant number of New-Molecular-Entity approvals (46, one more than the recent high in 2015), clinical progress, M&A and the deregulation efforts of the Trump administration all contributed to fuel this strong performance.

Our brief review of 2017 would not be complete without a brief discussion of emerging markets. Fueled by improving macroeconomic conditions, emerging markets did very well in 2017, with the MSCI Emerging Markets Index up 37.3%. Healthcare stocks, which had lagged because of their defensive nature and premiums to their local markets, also turned in a stellar performance in the last quarter, with the MSCI Emerging Markets Healthcare Index up 16.6%, on improving corporate earnings and liquidity-driven increases in markets such as Korea.

TREES DON'T GROW INTO THE SKY

With markets hovering at all-time highs and valuations stretched (save maybe when considering the low level of real rates), the old saying that "Trees don't grow

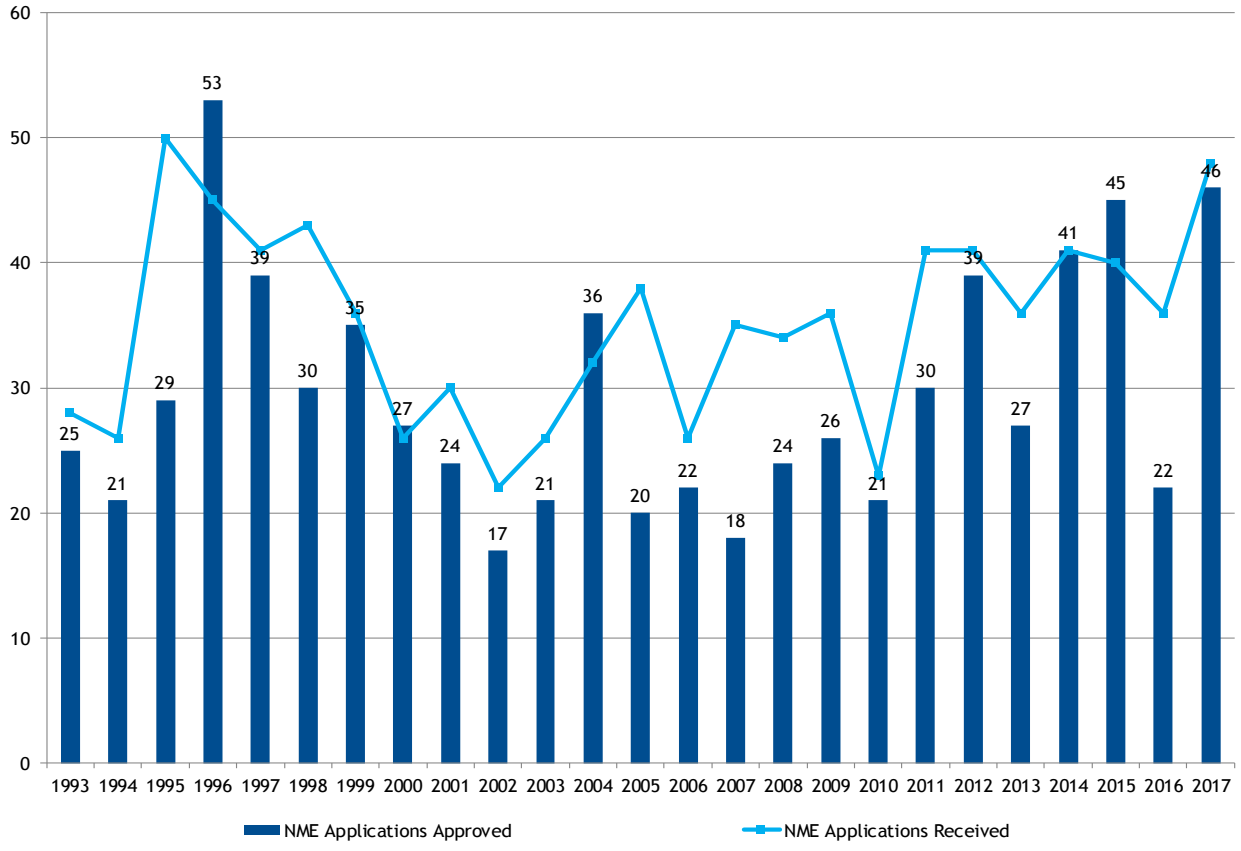

Figure 1: FDA New Molecular Entity Applications for Approval and Approvals by Year. Source: FDA, accessed January 2, 2018.

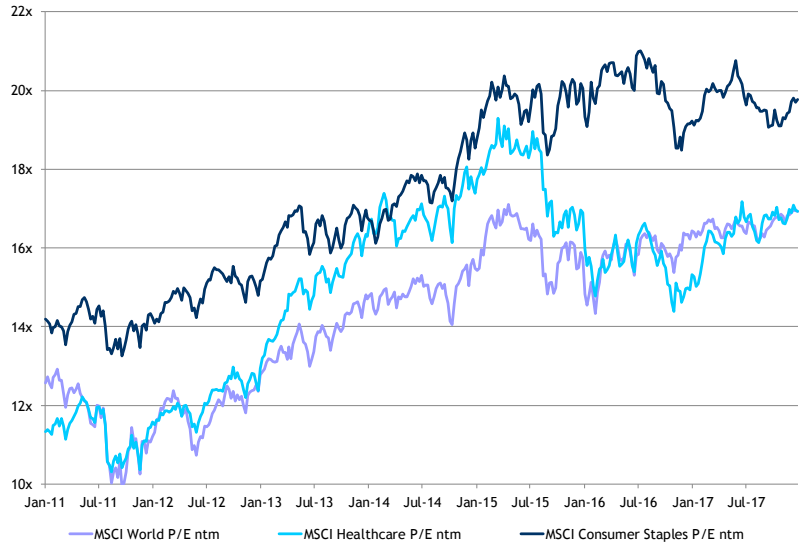

Figure 2: Valuation P/E NTM World, Healthcare and Consumer Staples. Source: Bloomberg, as of December 29, 2017.

GROWTH P.A. 2018-2020E					
	SALES	EPS	PE18E	EV/SALES18E	COGS
MSCI World Pharma	4%	7%	16x	4.0x	27%
MSCI World Biotech	7%	13%	16x	5.5x	17%
MSCI World Equip and Supplies	6%	11%	22x	4.3x	39%
MSCI World Healthcare Providers	12%	11%	17x	0.6x	83%

into the sky" has resonance for many. While the positive economic outlook and persistent, but slowly rising, low rates could continue to support markets, return expectations should, at a minimum, be lower entering 2018.

In this context, healthcare finds itself in an attractive spot. It is cheaper than global markets, with robust long-term drivers (ie, our aging population and demographics, growth opportunities afforded by the emerging markets, and innovation); a currently constructive regulatory environment; deregulation in the US, the industry's main geographic market; and increasing topline momentum due to a slew of recent approvals in biopharmaceuticals, as well as in medtech. All of these factors should favour healthcare stocks over the next 12 to 18 months. At one end of the spectrum, the stable earnings and low multiples of large-caps (pharma and biotechs, in particular) have defensive characteristics, which should appeal to investors if economic growth falls short of expectations. At the other end, the innovative power of small- and mid-cap biotechs and medtechs should appeal to investors, particularly so long as markets remain in "risk-on" mode. The healthcare sector's key struggle will continue: the continuing strong stream of innovation (especially in drugs) propelling the sector forward on the one-hand partly offset by healthcare spend financing concerns in general and US drug mispricing, on the other.

We advocate a strategy in which defensive large-cap exposure is mixed with high conviction ideas among small- and mid-caps. With respect to large-caps, we prefer selected pharmas and biotechs, with both solid fundamentals and attractive valuation. Still more selectivity is warranted for medtechs, where valuations have reached historically high levels, as well as among services, where managed care is our preference because of its greater visibility. Among small- and mid-caps, biotechs are to be privileged, based on their high commercial momentum, pipeline progress, potential for M&A, and valuation levels that remain below recent historical highs. In addition, selected innovative small- and mid-cap service and medtech companies can be added to the mix. Finally, the recent gain in momentum of emerging-market healthcare stocks should continue, arguing for direct exposure to stocks in the key economic regions.

Michael Sjöström, CFA
Chief Investment Officer

NORTH AMERICAN SPINE SOCIETY ANNUAL MEETING (NASS)

INTRODUCTION

In October 2017, we attended the 32nd annual meeting of the North American Spine Society in Orlando, Florida. This meeting brings together spine companies (large and small, public and private, diversified and pure-play) with surgeons, researchers, key opinion leaders, and various industry decision-makers. Companies showcased their product portfolios and innovations, while the medical community presented and debated the latest research data. It is the most attended spine conference of the year.

MARKET DYNAMICS AND TRENDS

The spine market comprises three broad groups of device manufacturers: the large-cap diversified medtech/orthopaedic, mid-cap pure-play spine portfolio, and small-cap (or private) pure-play companies.

In the large-cap group, we include such players as Medtronic, J&J's DePuy Synthes, Stryker and Zimmer Biomet. For these companies, "spine" is a segment of the overall business and can be subject to shifts in resource allocation, depending on market conditions and management priorities. At the same time, they benefit from synergies in their important commercial infrastructures, which also serve other products lines, such as orthopaedics or cardiology.

The mid-cap pure-play group includes Nuvasive, Globus Medical, K2M Group, and other such companies. They are spine specialists that differentiate themselves by offering a broad portfolio of products addressing the needs of spine physicians, developing spine-specific relationships, and commercializing leading innovations, either developed internally or acquired. These companies have gained a significant share of the market over the past years.

The third group comprises the small-cap and private spine companies. These are typically focused on a single technology or group of related technologies, their development, and early commercialization. Some may build a small portfolio of products to support a limited commercial effort. However, the most innovative technologies often get acquired by the larger players, which can create greater value via their broader portfolios and commercial infrastructures.

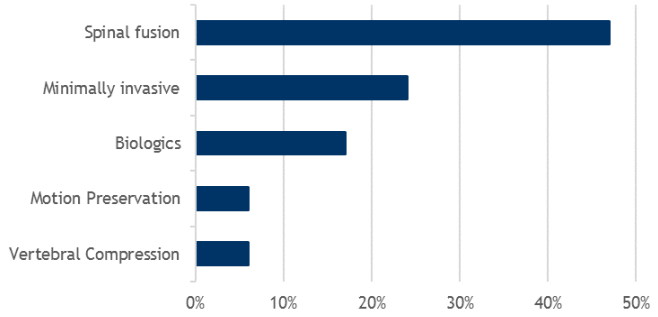

Figure 1. Share of market sales by product category. Source: Vizient, Technology Watch 2016.

Many procedures are served by the products of the spine market, but the most important treatment remains spinal fusion, in which two vertebrae are fused into a single segment. Biologics support the growth of bone and promote fusion. Minimally invasive surgery has seen important growth in the last decade and now represents approximately 25% of all procedures.

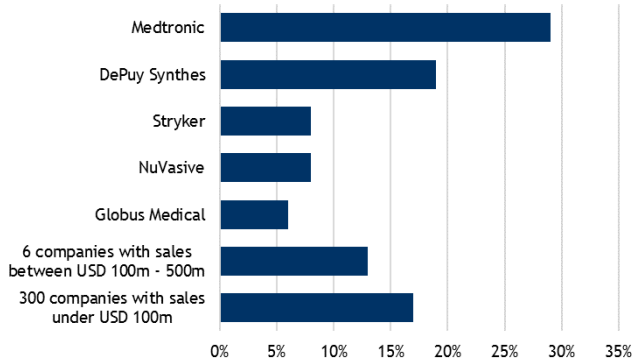

Figure 2. Market share in spine. Source: OrthoWorld 2016.

Sales in the global spine market are projected to continue growing at approximately 2% per year, surpassing USD9.4bn by 2020. Five companies generate approximately 70% of the market's sales.

From our perspective at the conference, it was apparent that vendors, especially in the first two groups, fiercely compete to attract surgeons and win accounts to which they can sell their spinal-surgery portfolio of products. Analysts highlight that larger players such as Medtronic are regaining share from the pure-play companies, reversing a recent trend. The overall spine market is believed to be growing in the low-to-mid single digits, with low single-digit growth in the US, including pricing pressure of 1-2%, which is offset by increases in procedural volumes. The pricing pressure may be explained by payer pushback and the large players' focus on leveraging price discounts and scale to win back market share.

Traditional high-volume products such as screws, plates, and interbody cages for spinal fusion are showing signs of commoditization and the ensuing pricing pressure. Given that hospitals and surgery centers are increasingly being selective and reducing their roster of vendors, these devices will remain a mainstay of any competitive spine-product portfolio. In addition, the more premium orthobiologics, among them stem-cell products, are seeing pushback from payers, who argue that the incremental clinical benefit from bone in-growth may not be worth the extra cost, especially given the advances in implant materials and coatings. As margins are being pressured, vendors are required to diversify and expand their portfolios into innovative areas to remain competitive.

A notable US market trend has been the increase in outpatient surgeries. Between 2005 and 2015, the share of US spine surgery done in the outpatient setting rose from 5% to 45%. This growth was enabled by innovations in minimally-invasive-surgery (MIS) implants and techniques. The available navigation and robotics systems to support MIS surgeries increased concurrently. The USD1bn acquisition of LDR by Zimmer in the summer of 2016 also highlights the expected market expansion in artificial disc replacement for the cervical spine. We will discuss these areas of innovation below.

MINIMALLY INVASIVE SURGERY

MIS presents obvious benefits in limiting damage to the structures surrounding the treatment site. Depending on the approach (ie, posterior, anterior, or lateral), accessing the spine can be complicated by the array of tissues, organs, vessels, nerves, and other structures in the region. Traditional open surgery either significantly damages or risks damaging these structures to access the target site of the spine. MIS promises less traumatic treatments, shorter stays in healthcare facilities, and lower risks of complications. However, the physician must be able to navigate through the body to reach the spine, and then, with limited access, proceed with the surgery. This type of procedure requires technological innovation in imaging, navigation, neuromonitoring, procedure and access instruments, implants, and interbody device designs.

For example, expandable devices enable the implantation of vertebral interbody fusion cages via a much smaller access than the traditional monobloc devices.

Figure 3. Globus RISE® expandable lumbar fusion device. Source: Globus Medical website, accessed December 15, 2017.

Some players have led the development of these innovative devices. However, the required US FDA 510(k) clearance for most devices is a lower barrier to entry than a premarket approval (PMA), and therefore

most companies have, or are soon launching, expandable cages as part of their portfolio.

Headwinds to the adoption of MIS include both the limited sub-segment of cases that can be treated and the need for surgeons to be trained in new advanced techniques. However, when appropriate, MIS promises benefits to the patient. It also serves as a great marketing tool and is a key factor in driving patient volumes. As patients are increasingly educating themselves, they are further driving adoption among surgeons by asking for these innovative surgical approaches.

While there is important innovation in many areas of MIS-enabling technologies, in the remainder of this article we will focus on imaging, navigation, and robotics.

IMAGING

Intra-operative fluoroscopy is an imaging modality in which a continuous x-ray picture is shown on a monitor. It has traditionally been used most often in fusion procedures to locate and guide instruments and treatment; today the tool is increasingly being used as MIS approaches are adopted. Fluoroscopy relies on harmful ionizing radiation from x-rays, which flow continuously during image acquisition. Patients, surgeons, and operating room (OR) staff are exposed to significant levels of radiation. In fact, compared with hip surgeons, spine surgeons have a 50-fold increase in lifetime exposure. Development of thyroid carcinoma, leukemia, skin erythema, and cataracts have been linked to exposure to this type of radiation.

Recent advances in radiation exposure reduction include Nuvasive's LessRay technology. LessRay imaging amplifies lower resolution fluoroscopy images via a computer algorithm to provide similar image quality with less radiation exposure. The demonstrations at Nuvasive's booth attracted many, and the message of reduced radiation exposure resonated.

COMPUTER-ASSISTED NAVIGATION

As promising as is the new fluoroscopy, advances in navigation technologies via computer-assisted approaches have an even greater potential to eliminate all intra-operative radiation exposure. Computer-assisted navigation (CAN) offers the operative techniques involved in MIS with a suitable alternative to high-radiation fluoroscopy. More specifically, CAN processes and reconstructs images to develop a three-dimensional model of the spine. This model is then used for pre-operative planning as well as during the surgery itself. Current CAN systems for spine procedures include those manufactured by BrainLab, Stryker, Medtronic, and Ziehm Imaging.

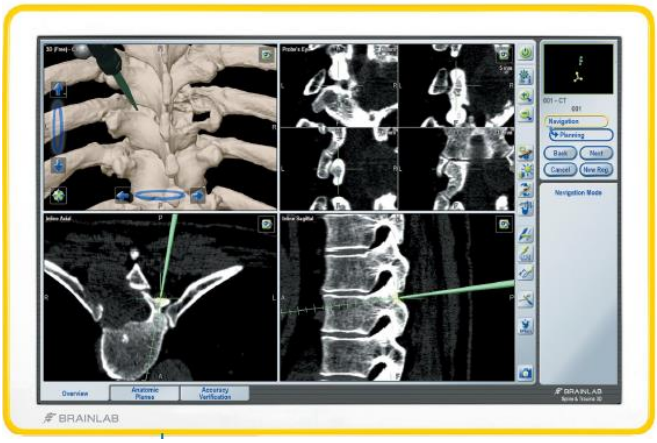

Figure 4. Brainlab Spine Navigation. Source: Brainlab website, accessed on December 15, 2017.

For intra-operative use, systems rely on reference points that are continuously scanned by the system's stereotactic camera, providing real-time guidance. The position of adapted instruments is then referenced to the spine by the navigation system. The imaging allows the surgeon to position his manoeuvres without the reliance on harmful radiation from intraoperative fluoroscopy.

Large meta-analyses have demonstrated that navigation-assisted pedicle-screw placement has significantly improved accuracy, compared with free-hand techniques. One would expect that outcomes

would be improved, but at present, not enough data are available to support this expectation. Headwinds to adoption also include the surgeon's learning curve, the capital cost of the equipment, and CAN's dependence on the accuracy of many variables, both technical and surgeon-related. Today, approximately 15% of surgeons use navigation systems.

Advances in CAN not only reduce the reliance on harmful radiation used in intra-operative fluoroscopy, but also enable the next step in surgery assistance, which can mitigate some of the headwinds mentioned above: robotics.

ROBOT-ASSISTED SURGERY

In development for over a decade, robotics are starting to garner more attention from the spine community. Their application in spine surgery is in the early stages of implementation and is currently limited to guiding the surgeon in placement of taps and pedicle screws. In this setting, robotics provides an additional guidance to navigation technologies and may improve accuracy.

The short-term promise of robots includes improved screw placement, a lowered revision rate, and less radiation exposure, relative to free-hand MIS. Over time, they could improve procedural workflow by taking more responsibilities from the surgeon, reducing fatigue-related variability, improving outcomes by achieving more accurate and complex manoeuvres, and enabling tele-surgery.

Figure 5. Da Vinci Surgical System. Source: Intuitive Surgical website, accessed on December 15, 2017.

Intuitive Surgical's da Vinci Surgical System represents the leading edge of surgical robotic technology. This system allows tele-surgery, where the surgeon operates from a remote console. Its benefits include enhanced visualization (via 3D-imaging, 10x magnification, and high definition), and dexterity (through tremor filtering and by enabling a limitless range of wrist motion). Although the da Vinci system is widely used in general surgery, urology, and gynecology, it is not currently approved for spinal surgery.

Three robots were highlighted at the NASS annual meeting: Zimmer Biomet's Rosa, Globus' Excelsius GPS, and the Mazor X from Mazor and Medtronic. The Excelsius GPS and Mazor X systems gathered the most interest.

Figure 6. Globus Excelsius GPS. Source: Globus Medical website, accessed on December 15, 2017.

Once paired with an intraoperative CT/cbCT scanner, the setup cost can range from approximately USD1.4 - 2.3m. The high capital cost and currently limited applications explain the restrained adoption by providers. In addition, the equipment requires significant operating-room space, which may not be readily available in many centers.

For adoption to increase, the value proposition must improve. Expanded applications (eg, Globus' modular arms) should be the next step. In addition, more data should be generated to demonstrate the clinical (eg, improved accuracy and reproducibility) and economic (eg, procedure speed and patient volume) benefits to help justify the purchase and maintenance costs.

ARTIFICAL DISC REPLACEMENT

An additional field of innovation is the motion-preserving alternative to spinal fusion, artificial disc replacement (ADR). Especially for the cervical spine, ADR is an area ripe for market expansion. Clinical data have accumulated over the past decade demonstrating the clinical and economic value of this procedure, compared with fusion. A recent meta-analysis (Hu Y 2016) of US Investigational Device Exemption (IDE) studies has demonstrated the superiority of artificial discs over fusion in the cervical spine. Worth noting, too, is that ADR was one of the most widely covered research subjects on technological innovation at NASS, with six presentations addressing the clinical value and two more on the economic benefits of cervical-disc replacement. Based on our internal research, we project the market for cervical ADR procedures in the US could reach USD1bn over the next 4 years, with two-level (two adjacent cervical discs replacements) procedures accounting for half of this market.

Artificial discs differ from comparable devices because they require a PMA from the FDA. To date, the agency has approved six artificial discs: Zimmer's Mobi-C, Centinel's ProDisc-C, Medtronic's Prestige LP and Bryan, Globus' Secure-C, and Nuvasive's PCM. Of these, only two are approved for two-level procedures: Mobi-C and Prestige LP.

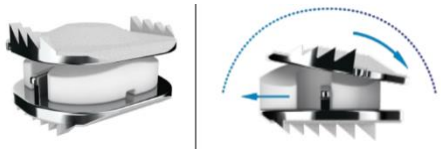

Figure 7. Mobi-C. Source: Zimmer Biomet website, date accessed on November 2, 2017.

Mobi-C, with its mobile core, presents the most advanced technology and generates approximately half of all sales in this segment. Since Zimmer acquired the disc as part of their USD1bn acquisition of LDR in 2016, Mobi-C has become one of the company's flagship products. The giant scaled-up model demonstrating the motion of the disc, which was featured at Zimmer's NASS booth, was clear evidence of its importance to the company.

In addition, DePuy Synthes recently sold the ProDisc, a first-generation ball-and-socket disc, to Centinel Spine. ProDisc is now the only such product available to independent distributors. We talked with these distributors and learned they are eager to offer a product in this fast-growing market, and are now looking to discuss distribution deals with Centinel Spine to add an artificial disc to their portfolio.

There is a clear need for an artificial disc in any competitive spine portfolio. Many of the largest players still do not have one and cannot adequately address this market opportunity. Among them, we've identified DePuy Synthes (a J&J company), Stryker, Nuvasive, Orthofix, and all the other pure-play spine companies. Vendors who are currently selling discs, such as Medtronic and Globus, may also wish to renew their offering to better compete with Zimmer's Mobi-C.

To bring a new disc to market, companies must go through the FDA's PMA process. In so doing, they must enroll hundreds of US patients in IDE clinical trials, comparing their disc with traditional fusion over a two-year follow up period. In addition, separate trials are required for approvals in the one-level indication and two-level indication. The requirements present substantial barriers to market entry, both in terms of costs and time.

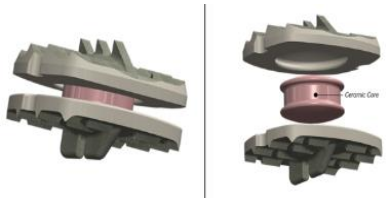

Figure 8. Simplify Disc. Source: Simplify Medical website, accessed on November 2, 2017.

Only two companies are currently running IDE trials and seeking FDA approval: Simplify, for both one-level and two-level indications, and Spinal Kinetics for the one-level indication.

CONCLUSION

The spinal-surgery market is showing low, but stable, growth. However, there are important shifts within the market, including the increased use of MIS and its enabling technologies. We see investment opportunities in those companies offering a broad portfolio of mainstay products and innovative solutions that support MIS procedures. Furthermore, companies developing these innovative solutions and other high-barrier technologies (ie. requiring PMA approval) can also offer valuable investment opportunities.

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SOURCES

- Nottmeier, E. Current Options in Robotic Spine Surgery, NASS 2017.
- Overley, S et al., Navigation and Robotics in Spinal Surgery: Where Are We Now? Neurosurgery 80:S86-S99, 2017
- Hu Y, Lv G, Ren S, Johansen D (2016) Mid- to Long-Term Outcomes of Cervical Disc Arthroplasty versus Anterior Cervical Discectomy and Fusion for Treatment of Symptomatic Cervical Disc Disease: A Systematic Review and Meta-Analysis of Eight Prospective Randomized Controlled Trials. PLoS ONE11(2): e0149312. https://doi.org/10.1371/journal.pone.0149312
- The Orthopaedic Industry Annual Report, OrthoWorld, 2016
- Technology Watch 2016, Vizient, 2016
- Ryan Zimmerman, BTIG Equity Research, October 2017

SECTORAL
ASSET MANAGEMENT

NEWSLETTER

FOURTH QUARTER 2017

ABOUT SECTORAL ASSET MANAGEMENT

Sectoral Asset Management was founded in 2000 and is exclusively focused on managing global healthcare portfolios. Sectoral continuously aims to achieve superior returns for our investors by concentrating on primary research. Sectoral has one of the world's longest track records in managing biotech equities and is a sub-advisor of numerous healthcare and biotech funds offered by partners in Europe and Asia. The firm is employee owned and registered with the SEC, AMF, FINMA and the SFC.

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Michael Sjöström, CFA - Chief Investment Officer	**Adrian Lam** – Financial Analyst
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Mina Marmor, Ph.D., CFA – Portfolio Manager	**Vasilios Tsimiklis, CFA** – Economist
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